Effective Health Care Program

Comparative Effectiveness Review
Number 55

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

Agency for Healthcare Research and Quality
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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10056-I

Prepared by:
RTI International–University of North Carolina Evidence-based Practice Center
Research Triangle Park, NC

Investigators:
Katrina E. Donahue, M.D., M.P.H.
Dan E. Jonas, M.D., M.P.H.
Richard A. Hansen, Ph.D.
Robert Roubey, M.D.
Beth Jonas, M.D., M.P.H.
Linda J. Lux, M.P.A.
Gerald Gartlehner, M.D., M.P.H.
Elizabeth Harden, M.P.H.
Tania Wilkins, M.S.
Visali Peravali, M.S.
Shrikant I. Bangdiwala, Ph.D.
Andrea Yuen, B.S.
Patricia Thieda, M.A.
Laura C. Morgan, M.A.
Karen Crotty, Ph.D.
Rishi Desai, M.S.
Megan Van Noord, M.S.I.S.

Errata: Tables 2, 3, and 4 have been corrected.

AHRQ Publication No. 12-EHC025-EF
Updated June 2012

This report is based on research conducted by the RTI International–University of North Carolina (RTI–UNC) Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10056-I).
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None of the investigators has any affiliations for financial involvement that conflicts with the material presented in this report.

Suggested Citation:
Donahue KE, Jonas DE, Hansen RA, Roubey R, Jonas B, Lux LJ, Gartlehner G, Harden E, Wilkins T, Peravali V, Bangdiwala SI, Yuen A, Thieda P, Morgan LC, Crotty K, Desai R, Van Noord M. Drug Therapy for Rheumatoid Arthritis in Adults: An Update. Comparative Effectiveness Review No. 55. (Prepared by RTI-UNC Evidence-based Practice Center under Contract No. 290-02-0016-I.) Rockville, MD: Agency for Healthcare Research and Quality. April 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Centre for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Agency for Healthcare Research and Quality

Carmen Kelly, Pharm.D., R.Ph.
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

Acknowledgements

We acknowledge the Director of the AHRQ Evidence-based Practice Center (EPC) Program, Stephanie Chang, M.D., M.P.H., and Carmen Kelly, Pharm.D., the AHRQ Task Order Officer for this project.

We extend our appreciation to our Technical Expert Panel. All provided thoughtful advice and input during our research process.

The investigators deeply appreciate the considerable support, commitment, and contributions of the EPC team staff at RTI International and the University of North Carolina at Chapel Hill. We express our gratitude to research analysts: Tammeka Swinson Evans, M.O.P., Stacey Lloyd, M.P.H., and Loraine Monroe, our EPC publications specialist.

Technical Expert Panel

Teresa J. Brady, Ph.D.
Patient Representative

Jeffrey R. Curtis, M.D., M.P.H.
Assistant Professor
Division of Clinical Immunology and Rheumatology
Associate Director
Center for Education and Research on Therapeutics of MSK disorders
University of Alabama at Birmingham
Birmingham, AL

Marion McDonagh, Pharm.D.
Assistant Professor
Informatics and Clinical Epidemiology
Oregon Health & Science University
Portland, OR

Christopher T. Ritchlin, M.D., M.P.H.
Internal Medicine, Rheumatology
School of Medicine and Dentistry
University of Rochester
Rochester, NY

Peer Reviewers

Joan M. Bathon, M.D.
Professor of Medicine
Division of Rheumatology
Department of Medicine
Johns Hopkins University
Director, Johns Hopkins Arthritis Center
Co-Deputy Director, Division of Rheumatology
Bayview Medical Center
Baltimore, MD

Louis Bridges, Jr., M.D., Ph.D.
Professor of Medicine and Microbiology
Director of the Division of Clinical Immunology and Rheumatology
Deputy Director of the Comprehensive Arthritis, Musculoskeletal, and Autoimmunity Center
University of Alabama at Birmingham
Birmingham, AL

Marion McDonagh, Pharm.D.
Assistant Professor
Informatics and Clinical Epidemiology
Oregon Health & Science University
Portland, OR

James O'Dell, M.D.
Professor and Program Director
Department of Internal Medicine
University of Nebraska
Lincoln, NE

Nancy Olsen, M.D.
McGee Foundation Distinguished Professor in Arthritis Research
Internal Medicine – Rheumatic Diseases
UT Southwestern Medical School
Dallas, TX

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

Structured Abstract

Objectives: Compare the benefits and harms of corticosteroids, oral and biologic disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis.

Data Sources: English-language articles from 1980 to February 2011 identified through PubMed, Embase, Cochrane Library, and International Pharmaceutical Abstracts; unpublished literature including dossiers from pharmaceutical companies.

Methods: Two people independently selected relevant head-to-head trials of any sample size, prospective cohort studies with at least 100 participants, and relevant good- or fair-quality meta-analyses that compared benefits or harms of 14 drug therapies. Retrospective cohort studies were also included for harms. For biologic DMARDs, placebo-controlled, double-blind RCTs were also included. We required trials and cohort studies to have a study duration of at least 12 weeks. Literature was synthesized qualitatively within and between the two main drug classes (oral and biologic DMARDs). Network meta-analysis also was performed to examine the relative efficacy of biologic DMARDs and comparing withdrawal rates from placebo controlled trials.

Results: Head-to-head trials showed no clinically important differences in efficacy among oral DMARD comparisons (methotrexate, sulfasalazine, leflunomide). The only head-to-head trial comparing biologic DMARDs (abatacept vs. infliximab) found no clinically important differences. Combination therapy of biologic DMARDs plus methotrexate improved clinical response rates and functional capacity more than monotherapy with methotrexate. Network meta-analyses found higher odds of reaching ACR 50 response for etanercept compared with most other biologic DMARDs (abatacept, adalimumab, anakinra, infliximab, rituximab, tocilizumab) for methotrexate-resistant patients with active rheumatoid arthritis. Similar overall tolerability profiles were found among oral and biologic DMARDs, but short-term adverse events were more common with biologic DMARDs. Adjusted indirect comparisons of biologic DMARDs found that certolizumab had the most favorable overall withdrawal profile, followed by etanercept and rituximab. Certolizumab had lower relative withdrawal rates due to lack of efficacy than adalimumab, anakinra, and infliximab. Certolizumab and infliximab had more, while etanercept had fewer withdrawals due to adverse events than most other drugs. Evidence was insufficient to assess comparative risk of serious adverse events among biologic DMARDs. Combinations of biologic DMARDs have higher rates of serious adverse events than biologic DMARD monotherapy. Limited data existed for subgroups.

Conclusions: Limited head-to-head comparative evidence does not support one therapy over another for adults with rheumatoid arthritis. Network meta-analyses from placebo-controlled trials of biologics suggest some differences, including higher odds of reaching ACR 50 response, but strength of evidence was low.

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Executive Summary

Background

Rheumatoid arthritis (RA), which affects 1.3 million adult Americans, is an autoimmune disease that involves inflammation of the synovium (a thin layer of tissue lining a joint space) with progressive erosion of bone leading in most cases to misalignment of the joint, loss of function, and disability. The disease tends to affect the small joints of the hands and feet in a symmetric pattern, but other joint patterns are often seen. The diagnosis is based primarily on the clinical history and physical examination with support from selected laboratory tests. Treatment of patients with RA aims to control pain and inflammation and, ultimately, the goal is remission or at least low disease activity for all patients. Available therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs or DMARDs (hydroxychloroquine, leflunomide, methotrexate [MTX], and sulfasalazine), and biologic DMARDs (five anti-tumor necrosis factor drugs [anti-TNF]: adalimumab, certolizumab, etanercept, golimumab, infliximab; and others including abatacept, anakinra, rituximab, and tocilizumab).

Treatment strategies for RA continue to evolve. Early use of DMARDs is considered crucial to avoid persistent and erosive arthritis. Clinicians frequently start treatment regimens with oral DMARD monotherapies and adjust dosages as appropriate to achieve a low disease activity or remission. Clinical experience supports the use of MTX as the oral DMARD of choice unless there are contraindications (e.g., liver impairment, alcohol abuse, pregnancy, lung disease). Experts have not arrived at consensus about the comparative effectiveness of corticosteroids, oral DMARDs, and biologic DMARDs. More importantly, it is unclear how the effectiveness and safety of different types of combination therapy compare, for example, oral DMARDs with corticosteroids, oral DMARDs with biologic DMARDs, or a triple combination of corticosteroids, oral DMARDs, and biologic DMARDs. In addition, there is debate about how early in the disease process combination therapy should be initiated. Many questions remain about the risks of these agents across a spectrum of adverse events, from relatively minor side effects such as injection site reactions to severe and possibly life-threatening problems such as severe infections or infusion reactions. Finally, very little is known about the benefits or risks of these drugs in different patient subgroups, including ethnic minorities, the elderly, pregnant women, and patients with other comorbidities.

Objectives

This report summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with RA. This report updates a previous version published in 2007. The Key Questions (KQs) are as follows:

KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?

KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?

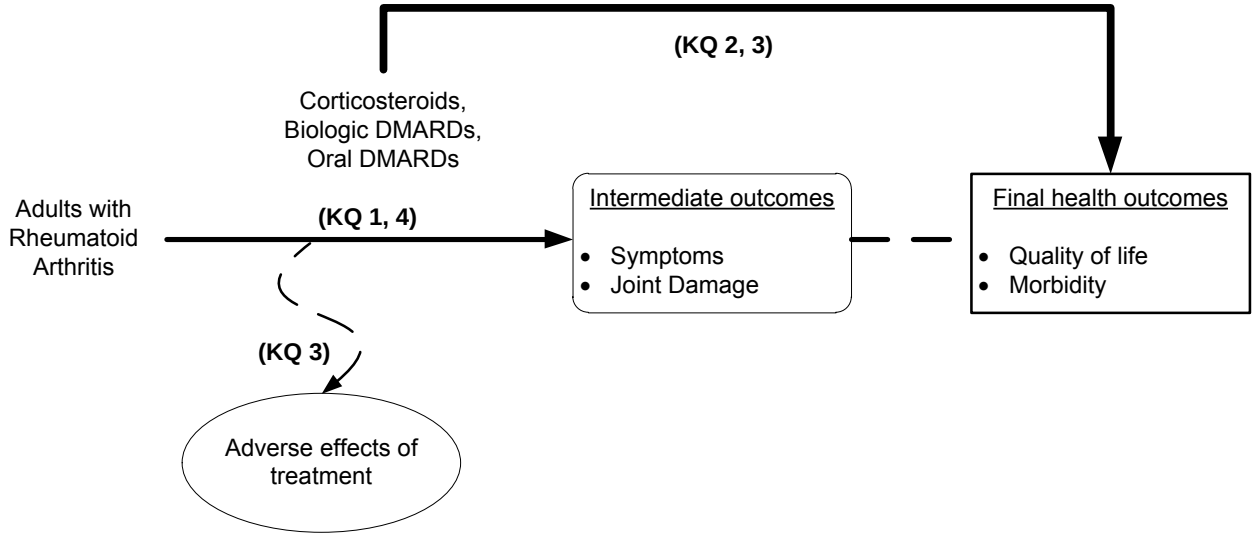
KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Analytic Framework

Figure A depicts the analytic framework for rheumatoid arthritis.

Figure A. Analytic framework for treatment for rheumatoid arthritis



Methods

A Technical Expert Panel was employed for the finalization of the KQs and review of the planned analysis strategy. Our KQs and protocol were posted on the Agency for Healthcare Research and Quality Web site for public review and comment. Individuals who were experts in rheumatology and various stakeholder and user communities performed an external peer review of the report. The report was also posted for public review. We compiled all comments and addressed each one individually, revising the text as appropriate.

We searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts to identify relevant articles. We limited the electronic searches to "human" and "English language." For this update, the searches went up to January 2011. Hand searches were conducted on the Center for Drug Evaluation and Research (CDER) database of the U.S. Food and Drug Administration and unpublished literature including dossiers from pharmaceutical companies.

Study eligibility (inclusion and exclusion) criteria were designed in respect to study design or duration, patient population, interventions, outcomes, and comparisons for each KQ. For efficacy and effectiveness, we focused on head-to-head trials and prospective cohort studies comparing one drug with another. For biologic DMARDs, we also included placebo-controlled, double-blind randomized controlled trials (RCTs). For harms and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and observational studies. We included studies with sample sizes of at least 100 and duration of at

least 3 months. We only included studies that used doses within the recommended dosing range or that used doses that could be considered equivalent to recommended doses.

Two individuals independently reviewed abstracts identified by searches. If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles. Two individuals again independently reviewed the full text of all remaining articles to determine whether they should be included. We designed and used a structured data abstraction form to ensure consistency of appraisal for each included study. Trained reviewers abstracted data from each study. A senior evaluated the completeness of each data abstraction.

We rated the quality of individual studies using the predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)[1] and the National Health Service Centre for Reviews and Dissemination.[2] Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. We gave a good-quality rating to studies that met all criteria. We gave a poor-quality rating to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. We graded the strength of evidence as high, moderate, low, or insufficient based on methods guidance for the Evidence-based Practice Program.[3,4] We graded strength of evidence for the outcomes determined to be most important: measures of disease activity (e.g., American College of Rheumatology [ACR] 20/50/70, Disease Activity Score [DAS]), radiographic changes, functional capacity, quality of life, withdrawals due to adverse events, and specific adverse events if data were available (e.g., injection-site reactions, infections, malignancy). We generally synthesized the literature qualitatively, but we did conduct meta-analyses comparing the relative efficacy of biologic DMARDs and comparing withdrawal rates from placebo-controlled trials. To compare the relative efficacy of biologic DMARDs, we conducted a mixed treatment comparison (MTC) meta-analysis using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) techniques. The primary efficacy outcome of our MTC meta-analysis was the ACR 50.

Results

We identified 3,868 citations from our searches. We included 258 published articles reporting on 211 studies: 31 head-to-head RCTs, 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies. We identified 30 studies for quantitative synthesis for KQ1 and 42 studies for quantitative syntheses for KQ3. Most studies were of fair quality.

Our major findings are presented in this section by type of drug comparison for benefits and harms (Table A). Subpopulation analyses are described after Table A because the evidence is very limited.

Table A. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. **Low** No clinically significant difference for functional capacity. **Low** Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. **Low**	No consistent differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Leflunomide vs. sulfasalazine	Mixed ACR response rates. **Insufficient** No differences in radiographic changes. **Low** Greater improvement in functional capacity for leflunomide **Low**	No differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes.[†] **Moderate** No differences for functional capacity.[†] **Moderate**	No differences in tolerability; more patients stayed on MTX long term. **Low** Mixed results for specific adverse events. **Insufficient**
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. **Moderate** No differences in functional capacity. **Moderate**	Withdrawal rates attributable to adverse events higher with combination. **Low** Insufficient evidence for specific adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. **Insufficient** Less radiographic progression in patients on DMARD plus prednisone. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded. joints **Low** Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. **Moderate** No difference in quality of life. **Low**	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. **Moderate** No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications. **Low**
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. **Low**	Discontinuation rates and severe adverse events higher with infliximab. **Low**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic vs. biologic *(Mixed treatment comparisons)*	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. **Low** Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. **Low**	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. **Low**
Biologic vs. biologic *(Mixed treatment comparisons)* (continued)	Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. **Low**	Risk for injection site reactions apparently highest with anakinra. **Low** Mixed results for specific adverse events. **Insufficient**
Biologic DMARDs vs. Oral DMARDs		
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. **Moderate** No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. **Low**; **Insufficient** Faster improvement in quality of life with etanercept than MTX. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. **Low**	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. **Moderate**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. **Moderate** In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. **Low** In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (**Moderate**) and quality of life (**Low**) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events **Insufficient**
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. **High** for clinical response and functional capacity, **Moderate** for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis. **Low** Mixed evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Strategies in Early RA		
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. **Low** More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. **Low**	No differences in discontinuation rates. **Moderate**
Three oral DMARDs plus prednisone vs. one oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints **Low**	No differences in discontinuation rates. **Moderate**
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. **Low**	No differences in serious adverse events between groups. **Low**

† at MTX doses ranging from 7.5-25 mg per week

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; MTC = mixed treatment comparisons; MTX = methotrexate; RA = rheumatoid arthritis; vs = versus

Subpopulations. Limited good or fair evidence for benefits or harms of subpopulations exists; therefore, the strength of evidence was low and results should be interpreted cautiously. Patients with moderate RA had significant improvements and better overall functional status than those with severe RA, but those with severe RA had the greatest improvements from baseline in disease activity. For MTX, the odds for major clinical improvement dropped slightly as the age of clinical trial patients increased; age did not affect MTX efficacy or the rate of side effects. Biologics neither decreased nor increased cardiovascular risks in the elderly. Those taking anakinra and concomitant diabetic, antihypertensive, or statin medications did not have higher adverse events rates. Toxicity was more likely with MTX in patients with greater renal impairment. Those with high-risk comorbidities (cardiovascular events, diabetes, malignances, renal impairment) and taking anakinra did not experience an increase in serious adverse events or overall infectious events.

Discussion

Existing comparative evidence did not support the superiority of one oral DMARD over another. Limitations to these trials included the wide range of MTX dosing in the trials. Biologic DMARD comparisons are limited to mostly observational studies and findings from MTC meta-analyses. Our MTC meta-analyses, suggest some differences, such as etanercept having a higher probability of improvement in disease activity than most other biologic DMARDs, but are limited primarily to indirect evidence (low strength of evidence) and therefore should be interpreted with caution. The limited evidence precludes drawing firm conclusions about whether one combination strategy is better than another in early RA. Overall tolerability is similar among biologic and among oral DMARDs; however, several studies suggest that adverse events are more common with biologic DMARDs compared with oral DMARDs. Limited evidence does not suggest an increased risk of severe adverse events, including cardiovascular or cancer, with oral DMARDs. Most studies found no risk of cardiovascular events and malignancy with biologic DMARDs, except for cohort studies, which describe an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with oral DMARDs.

Common problems for RA studies included the lack of effectiveness information, that is, studies and findings with a high level of applicability to community populations. Future investigations need to take into account factors such as varying adherence because of administration schedules, costs, and adverse events. Information is also needed about the performance of these drugs in subgroups of patients defined by health status, sociodemographic, or other variables.

To address problems with current literature, future studies should include using designs of longer duration and followup, enrolling patients representing key subgroups (or reporting on them when they are enrolled), and ensuring that quality of life (or other patient-centered outcomes) is measured, in addition to clinician-centered measures such as joint erosion. Ideally, studies need to mimic clinical decisionmaking, where if a patient is not doing well after a specified time, the protocol gives them something different. Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) timing of initiation of therapies, and (3) applicability of combination strategies and biologic DMARD therapy in community practice. The results of the MTC meta-analyses suggested some differences. However, the strength of evidence was low for the MTC findings, and head-to-head

studies are needed to confirm or refute these results before any firm clinical recommendations can be made.

Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases. Studies of longer duration and followup will be beneficial, given that RA is a progressive, chronic condition. Such studies will also help to clarify whether early initiation of any regimen can improve the long-term prognosis of RA and, particularly, whether early use of biologic DMARDs is helpful.

Abbreviations

ACR	American College of Rheumatology
Anti-TNF	Anti-tumor necrosis factor drugs
CDER	Center for Drug Evaluation and Research
DMARD	Disease-modifying antirheumatic drug
MCMC	Markov chain Monte Carlo techniques
MTC	Mixed-treatment comparisons
MTX	Methotrexate
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SF36	Short Form 36

References

1. Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35.

2. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001.

3. Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0. Rockville, MD: Agency for Healthcare Research and Quality; October 2007 (draft). http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf.

4. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2010 May;63(5):513-23.

Introduction

Arthritis and other rheumatic conditions constitute the leading cause of disability among U.S. adults,[1] with more than 46 million Americans reporting doctor-diagnosed arthritis.[2] Noninflammatory arthritic conditions (e.g., osteoarthritis) are most common, but inflammatory arthritides such as spondyloarthropathies (e.g., ankylosing spondylitis, psoriatic arthritis [PsA]), and reactive arthritis) and rheumatoid arthritis (RA) can be equally or more disabling.

Among patients with RA, the burden of disease is evidenced by decreased quality of life,[3-6] decreased employment rates,[7, 8] and increased direct and indirect costs.[9-12] In 2003, arthritis and other rheumatic conditions cost the United States $127.8 billion ($80.8 billion in medical care expenditures and $47.0 billion in lost earnings).[13] Annually, approximately 9 million physician office visits and more than 250,000 hospitalizations occur as the result of RA. The mean total annual direct cost to patients with RA is estimated to be $9,519 per person,[9] and most studies have reported indirect costs to be roughly twofold greater than direct costs.[14]

Causes and Diagnosis

RA is an autoimmune disease that affects 1.3 million adults in the United States.[2] Disease onset generally occurs between ages 30 and 50 years, and incidence is higher in women and older adults. RA presentations range from mild to severe. Some people are affected for as little as a few months, whereas others are affected for a lifetime and suffer severe joint damage and disability.

The hallmarks of the disease are inflammation of the synovium (a membrane that lines the joint capsule and produces lubricating fluid in the joint) with progressive erosion of bone leading to malalignment of the joint. As the inflamed synovium destroys the joint, the surrounding muscles and tendons become weak, leading to disability in most cases. Unlike osteoarthritis, RA can affect other areas in addition to joints. Most patients develop anemia. Some patients have dry eyes and mouth (sicca syndrome). Rarely, patients develop inflammation in the lining of the lung (pulmonary fibrosis), various layers of the eye wall (episcleritis and scleritis), small vessels (vasculitis), and the outer covering of the heart (pericarditis).

The exact etiology of RA is not completely understood, but genetic susceptibility plays an important role.[15, 16] Studies have shown the importance of T cells, B cells, and cytokines in the pathogenesis of RA.[17, 18] Cytokines of particular interest are tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6.

TNF plays a central role in the pathobiology of RA. It is an important regulator of other proinflammatory molecules and stimulates the secretion of matrix metalloproteinases. It also exerts a direct effect on the multiple tissues inside the joint including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. Together, its action leads to inflammation and the formation of pannus, a mass of tissue that causes localized joint destruction.[18]

The diagnosis of RA is primarily a clinical one, based on multiple patient symptoms. No single laboratory test confirms RA. Constitutional symptoms including low-grade fever, fatigue, or malaise are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. A serum rheumatoid factor is present in up to 75 percent of patients with RA but is frequently negative in early disease. A more specific marker, anticyclic citrullinated peptide

(CCP) antibody, has recently been described and may be a useful marker in patients with early disease.[19, 20] Table 1 presents the 1988 diagnostic criteria for RA developed by the American College of Rheumatology (ACR) and used by many of the studies in this review.[21] Patients are said to have RA if they meet four of the seven criteria in the table.[21] It should be noted that these criteria are relatively insensitive for early disease and efforts are underway to revise the criteria to address this issue. In 2010, a collaborative work group of the ACR and the European League Against Rheumatism (EULAR) released new classification criteria that are sensitive to the current treatment goals—remission or at least low disease activity in all patients.[22] (Further information on these criteria can be found at the end of Appendix G).

Table 1. ACR criteria for the diagnosis of rheumatoid arthritis

Criteria
1. Morning stiffness lasting greater than 1 hour
2. Arthritis in three or more joint areas
3. Arthritis of the hand joints (metacarpophalangeal [MCP], proximal interphalangeal [PIP], wrists)
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes: erosions or unequivocal periarticular osteopenia

Source: Arnett et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar; 31(3):315-24.[21]

Treatment of Rheumatoid Arthritis

Treatment of patients with RA aims to control pain and inflammation and, ultimately the goal is remission or at least low disease activity for all patients. This review focuses on treatments commonly used for RA in the United States.[a]

Corticosteroids. Corticosteroids—sometimes referred to as glucocorticoids or steroids—are used for many inflammatory and autoimmune conditions. As a class, corticosteroids have been used since the discovery of cortisone in the 1940s. Commonly used oral corticosteroids include methylprednisolone, prednisone, and prednisolone.

Corticosteroids are a synthetic form of cortisol, a hormone produced by the adrenal glands. They produce their anti-inflammatory and immunosuppressive response by interacting with steroid-specific receptors in the cytoplasm of cells, thereby inhibiting the movement of inflammatory cells into the site of inflammation, inhibiting neutrophil function, and inhibiting prostaglandin production. They are widely prescribed as an oral treatment for RA because of their ability to reduce inflammation and subsequent joint pain and swelling.

Oral disease-modifying antirheumatic drugs (DMARDs). Oral DMARDs such as methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide modify the course of inflammatory conditions, presumably through their effects on the immune system. Most of the oral DMARDs have been used in clinical practice for more than 20 years. MTX was developed in the 1940s as a treatment for leukemia but was not approved for the treatment of arthritis until 1988. Sulfasalazine also has been available since the 1940s; it is a combination salicylate (acetylsalicylic acid) and antibiotic (sulfapyearidine) that originally was used to treat patients with inflammatory bowel disease. Hydroxychloroquine, approved in the 1950s for the treatment of malaria, is believed to work in arthritis by interfering with antigen presentation and the activation of immune response by increasing the pH within macrophage phagolysosomes. Additionally, hydroxychloroquine possibly inhibits toll-like receptors that mediate

[a] Minocycline, gold cyclosporine, and azathioprine are not included in this review.

proinflammatory cytokine production. Only leflunomide, an isoxazole immunomodulatory agent, was specifically developed for treating inflammatory arthritis; the U.S. Food and Drug Administration (FDA) approved its use in 1998.

Oral DMARDs are not members of a single drug family. They are classified together, however, because they all are slow acting with the aim of improving symptoms, reducing or preventing joint damage, and preserving structure and function in patients with inflammatory disease. All the oral DMARDs covered in this review can be given orally, although MTX can also be injected (subcutaneous [SQ] or intramuscular [IM]).

Biologic DMARDs. Biologic DMARDs—commonly referred to as biological response modifiers or simply biologics—are a relatively new injectable category of DMARDs that differ from oral DMARDs in that they target specific components of the immune system. The FDA approved the first of the biologics (infliximab) in 1998; this report covers eight additional agents approved since that time: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), rituximab (2006), certolizumab pegol (2008), golimumab (2009), and tocilizumab (2010). Of the nine agents, all are currently FDA approved for treating RA.

The biologic DMARDs work by selectively blocking mechanisms involved in the inflammatory and immune response. Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are known as TNF inhibitors (i.e., drugs that block specific proinflammatory mediators known as cytokines). They produce their primary effect by blocking TNF from interacting with cell surface TNF receptors. Adalimumab, infliximab, and golimumab are monoclonal antibodies. Adalimumab is a fully human monoclonal antibody that binds specifically to TNF, blocking its interaction with both the p55 and p75 cell surface TNF receptor. Golimumab is also a human monoclonal antibody that binds to TNF alpha with high affinity. Infliximab is a chimeric (i.e., made from human and mouse proteins) monoclonal antibody that binds specifically to human TNF alpha. Etanercept is not a monoclonal antibody, but rather a TNF-soluble receptor protein. More specifically, it is a soluble dimeric form of the p75 TNF receptor linked to the Fc portion of human immunoglobulin G1 (IgG1). Etanercept exerts its action by binding circulating TNF and preventing it from interacting with a cell surface receptor. It does not form neutralizing antibodies or mediate cell lysis in the presence or absence of complement. Certolizumab pegol is a pegylated humanized antibody fragment of TNF monoclonal antibody. The drug binds to the TNF alpha-receptor and blocks TNF alpha actvity. It only possesses the Fab fragment and lacks the Fc region. Hence, it does not induce antibody-dependant cell mediated apoptosis or toxicity.

IL-1, another naturally occurring cytokine, has both immune and proinflammatory actions. Anakinra, an IL-1 receptor antagonist, is a human recombinant protein that competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agent abatacept produces its immune response by interfering with T lymphocyte activation. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of IgG1.

Rituximab, a chimeric murine/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes. Thus, it removes circulating B cells from the pre-B cell stage through the activated B cells. B cells are believed to play a role in autoimmune and inflammatory processes, such as those involved in RA.

IL-6 is a naturally occurring cytokine involved in the regulation of immune responses and inflammation. Tocilizumab is a monoclonal antibody that inhibits interleukin-6 (IL-6) receptors,

blocking the action of IL-6, and leading to a reduction in cytokine and inflammatory response. Tables 2 through 4 provide detailed information (names, manufacturers, and available dosage forms) on agents used in the treatment of RA that we have included in this review. Also presented are routes of administration, labeled uses, and usual (recommended) adult doses and frequency for RA.

Table 2. Pharmaceutical treatments for rheumatoid arthritis: Corticosteroids

Generic Name	Manufacturer U.S. Trade Name(s)*	How Supplied	Usual Adult Dose
Cortico-steroids: Methyl-prednisolone	Multiple Medrol®, Depo-Medrol®, Solu-Medrol®	Acetate - Injectable IM—20, 40, and 80 mg/ml Sodium succinate - Injectable IM—40, 125, and 500 mg, 1 and 2 g vials Oral: Tabs—2, 4, 8, 16, and 32 mg	Acetate: IM—10 to 80 mg every 1 to 2 weeks Intra-articular, intralesional—4 to 80 mg every 1 to 5 weeks Sodium succinate: IM—10 to 80 mg daily IV—10 to 40 mg every 4 to 6 hours; up to 30 mg/kg every 4 to 6 hours Oral: 2 to 60 mg in 1 to 4 divided doses to start, followed by gradual reduction
Prednisone	Multiple Deltasone®, Sterapred®, LiquiPred	Oral Solution—1 and 5 mg/ml Tabs—1, 2.5, 5, 10, 20, and 50 mg	Use lowest effective dose. Usually ≤ 10 mg/day, but doses range from 5-60 mg/day
Prednisolone	Multiple Orapred®, Pediapred®, Prelone®, Delta-Cortef®, Econopred®	Oral Solution/Syrup—5, 15, and 20 mg/5 ml Oral Tabs—5 and 15 mg	Use lowest effective dose (5 to 7.5 mg/day), up to 60 mg/day

IM = intramuscular; IV = intravenous; kg = kilogram; mg = milligram; ml = milliliter

*Listed trade names are limited to commonly prescribed U.S. products when multiple trade names are available.

Table 3. Pharmaceutical treatments for rheumatoid arthritis: Oral DMARDs

Generic Name	Manufacturer U.S. Trade Name(s)*	How Supplied	Usual Adult Dose
Hydroxy-chloroquine	Multiple Plaquenil®	Oral Tabs—200 mg	200 to 400[a] mg/day in 1 or 2 divided doses
Leflunomide	Multiple Arava®	Oral Tabs—10 and 20 mg	10 to 20 mg/day in a single dose. May give loading dose of 100 mg/day for 3 days in patients with low risk of hepatic or hematologic toxicity.
Methotrexate	Multiple Trexall®, Folex®, Rheumatrex®	Injectable—25 mg/ml, 20 mg and 1 g vials Oral Tabs—2.5, 5, 7.5, 10, and 15 mg	IM, SQ, oral—7.5 to 20 mg/week in a single dose
Sulfasalazine	Multiple Azulfidine®, EN-tabs®, Sulfazine®	Oral Suspension—250 mg/5 ml Oral Tabs—500 mg	500 to 3,000 mg/day in 2 to 4 divided doses

g = gram; IM = intramuscular; mg = milligram; ml = milliliter

*Listed trade names are limited to commonly prescribed U.S. products when multiple trade names are available.

[a]Initial dose is 400 to 600 mg/day for 4 to 12 weeks.

Table 4. Pharmaceutical treatments for rheumatoid arthritis: Biologic DMARDs

Generic Name	Manufacturer U.S. Trade Name(s)*	Injectable Supply	Usual Adult Dose
Abatacept	Bristol Myers Squibb Orencia®	250 mg vial	IV—Dosed according to body weight (< 60 kg = 500 mg; 60-100 kg = 750 mg; > 100 kg = 1,000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter SQ—may give weight-based IV loading dose, then 125 mg SQ once weekly
Adalimumab	Abbott Humira®	40 mg/0.8 ml, 20 mg/0.4 ml prefilled syringe	SQ—40 mg every other week; may increase to 40 mg per week in patients not taking concomitant MTX
Anakinra	Amgen Kineret®	100 mg/0.67 ml syringe	SQ—100 mg/day; dose should be decreased to 100 mg every other day in renal insufficiency
Certolizumab Pegol	UCB Cimzia®	200 mg powder for reconstitution, 200 mg/ml solution	SQ—Initial dose of 400 mg, (as 2 SQ injections of 200 mg), repeat dose 2 and 4 weeks after initial dose; maintenance dose is 200 mg every other week (may consider maintenance dose of 400 every 4 weeks)
Etanercept	Amgen Pfizer Immunex Enbrel®	50 mg/ml in 25 mg or 50 mg single use prefilled syringe	SQ—50 mg once weekly with or without MTX
Golimumab	Centocor or Ortho Biotech Simponi®	50 mg/0.5 ml syringe	SQ—50 mg once per month in combination with MTX
Infliximab	Centocor or Ortho Biotech Remicade®	100 mg in a 20 ml vial	IV—3 mg/kg in combination with MTX at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treat as often as every 4 weeks
Rituximab	Biogen Idec / Genentech Rituxan®	100 mg/10 ml and 500 mg/50 ml vial	IV—1,000 mg IV infusion separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks
Tocilizumab	Genentech / Roche Actemra®, RoActemra®	80 mg/4 ml, 200 mg/10 ml, 400 mg/20 ml vial	IV—4 mg/kg every 4 weeks; increase to 8 mg/kg every 4 weeks based on clinical response

kg = kilogram; mg = milligram; ml = milliliter; MTX = methotrexate; IV = intravenously SQ = subcutaneously
*Listed trade names are limited to commonly prescribed U.S. products when multiple trade names are available.

Treatment Strategies

In RA, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in early or mild disease, but they do not have any disease-modifying properties. The oral DMARD MTX is the cornerstone of treatment, as it has demonstrated good disease control. However, MTX toxicity may limit its use, and many patients do not adequately respond to MTX monotherapy. Leflunomide, hydroxychloroquine, and sulfasalazine are alternative oral DMARDs that can be given as monotherapy or in combination; recommendations for their use are largely based on disease duration, degree of disease activity, and prognostic features.[23]

Combination therapies serve an important role because treatment with a single DMARD often does not adequately control symptoms. Low-dose systemic corticosteroids (prednisone 7.5-10 mg/day) or intra-articular corticosteroids are used as an adjunct to DMARDs. In patients with persistent disease despite aggressive management with standard agents, biologic agents, often in combination with MTX, are now considered the standard of care. Although combination therapies improve response rates in patients initially receiving monotherapy, available evidence does not predict which combination strategy will provide the best outcome.[24]

There is debate about which types of combination therapy are preferred and how early in the disease process to initiate this intervention. No settled opinion exists as to whether treatment should proceed in a sequential step-up approach (progressing from single therapy to combination therapy) or in a step-down approach (beginning with combination therapy and stepping down treatment when symptoms are under control). Additional uncertainty remains regarding risks and benefits of therapies in patient subgroups.

Recent reports have examined treatment of RA, supporting the overall efficacy of treatments.[25-29] However, additional agents have since been introduced on the market, necessitating an update of the evidence. A further examination of the comparative efficacy and effectiveness of various treatments and treatment strategies, as well as long-term outcomes and subpopulations, is warranted.

Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with RA. We address the following four Key Questions (KQs):

- KQ 1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?
- KQ 2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
- KQ 3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?
- KQ 4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Organization of the Report

The remainder of this comparative effectiveness review describes our methods to review and synthesize this literature, presents our results by KQ, and discusses the implications of those results for clinical applications and future research. Appendix A describes our search strategy; Appendix B presents our review and abstraction forms; Appendix C lists our articles by database searched; Appendix D lists excluded studies and the reasons for exclusion; Appendix E contains our evidence tables; Appendix F presents the criteria for assessing the quality of individual studies; Appendix G describes clinical assessment scales commonly used in arthritis trials; Appendix H contains our Poor Quality studies; Appendix I, our Strength of Evidence tables; Appendix J, the sensitivity analysis methods for the Mixed Treatment Comparisons; and Appendix K, the ACR 20 and ACR 70 results for the Mixed Treatment Comparisons.

Methods

In this chapter, we document the procedures that the RTI International–University of North Carolina Evidence-based Practice Center (RTI–UNC EPC) used to develop this comparative effectiveness review (CER) on pharmacologic treatments for rheumatoid arthritis. We briefly describe the topic development process below. We then document our literature search and retrieval process and describe methods of abstracting relevant information from the eligible articles to generate evidence tables. We also document our criteria for rating the quality of individual studies and for grading the strength of the evidence as a whole.

Topic Development

This report is an update of a CER completed in 2007.[26] The topic of the original report and the preliminary Key Questions (KQs) arose through a public process involving the public, the Scientific Resource Center (SRC, at www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#RC) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov), and various stakeholder groups (www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#SG). Investigators from the RTI-UNC EPC then refined the original questions into the KQs used for the original report, in consultation with AHRQ, the SRC, and the Technical Expert Panel (TEP) during multiple conference calls. For this update, the original KQs were again refined into the final set of KQs cited in the introduction. No substantive changes to the KQs were made for this update other than adding new medications that have been approved since the previous report. The protocol for the project was posted on the AHRQ Web site (www.effectivehealthcare.ahrq.gov). The original report included both rheumatoid arthritis (RA) and psoriatic arthritis (PsA). When updating the material, the decision was made to divide into the material into two separate reports, one for RA and one for PsA. This report includes only the information related to patients with RA. This report is intended to replace the original report; it includes the information from the original report as well as the new information we identified.

Literature Search

To identify articles relevant to each KQ, we searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix A. We conducted this review at the same time as a review on PsA; the literature searches and review processes were conducted in parallel, shown in Appendix A. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (RA, PsA), drug interactions, and adverse events with a list of included medications. We included the following medications: corticosteroids (methylprednisolone, prednisone, and prednisolone), four oral disease-modifying antirheumatic drugs (DMARDs) (methotrexate [MTX], leflunomide, sulfasalazine, and hydroxychloroquine), and nine biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab). We limited the electronic searches to “human” and “English language.” For the original report, sources were searched from 1990 to September 2006. For this update, sources were searched from June 2006 to January 2011. We overlapped the update search with the original search to account for delays in indexing. We used the National Library of Medicine publication type tags to identify reviews,

randomized controlled trials (RCTs), and meta-analyses. We manually searched reference lists of pertinent review articles and letters to the editor to supplement searches for the original report. We used the Scopus™ abstract and citation database to supplement searches for this update. We imported all citations into an electronic database (EndNote X.0.2). Additionally, we hand-searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the U.S. Food and Drug Administration (FDA). The SRC contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from five pharmaceutical companies (Abbott, Amgen, Bristol-Myers Squibb, Centocor, and Genentech) for the original report. We received dossiers from six pharmaceutical companies (Abbott, Amgen, Centocor, Horizon, Genentech, and UCB) for this update. The SRC also searched the following for potentially relevant unpublished and ongoing literature: FDA Web site; Health Canada; Authorized Medicines for EU; ClinicalTrial.gov; Current Controlled Trials, Clinical Study Results, WHO Clinical Trials, Conference Papers Index; Scopus; NIH RePORTER; HSRPROJ; Hayes, Inc. Health Technology Assessment; and the New York Academy of Medicine's Grey Literature Index.

Study Selection

We developed eligibility (inclusion and exclusion) criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons for each KQ, as described in Table 5. For efficacy and effectiveness, we focused on head-to-head trials and prospective cohort studies comparing one drug with another. For biologic DMARDs, we also included placebo-controlled, double-blind RCTs. For harms and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and observational studies.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and harms. We defined head-to-head trials as those comparing one drug of interest with another. RCTs or prospective cohort studies of at least 3 months' duration were eligible for inclusion. Because multiple large RCTs had been conducted on this topic, we adopted a minimum sample size requirement ($N \geq 100$) to focus on the best available evidence. However, we did not use a sample size cutoff for our meta-analyses (RCTs of any sample size were eligible for our mixed treatment comparisons). For harms (i.e., evidence pertaining to tolerability, adverse effects, and adverse events), we examined data from both experimental and observational studies. We included RCTs and observational studies with sample sizes of at least 100 patients that last at least 3 months, and that reported an outcome of interest.

As equipotency among the reviewed drugs is not well established, we assumed that comparisons made within the recommended dosing ranges in the Introduction chapter are appropriate. Dose comparisons made outside the recommended daily dosing range are not in our report. Doses that that could be considered equivalent to the recommended doses, but were not identical to recommended doses are included in the report. For example, 40 mg every other week is a recommended dose for adalimumab and some studies used a 20 mg weekly dosing (not a recommended dose). We considered the 20 mg weekly dose to be equivalent to 40 mg every other week and included studies using the 20 mg every week dose.

Table 5. Outcome measures and study eligibility criteria

Key Questions, Outcomes of Interest, and Specific Measures	Study Eligibility Criteria
KQ 1/KQ 2:[a] **Efficacy/effectiveness** **KQ 1:** • Disease activity[b] • Radiographic joint damage • Remission **KQ 2:** • Functional capacity • Quality of life • Patient-reported symptoms	**Study Design** • Head-to-head double-blind RCTs • Systematic reviews • Prospective, controlled cohort studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Ages 19 or older • Patients with RA **Sample Size** • RCT N ≥100 • Observational N ≥100
KQ 3: **Harms, tolerability, adherence, adverse effects**	**Study Design** • Head-to-head double-blind RCTs • Systematic reviews • Observational studies, prospective and retrospective **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Ages 19 or older • Patients with RA **Sample Size** • RCT N ≥100 • Observational N ≥100
KQ 4: **Benefits and harms in subgroups based on stage, history of prior therapy, demographics, concomitant therapies, comorbidities**	**Study Design** • Head-to-head double-blind RCTs • Systematic reviews • Observational studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Ages 19 or older • Patients with RA **Sample Size** • RCT N ≥100 • Observational N ≥100

KQ = Key Question; N = number of subjects enrolled (i.e. sample size); RA = rheumatoid arthritis; RCT = randomized controlled trial

[a] We divided the assessment of efficacy/effectiveness into two KQs based on two groups of outcomes: those addressing disease activity, radiographic measures, and remission (KQ 1) and those addressing functional capacity, quality of life, and other patient reported symptoms (KQ 2). We did this to group measures that are based on more objective measures under KQ 1 and those that are based more on subjective patient reported outcomes under KQ 2.

[b] Disease activity reflects the overall RA activity. Measures of disease activity, such as the American College of Rheumatology 20 percent response (ACR 20), 50 percent response (ACR 50), 70 percent response (ACR 70), and the Disease Activity Score (DAS), include assessment of some or all of the following: the number of swollen and tender joints, the patient's global assessment of his/her disease activity, the physician's global assessment of the patient's disease activity, patient's pain score, patient's physical function score, and acute phase reactants (C-reactive protein). Appendix G provides additional details about these measures.

Two individuals independently reviewed abstracts (Appendix B contains review criteria for title/abstract stage). If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility

criteria (Appendix B) to determine which, if any, to exclude at this stage. Appendix C lists our full bibliography and their source database. Appendix D summarizes reasons for excluding studies that were reviewed as full-text articles but did not meet eligibility criteria. We did not include studies that met eligibility criteria but were reported as an abstract only.

We reviewed studies that reported health outcomes for efficacy or effectiveness. For example, these outcomes included clinical response to treatment, remission, functional capacity, and quality of life. In addition, we included radiographic outcomes as intermediate outcome measures. For harms, we looked for both total adverse events and specific adverse events ranging in severity (e.g., serious infections, malignancies, hepatotoxicity, hematological adverse events, infusion and injection reactions, and nausea), withdrawals attributable to adverse events, and drug interactions. We included systematic reviews and meta-analyses in our evidence report if we found them to be relevant for a KQ and of good or fair methodological quality. We did not abstract individual studies if they had been used in an included systematic review or meta-analysis of good quality. However, we reviewed them to determine whether any other outcomes of interest were reported.

Data Extraction

We designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Trained reviewers abstracted data from each study. A senior reviewer read each abstracted article and evaluated the completeness of the data abstraction.

We abstracted the following data from included articles: study design, eligibility criteria, intervention (drugs, dose, and duration), additional medications allowed, methods of outcome assessment, population characteristics (such as age, sex, race or ethnicity, or mean disease duration), sample size, loss to followup, withdrawals because of adverse events, results, and adverse events reported. We recorded intention-to-treat (ITT) results if available. All data abstraction employed SRS 4.0, Mobius Analytics™. Evidence tables containing all abstracted data of included studies are presented in Appendix E.

Quality Assessment

To assess the quality (internal validity) of trials, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)[30] and the National Health Service Centre for Reviews and Dissemination.[31] Elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis (i.e., all patients were analyzed as randomized), adequacy of blinding, and overall and differential loss to followup.

In general terms, a "good" study has a low risk of bias and results are considered to be valid. A "fair" study is susceptible to some risk of bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant risk of bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results.

To assess the quality of observational studies, we used criteria outlined by Deeks et al.[32] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis. To assess the quality of systematic reviews and meta-analyses, we assessed the following: whether the review was based on a clear question, clear reporting of inclusion criteria, methods used for identifying

literature (the search strategy), whether two reviewers independently reviewed publications to determine eligibility, whether authors used a standard method of critical appraisal (or quality rating or validity assessment), assessment of heterogeneity, assessment of publication bias, and statistical analysis. Systematic reviews were categorized as good when all criteria were met.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. Appendix F details the predefined criteria used for evaluating the quality of all included studies. We gave a good-quality rating to studies that met all criteria. We gave a poor-quality rating to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. Poor-quality studies and reasons for that rating are presented in Appendix H.

Applicability Assessment

We used the parameters for evaluation on guidance provided by AHRQ's Methods Guide for Comparative Effectiveness Reviews,[33] to evaluate the applicability of the included studies. Applicability is similar to generalizability or external validity of the studies included in the evidence base. We evaluated applicability using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of followup, and setting. We specifically considered whether populations enrolled in these trials or studies differed from target populations as laid out in the Introduction, whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings.

Grading Strength of Evidence

We evaluated the strength of evidence based on methods guidance for the EPC program.[33, 34] For this report, we graded the strength of evidence for the outcomes determined to be most important: measures of disease activity (e.g., ACR 20/50/70, DAS), radiographic changes, functional capacity, quality of life, withdrawals due to adverse events, and specific adverse events if data were available (e.g., injection-site reactions, infections, malignancy). The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains (Table 5): risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships).

As described in Owens et al., the evaluation of risk of bias includes assessment of study design and aggregate quality of studies.[34] We judged good-quality studies to result in evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same direction. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. We graded evidence as being precise when results had a low degree of uncertainty. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions.[34]

We dually evaluated the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain and reconciled all disagreements. The levels of strength of evidence are shown in Table 6.

Table 6. Strength of evidence grades and their definitions[34]

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

A direct comparative effectiveness assessment of two treatments was available if a comparative study of the two treatments has been conducted. Ideally, this would be a randomized controlled trial that directly compares the two treatments. However, many competing treatments have not been compared directly. In such cases, indirect methods that utilize data from common comparators (e.g., placebo) were available. There were very few head-to-head studies of biologic DMARDS, but there were numerous placebo-controlled studies. Using MTC meta-analysis allowed us to incorporate both direct evidence (from head-to-head studies) and indirect evidence (from placebo-controlled studies) to determine how biologic DMARDs compare with each other."

Throughout this CER, we generally synthesized the literature qualitatively. The exceptions are the meta-analysis comparing the relative efficacy of biologic DMARDs and the meta-analyses comparing withdrawal rates from placebo-controlled trials. Comparisons of the drugs that were not quantitatively analyzed in any of the included meta-analyses were either limited to fewer than three good or fair RCTs or had heterogeneous/noncomparable study populations. Therefore, we did not attempt any quantitative analyses of such comparisons.

To compare the relative efficacy of biologic DMARDs, we used a mixed treatment comparison (MTC) meta-analysis. MTC is a generalization of standard pairwise meta-analysis that allows for simultaneous pairwise comparisons based on a network of evidence.[35] One advantage of MTC using a Bayesian framework is that it allows for the combination of both direct head-to-head evidence and indirect evidence (e.g., different treatments with a common comparator) in a way that preserves randomization and minimizes bias.[36] Another advantage is that the Bayesian framework allows for a ranking of treatments based on the probability of which treatment is best.[37]

We conducted the MTC meta-analysis using the methods developed by the Multi-Parameter Evidence Synthesis (MPES) Research Group at the University of Bristol.[35, 36, 38] We used a random effects logistic regression model that adjusted for correlations between arms within each study. The analysis was performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) techniques.[39] We used WinBUGS code developed by the MPES Research Group, which is available from their program Web site.[40] For our analysis, study effect and treatment effect parameters were modeled by noninformative (flat) prior distributions that were normal (0, 10,000). For the heterogeneity of the random-effects model, we used a uniform prior distribution centered at zero with sufficiently large variance. The first 20,000 simulations were discarded to allow for model convergence, and then an additional 80,000 simulations were used in estimating the posterior probabilities. Satisfactory convergence was verified by trace plots and calculation of the Monte Carlo error for each parameter.

In conducting any meta-analysis, it is important to consider various sources of heterogeneity and bias. Valid inferences are based on the assumption of studies of similar design, similar patient populations, and a network of evidence with a common comparator. Evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials.[41-43]

For the MTC meta-analyses for efficacy, we included studies with a good or fair quality rating that compared biologic DMARDs to a placebo- or active-control in patients with active RA despite MTX therapy. Patients could be on a background dose of MTX, but both treatment and placebo arms needed to be on comparable doses. Only studies with durations greater than 3 months were considered. For MTC meta-analyses for efficacy, we excluded trials enrolling either (1) patients who were MTX-naïve, or (2) patients who previously failed treatment with biologic DMARDs. This population reflects a clinically relevant subset, because in general, biologics are prescribed when patients are resistant to MTX and many of the studies were conducted in MTX-resistant patients who are new to biologic therapy. In addition, patients who are MTX-naïve or who have previously failed treatment with biologic DMARDs may have different response to treatments. We felt that an inadequate number of studies examined other populations, such as MTX-naïve patients, to allow us to conduct MTC meta-analyses for efficacy for other populations.

For MTC meta-analyses of withdrawals, we did not exclude studies enrolling patients who were MTX-naïve or patients who previously failed treatment with biologic DMARDs because we did not consider these factors to be significant in evaluating tolerability profiles. Unlike efficacy, we believe that tolerability is more likely to be a function of the specific treatment regimen than it is to be related to how patients previously have responded to other treatments (i.e., MTX naive and anti-TNF failure).

Our outcome measures of choice were American College of Rheumatology (ACR) response rates and withdrawals (overall, due to lack of efficacy, and due to adverse events).[44] The primary efficacy outcome of our MTC meta-analysis is the ACR 50; results are reported in the Results chapter. The results from the analysis of ACR 20 and ACR 70 are presented in Appendix J. We present the relative efficacies of biologic DMARDs as odds ratios and 95 percent Credible Intervals (CrI).

A total of 34 studies were identified for potential inclusion in the MTC meta-analysis of ACR response rates, and were further reviewed to explore sources of heterogeneity before conducting the MTC. We excluded four studies from the main analysis because of heterogeneity due to study design, whereas other sources of heterogeneity were explored through sensitivity analyses (Appendix K). The four excluded studies had early escape designs, a large number of crossovers from placebo to active treatment, and no ACR outcomes reported prior to the crossover. All potentially eligible studies of certolizumab were among these four studies. A total of 30 studies were included in the final MTC meta-analysis for efficacy, evaluating eight biologic DMARDs: abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Detailed information on the included studies for the efficacy analysis can be found in the Results chapter.

The meta-analysis comparing withdrawal rates from placebo-controlled trials used a random effects model to calculate pooled odds ratios of treatment withdrawals for each biologic DMARD relative to placebo. In these analyses, certolizumab pegol was included (because outcomes were reported prior to, or at the time of, crossover) in addition to the eight biologic DMARDs listed above. The outcomes of interest were rates of overall withdrawals, withdrawals

due to lack of efficacy, and withdrawals due to adverse events. For each analysis, we conducted a test of heterogeneity (I^2 statistic) and assessed publication bias with funnel plots. These analyses were performed using Stata 10. Additional meta-analyses comparing withdrawal rates between the biologic DMARDs were performed using an MTC meta-analysis.

Peer Review

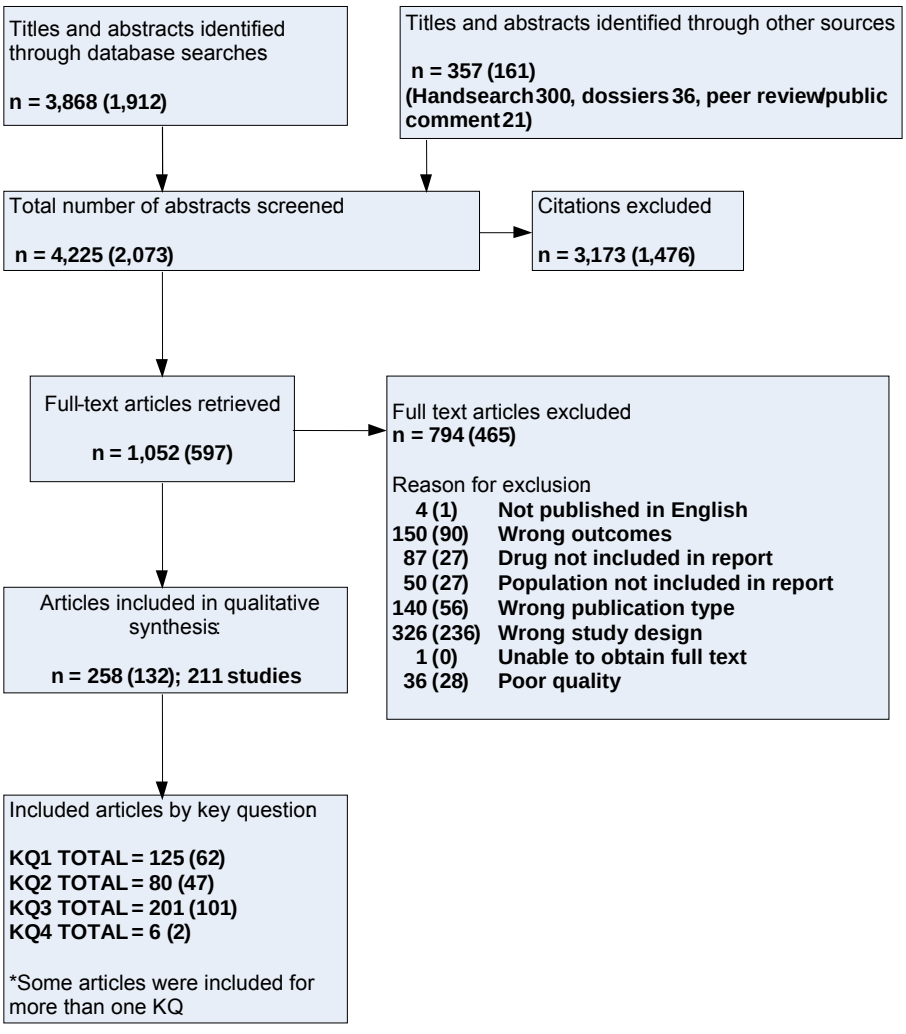
Individuals who were experts in rheumatology and various stakeholder and user communities (listed in the front matter) performed an external peer review on this CER. The SRC oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we had conceptualized and defined the topic and KQs. Our peer reviewers (listed in the front matter) gave us permission to acknowledge their review of the draft. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. In addition, the SRC placed the draft report on the AHRQ Web site (http://effectivehealthcare.ahrq.gov) and compiled the comments for our review.

Results

Introduction

Figure 1 depicts the disposition of identified articles. We included 258 published articles reporting on 211 studies: 31 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies. Our findings include studies rated good or fair for internal validity, unless a particular study rated poor provides some unique information that we judged to be of interest. Most studies were of fair quality; we designate in the text only those of good or poor quality. Evidence tables for included studies, by Key Question (KQ), can be found in Appendix E.

Figure 1. Disposition of articles (PRISMA figure)



KQ, key question; n, number of studies; PRIMSA, Preferred Reporting Items for Systematic Reviews and Meta Analyses

*The first number listed includes all references identified in both the original and update reports

Of the 211 included studies, 104 (49 percent) were supported by pharmaceutical companies; 42 (20 percent) were funded by governmental or independent funds; and 20 (10 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 45 (21 percent) studies.

This chapter is organized by Key Question. We then present findings in order by class of drugs and combinations of drugs as appropriate to the particular key question. Generally, the chapter is organized using the following categories: individual oral disease-modifying antirheumatic drug (DMARD) versus oral DMARD, oral DMARD combinations (with or without corticosteroids) versus oral DMARD combinations, biologic versus biologic, biologic versus oral DMARD, biologics plus oral DMARD versus biologic, biologic plus oral DMARD versus oral DMARD, and early RA strategies. For purposes of this review, we defined strategies as studies where drug regimens were not fixed, but rather when a clinician made dose adjustments or drug changes according to patient response.

Across all Key Questions, we included head-to-head studies, observational studies, and systematic reviews. When comparative evidence is available, we discuss it before presenting indirect analyses of placebo-controlled trials.

Table 7 gives the numbers of trials for drug class comparisons reported only from head-to-head studies; when some groupings have important subcomparisons, we note these as well. Additionally, we included 107 observational studies in the report.

Table 7. Number of head-to-head trials by drug comparison for rheumatoid arthritis

Drug Comparison	Number of Trials;[†] Quality Rating
Oral DMARDs vs. oral DMARDs	8 fair; 1 good
Oral DMARD combinations	3 fair; 3 good
Biologic DMARDs vs. biologic DMARDs	1 fair
Biologic DMARDs vs. oral DMARDs	4 fair; 1 good
Biologic DMARD+oral DMARD combinations	9 fair; 3 good
Early RA Strategies	1 fair; 3 good

DMARD = disease modifying anti-rheumatic drug

[†] Trials may fall into more than one drug comparison category, depending on the treatment arms discussed in the report.

Table 8 lists abbreviations and full names of diagnostic scales and health status or quality-of-life instruments encountered in these studies, as well information about clinical significance when available. For further details about such instruments and scales, see Appendix G.

Table 8. Disease activity, radiographic progression, functional capacity, and quality-of-life measures

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by	Clinically Significant Improvement
ACR-N	American College of Rheumatology percent improvement from baseline to endpoint	0 to 100 percent	Increase	--
ACR 20/50/70*	American College of Rheumatology response scores based on 20, 50, or 70 percent criteria for improvement	0 to 100 percent	Increase	ACR 20 is 20% minimal improvement; ACR 50/70 considered more clinically significant[45]
ASHI	Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific Health Index)	0 to 100	Increase	--
DAS*	Disease Activity Score	0 to 10	Decrease	DAS <1.6 correlates with remission[45, 46]
DAS 28	Disease Activity Score Short Form	0 to10	Decrease	DAS28 <2.6 correlates with remission [45, 47]
DLQI	Dermatology Life Quality Index	0 to 30	Decrease	--
EQ-5D*	EuroQol EQ-5D Quality of Life Questionnaire	0 to 1	Increase	--
EULAR response	European League Against Rheumatism response	N/A	N/A	--
HAQ*(D-HAQ)	Health Assessment Questionnaire (Dutch Version)	0 to 3	Decrease	HAQ >= 0.22 change[48]
HAQ-DI	Disability Index of the Heath Assessment Questionnaire	0 to 3	Decrease	--
SF-36*	Medical Outcomes Study Short Form 36 Health Survey	0 to 100	Increase	SF36 physical or mental component two standard error of the mean (SEM)[49-52]
SHS*	Sharp/van der Heijde Method (SHS) for Scoring Radiographs (SHS is frequently modified by individual authors to meet study requirements and needs; there is no standard modified SHS)	Erosion: 0 to 160 for hands; 0 to 120 for feet Joint space narrowing: 0 to 168 Total: 0 to 448	Decrease	Changes in joint damage around the level of 5 units of the Sharp/van der Heijde method as minimally clinically important[53]

* These key scales are defined in Appendix G.
-- = less commonly used measures for which there is little or no research regarding what constitutes a clinically significant improvement

Key Question 1: Reductions in Disease Activity, Limitations of Disease Progression, and Maintenance of Remission

This Key Question concerned three main topics. Specifically, for patients with rheumatoid arthritis (RA), do drug therapies differ in their ability to reduce disease activity, to slow or limit progression of radiographic joint damage, or to maintain remission? Evidence Tables in Appendix E document details about all these studies.

Overview

Individual study details are found in the Evidence Tables, Appendix E. The main drug classes that we compared include oral disease-modifying antirheumatic drug (DMARDs), biologic DMARDs (also referred to simply as biologics), and various combined therapies.

Overall strength of evidence by disease activity and radiographic changes, when available, is listed in Table 9. Table 10 provides information on comparisons made, symptom response, and quality ratings. Table 11 provides information on radiographic joint damage, indicating whether the study populations included patients with early RA. When possible, we describe whether treatment effects reach minimal clinically important differences (MCIDs). In this section, achieving at least an American College of Rheumatology 20% improvement criteria (ACR), a disease activity score (DAS)<1.6, a DAS28<2.6, or a Sharp/van de Heijde change in joint damage of 5.0 are considered minimally clinically important (Table 9).

Oral DMARD versus oral DMARD. One trial found no statistically significant difference by ACR 20 between budesonide and prednisolone for disease activity outcomes.[54] The strength of evidence is low.

Two trials found no statistically significant difference by ACR 20 between methotrexate (MTX) and leflunomide for disease activity outcomes at 2 years or radiographic changes. These results are limited by the use of lower doses of MTX.[55, 56] The strength of evidence is low.

Three trials did not find a significant difference by ACR 20 between MTX and sulfasalazine for disease activity outcomes. These results are limited by the lower doses of MTX used in the earlier studies[57-59] The strength of evidence is low.

One trial found that leflunomide lessens disease activity outcomes by ACR 20 at 2 years compared to sulfasalazine but did not detect differences in radiographic changes.[60] The strength of evidence is insufficient for disease activity and low for radiographic changes.

No fair or good evidence exists for comparing hydroxychloroquine monotherapy with other oral DMARD monotherapy.

Oral DMARD combinations. Combination therapy with sulfasalazine and MTX compared to monotherapy provides different results depending on the population.[57-59] Two trials and one cohort of DMARD naïve patients with early RA showed no difference in ACR 20 response between combination sulfasalazine and MTX versus monotherapy.[57, 58] The strength of evidence is moderate. The one trial in those without early RA (up to 10 years duration) supported combination therapy with sulfasalazine and MTX versus monotherapy with either drug; the changes in DAS scores were greater for combination therapy than for monotherapy, but MCID was not reached by ACR 20 response.[57] The strength of evidence is low

The strength of evidence is low for suggesting that sulfasalazine and MTX compared with monotherapy alone limit progression of radiographic joint damage.

The strength of evidence is moderate for suggesting that combinations of MTX, sulfasalazine, and hydroxychloroquine lessen disease activity by ACR 20 resonse compared to one or two drugs.[61, 62]

Low doses of glucocorticoids taken with an oral DMARD (generally MTX or sulfasalazine) reduce x-ray progression over 1-2 years.[63-65] The strength of evidence is low. However, the evidence is conflicting for change in DAS over 2 years; one study found significant change and one did not.[64, 65] The strength of evidence is insufficient.

Biologic DMARDs. We found one head-to-head randomized controlled trial (RCT) that compared one biologic DMARD with another[66]providing low strength of evidence that abatacept lessens disease activity at 1 year compared with infliximab. However, remission by DAS did not

reach significance at 1 year. Other existing direct head-to-head evidence is limited to a nonrandomized, open-label effectiveness trial[67] and six prospective cohort studies.[68-73] Because of the methodological limitations of observational studies, findings of these studies must be interpreted cautiously. The studies that compared etanercept with infliximab reported a faster onset of response for etanercept during the first months of therapy but no differences in efficacy by ACR 20 and ACR 50 thereafter.[67-71, 73] The faster onset of etanercept might be attributable partly to necessary dose adjustments for patients treated with infliximab. The strength of evidence is low.

Adalimumab lessens disease activity over 1 year compared with infliximab by DAS28, but MCID can not be determined.[71, 73] Evidence is limited to two cohort studies. There were no differences in achievement of ACR 70 for adalimumab compared with etancercept.[73] The strength of evidence is low for both of these comparisons.

A cohort of patients who had failed at least one anti-tumor necrosis factor (TNF) drug were subsequently treated with rituximab, and their outcomes were compared with those of patients treated with other anti-TNF agents. The results indicated that the patients treated with rituximab had a greater reduction in disease activity at 6 months than the patients treated with the other anti-TNF agents. The MCID can not be determined.[72] The strength of evidence is low.

Mixed treatment comparisons performed in this report suggest higher efficacy for improving disease activity (ACR 50) for etanercept compared with individual biologics including abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab; nonsignificant differences with golimumab were reported. The strength of evidence is low and should be interpreted cautiously given the indirectness of the evidence.

Anakinra appears to have lower efficacy based on our mixed treatment comparisons. However, ACR 50 was significant only for for adalimumab and etanercept. Prior indirect comparisons have found similar results.[74, 75] The strength of evidence is low and should be interpreted cautiously given the indirectness of the evidence.

Mixed treatment comparisons found no significant differences in disease activity with abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab. The strength of evidence is low and should be interpreted cautiously given the indirectness of the evidence.

Biologic DMARD versus oral DMARD. Population-based, observational evidence from prospective cohort studies and RCTs of individual drugs indicated that biologic DMARDs as a class (adalimumab, anakinra, etanercept, infliximab) were more efficacious by ACR 20, 50 and remission by DAS28 than oral DMARDs as a class (MTX, leflunomide).[67, 68, 76-78] The strength of evidence for available comparisons is moderate.

Radiographic outcomes were significantly better in patients treated with biologic DMARDs adalimumab and etanercept than in patients treated with MTX. How such intermediate outcomes translate to the long-term clinical progression of the disease remains unclear. The strength of the evidence for the available comparisons is low.

Individual trials of adalimumab and etanercept favor approved doses of biologic versus MTX. The strength of evidence for these comparisons is low.

Biologic DMARD combinations. There are no synergistic effects of a combination treatment of etanercept and anakinra[79] or etanercept and abatacept by ACR/20/50 response[80] compared with etanercept monotherapy. The strength of evidence is low.

Overall, moderate evidence suggests that some benefit in ACRresponse to biologic DMARD combinations over monotherapy, at least in relation to combining MTX with adalimumab, infliximab, or rituximab. A combination of MTX with either adalimumab,[76] or infliximab,[68, 81-83]

or rituximab[84] led to statistically significantly greater improvements in ACRresponse and radiographic progression than with biologic DMARD monotherapy. A combination of etanercept with MTX trended toward greater improvements in disease activity and radiographic outcomes than with monotherapy but not all studies reached statistical significance.[68, 81, 85-88] A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy at 1 year.[85] All RCTs were funded by the makers of the biologic DMARDs. Except for the PREMIER study on adalimumab,[76] none of these trials was conducted in patients with early RA. The strength of evidence is low for the individual comparisons. No evidence is available on abatacept, anakinra, certolizumab pegol, golimumab, tocilizumab, and combinations with oral DMARDs.

Overall, the evidence is high for combination of biologic DMARDs with oral DMARDs versus oral DMARDs. A combination of MTX with abatacept,[89] adalimumab,[76] etanercept,[86, 90, 91] golimumab,[92] or infliximab[82] led to significantly greater improvements in disease activity by ACR 20/50 response than MTX alone.

Evidence from two prospective cohorts for anti-TNF drugs with MTX compared to anti-TNF with leflunomide note similar efficacy.[93, 94] Anti-TNF drugs included anakinra, etanercept, and adalimumab. The strength of evidence is low.

None of the RCTs can be considered an effectiveness study. Of four population-based prospective cohort studies, only one was conducted in the United States. The generalizability of results to the average population of community rheumatology patients, therefore, remains unclear. All RCTs were funded by the makers of the biologic DMARDs.

Strategies limited to early RA. Combination therapy, which included two oral DMARDs (MTX and sulfasalazine) plus a stepped-down prednisolone treatment, demonstrated less radiographic progression by modified Sharp/van der Heijde score (5.6 vs. 8.6; P=0.001) than sulfasalazine alone.[95, 96] The strength of evidence is low.

Combination of three oral DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone led to less radiographic change than one oral DMARD (sulfasalazine, which could be changed to MTX).[97, 98] The MCID can not be determined. The strength of evidence is low.

Evidence from one trial found that in patients not responding to methotrexate in DAS response-driven treatment, combination of three oral DMARDs (MTX, sulfasalazine, and hydroxychloroquine) resulted in less response by European League Against Rheumatism (EULAR) criteria compared to infliximab plus MTX.[99] The MCID cannot be determined. The strength of evidence is low.

A strategy of either (1) MTX, sulfasalazine, and tapered high-dose prednisone, or (2) MTX and infliximab resulted in less radiographic change over 12 months than (3) sequential DMARD therapy or (4) stepped-up combination therapy.[100] At 4 years, the remission by DAS among groups was similar.[101-103] The strength of evidence is low.

Rheumatoid Arthritis: Detailed Analysis

Oral DMARD versus oral DMARD. Table 9 presents disease activity and remission and Table 10 presents radiographic joint damage results in these comparisons.

Corticosteroids versus corticosteroids. We found one head-to-head RCT (N=143) comparing two corticosteroids (Table 9).[54] It examined the efficacy of low-dose budesonide (3 mg/day), high-dose budesonide (9 mg/day), and prednisolone (7.5 mg/day) over 12 weeks. Mean disease duration of RA was 9 years. When comparing drugs, the percentage achieving ACR 20 response criteria for high-dose budesonide (9 mg) was significantly greater than that for lower- dose

budesonide (3 mg) (42 percent vs. 22 percent; $P<0.001$), but the percentages for high-dose budesonide and prednisolone did not differ significantly (42 percent vs. 56 percent; $P=0.11$). Similarly, high-dose budesonide and prednisolone did not differ significantly for tender joint count, swollen joint count, and the DAS.

Leflunomide versus MTX. We found two trials comparing leflunomide (20 mg/day) with MTX (studies ranging from 7.5 mg/week to 15 mg/week) and two systematic reviews with meta-analysis of leflunomide.[55, 104-106] We describe these two studies in detail here first. One trial randomized 482 patients to leflunomide (n=182) or MTX (n=182) over 12 months.[104] Mean disease duration of RA across these groups was 6.5 years to 7 years. The proportion of patients meeting ACR 20 response criteria at 12 months was higher for leflunomide than MTX but not statistically significantly so (52 percent vs. 46 percent; P=NR). Proportions meeting ACR 50 and ACR 70 criteria also did not differ significantly. Leflunomide had less disease progression by Sharp score than MTX (respectively, 0.53 vs. 0.88; $P=0.05$) (Table 10).

A continuation study followed the same cohort for 2 years (leflunomide, n=98; MTX, n=101).[56] At 2 years, leflunomide was associated with a higher proportion of patients meeting ACR 20 response criteria than MTX (79 percent vs. 67 percent; $P=0.049$). The percentage of patients meeting either ACR 50 or ACR 70 criteria at 2 years did not differ significantly, and the change in total Sharp score also did not differ significantly at 2 years (1.6 vs. 1.2; $P=0.659$).

These 2-year follow-up results are limited by the 45 percent attrition rate from the initial study.

The other trial comparing leflunomide to MTX examined 999 patients for 12 months with an optional second year (leflunomide, n=501; MTX, n=498).[105] Mean disease duration across the groups was 3.5 to 3.8 years. At 12 months, the proportion of patients meeting ACR 20 response criteria was lower for leflunomide than for MTX (50.5 percent vs. 64.8 percent; $P<0.001$), but differences were not significant at 2 years (64.3 percent vs. 71.7 percent; P=not significant [NS], not reported [NR]). Radiological outcomes at 12 months using Larsen Scale scores for joint narrowing were statistically equivalent (0.03 increase in both groups). After 2 years, no further increase in joint damage occurred in patients treated with leflunomide; patients taking MTX had a small improvement (data NR). The overall result was a small significant difference in Larsen Scale scores favoring MTX after 2 years (data NR).

In the systematic review that included two trials comparing leflumonide with MTX (n=1,348), there were no differences in achieving an ACR 20 response at12 months (odds ratio [OR], 1.08; 95% CI, 0.75 to 1.55) or at 2 years (OR, 1.05; 95% CI, 0.81 to 1.37). Patients receiving leflunomide and MTX did not differ in ACR 50 and ACR 70 responses, and the two drugs also did not differ in delaying bone erosions or joint damage assessed by total Sharp score.[55] This systematic review was limited by the small number of studies that the authors could use for the individual comparisons in the meta-analysis. Similarly, the second systematic review examined the efficacy and safety of oral DMARDs in adults with RA to inform the EULAR recommendations.[106] In the four studies included comparing leflunomide with MTX (N=1,889), there were no differences in ACR 20 response (MTX, OR, 1.04; 95% CI, 0.60 to 1.79). It should be noted that the mean dose of MTX was 12.5 mg/week. MTX could be increased to ≥15 mg/week in all studies, but dosing was not as high as currently recommended in most studies.

Table 9. Disease activity and remission for oral DMARD versus oral DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Corticosteroid vs. Corticosteroid					
Kirwan et al., 2004[54]	RCT 143 12 weeks	Population-based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	No significant difference between 9 mg BUD and PNL for ACR 20, DAS (ACR 20: 42% vs. 56%; *P*=0.11) at 12 weeks	Fair
Leflunomide vs. MTX					
Emery et al., 2000[105]	RCT 999 1 year with optional 2nd year	Mean disease duration 3.5 to 3.8 years	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Lower ACR 20 responses at 12 months (50.5% vs. 64.8%; *P*<0.001); no significant differences in ACR at 2 years (64.3% vs. 71.7%; *P*=NS, NR)	Fair
Strand et al., 1999[56, 104]	RCT 482 12 months (1 year continuation)	Mean disease duration 6.5 to 7 years	LEF (20 mg/day) vs. MTX (7.5 to 15 mg/week)	At 1 year, ACR 20 numerically higher for LEF but not significant (52% vs. 46%; *P*=NR); at 2 years, ACR 20 difference not significant (79% vs. 67%; *P*=0.049)	Fair
Leflunomide vs. Sulfasalazine					
Smolen et al., 1999;[107] Smolen, 1999;[108] Larsen et al., 2001[60]	RCT 358 24 weeks (12- and 24-month followup)	Mean disease duration 5.7 to 7.6 years	LEF (20 mg/day) vs. SSZ (2 g/day)	Similar ACR 20 response rates (48% vs. 44%; *P*=NR)	Fair
Sulfasalazine vs. MTX					
Capell et al., 2006[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Scotland; multicenter; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	At 18 months, no significant difference in DAS for SSZ vs. MTX (-0.30 vs. -0.26; *P*=0.79); no significant difference in any ACR responses	Fair
Dougados et al., 1999[57]	RCT 209 (146) 52 weeks (5-year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in DAS between SSZ vs. MTX (-1.15 vs. -0.87; *P*=NS, NR); no significant difference in ACR 20 responses; *P*=NR	Fair
Haagsma et al., 1997[58]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week	No significant difference in DAS for SSZ vs. MTX (-1.6 vs. -1.7; *P*=NS, NR)	Fair

ACR = American College of Rheumatology; BUD = budesonide; CI = confidence interval; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; g = gram; LEF = leflunomide; MTX = methotrexate; mg = milligram; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Table 10. Radiographic joint damage in oral DMARD versus oral DMARD

Study	Study Design N Duration	Population with Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Leflunomide vs. MTX				
Emery et al., 2000[105]	RCT 999 1 year with optional 2nd year	No	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Larsen score change at 1 year: 0.3 vs. 0.3; *P*=NS Larsen score change at 2 years: 1.27 vs. 1.31; *P*=NS, NR
Strand et al., 1999[104]	RCT 482 12 months (1 year continuation)	No	LEF (20 mg/day) vs. MTX (7.5 to 10 mg/week)	Total Sharp score change at 1 year: 0.53 vs. 0.88;*P*=0.05 Total Sharp score at 2 years: 1.6 vs. 1.2; *P*=0.659
Leflunomide vs. Sulfasalazine				
Smolen et al., 1999;[107] Larsen, et. al., 2001;[60] Sharp et al., 2000[109]	RCT 358 24 weeks (12- and 24-month followup)	No	LEF (20 mg/day) vs. SSZ (2 g/day)	Larsen score change at 24 weeks: 0.01 vs. 0.01; *P*=NS Larsen score change at 1 year: 0.02 vs. 0.02; *P*=NS Larsen score change at 2 years: -0.07 vs. -0.03; *P*=NR
Sulfasalazine vs. MTX				
Capell et al., 2006[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Yes (70% 1 year or less)	SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	No significant difference in total modified Sharp/van der Heijde score change (data NR)
Dougados et al., 1999[57]	RCT 209 (146) 52 weeks (5 years)	Yes	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Total modified Sharp/van der Heijde score change: 4.64 vs. 4.50 vs. 3.36; *P*=NS,NR; change at 5 years: 8.5 vs. 7.5; *P*=0.7

DMARD = disease-modifying antirheumatic drug; g = gram; LEF = leflunomide; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Leflunomide versus sulfasalazine. One study[107] with a 2-year followup[60] compared leflunomide with sulfasalazine (Tables 9 and 10). In addition, one systematic review did a meta-analysis of leflunomide against sulfasalazine.[55] Given that the systematic review included only one trial with this comparison, we describe it in detail first.[107, 108] This study was a 24-week, double-blind, multinational RCT of 358 patients on 20 mg/day leflunomide (n=133) or 2 g/day sulfasalazine (n=133).[107] Mean disease duration across groups was 5.7 to 7.6 years. ACR 20 response at 24 weeks was similar for leflunomide and sulfasalazine (48 percent vs. 44 percent; *P*=NR). The percentage achieving ACR 50 response criteria was also similar in the two groups (33 percent leflunomide, 30 percent sulfasalazine). Larsen Scale scores were also similar for leflunomide and sulfasalazine, and the Larsen Scale change score at endpoint was 0.01 for both drugs (Table 10). In the followup study, patients who completed the first study could opt to continue on the 12- and 24-month double-blind extension.[60] At 12 months (leflunomide, n=80; sulfasalazine, n=76), ACR 20 response was similar for leflunomide and sulfasalazine (77 percent

vs. 73 percent; *P*=NR). At 24 months (leflunomide, n=28; sulfasalazine, n=27), ACR 20 response was significantly greater for leflunomide than for sulfasalazine (82 percent vs. 60 percent; *P*=0.0085). Changes in Larsen Scale scores were also similar for leflunomide and sulfasalazine (mean change: 0.02 vs. 0.02 at 12 months, -0.07 vs. -0.03 at 24 months; *P*=NR). Changes in Sharp scores were also not significantly different (mean change: 0.97 vs. 1.38; *P*=0.685). However, these long-term results are significantly limited by the attrition rates of 65 percent to 70 percent.

The systematic review with a meta-analysis compared leflunomide (10 to 20 mg/day) with sulfasalazine (2 g/day).[55] The analysis included the study described above.[60, 107-109] Response to the two drugs did not differ as measured by either ACR 20 or ACR 50 criteria at 6 months and 12 months. However, leflunomide was more efficacious at 24 months (ACR 20: OR, 0.73; 95% CI, 0.57 to 0.93; *P*=0.012; ACR 50: OR, 0.48; 95% CI, 0.28 to 0.80; *P*=0.0048). The groups did not differ in the ACR 70 at 6, 12, or 24 months. Leflunomide and sulfasalazine also did not differ in delaying bone erosions or joint damage by Sharp score or Larsen Scale score at 6, 12, or 24 months. Again, these results are significantly limited because they include only the one study.[107]

Sulfasalazine versus MTX. Three RCTs.[57-59] and one systematic review[106] examined the efficacy of sulfasalazine and MTX (Tables 9 and 10). Overall, findings from these studies showed similar improvement rates between sulfasalazine and MTX for any ACR, DAS, and radiological outcomes. Two of the trials included patients with disease burden of less than 1 year and used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States.[57, 58] These trials also included a combination therapy arm, which we describe below (in the section on *Oral DMARD combinations versus oral DMARD combinations or oral DMARD monotherapy).*

One trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine (n=68), 7.5 mg/week to 15 mg/week MTX (n=69), or a combination of sulfasalazine and MTX (n=68) for 52 weeks.[57] Mean disease duration for the groups ranged from 2.3 months to 3.4 months. The trial did not detect any differences between the MTX and sulfasalazine groups in improvement as measured on the ACR 20 (59 percent sulfasalazine; 59 percent MTX; *P*=NR). The DAS change score favored sulfasalazine therapy (-1.15, sulfasalazine; -0.87, MTX; *P*=NR), but the statistical analysis examined only the comparison with combination therapy (reported under *Oral DMARD combinations versus oral DMARD combinations or oral DMARD monotherapy*). The mean total modified Sharp/van der Heijde scores of 8.5 for sulfasalazine and 7.5 for MTX indicated that the radiological scores at 5 years did not differ significantly (*P*=0.7).

Another RCT, lasting 52 weeks (N=105), also demonstrated similar ACR 20 and DAS results for sulfasalazine and MTX.[58] This trial compared 1 g/day to 3 g/day sulfasalazine (n=34) with 7.5 mg/week to 15 mg/week MTX (n=35) and with a combination (discussed later in this chapter); mean disease duration was 2.6 to 3.1 months. The mean change in DAS over 52 weeks was -1.6 in the sulfasalazine group and -1.7 in the MTX group (*P*=NS). The percentage of patients achieving improvement on the ACR 20 was 25 percent for sulfasalazine and 25 percent for MTX.

Finally, one trial included a population with disease duration of up to 10 years.[59] The investigators gave 687 patients sulfasalazine (up to 4 g/day) for 6 months. Those with DAS ≥2.4 were offered inclusion into a Phase II study and randomized to (1) sulfasalazine (n=55), (2) MTX (n=54) (maximum dose, 25 mg/week), and (3) sulfasalazine plus MTX (n=56). At 18 months, the DAS change was similar for sulfasalazine and MTX alone (-0.30 vs. -0.26; *P*=0.79). The ACR 20, 50, and 70 responses were also similar (ACR 20, 18 percent vs. 15

percent; ACR 50, 6 percent vs. 7 percent; ACR 70, 2 percent vs. 2 percent; *P*=NR). The groups also did not differ in modified Sharp/van der Heijde score, total erosions, and joint space narrowing (data NR) (Table 9). However, 18 months is a short period for observing radiological outcomes, and this study was not powered to detect radiological progression.

Similarly, a systematic review that examined the efficacy and safety of oral DMARDs in adults with RA to inform the EULAR recommendations.[106] In the two studies (N=193), there were no differences in ACR 50 response (MTX, OR, 1.57; 95% CI, 0.82 to 3.00). The mean dose of MTX was 14.2 mg/week, which is lower than currently recommended.

Oral DMARD combinations versus oral DMARD combinations or oral DMARD monotherapy, with or without corticosteroids. Table 11 presents disease activity and remission and Table 12 provides radiographic joint damage results for these comparisons.

Sulfasalazine plus MTX versus sulfasalazine or MTX. Three RCTs,[57-59] one systematic review and one observational cohort[110]compared the efficacy of sulfasalazine and MTX versus that of either sulfasalazine or MTX alone (Tables 11 and 12). Findings from two of these randomized trials consistently reported no significant differences in ACR, DAS, or radiological outcomes.[57, 58] They included patients with disease duration of less than 1 year and again used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States.[57, 58] The third trial included patients with RA duration of up to 10 years, and their DAS results favored the sulfasalazine-MTX combination therapy over monotherapy.[59]

Table 11. Disease activity and remission for oral DMARD combinations versus monotherapy or combinations with or without corticosteroid studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Sulfasalazine+MTX vs. Sulfasalazine or MTX monotherapy					
Capell et al., 2006[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Scotland, 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤4 g/day)+MTX (≤25 mg/week) vs. SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	Combination therapy better than monotherapy MTX or SSZ for DAS (-0.67, -0.30, -0.26; *P*=0.039 for SSZ+MTX vs. SSZ*; P*= 0.023 for SSZ+MTX vs. MTX) No significant difference in ACR responses	Fair
Dougados et al., 1999[57] Maillefert et al., 2003[111]	RCT 209 (146) 52 weeks (5-year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR responses (65 vs. 59 vs. 59; *P*=NS, NR) DAS change (-1.26 vs. -1.15 vs. -0.87; *P*=0.019) DAS change NS at year 5	Fair

Table 11. Disease activity and remission for oral DMARD combinations versus monotherapy or combinations with or without corticosteroid studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Haagsma et al., 1997[58]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week) vs. SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR or DAS responses	Fair
*Schipper et al., 2008[110]	Prospective cohort 230 52 weeks (primary outcome at 6 months)	Netherlands;early RA;sulfasalazine resistant; mean disease duration 3 months-1 year	SSZ (750 to 3g/day)+MTX (7.5-30 mg/week) vs. MTX (7.5-30 mg/week)	No significant difference for DAS responses DAS28 change (-0.8 vs. -0.9; *P* 0.737)	Fair
MTX+Hydroxychloroquine+Sulfasalazine vs. one or two oral DMARDs					
O'Dell et al., 2002[61]	RCT 171 2 years	Mean disease duration 5.8 to 7.9 years	1: MTX (7.5 titrated to 17.5 mg/week)+SSZ (2 g/day)+HCQ (400 mg/day) vs. 2: MTX+HCQ vs. 3: MTX+SSZ	ACR 20: 78%, 60%, 49% 1 vs. 2: *P*=0.05 1 vs. 3: *P*=0.002	Good
O'Dell et al., 1996[62]	RCT 102 2 years	Poor response to at least 1 DMARD; mean disease duration 6 to 10 years	1: MTX (7.5 to 17.5 mg/week)+SSZ (1 g/day)+HCQ (400 mg/day) vs. 2: MTX vs. 3: SSZ (+ HCQ	50% improvement (defined by authors): 77%, 40%, 33% 1 vs. 3: *P*<0.001 1 vs. 2: *P*=0.003	Good
Oral DMARD+Corticosteroid vs. Oral DMARD					
*Choy, et al., 2008[64]	RCT 467 2 years	England/Wales, Multicenter: early RA; mean disease duration 2.7-5.1 months	MTX (≤15 mg/week)+PNL (60 mg/day stepped down and stopped at 34 weeks) vs. MTX	No significant differences for DAS (-1.37 vs. -1.42; *P*=0.19); DAS 28 remission 20% vs. 18%; *P*=NR	Good
Svensson et al., 2005[65]	Open-label trial 250 2 years	Population-based; active RA; early RA	DMARD (SSZ or MTX, dosages NR)+PNL (7.5 mg/day) vs. DMARD	More patients in DMARD+PNL combination group achieve remission (DAS<2.6) than DMARD-only group (55.5% vs. 43.8%; *P*=0.0005)	Fair

* New study added since last review

ACR = American College of Rheumatology; DAS = disease activity score, DMARD = disease-modifying antirheumatic drug; g = gram; HQC = hydroxychloroquine; MTX = methotrexate; mg = milligram; NHS = National Health Service; NR = not reported; NS = not significant; PNL = prednisolone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Table 12. Radiographic joint damage in oral DMARD combinations versus monotherapy combinations with or without corticosteroid studies

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Sulfasalazine+MTX vs. Sulfasalazine or MTX				
Capell et al., 2006[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Yes (70% 1 year or less)	SSZ (≤4 g/day)+MTX (≤25 mg/week) vs. SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	No significant difference in total Sharp score (data NR)
Dougados et al., 1999;[57] Maillefert et al., 2003[111]	RCT 209 (146) 52 weeks (5-year followup)	Yes	SSZ (2 to 3 g/day)+ MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	5-year mean modified Sharp/van der Heijde score change: 8.5 vs. 7.5; *P*=0.7
Oral DMARD+Corticosteroid vs. Oral DMaRD				
*Choy, et al., 2008[64]	RCT 467 2 years	Yes	MTX (≤15 mg/week)+PNL (60 mg/day stepped down and stopped at 34 weeks) vs. MTX	Larsen score change 7.41 vs. 4.70; *P*=0.008
Svensson et al., 2005[65]	Open-label RCT trial 250 2 years	Yes	DMARD (SSZ or MTX, dosages NR)+PNL (7.5 mg/day) vs. DMARD	Median modified Sharp/van der Heijde score change: 1.8 vs. 3.5; *P*=0.019 Erosion score median change: 0.5 vs. 1.25; *P*=0.007 Joint space narrowing score median change: 1.0 vs. 2.0; *P*=0.08

*New study added since last review.
ACR = American College of Rheumatology; DAS = disease activity score, DMARD = disease-modifying antirheumatic drug; g = gram; HQC = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; mg = milligram; NR = not reported; NS = not significant; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Biologic DMARDs versus biologic DMARDs. We identified one head-to-head RCT,[66] one nonrandomized, open-label effectiveness trial,[67] and six prospective cohort studies (Table 13);[68-73] all but three studies[66, 71, 72] compared etanercept with infliximab. Other comparisons included adalimumab with infliximab,[71, 73] adalimumab with etanercept,[73] abatacept with infliximab[66] and rituximab compared with other anti-TNF agents.[72] All studies had minimal exclusion criteria, enrolling patients who were starting treatments with biologic DMARDs. Mean disease durations ranged from 7.3 years to 14.5 years, indicating that most patients suffered from advanced RA; the proportion of patients with early RA in these studies remains unclear. One study contained a multinational patient population,[66] one was conducted in the United States;[68] the other six were carried out in Sweden,[67, 69, 72] Denmark,[73] the Netherlands,[71] and Spain.[70]

Table 13. Disease activity and remission for biologic DMARD versus biologic DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Abatacept vs. Infliximab					
*Schiff, et al., 2008[66] ATTEST study	RCT 431 1 year	Patients who have failed MTX; active RA; mean disease duration 7.3-8.4 years	ABA (~10 mg/kg every 4 weeks) vs. INF (3 mg/kg every 8 weeks)	Greater decrease in DAS28 for ABA vs. INF at 1 year (estimate of difference -0.62 95% CI, -0.96 to -0.29). Trend toward greater remission for ABA vs. INF at 1 year (estimate of difference 6.5%; 95% CI, -2.2 to 15.2, *P*=NS, NR)	Fair
*Hetland et al., 2010[73] DANBIO	Prospective cohort 2,326 6 months (48 months)	Patients with RA initiating therapy with biologic DMARDs	ADA (mean: 40 mg) wks) vs. ETN (mean 45 mg) vs. INF (mean 3.5 mg/kg)	Higher achievement of ACR 70 response after 6 months for ADA than INF (OR 2.05, 95% CI, 1.52 to 2.76, *P*=NR)	Fair
*Kievit et al., 2008[71]	Prospective cohort 707 1 year	Population-based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ADA vs. INF (dosages NR)	Greater decrease in DAS28 for ADA vs. INF at 1 year (ADA -1.8, INF -1.2; *P*<0.05)	Fair
Adalimumab vs. Etanercept					
*Hetland et al., 2010[73] DANBIO	Prospective cohort 2,326 6 monhs (48 months)	Patients with RA initiating therapy with biologic DMARDs	ADA (mean: 40 mg) wks) vs. ETN (mean 45 mg) vs. INF (mean 3.5 mg/kg)	No difference in achievement of ACR 70 response after 6 months for ADA vs. ETN (OR 1.15, 95% CI, 0.82 to 1.60, *P*=NR)	Fair
Etanercept vs. Infliximab					
Geborek et al., 2002[67]	Nonrandomized, open-label trial 369 1 year	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher)	Higher ACR 20 responses for ETN at 3 (data NR; *P*<0.02) and 6 months (data NR; *P*<0.05); no significant differences in ACR response rates at 1 year (data NR)	Fair
*Fernandez-Nebro et al., 2007[70]	Prospective cohort 161 6 years	Tertiary care center, Spain; Anti-TNF naïve patients; mean disease duration 9.5 -9.9 years	ETN vs. INF (dosages NR)	Significantly greater decrease t in DAS28 at 6 months for ETN vs. INF (-1.7 vs. -1.3; *P*=0.03); No difference in EULAR responses between ETN vs. INF at 6 months	Fair

Table 13. Disease activity and remission for biologic DMARD versus biologic DMARD studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
*Hetland et al., 2010[73] DANBIO	Prospective cohort 2,326 6 monhs (48 months)	Patients with RA initiating therapy with biologic DMARDs	ADA (mean: 40 mg) wks) vs. ETN (mean 45 mg) vs. INF (mean 3.5 mg/kg)	Higher achievement of ACR 70 response after 6 months for ETN vs. INF (OR 1.78, 95% CI, 1.28 to 2.50, *P*=NR)	Fair
*Kievit et al., 2008[71]	Prospective cohort 707 1 year	Population-based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ETN vs. INF (dosages NR)	Greater decrease in DAS28 for ETN vs. INF at 1 year (ETN -1.8, INF -1.2; *P*<0.05)	Fair
Kristensen et al., 2002[69]	Prospective cohort 949 3 years	Population-based, Inadequate response to at least 2 DMARDs	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher)	No difference in ACR 50 response at 3 years (data NR)	Fair
Weaver et al., 2006[68]	Prospective cohort 1,371 1 year	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETN (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Higher ACR 20 response rates for ETN than INF at 1 year (41% vs. 26%; *P*=NR)	Fair
Rituximab vs. Anti-tumor Necrosis Factor Therapies					
*Finckh et al., 2007[72]	Prospective cohort 116 6 months	Population-based, Switzerland; Patients who have failed at least 1 Anti-TNF treatment; mean disease duration 9-10 yrs	RTX (2 infusions, 1000 mg) vs. anti-TNF agent (INF, ETN or ADA, dosages NR)	Greater reduction in DAS28 at 6 months for RTX vs. Anti-TNF (-1.6 vs. -0.98; *P*=0.01)	Fair

* New study added since last review.
ACR = American College of Rheumatology; ADA = adalimumab; ATTEST = Abatacept or infliximab vs. placebo, a trial for tolerability, efficacy, and safety in treating rheumatoid arthritis; CI = confidence interval; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ETN = etanercept; INF = infliximab; mg/kg = milligram/kilogram; mACR = modified American College of Rheumatology; NR = not reported; NS = not significant; PCS = physical component score; RA = rheumatoid arthritis; TNF = tumor necrosis factor; US = United States; vs. = versus

Abatacept versus infliximab. One head-to-head multinational RCT (N=431) examined the effectiveness of abatacept (10 mg/kg every 4 weeks) and infliximab (3 mg/kg every 8 weeks) over 1 year.[66] All participants had active RA, were MTX-resistant, and continued on background MTX for the study. At 1 year abatacept had a greater reduction in DAS28 than infliximab (-2.88 vs. -2.25; estimate of difference -0.62; 95% CI, -0.96 to -0.29). There was also a nonsignificant trend in DAS, ESR (erythrocyte sedimentation rate) defined, remission (18.7% vs. 12.2%; estimate of difference 6.5; 95% CI, -2.2 to 15.2). Additionally, ACR 20 response was significantly higher for abatacept than infliximab (72.4 percent vs. 55.8 percent, estimate of difference 16.7 percent; 95% CI, 5.5 to 27.8) but ACR 50 and ACR 70 did not reach statistical significance. This study is limited by the fixed dosing of infliximab, which may be lower than

generally used in practice. Additionally, the study was powered only to detect differences between the biologics with placebo at 197 days.

Adalimumab versus etanercept. One 52-week prospective observational study used the nationwide Danish DANBIO registry to examine TNF inhibitors adalimumab, etanercept, and infliximab in patients (n=2,326) with RA in whom the first biologic treatment was initiated.[73] Twenty-nine percent received adalimumab (mean: 40 mg), 22 percent received etanercept (mean: 45 mg), and 49 percent received infliximab (mean: 3.5 mg/kg). After correction for differences in sex, age, disease duration, seropositivity, DAS28, concomitant MTX and prednisolone treatement, number of previous DMARDs, Health Assessment Questionnaire (HAQ) at baseline, the odds of achieving an ACR 70 at 6 months was not significant for adalimumab compared with etanercept (OR 1.15; 95% CI, 0.82 to 1.60). However, achieving a good EULAR response was higher for adalimumab (OR 1.49; 95% CI, 1.13 to 1.96). Results were similar at 12 months (data NR). This study is limited by the lack of blinding to treatment

Etanercept versus infliximab. The nonrandomized, open-label effectiveness study (N=369) assessed the effectiveness and safety of etanercept (25 mg twice weekly) and infliximab (3 mg/kg or higher every 8 weeks).[67] Study duration was 12 months. Comparisons of etanercept and infliximab with the leflunomide arm are reported in the section below comparing oral DMARDs with biologic DMARDs. Etanercept had significantly greater improvement on the ACR 20 at 3 months ($P<0.02$; data NR) and 6 months ($P<0.05$; data NR) and on the ACR 50 at 3 months ($P<0.005$; data NR) than infliximab. The authors attributed these differences partly to a high need of dose adjustments (57 percent) in the infliximab group during the first months of the study. No significant differences between the therapy groups could be detected after 6 months.

Three prospective cohort studies provide similar results, initially favoring etanercept, but with differences lessening over longer time periods.[69-71] The first prospective cohort study (N=161) in anti-TNF naïve patients found a higher change in DAS28 at 6 months for etanercept than infliximab (- 1.7 vs. -1.3; $P=0.03$), but no differences in EULAR responses.[70] The second prospective cohort (N=707) in anti-TNF naïve patients found a higher change in DAS28 at 12 months for etanercept than infliximab (-1.8 vs. -1.2, $P<0.05$). A prospective cohort (N=949) with longer followup found that etanercept treatments led to greater improvement on the ACR 50 than infliximab during the first months of treatment, but no differences were noted thereafter for up to 36 months.[69] The authors of this study created an index called the LUNDEX (an index of drug efficacy in clinical practice developed at Lund University in Sweden, calculated as the proportion of starters still on the drug at time T times the proportion responding at time T), which takes adherence and efficacy together into consideration. Patients on etanercept achieved higher LUNDEX scores than patients on infliximab, which reflected a significantly lower level of adherence of patients on infliximab compared with those on etanercept (data NR; $P<0.001$).

Findings from the U.S. prospective cohort study, which was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program and funded by the maker of etanercept, reported similar results.[68] Etanercept-treated patients had greater responses than infliximab-treated patients on the modified ACR 20 (mACR 20, which omits ESR and C-reactive protein [CRP] values because they are infrequently measured in clinical practice); percentage improvement rates were 43 percent for etanercept plus MTX, 41 percent for etanercept monotherapy, 35 percent for infliximab plus MTX, and 26 percent for infliximab monotherapy (P=NR). Similarly a Danish cohort (described above in adalimumab vs. etanercept) found a higher odds of achieving an ACR 70 and a good EULAR response at 6 months for

etanercept compared with infliximab (good EULAR for etanercept: OR, 1.41; 95% CI, 1.09 to 1.84).[73]

Adalimumab versus infliximab. In addition to examining the effects of etanercept, two prospective cohort studies examined adalimumab with infliximab.[71, 73] The first (N=116) examined adalimumab with infliximab in anti-TNF naïve patients as part of the Dutch Rheumatoid Arthritis Monitoring (DREAM) register. Adalimumab-treated patients had a greater decrease in DAS28 than infliximab-treated patients at 1 year (- 1.8 vs. -1.2, $P<0.05$).[71] Similarly, the Danish cohort (described above in adalimumab vs. etanercept) found a higher odds of achieving an ACR 70 and good EULAR response at 6 months for adalimub compared with infliximab (good EULAR for adalimumab: OR 2.10; 95% CI 1.66 to 2.66).[73]

Rituximab versus anti-TNF. One cohort study (N=116) examined the effectiveness of rituximab (1,000 mg x 2 with concomitant IV glucocorticoids) compared to other anti-TNF agents in patients who had inadequate response to previous ant-TNF therapy.[72] The population included Swiss patients receiving anti-TNF therapy in 2003. Patients included in this analyses had an inadequate response to at least one anti-TNF agent (infliximab, etanercept, or adalimumab) and initiated a second or third anti-TNF or rituximab. At 6 months, rituximab-treated patients had a greater decrease in DAS28 than patients treated with an alternative anti-TNF agent (-1.6 vs. -0.98, $P=0.01$).[72]

Indirect head-to-head comparisons of biologic DMARDs. Multiple placebo-controlled RCTs and meta-analyses[25, 29, 112] provide evidence on the efficacy of abatacept,[66, 113-117] adalimumab,[118-127] anakinra,[75, 128-134] etanercept,[86, 126, 135-145] infliximab,[66, 126, 135, 146-156], rituximab,[84, 157-163] certolizumab pegol,[164-168] golimumab,[166, 169-171] and tocilizumab.[164, 172-178] Most of these studies were conducted in patients who previously failed oral DMARD treatment.

Using information from these placebo-controlled trials, several research groups did meta-analyses to produce adjusted indirect comparisons of biologic DMARDs.[28, 74, 75, 179, 180] The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[181] In the more recent analysis, findings suggested that efficacy does not differ substantially for adalimumab, etanercept, and infliximab, abatacept, and rituximab.[27, 74, 180] However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty. Compared with anakinra, point estimates favored adalimumab, etanercept, and infliximab, but the results were not all statistically significantly different.[74, 180] Adjusted indirect comparisons of anti-TNF drugs as a class with anakinra showed a statistically significantly greater efficacy of the anti-TNF drugs on ACR 20 but not on ACR 50.[74]

Mixed treatment comparisons. Our team conducted mixed treatment comparisons (MTC) meta-analyses using Bayesian methods for ACR 20/50/70 that included RCTs of abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab in MTX-resistant patients. A summary of the studies included and network diagram are described in Table 14 and Figure 2. In the analysis of ACR 50, the data show that etanercept has the highest mean treatment response and anakinra the lowest mean response. Point estimates favor other biologics over anakinra; but the differences were only statistically significant for comparisons with adalimumab and etanercept for ACR 50. In addition, point estimates for etanercept are

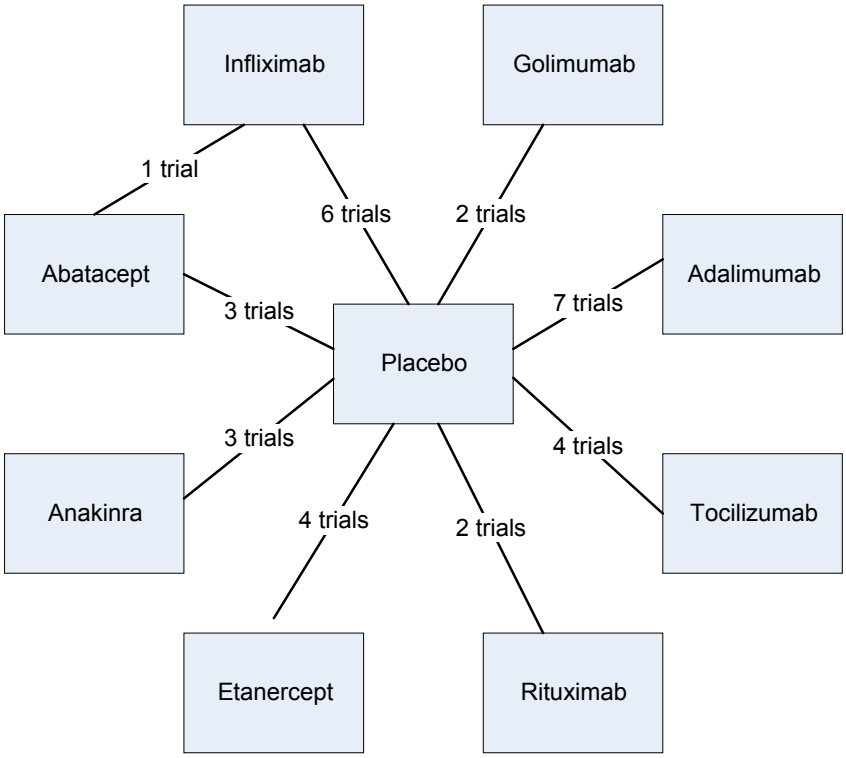
Table 14. Summary of the 30 studies included in mixed treatment comparison meta-analysis

Treatment	Author and Year	Study Name	Time-Point for ACR 50 (weeks)	Total N
Abatacept	Kremer, 2006[116]	AIM	24	652
	Kremer, 2003[113]	NR	24	234
	Schiff, 2008[a,66]	ATTEST	28	266
Adalimumab	Weinblatt, 2003[123]	ARMADA	24	129
	Furst, 2003[121]	STAR	24	636
	Keystone, 2004[120]	NR	52	619
	van de Putte, 2004[122]	NR	26	438
	van de Putte, 2003[119]	NR	12	212
	Kim, 2007[127]	NR	24	128
	Chen, 2008[182]	NR	12	47
Anakinra	Cohen, 2002[131]	NR	24	153
	Cohen, 2004[133]	NR	24	506
	Bresnihan, 1998[128]	NR	24	353
Etanercept	Moreland, 1999[140]	NR	26	158
	Weinblatt, 1999[142]	NR	24	89
	Lan, 2004[143]	NR	12	58
	Moreland, 1997[144]	NR	12	88
Golimumab	Keystone, 2009[169]	GO-FORWARD	14	222
	Kay, 2008[166]	NR	16	70
Infliximab	Abe, 2006[153]	NR	14	147
	Kavanaugh, 2000[154]	NR	12	21
	Zhang, 2006[156]	NR	18	173
	Maini, 1999[148]	ATTRACT	30	428
	Westhovens, 2006[155]	START	22	1,084
	Schiff, 2008[a,66]	ATTEST	28	275
Rituximab	Edwards, 2004[84]	NR	24	80
	Emery, 2010[162]	SERENE	24	512
Tocilizumab	Kremer, 2010[178]	LITHE	24	1,196
	Smolen, 2008[164]	OPTION	24	623
	Genovese, 2008[176]	TOWARD	24	1,220
	Maini, 2006[174]	CHARISMA	16	148

NR = not reported

[a] Schiff 2008 (ATTEST) is listed twice as the study included comparisons with both abatacept and infliximab.

Figure 2. Evidence network for ACR 50 mixed treatment comparisons



Note: The total number of trials does not appear to equal30 (the total number of studies included in the analysis) because some trials have multiple arms that were included.

favored over the other included biologics (ACR 50 OR range for etanercept 2.39-5.20). The differences showed statistically significant improvements in disease activity with etanercept than with abatacept, adalimumab, anakinra, infliximab, rituximab, or tocilizumab, but no statistically significant differences between etanercept and golimumab.

As described in Appendix K four sensitivity analyses were conducted to examine various sources of potential heterogeneity. The four analyses are described below and results are presented in Table 15.

- Sensitivity Analysis 1: Four trials with early escape designs were removed in the main MTC analysis because a large number of crossovers (from placebo to active treatment) in these studies might have led to inaccurate calculations of treatment effects. These four studies were included in a sensitivity analysis to gauge potential impact on overall results.
- Sensitivity Analysis 2: Some trials included in the MTC did not have patients in the relevant arms on a background dose of MTX. To separate the effects that combination therapy may have on the relative treatment effects, monotherapy trials were removed in a sensitivity analysis.
- Sensitivity Analysis 3: To evaluate whether study duration influenced our findings, and to compare with other analyses that have used a 6-month cutoff, the ACR 50 analysis was rerun with studies of durations of 22 weeks or longer.
- Sensitivity Analysis 4: Two trials with etanercept, Lan 2004[143] and Moreland 1997,[144] had both a high ACR 50 response and low placebo response. Due to the relatively large differences between treatment and placebo response, we removed these two trials in a sensitivity analysis.

Table 15. Expected (mean) ACR 50 treatment response of biologic DMARDs

	Scenario				
Treatment	ACR 50	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3	Sensitivity Analysis 4
Placebo	0.0943	0.0874	0.1029	0.0922	0.0964
Abatacept	0.2767	0.2603	0.2972	0.2762	0.2818
Adalimumab	0.3591	0.3381	0.3734	0.3377	0.3824
Anakinra	0.2220	0.2076	0.2663	0.2171	0.2283
Certolizumab	NA	0.4837	NA	NA	NA
Etanercept	0.6353	0.6129	0.6844	0.6088	0.7129
Golimumab	0.3909	0.3691	0.4173	NA	0.3986
Infliximab	0.2810	0.2643	0.3017	0.2960	0.2861
Rituximab	0.2957	0.2770	0.3179	0.2911	0.3041
Tocilizumab	0.3118	0.2948	0.3300	0.3324	0.3153

NA = not applicable

In the analysis of ACR 50, the data show that etanercept has the highest mean treatment response and anakinra the lowest mean response. Under each scenario, this trend was maintained. Ranking of the other biologics show that golimumab and adalimumab have the second and third highest response in the ACR 50 analysis and Sensitivity Analyses 2 and 4. In Sensitivity Analysis 3, which included studies with durations of 22 weeks or more, adalimumab and tocilizumab rank behind etanercept, respectively (there are no longer any studies of golimumab included in this analysis). In the sensitivity analysis including all 34 potential studies (Sensitivity Analysis 1), certolizumab pegol has the second highest response, but this relative ranking may be due to the difference in study design, with the required early escape biasing results in favor of active treatment. The results from the sensitivity analyses show the model to be fairly robust.

These findings are consistent with a good-quality German retrospective cohort study based on the RABBIT (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) database, which reports higher discontinuation rates due to lack of efficacy for patients on anakinra than for patients on either etanercept or infliximab after 12 months of treatment (30 percent vs. 20 percent vs. 20 percent; P=NR).[88] In addition, they are consistent with several cohort studies reporting greater improvements in disease activity with etanercept than with infliximab.[68-71] Similarly, one meta-analysis of short-term (12-30 week) treatment of etanercept, adalimumab, and infliximab found higher risk ratios for reaching ACR 50 for etanercept than adalimumab and infliximab (ACR 50 for etanercept 5.28, 95% CI, 3.12 to 8.92; adalimumab 3.50, 95% CI, 2.75 to 4.44, infliximab 2.68, 95% CI, 1.79 to 3.99.[183]

Comparisons with other MTC meta-analyses of biologic DMARDs. We compared our analysis with four other reviews using MTC meta-analyses that compared biologic DMARDs (Nixon 2007,[184] Devine 2011,[185] Bergman 2010,[186] and CADTH 2010[187]). All the meta-analyses present arm-based random effects logistic regression models within a Bayesian framework. Two of the MTC analyses, Devine 2011 and Nixon 2007, use meta-regression to adjust for study-level covariables. Some differences exist between the inclusion/exclusion criteria of our analysis compared with the others, shown in Table 16.

Table 16. Exclusion criteria of MTC meta-analyses

	Exclusions				
Study	**6-Month Duration**	**MTX Naïve**	**Monotherapy**	**Biologic Failure**	**Low-Dose MTX**
Devine, 2011	x			x	
Bergman, 2010	x	x			
CADTH, 2010	x	x	x	x	x
Nixon, 2007	x		x		
RTI-UNC EPC 2011 analysis	Limited to 6-month duration In sensitivity analysis	x	Removed these studies in a sensitivity analysis	x	

These differences in criteria led to a different set of studies included in the MTC. Studies included in the other meta-analyses, including our MTC meta-analysis, are listed in Table 14. Reasons for exclusion from our MTC are listed beside trial name. Figure 3 illustrates the relative treatment effect for ACR response.

Biologic DMARD versus oral DMARD. Four RCTs, a nonrandomized trial, and a prospective cohort study determined the comparative efficacy and safety of various biologic and oral DMARDs with approved doses. The RCTs compared adalimumab,[76] etanercept,[77, 86] and tocilizumab[173] with MTX; the nonrandomized trial compared etanercept and infliximab with leflunomide;[67] and the cohort study assessed differences in class effects (Table 17).[78] No evidence exists on abatacept, anakinra, and rituximab, certolizumab, golimumab, or on oral DMARDs other than MTX and leflunomide. Disease activity and remission results are presented in Table 17 and radiographic damage in Table 18.

Biologic DMARDs as a class versus oral DMARDs as a class. A prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab (n=818) and oral DMARDs as a class (n=265) in patients who had failed two previous DMARD treatments.[78] This study was population-based and part of RABBIT, a German long-term, prospective cohort study of RA patients who had required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. In a multivariate logistic regression, adjusting for baseline confounders, the investigators determined that patients on biologics had a statistically significantly greater chance of remission (DAS<2.6) after 12 months of treatment (OR, 1.95; 95% CI, 1.20 to 3.19). Likewise, patients treated with biologics had an almost four times higher likelihood of achieving functional independence than patients treated with oral DMARDs (OR, 3.88; 95% CI, 1.71 to 8.79). Nevertheless, both groups had a substantial risk of relapse during the treatment period. Approximately one-half of the patients who were in remission at 6 months achieved a sustained remission until 12 months (biologics, 55 percent; oral DMARDs, 58 percent).

Adalimumab versus MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration<3 years), aggressive RA.[76] This multinational study randomized 799 patients with early RA to a combination of adalimumab (40 mg every other week) and MTX (20 mg/week), adalimumab monotherapy (40 mg every other week), or MTX monotherapy (20 mg/week). Two treatment arms of this 2-year study assessed differences in the efficacy of adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). After 2 years, the proportion of patients who met ACR 50 criteria was lower for those on

Figure 3. Relative treatment effect for ACR 50 response for biologics

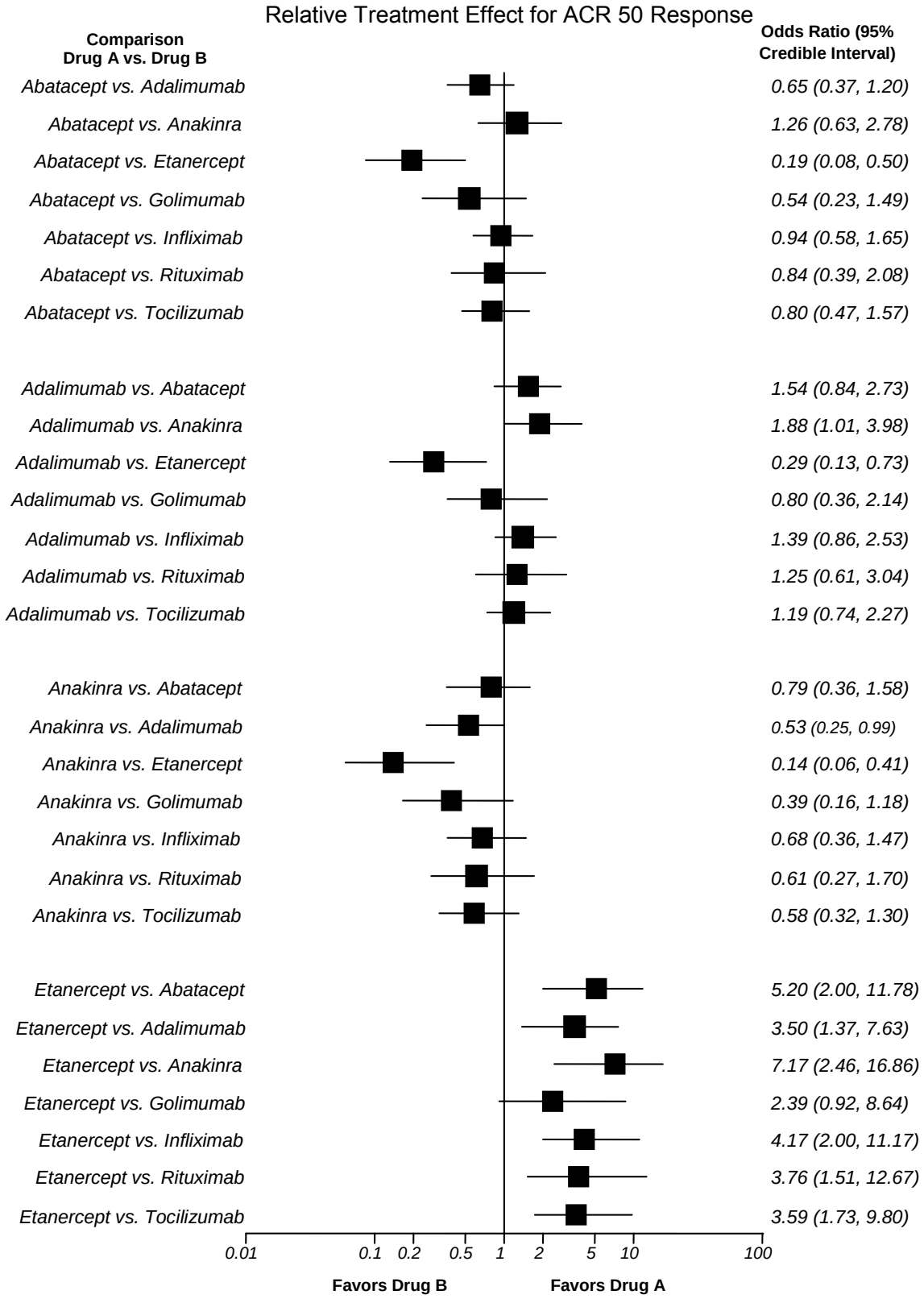


Figure 3. Relative treatment effect for ACR 50 response for biologics (continued)

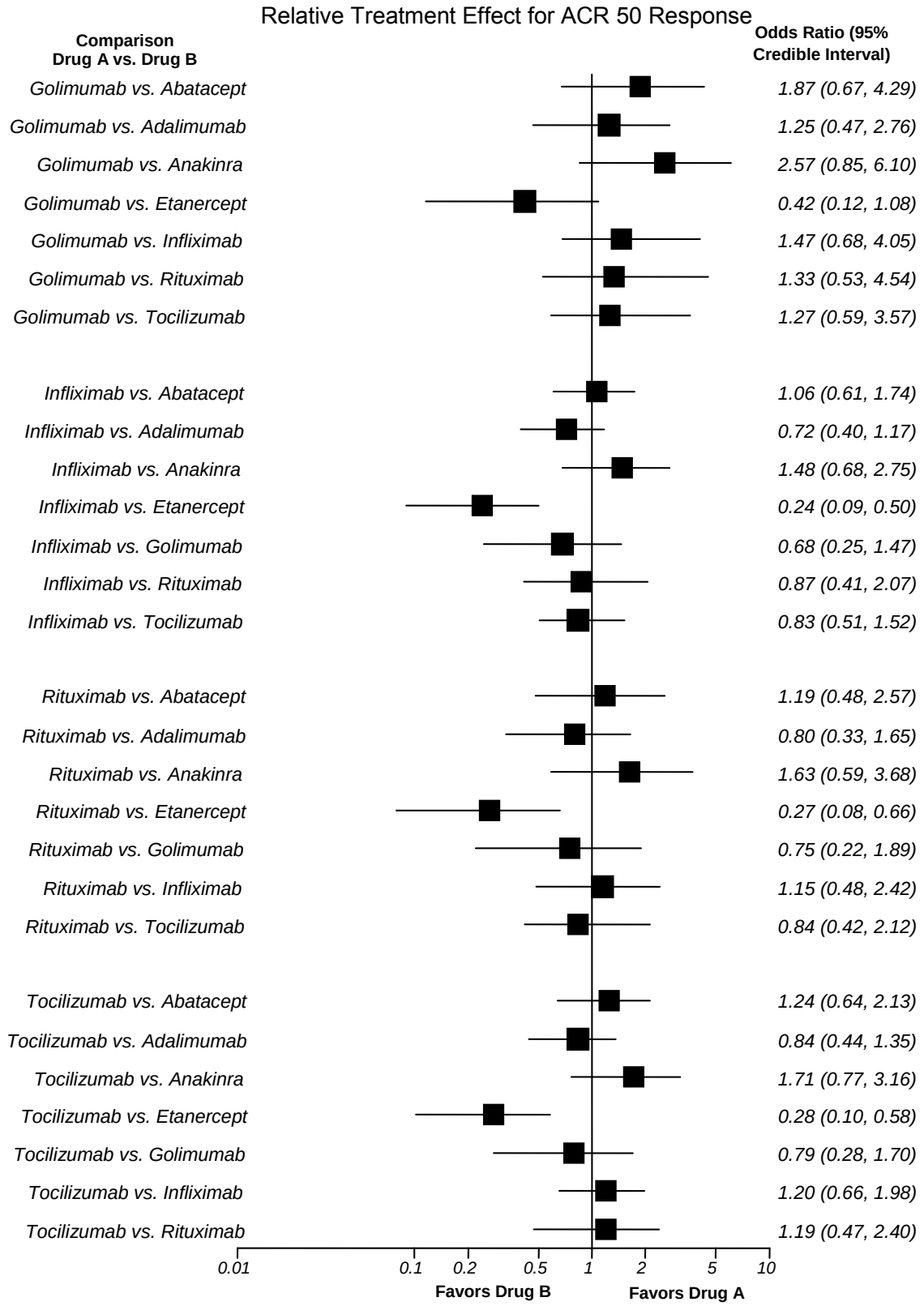


Table 17. Disease activity and remission for biologic DMARD versus oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Adalimumab vs. Oral DMARD					
		(DMARD naïve)			
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (<3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Lower ACR 50 response rates for ADA than MTX (37% vs. 43%; *P*=NR)	Fair
Etanercept vs. Oral DMARD					
		(DMARD naive)			
Bathon et al., 2000;[77] Genovese et al., 2002;[188] Genovese et al., 2005[189] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Similar ACR 20 at 12 months for ETN vs. MTX (72% vs. 65%; *P*=0.16)	Fair
		(Prior DMARD failure)			
Klareskog et al., 2004[86] van der Heijde et al., 2006[136] van der Heijde et al., 2006[138] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETN (25 mg twice weekly) vs. MTX (7.5 titrated to 20 mg/week)	Higher area under curve of ACR-N for ETN than MTX(14.7%-years vs. 12.2%-years; *P*= NR) at 24 weeks; but similar ACR 20 at 52 weeks (76% vs. 75%, *P*=NR)	Fair
Geborek et al., 2002[67]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher) vs. LEF (20 mg/day)	Higher ACR 20/50 responses for ETN and INF vs. LEF at 3 months (data NR; *P*<0.05) and for ETN vs. LEF at 6 months (data NR; *P*<0.05); results for 12 months: NR	Fair
Tocilizumab vs. MTX					
		(DMARD naïve)			
*Nishimoto et al., 2009[173] SATORI study	RCT 127 24 weeks	Active RA; inadequate response to MTX	TCZ (8 mg every 4 weeks) vs. MTX (8 mg/week)	Higher ACR 20 response for TCZ than MTX (80.3% vs. 25.0%; *P*<0.001)	Fair
Biologic class vs. DMARD class					
Listing et al., 2006[78]	Prospective cohort 1,083 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.6 years	Biologics as a class (ADA, ANA, ETN, INF; dose NR) vs. DMARDs as a class (dose NR)	Significantly higher chance of remission for biologics than oral DMARDs (OR, 1.95; 95% CI, 1.20 to 3.19)	Fair

* New study added since last review.

ACR = American College of Rheumatology; ADA = adalimumab; ANA = anakinra; CI = confidence interval; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ETN = etanercept; INF = infliximab; LEF = leflunomide; mg = milligram; MTX = methotrexate; NR = not reported; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; vs. = versus

Table 18. Radiographic joint damage in biologic DMARDs versus oral DMARD studies

Study	Study Design N Duration	Population With Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Adalimumab vs. Oral DMARD				
Breedveld et al., 2006[76], *Hoff et al., 2009[190] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Total modified Sharp score change: 5.5 vs. 10.4; *P*<0.001 Erosion score change: 3.0 vs. 6.4; *P*<0.001 Joint space narrowing score change: 2.6 vs. 4.0; *P*<0.001
Etanercept vs. Oral DMARD				
Bathon et al., 2000;[77] Genovese et al., 2002;[188] Genovese et al., 2005[189] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Yes; MTX-naive patients with early, aggressive RA	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Total Sharp score change: 1.0 vs. 1.59; *P*= 9,111 Erosion score change: 0.47 vs. 1.03; *P*=0.006
Klareskog et al., 2004[86] van der Heijde et al., 2006[136] van der Heijde et al., 2006[138] TEMPO study	RCT 686 (503 for 2-year results) 52 weeks (2 years, 100 weeks)	No	ETN (25 mg twice weekly) vs. MTX (7.5 titrated to 20 mg/week)	At 1 year: Total modified Sharp score change: 0.52 vs. 2.80; *P*=0.047 Erosion score change: 0.21 vs. 1.68; *P*<0.008 Joint space narrowing score change: 0.32 vs. 1.12; *P*=NR (NS)

* New study added since last review.
ADA = adalimumab; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ETN = etanercept; INF = infliximab; LEF = leflunomide; mg = milligram; MTX = methotrexate; NR = not reported; P=NR (NS), p value not reported but authors stated it was not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; TEMPO = Trial of etanercept and Methotrexate with radiographic patient outcomes; vs. = versus

adalimumab than for those on MTX monotherapy (37 percent vs. 43 percent; *P*=NR). In contrast, radiographic progression was statistically significantly lower in patients treated with adalimumab than with MTX (5.5 vs. 10.4 Sharp units; *P*<0.001) (Table 18). No difference was apparent in clinical remission (DAS 28<2.6) between the two treatment groups (both 25 percent); discontinuation rates due to lack of efficacy were similar in the adalimumab and MTX groups (19.0 percent vs. 17.9 percent; *P*=NR). We report on results of the other comparisons of the PREMIER study in the respective sections (below) on *Biologic DMARD plus oral DMARD versus biologic DMARD* and *Biologic DMARD plus oral DMARD versus oral DMARD.*

Etanercept versus MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week) over 52 weeks.[77, 86, 136, 138, 188, 189] The ERA (Early Rheumatoid Arthritis) study (N=632) was conducted in patients with early RA who were MTX-naive.[77, 188, 189] The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) trial[86, 136, 138] randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week MTX), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week).[86, 136, 138] Patients had active RA and had failed at least one DMARD other than MTX. About 57 percent of the study population was MTX naive. Patients

who had either failed prior MTX treatment or experienced toxic effects were excluded from this study.

Both studies failed to show statistically significant differences between etanercept and MTX in clinical and health outcome measures (SF-36, the Health Assessment Questionnaire [HAQ], the Arthritis-Specific Health Index [ASHI]), and ACR 20/50/70 responses at study endpoints (52 weeks). By contrast, radiographic outcomes were significantly better in patients on etanercept than in those on MTX. For example, in the ERA trial, 72 percent of patients on etanercept and 60 percent on MTX had no radiographic progression of disease (P=0.007). Improved radiographic outcomes were maintained during an open-label extension of the ERA study to 2 years[188] and 5 years.[189]

Etanercept or infliximab versus leflunomide. No RCT compared biologic DMARDs to leflunomide. The only head-to-head evidence came from a nonrandomized, open-label study (N=369) that accessed the efficacy and safety of etanercept (25 mg twice weekly), infliximab (3 mg/kg or higher every 8 weeks), and leflunomide (20 mg/day).[67] This study has been described in greater detail in the section (above) on *Biologic DMARD versus biologic DMARD*. At 3 months and 6 months, a greater percentage of patients on etanercept met ACR 20 and ACR 50 criteria than those on leflunomide (data NR; P<0.05). A greater percentage of patients on infliximab achieved ACR 20 and ACR 50 criteria at 3 months than those on leflunomide (data NR; P<0.05). The authors did not report 12-month data. Both etanercept and infliximab led to significant reductions in prednisolone dosage; by contrast, the investigators did not find any reduction in prednisolone dosage with leflunomide. These findings must be viewed cautiously. Baseline characteristics of patients differed substantially between the leflunomide group and the biologic groups. Leflunomide patients were older and had significantly more joint damage than patients on etanercept or infliximab. Such differences can potentially confound results, introducing bias that would support differences in results among these treatment groups.

Golimumab versus MTX. Two RCTs compared unapproved doses of golimumab (100 mg) with MTX.[92, 169] These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 17 and 18, the overview, our conclusions, or in strength of evidence tables due to the use of unapproved doses in the golimumab plus placebo arms, because it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) with MTX.

The GO-FORWARD study was a phase III, multicenter 52-week trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 50 mg injections plus MTX 52.[169] At week 16, patients in the first three groups who had less than 20% improvement in tender and swollen joints were allowed to enter an early escape The trial found no difference in the ACR 20 response between those treated with golimumab 100 mg and those treated with MTX at 52 weeks (ACR 20 45 percent vs. 44 percent, P=NS, NR).

The GO-BEFORE study was a phase III, multicenter trial that randomized subjects to subcutaneous placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 100 mg injections plus MTX capsules.[92] At week 24, there were no differences in ACR 20, 50, or 70 between those treated with golimumab 100 mg and those treated with MTX (ACR 50: 32.7 percent vs. 29.4 percent, P=NR) data NR).

Tocilizumab versus MTX. The SATORI study, a multisite RCT in Japan, examined 127 patients with active RA and an inadequate response to MTX.[173] Subjects were randomized to MTX (8 mg/week) plus placebo or to tocilizumab (8 mg/kg every 4 weeks) plus placebo. After 24 weeks, those treated with tocilizumab had significantly higher ACR 20 response than those treated with MTX (80.3 percent vs. 25.0 percent, $P<0.001$). The study findings are limited by a high withdrawal rate; 48% of patients in the MTX group, compared with 11% in the tocilizumab group withdrew during the study, mostly due to unsatisfactory response. Additionally, the dose of MTX used in this study is below the dose usually considered therapeutic. Mulitnational evidence-based recommendations suggest starting MTX at 10-15 mg/week, with the escalation of 5 mg every 2-4 weeks up to 20-30 mg week.[191] Thus, this study does not provide evidence that is relevant to determine how tocilizumab compares with MTX as it is generally used in clinical practice.

Biologic combinations: Biologic DMARD plus biologic DMARD versus biologic DMARD. A 24-week RCT did not detect any synergistic effects of a combination treatment of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy (Table 19).[79] Overall, 242 patients who were on stable doses of MTX treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept only. Furthermore, the frequency of serious adverse events was substantially higher in the combination groups (14.8 percent for 50 mg etanercept plus anakinra, 4.9 percent for 25 mg etanercept plus anakinra, and 2.5 percent for etanercept only; P=NR). Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6 percent vs. 7.4 percent; P=NR).

Table 19. Disease activity and remission for biologic DMARD+biologic DMARD versus biologic DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
ETN+AKA vs. ETN					
Genovese et al., 2004[79]	RCT 242 24 weeks	Inadequate control of disease with MTX; mean disease duration 9.9 years	ETN (25 mg twice weekly)+ANK (100 mg/day) vs. ETN (25 mg/week)	Higher ACR 50 response rates for ETN monotherapy (31% vs. 41%; P=0.914)	Fair
ETN+ABA vs. ETN					
*Weinblatt, et al., 2007[80]	RCT 121 1 year 2-year long-term extension	Patients on ETN; mean disease duration 12.8-13 yrs	ETN (25 mg twice weekly)+ABA 2g/kg increased to 10 mg/kg after 1 year) vs. ETN (25 mg twice weekly)	No difference in mACR 20/50/70 response rates at 1 year	Fair

* New study added since last review.
ABA = abatacept; ACR = American College of Rheumatology; ANK = anakinra; ETN = etanercept; kilogram = kg; mACR = modified American College of Rheumatology; milligram = mg; RCT = randomized controlled trial; vs. = versus; yr = year

Similarly, a 1-year RCT (N=121) followed by a 2-year open-label long-term extension (N=80) found no significant differences in modified ACR 20 at 1 year or at 2 and 3 years in the long-term extension for patients treated with abatacept (2 mg/kg for RCT, 10 mg in long-term extension) combined with etanercept (25 mg twice weekly) compared to etanercept only (Table 19).[80] Although the initial RCT dosing of abatacept was lower than currently used clinically, the

frequency of serious adverse events was higher in the abatacept combined with etanercept-treated patients than in the etanercept-only treated patients.

Biologic DMARD plus oral DMARD versus biologic DMARD. The majority of trials assessed a combination of a biologic DMARD and MTX against a monotherapy of the respective biologic DMARD.[68, 76, 81, 84, 86, 87, 126] Only one trial used sulfasalazine as a oral DMARD in combination with a biologic DMARD.[85] No evidence is available on combination treatments of abatacept or anakinra. Disease activity and remission results are presented in Table 20 and radiographic joint damage in Table 21.

Adalimumab plus MTX versus adalimumab. The PREMIER study was conducted in MTX-naive patients with early (disease duration<3 years), aggressive RA.[76] Details of this study are reported above in *Biologic DMARD versus oral DMARD.* After 2 years, significantly more patients on the combination therapy achieved response criteria on ACR 50 than patients on adalimumab monotherapy (59 percent vs. 37 percent; $P<0.001$); in addition, they had statistically significantly less progression on a modified Sharp/van der Heijde score (1.9 vs. 5.5 Sharp units; $P<0.001$). After 2 years of treatment, 49 percent of patients on the combination therapy and 23 percent on adalimumab monotherapy achieved remission (DAS 28<2.6; $P<0.001$). Discontinuation rates because of lack of efficacy were lower in the combination group than in the monotherapy group (4.2 percent vs. 19.0 percent; P=NR). We report on results of the other comparisons of the PREMIER study in the respective sections on *Biologic DMARD versus oral DMARD* and *Biologic DMARD plus oral DMARD versus oral DMARD*.

Etanercept plus MTX versus etanercept. Two RCTs (in four publications)[86, 87, 136, 138] and two prospective cohort studies[68, 81] assessed differences in efficacy between an etanercept-MTX combination and etanercept monotherapy in patients with active, DMARD-resistant disease. Findings of these studies consistently supported greater efficacy for the combination therapy than for the etanercept monotherapy.

The TEMPO trial (described above in *Biologic DMARD versus oral DMARD)* enrolled a mixed population of MTX-naive patients (about 57 percent) and patients who had been on prior MTX treatment (about 43 percent). Patients who had either failed prior MTX treatment or experienced toxic effects were excluded from this study. Results of the etanercept-MTX combination (25 mg twice weekly plus up to 20 mg/week) and the etanercept monotherapy (25 mg twice weekly) arms showed that the combination treatment was significantly more efficacious than etanercept alone. After 52 weeks, 69 percent in the combination group and 48 percent in the etanercept group achieved ACR 50 response criteria ($P<0.0001$). Likewise, a statistically significantly higher proportion of patients in the combination than in the monotherapy group met ACR 20 and ACR 70 response criteria. The proportion of patients achieving remission (DAS<1.6) was 35 percent in the combination group and 16 percent in the monotherapy group ($P<0.0001$). In addition, the combination regimen led to significantly better radiographic outcomes (changes in total Sharp score: -0.54 vs. 0.52; $P<0.0001$) than the etanercept monotherapy.[136]

Table 20. Disease activity and remission for biologic DMARD+oral DMARD versus biologic DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Adalimumab+MTX vs. Adalimumab					
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (<3 years)	ADA (40 mg biweekly)+MTX (20 mg/week) vs. ADA (40 mg biweekly)	Significantly higher ACR 50 response rates for ADA+MTX than ADA (59% vs. 37%; *P*<0.001)	Fair
Etanercept+vs. Etanercept					
Combe et al., 2006[85]	RCT 260 24 weeks	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly)+SSZ (2, 2.5, or 3 g/day) vs. ETN (25 mg twice weekly)	Similar ACR 20 response rates between ETN+SSZ and ETN (74% vs. 74%; *P*=NR)	Fair
Klareskog et al., 2004;[86] van der Heijde et al., 2006;[136] van der Heijde et al., 2006;[138] *Kavanaugh et al., 2008[192] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETN+MTX than ETN (18.3%-years vs. 14.7%-years; *P*<0.0001) at 24 weeks	Fair
Van Riel et al., 2006[87]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX; mean disease duration 10.9 years	ETN (25 mg twice weekly)+MTX (>12.5 mg/week) vs. ETN (25 mg twice weekly)	Similar proportions of patients achieved an improvement of >1.2 units of DAS 28 (75% vs. 73%; *P*=0.66)	Fair
Hyrich et al., 2006[81]	Prospective cohort 2,711 6 months	Population-based; patients with active RA who required change in therapy; mean disease duration 14.3 years	ETN (25 mg twice weekly)+MTX (dose NR) vs. ETN (25 mg twice weekly)+other DMARD (dose NR) vs. ETN (25 mg twice weekly)	Significantly higher EULAR response rates for ETN+MTX than ETN (OR, 1.98; 95% CI, 1.45-2.71)	Good
Weaver et al., 2006[68]	Prospective cohort 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly)+MTX (dose NR) vs. ETN (25 mg twice weekly)	Similar mACR 20 response rates for ETN+MTX and ETN (43% vs. 41%; *P*=NR)	Fair
Zink et al., 2005[88]	Retrospective cohort 1,523	Patients with RA who had a change in treatment regimen	ETN+MTX vs. ETN (dosages NR)	Discontinuation due to lack of efficacy: Greater in ETN monotherapy vs. combination (ETN+MTX: 16.9%; ETN: 19.9%; *P*=NR)	Good

Table 20. Disease activity and remission for biologic DMARD+oral DMARD versus biologic DMARD studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Infliximab+MTX vs. Infliximab					
Zink et al., 2005[88]	Retrospective cohort 1,523 1 year	Patients with RA who had a change in treatment regimen	INF+MTX vs. INF, (dosages NR)	Greater in INF monotherapy than combination (INF+MTX: 17.9%, INF: 45%)	
Hyrich et al., 2006[81]	Prospective cohort 2,711 6 months	Population-based; patients with active RA who required change in therapy; mean disease duration 14.3 years	INF (3 mg/kg)+MTX (dose NR) vs. INF (3 mg/kg)+other DMARD (dose NR) vs. INF (3 mg/kg)	Higher EULAR response rates for INF+MTX than INF (OR, 1.35; 0.92-2.00)	Good
Rituximab+MTX vs. MTX					
Edwards et al., 2004[84]	RCT 161 24 weeks	Active RA despite MTX treatment; mean disease duration 10.4 years	RTX (1,000 mg/days 1 & 15)+MTX (>10 mg/day) vs. RTX (1,000 mg/days 1 & 15)	Higher ACR 50 response rates for the RTX+MTX combination than for RTX monotherapy (43% vs. 33%; *P*=NR)	Fair

* New study added since last review.

ACR = American College of Rheumatology; ACR-N = American College of Rheumatology percent improvement from baseline to endpoint; ADA = adalimumab; CI = confidence interval; ETN = etanercept; ETN+ABA = etanercept plus abatacept; ETN+AKA = etanercept plus anakinra; EULAR = European League Against Rheumatism response; INF = infliximab; kg = kilogram; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; SSZ = sulfasalazine; vs. = versus

Table 21. Radiographic joint damage biologic DMARD+oral DMARD versus biologic DMARD studies

Study	Study Design N Duration	Population with Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Adalimumab+MTX vs. Adalimumab				
Breedveld et al., 2006;[76] *Hoff et al., 2009[190] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly)+MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 5.5; *P*<0.001 Erosion score change: 1.0 vs. 3.0; *P*<0.001 Joint space narrowing score change: 0.9 vs. 2.6; *P*<0.001
Etanercept+MTX vs. Etanercept				
Klareskog et al., 2004;[86] van der Heijde et al., 2006;[136] van der Heijde et al., 2006[138] TEMPO study	RCT 686 52 weeks	No	ETN (25 mg twice weekly)+MTX (20 mg/week) vs. ETN (25 mg twice weekly)	At 1 year: Total modified Sharp score change: -0.54 vs. 0.52; *P*=0.0006 Erosion score change: -0.30 vs. 0.21; *P*<0.0001 Joint space narrowing score change: -0.23 vs. 0.32; *P*=0.0007 At 2 years: Total modified Sharp score change: -0.56 vs. 1.10; *P*<0.05 Erosion score change: -0.76 vs. 0.36; *P*<0.05 Joint space narrowing score change: 0.20 vs. 0.74; *P*=NR (NS)

* New study added since last review.
ADA = adalimumab; CI = confidence interval; ETN = etanercept; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; P=NR (NS) = p value not reported but authors stated it was not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; vs. = versus

A German retrospective cohort study based on the RABBIT database did not find differences in discontinuation rates due to lack of efficacy between patients on etanercept monotherapy and those on an etanercept-MTX combination (19.9 percent vs. 16.9 percent; *P*=NR).[88]

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of findings from efficacy RCTs.[138] ACR response criteria, DAS remission rates, quality-of-life measures, and radiographic progression were statistically significantly better in the combination group than in the etanercept monotherapy group. Attrition was 39 percent after 2 years and could compromise the internal validity of the long-term results.

The other three studies included a 16-week, open-label RCT (N=315),[87] a 12-month prospective cohort study,[68] and a 6-month prospective cohort study.[81] Their results were generally consistent with findings from the TEMPO trial. Both prospective cohort studies were population-based, one in the United States[68] and the other in the United Kingdom,[81] and both have a high generalizabilty.

The UK study also compared the effectiveness of the etanercept-MTX combination and a combination of etanercept and other DMARDs (leflunomide, azathioprine, sulfasalazine, hydroxychloroquine, cyclosporine A, penicillamine, gold, minocycline) as a class.[81] After adjusting for potential confounders, the investigators reported statistically significantly higher response rates for MTX as a cotherapy than for other DMARDs (OR, 1.66; 95% CI, 1.14 to 2.42).

Etanercept plus sulfasalazine versus etanercept. A 24-week RCT assessed the comparative efficacy of etanercept and sulfasalazine combination therapy (respectively, 25 mg twice weekly plus 2, 2.5, or 3 g/day), etanercept monotherapy (25 mg twice weekly), and sulfasalazine monotherapy (2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[85] Because sulfasalazine monotherapy resembles a placebo treatment (patients had to have failed it to be eligible), we focus on results from the combination (n=101) and etanercept monotherapy (n=103) arms. After 24 weeks, both groups had similar clinical responses on multiple outcome measures (ACR 20/50/70, DAS28). On ACR 20, the primary efficacy variable, 74 percent of patients in both groups met the relevant response criteria. Likewise, results on patient-reported measures of quality of life (HAQ, EuroQOL, general health VAS) were similar for patients on the combination and monotherapy interventions.

Golimumab plus MTX versus golimumab. Two RCTs compared golimumab plus MTX with unapproved does of golimumab (100 mg).[92, 169] These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 20 and 21 the overview, our conclusions, because it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) plus MTX.

The GO-BEFORE study was a phase III, multicenter trial that randomized subjects to subcutaneous placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 100 mg injections plus MTX capsules.[92] The GO-FORWARD study was a phase III, multicenter 52-week trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 50 mg injections plus MTX 52.[169] For both trials, the golimumab plus placebo arm of the trial used an unapproved dose of golimumab, thus it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks and combination therapy with golimumab plus MTX.

Infliximab plus MTX versus infliximab. No RCT examined the comparative efficacy and effectiveness of a combination of infliximab and MTX against infliximab monotherapy in patients with RA. Of note, infliximab is not FDA approved for use as monotherapy. The only comparative evidence includes one U.S. and one U.K. prospective cohort study (already described).[68, 81] Both studies indicated that EULAR and modified ACR response criteria were greater for patients in the studies' infliximab combination groups. Remission rates, however, were similar in both studies for the two regimens. At 6 months, U.K. patients in the combination group had higher EULAR response rates than those in the monotherapy group (OR, 1.35; 95% CI, 0.92 to 2.00).[81] At 12 months, mACR 20 responses were similar for U.S. patients in the combination and the monotherapy groups (OR, 0.96; 95% CI, 0.76 to 1.21; P=0.72).[68]

A German retrospective cohort study assessing discontinuation rates in clinical practice reported findings similar to those noted above. Discontinuation rates because of lack of efficacy were higher among patients on an infliximab monotherapy than among those on an infliximab-MTX combination regimen (45 percent vs. 18 percent; P=NR).[88] Overall discontinuation rates, however, were statistically significantly higher in the monotherapy than in the combination group (56 percent vs. 34 percent; hazard ratio, 1.9; 95% CI, 1.1 to 3.1).

Rituximab plus MTX versus rituximab. One RCT enrolled patients with highly active, long-standing, DMARD-resistant RA to compare the efficacy of rituximab and MTX (1,000 mg on day 1 and day 15 plus MTX 10 mg or more/week), rituximab monotherapy (1,000 mg on day 1

and day 15), rituximab and cyclophosphamide, and MTX monotherapy.[84] Because cyclophosphamide is not a drug of interest for this report and because MTX monotherapy resembles a placebo treatment (patients had to have failed MTX treatment to be eligible), we focus on results of the rituximab-MTX combination (n=40) and the rituximab monotherapy (n=40) arms. After 24 weeks, patients on the combination intervention experienced changes in DAS outcomes similar to those for patients on rituximab monotherapy (-2.6 vs. -2.2; *P*=NR). A similar proportion of patients in both treatment groups achieved a good or moderate EULAR response (83 percent vs. 85 percent; *P*=NR). However, the proportion of patients meeting all three ACR response criteria was higher for patients treated with the rituximab combination treatment than for patients on rituximab monotherapy (ACR 20, 73 percent vs. 65 percent; ACR 50, 43 percent vs. 33 percent; ACR 70, 23 percent vs. 15 percent; *P*=NR). Higher ACR response rates for the combination treatment were maintained during a 48-week, double-blinded followup. After 48 weeks, 35 percent of patients on the combination regimen and 15 percent of patients on rituximab monotherapy met the ACR 50 response criteria.

Biologic combinations: Biologic DMARD plus oral DMARD versus oral DMARD. The evidence is limited to six studies and one systematic review[193]comparing a combination regimen of abatacept plus MTX[89] adalimumab plus MTX[76] or a combination of etanercept plus MTX[86, 90] or a combination regimen of infliximab plus MTX[82] with MTX monotherapy. One study examined etanercept plus sulfasalazine versus sulfasalazine monotherapy.[85] Four studies and a systematic review[193] were conducted in patients with early, aggressive RA.[76, 82, 89, 90] Table 22 presents disease activity and remission results, followed by radiographic joint damage in Table 23.

Table 22. Disease activity and remission for biologic DMARD+oral DMARD versus oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Abatacept+MTX vs. MTX					
*Westhovens et al., 2009[89]	RCT 509 2 year (1 year reported)	Early RA, MTX-naïve or previous MTX ≤10 mg/week for 3 weeks or less, with none for prior 3 months	Abatacept (~10 mg/kg)+MTX vs. MTX	Significantly higher ACR 50 response rates for ABA+MTX than MTX (57.4% vs. 42.3%; *P*<0.001) Higher remission rates for ABA+MTX than MTX (41.4% vs. 23.3%; *P*<0.001)	Good
Adalimumab+MTX vs. MTX					
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (<3 years)	ADA (40 mg biweekly)+MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly higher ACR 50 response rates for ADA+MTX than MTX (59% vs. 43%; *P*<0.001)	Fair
Etanercept+MTX vs. MTX					
*Emery et al., 2008[90]; Emery et al., 2010[91] COMET study	RCT 542 52 weeks† 2 years[91]	MTX-naïve patients; Early RA, mean disease duration 9 months	ETN (50 mg/week)+MTX 7.5 mg vs. MTX	Higher ACR 20 response rates between ETN+MTX vs. MTX (86%, 67%, *P*<0.001) Higher remission between ETN+MTX vs. MTX (50%, 28%, *P*<0.001)	Fair

Table 22. Disease activity and remission for biologic DMARD+oral DMARD versus oral DMARD (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Klareskog et al., 2004;[86] van der Heijde et al., 2006;[136] van der Heijde et al., 2006,[138] *Kavanaugh et al., 2008[192] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETN+MTX than MTX (18.3%-years vs. 12.2%-years; *P*<0.0001) at 24 weeks	Fair
Etanercept+Sulfasalazine vs. Sulfasalazine					
Combe et al., 2006[85] *Combe et al., 2009[145]	RCT 260 24 weeks 2 years	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly)+SSZ (2, 2.5, or 3 g/day) vs. SSZ (2, 2.5, or 3 g/day)	Higher ACR 20 response rates between ETN+SSZ and SSZ (74% vs. 28%; *P*=NR) Higher remission at 2 years ETN+SSZ than SSZ (DAS <2.5; 57% vs.4.0%; *P*<0.01)	Fair
Golimumab+MTX vs. MTX					
*Emery et al., 2009[92] GO-BEFORE	RCT 637 24 weeks	MTX-naïve patient with active RA	GOL (50 mg)+MTX vs. MTX	Higher ACR 50 response rates between GOL+MTX and MTX (40.3% vs. 29.4%; *P*=0.042)	Fair
Infliximab+MTX vs. MTX					
St Clair et al., 2004;[82] Smolen et al., 2006;[83] *Smolen et al., 2009[194] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks)+MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks)+MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly greater improvement of ACR-N for INF 3 mg+MTX and INF 6 mg+MTX than MTX (38.9% vs. 46.7% vs. 26.4%; *P*<0.001) Higher remission in INF+MTX vs. MTX (DAS28-ESR<2.6; 21.3%, 12.3%; *P*<0.001)	Fair

* New study added since last review.

†In COMET, subjects were randomized to one of four treatment groups: (1) ETN+MTX for year 1 followed by the same treatment for year 2, (2) ETN+MTX for year 1 followed by ETN alone for year 2, (3) MTX for year 1 followed by ETN+MTX for year 2, or (4) MTX for year 1 followed by continued MTX for year 2. Thus, all subjects were treated with ETN+MTX or MTX for 1 year and we present the 52-week outcomes in this table

ADA = adalimumab; ETN = etanercept; mg = milligram; MTX = methotrexate; RA = rheumatoid arthritis; RCT = randomized controlled trial; TEMPO = Trial of etanercept and Methotrexate with radiographic patient outcomes; vs. = versus

Table 23. Radiographic joint damage of biologic DMARD+oral DMARD versus oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results
Abatacept+MTX vs. MTX				
*Westhovens et al., 2009[89]	RCT 509 2 year (1 year reported)	Early RA, MTX-naïve or pervious MTX ≤10 mg/week for 3 weeks or less, with none for prior 3 months	Abatacept (~10 mg/kg)+MTX vs. MTX	Genant modified Sharp total score mean change 0.63 vs. 1.06; *P*<0.040
Adalimumab+MTX vs. MTX				
Breedveld et al., 2006,[76] *Hoff et al., 2009[190] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly)+MTX (20 mg/week) vs. MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 10.4; *P*<0.001 Erosion score change: 1.0 vs. 6.4; *P*<0.001 Joint space narrowing score change: 0.9 vs. 4.0; *P*<0.001
Etanercept+MTX vs. MTX				
*Emery et al., 2008;[90] Emery et al., 2010[91] COMET study	RCT 542 52 weeks† 2 years[91]	MTX-naïve patients; early RA, mean disease duration 9 months	ETN (50 mg/week)+MTX 7.5 mg vs. MTX	Lower radiographic progression between ETN+MTX vs. MTX (mTSS -2.44, -0.27 *P*<0.001)

* New study added since last review.

†In COMET, subjects were randomized to one of four treatment groups: (1) ETN+MTX for year 1 followed by the same treatment for year 2, (2) ETN+MTX for year 1 followed by ETN alone for year 2, (3) MTX for year 1 followed by ETN+MTX for year 2, or (4) MTX for year 1 followed by continued MTX for year 2. Thus, all subjects were treated with ETN+MTX or MTX for 1 year and we present the 52-week outcomes in this table.

ADA = adalimumab; ETN = etanercept; mg = milligram; MTX = methotrexate; RA = rheumatoid arthritis; RCT = randomized controlled trial; TEMPO = Trial of etanercept and Methotrexate with radiographic patient outcomes; vs. = versus

Abatacept plus MTX versus MTX. One multinational RCT randomized 509 subjects with early RA to receive abatacept plus MTX or placebo plus MTX.[89] The trial enrolled subjects with early agressive RA who were MTX-naïve and seropositive for rheumatoid factor, anti-cyclic citrullinated protein type 2, or both, and had radiographic evidence of joint erosions. At 1 year, subjects treated with abatacept plus MTX had statistically significantly greater improvement in ACR 50 measures, remission defined by DAS28 less than 2.6 (41.4 percent vs. 23.3 percent; *P*<0.001) and less radiographic progression (mean change TS 0.63 vs. 1.06; *P* 0.040).

Adalimumab plus MTX versus MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration <3 years), aggressive RA[76] (see *Biologic DMARD plus oral DMARD versus biologic DMARD).* Two treatment arms of this 2-year study assessed differences in efficacy between a combination of adalimumab (40 mg every other week) and MTX (20 mg/week) and MTX monotherapy (20 mg/week).[76] After 2 years, statistically significantly more patients on the combination therapy met ACR 50 response criteria than patients on MTX monotherapy (59 percent vs. 43 percent; *P*<0.001); in addition, they had statistically significantly less progression on the modified SHS score (changes in total Sharp score: 5.5 vs. 10.4; *P*<0.001). After 2 years of treatment, 49 percent of patients on the combination therapy

and 25 percent on MTX monotherapy achieved remission (DAS28<2.6; *P*<0.001). Discontinuation rates because of lack of efficacy were lower in the combination than in the MTX group (4.2 percent vs. 17.9 percent; *P*=NR).

Etanercept plus MTX versus MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly or 50 mg weekly) with MTX (20 mg/week) over 52 weeks.[86, 136, 138, 192] The COMET (Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis) study (N=542) was conducted in patients with early RA who were MTX-naïve.[90] The TEMPO trial,[86, 136, 138, 192] described above in the section, *Biologic DMARD versus biologic DMARD* randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week).[86, 136, 138] The COMET trial[90] compared 542 early RA patients with etanercept (50 mg weekly) plus MTX (7.5 mg weekly) versus MTX in year 1. However, subjects were actually randomized to one of four treatment groups: (1) etanercept plus MTX for year 1 and year 2 (EM/EM), (2) etanercept plus MTX for year 1 followed by etanercept alone for year 2 (EM/E), (3) MTX for year 1 followed by year 2 (M/EM), or (4) MTX for year 1 followed by continued MTX for year 2 (M/M).[91]. Both studies showed statistically significant differences between etanercept plus MTX versus MTX in achieving ACR 20 response criteria at 24 weeks[86] and 52 weeks.[90] In the COMET study, patients treated with etanercept plus MTX had a higher remission (50 percent vs. 28 percent, *P*<0.001) and less radiographic progression than MTX only.[90] After 2 years, remission remained higher for patients in the EM/EM group compared with the M/M group (57 percent vs. 35 percent, *P*=0.002) and radiographic progression was also less (10 percent vs. 33 percent, *P*=0.009).[91]

Golimumab plus MTX versus MTX. The GO-BEFORE study was a phase III, multicenter RCT in MTX-naïve patients with active RA that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules.[92] The trial reported a higher ACR 50 response at week 24 for golimumab 50 mg plus MTX than MTX only (ACR 50: 40.3 percent vs. 29.4 percent; *P*=0.042).

Infliximab plus MTX versus MTX. The ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset) trial enrolled 1,049 patients with early RA (disease duration <3 years) who were MTX-naive.[82] This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or of using two different combinations of MTX and infliximab (3 mg/kg or 6 mg/kg) over 54 weeks. At endpoint, patients in the combination groups had significantly higher ACR-N (ACR-N is the percentage of ACR improvement from baseline to endpoint) scores than patients on MTX monotherapy (38.9 percent [3 mg infliximab plus MTX] versus 46.7 percent [6 mg infliximab plus MTX] versus 26.4 percent [MTX]; *P*<0.001); remission rates were 31 percent, 21 percent, and 15 percent, respectively. The patients treated with infliximab plus MTX also had higher remission rates than patients treated with MTX alone (DAS28 ESR <2.6; 21.3 percent vs. 12.3 percent, *P*<0.001).[194]

Biologic plus MTX versus MTX. One systematic review with meta-analysis of seven trials (N=2,763 patients) examined four combinations of biologics with MTX, including infliximab, adalimumab, etanercept, and abatacept, compared to MTX only.[193] Overall, clinical remission was higher for the compination therapy as compared with MTX only (RR, 1.74; 95% CI, 1.54 to 1.98). Radiographic nonprogression was also higher for combination therapy (RR, 1.30; 95% CI,

1.01 to 1.68). These results are limited by the heterogeneity in the definity of clinical remission and radiographic nonprogression. None of the included trials lasted more than 1 year.

Biologic combinations: Biologic DMARD plus oral DMARD versus biologic DMARD plus oral DMARD. Three prospective cohorts compared patients taking an anti-TNF plus oral DMARD to patients taking another anti-TNF plus oral DMARD.[93, 94, 195] Each compared a different anti-TNF-oral DMARD combination and followup ranged from 6 months to 17 months. Comparisons included anakinra plus MTX versus anakinra plus LEF,[93] etanercept plus oral DMARD versus infliximab versus oral DMARD,[195] and 'anti-TNF' (infliximab, etanercept or adalimumab) plus MTX versus anti-TNF plus MTX.[94] Overall, all three studies found similar disease activity responses (measured by ACR 20, EULAR and DAS28) for patients on anti-TNF plus oral DMARD compared to patients taking another anti-TNF plus oral DMARD. Similarly, radiographic progression was similar among anti-TNF+MTX groups.[94] Table 24 presents disease activity and remission while Table 25 presents radiographic joint damage.

Table 24. Disease activity and remission for biologic DMARD+oral DMARD versus biologic DMARD+oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Anakinra+MTX vs. Anakinra+Leflunomide					
*Karanikolas, et al., 2008[93]	Prospective cohort 128 48 weeks	Patients failed oral DMARD	ANK (100 mg/day)+MTX (25 mg/week) vs. ANK+LEF (20 mg/week)	No significant difference in ACR 20 response between ANK +MTX and ANK+LEF (65%, 81%; *P*=NS, NR)	Fair
Etanercept+Oral DMARD vs. Infliximab+Oral DMARD					
*Hyrich, et al., 2006[195]	Prospective cohort 2,879 6 months	Population-based, UK; patients failed at least 2 DMARDs; mean disease duration 14 years	ETN (dose NR) vs. INF (NR) (98% also received MTX)	Similar good EULAR response between ETN and INF (17.3% vs. 18.7%; *P*=NR	Fair
Anti-TNF+MTX vs. Anti-TNF+Leflunomide					
*Finckh et al., 2009[94] SCQM cohort	Prospective Cohort 1,218 17 months (mean)	Population-based: treatment with INF, ETN or ADA; mean disease duration 8.4-8.9 years	Anti-TNF(INF or ETN or ADA)(dose NR)+MTX (NR) vs. anti- TNF (INF or ETN or ADA) (NR)+LEF	Similar DAS 28 improvement at 1 yr for anti-TNF+MTX and anti-TNF+LEF (0.74; 95% CI, 0.63 to 0.84 vs. 0.63; 95% CI, 0.45 to 0.82, *P*=NR)	Fair

* New study added since last review.

ACR = American College of Rheumatology; ADA = adalimumab; ANK = anakinra; CI = confidence interval; DMARD = disease modifying anti-rheumatic drug; ETN = etanercept; EULAR = European League Against Rheumatism response; INF = infliximab; LEF = leflunomide; mg = milligram; NR = not reported; NS = not significant; SCQM = Swiss Clinical Quality Management; TNF = tumor necrosis factor; vs. = versus

Table 25. Radiographic joint damage for biologic DMARD+oral DMARD versus biologic DMARD+oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Anti-TNF+MTX vs. Anti-TNF+Leflunomide					
*Finckh et al., 2009[94] SCQM cohort	Prospective cohort 1,218 17 months (mean)	Population-based: treatment with INF, ETN or ADA; mean disease duration 8.4-8.9 years	Anti-TNF(INF or ETN or ADA)(NR)+MTX (NR) vs. anti-TNF (INF or ETN or ADA) (NR)+LEF	Similar nonsignificant radiographic progression for anti-TNF +MTX and anti-TNF+LEF (0.91%; 95% CI, 0.54 to 1.27 vs. 0.74%; 95% CI, 0.21 to 1.27, *P*=NS, NR)	Fair

* New study added since last review.
ADA = adalimumab; ASPIRE = Active-Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; SCQM = Swiss Clinical Quality Management; INF = infliximab; kg = kilogram; LEF = leflunomide; mg = milligram; NR = not reported; NS = not reported; RA = rheumatoid arthritis; RCT = randomized controlled trial; TNF = tumor necrosis factor; vs. = versus

Treatment strategies. Treatment strategies are guided by clinical response and may involve drug combinations. Disease activity and remission are presented in Table 26 and radiographic joint damage in Table 27. Available treatment strategy studies focus on early RA patients.

Two oral DMARDs plus corticosteroid versus oral DMARD. One multicenter RCT, known as COBRA (Combinatietherapie Bij Reumatoide Artritis), assessed differences in efficacy between a combination of stepped-down prednisolone, MTX, and sulfasalazine and sulfasalazine only.[95] The investigators randomized 155 Dutch patients with early RA for 56 weeks. Patients with active RA were included if they had had symptoms for fewer than 2 years and had not used DMARDs in the past. Patients were then followed indefinitely in an open-label prospective cohort (5-year follow-up data reported).[96] Combination therapy included a stepped-down prednisolone treatment (60 mg/day tapered over 28 weeks), MTX (7.5 mg/week stopped after 40 weeks), and sulfasalazine (2 g/day). Mean duration of RA was 4 months. The authors applied a pooled index, which yielded a weighted change score of five disease activity measures: tender joint count, grip strength, erythrocyte sedimentation rate (ESR), assessor's global assessment by visual analog scale (VAS), and the McMaster Toronto arthritis questionnaire (MACTAR) (score range not given). At 28 weeks, patients on combination therapy had an improved change score in this index (mean change 1.4 vs. 0.8; $P<0.0001$). At 52 weeks, however, the change results on the pooled index were no longer significant (mean change 1.1 vs. 0.9; $P=0.20$). In terms of radiographic progression, patients on combination therapy had statistically significantly less progression than the monotherapy patients on the modified Sharp/van der Heijde score at 28 weeks (1 vs. 4; $P<0.0001$), 56 weeks (2 vs. 6; $P<0.004$), and 80 weeks (4 vs. 12; $P<0.01$). Over 5 years, the modified Sharp/van der Heijde change score per year was lower for combination therapy than for monotherapy (5.6 vs. 8.6; $P=0.001$).[96]

Table 26. Disease activity and remission for early RA DMARD strategies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Two Oral DMARDs+Corticosteroid vs. Oral DMARD					
Boers et al., 1997;[95] Landewe et al., 2002[96] COBRA Study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2 g/day)+MTX (7.5 mg/day stopped after 40 weeks)+PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Pooled disease index: mean change better in combo group than SSZ alone at 28 weeks (1.4 vs. 0.8; *P*<0.0001) vs. no longer significant at 52 weeks (1.1 vs. 0.9; *P*=0.20) (Pooled index included tender joint count, grip strength, ESR, VAS, MACTAR questionnaire)	Good
Three Oral DMARDs+Corticosteroid vs. Oral DMARDs					
Mottonen et al., 1999;[97] Korpela et al., 2004[98] FIN-RACo study	RCT 199 24 months (5-year follow-up)	Multicenter; early RA; mean disease duration 7.3-8.6 months	MTX (7.5 to 10 mg/week)+HCQ (300 mg/day)+SSZ (2 g/day)+PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	Remission (defined by ACR preliminary criteria modified by authors) higher in combination group (37.9% vs. 18.4%; *P*=0.011); ACR 50 higher in combination group (71% vs. 58%; *P*=0.058); (5-year remission, NS, 28% vs. 22%; *P*=NS)	Fair
Three Oral DMARDs vs. Biologic+Oral DMARD					
Van Vollenhoven et alo., 2009[99] Swefot trial	RCT 258 12 months	Swedish, multicenter; early RA; mean disease duration 6.2-6.3 months	DAS-driven treatment; MTX up to 20mg /wk for 3-4 months, if DAS >3.2 randomized to MTX (up to 20 mg/week) +SSZ (1,000 mg twice/day)+HCQ (400 mg/day vs. MTX (up to 20 mg/week)+INF (3 mg/kg)	EULAR good response lower in combination oral DMARD group (25% vs. 39%; *P*=0.0160	Fair
Other Combination Strategies					
Goekoop-Ruiterman et al., 2005;[100] *Allaart et al., 2006;[101] *Goekoop-Ruiterman et al., 2007;[102] *van der Kooij, et al., 2009;[103] *van der Kooij et al., 2009;[196] *van der Kooij et al., 2008[197] BeSt study	RCT 508 12 months 2 years 4 years	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1 to 5); median duration of symptoms 23 weeks (IQR 14 to 53)	DAS-driven treatment; 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: stepped-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	DAS ≤2.4: 53%, 64%, 71%, 74%; *P*=0.004 for 1 vs. 3; *P*=0.001 for 1 vs. 4; *P*=NS for other comparisons Shorter time to DAS<2.4 for initial combination therapy groups (groups 3 and 4) than monotherapy groups (groups 1 and 2) (Median months; 3,3,9,9 *P*<0.001) Similar remission among groups at 4 years (DAS<1.6; 50%, 41%, 38%, 42%; *P*=0.40)	Good

* New study added since last review.

BeST = Dutch acronym for Behandel Sstrategieen; COBRA = Combinatietherapie Bij Reumatoide Artritis; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ESR = erythrocyte sedimentation rate; ETN = etanercept; g = gram; HCQ = hydroxychloroquine; INF = infliximab; IQR = interquartile range; kilogram = kg; MACTAR = McMaster Toronto Arthritis Questionnaire mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; VAS = visual analog scale; vs. = versus

Table 27. Radiographic joint damage in early RA strategy studies

Study	Study Design N Duration	Population with Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Two Oral DMARDs+Corticosteroid vs. Oral DMARD				
Boers et al., 1997;[95] Landewe et al., 2002[96] COBRA Study	RCT 155 (148) 56 weeks (5-year followup)	Yes	SSZ (2 g/day)+MTX (7.5 mg/day stopped after 40 weeks)+PNL (60 mg/day tapered over 28 weeks) vs. SSZ	56 week Modified Sharp/van der Heijde 5.6 vs. 8.6; *P*=0.001
Two Oral DMARDs+Corticosteroid vs. Oral DMARD				
Mottonen et al., 1999;[97] Korpela et al., 2004[98] FIN-RACo study	RCT 199 24 months (5 years)	Yes	MTX (7.5 to 10 mg/week)+HCQ (300 mg/day),+SSZ (2 g/day)+PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	2-year Larsen score change: 2 vs. 10; *P*=0.002 2-year erosion score change: 2 vs. 3; *P*=0.006 5-year median Larsen score: 11 vs. 24; *P* =0.001
Other combination strategies				
Goekoop-Ruiterman, 2005[100] *Allaart et al., 2006;[101] *Goekoop-Ruiterman et al., 2007;[102] *van der Kooij, et al., 2009;[103] *van der Kooij, et al., 2009;[196] *van der Kooij et al., 2008[197] BeST study	RCT 508 12 months (2 years, 4 years)	Yes	DAS-driven treatment: 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: stepped-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/day-7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	Median modified Sharp/van der Heijde score change: 2.0, 2.5, 1.0, 0.5; *P*=0.003 for 1 vs. 3, *P*<0.001 for 1 vs. 4; *P*=0.007 for 2 vs. 3; *P*<0.001 for 2 vs. 4 In year 2, less joint damage in groups 3 and 4 (median modified Sharp/van der Heijde score change: 2.0, 2.0, 1.0, 1.0; *P*=0.004) In year 4, less joint damage in groups 3 and 4 (median modified Sharp/van der Heijde score change: 5.0, 5.5, 3.0, 2.5; *P*<0.05 for 1 and 2 vs. 4)

* New study added since last review.
BeST = Dutch acronym for Behandel Sstrategieen; COBRA = Combinatietherapie Bij Reumatoide Artritis; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ETN = etanercept; FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy; g = gram; HCQ = hydroxychloroquine; INF = infliximab; kg = kilogram; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Three oral DMARDs plus corticosteroid versus oral DMARD. The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) RCT assessed the efficacy of a complex combination of prednisolone (5 to 10 mg/day), MTX (7.5 to 10 mg/week), sulfasalazine (2 g/day), and hydroxychloroquine (300 mg/day) against that of monotherapy with a DMARD with or without prednisolone.[97] The investigators randomized 199 patients with early RA to either combination therapy or monotherapy. Patients on monotherapy were initially started on sulfasalazine (2 to 3 g/day) but could be changed to MTX (7.5 to 15 mg/week), then changed to a third DMARD if needed (azathioprine, auranofin, hydroxychloroquine, injectable gold, penicillamine, or podophyllotoxin). If patients reached remission in the first year, they could be tapered and prednisolone and MTX could be discontinued at 9 months and 18 months, respectively. Adding prednisolone (up to 10 mg/day) in the monotherapy group was left up to the

treating physician and allowed in patients with continuously active disease. After 2 years, remission (judged by the authors using modified ACR 20) was higher in the combination group than in the monotherapy group (37.9 percent vs. 18.4 percent; *P*=0.011); the proportion achieving ACR 50 response criteria was higher in the combination group than in monotherapy group but did not reach statistical significance (71 percent vs. 58 percent; *P*=0.058). Larsen Scale radiographic scores had also improved at 2 years in the combination group as compared with the monotherapy group (Larsen Scale score increase 2 vs. 10; *P*=0.002). Subsequently, patients in this trial were followed for 5 years.[98] Those in the monotherapy group were allowed to be treated with combinations of DMARDs if their response was insufficient. At 5 years, the median Larsen Scale score remained lower in the combination therapy group than in the monotherapy group (11 vs. 24; *P*=0.001). This trial can be considered an effectiveness trial given the flexibility of dosing in an effort to follow clinical practice.

Three oral DMARDs versus biologic plus oral DMARD. One multicenter RCT in Sweden examined the efficacy of an oral DMARD combination versus a biologic plus oral DMARD.[99] A total of 487 patients with early RA were initially treated MTX (up to 20 mg/wk) and if they did not respond after 3-4 months, they were randomized to MTX (up to 20 mg/wk) plus sulfasalazine (1000 mg twice/day) plus hydroxychloroquine (400 mg/day) versus MTX (up to 20 mg/wk) plus infliximab (3 mg/kg at week 0, 2, 6 and then every 2 months). Of the 487 patients enrolled, 29.8% (n=145) responded to MTX monotherapy and 258 were randomized to the combination oral DMARD arm versus the infliximab plus MTX arm. At 1 year, significantly more patients in the infliximab plus MTX arm achieved a good EULAR response, defined as a decrease of DAS28 score by at least 1.2 after randomization and a resulting DAS28 of 3.2 or lower (RR: 1.59, 95% CI 1.10 to 2.30). ACR 20 and 50 responses were also significantly higher for the infliximab plus MTX arm (ACR 50: 25% vs. 15%; *P* = 0.0424).

Other combination strategies. One good-quality RCT examined four different treatment strategies over 12 months.[100] The BeSt Study (Dutch acronym for Behandel Strategieen, "treatment strategies") randomized 508 patients with early RA to one of four groups: (1) sequential DMARD, starting with MTX (15 mg/week), (2) stepped-up combination therapy with MTX (15 to 30 mg/week) followed by sulfasalazine (2 g/day), hydroxychloroquine, and prednisone, (3) initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone 60 mg/day to 7.5 mg/day in 7 weeks, and (4) initial combination therapy with MTX 25 to 30 mg/week and infliximab 3 mg/kg every 8 weeks (dose titrated up to 10 mg/kg dependent upon DAS 44>2.4). This design called for frequent changes in treatment strategy; the DAS (i.e., DAS in 44 joints) was calculated every 3 months and if it was greater than 2.4, the therapeutic strategies were adjusted. At 12 months, more patients in group 3 (MTX, sulfasalazine, tapered high-dose prednisone) and in group 4 (MTX with infliximab) reached a DAS of 2.4 or less. Respectively, these proportions were 53 percent, 64 percent, 71 percent, and 74 percent (*P*=0.004 for group 1 vs. group 3; *P*=0.001 for group 1 vs. group 4; *P*=NS for other comparisons). Additionally, the median change in modified Sharp/van der Heijde score was lower for groups 3 and 4 than for groups 1 and 2 (2.0, 2.5, 1.0, and 0.5, respectively; *P*=0.003 for group 1 vs. group 3; *P*<0.001 for group 1 vs. group 4; *P*=0.007 for group 2 vs. group 3; *P*<0.001 for group 2 vs. group 4). Interestingly, at four years, the remission rates were similar among the groups (DAS<1.6; 50 percent, 41 percent, 38 percent, 42 percent, *P*=0.40).[196]

Key Question 2: Functional Capacity and Quality of Life

This question specifically examined the issue of whether drug therapies differed in their ability to improve functional capacity or quality of life for patients with RA. Findings are organized as for KQ 1. Table 8 (above) lists the abbreviated and full names of all instruments and scales referred to in this section. For the purposes of this report we divided outcomes into functional capacity and health-related quality of life. *Functional capacity, functional status, and functional ability* are three concepts often used interchangeably to refer to similar capabilities. We use these terms to refer to condition-specific measures, such as the Health Assessment Questionnaire (HAQ), developed to assess function in patients with RA or other rheumatic diseases. Quality of life is a far broader construct comprising physical health, mental or emotional health, a variety of symptom states (e.g., pain, fatigue), and coping, spiritual and other domains. We use the term *quality of life* when referring to generic measures, such as the Medical Outcomes Study Short Form 36 Health Survey (SF-36), that have been developed to assess health-related quality of life in both healthy persons and those with different conditions. Outcomes for functional capacity and health-related quality of life were often secondary outcomes in these studies.

Overview

Details of the individual studies are found in the Evidence Tables in Appendix E. Many of the studies in this section are described in more detail in the corresponding KQ 1 sections. For each comparison, tables in Appendix I provide the strength of evidence for functional capacity and quality-of-life outcomes.

Small differences in outcome measures may be statistically significant, yet clinically unimportant. Therefore, in the text below, we consider whether treatment effects reach minimal clinically important differences (MCIDs) for the HAQ and SF-36, the two most commonly reported outcome measures in this section. When we describe "no difference" between two treatments, we use this to indicate that the available evidence did not support a statistically or clinically significant difference between the two treatments. When we describe greater improvements with one treatment compared with another, the difference was both statistically significant and reached the threshold for a MCID. For the HAQ, we considered a difference of $\geq$0.22 to be a MCID.[48] For the SF-36, some have suggested an improvement of 3 to 5 for the MCID.[50, 198] Data from clinical trials of rheumatoid arthritis patients suggest slightly lower values, with ranges of 2.6-4.4 for the physical component score (PCS) and 2.2-4.7 for the mental component score (MCS).[49] We used these lower ranges to take a conservative approach on what might be a MCID.

Oral disease-modifying antirheumatic drugs (DMARDs) versus oral DMARD. One head-to-head RCT found that patients treated with prednisolone (7.5 mg/d) had greater improvements in functional capacity and quality of life than those treated with budesonide (3 or 9 mg/d) (low strength of evidence). The differences reached thresholds for MCIDs (difference in improvement in mean HAQ: 0.28 to 0.39 units, $P<0.01$; difference in improvement in SF-36 PCS: 3.7 to 5.4 units, $P<0.05$).[54]

The evidence from two RCTs[56, 104, 105, 199] does not support a clinically significant difference between leflunomide and methotrexate (MTX) for improvement in functional capacity (low strength of evidence), although some results reached statistically significant differences favoring leflunomide (mean improvement in HAQ-DI at 12 months: -0.45 vs. -0.26, $P \leq 0.01$). Evidence

from one study found greater improvement in quality of life with leflunomide than with MTX (SF-36 PCS mean improvement at 12 months of 7.6 vs. 4.6, $P<0.01$, low strength of evidence).

One RCT[107] with a 2-year followup[200] provides low strength of evidence that leflunomide yields greater improvements in functional capacity at 24 weeks, 6 months, and 24 months than sulfasalazine (improvement in HAQ at 24 months: -0.65 vs. -0.36, $P<0.01$).

Evidence from three RCTs[57-59] provides moderate strength of evidence that there is no difference in functional capacity between patients treated with sulfasalazine and MTX.

Oral DMARD combinations. Three RCTs compared a combination of two oral DMARDs (sulfasalazine plus MTX) to monotherapy with either drug and provide moderate strength of evidence that there is no statistically significant difference in functional capacity (between-group differences for change in HAQ ranged from 0.03 to 0.25, all *P* values=NS).[57-59]

Two RCTs provide moderate strength of evidence that using corticosteroids and one oral DMARD results in greater improvements in functional capacity than using oral DMARD monotherapy (difference in mean change in HAQ -0.28, $P=0.02$).[64, 65] One RCT provides low strength of evidence supporting no difference in quality-of-life outcomes for the same comparison.[64]

Biologic DMARD versus biologic DMARD. We found one head-to-head RCT and three prospective cohort studies that compared one biologic DMARD with another.[66, 68, 70, 71] The head-to-head RCT[66] provides low strength of evidence that there is no difference in functional capacity between those treated with abatacept and infliximab; the difference for quality-of-life outcomes was statistically significant, but the difference did not reach the MCID (difference in SF-36 PCS at 1 year 1.93, 95% CI, 0.02 to 3.84).

Data from the three prospective cohort studies do not provide any convincing evidence of a difference between biologic treatments.[68, 70, 71] Overall, the strength of evidence (Appendix I) for all comparisons of biologic DMARDs from these studies was low or insufficient and does not suggest a significant difference between etanercept, infliximab, and adalimumab. Some individual studies reported statistically significant differences favoring etanercept over infliximab for functional capacity (one of three studies) or for quality of life (one study), or adalimumab over infliximab for functional capacity and quality of life (one study), but differences did not reach MCIDs or data were not reported. We rated the risk of bias moderate to high for this body of evidence. Because of the methodological limitations of observational studies, findings of these studies should be interpreted cautiously.

Biologic DMARD versus oral DMARD. We found four RCTs[76, 77, 86, 173] and one prospective cohort study[78] that included comparisons of monotherapy with a biologic DMARD to monotherapy with an oral DMARD. We found no evidence on approved doses of biologic DMARDs other than etanercept, adalimumab, and tocilizumab and no studies comparing biologics with oral DMARDs other than MTX. The evidence from these studies is mixed. Overall, the strength of the evidence is insufficient for biologics as a class compared to oral DMARDs as a class. Two of the RCTs found no differences when comparing either adalimumab[76] or etanercept[86] with MTX. One RCT[77] found that etanercept resulted in better improvement of function and quality of life during the first 12 weeks of treatment, and that a greater percentage of patients treated with etanercept 25 mg or etanercept 10 mg had significant improvements in functional capacity compared with MTX at 24 months (≥0.5 unit improvement in HAQ-DI: 55 percent vs. 43 percent vs. 37 percent, $P=0.021$ and<0.001, respectively). One RCT found subjects treated with tocilizumab had significantly greater improvements in functional capacity than those treated with MTX, but this trial used a dose of MTX below the

dose usually considered therapeutic; thus, it does not provide evidence to determine how tocilizumab compares with MTX as it is generally used in clinical practice.[173] All RCTs were funded by the makers of the biologic DMARDs. Population-based, observational evidence from the cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than oral DMARDs as a class in patients with active RA who required a change in therapy.[78]

Biologic DMARD combinations. One RCT provides low strength of evidence that there is no difference in functional capacity between a combination of etanercept plus abatacept compared with etanercept alone.[80] The same RCT provides low strength of evidence that the combination results in statistically significantly greater improvement in physical, but not mental, health-related quality of life (as measured by the SF-36 PCS and MCS, respectively). Of note, the study concluded that abatacept in combination with etanercept should not be used for patients with RA due to limited efficacy findings and safety concerns (more serious adverse events).

For studies comparing a biologic DMARD plus an oral DMARD versus a biologic DMARD, we stratified by population. Based on results of two RCTs, we conclude that biologic DMARDs plus MTX result in greater improvements in functional capacity (difference in improvement in HAQ-DI at 1 year -0.3, $P \leq 0.002$, moderate strength of evidence) and quality of life (low strength of evidence) than biologic DMARDs alone for MTX naïve subjects or those not recently on MTX.[76, 86] However, for subjects with active RA despite treatment with the same oral DMARD used in the combination therapy, we conclude that there is no difference in improvements in functional capacity or quality of life (moderate strength of evidence) between a biologic DMARD plus an oral DMARD and biologic DMARD monotherapy.[68, 85, 201] For most individual medications in these comparisons, the evidence is limited to a single study. All RCTs were funded by the makers of the biologic DMARDs. No evidence (for biologic DMARD plus oral DMARD vs. biologic DMARD) was available for approved doses of biologic DMARDs other than adalimumab, etanercept, or infliximab and combinations with oral DMARDs other than MTX and sulfasalazine.

Results from seven RCTs and one prospective cohort study suggest greater improvement in functional capacity with combination treatment with a biologic DMARD plus an oral DMARD than with oral DMARD monotherapy (high strength of evidence).[68, 76, 82, 85, 86, 89, 90, 92, 136, 138, 145] Five of the RCTs enrolled all or a majority of subjects with early RA;[76, 82, 89, 90, 92] Effect sizes for studies finding a clinically important and statistically significant difference between groups ranged from 0.3 to 0.35 for difference in improvement in HAQ-DI and from 9 percent to 38 percent for difference in percentage of subjects with clinically significant improvement in HAQ. All but two of the trials reported results that reached MCIDs; for the two that did not, point estimates were in the direction favoring combination therapy.[89, 92] Four of the RCTs also reported quality-of-life outcomes, finding greater improvement in the biologic DMARD plus oral DMARD combination therapy group (moderate strength of evidence).[82, 86, 89, 90, 136, 138] The specific comparisons in these studies were a combination regimen of abatacept plus MTX,[89] adalimumab plus MTX,[76] golimumab plus MTX,[92] infliximab plus MTX,[68, 82] or etanercept plus MTX[68, 86, 90, 136, 138] with MTX monotherapy; and a combination of etanercept plus sulfasalzine with sulfasalazine monotherapy.[85, 145]

Treatment strategies for early RA. Based on the results of two RCTs (three publications),[95, 97, 98, 202] we concluded that combination strategies using corticosteroids plus multiple oral DMARDs result in more rapid improvement in functional capacity (difference in mean change in HAQ at 28 weeks -0.5, $P<0.0001$) and less work disability (median 12.4 days

per patient-observation year vs. 32.2 days, $P<0.008$) than oral DMARD monotherapy (low strength of evidence for each outcome).

One RCT (the BeSt study) in patients with early RA found that patients treated with initial combination therapy with prednisone (study group 3) or initial combination therapy with infliximab (group 4) had more rapid improvement in functional ability than those treated with sequential DMARD monotherapy (group 1) or with step-up combination therapy (group 2) (statistically significantly greater improvements at 3, 6, 9, and 12 months).[100-103, 196] By 2 years, improvement was maintained in all groups, but there were no statistically significant differences between groups (low strength of evidence).

Detailed Analysis

Oral DMARD versus oral DMARD. Functional capacity and health-related quality-of-life outcomes are presented in Table 28.

Corticosteroids versus corticosteroids. One 12-week head-to-head RCT (N=143) compared budesonide (3 mg/day or 9 mg/day; n=37 and 36, respectively) and prednisolone (7.5 mg/day; n=39).[54] Mean disease duration of RA was 9 years. Overall, prednisolone produced greater improvement in functional capacity and health-related quality of life than either dose of budesonide. At 12 weeks, those treated with prednisolone had better improvement in mean HAQ scores than budesonide (Table 28). Those treated with prednisolone also had better improvement in health-related quality of life as measured by the physical subscale of the SF-36. Improvement on the mental subscale of the SF-36 was not statistically significantly different between groups. Of note, functional capacity and health-related quality of life were secondary outcome measures; the study had not been designed to compare differences in either the HAQ or the SF-36.

Leflunomide versus MTX. We found two RCTs[104, 105] comparing leflunomide (20 mg/day) with MTX (7.5 mg/week to 15 mg/week)[104, 105] and two systematic reviews.[55, 106] We describe the individual studies first.

The first trial randomized 482 patients to leflunomide (n=182) or MTX (n=182) over 12 months.[104, 199] Patients receiving leflunomide reported greater mean improvement in the HAQ-DI that was statistically significant (Table 28), but the difference between groups did not reach the MCID. Those receiving leflunomide had greater improvement on the SF-36 physical component than those receiving MTX at 12 months that was statistically significant and reached the MCID. At 12 months, the two groups did not differ significantly in improvement in the SF-36 mental summary score or in work productivity. A 2-year followup of 235 patients (leflunomide, n=98; MTX, n=101) found greater mean improvement in the HAQ-DI (-0.60 vs. -0.37; $P=0.005$) and MHAQ scores (-0.43 vs. -0.28; $P \leq 0.05$) with leflunomide than with MTX.[56] The groups did not differ significantly in mean improvement in the SF-36 physical or mental summary scores at 24 months. These 2-year results are limited by the high attrition rate (45 percent) from the initial study.

A 1-year multinational RCT (N=999) comparing leflunomide and MTX with an optional second year enrolled RA subjects with a mean disease duration of 3.5 years to 3.8 years.[105] At 12 months, a statistically significant but minimal quantitative difference (number not reported, shown in bar graph)[105] for change in the HAQ ($P<0.05$) was reported between the two groups; at 24 months, however, the groups did not differ significantly.

Table 28. Oral DMARD versus oral DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Corticosteroid vs. Corticosteroid						
Kirwan et al., 2004[54]	RCT 143 12 weeks	Population-based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	Improvement in mean HAQ scores: PNL 0.393 units better than BUD 3 mg; *P*<0.001 PNL 0.276 units better than BUD 9 mg; *P*<0.01	Improvement in SF-36 physical component: mean change 5.4 units better for PNL than BUD 3 mg, *P*<0.01; 3.7 units better than BUD 9 mg, *P*<0.05	Fair
Leflunomide vs. MTX						
Emery et al., 2000[105]	RCT 999 1 year with optional second year	Mean disease duration 3.5 to 3.8 years	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Change in HAQ at 12 months, minimal quantitative (data NR) but significant (*P*<0.05); at 24 months, difference NS	NR	Fair
Strand, et al., 1999[104] Cohen et al., 2001[56, 199]	RCT 482 12 months (1-year continuation)	Mean disease duration 6.5 to 7 years	LEF (20 mg/day) vs. MTX (7.5 to 15 mg/week)	Mean improvement in HAQ-DI greater in LEF than MTX at 12 months (-0.45 vs. -0.26; *P* ≤0.01) and MHAQ (-0.29 vs. -0.15; *P*<0.01)	Mean improvement in SF-36 physical greater in LEF than MTX at 12 months (7.6 vs. 4.6; *P*<0.01) but not mental component (1.5 vs. 0.9; *P*=NS)	Fair
Leflunomide vs. Sulfasalazine						
Smolen et al., 1999[107] Scott et al., 2001[200]	RCT 358 (146) 24 weeks (12- and 24-month followup)	Mean disease duration 5.7 to 7.6 years	LEF (20 mg/day) vs. SSZ (2 g/day)	Improvement in HAQ scores at 24 weeks greater in LEF than SSZ (-0.50 vs. -0.29; *P*<0.03) and continued in 2-year followup group at 6 and 24 months (-0.50 vs. -0.29; -0.65 vs. -0.36; both *P*<0.01)	NR	Fair
Sulfasalazine vs. MTX						
Capell et al., 2007[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	No significant difference between groups in change from baseline HAQ (SSZ: -0.25; MTX: -0.19; *P*=0.99)	NR	Fair

Table 28. Oral DMARD versus Oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Dougados et al., 1999[57]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ -0.74 vs. MTX -0.73; *P*=NS)	NR	Fair
Haagsma et al., 1997[58]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks not significant (SSZ -0.32; 95% CI, -0.53 to -0.10, MTX -0.46; 95% CI, -0.68 to -0.25; *P*=NR)	NR	Fair

BUD = budesonide; combo = combination therapy; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ETN = etanercept; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; HCQ = hydroxychloroquine; INF = infliximab; LEF = leflunomide; mg = milligram; MTX = methotrexate; NHS = National Health Service; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; SOFI = Signals of Functional Impairment Scale; SSZ = sulfasalazine

One systematic review with meta-analysis included 33 trials comparing leflunomide, either as monotherapy or combined with another medication, with placebo or other oral DMARDs in patients with active RA.[55] MHAQ scores improved significantly more in patients treated with leflunomide than in those treated with MTX at 6, 12, and 24 months. The leflunomide group and the MTX group did not differ in improvement on the HAQ index at either 12 months or 24 months. Work productivity did not improve significantly in the leflunomide group when compared with the MTX group (weighted mean difference [WMD], -2.3 points; 95% CI, -6.37 to 1.77). When comparing leflunomide with MTX, changes in SF-36 scores showed better improvement in the physical summary score with leflunomide (WMD, -3.0 points; 95% CI, -5.41 to -0.59) but not the mental summary score (WMD, -0.6 points; 95% CI, -3.01 to 1.81). The only study that contributed to this outcome (SF-36 physical summary score) was the RCT (N=482) described above in this section.[104, 199] This systematic review was limited by the number of studies included for meta-analysis; only one study was available for each individual functional capacity or quality-of-life outcome measure except for change in HAQ scores.

The second systematic review aimed to assess the efficacy and safety of oral DMARDs in adults with RA to inform the European League Against Rheumatism (EULAR) recommendations.[106] The review included a total of 97 RCTs (14,159 patients) covering a variety of comparisons. The results were not significantly different for leflunomide and MTX for pain (four studies, 1,475 patients, SRM -0.04, 95% CI, -0.33 to 0.26) or for disability (four studies, 1,465 patients, SRM -0.09, 95% CI, -0.30 to 0.11). The mean dose of MTX, reported in three studies, was 12.5 mg/week. MTX could be increased to ≥15 mg/week in all studies, but dosing was not as high as currently recommended in most studies.

Leflunomide versus sulfasalazine. One RCT[107] with a 2-year followup[200] compared leflunomide (20 mg/day) with sulfasalazine (2 g/day) and placebo; one systematic review included a meta-analysis of leflunomide.[55] The RCT was a multinational, multicenter study of 358 patients (leflunomide, n=133; sulfasalazine, n=133; placebo, n=92).[107] Baseline HAQ scores were similar for all groups. The leflunomide group had significantly greater improvement in HAQ scores at 24 weeks, 6 months, and 24 months compared with the sulfasalzine group (Table 28).[200] Subjects completing the first 6 months were given the option to continue. Those in the placebo group were switched to sulfasalazine if they continued in the study. The study was limited by only including 146 (leflunomide, n=60; sulfasalazine, n=60; placebo then sulfasalzine, n=26) of the original 358 subjects and having a 21 percent attrition rate (116 completed the study).

One systematic review with meta-analysis compared leflunomide (10 to 20 mg/day) with other DMARDs in patients with active RA.[55] For the comparison of leflunomide and sulfasalazine, the meta-analysis included one study (N=229) with changes in HAQ at 6, 12, and 24 months.[200] At 6 and 24 months, the leflunomide group had greater improvements in the HAQ-DI than the sulfasalazine group (WMD -0.25 point; 95% CI, -0.42 to -0.08; WMD -0.29 point; 95% CI, -0.57 to -0.01, respectively). This evidence is limited because the meta-analysis included only one study for this outcome; they did not pool data from multiple studies.

Sulfasalazine versus MTX. Three RCTs[57-59] and one systematic review[106] compared sulfasalazine with MTX. Their findings are consistent and do not support a difference in functional capacity between the groups (Table 28). These included a multinational 52-week RCT of 209 DMARD-naive subjects,[57] a 52-week RCT of 105 DMARD-naive subjects in academic and peripheral clinics in the Netherlands,[58] and an 18-month RCT of 165 subjects at eight sites in Scotland.[59]

The systematic review aimed to assess the efficacy and safety of oral DMARDs to inform the EULAR recommendations and included a variety of comparisons.[106] The results were not significantly different for sulfasalazine versus MTX for disability (two studies, 208 patients, SRM 0.62, 95% CI, −0.86 to 2.10).

Oral DMARD combinations: MTX plus sulfasalazine versus monotherapy with MTX or sulfasalazine. Three RCTs (four publications) compared MTX plus sulfasalazine to either drug alone.[57-59, 111] Two of the RCTs included patients with disease duration of less than 1 year;[57, 58] the third included patients with RA of up to 10 years.[59] Findings of these studies do not support a difference in functional capacity between combination therapy and either monotherapy. Study data are presented in Table 29.

Table 29. Oral DMARD combination studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Sulfasalazine+MTX versus Sulfasalazine or MTX Monotherapy						
Capell et al., 2007[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤4 g/day)+MTX (≤25 mg/week) vs. SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	Change from baseline HAQ: no significant difference between groups (SSZ+MTX -0.50 vs. SSZ -0.25; *P*=0.51), (SSZ+MTX -0.50 vs. MTX -0.19; *P*=0.57)	NR	Fair
Dougados et al., 1999[57] Maillefert et al., 2003[111]	RCT 209 (146) 52 weeks (5-year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) plus MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ+MTX -0.70 vs. SSZ -0.74 vs. MTX -0.73; *P*= NS) or in mean HAQ at 5 years (combination 0.6 vs. either single therapy 0.6; *P*=0.9)	NR	Fair
Haagsma et al., 1997[58]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks NS (SSZ+MTX -0.51: 95% CI, -0.76 to -0.26 vs. SSZ -0.32: 95% CI, -0.53 to -0.10 vs. MTX -0.46: 95% CI, -0.68 to -0.25; *P*=NR)	NR	Fair

Table 29. Oral DMARD combination studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Oral DMARD+Corticosteroid vs. Oral DMARD						
*Choy et al., 2008[64]	RCT 467 2 years	England/Wales, Multicenter: early RA; mean disease duration 2.7 to 5.1 months	MTX (≤15 mg/week)+PNL (60 mg/day stepped down and stopped at 34 weeks) vs. MTX	Difference in mean change in HAQ: -0.28 with additional PNL compared to MTX alone (*P*=0.02)	Mean change in SF-36 PCS and MCS: No difference between groups (*P*=0.22 and NR, respectively)	Good
Svensson et al., 2005[65]	Open-label trial 250 2 years	Population-based; active RA; duration 1 year or less	DMARD (SSZ or MTX, dosages NR)+PNL (7.5 mg/day) vs. DMARD	Greater improvement in DMARD+PNL group than DMARD-only group (from mean HAQ of 1.0 to 0.4 at 1 year and 0.5 at 2 years vs. 1.0, 0.6, and 0.7; *P*=NR) Mean SOFI index decreased from 8 at baseline to 4 at 1 year and 4 at 2 years vs. 9, 6, and 7 respectively; *P*=NR)	NR	Fair

* New study added since last review.

CI = confidence interval; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; g = gram; HAQ = Health Assessment Questionnaire; mg = milligram; MTX = methotrexate; NHS = National Health Service; NR = not reported; NS = not significant; PCS = physical component score; PNL = prednisolone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; SOFI = Signals of Functional Impairment Scale; SSZ = sulfasalazine; vs. = versus; yrs = years

A multinational RCT of 209 DMARD-naive subjects compared sulfasalazine (n=68), MTX (n=69), and the sulfasalazine-MTX combination (n=68) for 52 weeks. No statistically significant difference in changes in HAQ scores occurred from baseline to 1 year.[57] A long-term followup comparing the combination therapy to monotherapy (combining the two monotherapy groups) did not find a significant difference in mean HAQ scores at 5 years (combination 0.6; monotherapy 0.6; *P*=0.9).[111]

A 52-week RCT of 105 DMARD-naive subjects in Dutch academic and peripheral clinics reported a change in HAQ scores between baseline and 52 weeks of -0.51 (95% CI, -0.76 to -0.26) for the MTX-sulfasalazine combination therapy, a change of -0.32 (95% CI, -0.53 to -0.10; *P*=NR) for sulfasalazine, and a change of -0.46 (95% CI, -0.68 to -0.25; *P*=NR) for MTX.[58] The HAQ was a secondary outcome in this study; the authors did not attempt to explain these results or compare the values, but the differences between groups did not reach thresholds for MCIDs and the 95% CIs overlap between all groups.

The third study was an 18-month RCT of 165 subjects at eight sites in Scotland. The investigators found no significant difference between the combination therapy and the monotherapy groups in changes from baseline HAQ scores.[59]

Oral DMARD plus corticosteroid versus oral DMARD. We found two RCTs; both found that corticosteroids and one oral DMARD results in greater improvements in functional capacity than using oral DMARD monotherapy (Table 29).[64, 65] The first was a 2-year RCT (N=467) comparing MTX plus prednisolone (60 mg/day stepped down and stopped at 34 weeks) with MTX monotherapy in subjects with early RA.[64] The study reported greater improvements in functional capacity for subjects treated with MTX plus prednisolone than subjects treated with MTX alone, but found no difference in quality of life between groups.

One open-label RCT compared oral DMARD use with and without prednisolone in patients with active RA for 1 year or less.[65] This 2-year study compared prednisolone (7.5 mg/day) added to an initial DMARD (chosen by the treating physician) with an oral DMARD only in patients with early RA**.** The authors reported greater improvement in functional capacity for the prednisolone group than the nonprednisolone group. The DMARD plus prednisolone group also had greater improvement in the mean Signals of Functional Impairment (SOFI) index. Scores on the HAQ and the SOFI index were not statistically compared for the two groups; the clinical relevance of these results is uncertain. In addition, the results should be interpreted cautiously, given the open-label design and potential for bias.

Biologic DMARD versus biologic DMARD. We identified one head-to-head RCT and three prospective cohort studies meeting our inclusion criteria (Table 30).[66, 68, 70, 71] Three of these included comparisons of etanercept with infliximab;[68, 70, 71] one study compared each of the following: adalimumab versus etanercept,[71] abatacept versus infliximab,[66] and adalimumab versus infliximab.[71] Mean disease durations ranged from 6 years to 9.9 years; the proportion of patients with early RA in these studies remains unclear. One study was conducted in the United States;[68] the others were carried out in the Netherlands,[71] Spain,[70] or were multinational.[66]

Abatacept versus infliximab. One head-to-head multinational RCT (N=431) conducted in subjects with active RA who had an inadequate response to MTX did not find a difference in functional capacity between those treated with abatacept and infliximab. It found greater improvement in health-related quality of life for those treated with abatacept that reached statistical significance, but did not reach the threshold for a MCID (SF-36 PCS: difference of 1.93 at 1 year, 95% CI, 0.02 to 3.84).[66]

Etanercept versus infliximab. Two of the three cohort studies comparing etanercept with infliximab reported no difference in functional capacity outcomes; one reported greater improvement with etanercept.[68] Only one of the three studies reported a quality-of-life outcome, finding greater improvement in the SF-36 PCS with etanercept than with infliximab.[71]

The first cohort study (N=161) was conducted in anti-tumor necrosis factor (TNF) naïve patients and found no difference in functional capacity between etanercept than infliximab.[70] The second cohort study (N=707) was conducted in anti-TNF naïve patients that had failed at least two DMARDs and also found no difference in functional capacity between etanercept than infliximab, but reported statistically significantly greater improvement in health-related quality of life for those treated with etanercept, but the actual data were not reported.[71]

Table 30. Biologic DMARD versus biologic DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Abatacept vs. Infliximab						
*Schiff et al., 2008[66] ATTEST	RCT 431 1 year	Multinational; Active RA with inadequate response to MTX	ABA (~10 mg/kg every 4 weeks) vs. INF (3 mg/kg every 8 weeks) Study also had a third arm (placebo)	Percentage of patients with improvement in HAQ-DI at 1 year: 57.7% vs. 52.7%; estimate of difference (95% CI, 5.0 (-6.5 to16.5)	SF-36 PCS: between group difference at 1 year favoring ABA of 1.93, 95% CI, 0.02 to 3.84 SF-36 MCS: difference of 1.92, 95% CI, -0.30 to 4.15	Fair
Etanercept vs. Infliximab						
*Fernandez-Nebro et al., 2007[70]	Prospective cohort 161 6 years	Tertiary care center, Spain; Anti-TNF naïve patients; mean disease duration 9.5 to 9.9 years	ETN vs. INF (dosages NR)	Mean change in HAQ at 6 months: -0.46 vs. -0.32; *P*=0.218	NR	Fair
*Kievit et al., 2008[71] DREAM register	Prospective cohort study 707 1 year	Population-based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6 to 7.7 years	ETN vs. INF (dosages NR)	Mean change in HAQ at 12 months: -0.35 vs. -0.26; *P*=NS	SF-36 PCS: ADA and ETN patients had greater improvement than INF; *P*=0.001 (data NR, in Figure only)	Fair
Weaver et al., 2006[68]	Prospective cohort study 1,371 12 months	Population-based, US; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETN (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Mean percentage improvements in HAQ at 12 months: 17% vs. 1%; *P*=NR	NR	Fair

Table 30. Biologic DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab vs. Etanercept						
*Kievit et al., 2008[71] DREAM register	Prospective cohort study 707 1 year	Population-based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6 to 7.7 years	ADA vs. ETN (dosages NR)	Mean change in HAQ at 12 months: -0.42 vs. -0.35; *P*=NS	SF-36 PCS: ADA and ETN patients had greater improvement than INF; *P*=0.001 (data NR, in Figure only)	Fair
Adalimumab vs. Infliximab						
*Kievit et al., 2008[71] DREAM register	Prospective cohort study 707 1 year	Population-based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6 to 7.7 years	ADA vs. INF (dosages NR)	Mean change in HAQ at 12 months: -0.42 vs. -0.26; *P*<0.05)	SF-36 PCS: ADA and ETN patients had greater improvement than INF; *P*=0.001 (data NR, in Figure only)	Fair

* New study added since last review.
ADA = adalimumab; CI = confidence interval; DMARD = disease modifying antirheumatic drug; ETN = etanercept; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; INF = infliximab; MCS = mental component score; mg/kg = milligram/kilogram; NR = not reported; NS = not significant; PCS = physical component score; RA = rheumatoid arthritis; SF-36 = Medical Outcomes Test, Short Form 36; TNF = tumor necrosis factor; US = United States; vs. = versus

The third cohort study comparing etanercept with infliximab was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program. RADIUS was a primary care-based U.S. study that enrolled patients who were initiating any new DMARD at study entry.[68] Mean disease duration was 9.3 years, indicating that most patients suffered from advanced RA. The percentage of patients with early RA was not reported. Patients treated with etanercept had a greater mean percentage improvement on the HAQ at 12 months than patients treated with infliximab (17 percent vs. 1 percent; *P*=NR). Among patients older than 65 years, after adjusting for baseline covariates, the authors reported that the etanercept-treated patients had a greater mean percentage improvement in the HAQ at 12 months than infliximab-treated patients (22 percent vs. 4 percent; *P*=NR). However, the authors did not describe direct statistical comparisons between etanercept and infliximab. The study was designed to compare combinations of etanercept or infliximab with MTX to monotherapy with etanercept, infliximab, or MTX.

Adalimumab versus etanercept. One cohort study (N=707) conducted in anti-TNF naïve patients that had failed at least two DMARDs reported no difference in functional capacity or health-related quality of life between adalimumab and etanercept.[71]

Adalimumab versus infliximab. One cohort study (N=707) conducted in anti-TNF naïve patients that had failed at least two DMARDs reported greater improvement in functional capacity that reached statistical significance but did not reach the MCID (mean change in HAQ at 12 months: -0.42 vs. -0.26, $P<0.05$). It also reported greater improvement in health-related quality of life (data NR, $P=0.001$) for subjects treated with adalimumab than for those treated with infliximab.[71]

Placebo-controlled studies. Multiple placebo-controlled RCTs and systematic reviews of placebo-controlled trials provide evidence on the efficacy of abatacept,[66, 113, 116, 203-207] adalimumab,[119-125] anakinra,[75, 128, 129, 131-134] etanercept,[86, 136-145] infliximab,[66, 135, 148-156] rituximab,[84, 158-161, 208] certolizumab pegol,[164, 165, 168, 209] golimumab,[166, 169, 170, 210] and tocilizumab.[164, 172, 174-178] Most of these studies were conducted in patients who had failed oral DMARD treatment.

Biologic DMARD versus oral DMARD. We found four RCTs and one prospective cohort study that included comparisons of approved doses of biologic DMARD monotherapy with oral DMARD monotherapy (Table 31). The RCTs compared etanercept with MTX,[77, 86] adalimumab with MTX,[76] and tocilizumab with MTX;[173] the cohort study assessed differences in class effects.[78] No head-to-head evidence exists for the other biologic DMARDs or for oral DMARDs other than MTX (although anakinra and infliximab were included in the prospective cohort study comparing biologics as a class to oral DMARDs as a class).

Table 31. Biologic DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab vs. MTX						
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (<3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	At 1 year, ADA and MTX monotherapy groups had similar improvement in HAQ-DI (-0.8 vs. -0.8; P=NR). Improvements remained similar after 2 years	NR	Fair
Etanercept vs. MTX						
Bathon et al., 2000;[77] Genovese et al., 2002;[188] Genovese et al., 2005;[189] Kosinski et al., 2002[211] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Better improvement in HAQ early in treatment (first 12 weeks) for ETN than MTX ($P<0.0001$). No significant difference in HAQ scores during weeks 16 to 52 Significantly greater percentage of patients with at least a 0.5 unit improvement in HAQ-DI at 24 months for ETN 25 mg than for either ETN 10 mg or MTX (55% vs. 43% vs. 37%; $P=0.021$ and $P<0.001$, respectively)	Better improvement in SF-36 physical summary and SF-36 arthritis-specific health index for ETN group than the MTX group during first 12 weeks ($P<0.0001$) No significant difference in weeks 16 to 52	Fair

Table 31. Biologic DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Klareskog et al., 2004;[86] van der Heijde et al., 2006;[136] van der Heijde et al., 2006[138] TEMPO study	RCT 686 (503 for 2-year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly) vs. MTX (20 mg/week)	Similar improvement in mean HAQ scores for MTX and ETN (scores fell from 1.7 to 1.1 and 1.7 to 1.0; *P*=0.3751)	NR	Good
Tocilizumab vs. MTX						
*Nishimoto et al., 2009[173] SATORI	RCT 127 24 weeks	Active RA with inadequate response to MTX	TCZ (8 mg every 4 weeks) +placebo vs. MTX (8 mg/week)+placebo	Percentage of patients with a decrease of at least 0.22 units in MHAQ at last observation: 67% vs. 34% (*P*<0.001)	NR	Fair
Biologic Class vs. Oral DMARD Class						
Listing et al., 2006[78]	Prospective cohort study 1,083 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.6 years	Biologics as a class (ADA, ANA, ETN, INF; dose NR) vs. DMARDs as a class (dose NR)	Severely disabled patients (≤50% of full function) in biologic group more likely to achieve physical independence (≥67% of full function, Hanover Functional Status Questionnaire) than DMARD group (OR, 3.88; 95% CI, 1.7 to 8.8) Functional remission (≥83% of full function) more often achieved in biologic group than in DMARD group (OR, 2.18; 95% CI, 1.04 to 4.6)	NR	Fair

* New study added since last review.
ADA = adalimumab; ANA = anakinra; CI = confidence interval; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ETN = etanercept; GOL = Golimumab; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; INF = infliximab; mg = milligram; MHAQ = modified Health Assessment Questionnaire; MTX = methotrexate; NR = not reported; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; TCZ = tocilizumab

Adalimumab versus MTX. The only data come from the PREMIER study, a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX.[76] Two treatment arms of this 2-year study were adalimumab monotherapy and MTX monotherapy. After 1 year, the adalimumab and MTX monotherapy groups had no difference in improvements in functional status measured using the HAQ-DI. Improvements remained similar after 2 years (-0.9 vs. -0.9; *P*=NR). After 2 years, 19 percent of patients in both monotherapy groups had HAQ-DI scores of zero.

Etanercept versus MTX. Two trials (seven publications) compared etanercept with MTX over 52 weeks.[77, 86, 136, 138, 188, 189, 211] ERA was a 52-week multicenter RCT of 632 patients with early

RA in the United States that compared etanercept with MTX.[77, 188, 189, 211] The treatment groups were similar at baseline. Most patients were female, white, and rheumatoid factor positive and had had RA for fewer than 18 months. Patients treated with etanercept had better early responses for functional status and health-related quality of life. Compared with patients treated with MTX, patients treated with etanercept showed better improvement early in treatment (during the first 12 weeks) on the HAQ ($P<0.0001$), the SF-36 physical subscale ($P<0.0001$), and the SF-36 arthritis-specific health index (ASHI) ($P<0.0001$). From weeks 16 to 52, these measures did not differ significantly; both groups showed similar improvement. These results may be attributed to an earlier response to etanercept than to MTX and the fact that patients were increased to the maximum MTX dose over 2 months. After 12 months, approximately 55 percent of patients in both the MTX and the 25- mg etanercept groups had at least a 0.5 unit improvement in the HAQ-DI. At 24 months, 55 percent of the 25- mg etanercept group had this level of improvement, as did 37 percent of the MTX group ($P<0.001$) and 43 percent of the 10- mg etanercept group ($P=0.021$).

TEMPO was a 52-week RCT of RA patients who had failed previous DMARD therapy that compared etanercept with MTX and with combination therapy with both drugs.[86] Baseline HAQ scores were similar for all three groups. At 52 weeks, improvement of functional status did not differ significantly between the MTX group and the etanercept group.

Golimumab versus MTX. Two RCTs compared unapproved doses of golimumab (100 mg) with MTX.[92, 169] These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 31, the overview, our conclusions, or in strength of evidence tables due to the use of unapproved doses in the golimumab plus placebo arms, because it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) with MTX.

The GO-FORWARD study was a phase III, multicenter trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 50 mg injections plus MTX capsules.[169] The trial found no difference in the improvement in functional capacity (change in median HAQ-DI) between those treated with golimumab 100 mg and those treated with MTX at 24 weeks.

The GO-BEFORE study was a phase III, multicenter trial that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules.[92] The trial reported a median percent improvement in HAQ-DI of 36.95 for the MTX group compared with 31.05 for the golimumab 100 mg plus placebo group (P=NR).

*Tocilizumab versus MTX***.** The only data come from the Study of Active controlled TOcilizumab monotherapy for Rheumatoid arthritis patients with an Inadequate response to methotrexate (SATORI), a 24-week RCT of 127 patients with active RA and an inadequate response to MTX conducted at 25 sites in Japan.[173] Subjects were randomized to MTX monotherapy (8 mg/week) plus tocilizumab placebo or to tocilizumab plus MTX placebo. After 24 weeks, those treated with tocilizumab had significantly greater improvements in the percentage of subjects achieving at least a 0.22 unit improvement in MHAQ scores, which was considered significant clinical improvement and the MCID. Of note, the dose of MTX used in this study is below the dose usually considered therapeutic. Multinational evidence-based recommendations suggest starting MTX at 10-15 mg/week, with escalation of 5 mg every 2-4

weeks up to 20-30 mg/week.[191] Thus, this study does not provide evidence that is relevant to determine how tocilizumab compares with MTX as it is generally used in clinical practice.

Biologic DMARD as a class versus oral DMARD as a class. One prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab; n=818) and oral DMARDs as a class (n=265) in patients who had failed two previous oral or biologic DMARD treatments.[78] This study was population-based and part of the RABBIT study, a German long-term, prospective cohort study of RA patients who required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. Severely disabled patients receiving biologic therapies were more likely to achieve physical independence than controls on conventional oral DMARD therapy (Table 31). Functional remission was more often achieved in patients receiving biologics than in controls.

Biologic combinations: biologic DMARD plus biologic DMARD versus biologic DMARD. We found a single 1-year RCT (N=121) followed by a 2-year open label long-term extension (N=80) that reported no significant differences in functional capacity for patients treated with abatacept combined with etanercept compared with etanercept only (Table 32).[80] The study reported greater improvement in quality of life measured by the physical component summary of the SF-36 (data NR), but not the mental component summary. Although the initial RCT dosing of abatacept was lower than currently used clinically, the frequency of serious adverse events was higher in the abatacept combined with etanercept treated patients than the etanercept-only treated patients. The study concluded that abatacept in combination with etanercept should not be used for patients with RA due to limited efficacy findings and safety concerns (more abatacept and etanercept-treated patients experienced serious adverse events).

Table 32. Biologic DMARD plus biologic DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Etanercept+Abatacept vs. Etanercept						
*Weinblatt et al., 2006[80]	RCT 121 1-year double-blind phase 2-year long term-extension	Patients with active RA despite ETN; mean disease duration 12.8 to 13 years	ETN (25 mg twice weekly)+ABA 2g/kg increased to 10 mg/kg after 1 year) vs. ETN (25 mg twice weekly)	Mean change in mHAQ at 12 months: -0.3 vs. -0.2; *P*=NR Mean change in mHAQ from 1 year to 2 years: -0.1 vs. 0; *P*=NR)	Greater improvement in the SF-36 PCS for ETN+ABA group (data NR) Mean change in SF-36 MCS: 3.9 vs.1.06; *P*=NS	Fair

*New studies since last review.
ABA = abatacept; ETN = etanercept; g/kg = gram/kilogram; mg = milligram; mg/kg = milligram/kilogram; mHAQ = modified health assessment questionnaire; NR = not reported; NS = not significant; PCS = physical component score; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; vs. = versus; yr = year

Biologic combinations: biologic DMARD plus oral DMARD versus biologic DMARD. We found five studies, four RCTs[76, 85, 86, 201] and one prospective cohort study,[68] comparing the combination of a biologic DMARD plus an oral DMARD with approved doses of biologic DMARD monotherapy (Table 33). The majority of these studies compared a combination of a biologic DMARD and MTX with monotherapy of the same biologic DMARD.[68, 76, 86, 201] One trial used sulfasalazine as a oral DMARD in combination with a biologic DMARD.[85] Three of

the studies found no difference between combination therapy and biologic DMARD monotherapy; two reported greater improvement with combination therapy. The two RCTs finding that combination therapy resulted in greater improvement in functional capacity or quality of life enrolled subjects that were MTX-naïve[76] or had not been on MTX for at least 6 months prior to enrollment.[86] The studies finding no difference enrolled subjects with active RA despite treatment with the same oral DMARD that was used in the combination therapy arm of the trial.

Table 33. Biologic DMARD plus oral DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab +MTX vs. Adalimumab						
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (<3 years)	ADA (40 mg biweekly)+MTX (20 mg/week) vs. ADA (40 mg biweekly)	At 1 year, ADA+MTX group had greater improvements in HAQ-DI than ADA alone (mean, -1.1 units vs. -0.8; *P*=0.002). After 2 years, there was no difference (-1.0 vs. -0.9; *P*=0.058) After 2 years, more ADA+MTX patients had improvement of ≥0.22 in HAQ-DI than ADA patients (72% vs. 58%; *P*<0.05); had a greater percentage with HAQ-DI scores of 0 (33% vs. 19%; *P*<0.001)	NR	Fair
Etanercept+Oral DMARD vs. Etanercept						
Combe et al., 2006[85] *Combe et al., 2009[145]	RCT 260 24 weeks 2 years	Europe multicenter; active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly)+SSZ (2, 2.5, or 3g/day) vs. ETN (25 mg twice weekly)	Mean percentage improvements in HAQ were similar for ETN+SSZ and ETN alone at 24 weeks (40.2% vs. 35.3%, *P*=NS). At 2 years, clinically significant improvement in HAQ was seen for 78% vs. 76% (*P*=NS)	Mean percentage improvements in EuroQOL VAS were similar for ETN+SSZ and ETN alone at 24 weeks (67.6% vs. 64.6%; *P*=NS)	Fair
Klareskog et al., 2004;[86] van der Heijde et al., 2006;[136] van der Heijde et al., 2006[137, 138] TEMPO study	RCT 686 (503 for 2-year results) 52 weeks (2 years, 100 weeks)	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (20 mg/week) vs. ETN (25 mg twice weekly)	At 52 weeks ETN+MTX was more likely to attain HAQ-DI scores similar to population norms (<0.5) than ETN alone (*P*<0.05). Combination group had greater improvement in mean HAQ scores (mean fall from 1.8 to 0.8 vs. 1.7 to 1.0; *P*<0.001; mean improvement from baseline HAQ 1.0 vs. 0.7; *P*<0.01)	ETN+MTX patients reported better quality of life than ETN-only patients (mean EQ-5D VAS 72.7 vs. 66.8; *P*<0.05)	Good

Table 33. Biologic DMARD plus oral DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
*Van Riel et al., 2008[201] ADORE trial	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX; mean disease duration 10.9 years	ETN (25 mg twice weekly)+MTX (>12.5 mg/week) vs. ETN (25 mg twice weekly)	Mean change in HAQ DI at 16 weeks: -0.59 vs. -0.59; difference between groups 0.029 (95% CI, -0.115 to 0.172)	Mean change in EQ-5D VAS: 21.00 vs. 19.76; difference between groups -2.593 (95% CI, -7.667 to -2.482)	Fair
Weaver et al., 2006[68]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly)+MTX (dose NR) vs. ETN (25 mg twice weekly)	Patients treated with ETN+MTX had similar improvements in functional capacity to those treated with ETN only (mean percentage improvements in HAQ at 12 months: 17% vs. 17%; *P*=NR)	NR	Fair

* New study added since last review.
ADA = adalimumab; CI = confidence interval; EQ-5D VAS = European Quality of Life-5 Dimensions Visual Analogue Scale; EuroQOL VAS = European Quality of Life Health Status Visual Analogue Scale; ETN = etanercept; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; MTX = methotrexate; NR = not reported; NS = not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Adalimumab plus MTX versus adalimumab. The PREMIER study was conducted in MTX-naive patients with early (<3 years), aggressive RA.[76] This 2-year multinational study randomized 799 patients to a combination of adalimumab and MTX, adalimumab monotherapy, or MTX monotherapy. After 1 year, the combination group had greater improvements in HAQ-DI scores than the adalimumab group. After 2 years, the combination group and the adalimumab-only group did not differ significantly for improvements in the HAQ-DI. After 2 years, more patients in the combination group had achieved improvement of ≥0.22 (the clinically relevant threshold) in HAQ-DI than the adalimumab group. In addition, 33 percent of patients in the combination group and 19 percent of those in the adalimumab group had HAQ-DI scores of zero ($P<0.001$).

Etanercept plus MTX versus etanercept. Two RCTs (four publications)[86, 136, 138, 201] and one prospective cohort study[68] assessed differences in efficacy between a combination of etanercept and MTX and etanercept monotherapy. One RCT showed greater improvements for functional capacity and quality of life for combination therapy; one RCT found no difference; the cohort study found no difference. The study showing greater improvements for combination therapy enrolled subjects who had not taken MTX during the prior 6 months. The studies that found no difference enrolled subjects with active RA despite current MTX use.

The first RCT, the 52-week TEMPO trial, involved 686 patients with active RA who had failed previous DMARD therapy.[86, 136-138] Subjects were included only if they had not taken MTX for the 6 months prior to enrollment. Baseline HAQ scores were similar. At 52 weeks, patients in the combination group were significantly more likely to attain HAQ-DI scores similar to population norms (<0.5) than patients in the monotherapy group ($P<0.05$) and had greater

improvement in HAQ scores. In addition, those receiving combination therapy achieved better quality-of-life scores than etanercept monotherapy.[136] Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings.[138] Improvement in disability (based on HAQ) remained significantly better in the combination group than in the etanercept monotherapy group ($P<0.01$). However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

The second RCT, the ADORE trial,[201] randomized subjects (N=315) with active RA despite MTX treatment to 16 weeks of etanercept plus MTX or to etanercept monotherapy. The study reported no difference in change in functional capacity or quality of life between groups. Unlike the TEMPO trial described above, that enrolled subjects who had not been on MTX for the prior 6 months, the ADORE trial enrolled patients with active RA despite MTX use.

The prospective cohort study was based on the RADIUS program[68] (see Biologic DMARD versus biologic DMARD above). Mean percentage improvements in HAQ at 12 months did not differ between patients treated with etanercept plus MTX and those treated with etanercept monotherapy.

Etanercept plus sulfasalazine versus etanercept. A 24-week multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy, sulfasalazine monotherapy, and an etanercept-sulfasalazine combination in patients with active RA who had failed previous sulfasalazine treatment.[85] Two-year outcomes were also published for the trial.[145] Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. The mean percentage improvement for HAQ was similar for the combination group and the etanercept group (P=NS). The mean percentage improvement for health-related quality of life measured by the EuroQOL VAS was also similar. After 2 years, a clinically significant improvement in functional capacity (HAQ improvement of ≥0.22) was similar for both groups (Table 34).[145]

Table 34. Biologic DMARD plus oral DMARD versus oral DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Abatacept+MTX vs. MTX						
*Westhovens et al., 2009[89]	RCT 509 2 years	Early RA, MTX-naïve or pervious MTX ≤10 mg/week for 3 weeks or less, with none for prior 3 months	Abatacept (~10 mg/kg)+MTX vs. MTX	Adjusted mean change from baseline in HAQ-DI: -0.96 vs. -0.76, between group difference -0.20, 95% CI -0.31 to -0.08	Adjusted mean change from baseline in SF-36 PCS: 11.68 vs. 9.18, P=0.005 For SF-36 MCS: 8.15 vs. 6.34, P=0.046	Good

Table 34. Biologic DMARD plus oral DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab+MTX vs. MTX						
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration <1 year	ADA (40 mg biweekly)+MTX (20 mg/week) vs. MTX (20 mg/week)	At 1 year, mean improvement in HAQ-DI: -1.1 units vs. -0.8; *P*<0.001. After 2 years: -1.0 vs. -0.9; *P*<0.058 After 2 years, percentage of subjects with improvement of ≥0.22 in HAQ-DI: 72% vs. 63%; *P*<0.05 Percentage with HAQ-DI scores of 0: 33% vs. 19%; *P*<0.001	NR	Fair
Etanercept+MTX vs. MTX						
*Emery et al., 2008;[90] Kekow, 2010[212] Emery, 2010[91] COMET study	RCT 542 52 weeks† 2 years[91]	MTX naïve patients; Early RA, mean disease duration 9 months	ETN (50 mg/week)+MTX (7.5-20 mg/week) vs. MTX (7.5 to 20 mg/ week)	Percent improvement in HAQ DI: 61% vs. 44%; *P*<0.0001 Mean improvement in HAQ: -1.02 vs. -0.72; *P*<0.001 Percent of subjects achieving normal HAQ-DI (score<0.5): 55% vs. 39%; *P*=0.0004	Mean improvement in SF-36 PCS: 13.7 vs. 10.7, *P*=0.003 Mean improvement in SF-36 MCS: 6.8 vs. 6.1, *P*=NS Mean improvement in EQ-5D VAS: 26.6 vs. 21.7, *P*=0.003	Fair
Klareskog et al., 2004;[86] van der Heijde et al., 2006;[136] van der Heijde et al., 2006[137, 138] TEMPO study	RCT 686 (503 for 2-year results) 52 weeks (2 years, 100 weeks)	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (20 mg/week) vs. MTX (20 mg/week)	Combination group had greater improvement in mean HAQ scores (mean improvement from baseline HAQ 1.0 vs. 0.65; *P*<0.01)	ETN+MTX patients reported better quality of life than MTX-only patients (mean EQ-5D VAS 72.7 vs. 63.7; *P*<0.01)	Good
Weaver et al., 2006[68]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly)+MTX (dose NR) vs. MTX	Greater mean percentage improvements in HAQ at 12 months for ETN+MTX than MTX (17% vs. 7%; *P*<0.01) Similar mean percentage improvements in HAQ at 12 months for INF+MTX and MTX (3% vs. 7%; *P*=NS)	NR	Fair

Table 34. Biologic DMARD plus oral DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Etanercept+SSZ vs. SSZ						
Combe et al., 2006[85], *Combe et al., 2009[145]	RCT 260 24 weeks 2 years	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly)+SSZ (2, 2.5, or 3g/day) vs. SSZ (2, 2.5, or 3g/day)	Percentage of patients who achieved a clinically significant improvement in HAQ at 2 years: 78% vs. 40%; *P*<0,01	NR	Fair
Golimumab+MTX vs. MTX						
*Emery et al., 2009[92] GO-BEFORE	RCT 637 24 weeks	MTX-naïve patients with active RA	GOL (50 mg)+MTX vs. GOL (100 mg)+MTX vs. MTX vs. GOL (100 mg)	Median % improvement from baseline in HAQ-DI: 43.65 vs. 48.55 vs. 36.95 vs. 31.05 (*P*=0.141 for GOL 50+MTX vs. MTX)‡	NR	Fair
Infliximab+MTX vs. MTX						
St Clair et al., 2004;[82] Smolen et al., 2006[83] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks)+MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks)+MTX (20 mg/week) vs. MTX (20 mg/week)	Median decrease in HAQ: 0.78 vs. 0.79 vs. 0.75; *P*=0.03 for INF 3+MTX vs. MTX and *P*<0.001 for INF 6+MTX vs. MTX. Combination therapy was more effective for improving HAQ by at least 0.22 units (76.0% and 75.5% vs. 65.2%; *P*=0.003; *P*=0.004)	Significantly greater improvement in SF-36 PCS for INF 6 mg+MTX vs. MTX (13.2 vs. 10.1; *P*=0.003) but not for INF 3 mg+MTX vs. MTX (11.7 vs. 10.1; *P*=0.10)	Fair

* New study added since last review.
†In COMET, subjects were randomized to one of four treatment groups: (1) ETN+MTX for year 1 followed by the same treatment for year 2, (2) ETN+MTX for year 1 followed by ETN alone for year 2, (3) MTX for year 1 followed by ETN+MTX for year 2, or (4) MTX for year 1 followed by continued MTX for year 2. Thus, all subjects were treated with ETN+MTX or MTX for 1 year and we present the 52 week outcomes in this table.
‡*P*=0.006 for GOL 100+MTX vs. MTX, but GOL 100 mg is an unapproved dose.
ADA = adalimumab; ETN = etanercept; EQ-5D VAS = European Quality of Life-5 Dimensions Visual Analogue Scale; GOL = golimumab; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; INF = infliximab; MTX = methotrexate; NR = not reported; NS = not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 PCS = Medical Outcomes Test, Short Form 36, physical component score; SSZ = sulfasalazine

Golimumab plus MTX versus golimumab. Two RCTs compared golimumab plus MTX with unapproved doses of golimumab (100 mg).[92, 169] These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 34, the overview, our conclusions, or in strength of evidence tables due to the use of unapproved doses in the golimumab plus placebo arms, because it is difficult to draw conclusions about the comparative effectiveness of golimumab plus MTX with the approved use of golimumab (50 mg every 4 weeks).

The GO-BEFORE study was a phase III, multicenter RCT that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo

capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules.[92] The trial reported a median percent improvement in HAQ-DI of 43.65 for golimumab 50 mg plus MTX compared with 48.55 for golimumab 100 mg plus MTX compared with 31.05 for the golimumab 100 mg plus placebo group (*P*=NR for golimumab plus MTX compared with golimumab).

The GO-FORWARD study was a phase III, multicenter trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 50 mg injections plus MTX capsules.[169] The golimumab plus placebo arm of the trial used an unapproved dose of golimumab; thus, it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) and combination therapy with golimumab plus MTX.

Infliximab plus MTX versus infliximab. No RCT compared the infliximab-MTX combination to infliximab monotherapy. The only comparative evidence comes from a cohort study from the RADIUS program (see *Etanercept plus MTX versus etanercept*).[68] The mean percentage improvements in the HAQ at 12 months were similar for patients treated with the infliximab-MTX combination and those treated with infliximab monotherapy (3 percent vs. 1 percent; *P*=NR).

Biologic combinations: biologic DMARD plus oral DMARD versus oral DMARD. We included seven studies comparing a biologic DMARD plus an oral DMARD with oral DMARD monotherapy (Table 34). We found five RCTs[76, 82, 89, 90, 92] and one prospective cohort study[68] comparing a combination regimen of abatacept plus MTX,[89] adalimumab plus MTX,[76] golimumab plus MTX,[92] infliximab plus MTX,[68, 82] or etanercept plus MTX[68, 90] with MTX monotherapy. We found one RCT comparing a combination of etanercept plus sulfasalzine with sulfasalazine monotherapy.[85, 145] Four RCTs were conducted in subjects with early RA;[76, 82, 89, 90] another enrolled a majority of subjects with early RA (about 70 percent of subjects had RA for 3 years or less).[92] All of the RCTs found greater improvement in functional capacity with combination therapies than with monotherapy, although findings in two of the studies did not reach both clinical and statistical significance.

Abatacept plus MTX versus MTX. One multinational RCT randomized 509 subjects with early RA to receive abatacept plus MTX or placebo plus MTX.[89] The trial enrolled subjects with early RA who were MTX naïve and seropositive for rheumatoid factor, anti-cyclic citrullinated protein type 2, or both, and had radiographic evidence of joint erosions. At 1 year, subjects treated with abatacept plus MTX had statistically significantly greater improvement in measures of functional capacity (HAQ-DI) and quality of life (SF-36 PCS), but neither difference reached the threshold for MCID (Table 34).

Adalimumab plus MTX versus MTX. The PREMIER study was a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX; it compared adalimumab monotherapy, MTX monotherapy, and the combination of adalimumab plus MTX[76] (see KQ 1 section on *Biologic DMARD plus oral DMARD versus biologic DMARD*). After 1 year, the combination group had greater improvements in HAQ-DI scores than the MTX group. After 2 years, the combination was superior to MTX. More patients in the combination group had achieved improvement of ≥0.22 in the HAQ-DI than the MTX group. In addition, 33 percent of patients in the combination group and 19 percent of those in the MTX group had HAQ-DI scores of zero ($P<0.001$).

Etanercept plus MTX versus MTX. The COMET study randomized 542 subjects with active, early, moderate to severe early RA to 52 weeks of MTX monotherapy or a combination of MTX and etanercept.[90, 212] Subjects in the combination therapy group had greater improvements in functional capacity and quality of life (Table 34). In addition, among subjects that were working full- or part-time at baseline, fewer patients needed to stop work for at least 1 week in the combination therapy group (9 percent vs. 24 percent, *P*=0.004). In COMET, although year 1 of the study compared combination therapy with etanercept and MTX with MTX alone, subjects were actually randomized to one of four treatment groups at the outset: (1) etanercept plus MTX for year 1 followed by the same treatment for year 2 (EM/EM), (2) etanercept plus MTX for year 1 followed by etanercept alone for year 2 (EM/E), (3) MTX for year 1 followed by etanercept plus MTX for year 2 (M/EM), or (4) MTX for year 1 followed by continued MTX for year 2 (M/M). After 2 years, a greater proportion of subjects had normal HAQ DI scores in the EM/EM group compared with the M/M group (62 percent vs. 44 percent, *P*<0.011).[91]

The 52-week TEMPO trial involved 686 patients with active RA who had failed previous DMARD therapy.[86, 136-138] Subjects were included only if they had not taken MTX for the 6 months prior to enrollment. We focus here on results of the etanercept-MTX combination and the MTX monotherapy arms; their baseline HAQ scores were similar. The combination therapy group had better improvement in functional status than the MTX monotherapy group. At 52 weeks, the combination group had greater improvement in functional capacity than the monotherapy group. In addition, those receiving combination therapy achieved better quality-of-life scores than MTX monotherapy (EQ 5-D VAS).[136] Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings.[138] Improvement in disability (based on HAQ) remained significantly better in the combination group. However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

A prospective cohort study from the RADIUS program showed that patients treated with the etanercept-MTX combination had statistically significantly greater mean percentage improvements in HAQ scores at 12 months than those treated with MTX alone.[68]

Etanercept plus sulfasalazine versus sulfasalazine. A 2-year multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy, sulfasalazine monotherapy, and an etanercept-sulfasalazine combination in patients with active RA who had failed previous sulfasalazine treatment.[85] Two-year outcomes were also published for the trial.[145] Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. A greater percentage of subjects treated with combination therapy achieved a clinically significant improvement in functional capacity (HAQ improvement of ≥0.22) at 2 years.[145]

Golimumab plus MTX versus MTX. The GO-BEFORE study was a phase III, multicenter RCT that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules.[92] The trial reported a median percent improvement in HAQ-DI of 43.65 for golimumab 50 mg plus MTX compared with 48.55 for golimumab 100 mg plus MTX compared with 36.95 for the MTX group. Although the difference was statistically significant for the 100 mg dose of golimumab plus MTX compared with MTX, the difference was not statistically significantly for the approved dose of golimumab (50 mg) plus MTX compared with MTX (*P*=0.141 for GOL 50+MTX vs. MTX; *P*=0.006 for golimumab 100 mg plus MTX compared with MTX).

Infliximab plus MTX versus MTX. The ASPIRE trial enrolled 1,049 patients with early RA (disease duration<3 years) who were MTX-naive.[82, 83] This study compared the benefits of initiating treatment with MTX alone or with a combination of MTX and infliximab over 52 weeks. HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX-only group. The median decrease in the HAQ score was greater for the combination groups than for the MTX-only group (Table 34). In addition, more patients in the combination groups improved their HAQ scores by at least 0.22 units than in the MTX-only group. The mean increases in SF-36 physical component summary scores were 11.7 and 13.2 for the combination groups and 10.1 for the MTX-only group (P=0.10 and P=0.003, respectively). Patients on the combination treatment also had a higher probability of maintaining their employability than did those on MTX alone (P<0.001).[83]

One prospective cohort study from the RADIUS program in the United States (described above in the *Etanercept plus MTX versus etanercept section)* involved patients who were initiating any new DMARD.[68] The mean percentage improvements in the HAQ at 12 months were not significantly different between patients treated with the infliximab-MTX combination and those treated with MTX monotherapy.

Biologic combinations: biologic DMARD plus oral DMARD versus biologic DMARD plus oral DMARD. One prospective cohort compared patients taking an anti-TNF plus oral DMARD to patients taking another anti-TNF plus oral DMARD (Table 35).[94] The study compared anti-TNF (infliximab, etanercept or adalimumab) plus MTX versus anti-TNF plus leflunomide.[94] The study reported no difference in functional capacity between groups (mean improvement in HAQ at 1 year).[94]

Table 35. Biologic DMARD plus oral DMARD versus biologic DMARD plus oral DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Anti-TNF+MTX vs. Anti-TNF+LEF						
*Finckh et al., 2008[94] SCQM cohort	Prospective Cohort 1,218 17 months (mean)	Population-based: Treatment with INF, ETN or ADA; mean disease duration 8.4 to 8.9 years	Anti-TNF (INF or ETN or ADA) (NR)+MTX (NR) vs. Anti-TNF (INF or ETN or ADA) (NR)+LEF	Mean improvement in HAQ at 1 year: 0.12 vs. 0.14; P=0.09	NR	Fair

* New study added since last review.

ADA = adalimumab; ETN = etanercept; HAQ = Health Assessment Questionnaire; INF = infliximab; LEF = leflunomide; NR = not reported; SCQM = Swiss Clinical Quality Management; TNF = tumor necrosis factor

Strategies in early RA. Functional capacity and health related quality-of-life outcomes are presented in Table 36.

Table 36. Early RA strategies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Two Oral DMARD+Corticosteroid vs. Oral DMARD						
Boers et al., 1997;[95] Landewe et al., 2002[96], COBRA study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2g/day)+MTX (7.5 mg/day stopped after 40 weeks)+PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Mean change in HAQ: SSZ+MTX combination had greater improvements in functional capacity at 28 weeks (mean change in HAQ -1.1 vs. -0.6; *P*<0.0001) but difference not significant at 56 weeks (-0.8 vs. -0.6; *P*<0.06)	NR	Good
Two Oral DMARD+Corticosteroid vs. Oral DMARD						
Mottonen et al., 1999;[97] Korpela et al., 2004;[98] Puolakka et al., 2004[202], FIN-RACo study	RCT 199 24 months (5-year followup)	Multicenter; early RA; mean disease duration 7.3 to 8.6 months	MTX (7.5 to 10 mg/week)+HCQ (300 mg/day)+SSZ (2g/day)+PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL	Less work disability for combination group than monotherapy group (median 12.4 days per patient-observation year vs. 32.2; *P*=0.008)	NR	Fair
Other Combination Strategies						
Goekoop-Ruiterman et al., 2005;[100] *Allaart et al., 2006;[101] Goekoop-Ruiterman et al., 2007;[102] van der Kooij et al., 2009;[103] van der Kooij et al., 2009[196] BeSt study	RCT 508 12 months 2 years 4 years	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1 to 5), median duration of symptoms 23 weeks (IQR 14 to 53)	DAS-driven treatment; 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/d) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	All groups improved; greater improvement for groups 3 and 4 than groups 1 or 2 at 3 months (improvement in D-HAQ for strategies 1 through 4: 0.4 vs. 0.4 vs. 0.8 vs. 0.8); better functional ability after 12 months for patients in group 3 or 4 than in group 1 (improvement in mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.9, and 0.9, respectively; *P*<0.05 for 1 vs. 3 and 4, NS for other comparisons); No difference between groups at 24 months (0.7, 0.8, 0.9, and 0.9; *P*=0.26); improvements were maintained at 4 years, with no significant differences between groups (0.8, 0.7, 0.8, 0.8; *P*=0.64)	SF-36 PCS: Greater improvement at 3 months and 6 months for groups 3 and 4 than groups 1 and 2 (*P*<0.001); no difference at 1 and 2 years (*P*=0.10 and 0.95, respectively) difference SF-36 MCS: No differences between groups at 3 months, 6 months, 1 year, or 2 years (*P*=0.22, 0.17, 0.83, 0.97, respectively)	Good

* New study added since last review.

BeST = Dutch acronym for Behandel Sstrategieen; COBRA = Combinatietherapie Bij Reumatoide Artritis; DAS = disease activity score; D-HAQ = Health Assessment Questionnaire – Disability Index; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy; g/day = gram per day; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; INF = infliximab; MCS = mental component score; mg/d = milligram per day; MTX = methotrexate; NR = not reported; NS = not significant; PCS = physical component score; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; SSZ = sulfasalazine

Two oral DMARDs plus corticosteroid versus oral DMARD. The COBRA study assessed differences in efficacy between a combination of sulfasalazine, MTX, and prednisolone and sulfasalazine only.[95, 96] This RCT evaluated 155 patients with early RA over 56 weeks. Combination therapy included sulfasalazine, MTX, and prednisolone treatment. Compared with patients treated with sulfasalazine alone, patients treated with combination therapy had greater improvements in functional capacity at 28 weeks. The difference was no longer statistically significant at 56 weeks.

Three oral DMARDs plus corticosteroid versus oral DMARD. The FIN-RACo RCT assessed the efficacy of a combination of MTX, sulfasalazine, hydroxychloroquine, and prednisolone against monotherapy with a DMARD with or without prednisolone.[97] This study randomized 199 patients with early RA to combination therapy or monotherapy. Combination therapy included sulfasalazine, MTX, hydroxychloroquine, and prednisolone. Patients on monotherapy were initially started on sulfasalazine (2 g/day to 3 g/day), but they could be changed to MTX (7.5 mg/week to 15 mg/week) or to a third DMARD if needed. The study is described further in the KQ 1 section titled *Three oral DMARDs plus corticosteroid versus oral DMARD*. The initial publication reported no functional capacity or quality of life outcomes at 2 years. A 5-year follow-up trial reported that patients in the combination therapy group had significantly less work disability than patients in the monotherapy group.[202] After 2 years, the drug treatment strategy was no longer restricted and was left to the discretion of individual physicians.

Other combination strategies. The BeSt RCT examined four different treatment strategies over 12 months.[100-103, 196] Patients (N=508) with early RA were randomized to one of four strategies: (1) sequential DMARD starting with MTX (15 mg/week); (2) step-up combination therapy of MTX (15 to 30 mg/week) followed by sulfasalazine (2g/day), hydroxychloroquine, and prednisone; (3) initial combination therapy of MTX, and sulfasalazine with tapered high-dose prednisone (60 mg/day to 7.5 mg/day in 7 weeks); and (4) initial combination therapy with infliximab (3 mg/kg) and MTX (25 to 30 mg/week). Adjustments were made in each strategy when the DAS 44 (disease activity score in 44 joints) was greater than 2.4. All groups had similar D-HAQ (Dutch version of the HAQ) scores at baseline (1.4 ± 0.7 or 1.4 ± 0.6). Functional ability, measured by the D-HAQ, was a primary end point. Subjects in groups 3 and 4 had more rapid improvement in functional ability (statistically significant greater improvements at 3, 6, 9, and 12 months). After 12 months of treatment, patients treated with strategy 3 or 4 had statistically significant better functional ability than those treated with strategy 1. By 2 years, improvement was maintained in all groups, but there were no statistically significant differences between groups. Improvements were maintained at 4 years, with no significant differences between groups. Subjects in groups 3 and 4 had more rapid improvement in physical health-related quality of life; with greater improvement at 3 months and 6 months for groups 3 and 4 than groups 1 and 2 on the SF-36 PCS ($P<0.001$); but all groups had similar improvement by the end of 1 and 2 years ($P=0.10$ and 0.95, respectively). There were no differences at any point in mental health-related quality of life as measured by the SF-36 MCS.

Key Question 3: Harms, Tolerability, Adverse Effects, or Adherence

This key question examines whether drug therapies differ in harms, tolerability, or adverse effects in patients with RA. We describe overall tolerability, then specific adverse events for each drug class, followed by studies reporting on adherence. Evidence Tables in Appendix E describe details about these studies, some of which were described for efficacy in KQ 1, above.

Overview

A total of 66 randomized controlled trials (RCTs), one nonrandomized controlled trial, 99 observational studies, and 18 systematic reviews reported on tolerability, harms, and adherence (see Evidence Tables in Appendix E).

As with earlier KQs, the main drug classes examined are corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. Studies often defined comparator groups that were not specific to a particular agent, but instead encompassed any agent in a family of treatments (e.g., an oral DMARD). In cases of biologic DMARDs, studies often required all patients to already be on an oral DMARD such as methotrexate (MTX). In RCTs where the biologic DMARD plus MTX is compared with MTX monotherapy, we discuss these as placebo-controlled trials since the MTX is given to all patients. We differentiate this issue in the text when study designs may not otherwise be clear.

Most studies that examined the comparative efficacy of our drugs of interest also determined their harms. Methods of adverse events assessment, however, differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often, determining whether assessment methods were unbiased and adequate was difficult. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events.

Because few studies used the term *serious adverse events* as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,[213] we describe serious adverse events as the individual studies identified and reported them.

Rheumatoid Arthritis: Key Points

Tolerability and adverse events. *Corticosteroids.* Comparative tolerability and overall adverse events between corticosteroids were similar but comparative data were limited to one 3-month trial.[54] The strength of evidence is low (Appendix I).

Mixed results from one RCT and four observational studies suggest that corticosteroids may increase risk of cardiovascular events.[64, 214-217] One study showed a protective effect against cardiovascular morbidity with corticosteroids.[215] The strength of the evidence is low.

Corticosteroid use significantly predicted the risk of serious infections, with increased risk of infection demonstrated in nine observational studies.[218-226] The strength of evidence for risk of infection with corticosteroids is moderate.

Low strength evidence suggests that corticosteroid treatment is associated with an increased risk of septic (infectious) arthritis[227] and interstitial lung disease.[228]

Oral DMARDs and combinations. Three efficacy trials and one meta-analysis indicated similar tolerability and discontinuation rates of leflunomide, MTX, and sulfasalazine in data up to 2 years.[55, 56, 104, 105, 107, 108] A retrospective cohort study found improved tolerability with leflunomide.[229] In another meta-analysis, the proportion of patients who stayed on MTX was higher than the proportion remaining on sulfasalazine at 5 years based on analysis of 71 RCTs and 88 observational studies (36 percent vs. 22 percent, P=NR [not reported]).[230] The strength of evidence for comparisons of monotherapy with oral DMARDs is low (Appendix I).

Seven studies and two meta-analyses involving combinations of two or three DMARDs, including sulfasalazine, MTX, hydroxychloroquine, and etanercept (a biologic DMARD) versus one or two DMARDs have similar withdrawal rates attributable to adverse events.[29, 57-59, 61, 62, 95, 110, 231, 232] Although discontinuation rates were similar for these pharmaceuticals, the number of patients with adverse events (nausea, erythema, elevated transaminases) were higher in two studies of sulfasalazine plus MTX than in monotherapy with either drug.[57, 58] The strength of evidence comparing combinations of DMARDs with DMARD monotherapy is low.

Three studies of combinations including prednisone with one or more DMARD indicated similar discontinuation rates between groups.[65, 98, 100-102, 196] The BeST study compared various strategies of combining corticosteroids with oral and biologic DMARDs and found similar rates of serious adverse events.[100-102, 196] A retrospective cohort study of 154 patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months ($P<0.05$).[233] The level of evidence is moderate.

Four observational studies assessed cardiovascular or cerebrovascular outcomes with monotherapy or combinations of oral DMARD treatment.[214, 215, 234, 235] All found either a decrease or no difference in risk of these events for patients treated with oral DMARDs. The reduction in risk was largest for leflunomide based on two studies.[215, 234] The strength of the evidence is low.

Hepatic events appeared to be similar among patients treated with MTX, leflunomide, hydroxychloroquine, sulfasalazine, infliximab, and etanercept in two retrospective studies over 2 years to 3 years.[229, 236] Longer-term evidence is lacking. The level of evidence is low.

Mixed evidence from 12 studies suggests that oral DMARDs do not significantly affect risk of infections.[218, 220, 221, 223, 224, 226, 229, 237-240] Evidence is inconclusive for comparing among oral DMARDs. One good-rated nested case-control study showed a lower rate of infection with MTX and hydroxychloroquine. Four other observational studies found no difference in risk with oral DMARDs,[218, 220, 221, 239] while five fair-rated observational studies suggest that risk of infection was increased with oral DMARDs. Because of these inconsistencies, the level of evidence is low.

In one 5-year retrospective cohort, interstitial lung disease appeared to be significantly higher with leflunomide use than with use of other DMARDs (relative risk [RR], 1.9; 95% CI, 1.1 to 3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8 to 2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4 to 1.5).[217] Overall, the rate of hospitalizations because of interstitial lung disease in the entire cohort was 8.1 per 10,000 patient years. In a second study, the risk of interstitial lung disease was similar for leflunomide and other oral DMARDs. The level of evidence is insufficient.

Estimates of cancer risk were limited to retrospective cohort studies. No risk of lymphoma was found for MTX or sulfasalazine in a 30-year retrospective cohort.[241] For the comparison of oral DMARDs, the strength of the evidence is low. Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (hazard ratio [HR], 1.28; $P=0.014$).[242]

Additional studies suggest that oral DMARDs increase risk of septic (infectious) arthritis,[227] and that leflunomide increases risk of wound healing complications compared with MTX,[243] but hydroxychloroquine, leflunomide, MTX, and sulfasalazine do not increase risk of sinus problems[244] A good-rated RCT found that combination DMARD therapy did not increase risk of renal failure.[245] Evidence is insufficient regarding risks for fertility, pregnancy, and lactation.[246]

The strength of this evidence is low because only a single study addresses each of these questions.

Biologic DMARDs. Meta-analysis of withdrawal rates from placebo-controlled trials indicate that fewer patients randomized to a biologic DMARD discontinue treatment compared with patients randomized to placebo or MTX monotherapy (oddsratio [OR] of discontinuation, 0.51; 95% CI, 0.40 to 0.65). This difference is largely driven by withdrawals because of lack of efficacy. In a meta-analysis of withdrawals because of lack of efficacy, the patients treated with a biologic DMARD were much less likely to withdraw than placebo- or MTX-treated patients (OR, 0.21; 95% CI, 0.17 to 0.27). Withdrawals because of adverse events were higher among patients treated with a biologic DMARD compared with placebo- or MTX-treated patients (OR, 1.43; 95% CI, 1.18 to 1.74). Because the *overall* withdrawals rates favored biologic DMARDs over placebo, we concluded that efficacy had a stronger influence on the likelihood of treatment continuation than adverse events. Adjusted indirect comparisons based on the same efficacy trials found no difference in overall withdrawals, with the exception of a more favorable withdrawal profile for certolizumab pegol. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals.

Strength of evidence is presented in Appendix I; overall the strength of evidence is low.

Overall tolerability: *studies on discontinuation rates not otherwise covered in quantitative analyses.* Studies that assessed overall tolerability but were not eligible for inclusion in quantitative analyses are summarized in Table 38. One good-quality RCT compared etanercept with the combination of etanercept and abatacapt.[80] Withdrawals due to adverse events occurred more in the combination group (11.8 percent) than in the monotherapy etanercept group (2.8 percent). Additional evidence on comparative discontinuation rates is provided by observational studies.[88, 93, 247-251] While some studies did not find clinically or statistically significant differences in drug discontinuation rates,[247, 249] others did, generally suggesting higher discontinuation rates with infliximab, adalimumab, and anakinra.[73, 88, 210, 248, 250-252] One good-rated meta-analysis reported an elevated risk of withdrawals due to adverse events for infliximab,[126] and another good-rated meta-analysis reported higher withdrawals due to adverse events or adalimumab, anakinra, and infliximab compared with etanercept.[27, 180]

Two studies compared adverse event rates and serious adverse events with biologic DMARDs; one randomized controlled trial[66] and one retrospective cohort study.[253] Both studies found more serious adverse events among patients treated with infliximab compared with abatacept, adalimumab, and etanercept. No other studies directly compared one biologic DMARD with another biologic DMARD with regard to tolerability or serious adverse events. The strength of this evidence is low.

Indirect evidence from additional efficacy trials, cohort studies, and meta-analyses suggests that the overall tolerability profiles are similar among biologic and oral DMARDs, or combinations of biologic and oral DMARDs.[67, 70, 76, 84, 86, 87, 89, 90, 116, 121, 127, 136, 138, 156, 170, 175, 177, 178, 183, 210, 254-256] However, several studies suggested that adverse events were more common with biologic DMARDs, given alone or in combination with an oral DMARD.[120, 145, 164-167, 173] One good-rated[126] and one fair-rated[183] systematic review and meta-analysis provide indirect evidence

that adverse event rates may be more common with infliximab than with adalimumab or etanercept. One prospective cohort study found a slightly lower rate of serious adverse events among patients who had an oral DMARD added to adalimumab, compared with patients who only received adalimumab (5.3 percent vs. 7.3 percent, respectively; *P*=NR).[257] In contrast, in an RCT of MTX-naïve patients that compared golimumab monotherapy, MTX monotherapy, and golimumab plus MTX, serious adverse events were least common among the golimumab monotherapy group (3.2 percent vs. 6.9 percent vs. 6.3 percent, respectively; *P*=NR).[92]

Four RCTs were designed to assess adverse events as primary outcomes.[121, 155, 258, 259] Overall, adverse event rates were similar for abatacept,[258] adalimumab,[121] anakinra,[259] or infliximab[155] and placebo. Other efficacy trials suggested that overall adverse events are higher with biologic DMARDs than with placebo.

Two trials indicated that a combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy.[79, 258] The evidence, however, is limited to combinations of anakinra with etanercept, and abatacept with anakinra, adalimumab, etanercept, or infliximab. The strength of the evidence is moderate.

Five long-term extension studies of adalimumab,[124] anakinra,[129] etanercept,[260] and infliximab[149, 261] indicated that the rate of adverse events does not increase over time. The strength of the evidence is moderate. No evidence is available on the long-term tolerability of abatacept and rituximab.

Specific adverse events. The risk for long-term, rare but serious adverse events such as serious infections, malignancies, congestive heart failure, or autoimmunity is a cause of concern for all biologic DMARDs. We could not, however, reliably assess the *comparative* risk among biologic DMARDs for most serious adverse events because of insufficient evidence. A summary of studies assessing specific events can be found below later on in Table 39.

Cardiovascular and cerebrovascular events. No studies compared the risk of cardiovascular or cerebrovascular events with one biologic DMARD to another. Studies assessing class effects or individual biologic DMARDs provide mixed results. For example, one observational study reported lower rates of congestive heart failure.[262] for RA patients on anti-tumor necrosis factor (TNF) therapy than for those on conventional RA therapies. This study is contrasted by three other cohort studies that found an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with no treatment or oral DMARD.[263-265] Three observational studies assessed the risk of broadly defined cardiovascular events.[215, 216, 266] One study found no statistically significant association between use of biologic DMARDs and cardiovascular events,[216] while two studies reported a decreased risk of cardiovascular events with biologic DMARDs.[215, 266] One nested case-control study found a slight decrease in the risk of stroke with adalimumab, etanercept, and infliximab (OR, 0.79; 95% CI, 0.34 to 1.82; *P*=NS),[214] and two cohort studies found no statistically significant differences in the risk of myocardial infarction (MI) (although results trended towards an increased risk of MI for these biologic DMARDs).[234, 267]

Infection. The best comparative evidence for risk of infection stems from an RCT[66] and two prospective cohort studies.[268, 269] The trial abatacept plus MTX with infliximab plus MTX and reported that serious infections were more common in the infliximab group than the abatacept group (*P*=NR).[66] One prospective cohort study suggested that risks do not differ for adalimumab, etanercept, and infliximab.[268] A second cohort study conducted in the British Society for Rheumatology Biologics Register (BSRBR) reported that anti-TNF drugs as a class increased risk of serious infections (HR, 1.2; 95% CI, 1.1 to1.5).[269] No statistically significant difference in

the incidence rate was observed comparing across the individual drugs. Six systematic reviews and meta-analyses have assessed serious adverse events with biologic DMARDs, with some showing elevated risk of infection for biologic DMARDs.[126, 183, 255, 270-272] Some of these analyses provide drug-specific effect size estimates that trended to be higher than for some drugs, although none of these analyses provide adjusted indirect comparisons or mixed treatment comparisons to adequately compare risk of infection among biologic DMARDs. Long-term observational studies generally support an increased risk of infection with biologic DMARDs, although not in across all studies.[158, 218, 222, 223, 226, 240, 273-279] Numerous studies suggest that biologic DMARDs have increased risk of tuberculosis (TB) or granulomatous infections,[219, 279-287] with one study indicating the risk may be higher for adalimumab and infliximab compared with etanercept.[279] Two studies indicated that the general risk of biologic DMARDs for serious infections is dose dependent. The evidence, however, is limited to adalimumab[271] and infliximab.[155] The strength of comparative evidence is low, and the strength of general evidence of infection is moderate.

Infusion and injection site reactions. In efficacy studies, infusion reactions (abatacept, infliximab, rituximab, tocilizumab) and injection site reactions (adalimumab, anakinra, certolizumab, etanercept, golimumab) were the two most commonly and consistently reported adverse events. Overall, 0.5 percent of patients treated with infliximab had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions.[273] Fatal infusion reactions have also occurred with rituximab.[288] Of existing comparative evidence, reactions with infliximab were reported more commonly than with other biologic DMARDs in an RCT comparing abatacept and infliximab,[66] and in a retrospective cohort study comparing adalimumab, etanercept, and infliximab.[253] A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1 to 27.9) for adalimumab, 22.4 percent (95% CI, 8.5 to 36.3) for etanercept, and 67.2 percent (95% CI, 38.7 to 95.7) for anakinra.[74]

Interstitial lung disease. Only one study assessed the risk of interstitial lung disease with biologic DMARDs. This prospective cohort study found that current treatment with etanercept and infliximab was not associated with hospitalization for interstitial lung disease.[228] However, past treatment with etanercept (HR, 1.7; 95% CI, 1.0 to 3.0; P=0.056) and infliximab (HR, 2.1; 95% CI, 1.1 to 3.8; P=0.019) was associated with hospitalization for interstitial lung disease.[228]

Malignancies. Data from controlled trials do not provide sufficient evidence concerning an increase in the risk of cancer attributable to the use of either biologic DMARDs or a combination of biologic and oral DMARDs. In a large prospective cohort study the risk of lymphoma was higher for patients on anti-TNF therapies than for those on oral DMARDs, although not statistically significantly so (standardized incidence ratio: MTX, 1.7 (95% CI, 0.9 to 3.2); infliximab, 2.6 (95% CI, 1.4 to 4.5); and etanercept, 3.8 (95% CI, 1.9 to 7.5).[289] An update of this analysis with additional patients and follow-up time confirmed that the risk of lymphoma was not increased among patients taking adalimumab, etanercept, and infliximab.[290] Similarly, three retrospective cohort studies did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on oral DMARDs.[291-293] The largest study included 4,160 patients treated with anti-TNF drugs.[292] Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6 to 2.1) for anti-TNF patients relative to patients on oral DMARDs. Four meta-analyses have evaluated risk of overall malignancy with anti-TNF drugs.[183, 255, 271, 294] Effect size estimates were not statistically significant in three of these analyses, but one fair-rated meta-analysis reported a pooled odds ratio for malignancies of 3.3 (95% CI, 1.2 to 9.1). Five large

cohort studies do not suggest a statistically significant increase in risk of malignancy.[276, 293, 295-297] The strength of the evidence is low.

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity. Reports based on data from the FDA's Adverse Events Reporting System (AERS) indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[298, 299] Similar cases have been seen in regulatory trials of adalimumab.[300] Reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases.[273, 301-303] Lupus-like syndromes have also been reported for adalimumab.[298]

Hepatotoxicity has been reported for infliximab.[301] One study also reported elevated liver enzymes in patients treated with tocilizumab.[174]

A prospective cohort study indicated that patients on anti-TNF treatments were more likely to develop dermatological conditions (skin infections, eczema, drug-related eruptions).[304] Another retrospective cohort study found no overall association of anti-TNF drugs with risk of psoriasis.[305] Among the three biologic DMARDs included, adalimumab had a significantly increased risk of psoriasis compared with those treated with etanercept (incidence rate ratio [IRR], 4.6; 95% CI, 1.7 to 12.1) and infliximab (IRR, 3.5; 95% CI, 1.3 to 9.3).

One cross-sectional analysis of data from 7,243 patients reported a small elevated risk of sinus problems with etanercept (OR, 1.21; 95% CI, 1.02 to 1.42).[244] No statistically significant increased risk of sinus problems was observed with adalimumab (OR, 1.09; 95% CI, 0.79 to 1.51) or infliximab (OR, 1.00; 95% CI, 0.88 to 1.15).

Adherence. Few efficacy studies reported rates of adherence. Results of efficacy trials do not indicate any differences in adherence among drug therapies used to treat RA. However, the quality of reporting and assessment of adherence was limited.

Findings from highly controlled efficacy studies may have limited generalizability to "real world" practice, especially because of the overall short duration of these trials. The evidence is insufficient to draw any conclusions about adherence from effectiveness studies.

For the comparison of one biologic DMARD with another, five observational studies provided mixed results. A review of a large, managed care database suggested that infliximab might have greater adherence than etanercept or MTX.[306] This finding is supported by a second analysis that found greater adherence with infliximab compared with etanercept and anakinra.[307] In contrast, two prospective cohort studies found that etanercept had better adherence than infliximab.[69, 73] One of these studies suggested that etanercept had a better response rate than infliximab attributable to greater adherence.[69] Another prospective cohort study failed to find any differences in adherence between etanercept and infliximab.[81] Overall strength of evidence is low or insufficient for adherence.

Detailed Analysis

Tables 37 to 56 provide information on harms, divided into separate sections for the three main categories of drugs covered in this review. In each section, we cover overall tolerability and then specific adverse events. When sufficient data are available, we break out specific events by type (e.g., hepatic, infection, etc). The overall tolerability section for biologic DMARDs is divided further to present results of quantitative analyses.

Corticosteroids: overall tolerability. Corticosteroids are associated with several well-known side effects (noted already in Tables 38 to 40). The prescription information for long-term use of corticosteroids highlights precautions including osteoporosis with secondary fractures, infection, glucose intolerance, peptic ulcer disease, gastrointestinal bleeding, cataracts, and glaucoma.[308-312]

Comparatively, the tolerability for corticosteroids appears to be similar among different corticosteroids, although the information is limited by short study duration and the fact that only one comparative study is available (Table 37). This head-to-head RCT, described more in detail for KQ 1, compared budesonide (3 mg/day), high-dose budesonide (9 mg/day), prednisolone (7.5 mg/day), and placebo over 12 weeks.[54] Overall rates of adverse events were similar among groups (89 percent, 3 mg/day budesonide; 94 percent, 9 mg/day budesonide; 85 percent, prednisone; 90 percent, placebo; *P*=NR). Few adverse events caused patients to discontinue the drug; gastrointestinal symptoms, heart symptoms, and mood swings or insomnia were similar in all patient groups (*P*=NR).

Table 37. Overall tolerability in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Kirwan et al., 2004[54]	RCT 143 12 weeks	Active RA	BUD PNL	Similar in all groups	Fair
Saag et al., 1994[313]	Retrospective cohort 224 ≥1 year	RA patients on low-dose PRED (15 mg/day or less)	PRED No PRED	PRED 10 mg to 15 mg/day most related to development of AE (OR, 32.3; 95% CI, 4.6 to 220) PRED 5 mg to 10 mg/day (OR, 4.5; 95% CI, 2.1 to 9.6) No increase in AE for PRED<5 mg/day Fracture: OR, 3.9 (95% CI, 0.8 to 18.1; *P*<0.09) First infection: OR, 8.0 (95% CI, 1.0 to 64.0; *P*<0.05) First GI event: OR, 3.3 (95% CI, 0.9 to 12.1; *P*<0.07)	Fair

AE = adverse event; BUD = budesonide; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; mg = milligram; HR = hazard ratio; OR = odds ratio; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial

One retrospective cohort study of 224 RA patients directly assessed the toxicity of low-dose, long-term corticosteroid therapy (mean 4.9 years).[313] In three outpatient rheumatology clinics, 112 patients on low-dose prednisone (<15 mg/day) for more than 1 year were matched with 112 patients not using prednisone. Investigators abstracted records from the date of prednisone initiation to the date of a predetermined adverse event (fracture, avascular necrosis of bone, new onset diabetes or diabetes out of control, infection requiring hospital or surgical intervention, herpes zoster, MI, cerebrovascular event, gastrointestinal (GI) bleeding or peptic ulcer disease, cataracts, glaucoma, and death). Low-dose and high-dose long-term prednisone use (>5 mg/day) was correlated with dose-dependent specific adverse events (adverse event at 10 to 15 mg/day:

OR, 32.3; 95% CI, 4.6 to 220; P=0.0004; adverse event at 5 to 10 mg/day: OR, 4.5; 95% CI, 2.1 to 9.6; P=0.0001; and adverse event at 0 to 4 mg/day: OR, 1.9; 95% CI, 0.8 to 4.7; P=0.15). Patients on long-term prednisone (any dose) were at higher risk for fracture (OR, 3.9; 95% CI, 0.8 to 18.1; P<0.09), infection (OR, 8.0; 95% CI, 1.0 to 64; P<0.09) and GI event (OR, 3.3; 95% CI, 0.9 to 12.1; P<0.07) than were those on shorter-term prednisone use.

Corticosteroids—specific adverse events. We found no comparative study of corticosteroids directly assessing specific serious adverse events. Sixteen studies assessed single agents or class effects of corticosteroids, and these studies are highlighted here for cardiovascular and cerebrovascular events (Table 38), infection (Table 39), and other specific events (Table 40).

Cardiovascular and cerebrovascular events. Four observational studies[214-216, 234] and one RCT[64] provide mixed evidence that corticosteroid treatment in patients with RA increases risk of cardiovascular events, and possibly cerebrovascular events (Table 38). Of the studies of cardiovascular outcomes, one fair-rated cross-sectional analysis of 4,363 patients with RA sampled from 15 countries reported a small reduction in risk of cardiovascular morbidity (HR, 0.95; 95% CI, 0.92 to 0.98).[215] Three studies reported an increased risk of cardiovascular events.[64, 216, 234] A fair-rated RCT of patients with early RA reported that prednisolone was associated with an increased risk of developing hypertension (OR, 2.16; 95% CI, 1.07 to 4.36).[64] A fair-rated nested-case control study of Pennsylvania Medicare enrollees with RA found a glucocorticoid-related increased risk of cardiovascular events (OR, 1.5; 95% CI, 1.1 to 2.1),[216] and a fair-rated retrospective cohort study of U.S. commercially insured patients found that glucocorticoid use was associated with small increased risk of acute MI (RR, 1.32; 95% CI, 1.02 to 1.72).[234] Only one study assessed cerebrovascular outcomes; this nested case-control study from the National Data Bank for Rheumatic Diseases (NDB) study found a statistically nonsignificant increased risk of ischemic stroke with prednisolone treatment (OR, 1.75; 95% CI, 0.87 to 3.53).

*Infection***.** Nine observational studies (Table 39) provide consistent evidence that corticosteroid use in patients with RA is associated with an increased risk of infection, including infections like TB and herpes zoster.[218-226] These studies represent large treated populations with RA, varying in setting from U.S. commercially insured populations, Medicare patients in a single U.S. state, a U.S. registry, and populations in the UK and Canada. A risk of serious bacterial infection was shown in five fair-quality studies[218, 220-222, 226] and one good-quality study.[223] One fair-[224] and one good-rated study[225] demonstrated an increased risk of herpes zoster infection with corticosteroids, and one fair-rated study[219] demonstrated an increased risk of TB with corticosteroids. Across all of these studies of patients with RA (regardless of type of infection), the risk of infection increased by approximately 50 percent to 150 percent with use of corticosteroids.

Table 38. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Cardiovascular and Cerebrovascular Events					
*Choy et al., 2008[64] CARDERA trial	RCT 467 2 years	Pts with early, active RA	MTX+PNL	The number need to harm (NNH) with added PNL for any adverse event leading to withdrawal was 14 (95% CI, 6 to 65). PNL use associated with hypertension (OR, 2.16; 95% CI, 1.07 to 4.36).	Fair
*Nadareishvili et al., 2008[214]	Nested case-control 269 cases among 7,045 patients 8 years	RA pts in National Data Bank for Rheumatic Diseases	PRED	Association of PRED therapy with ischemic stroke: OR,1.75; 95% CI, 0.87 to 3.53; *P*=0.114)	Fair
*Naranjo et al., 2008[215]	Cross-sectional 4,363 Clinician and patient recall	Sample of RA pts across 15 countries	Glucocorticoids	Glucocorticoids associated with reduced risk for CV morbidity (HR, 0.95; 95% CI, 0.92 to 0.98).	Fair
*Solomon et al., 2006[216]	Nested case-control study 3,501 24 months	Pennsylvania Medicare enrollees with RA	Glucocorticoids	Glucocorticoid monotherapy associated with increased risk for cardiovascular events (OR, 1.5; 95% CI, 1.1 to 2.1).	Fair
*Suissa et al, 2006[234]	Retrospective cohort 107,908 14 months	RA pts from PharMetrics data (US)	Glucocorticoids	Glucocorticoid use associated with acute MI (RR,1.32; 95% CI, 1.02 to 1.72)	Fair

* New study added since last review.

AE = adverse event; BUD = budesonide; CI = confidence interval; CV = cardiovascular; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; mg = milligram; HR = hazard ratio; MI = myocardial infarction; MTX = methotrexate; NNH = number needed to harm; OR = odds ratio; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial

Table 39. Infection in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et al., 2007[218]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Glucocorticoids	The risk for all infections requiring hospitalization was most elevated with glucocorticoid agents (RR, 2.6; 95% CI, 2.3 to 2.9); Similar effects were seen with pneumonia as the outcome (RR, 2.1; 95% CI, 2.4 to 3.1).	Fair
*Brassard et al., 2006[219]	Retrospective cohort study 112,300 Up to 5 years	RA pts from PharMetrics data (U.S.)	Several oral DMARDs, biologic DMARDs, corticosteroids	Adjusted rate ratio of developing TB with corticosteroids: 1.7 (95% CI, 1.3 to 2.2).	Fair
Doran et al., 2002[220]	Retrospective cohort 609 39 years	RA patients	Several oral DMARDs, corticosteroids	In patients hospitalized for infection, corticosteroid use increased risk (HR, 1.56; 95% CI, 1.20 to 2.04)	Fair
*Lacaille et al., 2008[221]	Retrospective cohort 27,710 162,720 person years	Pts with RA from British Columbia, Canada	Oral DMARDs, corticosteroids	Adjusted Rate Ratio for serious infections: DMARDs+corticosteroids:1.63 (95% CI, 1.5 to 1.77); corticosteroids alone: 1.9 (95% CI, 1.75 to 2.05)	Fair
*Greenberg et al., 2010[226] CORRONA	Prospective cohort 7,971 15,047 person-years	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	MTX, oral DMARDs, anti-TNF agents, PRED	Adjusted incidence rate ratio of infection and opportunistic infection for PRED compared with oral DMARDs, respectively: IRR 1.05 (0.97-1.15, *P*=0.251); IRR 1.63 (1.20-2.21, *P*=0.002) PRED above 10 mg daily associated with risk of infection (IRR 1.30, 95% 1.11-1.53, *P*=0.001)	Fair
*Schneeweiss et al., 2007[222]	Retrospective cohort 15,597 Up to 8 years	Medicare beneficiaries ages 65 and older with RA	Glucocorticoids	Compared with MTX use, glucocorticoid use associated with serious bacterial infections (RR, 2.25; 95% CI, 1.57 to 3.22)	Fair
*Smitten et al., 2008[223]	Retrospective cohort 24,530 26.6 months	RA pts from PharMetrics data (U.S.)	Corticosteroids	Oral corticosteroid use increased risk of hospitalized infection (RR, 1.92; 95% CI, 1.67 to 2.21). Risk increased with dose.	Good
*Smitten et al., 2007[224]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	RA pts from PM database and UK GPRD	Corticosteroids	Risk of herpes zoster infection with corticosteroids only: (PM: OR, 2.51; 95% CI, 2.05 to 3.06 GPRD: 1.46; 95% CI, 1.24 to 1.70)	Fair

Table 39. Infection in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Strangfeld et al., 2009[225]	Prospective cohort 5,040 up to 36 months	RA pts initiating biologic therapy or switching to another DMARD	Glucocorticoids	Adjusted HR for herpes zoster. Glucocorticoids 1 mg to 9 mg (HR, 1.86; 95% CI, 0.92 to 3.78); Glucocorticoids 10+mg (HR, 2.52; 95% CI, 1.12 to 5.65)	Good

* New study added since last review.
AE = adverse event; BUD = budesonide; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; GPRD = General Practice Research Database; mg = milligram; HR = hazard ratio; MTX = methotrexate; OR = odds ratio; PM = Pharmetrics; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; TB = tuberculosis

*Other adverse events***.** Three additional observational studies assessed the risk of specific adverse events with corticosteroid treatment in patients with RA; one of septic (infectious) arthritis;[227] one of sinus problems;[244] and one of interstitial lung disease (Table 40).[228] A large fair-rated retrospective cohort study found that prednisolone was associated with roughly a threefold increased risk of developing septic (infectious) arthritis compared with those not receiving any DMARD (IRR, 2.94; 95% CI, 1.93 to 4.46).[227] A cross-sectional analysis of 6-month questionnaires from 7,243 patients enrolled in the NDB study found that prednisone use was not associated with an increased risk of sinus problems.[244] Analysis of a larger group of patients from the NDB study (n=17,598) found that current and past prednisone use was associated with hospitalization for interstitial lung disease (respectively, HR, 2.5; 95% CI, 1.5 to 4.1, $P<0.001$, and HR, 3.0; 95% CI, 1.0 to 8.9, $P=0.044$).[228]

Oral DMARDs: overall tolerability. MTX, sulfasalazine, hydroxychloroquine and leflunomide all can produce several well-known, and similar, reactions. Frequently reported adverse reactions for these drugs found in package inserts include the following:

- MTX: ulcerative stomatitis, nausea and abdominal distress, fatigue, chills and fever, dizziness, leukopenia, and decreased resistance to infection;[314]
- Sulfasalazine: stomatitis, nausea, dyspepsia, rash, headache, abdominal pain or vomiting, fever, dizziness, pruritus, and abnormal liver function tests;[315]
- Hydroxychloroquine: dizziness, headache, abdominal pain/nausea/vomiting/diarrhea, pruritus, weight loss, hair bleaching, and alopecia;[316] and
- Leflunomide: diarrhea, rash, elevated liver enzymes, and alopecia.[317]

Table 40. Other specific harms in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Edwards et al., 2007[227]	Retrospective cohort 136,997 15 years	RA pts (n=34,250)	Several oral DMARDs, PNL	PNL (adjusted IRR, 2.94; 95% CI, 1.93 to 4.46, *P*<0.001) was associated with an increased incidence of septic arthritis when compared with those not receiving any DMARD.	Fair
*Michaud and Wolfe, 2006[244]	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the NDB study	PRED	Association of PRED treatment with visits to physician for sinus problems was OR,0.98; 95% CI, 0.86 to 1.11; *P*=0.776).	Fair
*Wolfe et al., 2007[228]	Prospective cohort 17,598 Up to 3.5 years	RA pts in the NDB	PRED	Current treatment with PRED associated with hospitalization for interstitial lung disease (HR, 2.5; 95% CI, 1.5 to 4.1, *P*<0.001). Past treatment with PRED was also associated with hospitalization for interstitial lung disease (HR, 3.0; 95% CI, 1.0 to 8.9, *P*=0.044)	Fair

* New study added since last review.
AE = adverse event; BUD = budesonide; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; mg = milligram; HR = hazard ratio; NDB = National Data Bank for Rheumatic Diseases; OR = odds ratio; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial

Tables 41 to 47 describe studies providing information on tolerability and various adverse events. Studies reporting overall tolerability of oral DMARDs and oral DMARD combinations are summarized in Table 41. For monotherapy with oral DMARDs, three trials[56, 104, 105, 107, 108] and a meta-analysis with up to 2 years of data,[55] all described in more detail for KQ 1, indicated similar levels of general tolerability among leflunomide, MTX, and sulfasalazine, including similar discontinuation rates and frequency of serious adverse events. A retrospective cohort study found leflunomide given as monotherapy or in combination with MTX had fewer adverse event reports than MTX alone or other oral DMARDs.[229] However, another meta-analysis of withdrawal rates from 71 RCTs and 88 observational studies, which included data up to 5 years, found that patients with RA stayed on MTX significantly longer than on either sulfasalazine or hydroxychloroquine.[230] At 5 years, 36 percent of patients had remained on MTX to continue their treatment; 22 percent had remained on sulfasalazine. Patients on sulfasalazine were more likely to have withdrawn from medication because of toxicity than those on MTX (52 percent vs. 35 percent; RR, 1.68; *P*<0.0001). Withdrawal rates were not found to differ between samples reported in observational studies and RCTs.

Table 41. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Oral DMARDs					
Cannon et al., 2004[229]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	AE rates in LEF and LEF+MTX were lower than or similar to AE rates for MTX and other DMARDs	Fair
Emery et al., 2000[105]	RCT 999 1 year with optional 2nd year	RA 4 months to 10 years	LEF, MTX	Frequency of SAEs similar between groups	Fair
Maetzel et al., 2000[230]	Meta-analysis (RCT and observational) 159 studies MTX=2,875 SSZ=1,418 5 years	RA pt studies including withdrawal information	MTX, SSZ, HCQ (and gold)	Withdrawals due to toxicity for 5 years: MTX 35%, SSZ 52% Pts treated with SSZ were 1.68 times more likely to fail therapy due to toxicity than MTX (RR, 1.68; *P*<0.0001)	Fair
*Osiri et al., 2009[55]	Systematic review and meta-analysis 6 studies 1,220 patients Mixed duration	Active RA	LEF, MTX, SSZ	Withdrawals due to adverse events were 10% (95%CI: 6-15%) greater with leflunomide than placebo. NNH: 10 (7 to 17) Adverse events and withdrawal rates simiar for LEF, SSZ, and MTX	Good
Smolen et al., 1999[107, 108]	RCT 358 24 weeks	Active RA	LEF, SSZ	Withdrawal due to AEs 14% vs. 19%	Fair
Strand, et al., 1999[56, 104]	RCT 482 12 months (1 year continuation)	RA for at least 6 months, MTX-naive	LEF, MTX	AEs constant over time for LEF and MTX 12 months: Higher discontinuation rate for LEF (22% vs. 10.4%, *P*=NR)	Fair
Oral DMARD Combinations					
Boer et al., 1997[95] COBRA study	RCT 155 56 weeks	Early RA, DMARD naive	PNL taper+MTX+SSZ vs. SSZ	Lower withdrawal rate due to AEs (2.6% vs. 7.6%, *P*=NR)	Fair
Capell et al., 2006[59]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Active RA	SSZ+MTX vs. SSZ or MTX	Similar withdrawal rate due to AEs	Fair

Table 41. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Dougados et al., 1999[57]	RCT 209 (146) 52 weeks (5-year followup)	DMARD naive, early RA	SSZ +MTX vs. SSZ or MTX	Discontinuation rate due to AEs similar among groups AEs higher in SSZ+MTX vs. SSZ vs. MTX (91% vs. 75% vs. 75%, *P*=0.025)	Fair
*Goekoop-Ruiterman et al., 2005[100-102, 196] BeSt study	RCT 508 12 months	Early RA	Sequential monotherapy (starting with MTX) vs. step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. combination (MTX, SSZ, tapered high-dose PRED) vs. combination with INF (3 mg/kg – could be titrated to 10 mg/kg based on DAS)	No significant differences in serious AEs in all groups	Good
Haagsma et al., 1997[58]	RCT 105 52 weeks	DMARD naive, early RA	SSZ+MTX vs. SSZ or MTX	No significant difference in number of withdrawals due to AEs	Fair
Korpela et al., 1999[98] FIN-RACo study	RCT 199 24 months	Early RA	MTX+HCQ+SSZ+PNL vs. DMARD ± PNL	Frequency of serious AEs similar in both groups Discontinuation due to AEs similar in both groups	Fair
*Malysheva et al., 2008[233]	Retrospective cohort 154 2-62 months	RA Pts	MTX vs. MTX +glucocorticoids vs. HCQ vs. HCQ+glucocorti-coids	Use of GC significantly increased the time until withdrawal of DMARD therapy due to AE (18.6 ± 2.3 months; *P*<0.05) compared with no use of GC (12.5 ± 1.4 months)	Fair
O'Dell et al., 2006[231]	Prospective cohort 119 48 weeks	Active RA, previous use of DMARDs	ETA +SSZ vs. ETA+HCQ	Similar discontinuation rates due to AEs	Fair
O'Dell et al., 2002[61]	RCT 171 2 years	RA pts not previously treated with combination drugs	MTX+SSZ+HCQ vs. MTX+HCQ vs. MTX+SSZ	Similar withdrawal rate due to AEs across groups	Good
O'Dell et al., 1996[62]	RCT 102 2 years	RA and poor response to at least 1 DMARD	MTX+SSZ+ HCQ vs. MTX vs. SSZ+HCQ	Similar withdrawal rate due to AEs across groups	Good

Table 41. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Osiri et al., 2009[55]	Systematic review and meta-analysis 6 studies 1,220 patients Mixed duration	Active RA	LEF+ MTX, MTX	Adverse events reported more frequently for LEF+ MTX than MTX. Withdrawal rates similar with LEF+MTX vs. MTX	Good
*Schipper et al., 2009[232]	Systematic review 515 24 to 52 weeks	Ra pts with insufficient response to SSZ or MTX and SSZ naive	MTX+SSZ vs. MTX vs. SSZ	Pts naïve to MTZ or SSZ on combination therapy experienced significantly more nausea. Those on MTX+SSZ who previously failed SSZ had comparable tolerability	Fair
*Schipper et al., 2009[110]	Nonrandomized inception cohort 230 52 weeks	RA pts that had failed SSZ treatment	SSZ+MTX vs. MTX switch	Rate of discontinuation significantly lower in MTX vs. SSZ+MTX group (*P*=0.01) Relative hazard to stop DMARD within 1 year in SSZ+MTX group vs. MTX group: 1.7 (95% CI, 1.11 to 2.46, *P*<0.01)	Fair
Svensson et al., 2005[65]	Open-label RCT 250 2 years	Early RA	DMARD+PNL vs. DMARD	Similar number of discontinuations between groups	Fair
Svensson et al., 2003[318]	Open-label RCT 245 2 years	Early RA	MTX+PRED SSZ+PRED	Lower withdrawal rate due to AEs or inefficacy for PRED+MTX group vs. PRED+SSZ group (11.5% vs. 33.3%, *P*=0.0005)	Fair

* New study added since last review.
AEs = adverse events; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; GC = glucocorticoids; hydroxychloroquine; HR = hazard ratio; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; PNL = prednisolone; PRED = prednisone; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; SAEs = serious adverse events; SSZ = sulfasalazine

For combination therapies, eight studies of DMARD combinations (one up to 5 years[57]) included MTX, sulfasalazine, hydroxychloroquine, and etanercept (described in detail under KQ 1). They generally had similar withdrawal rates attributed to adverse events.[55, 57-59, 61, 62, 110, 231, 232] One nonrandomized inception cohort fournd higher disciontinuation rates for sulfasalazine plus MTX compared with MTX monotherapy (*P*=0.01).[110] In two RCTs, discontinuation rates were similar, but rates of adverse events were higher for sulfasalazine plus MTX vs. MTX monotherapy (adverse events for combination therapy range from 53 percent to 91 percent; adverse events for monotherapy range from 50 percent to 75 percent).[57, 58] Side effects included nausea, erythema, and elevated transaminases. One systematic review of leflunomide plus MTX vs. MTX monotherapy found increased frequency of adverse event reports with combination therapy.[55] Three RCTs of combination therapy including prednisone with one or more DMARDs (described in detail in KQ 1) showed similar discontinuation rates between groups.[65, 98, 100] One open-label RCT of 155 patients comparing a prednisolone taper plus MTX plus sulfasalazine actually had a lower withdrawal rate because of adverse events than sulfasalazine only (2.6

percent vs. 7.6 percent, P=NR).[95] Another open-label RCT of 245 patients found the withdrawal rate for adverse events to be lower in the prednisone plus MTX group than in the prednisone plus sulfasalazine group (11.5 percent vs. 33.3 percent, P=0.0005).[318] A retrospective cohort study of 154 patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months (P<0.05).[233]

Oral DMARDs: specific adverse events. Oral DMARDs can produce several serious adverse events. The package inserts for MTX give several warnings.[314] It has been reported to cause congenital abnormalities. Severe and sometimes fatal bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of MTX and nonsteroidal anti-inflammatory drugs (NSAIDs). MTX-induced lung disease can occur with doses as low as 7.5 mg per week. Malignant lymphoma may also occur in patients on low-dose MTX. Severe, occasionally fatal skin reactions have also been reported.

Less common but severe adverse and potentially fatal events for sulfasalazine include blood dyscrasias, hypersensitivity reactions including Stevens-Johnson syndrome, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis.[315] The package insert for hydroxychloroquine describes irreversible retinal damage in some patients on long-term therapy or high dosage. Other serious reactions include blood dyscrasias, seizures, hypersensitivity reactions, and hepatotoxicity.[316] Potentially severe adverse reactions for leflunomide include blood dyscrasias, hepatotoxicity, and hypersensitivity reactions including Stevens-Johnson syndrome.[317] Studies of adverse events with oral DMARDs are summarized in Tables 42 to 47.

Cardiovascular and cerebrovascular events. Four observational studies assessed cardiovascular or cerebrovascular outcomes with oral DMARD treatment (Table 42).[214, 215, 234, 235] All found either a decrease or no difference in risk of these events for patients treated with oral DMARDs compared with no treatment or other comparator treatments.

Two studies found a decreased risk of broadly defined cardiovascular events with oral DMARDs.[215, 235] One study, the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) project, was a cross-sectional review of 4,363 patient records from 15 countries.[215] This fair-rated study reviewed clinical history and surveyed patients for information about cardiovascular events, including MI, angina, coronary disease, coronary bypass surgery, and stroke. Risk of all types of cardiovascular events was reduced among patients taking MTX, leflunomide, and sulfasalazine. The second study was a retrospective chart review of 613 patients from a single rheumatology clinic in the Netherlands.[235] Cardiovascular disease was defined as a verified medical history of coronary, cerebral, or peripheral arterial disease. Regression models considered patients treated with oral DMARD monotherapy, as well as combinations of MTX, hydroxychloroquine, and sulfasalazine. All oral DMARD monotherapy and combinations showed a decreased risk of cardiovascular disease (compared with no oral DMARD), although the risk reduction was only statistically significant for patients ever taking MTX and sulfasalazine (OR, 0.24; 95% CI, 0.07 to 0.85, P<0.05) and MTX, sulfasalazine, and hydroxychloroquine (OR, 0.27; 95% CI, 0.07 to 0.99, P<0.05).

Table 42. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Naranjo et al., 2008[215]	Cross-sectional 4,363 Clinician and patient recall	Sample of RA pts across 15 countries	MTX, LEF, SSZ	MTX, LEF, and SSZ associated with reduced risk for CV morbidity (HR, 0.85; 95% CI, 0.81 to 0.89; HR, 0.59; 95% CI, 0.43 to 0.79; HR, 0.92; 95% CI, 0.87 to 0.98; respectively).	Fair
*Nadareishvili et al., 2008[214]	Nested case-control 269 cases among 7045 patients 8 years	RA pts in National Data Bank for Rheumatic Diseases	MTX	Association of treatment with ischemic stroke: MTX: OR,0.63; 95% CI, 0.32 to 1.26; *P*=0.191)	Fair
*Suissa et al, 2006[234]	Retrospective cohort 107,908 14 months	RA pts in PharMetrics U.S. data	Traditional DMARDs	Traditional DMARD use associated with decreased acute MI: MTX: RR, 0.8; 95% CI, 0.60 to 1.08 LEF: RR, 0.28; 95% CI,0.12 to 0.64	Fair
*van Halm et al., 2006[235]	Case-control 613 Eligible diagnosis from 1953-2004	Pts with RA treated in a single clinic in Netherlands	MTX, HCQ, SSZ, MTX+HCQ, MTX+SSZ, SSZ+HCQ, MTX+HCQ+SSZ	Cardiovascular events compared with no DMARD treatment: MTX OR:0.47 (95% CI, 0.07 to 3.23), SSZ: 0.31 (95% CI, 0.07 to 1.33), HCQ: 0.45 (95% CI, 0.10 to 2.04), MTX+ SSZ: 0.24 (95% CI, 0.07 to 0.85, *P*<0.05), MTX+HCQ: 0.54 (95% CI, 0.08 to 3.66), SSZ+ HCQ: 0.34 (95% CI, 0.05 to 2.16), MTX+SSZ+HCQ: 0.27 (95% CI, 0.07 to 0.99, *P*<0.05)	Fair

* New study added since last review

CV = cardiovascular; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GI = gastrointestinal; HCQ = hydroxychloroquine; HR = hazard ratio; INF = infliximab; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; RR = rate ratio; SSZ = sulfasalazine

One fair-rated retrospective cohort study of 107,908 commercially insured patients with RA found a decreased risk of acute MI among patients taking MTX (RR, 0.81; 95% CI, 0.60 to 1.08) or leflunomide (RR, 0.28; 95% CI, 0.12 to 0.65).[234] A decreased risk also was observed among a heterogeneous group of "all other traditional DMARDs" (RR, 0.67; 95% CI, 0.46 to 0.97); this group included hydroxychloroquine and sulfasalazine among numerous other agents.

A fair-rated nested case-control study of 7,045 patients with RA from the NDB study found that while overall patients with RA have a significantly increased risk of stroke (OR, for all strokes 1.64; 95% CI, 1.16 to 2.30; OR, for ischemic strokes 2.66; 95% CI, 1.24 to 5.70),

treatment with MTX, hydroxychloroquine, leflunomide, and sulfasalazine does not increase this risk.[214]

Hepatic events. Two retrospective cohorts examined hepatic events in patients with rheumatoid arthritis.[229, 236] Both studies found similar hepatic event rates for leflunomide and MTX (Table 43).

Table 43. Hepatic events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Cannon et al., 2004[229]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Hepatic event: LEF 4.1/1,000 PY, MTX 6.2/1,000 PY, Other 4.2/1,000 PY, LEF+MTX 4.6/1,000 PY	Fair
Suissa et al., 2004[236]	2 retrospective cohorts (claims data) 41,885 3 years	RA diagnosis	LEF, biologics, traditional DMARDs, MTX	Serious hepatic events compared with MTX: LEF rate ratio: 0.9 (95% CI, 0.2 to 4.9), traditional DMARD: 2.3 (95% CI, 0.8 to 6.5), biologic DMARD: 5.5 (95% CI, 1.2 to 24.6)	Fair

* New study added since last review.
CI = confidence interval; DMARD = disease-modifying antirheumatic drug; LEF = leflunomide; MTX = methotrexate; Pts = patients; PY = person years; RA = rheumatoid arthritis

A 2-year retrospective cohort from a U.S. insurance claims database (N=40,594) examined the incidence rates of serious hepatic events in patients treated with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept).[229] The hepatic event rate for leflunomide was similar to that for other DMARDs (leflunomide, 4.1/1,000 person-years [95% CI, 2.4 to 7.0], MTX, 6.2/1,000 person-years [95% CI, 5.1 to 9.3]; other DMARDs, 4.2/1,000 person-years [95% CI, 3.3 to 5.3], *P*=NS, NR).

Another group examined data from claims databases for two retrospective cohorts of 41,885 patients over 3 years for serious hepatic events associated with treatment with leflunomide, MTX, traditional DMARDs (hydroxychloroquine, sulfasalazine, gold, minocycline, penicillamine, chlorambucil, cylcophosphamide and cyclosporine), or biologic DMARDs (infliximab, etanercept).[236] Overall, the rate of serious hepatic events for all drugs was 4.9 per 10,000 patient years. Using MTX as the reference, they observed no higher rates in serious hepatic events for leflunomide (RR, 0.9; 95% CI, 0.2 to 4.9) or for traditional DMARDs (RR, 2.3; 95% CI, 0.8 to 6.5), but they did report higher rates for biologic DMARDs (RR, 5.5; 95% CI, 1.2 to 24.6).

Infection. Mixed evidence from 12 studies suggests that oral DMARDs do not significantly affect risk of infections (Table 44).[218, 220, 221, 223, 224, 226, 229, 237-240] A good-rated retrospective cohort study found that some oral DMARDs may decrease risk of infection.[223] In this study, 24,530 U.S. commercially insured patients with RA were evaluated for hospitalized infection. A nested case-control analysis was conducted on 1,993 cases of infection and 9,965 controls. The adjusted rate ratio showed a statistically significantly lower rate of infection for MTX- (RR, 0.81; 95% CI, 0.70 to 0.93) and hydroxychloroquine-treated patients (RR, 0.74; 95% CI, 0.62 to 0.89). Risk of infection was not increased with leflunomide (RR, 1.02; 95% CI, 0.79 to 1.32) or sulfasalazine (RR, 0.82; 95% CI, 0.58 to 1.16). In contrast, a fair-rated cohort study from the

Consortium of Rheumatology Research of North America (CORRONA) registry found MTX to be associated with an increased risk of infection (IRR, 1.30; 95% CI, 1.12 to 1.5; $P<0.001$).[226]

Table 44. Infection in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et al., 2007[218]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Oral DMARDs including: MTX, LEF, HCQ, SSZ	Relative risk for infections requiring hospitalization: MTX 1.10 (95% CI, 0.98 to 1.23); all other DMARDs (includes LEF, SSZ) 0.99 (95% CI, 0.84 to 1.16); Antimalarial (includes HCQ) 1.06 (95% CI, 0.92 to 1.22)	Fair
*Brassard et al., 2009[238]	Retrospective cohort study 24,282 1980-2003 for cohort and 1992-2003 for TB incidence rates	RA pts from Quebec	Traditional DMARDs including MTX and LEF, corticosteroids	Rate ratio of TB associated with any DMARD use: 3.0 (95% CI, 1.6 to 5.8).	Fair
*Brassard et al., 2006[219]	Retrospective cohort study 112,300 Up to 5 years	RA pts from the PharMetrics Patient-Centric database	Several oral DMARDs, biologic DMARDs, corticosteroids	Adjusted rate ratio of developing TB with use of traditional DMARDs: 1.2 (95% CI, 1.0 to 1.5).	Fair
Cannon et al., 2004[229]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Respiratory infection: LEF 20/1,000 PY, MTX 38.9/1,000 PY, Other 36.9/1,000 PY	Fair
Doran et al., 2002[220]	Retrospective cohort 609 39 years	RA pts	Several oral DMARDs, corticosteroids	Compared with oral DMARDs, corticosteroids increased risk of hospitalized infection (HR, 1.56; 95% CI, 1.20 to 2.04)	Fair
*Greenberg et al., 2010[226] CORRONA	Prospective cohort 7,971 15,047 patient years	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	MTX, oral DMARDs, anti-TNF agents, PRED	Adjusted incidence rate ratio (IRR) for infections: MTX (IRR, 1.30; 95% CI, 1.12 to 1.50, $P<0.001$) Adjusted incidence rate ratio (IRR) for opportunistic infections: MTX (IRR, 0.93; 95% CI, 0.54 to 1.60, $P=0.781$)	Fair
*Grijalva et al., 2010[240]	Prospective cohort 28,906 3 years	Tennesee Medicaid-enrolled RA pts initiating DMARD use	MTX, LEF, SSZ, HCQ, biologic DMARDs, glucocorticoids	Compared with MTX; LEF, SSZ or HCQ did not increase risks of hospitalizations due to pneumonia or serious infections	Good
*Lacaille et al., 2008[221]	Retrospective cohort 27,710 162,720 person years	Pts with RA from British Columbia, Canada	Oral DMARDs, corticosteroids	Adjusted rate ratio for serious infections: DMARDs+corticosteroids:1.63 (95% CI, 1.5 to 1.77); DMARDs alone: 0.92 (95% CI, 0.85 to 1.0)	Fair

Table 44. Infection in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*McDonald et al., 2009[239]	Retrospective cohort 20,357 7 years	Pts with RA in the Veterans Affairs health care system	Traditional DMARDs	No increased risk of infection with oral DMARDs; SSZ associated with a lower risk of herpes zoster infection (HR, 0.44; 95% CI, 0.21 to 0.91)	Fair
*Smitten et al., 2008[223]	Retrospective cohort 24,530 26.6 months	Pts with RA from U.S. PharMetrics data	MTX, LEF, HCQ, SSZ	MTX and HCQ decreased risk of hospitalized infection (RR, 0.81; 95% CI, 0.70 to 0.93; RR, 0.74; 95% CI, 0.62 to 0.89; respectively).	Good
*Smitten et al., 2007[224]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	Pts with RA the PM database and UK GPRD	Corticosteroids, traditional DMARDs, biologic DMARDs	Risk of herpes zoster infection with traditional DMARDs alone (PM: OR,1.37; 95% CI, 1.18 to 1.59; GPRD, 1.27; 95% CI, 1.10 to 1.48)	Fair
Wolfe et al., 2006[237]	Prospective cohort 16,788 3.5 years	RA diagnosis	PRED, LEF, SSZ, MTX, ETA, INF, ADA	Risk for hospitalization for pneumonia: PRED HR, 1.7 (95% CI, 1.5 to 2.1), LEF HR, 1.3 (95% CI, 1.0 to 1.5). No significant differences for SSZ, MTX	Fair

* New study added since last review.
ADA = adalimumab; AERS = adverse events reporting system; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GI = gastrointestinal; GPRD = General Practict Research Database; HCQ = hydroxychloroquine; HR = hazard ratio; INF = infliximab; LEF = leflunomide; MTX = methotrexate; N/A = not applicable; NR = not reported; OR = odds ratio; PM = PharMetrics; PNL = prednisolone; PRED = prednisone; Pts = patients; PY = person years; RA = rheumatoid arthritis; RR = rate ratio; SSZ = sulfasalazine; TB = tuberculosis

Four other fair-rated studies showed no difference in infection rates with oral DMARDs.[218, 220, 221, 239] A 39-year population-based study of the Rochester, Minnesota, cohort examined potential risk factors for hospitalization for infection in RA patients (N=609).[220] The use of corticosteroids increased hospitalization for infection (HR, 1.56; 95% CI, 1.20 to 2.04), but oral DMARDs (including MTX, hydroxychloroquine, sulfasalazine, and leflunomide) had no increased risk of infection-related hospitalizations. This finding was similar in a retrospective cohort study of 27,710 patients with RA from British Columbia,[221] where oral DMARDs given in combination with corticosteroids were associated with an increased risk of infection (RR, 1.63; 95% CI, 1.5 to 1.77), but oral DMARDs alone were not associated with an increased risk of infection (RR, 0.92; 95% CI, 0.85 to 1.0). A nested case-control study of 23,733 patients with RA from a Quebec database[218] and a retrospective cohort study of 20,357 patients with RA treated at the U.S. Veterans Affairs health care system[239] also found no increased risk of infection with oral DMARDs.

Two fair-rated and one good-rated cohort studies examined the risk of hospitalization for pneumonia infection.[229, 237, 240] One study examined 16,788 patients from U.S. rheumatology practices and followed up semi-annually with questionnaires for 3.5 years.[237] Both prednisone and leflunomide use increased the risk of hospitalization for pneumonia compared with RA patients not on these drugs (HR, 1.7; 95% CI, 1.5 to 2.1; HR 1.3; 95% CI, 1.0 to 1.5); MTX, hydroxychloroquine, sulfasalazine, infliximab, etanercept, or adalimumab did not increase risks. A 2-year retrospective database study examined RA patients to determine the incidence rates of

adverse events during treatment with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept).[229] Respiratory infection rates per person-year were highest in the MTX group (38.9/1,000 person-years), next highest in the other DMARD group (36.9/1,000 person-years), and lowest in the leflunomide group (20/1,000 person-years) ($P<0.0001$). The good-rated study found that, compared with MTX, hydroxychloroquine, leflunomide, and sulfasalazine do not increase risk of hospitalization due to pneumonia (adjuster HR, 1.61; 95% CI, 0.85 to 3.03).[240]

Two retrospective cohort studies examined the risk of TB with oral DMARDs.[219, 238] Both showed an increased risk of TB with oral DMARD treatment. One study examined 24,282 patients with RA from Quebec, Canada and found the risk of TB to be increased among oral DMARD users (RR, 3.0; 95% CI, 1.6 to 5.8).[238] The risk was highest among leflunomide-treated patients (RR, 11.7; 95% CI, 2.1 to 65.1), although the sample size for this group was only 10 patients (3 cases, 7 controls). A similarly designed study using a U.S. claims database identified 112,300 patients with RA and found only a slight increase in risk of developing TB among oral DMARD users (RR, 1.2; 95% CI, 1.0 to 1.5).[219] Subgroup analyses from this study illustrate that the risk of developing TB is lower among patients concomitantly receiving corticosteroids (RR, 0.6; 95% CI, 0.4 to 1.0) compared with patients not receiving corticosteroids (RR, 1.4; 95% CI, 1.1 to 1.8).

One fair-rated retrospective cohort study examined the risk of herpes zoster infection with oral DMARDs.[224] This study analyzed data from a U.S. commercial claims database as well as data from the UK General Practice Research Database. Analyses from both databases revealed an increased risk of herpes zoster infection with oral DMARDs (U.S. data: OR, 1.37; 95% CI, 1.18 to 1.59; UK data: OR, 1.27; 95% CI, 1.10 to 1.48).

Interstitial lung disease. Two fair-rated observational studies evaluated the risk of interstitial lung disease with oral DMARD treatment (Table 45).[217, 228] One 5-year retrospective cohort study examined claims data from 62,734 patients with RA given a DMARD 1 year prior to the date of diagnosis of interstitial lung disease.[217] Patients were divided into four categories: leflunomide, MTX, biologic agents (infliximab, etanercept, adalimumab, anakinra), and traditional DMARDs (antimalarials, sulfasalazine, gold salts, minocycline, penicillamine, azathioprine, cyclosporine, other cytotoxic agents). In patients diagnosed with interstitial lung disease, those prescribed leflunomide were at increased risk compared with patients prescribed other DMARDs (RR, 1.9; 95% CI, 1.1 to 3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8 to 2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4 to 1.5).[217] The second study analyzed data from 17,598 patients with RA followed prospectively in the NDB study.[228] Cases of interstitial lung disease were identified by searching patient descriptive reports, hospital records, physician records, and mortality records. The incidence of hospitalization for interstitial lung disease was 260 per 100,000 patient years. No significant association was observed between current or past treatment with MTX, hydroxychloroquine, leflunomide, or sulfasalazine. Current and past treatment with prednisone, as well as current treatment with infliximab, etanercept, and cyclophosphamide was associated with an increased risk of interstitial lung disease.

Table 45. Interstitial lung disease in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Suissa et al., 2006[217]	Retrospective cohort (claims data) 62,734 5 years	RA diagnosis, on DMARD	MTX, LEF, biologics, traditional DMARDs	Risk of interstitial lung disease in LEF compared with other DMARDs: OR, 1.9 (95% CI, 1.1 to 3.6). No elevation noted in LEF pts with no history of MTX or no history of interstitial lung disease	Fair
*Wolfe et al., 2007[228]	Prospective cohort 17,598 Up to 3.5 years	RA pts in the National Databank for Rheumatic Diseases	MTX, LEF, HCQ, SSZ	No significant association between current and past MTX, LEF, HCQ, and SSZ use and hospitalization for interstitial lung disease.	Fair

* New study added since last review.
CI =confidence interval; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; SSZ = sulfasalazine

Malignancies. Two observational studies assessed the risk of malignancy with oral DMARDs (Table 46). One retrospective study examined 756 patients with RA to determine the risk of lymphoma over a 30-year period.[241] This was a matched case-control of consecutive Swedish RA patients in whom lymphoma was diagnosed. Controls were RA patients matched for sex, year of birth, year of RA diagnosis, and county of residence. The investigators found no association between lymphoma and use of DMARDs, including MTX (OR, 0.7; 95% CI, 0.3 to 1.6) or sulfasalazine (OR, 0.6; 95% CI, 0.3 to 1.1).

Table 46. Malignancies in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Baecklund et al., 2006[241]	Retrospective cohort 756 30 years	RA pts with diagnosis of lymphoma	MTX, SSZ	No significant risk for lymphoma for MTX or SSZ	Good
Chakravarty et al., 2005[242]	Retrospective cohort 15,789 (RA) 4 years	RA pts	PRED, LEF, MTX	PRED was associated with increased risk for nonmelanoma skin cancer PRED: HR 1.28 (95% CI, 1.05 to 1.55, *P*=0.014)	Fair

* New study added since last review.
CI = confidence interval; HR = hazard ratio; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; PRED = prednisone; Pts = patients; RA = rheumatoid arthritis; SSZ = sulfasalazine

Another retrospective cohort study examined the risk of nonmelanoma skin cancer in 15,789 U.S. patients with RA who were participating in a registry and returned semiannual questionnaires over a 4-year period in which they reported any current malignancies.[242] Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR, 1.28; *P*=0.014). They found no association between this neoplasm and leflunomide plus MTX.

Other adverse events. Five studies provided additional data on oral DMARD-related adverse events (Table 47). One study evaluated the relationship of treatment with the incident rate of septic arthritis;[227] one study examined whether MTX and leflunomide increased the risk of wound healing complications (both in combination with corticosteroids) in RA patients undergoing elective orthopedic surgery;[243] one study examined evidence of kidney damage from combination therapy compared with monotherapy with suflasalazine or prednisone;[245]one systematic review evaluated studies addressing fertility, pregnancy, and laction;[246] and one study assessed whether oral DMARDs were related to sinus problems.[244]

Table 47. Other specific adverse events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Edwards et al., 2007[227]	Retrospective case-control 136,997 15 years	RA pts (n=34,250)	Several oral DMARDs, including MTX, LEF, HCQ, SSZ	Incident rate of septic arthritis in RA pts receiving DMARDs: 2.14 (95% CI, 1.64 to 2.78; *P*<.001) times greater than in patients with RA not receiving DMARDs.	Fair
*Fuerst et al., 2006[243]	Prospective cohort 201 6 weeks+	Pts with RA or PsA (n=8) undergoing elective orthopedic surgery	MTX, LEF, both in combination with corticosteroids	LEF+corticosteroids significantly increased the risk for wound healing complications compared with MTX+corticosteroids (40.6% vs. 13.6%, *P*=0.01).	Fair
*Karstila et al., 2010[245]	RCT 195 Up to 11 years	Pts with new onset RA naïve to DMARD treatment	Combination therapy with SSZ, MTX, HCQ, or PRED vs. monotherapy with SSZ with or without PRED	Culmulative incidence of abnormal renal findings in combination vs. monotherapy groups were comparable	Good
*Martinez Lopez et al., 2009[246]	Systematic review 6 studies 366 patients	Studies addressing pregnancy, fertility, and lactation	MTX	Evidence is insufficient for conclusions	Fair
*Michaud and Wolfe, 2006[244]	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the NDB study	MTX, HCQ, LEF, SSZ	Association (OR) of treatment with visits to physician for sinus problems was • MTX: 1.06 (95% CI, 0.93 to 1.20; *P*=0.371); • HCQ: 1.08 (95% CI, 0.93 to 1.25; *P*=0.313) • LEF: 0.84 (95% CI, 0.70 to 0.99; *P*=0.041) • SSZ: 0.68 (95% CI, 0.51 to 0.90; *P*=0.007)	Fair

* New study added since last review.
DMARD, = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; SSZ = sulfasalazine

In a retrospective cohort study of 136,977 patients with RA from the UK General Practice Research Database, the incidence rate of septic (infectious) arthritis was increased for patients receiving oral DMARDs compared with patients not receiving oral DMARDs (IR, 2.14; 95% CI,

1.64 to 2.78; $P<0.001$).[227] The increased incidence rate varied by drug, and was highest for penicillamine (IRR, 2.51; 95% CI, 1.29 to 4.89), sulfasalazine (IRR, 1.74; 95% CI, 1.04 to 2.91), and prednisolone (IRR, 2.51; 95% CI, 1.93 to 4.46).

A prospective cohort study of 201 patients with RA undergoing orthopedic surgery assessed whether leflunomide or MTX given in combination with corticosteroids increased the risk of wound healing complications.[243] In comparison with patients who received MTX, the risk of postoperative wound healing complications was significantly higher than in patients who received leflunomide (MTX 13.6 percent vs. leflunomide 40.6 percent; $P=0.01$).

A good-rated RCT compared oral DMARD combination therapy with oral DMARD monotherapy in 195 DMARD-naïve patients with recent onset RA. Over an 11-year follow-up period, no statistically significant difference in renal complications was observed.[245]

A systematic review of studies addressing safety of MTX during pregnanancy, lactation, and related to fertility concluded that evidence is insufficient to adequately addreass the question.[246]

A cross-sectional analysis of 7,243 patients followed in the NDB study assessed whether treatment with oral DMARDs was associated with physician visits for sinus problems.[244] Treatment with MTX and hydroxychloroquine were not associated with an increased risk of sinus problems, and leflunomide and sulfasalazine had a slight protective effect (respectively, OR, 0.84; 95% CI, 0.70 to 0.99; $P=0.041$; and OR, 0.68; 95% CI, 0.51 to 0.90; $P=0.007$).

Biologic DMARDs. This section follows a similar format as the detailed analysis of corticosteroid and oral DMARD sections above, where results for overall tolerability are presented first, followed by general adverse events and then specific adverse events. This section follows a slightly different format to accommodate the presentation of quantitative analyses and detailed adverse event data. Data on tolerability and adverse events for biologic DMARDs are presented as follows: (1) results of quantitative analyses for withdrawal data; and (2) additional discontinuation data not captured by the quantitative analyses, (3) overall adverse event rates and reports of serious adverse events (not otherwise discussed in the specific adverse events section but that are reflective of tolerability profile), and (4) specific adverse events.

Overall tolerability quantitative analyses. RCTs identified by our systematic literature search were screened for inclusion in the meta-analysis of overall tolerability. This included mostly fair-to-good quality efficacy trials, as well as some RCTs otherwise included in a good-quality meta-analysis covered in KQ 1 or KQ 2 of this report. Trials were excluded if they did not meet preestablished eligibility criteria for study design or duration, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest. Eligible studies had to compare one more biologic DMARD with placebo. Concomitant use of MTX was allowed, as long as it was consistently used in the biologic DMARD and placebo groups. The outcome of interest was withdrawal (total, due to adverse events and due to lack of efficacy) of biologic DMARD treatment. These trials were not required to report adverse event data other than withdrawals, and thus not all of the studies are detailed further in other adverse event-related sections of this report. Trials had to be at least 12 weeks in duration. If multiple withdrawal rates were reported for more than one time point, we used the time point identified for the primary outcome measure. We limited included data to FDA-approved dosage ranges to achieve better equivalency across drugs. Note that sample sizes may not match sample sizes reported in individual trials since we excluded dosing arms outside of the FDA recommend range. We identified a total of 42 studies (43 comparisons) that were relevant for nine biologics. These included five studies for abatacept, eight for adalimumab, four for anakinra, three for certolizumab, six for etanercept, three for golimumab, six for infliximab, four for rituximab, and

four for tocilizumab. Table 48 lists trials included in the meta-analyses, along with the corresponding withdrawal rates overall and by reason.

Table 48. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses

				Number of Withdrawals by Reason		
Author, Year	Duration (weeks)	Comparison	N	Overall	Tolerability	Efficacy
Kremer, 2005[114]	52	Abatacept	115	26‡	6‡	13‡
		Placebo	119	48	11	30
Kremer, 2006[116]	52	Abatacept	433	48‡	18‡	13‡
		Placebo	219	57	4	40
Schiff, 2008[66]	26	Abatacept	156	9‡	2‡	2‡
		Placebo	55	3	1	1
Weinblatt, 2006[258]	52	Abatacept	959	123‡	52‡	NR
		Placebo	482	87	20	NR
*Westhovens, 2009[89]	52	Abatacept	256	24	9	0
		Placebo	253	26	11	8
Breedveld, 2006[76]	104	Adalimumab	268	65§	32	13
		Placebo	257	112	19	46
Furst, 2003[121]	24	Adalimumab	318	28‡	9‡	5‡
		Placebo	318	30	8	14
Kim, 2007[127]	18	Adalimumab	65	6‡	4‡	NR
		Placebo	63	4	4	NR
Keystone, 2004[120]	52	Adalimumab 20 mg	212	44‡	16‡	6‡
		Adalimumab 40 mg	207	48‡	26‡	6‡
		Placebo	200	60	13	23
Miyasaka, 2008[125]	24	Adalimumab	91	16‡	12‡	NR
		Placebo	87	7	4	NR
Van de putte, 2003[119]	12	Adalimumab 20 mg	72	10‡	0‡	2‡
		Adalimumab 40 mg	70	12‡	3‡	0‡
		Placebo	70	24	1	1
Van de putte, 2004[122]	26	Adalimumab 20 mg	112	33‡	3‡	27‡
		Adalimumab 40 mg biweekly	113	32‡	6‡	20‡
		Adalimumab 40 mg weekly	103	15‡	3‡	10‡
		Placebo	110	62	1	56
Weinblatt, 2003[123]	16	Adalimumab	67	NR	0‡	NR
		Placebo	62	NR	2‡	NR
Breshnihan, 1998[128]	24	Anakinra 75 mg/day	116	22‡	7‡	14‡
		Anakinra 150 mg/day	116	28‡	11‡	11‡
		Placebo	121	32	5	24
Cohen, 2002[131]	24	Anakinra 1 mg/kg/day	59	13‡	8‡	4‡
		Anakinra 2 mg/kg/day	72	19‡	11‡	4‡
		Placebo	74	14	3	5
Cohen, 2004[133]	24	Anakinra	250	NR	14‡	NR
		Placebo	251	NR	13‡	NR
Fleishmann, 2003[259]	24	Anakinra	1116	241‡	149‡	NR
		Placebo	283	53‡	26‡	NR
Fleishmann, 2009[165]	24	Certolizumab	111	35‡	5‡	24†
		Placebo	109	81	2	75
Keystone, 2008[168]	52	Certolizumab	390	116‡	22‡	68‡
		Placebo	199	156	3	125
Smolen, 2009[167]	24	Certolizumab	246	65‡	6‡	53‡
		Placebo	127	110	2	107
*Emery, 2008[90]	52	Etanercept	274	53‡	28‡	9‡
		Placebo	268	79	34	24

Table 48. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses (continued)

Author, Year	Duration (weeks)	Comparison	N	Number of Withdrawals by Reason		
				Overall	Tolerability	Efficacy
*Emery, 2010[91]	52	Etanercept	90	16‡	7‡	1‡
		Placebo	99	23	9	7
Klareskog, 2004[86]	52	Etanercept	231	38‡ 24	‡	6‡
		Placebo	228	69	32	21
Moreland,1997[144]	12	Etanercept	44	3‡ NR		2‡
		Placebo	44	21	NR	19
Moreland,1999[140]	26	Etanercept	78	19§	2†	12§
		Placebo	80	54	3	42
Weinblatt,1999[142]	24	Etanercept	59	2‡	2‡	0‡
		Placebo	30	6	1	4
*Emery, 2009[92]	24	Golimumab	158	8‡	5‡	0‡
		Placebo	160	10	1	1
*Kay, 2008[166]	16	Golimumab	35	4‡	2‡	2‡
		Placebo	35	6	3	3
*Keystone, 2009[169]	16	Golimumab	89	2‡	2‡	0‡
		Placebo	133	6	4	0
Abe, 2006[153]	14	Infliximab 3 mg/kg	49	NR	1‡ NR	
		Infliximab 10 mg/kg	51	NR	4‡ NR	
		Placebo	47	NR	1	NR
Lipsky, 2000[151]	54	Infliximab 3 mg/kg every 8 wks	86	23‡	5‡ 17	‡
		Infliximab 3 mg/kg every 4 wks	86	20‡	9‡ 19	‡
		Infliximab 10 mg/kg every 8 wks	87	12‡	4‡	6‡
		Infliximab 10 mg/kg every 4 wks	81	16‡	8‡	7‡
		Placebo	88	44	7	32
Schiff, 2008[66]	26	Infliximab	165	13‡	8‡	2‡
		Placebo	55	2	1	1
St. Clair, 2004[82]	54	Infliximab 3 mg/kg	373	66‡ 34	‡	7‡
		Infliximab 6 mg/kg	375	75‡ 35	‡ 12	‡
		Placebo	298	60	9	27
Westhovens, 2006[155]	22	Infliximab 3 mg/kg	360	26‡ 18	‡ NR	
		Infliximab 10 mg/kg	361	32‡ 20	‡ NR	
		Placebo	363	23	8	NR
Zhang, 2006[156]	18	Infliximab	87	9‡	6‡ NR	
		Placebo	86	15	4	NR
Cohen, 2006[158]	24	Rituximab	309	55‡	2‡ NR	
		Placebo	208	96	8	NR
Edwards, 2004[84]	24	Rituximab	40	1‡	1‡	1‡
		Placebo	40	3	0	2
Emery, 2006[157]	24	Rituximab	192	27‡	6‡ 16	‡
		Placebo	149	52	0	46
*Emery, 2010[162]	24	Rituximab	340	12‡	5‡	1‡
		Placebo	172	13	2	7
*Emery, 2008[175]	24	Tocilizumab 4 mg/kg	163	24‡ 10	‡	6‡
		Tocilizumab 8 mg/kg	175	23‡ 11	‡	4‡
		Placebo	160	30	10	19
*Genovese, 2008[176]	16	Tocilizumab	805	53‡ 32	‡ NR	
		Placebo	415	43	8	NR
*Kremer, 2010[178]	24	Tocilizumab	797	NR	61‡	3‡
		Placebo	393	NR	11	12

Table 48. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses (continued)

Author, Year	Duration (weeks)	Comparison	N	Number of Withdrawals by Reason		
				Overall	Tolerability	Efficacy
Smolen, 2008[164]	24 T	ocilizumab 4 mg/kg	214	25‡ 14	‡	2‡
		Tocilizumab 8 mg/kg	205	13‡ 12	‡	0‡
		Placebo 204		12	6	3

* New studies since last review.
Kg = kilogram; mg = milligram; NR = not reported; NS = not significant
† *P*=NS
‡ *P*=NR
§ *P*<0.01

Overall tolerability: quantitative analysis of total withdrawals for biologic DMARD versus placebo. Using random effects models, we calculated the pooled odds ratios of total treatment withdrawal for each biologic relative to placebo (Figure 4). Overall, patients on biologics were approximately half as likely to withdraw from the treatment as compared with the patients on placebo. Among the individual biologics, the pooled estimates were statistically significant for abatacept (OR, 0.58; 95% CI, 0.39 to 0.86), certolizumab (OR, 0.10; 95% CI, 0.06 to 0.18), etanercept (OR, 0.32; 95% CI, 0.18 to 0.57) and rituximab (OR, 0.29; 95% CI, 0.22 to 0.39). Patients taking these drugs were less likely to withdraw from a trial than patients taking placebo. The likelihood of withdrawal of adalimumab, anakinra, golimumab, infliximab, and tocilizumab was not statistically significantly different than placebo. We estimated heterogeneity using I2 statistic. I2 was found to be 86.5 percent overall, which suggested a high amount of heterogeneity among the studies. This heterogeneity may be attributed to several reasons. First, real heterogeneity may exist across study designs and patient populations. Second, the withdrawal outcome—which measures a combination of withdrawals due to adverse events and withdrawals due to lack of efficacy—can be a potential source of heterogeneity. These reasons for withdrawal may not be in agreement with each other, and introduce measurement concerns when combining studies. For example, total withdrawal for one drug can be higher because it is less efficacious while for another drug, it might just be because of high adverse events. This can lead to potential heterogeneity concerns when looking across all studies. We assessed publication bias using funnel plots. Visual examination of funnel plots illustrated potential for some publication bias. However, given the small number of component studies, results of these tests must be viewed cautiously.

Overall tolerability: quantitative analysis of withdrawals due to lack of efficacy for biologic DMARD versus placebo. We also calculated the pooled odds ratios of treatment withdrawal because of lack of efficacy for each biologic relative to placebo (Figure 5). Patients randomized to biologic DMARDs were nearly 5 times less likely to withdraw from the treatment due to lack of efficacy as compared with the patients on placebo (OR, 0.21; 95% CI, 0.17 to 0.27). All individual biologics, except golimumab, were less likely to be withdrawn compared with placebo for lack of efficacy. I2 was found to be 52.8 percent, which suggested slightly lower heterogeneity when just looking at lack of efficacy compared with overall withdrawals. This result suggests that some of the heterogeneity with the total withdrawals analysis was probably

Figure 4. Meta-analysis of overall withdrawals from randomized controlled trials of biologic DMARDs

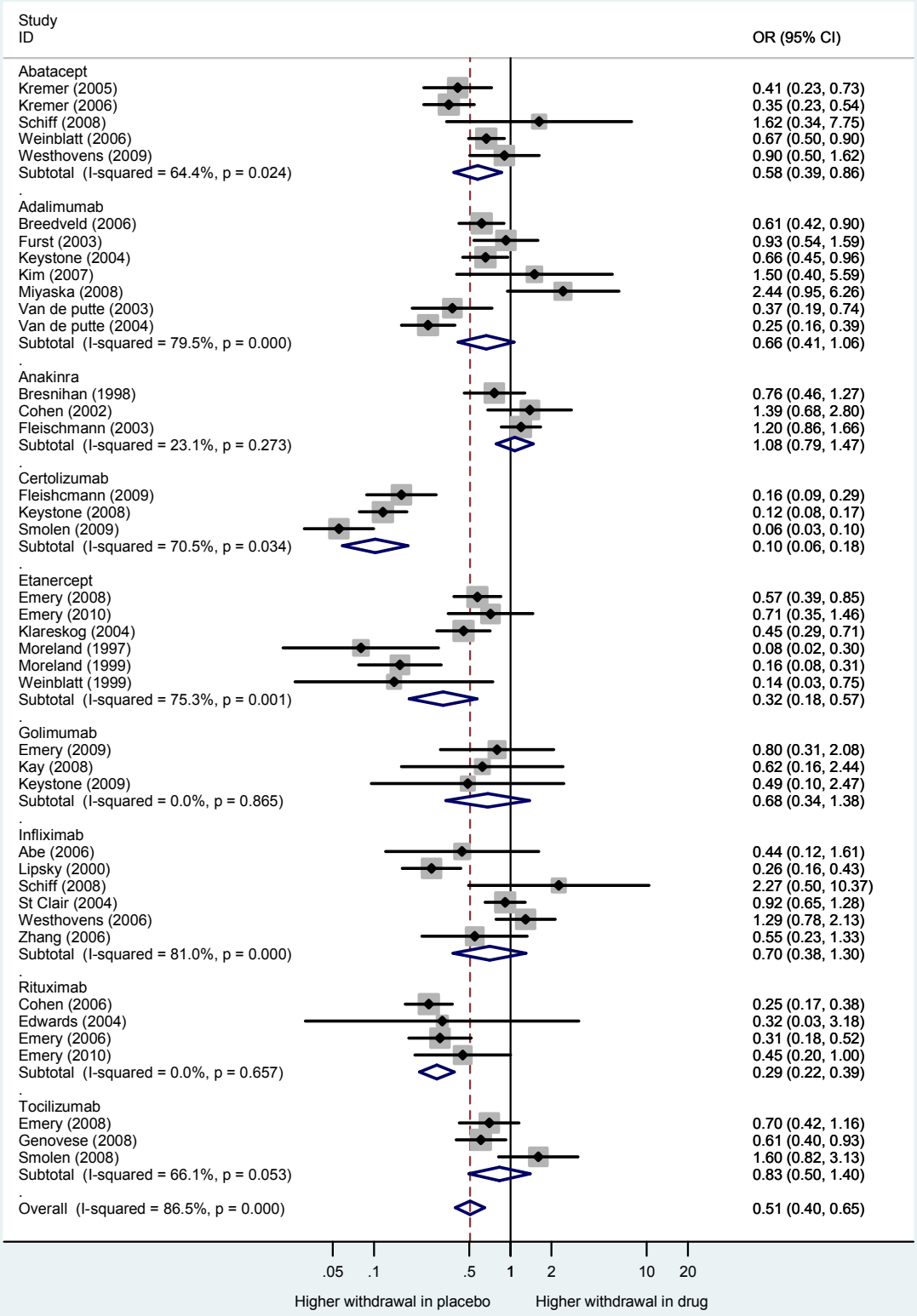
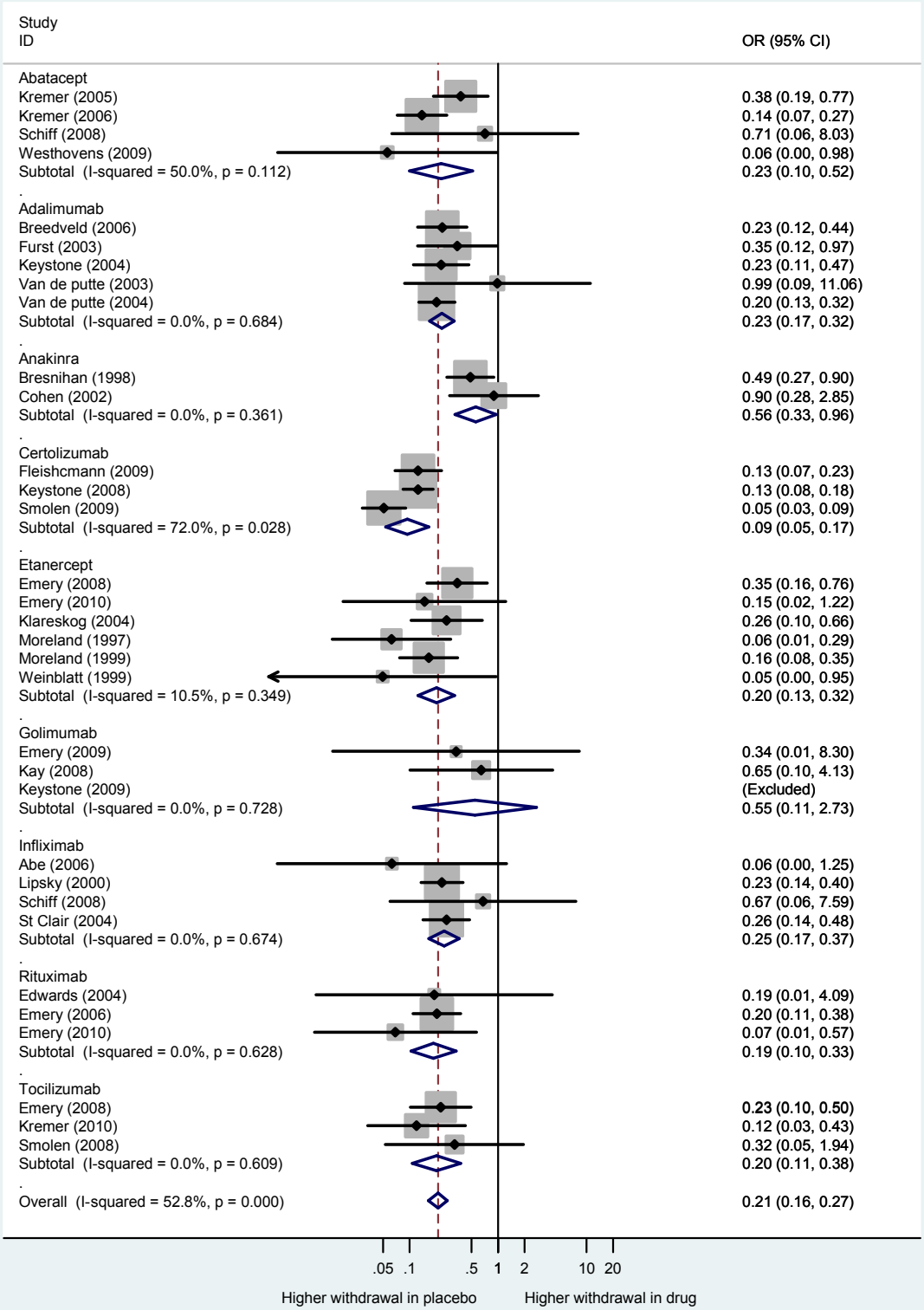


Figure 5. Meta-analysis of withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs



due to combining withdrawals for all the reasons together. Visual examination of funnel plots did not show evidence of publication bias.

Overall tolerability: quantitative analysis of withdrawals due to adverse events for biologic DMARD versus placebo. We also calculated the pooled odds ratios of treatment withdrawal because of adverse events for each biologic relative to placebo. Patients on biologics were 44 percent more likely to withdraw from the treatment due to adverse events compared with the patients on placebo (OR, 1.43; 95% CI, 1.18 to 1.74). Among individual biologics, the pooled estimates for adalimumab (OR, 1.60; 95% CI, 1.13 to 2.28), anakinra (OR, 1.59; 95% CI, 1.10 to 2.31), certolizumab (OR, 2.73; 95% CI, 1.18 to 6.31), infliximab (OR, 2.09; 95% CI, 1.38 to 3.18), and tocilizumab (OR, 1.94; 95% CI, 1.22 to 3.09) were statistically significant, suggesting that patients on these drugs were more likely to withdraw from the trial due to adverse events than patients on placebo. Heterogeneity I^2 was found to be 31.3 percent, which suggests relatively low heterogeneity among this outcome in these studies. Visual examination of funnel plots did not show evidence of publication bias.

Overall tolerability: mixed treatment comparisons for overall withdrawals. Indirect comparisons were made using the studies described in Table 49 and shown in meta-analyses (Figures 4 to 6). Thirty-eight studies contributed data to the analysis of overall withdrawals. Results are presented for each possible drug-drug comparison (Figure 7). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer total withdrawals for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable withdrawal rate. Most comparisons suggest no difference in overall withdrawals. A few exceptions were found: certolizumab pegol had a more favorable overall withdrawal profiles than all other biologic DMARDs. Etanercept and rituximab also had fewer overall withdrawals in some comparisons. For etanercept, results were statistically significant for the comparison with adalimumab (OR, 0.51; 95% CI, 0.22 to 0.97), anakinra (OR, 0.32; 95% CI, 0.12 to 0.70), infliximab (OR, 0.38; 95% CI, 0.18 to 0.89), and tocilizumab (OR, 0.33; 95% CI, 0.14 to 0.89). For rituximab, results were statistically significant for only the comparisons with anakinra (OR, 0.33; 95% CI, 0.11 to 0.78), infliximab (OR, 0.45; 95% CI, 0.17 to 1.00), and tocilizumab (OR, 0.32; 95% CI, 0.13 to 0.99). These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals. Plus, evaluating overall withdrawals provides only a rough proxy for tolerability.

Overall tolerability: mixed treatment comparisons for withdrawals due to lack of efficacy. Thirty-one studies contributed data to the analysis of withdrawals due to lack of efficacy. Results are presented for each possible drug-drug comparison (Figure 8). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer withdrawals due to lack of efficacy for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable efficacy-related withdrawal rate. Most comparisons suggest no difference in withdrawals due to lack of efficacy. Similar to the analysis of overall withdrawals, certolizumab pegol had lower rates of withdrawals due to lack of efficacy than adalimumab (OR, 0.41; 95% CI, 0.18 to 0.76), anakinra (OR, 0.18; 95% CI, 0.06 to 0.39), and infliximab (OR, 0.33; 95% CI, 0.16 to 0.77). Withdrawals due to lack of efficacy were lower for abatacept (OR, 0.31; 95% CI, 0.13 to 0.93), etanercept (OR, 0.33; 95% CI, 0.11 to 0.74), rituximab (OR, 0.31; 95% CI, 0.08to 0.78), and tocilizumab (OR, 0.37; 95% CI, 0.11 to 0.93) than for anakinra. These results should be interpreted cautiously because of the relatively small

Figure 6. Meta-analysis of withdrawals due to adverse events in randomized controlled trials of biologic DMARDs

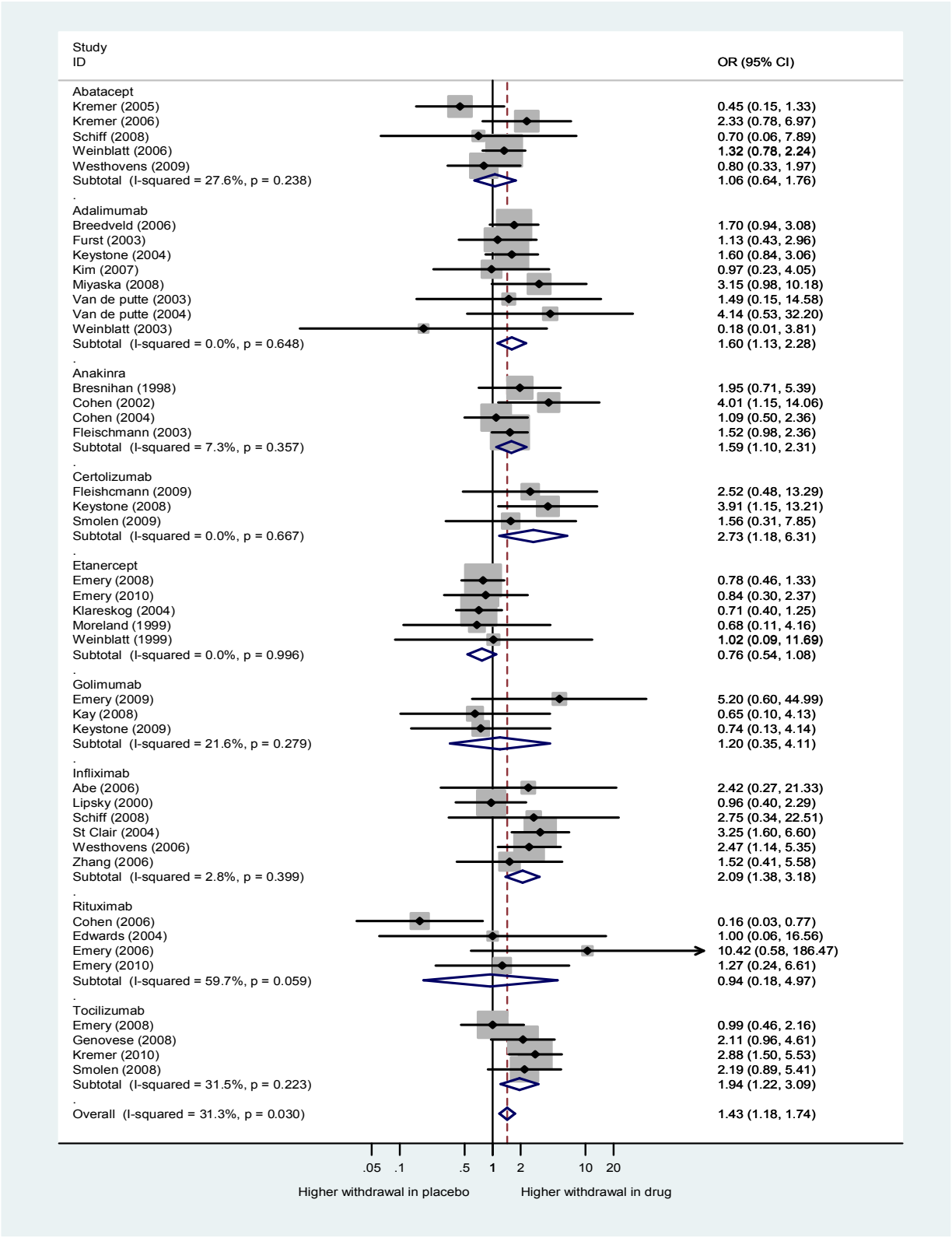


Figure 7. Mixed treatment comparisons for overall withdrawals in randomized controlled trials of biologic DMARDs

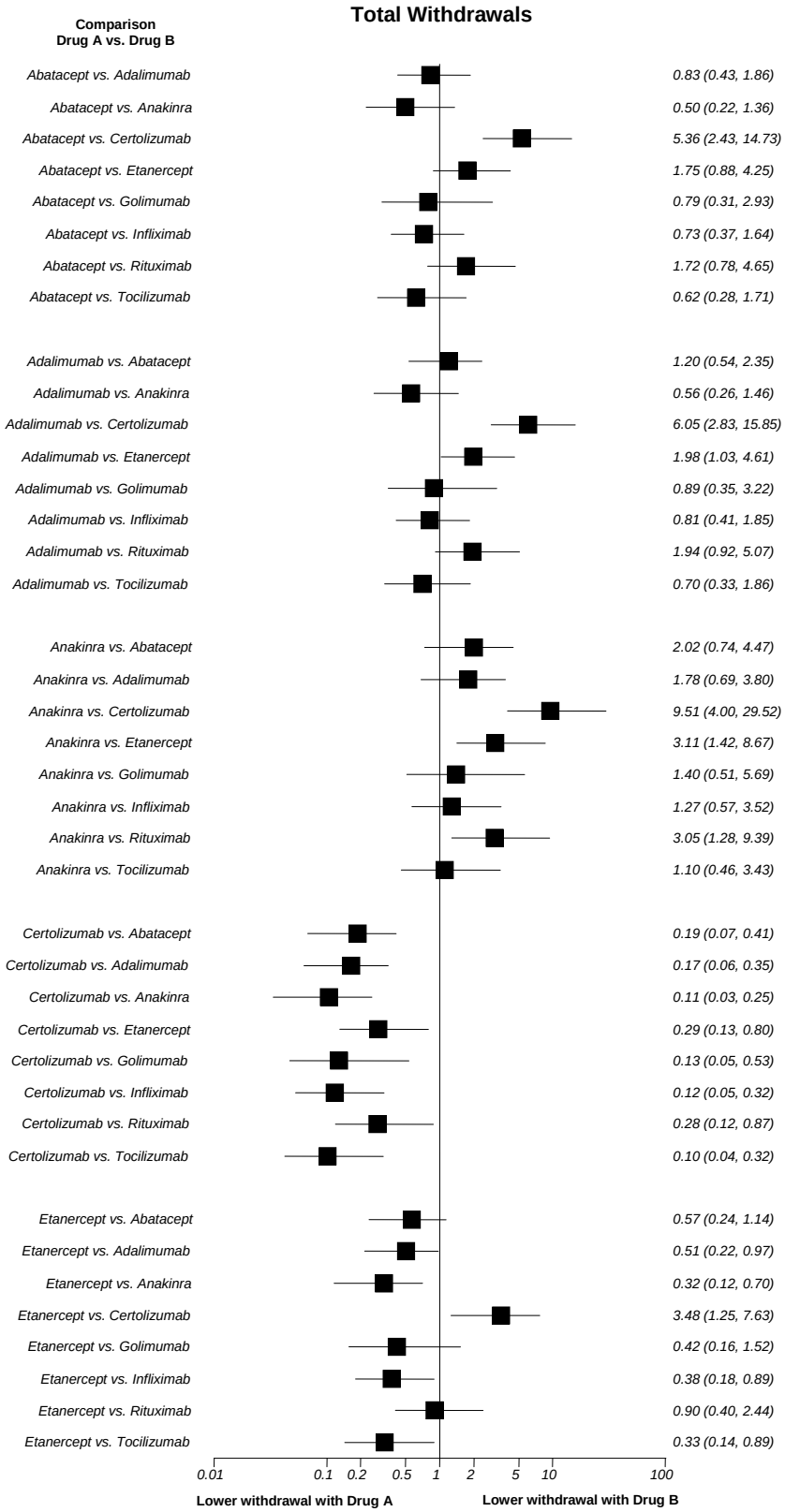


Figure 7. Mixed treatment comparisons for overall withdrawals in randomized controlled trials of biologic DMARDs (continued)

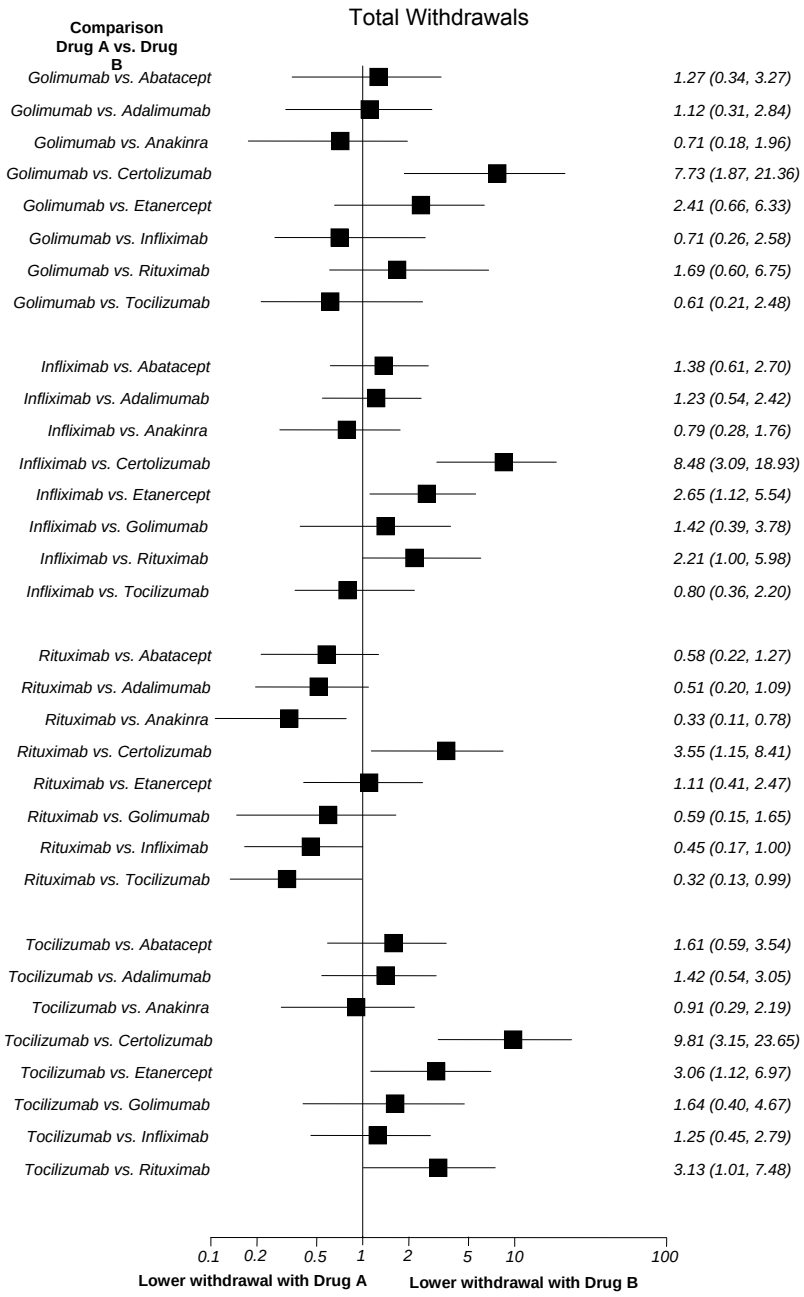


Figure 8. Mixed treatment comparisons for withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs

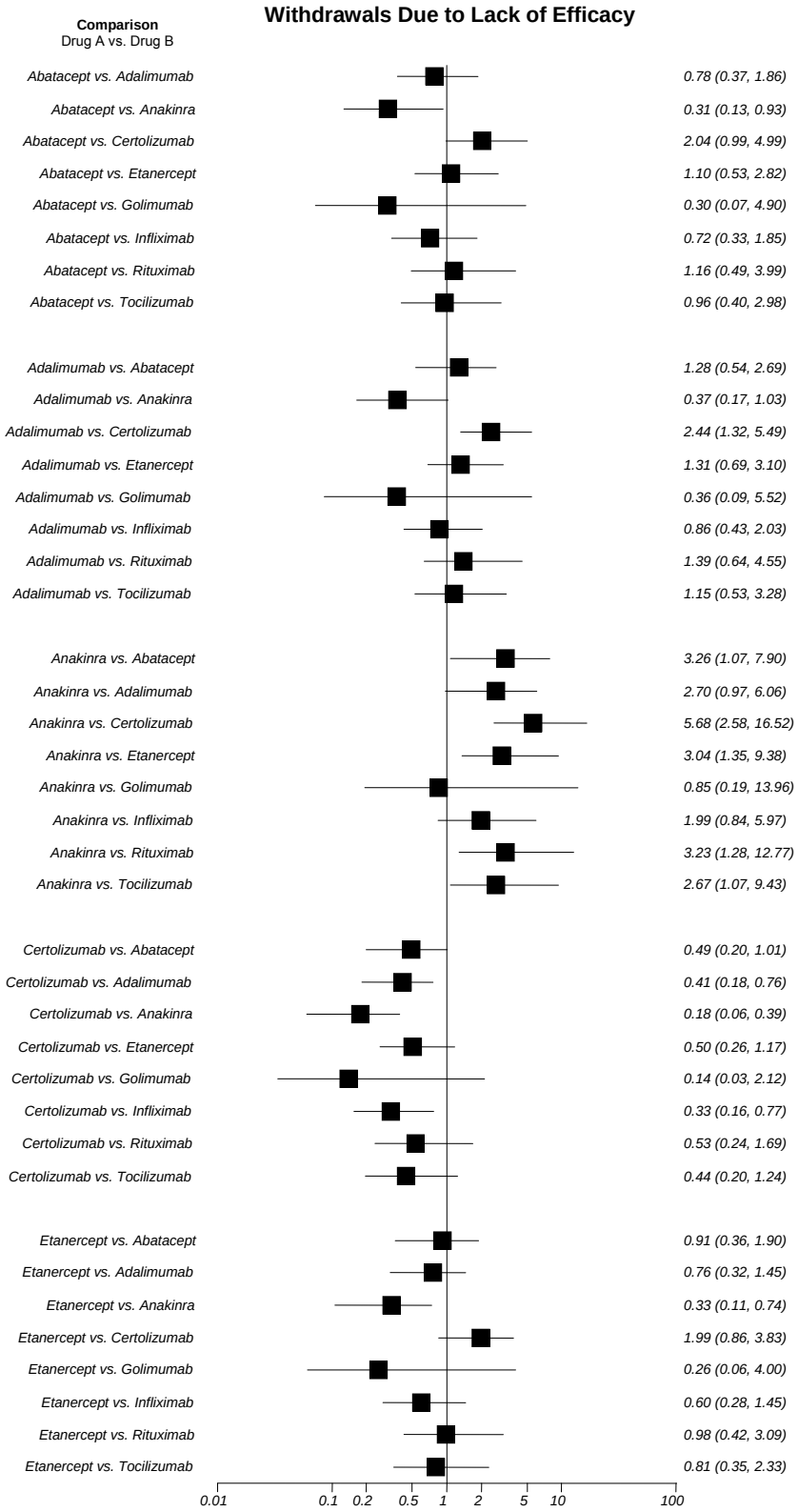
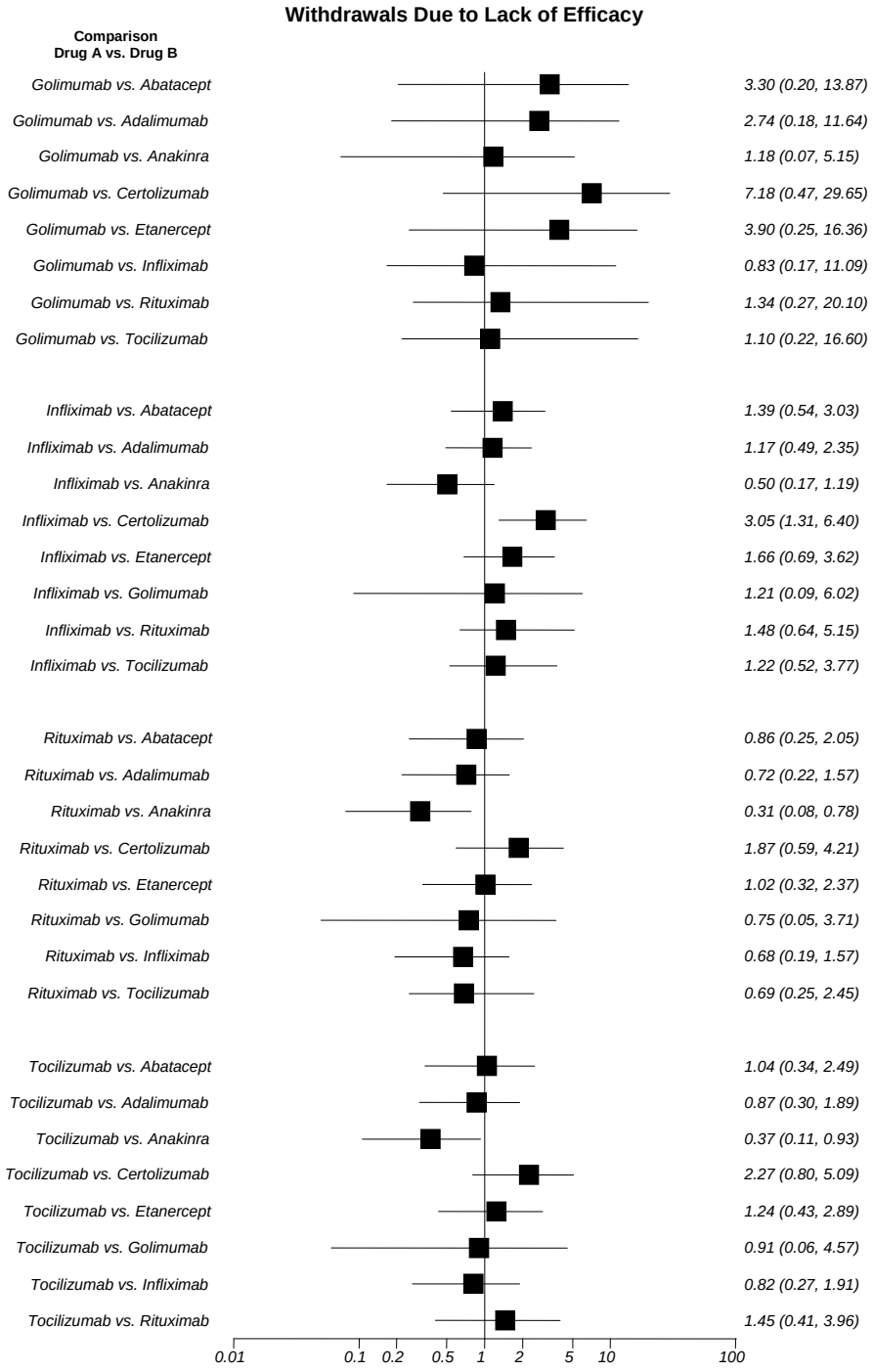


Figure 8. Mixed treatment comparisons for withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs (continued)



number of contributing studies and the corresponding wide confidence intervals. Plus, evaluation of withdrawals due to lack of efficacy is only a rough proxy for tolerability.

Overall tolerability: mixed treatment comparisons for withdrawals due to adverse events. Indirect comparisons were made using the studies described in Table 48 and shown in meta-analyses (Figure). Forty-one studies contributed data to the analysis of withdrawals due to adverse events. Results are presented for each possible drug-drug comparison (Figure 9). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer withdrawals due to adverse events for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable adverse-event-related withdrawal rate. Most comparisons suggest no difference in withdrawals due to adverse events, with a few exceptions. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than some other drugs. For certolizumab, the likelihood of withdrawal because of an adverse event was greater than for abatacept (OR, 3.28; 95% CI, 1.05 to 8.53), etanercept (OR, 3.48; 95% CI, 1.44 to 11.65) and rituximab (OR, 2.82; 95% CI, 1.01 to 13.26).

For infliximab, the likelihood of withdrawal because of an adverse event was greater than for abatacept (OR, 2.35; 95% CI, 1.20 to 4.22), etanercept (OR, 3.31; 95% CI, 1.62 to 6.07), and rituximab (OR, 2.40; 95% CI, 1.00 to 7.43). Withdrawals because of adverse events tended to be lower with abatacept and etanercept when comparing them with some other drugs. For abatacept, statistically significantly fewer withdrawals occurred due to adverse events when compared with certolizumab (OR, 0.30; 95% CI, 0.12 to 0.96), infliximab (OR, 0.43; 95% CI, 0.24 to 0.83), and tocilizumab (OR, 0.50; 95% CI, 0.27 to 1.00), and for etanercept, differences were statistically significant for comparisons with adalimumab (OR, 0.50; 95% CI, 0.25 to 0.91), anakinra (OR, 0.48; 95% CI, 0.23 to 0.85), certolizumab (OR, 0.29; 95% CI, 0.09 to 0.69), infliximab (OR, 0.30; 95% CI, 0.16 to 0.62), and tocilizumab (OR, 0.35; 95% CI, 0.20 to 0.73). All of these results should be interpreted cautiously because of the relatively small number of contributing studies and the very wide confidence intervals.

Biologic DMARDs—overall tolerability: studies on discontinuation rates not otherwise covered in quantitative analyses. Table 49 presents studies providing discontinuation data not otherwise covered by quantitative analyses. One good-quality RCT compared etanercept with the combination of etanercept and abatacapt.[80] This RCT was not included in our meta-analysis of withdrawal rates because it compared two biologic DMARDs with a single biologic DMARD. Withdrawals due to adverse events occurred more in the combination group (11.8 percent) than in the monotherapy etanercept group (2.8 percent).

Figure 9. Mixed treatment comparisons for withdrawals due to adverse events in randomized controlled trials of biologic DMARDs

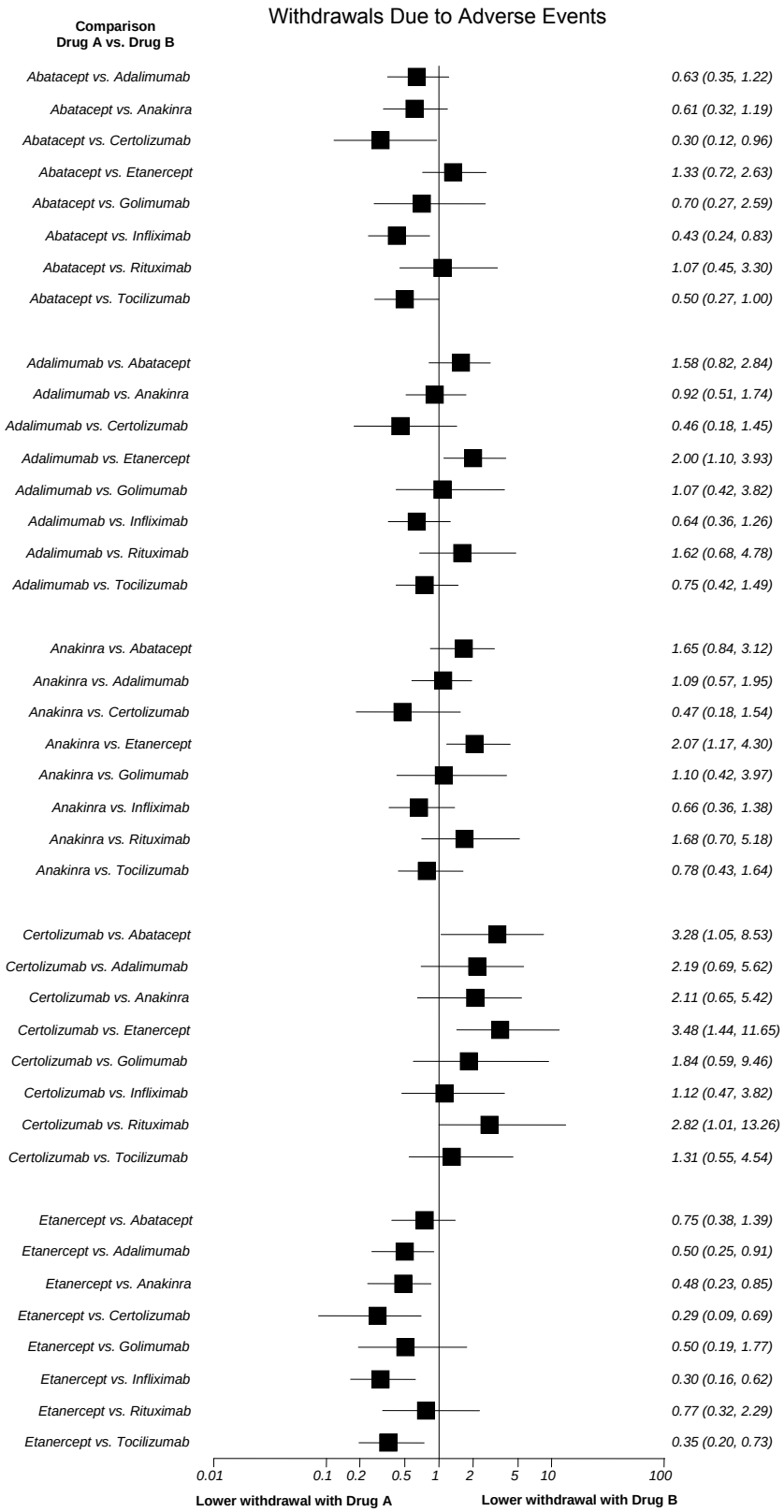


Figure 9. Mixed treatment comparisons for withdrawals due to adverse events in randomized controlled trials of biologic DMARDs (continued)

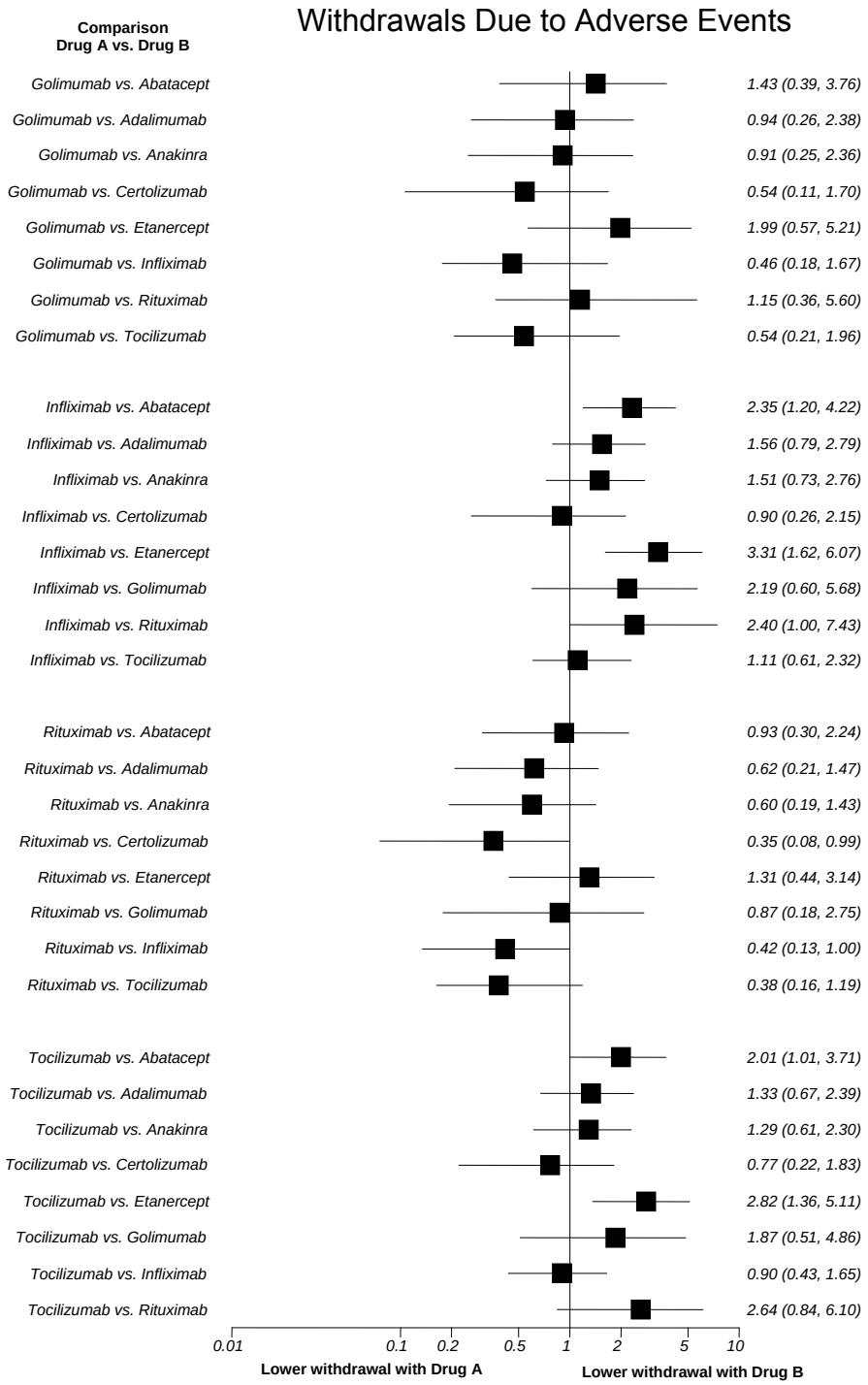


Table 49. Overall tolerability: discontinuation data not otherwise covered by quantitative analyses

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Alonoso-Ruiz et al. 2008[126]	Systematic review and meta-analysis 13 trials 7,087 patients At least 6 months	Pts with RA	ADA ETA, INF	Relative risk of withdrawal due to adverse event compared with control group: ADA (RR, 1.4; 95% CI, 1.0 to 2.0); ETA (RR, 0.7; 95% CI, 0.5 to 0.9); INF (RR, 2.0; 95% CI, 1.3 to 3.1)	Good
*Duclos et al., 2006[248]	Retrospective cohort 770 7 years	Pts with inflammatory rheumatism (mostly RA) that received an anti-TNF agent	ADA, ETA, INF	Trend towards better tolerability with ETA and ADA compared with INF (*P*=0.06)	Fair
Flendrie et al., 2003[247]	Retrospective cohort study 230 NR	Pts with RA initiating therapy with biologic DMARDs	ADA, ETA, INF	No significant differences in discontinuation rates among anti-TNF drugs	Fair
*Hetland et al., 2010[73] DANBIO	Prospective cohort 2,326 48 months	Pts with RA initiating therapy with biologic DMARDs	ADA, ETA, INF	Hazard ratio for drug withdrawal: INF vs. ETA HR 1.98 (95% CI, 1.63 to 2.40); INF vs. ADA 1.35 (95% CI, 1.15 to 1.58); ADA vs. ETA 1.47 (95% CI, 1.20 to 1.80)	Fair
*Hjardem et al., 2007[249]	Retrospective cohort 235 Varied	RA pts who had received 2+ biologics (INF, ETA, or ADA only)	ADA,ETA, INF	Similar reasons for switching treatments: Lack of efficacy; ADA 54%; ETA 44%; INF 45%. Adverse events: ADA 21%; ETA 22%; INF 34%	Fair
*Hyrich et al., 2007[250]	Prospective cohort 6,739 Minimum 6 months	Pts with RA in the British Society for Rheumatology Biologics Register	ADA, ETA, INF	Differences in reason for discontinuation (*P*=NR): Lack of efficacy; ADA 6.7%; ETA 4.8%; INF 10%. Adverse events: ADA 2.9%; ETA 2.6%; INF 8.4%	Fair
*Karanikolas et al., 2008[93]	Prospective cohort 128 48 weeks	Pts with RA with inadequate response to traditional DMARD	MTX+ ANK LEF+ANK	No statistically significant differences in number of withdrawals due to adverse events	Fair
Kristensen et al., 2006[251]	Prospective cohort 1,161 Up to 6 years	Pts with RA in southern Sweden	ETA, ETA+MTX, INF, INF+MTX, other DMARDs	Early discontinuation threefold higher for INF than for ETA (*P*<.001). Addition of MTX improved treatment continuation rates (*P*<0.01).	Fair
*Marchesoni et al., 2009[252] LOHREN	Prospective cohort 1,064 23.32 months	Pts with RA treated with at least one dose of an anti-TNF agent	ADA, ETA, INF	Risk of discontinuation due to adverse events higher for ADA than ETA	Fair

Table 49. Overall tolerability: discontinuation data not otherwise covered by quantitative analyses (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Mertens and Singh, 2009[134]	Meta-analysis 2,876 5 trials	Pts with RA included in placebo-controlled RCTs	ANK	No difference in total number of withdrawals, adverse events, or serious adverse events for ANK vs. placebo	Fair
*Singh et al., 2009[27, 180]	Review of Cochrane reviews and network meta-analysis	Pts with RA	ABA, ADA, ANK, ETA, INF, RTX	ADA, ANK, and INF more likely to have withdrawals due to adverse events vs. ETA: (OR, 1.89; 95% CI, 1.18 to 3.04; OR, 2.05; 95% CI, 1.27 to 3.29; OR, 2.70; 95% CI, 1.43 to 5.26, respectively)	Good
*Singh et al., 2010[177]	Systematic review and meta-analysis 8 studies 3,334 patients 8 to 52 weeks	Pts with RA	TCZ	Fewer overall trial withdrawals with TCZ than placebo; no statistically significant diffence in withdrawals due to adverse events	Fair
*Singh et al., 2010[210]	Systematic review and meta-analysis 4 studies 1,231 patients 20 to 52 weeks	Pts with RA	GOL+MTX, MTX	Fewer overall withdrawals for GOL+MTX than MTX alone	Good
*Weinblatt et al., 2007[80]	RCT 121 1 year (LTE: 2 years)	Pts with active RA	ETA, ABA+ETA	Discontinuation due to adverse events occurred more in ABA+ETA group (11.8%) vs. ETA group (2.8%).	Good
Zink et al., 2005[88]	Retrospective cohort study 1,523 1 year	Pts with RA who had a change in treatment regimen	ANK, ETA, INF, LEF	Significantly higher overall discontinuation rates for ANK than ETA and INF after 12 months; no differences in discontinuation rates due to adverse events	Good

* New study added since last review.
ABA = abatacept; ADA = adalimumab; AE = adverse event; ANK = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GOL = golimumab; INF = infliximab; LEF = leflunomide; LOHREN = Italian Lombardi Rheumatology Network; MTX = methotrexate; NR = not reported; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; TCZ = tocilizumab; TNF = tumor necrosis factor

Additional evidence on comparative discontinuation rates is provided by systematic reviews[27, 126, 134, 177, 180, 210] and observational studies.[73, 88, 93, 247-252] While some studies did not find clinically or statistically significant differences in drug discontinuation rates,[247, 249] others did. Consistent with our mixed treatment comparisons analysis, a good-rated meta-analysis found etanercept to have fewer withdrawals due to adverse events than adalimumab, anakinra, and infliximab.[27] A second good-rated meta-analysis found the highest rate of withdrawals due to adverse events for infliximab and the lowest rate for adalimumab.[126]

Observational evidence generally supports these findings.[73, 88, 248, 250-252] A Swedish population-based, prospective cohort study reported statistically significantly higher rates of

overall discontinuation (HR, 2.92; 95% CI, 2.32 to 3.69; $P<0.001$) for patients on infliximab than for those on etanercept.[251] These differences were not statistically significant for discontinuations due to adverse events or due to lack of efficacy. A German retrospective, population-based cohort study, based on the RABBIT database, reported that overall discontinuation rates among biologics were significantly higher for anakinra-treated patients (41 percent) than for patients on etanercept (31 percent; $P=0.004$ for anakinra vs. etanercept) or those on infliximab (35 percent; $P=0.03$ for anakinra vs. infliximab).[88] Treatment discontinuations because of adverse events, after 12 months of treatment, were lowest for etanercept (13 percent for etanercept, 16 percent for anakinra, and 19 percent for infliximab; P=NR). This finding is also consistent with a retrospective cohort study of patients treated with adalimumab, etanercept, and infliximab, where there was a trend towards better tolerability with adalimumab and etanercept compared with infliximab ($P=0.06$).[248] Another prospective cohort study reported higher rates of switching treatments with infliximab compared with adalimumab and etanercept (P=NR).[250] In the Danish DANBIO registry, the hazard ratios for drug withdrawal were 1.98 for infliximab versus etanercept (95% CI, 1.63 to 2.40), 1.35 for infliximab versus adalimumab (95% CI, 1.15 to 1.58), and 1.47 for adalimumab versus etanercept (95% CI, 1.20 to 1.80).[73] In the Italian Lombardi Rheumatology Network (LOHREN) registry, the risk of discontinuation due to adverse events was higher for adalimumab than for etanercept (AHR 2.09; 95% CI, 1.29 to 3.38).[252]

Biologic DMARDs—overall tolerability: adverse event rates and serious adverse events. Table 50 presents the comparative harms for biologic DMARDs. Only two studies compared adverse event rates and serious adverse events with biologic DMARDs; one RCT[66] and one retrospective cohort study.[253] Both studies found more serious adverse events among patients treated with infliximab. The RCT included 431 patients with RA who were receiving MTX and were naïve to biologic DMARDs. Patients were randomized to abatacept plus MTX, infliximab plus MTX, or placebo plus MTX. At 6 months, 5.1 percent of the abatacept group reported serious adverse events, but 11.8 percent and 11.5 percent of the placebo and infliximab groups, respectively, reported serious adverse events (P=NR). After 1 year, 18.2 percent of infliximab-treated and 9.6 percent of abatacept-treated reported a serious adverse event (P=NR; placebo arm stopped at 6 months). Acute infusional events were lower with abatacept (7.1 percent) than with infliximab (24.8 percent). The retrospective cohort study followed 2,364 patients with RA newly treated with an anti-TNF agent in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry. There was an increased risk of adverse events in the infliximab compared with adalimumab and etanercept groups (HR, 1.4; 99% CI, 1.0-1.96). More specifically, there was an increased risk of infusion or systemic allergic reactions with infliximab compared with adalimumab and etanercept ($P=0.018$).

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
		Biologic DMARDs Overall Tolerability			
*Alonoso-Ruiz et al., 2008[126]	Systematic review and meta-analysis 13 trials 7,087 patients at least 6 months	Pts with RA	ADA ETA, INF	Relative risk of serious adverse events compared with control group: ADA (RR, 1.0; 95% CI, 0.7 to .4); ETA (RR, 1.0; 95% CI, 0.5 to 1.6), INF (RR, 1.4; 95% CI, 1.0 to 2.0)	Good
Bathon et al., 2000[77, 188, 189] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive	ETA, MTX	Significantly more patients on MTX than on ETA had nausea (29% vs. 15%; *P*<0.05) or mouth ulcers (14% vs. 5%; *P*<0.05)	Fair
Breedveld et al., 2006[76] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive	ADA, MTX, ADA+MTX	No statistically significant differences in adverse events	Fair
*Burmester et al., 2007[257] ReACT trial	Prospective cohort 6,610 12 weeks	Pts with RA with treatment failure to at least one traditional DMARD	ADA, ADA+DMARDs	Serious adverse events occurred in 7.3% of pts treated with ADA vs. 5.3% treated with ADA+DMARDs	Fair
*Combe et al., 2009[145]	RCT 260 2 years	Pts with active RA despite treatment with sulfasalazine	ETA, SSZ, ETA+SSZ	Noninfectious serious adverse events were significantly greater in patients receiving ETA (20.8% for the combination and 20.4% for ETA alone) compared with 4% for patients receiving SSZ (*P*<0.01)	Fair
Edwards et al., 2004[84]	RCT 161 24 weeks	Active RA despite MTX treatment	RTX, MTX, RTX+MTX, RTX+CYP	No significant differences in adverse events	Fair
*Emery et al., 2008[175] RADIATE study	RCT 499 24 weeks	Pts with active RA resistant to 1 or more TNF-alpha antagonist agents	MTX, TCZ +MTX	The overall occurrence of adverse events was similar among groups.	Fair
*Emery et al., 2008[90] COMET trial	RCT 542 52 weeks	Early, moderate to severe RA; MTX-naive	MTX, ETA+MTX	Serious adverse events were similar among groups	Fair

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Emery et al., 2009[92]	RCT 637 24 weeks	Pts with RA; MTX-naive	MTX, GOL, GOL+ MTX	More adverse events occurred in the GOL+MTX and MTX monotherapy group compared with GOL monotherapy (*P*=NR)	Fair
Feltelius et al., 2005[260]	Case series 1,073 2 years	Pts with RA initiating ETA therapy	ETA	Incidence of serious adverse events remained constant over time	Fair
*Fernandez-Nebro et al., 2007[70]	Prospective cohort 161 6 years	RA pts with no response to DMARDs, including MTX	ADA, ETA, INF	No difference in adverse events among groups	Fair
*Fleischmann et al., 2009[165] FAST4WARD	RCT 220 24 weeks	Pts with RA treatment resistant to at least one DMARD	CTZ	Overall, adverse events occurred in 75.4% of pts treated with CTZ and 57.8% of placebo pts	Fair
Fleischmann et al., 2003[259]	RCT 1,414 6 months	Pts with active RA despite MTX treatment	ANK No	statistically significant differences in adverse events (except infusion reactions)	Fair
Fleischmann et al., 2006[319]	Open-label extension of RCT 1,346 Up to 3 years	Pts with active RA despite MTX treatment	ANK	Incidence of serious adverse events remained constant over time	Fair
Furst et al., 2003[121] STAR study	RCT 636 6 months	Pts with active RA despite MTX treatment	ADA No	statistically significant differences in adverse events	Fair
Geborek et al., 2002[67]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs	ETA, LEF, INF	No statistically significant differences in adverse events	Fair
Genovese et al., 2002[188]	Open-label extension of RCT 632 2 years	Pts with early, aggressive RA; MTX-naive	ETA	Incidence of serious adverse events remained constant over time	Fair
Genovese et al., 2004[79]	RCT 242 24 weeks	Inadequate control of disease with MTX	ETA, ETA+AKA	Significantly higher rates of serious adverse events in combination group	Fair

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Genovese et al., 2005[189]	Uncontrolled extension of RCT 369 5 years	Pts with early, aggressive RA; MTX-naive	ETA	Rates of serious adverse events did not increase with long-term exposure	Fair
*Karanikolas et al., 2008[93]	Prospective cohort 128 48 weeks	Pts with RA with inadequate response to traditional DMARD	MTX+ANK, LEF+ANK	No statistically significant differences in adverse events	Fair
*Kay et al., 2008[166]	RCT 172 52 weeks	Pts with active RA despite treatment with MTX	MTX, GOL+MTX,	Serious adverse events occurred in 9% of pts treated with GOL vs. 6% in pts treated with MTX alone	Fair
*Keystone et al., 2004[120]	RCT 619 52 weeks	Pts with active RA on MTX therapy	MTX, ADA+MTX	Serious adverse events occurred more frequently in ADA pts (3.8%) vs. MTX pts (0.5%; *P*≤0.02*)*	Fair
*Kim et al., 2007[127]	RCT 128 24 weeks	Korean pts with RA with inadequate response to MTX	ADA+MTX, MTX	No statistically significant differences in adverse events	Fair
Klareskog et al., 2004[86, 136, 138] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 2 DMARDs	ETA, MTX, ETA+MTX	No statistically significant differences in adverse events	Good
*Kremer et al., 2011[178]	RCT 1,196 12 months	Pts with RA with inadequate response to MTX	TCZ+MTX, MTX	Rate of serious adverse events were not statistically significantly different between groups	Fair
Langer et al., 2003[320]	Postmarketing surveillance 454 6 months	Pts with RA, initiating AKA treatment	AKA	Rate of adverse events was generally similar to those reported in efficacy trials	Fair
*Leombruno et al., 2009[255]	Meta-analysis 18 trials 8,808 patients Average 0.8 years	RA pts on anti-TNF therapy	ADA, ETA, INF	Anti-TNF treatment did not increase death (OR, 1.39; 95% CI, 0.74 to 2.62) or serious adverse events (OR, 1.11; 95% CI, 0.94 to 1.32)	Fair

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Maini et al., 2004[149]	Open-label extension of RCT 259 2 years	Pts with active RA despite MTX treatment	INF	Incidence of serious adverse events remained constant over time	Fair
*Martin Du Pan et al., 2009[253]	Retrospective cohort 2,364 9 years	Pts with RA in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry treated with an anti-TNF agent	ADA, ETA, INF	Increased overall risk for adverse events in INF vs. ETA and ADA (HR, 1.4; 99% CI,1.00-1.96)	Fair
Moreland et al., 2006[261]	Open-label extension of clinical trials 714	Pts treated with ETA	ETA	Incidence of serious adverse events remained constant over time	Fair
*Nishimoto et al., 2009[173] SATORI	RCT 127 24 weeks	Pts with active RA despite MTX treatment	TCZ, MTX	Adverse events occurred in 91.8% of pts treated with TCZ vs. 71.9% of those treated with MTX	Fair
Nuki et al., 2002[129]	Uncontrolled extension of RCT 309 19 months	Pts with active RA despite MTX treatment	AKA	Incidence of serious adverse events remained constant over time	Fair
O'Dell et al., 2006[231]	Nonrandomized, open-label trial 119	Pts with active RA despite treatment with SSZ, HCQ, or gold	ETA+SSZ ETA+HCQ ETA+gold	No differences in adverse event rates among 3 treatment groups	Fair
*Russell et al., 2007[116, 254] AIM	RCT 652 12 months	Pts with RA despite treatment with MTX	ABA, ABA+MTX	Incidence of serious adverse events similar between groups	Good
*Schiff et al., 2008[66]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA +MTX, INF +MTX, MTX	The occurrence of serious adverse events was lower in those treated with ABA (9.6%) vs. INF (18.2%).	Fair
Schiff et al., 2006[298]	Retrospective data analysis of clinical trials; postmarketing surveillance 10,050 12,506 pt years	Pts treated with ADA	ADA	Incidence of serious adverse events remained constant over time	Fair

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Singh et al., 2010[177]	Systematic review and meta-analysis 8 studies 3,334 patients 8 to 52 weeks	Pts with RA	TCZ	Occurrence of adverse event in TCZ group compared with placebo (74% vs. 65%); RR, 1.17; 95% CI, 0.83 to 1.64	Fair
*Singh et al., 2010[210]	Systematic review and meta-analysis 4 studies 1,231 patients 20 to 52 weeks	Pts with RA	GOL+MTX, MTX	No difference in occurrence of adverse events in GOL+MTX vs. MTX (RR, 1.1; 95% CI, 0.9 to 1.2; *P*=0.44). No differences in GOL vs. placebo for serious adverse events	Good
*Smolen et al., 2008[164] OPTION study	RCT 623 32 weeks	Pts with RA that failed treatment with MTX	MTX, TCZ+MTX	Adverse events occurred more frequently in pts treated with TCZ (71%) vs. MTX monotherapy (63%)	Fair
*Smolen et al., 2009[167] RAPID 2 study	RCT 619 24 weeks	Pts with RA with prior MTX use for ≥6 months	MTX, CTZ+MTX	Serious adverse events occurred more frequently in CTZ pts vs. pts treated with MTX monotherapy	Fair
*Smolen et al., 2009[170]	RCT 461 24 weeks	Pts with RA treated with at least one dose of an TNF inhibitor	GOL	No statistically significant differences in adverse events	Fair
Van Riel et al., 2006[87]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX	ETA, ETA+MTX	No statistically significant differences in adverse events	Fair
Weinblatt et al., 2006[258] ASSURE study	RCT 1,456 1 year	Pts with active RA despite background biologic or synthetic DMARD treatment	ABA	Higher incidence of serious adverse events in pts on ABA and a biologic background DMARD	Fair
Weinblatt et al., 2006[124]	Uncontrolled extension of RCT 162 3.4 years	Pts with active RA despite MTX treatment	ADA	Incidence of serious adverse events remained constant over time	Fair
Westhovens et al., 2006[155] START study	RCT 1,084 22 weeks	Pts with active RA despite MTX treatment	INF+MTX, MTX	No statistically significant differences in adverse events, except infection (higher in 10 mg/kg)	Good
*Westhovens et al., 2009[89]	RCT 509 1 year	RA pts naïve to MTX	ABA+ MTX, MTX	No statistically significant differences in adverse events	Fair

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Wiens et al., 2009[256]	Meta-analysis 2,385 8 weeks to 3 years	Pts with RA with or without concomitant MTX	ETA, MTX	No statistically significant differences in withdrawals due to adverse events, serious adverse events, serious infections, malignancies, or deaths.	Fair
*Wiens et al., 2010[183]	Meta-analysis 21 studies 6,503 patients 8 weeks to 3 years	Pts with RA with or without concomitant MTX	ADA, ETA, INF	Similar incidence of serious adverse events for ADA, ETA, and INF compared with placebo	Fair
*Zhang et al., 2006[156]	RCT 173 18 weeks	Pts with active RA despite treatment with MTX	MTX, INF+MTX	Rate of adverse events similar between groups	Fair

* New study added since last review.
ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CTZ = certolizumab; CYP = cyclophosphamide; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; INF = infliximab; IR = incidence rate; IRR = incidence rate ratio; LEF = leflunomide; MTX = methotrexate; NA = not applicable; NR = not reported; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = rate ratio; RTX = rituximab; SSZ = sulfasalazine; TCZ = tocilizumab; TNF = tumor necrosis factor

One good-rated[126] and one fair-rated[183] systematic review and meta-analysis provided indirect evidence regarding comparative differences in adverse events with adalimumab, etanercept, and infliximab. In the good-rated meta-analysis, the relative risk of serious adverse events for biologic DMARDs compared with control was statistically significant only for infliximab (RR, 1.4; 95% CI, 1.0 to 2.0; P=0.048).[126] The infliximab-treated patients in this analysis were more likely than control group patients to withdraw from studies because of adverse events, had more severe adverse events, infection, and infusion reactions. In the fair-rated meta-analyis of adalimumab, etanercept, and infliximab compared with placebo, no statistically significant differences were noted in serious adverse events, serious infections, malignancy, or death (P>0.05 for all comparisons).[183] Based on unadjusted comparison of risk ratios from meta-analyses, infliximab had the highest rate of withdrawal due to adverse events (RR, 2.05; 95% CI, 1.33 to 3.16).

Indirect evidence from additional efficacy trials, cohort studies, and meta-analyses suggests that the overall tolerability profiles are similar among biologic and oral DMARDs, or combinations of biologic and oral DMARDs.[67, 70, 76, 84, 86, 87, 89, 90, 116, 121, 127, 136, 138, 156, 170, 175, 177, 178, 210, 254-256] However, several studies suggested that adverse events were more common with biologic DMARDs, given alone or in combination with an oral DMARD.[120, 145, 164-167, 173] One prospective cohort study found a slightly lower rate of serious adverse events among patients who had an oral DMARD added to adalimumab, compared with patients who only received adalimumab (5.3 percent vs. 7.3 percent, respectively; P=NR).[257] In one RCT of MTX-naïve patients that compared golimumab monotherapy, MTX monotherapy, and golimumab plus MTX, serious adverse events were least common among the golimumab monotherapy group (3.2 percent vs. 6.9 percent vs. 6.3 percent, respectively; P=NR).[92]

Four RCTs were designed to assess adverse events as primary outcomes.[121, 155, 258, 259] Overall, adverse event rates were similar for abatacept,[258] adalimumab,[121] anakinra,[259] or infliximab[155] and placebo. Other efficacy trials suggested that overall adverse events are higher with biologic DMARDs than with placebo.

In placebo-controlled efficacy trials of biologic DMARDs, injection site reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were commonly reported adverse events.[74] The combination of two biologic DMARDs consistently had more adverse events than monotherapy. A 24-week RCT, described in more detail for KQ 1, assessed a combination treatment of etanercept (25 mg or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy.[79] The frequency of serious adverse events was substantially higher in the combination groups than the etanercept-only group (14.8 percent for 50 mg etanercept plus anakinra; 4.9 percent for 25 mg etanercept plus anakinra; 2.5 percent for etanercept only; *P*=NR). Furthermore, a study determining the efficacy of abatacept combined with different background treatments found substantially higher rates of serious adverse events in patients on abatacept combined with a biologic background treatment (22.3 percent) than in those not on a combination of two biologic DMARDs (12.5 percent).[258]

One nonrandomized open-label trial determined the comparative harms among combinations of biologic DMARDs and oral DMARDs other than MTX.[231] No differences in adverse events could be detected between a combination of etanercept and either sulfasalazine or hydroxychloroquine. Similar evidence of similarities in adverse events among background oral DMARDs comes from an RCT comparing rituximab, MTX, rituximab plus MTX, and rituximab plus cyclophosphamide,[84] and a prospective cohort study comparing anakinra plus MTX with anakinra plus leflunomide.[93] Both studies reported no significant differences in adverse events among these combinations of biologic and oral DMARDs.

The ERA study,[77] described in more detail in KQ 1, had an open-label extension of up to 2 years,[188] and an uncontrolled extension with etanercept (25 mg twice weekly) of up to 5 years.[189] The rates of adverse events for etanercept did not rise during long-term treatment compared with rates reported from the short-term RCT. These results are consistent with findings from long-term extension studies of efficacy RCTs on adalimumab,[124] anakinra,[129, 319] and infliximab.[149, 261] Likewise, safety analyses of postmarketing surveillance data showed that the incidence of adverse events did not rise over time in patients treated with adalimumab[298] and etanercept.[260]

Biologic DMARDs—specific adverse events. Biologic DMARDs can produce several serious adverse events (Table 51). Studies of adverse events with biologic DMARDs are summarized in Tables 51 to 56.

Cardiovascular and cerebrovascular events. No direct evidence compared the risk of cardiovascular or cerebrovascular events for one biologic DMARD with another. Eleven observational studies provide evidence for the risk of cardiovascular and cerebrovascular events (Table 51).[214, 216, 234, 262-267, 321] These studies use a variety of comparator groups, including oral DMARDs, "conventional" DMARDs, and placebo. In some cases, the comparison group is unclear. Whenever possible, we specify the comparator in the tables and summary text.

One additional RCT conducted in a population with CHF[322] is discussed because it provides general evidence for risk of using infliximab in patients with existing heart failure (even though these patients did not have RA).

Table 51. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Curtis et al., 2007[263]	Retrospective cohort study 2,121 5 years	Pts with RA (Also Crohn's disease but excluded here)	ETA, INF	Cumulative incidence of heart failure among pts treated with ETA or INF vs. those not: 4.4 cases per 1,000 persons and 1.0 case per 1,000 persons in the unexposed group (RR, 4.3; *P*=NS).	Fair
*Dixon et al., 2007[267] BSRBR	Prospective cohort 10,755 1.66 years median followup	Pts with RA in the British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF, oral DMARDs	IRR, of MI among anti-TNF users compared with oral DMARDs:1.44 (95% CI, 0.56 to 3.67)	Good
Jacobsson et al., 2005[266]	Retrospective cohort study 983 NR	Pts with RA in daily clinical care in Sweden	ETA, INF	Pts on anti-TNF treatment had a lower rate of cardiovascular events than pts on traditional RA therapy	Fair
*Listing et al., 2008[264]	Prospective cohort 4,248 5 years	Pts with RA enrolled in the RABBIT German biologics register	ADA, ETA, INF, oral DMARDs	HR for incident HF among those using anti-TNFs vs. conventional DMARDs: 1.66, (95% CI, 0.67 to 4.10;*P*=0.28); HR for worsening HF among prevalent cases: 1.18, (95% CI, 0.30 to 4.73;*P*=0.81)	Good
*Nadareishvili et al., 2008[214]	Nested case-control 269 cases among 7045 patients 8 years	RA pts in National Data Bank for Rheumatic Diseases	ADA, ETA, INF	Association of treatment with ischemic stroke: Anti-TNF: OR,0.79; 95% CI, 0.34 to 1.82; *P*=0.584)	Fair
*Naranjo et al., 2008[215]	Cross-sectional 4,363 Clinician and patient recall	Sample of RA pts across 15 countries	TNF-alpha antagonists (not specified)	Anti-TNF agents associated with reduced risk for CV morbidity (HR, 0.64; 95% CI, 0.49 to 0.83).	Fair
Kwon et al., 2003[321]	Database analysis AERS 47 cases of CHF NA, AERS data	Pts on ETA or INF therapy	ETA, INF	Most pts with CHF did not have preexisting conditions	Fair
*Setoguchi et al., 2008[265]	Retrospective cohort 5,593 10 years	Medicare pts with RA from 2 states	ADA, ETA, INF, MTX	Effect of anti-TNFs compared with MTX on heart failure and/or death; HR,1.70; 95% CI, 1.07 to 2.69	Good

Table 51. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Solomon et al., 2006[216]	Case-control study 3,501 24 months	Pennsylvania Medicare enrollees with RA	Biologic DMARDs	No statistically significant association between use of biologic DMARDs and cardiovascular events	Fair
*Suissa et al, 2006[234]	Prospective cohort 107,908 14 months	RA pts in U.S. PharMetrics data	ADA,ETA, INF	Biologic DMARD use slightly associated with acute MI (RR,1.30; 95% CI, 0.92 to 1.83)	Fair
Wolfe et al., 2004[262]	Retrospective cohort study 13,171 2 years	Pts with RA in daily clinical care in U.S.	ADA, ETA, INF	Pts on anti-TNF treatment had a lower rate of CHF than pts on traditional RA therapy	Fair

* New study added since last review.
ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CHF = congestive heart failure; CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HF = heart failure; HR = hazard ratio; INF = infliximab; IR = incidence rate; IRR = incidence rate ratio; LEF = leflunomide; MI = myocardial infarction; MTX = methotrexate; NA = not applicable; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = rate ratio; TCZ = tocilizumab; TNF = tumor necrosis factor; vs. = versus

The evidence on the risk of congestive heart failure (CHF) with anti-TNF therapy is mixed. One observational study reported lower rates of CHF[262] for RA patients on anti-TNF therapy than for those on conventional RA therapies. This large retrospective cohort study (N=13,171) reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 to -0.5; *P*=NR) for patients treated with anti-TNF therapy compared with those not treated with anti-TNF medications over a 2-year period.[262] This study contrasts with three other cohort studies that found an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with no treatment or oral DMARD.[263-265] While the increased risk was not statistically significant in two of these studies,[263, 264] one good-rated retrospective cohort study of 5,593 Medicare patients with RA from two U.S. states reported statistically significant increases in the risk of heart failure and death (HR, 1.70; 95% CI, 1.07 to 2.69).[265]

An analysis of the FDA AERS data reported that half of the patients who developed new onset CHF under etanercept or infliximab treatment did not have any identifiable risk factors.[321] Indirect evidence comes from three trials, two on etanercept[323] and one on infliximab,[322] that evaluated the efficacy of these drugs for the treatment of CHF. Study populations did not have any rheumatoid illnesses. One of the two etanercept trials was terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.[322] The package insert of infliximab issues a contraindication regarding use in patients with CHF; the package inserts of etanercept and adalimumab emphasize precaution.

Three observational studies assessed the risk of cardiovascular events (broadly defined).[215, 216, 266] One case-control study of Medicare patients with RA found no statistically significant association between use of biologic DMARDs and cardiovascular events,[216] while two studies

reported a decreased risk of cardiovascular events with biologic DMARDs.[215, 266] A good-quality Swedish retrospective cohort study (N=983), using data from population-based databases, reported a statistically significantly lower risk of cardiovascular events in patients treated with anti-TNF medications than in those on conventional therapy (age-sex adjusted rate ratio: 0.46/1,000 person-years; 95% CI, 0.25 to 0.85; P=0.013).[266] A cross-sectional analysis of patients from 15 countries participating in the QUEST-RA study reported that patients exposed to biologic DMARDs had a reduced risk of cardiovascular morbidity (HR, 0.42; 95% CI, 0.21 to 0.81; P<0.05).[215]

One nested case-control study assessed the risk of stroke with adalimumab, etanercept, and infliximab,[214] and two cohort studies assessed the risk of MI with these same biologic DMARDs.[234, 267] The study assessing stroke was conducted in the National Data Bank for Rheumatic Diseases, finding a slight decrease in the risk of stroke with adalimumab, etanercept, and infliximab (OR, 0.79; 95% CI, 0.34 to 1.82; P=NS).[214] The two studies assessing risk of MI also found no statistically significant differences in the risk of MI, although results trended towards an increased risk of MI for these biologic DMARDs. In a good-rated analysis of 10,755 patients from the British Society for Rheumatology Biologics Register, the incidence rate ratio was 1.44 (95% CI, 0.56 to 3.67) for biologic DMARDs compared with oral DMARDs. In a larger fair-rated analysis of 107,908 patients from a U.S. claims database, biologic DMARDs were associated with a similar nonstatistically significant increase in the risk of MI (RR, 1.30; 95% CI, 0.92 to 1.83).[234]

Infections. Because of the immunosuppressive nature of biologic DMARDs, serious infections including TB, pneumonia, osteomyelitis, progressive multifocal leucoencephalopathy (PML), and sepsis are of special concern. The FDA has issued black box warnings about an increased risk of infections for adalimumab and infliximab. The package inserts of anakinra and etanercept also contain bold letter warnings. Recently, the FDA issued an alert for health care professionals highlighting the death of two patients from PML who had been treated with rituximab for systemic lupus erythematosus.[324] The available head-to-head evidence is insufficient to draw firm conclusions about the comparative risk of biologic DMARDs.

The best comparative evidence stems from an RCT[66] and two prospective cohort studies.[268, 269] The trial randomized 431 patients with RA to MTX, abatacept plus MTX, or infliximab plus MTX. Serious infections were reported more often in the infliximab group than the abatacept group (P=NR).[66] One cohort study enrolled 8,973 patients with severe RA from the British Society for Rheumatology Biologics Register (BSRBR). Patients were treated with adalimumab (n=1,190), etanercept (n=3,596), infliximab (n=2,878), or oral DMARDs (n=1,354). The overall followup included 11,220 person-years. Results indicated no differences in risks among anti-TNF drugs. Compared with oral DMARDs, anti-TNF drugs did not lead to a higher overall risk for serious infections (IRR, 1.03; 95% CI, 0.68 to 1.57). The frequency of serious skin infections, however, was fourfold higher in patients treated with anti-TNF drugs than with oral DMARDs (IRR, 4.28; 95% CI, 1.06 to 17.17). A second cohort study conducted in BSRBR followed 15,396 patients with RA who were taking adalimumab, etanercept, or infliximab.[269] As a class, these anti-TNF drugs increased risk of serious infections (HR, 1.2; 95% CI, 1.1 to 1.5). No statistically significant difference in the incidence rate was observed comparing across the individual drugs.

Although the statistical analysis for the prospective cohort studies controlled for multiple confounding factors, residual confounding in such a study design is likely. Results, therefore,

must be interpreted cautiously. Event rates of serious infections in efficacy trials comparing anti-TNF drugs with oral DMARDs were generally too low to draw meaningful conclusions.

The following paragraphs summarize the evidence on the general risk of biologic DMARDs for serious infections (i.e., the risk of biologic DMARDs compared with that of placebo treatment). Table 52 presents studies reporting on infections in those patients treated with biologic DMARDs.

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Alonoso-Ruiz et al. 2008[126]	Meta-analysis 13 trials 7,087 patients St least 6 months	Pts with RA	ADA ETA, INF	Relative risk of infections compared with control group: ADA (RR, 1.1; 95% CI, 0.9 to 1,2); ETA (RR, 1.0; 95% CI, 0.9 to 1.0); INF (RR, 1.2; 95% CI, 1.1 to 1.3)	Good
Askling et al., 2005[281]	Retrospective cohort study 62,321 467,770 person-years	Pts with RA in daily clinical care in Sweden	ETA, INF	Fourfold increase of risk for TB for ETA and INF compared with conventional DMARDs	Good
Bergstrom et al., 2004[325]	Retrospective cohort study 985 3 years	Pts with inflammatory arthritis in daily clinical care, U.S.	ETA, INF	Pts treated with INF or ETA are more likely to develop symptomatic coccidiomycosis than pts on synthetic DMARDs	Fair
*Bernatsky et al., 2007[218]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Anti-TNFs (not specified), oral DMARDs, corticosteroids	No statistical association between anti-TNF use and risk for all infections requiring hospitalization (RR, 1.9; 95% CI, 0.7 to 5.3)	Fair
*Bernatsky et al., 2010[270]	Meta-analysis 7 studies of administrative claims or electronic health records	Studies estimating overall risk of serious infection in RA pts initiating biologic DMARDs	Biologic DMARD use vs. no use	Biologic DMARD use increased risk of serious infection (pooled adjusted RR, 1.37, 95% CI, 1.18 to 1.60)	Fair
Bongartz et al., 2006[271]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of serious infections for ADA and INF compared with placebo (3.6% vs. 1.7%; OR, 2.0; 95% CI, 1.3 to 3.1)	Fair
*Brassard et al., 2006[219]	Retrospective cohort 112,300 Up to 5 years	RA pts with ≥1 claim for anti-RA drugs in U.S. database	Several oral DMARDs, ANK, ETA, INF, corticosteroids	Adjusted rate ratio of developing TB: Biologic DMARDs:1.5 (95% CI, 1.1 to 1.9); INF:1.6 (95% CI, 1.0 to 2.6) ETA:1.2 (95% CI, 0.9 to 1.8) ANK:1.3 (95% CI, 0.8 to 2.1)	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Cohen et al., 2006[158] REFLEX Trial	RCT 520 24 weeks	Pts with RA with inadequate response to previous or current treatment with anti-TNF agents	RTX+MTX, MTX	The rate of serious infection was 5.2 and 3.7 per 100 pt-yrs in the RTX+MTX and MTX groups, respectively	Fair
Combe et al., 2006[145]	RCT 260 Up to 2 years	Active RA despite SSZ treatment	ETA, SSZ, ETA+SSZ	Significantly more infections in ETA and ETA+SSZ than in SSZ group (47% vs. 31% vs. 13%; *P*<0.05) at 6 months; similar pattern at 2 years (*P*<0.001)	Fair
*Curtis et al., 2007[277, 278]	Retrospective cohort study 5,326 Up to 67 months	Pts with RA enrolled in a large U.S. health care organization	MTX, TNF-alpha antagonists	Risk of hospitalization with a bacterial infection for those receiving TNF-alpha antagonists was 1.94 (95% CI, 1.32 to 2.83) compared with pts that received MTX only; risk highest in first 6 months – ETA: 1.61, 95% CI, (0.75 to 3.47) INF 2.40, 95% CI, (1.23 to 4.68)	Good
*den Broeder et al., 2007[326]	Retrospective cohort 1,219 1 year followup	RA pts that were TNF-alpha antagonist naïve	TNF-alpha antagonists	Perioperative continuation of anti-TNFs not associated with increased risk of surgical site infection. Wound dehiscence in patients that continued anti-TNFs compared with patients that temporarily discontinued anti-TNF treatment (OR, 11.2; 95% CI, 1.4 to 90).	Fair
Dixon et al., 2006[268]	Prospective cohort study 8,973 11,220 pt-years	Pts with active RA despite MTX treatment	ADA, ETA, INF	No differences among anti-TNF drugs for risk of serious infections. Similar risk for serious infections between anti-TNF drugs and oral DMARDs	Fair
*Dixon et al., 2010[279] BSRBR	Prospective cohort study 13,739 7,345 person-years (DMARD cohort) 34,025 person-years (anti-TNF cohort)	Pts with RA from the British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF vs. oral DMARDs	Adjusted incidence rate ratio of TB cases compared with ETA: INF 3.1 (95% CI, 1.0 to 9.5) and ADA 4.2 (1.4-12.4)	Fair
*Galloway et al., 2011[269] BSRBR	Prospective cohort study 15,396 3.9 years (anti-TNF cohort) 2.6 years (DMARD cohort)	Pts with RA from the British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF vs. oral DMARDs	Adjusted hazard ratio for serious infection in anti-TNF cohort: 1.2 (95% CI, 1.1 to 1.5). No significant difference in serious infection incidence between ADA, ETA, and INF	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Gomez-Reino et al., 2003[282]	Retrospective cohort study 1,540 1.1 years	Pts with RA in daily clinical care in Spain	ETA, INF	Higher risk of TB for ETA and INF than oral DMARDs	Fair
*Greenberg et al., 2010[226] CORRONA	Prospective cohort 7,971 15,047 person-years	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	MTX, oral DMARDs, anti-TNF agents, PRED	Adjusted incidence rate ratio (IRR) for infections withanti-TNF agents compared with oral DMARDs (IRR, 1.52; 95% CI, 1.30 to 1.78, $P<0.001$); opportunistic infections (IRR, 1.67; 95% CI, 0.95 to 2.94 $P=0.077$)	Fair
*Grijalva et al., 2010[240]	Retrospective cohort 28,906 Up to 180 days	Tennesee Medicaid-enrolled RA pts initiating DMARD use	MTX, LEF, SSZ, HCQ, biologic DMARDs (ADA, ETA, INF), steroids	Compared with MTX biologic DMARDs increased risk of hospitalization due to pneumonia (HR, 1.31; 95% CI, 0.78 to 2.19) or serious infections (HR, 1.65; 95% CI, 0.85 to 3.03)	Good
*Kawakami et al., 2010[327]	Case-control 128	Pts with RA that underwent joint surgery	ETN, INF, DMARDs	Higher risk of surgical site infections in anti-TNF group vs. oral DMARD group (OR, 21.80; 95% CI,1.231 to 386.1, $P=0.036$)	Fair
Keane et al., 2001[283]	Database analysis 70 cases of TB NA, AERS data	Pts treated with INF	INF	TB may develop soon after initiation of INF treatment	Fair
*Keystone et al., 2008[168] RAPID-1 Trial	RCT 982 52 weeks	Pts with RA that received MTX for ≥6 months prior to baseline	MTX, CTZ+MTX	Occurrence of serious infections was higher in pts treated with CTZ than those on MTX alone	Fair
Lee et al., 2002[286]	Database analysis 10 cases of histo-plasmosis NA, AERS data	Pts treated with ETA and INF	ETA, INF	Histoplasmosis infections may be a serious complication of treatment with anti-TNF agents; pts on INF had a higher rate of infections than pts on ETA	Fair
*Leombruno et al., 2009[255]	Meta-analysis 18 trials 8,808 patients Average 0.8 years	RA pts on anti-TNF therapy	ADA, ETA, INF	Anti-TNF treatment did not increase seirious infection (OR, 1.21; 95% CI, 0.89 to 1.63)	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Listing et al., 2005[274]	Prospective cohort study 1,529 Up to 12 months	Pts with RA in daily clinical care in Germany	AKA, ETA, INF	Higher risk of infections for AKA, ETA, INF compared with DMARDs	Fair
*Migliore et al., 2009[328]	Retrospective cohort 138 with RA Followup not specified	Pts 65 years old or more with RA, PsA, or Ankylosing Spondylitis	ETA, ADA, INF	Infection rate: ETN 18.51%, ADA 20.51%, INF 15.55%	Fair
Mohan et al., 2004[284]	Database analysis 25 cases of TB NA, AERS data	Pts treated with ETA	ETA	Median interval between first dose and diagnosis of TB was 11.5 months	Fair
*Salliot et al., 2009[272]	Meta-analysis 12 RCTs	RA patients receiving ABA, ANK, or RTX	ABA, ANK, RTX	No increase in risk of serious infection for ABA or RTX; high doses of ANK increased risk of serious infection	Fair
Salliot et al., 2006[275]	Case series 709 NR	Pts with different rheumatic diseases; primary care-based cohort	ADA, ETA, INF	Rates of serious infections in daily practice were higher than ones reported in efficacy trials	Fair
*Schiff et al., 2008[66]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA +MTX, INF +MTX, MTX	Serious infections were reported more with INF (8.5%) than ABA (1.9%)	Fair
*Schneeweiss et al., 2007[222]	Retrospective cohort 15,597 Up to 8 years	Medicare beneficiaries ages 65 and older with RA	TNF-alpha antagonists (ADA, ETA, INF)	Compared with MTX use, TNF-alpha did not increase risk of serious bacterial infections (RR, 1.04; 95% CI, 0.63 to 1.72)	Fair
Slifman et al., 2003[287]	Database analysis 15 cases of listeria infection NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of infections than pts on ETA	Fair
*Smitten et al., 2008[223]	Retrospective cohort 24,530 26.6 months	Pts with RA from U.S. PharMetrics data	ADA, ANK, ETA, INF	Biologic DMARDs slightly increased risk of hospitalized infection (RR, 1.21; 95% CI, 1.02 to 1.43).	Good

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Smitten et al., 2007[224]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	Pts with RA from the PharMetrics (PM) database and UK General Practice Research database (GPRD)	ANK, ETA, INF	Risk of herpes zoster infection with biologic DMARD: (PM: OR,1.54; 95% CI, 1.04 to 2.29)	Fair
*Smolen et al., 2009[167] RAPID 2 study	RCT 619 24 weeks	Pts with RA with prior MTX use for ≥6 months	MTX, CTZ+MTX	Serious infection occurred more frequently in CTZ pts vs. pts treated with MTX monotherapy	Fair
St. Clair et al., 2004[82] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive	MTX, INF+ MTX	Significantly more patients in the INF+MTX than in the MTX group had more than one serious infection (5.3 vs. 2.1%; *P*<0.05)	Fair
*Strangfeld et al., 2009[225]	Prospective cohort 5,040 up to 36 months	RA pts initiating biologic therapy or switching to another DMARD	ADA, ETA, INF	Adjusted HR for Herpes Zoster. All anti-TNFs: (HR, 1.63; 95% CI, 0.97 to 2.74) ADA or INF (HR, 1.82; 95% CI, 1.05 to 3.15) ETA (HR, 1.36; 95% CI, 0.73 to 2.55)	Good
Wallis et al., 2004[280]	Database analysis 649 cases of granulomatous infections NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of granulomatous infections than pts on ETA	Fair
*Wiens et al., 2010[183]	Meta-analysis 21 studies 6,503 patients 8 weeks to 3 years	Pts with RA with or without concomitant MTX	ADA, ETA, INF	Effect estimate of serious infections compared with placebo: ADA (2.22, 95% CI, 0.83 to 5.99, *P*=0.11), ETA (0.89, 95%CI, 0.54 to 1.48, *P*=0.66), INF (0.96, 95%CI, 0.39 to 2.38, *P*=0.93)	Fair
Westhovens et al., 2006[155] START study	RCT 1,084 22 weeks	Pts with active RA despite MTX treatment	INF+MTX, MTX	Risk of serious infections was similar between placebo and 3 mg/kg infliximab. 10 mg/kg infliximab led to increased risk of serious infections	Good
Wolfe et al., 2004[285]	Prospective cohort study with historic control 17,242 3 years	Pts with RA in daily clinical care in U.S.	INF, oral DMARDs	TB was more common in pts treated with INF than with oral DMARDs	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Wolfe et al., 2006[237]	Prospective cohort study 16,788 3.5 years	Pts with RA	ADA, ETA, INF	No increased risk for hospitalization for pneumonia for ADA, ETA, and INF compared with a historic control	Fair

* New study added since last review.
ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CI = confidence interval; CTZ = certolizumab; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HR = hazard ratio; INF = infliximab; kg = kilogram; LEF = leflunomide; mg = milligram; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = rate ratio; RTX = rituximab; SSZ = sulfasalazine; TB = tuberculosis; TCZ = tocilizumab; TNF = tumor necrosis factor

Most studies defined serious infections as those that required antibiotic treatment or led to hospitalization or death. In placebo-controlled safety RCTs, the incidence of serious infections was consistently higher in biologic-treated than in placebo-treated patients.[82, 85, 155, 158, 167, 168] Although clinically significant, these differences rarely reached statistical significance because of low power. For example, in one large safety RCT (N=1,414), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1 percent vs. 0.4 percent; P=0.068).[259] The START (Trial for Rheumatoid Arthritis with Remicade) study, another safety RCT (N=1,084) conducted to assess the risk of serious infections during infliximab treatment for RA, indicated a dose-dependent risk for patients on infliximab.[155] After 22 weeks of treatment, patients on 3 mg/kg infliximab had similar rates of serious infections as patients on placebo (1.7 percent vs. 1.7 percent; RR, 1.0; 95% CI, 0.3 to 3.1). Patients treated with 10 mg/kg infliximab had a significantly higher rate of serious infections than patients on placebo (5.0 percent vs. 1.7 percent; RR, 3.1; 95 percent CI, 1.2 to 7.9). The REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab) trial randomized 520 patients to 24 weeks of treatment with MTX or rituximab plus MTX.[158] The rate of serious infections was slightly higher among rituximab-treated patients (5.2 vs. 3.7 per 100 person-years). In both the RAPID1 and RAPID2 (RA Prevention of Structural Damage) trials,[167, 168] two trials assessing the efficacy of certolizumab in RA patients previously treated with MTX, serious infections occurred more frequently among the certolizumab-treated patients.

Six systematic reviews and meta-analyses have assessed serious infections with biologic DMARDs.[126, 183, 255, 270-272] Some of these analyses provide drug-specific effect size estimates, although none provide adjusted indirect comparisons or mixed treatment comparisons to adequately compare risk of infection among biologic DMARDs. Effect size estimates generally suggest that infection rates are increased with biologic DMARDs; several analyses found this increase to be statistically nonsignficant.[183, 255] In a fair-rate meta-analysis of efficacy studies of adalimumab- and infliximab-treated patients, the pooled odds ratio for serious infections was 2.0 (95% CI, 1.3 to 3.1) relative to placebo.[271] A fair-rated meta-analysis of large cohort studies (excluding trials) of anti-TNF drugs also found an increased risk of serious infections (RR, 1.37; 95% CI, 1.18 to 1.60).[270] In a good-rated meta-analysis of 13 trials (7,087 patients) of adalimumab, etanercept, and infliximab, a statistically significant increase in risk of infection was observed only among the infliximab group (RR, 1.2; 95% CI, 1.1 to 1.3).[126] Another fair

meta-analysis of 12 RCTs did not find an increased risk of serious infections with abatacept or rituximab, but found that high doses of anakinra did increase risk.[272]

Long-term observational studies generally support an increased risk of infection with biologic DMARDs, although not in across all studies.[158, 218, 222, 223, 226, 240, 273-279, 328] A large, French case series of 709 patients with various rheumatic diseases treated with adalimumab, etanercept, or infliximab in daily clinical practice reported a substantially higher rate of serious infections (10.5 per 100 person-years) than rates reported in phase 3 efficacy trials (3 to 4 per 100 person-years).[275] A prospective cohort study of 7,971 patients (15,047 patient years) with RA in the Consortium of Rheumatology Researchers of North America (CORRONA) registry reported an increased rate of infection for anti-TNF drugs compared with oral DMARDs (IRR, 1.52; 95% CI, 1.30 to 1.78).[226] A large good-rated U.S. cohort study (N=5,326) of patients with RA enrolled in a U.S. health care organization found an increased risk of hospitalization with bacterial infection for those treated with adalimumab, etanercept, or infliximab (HR, 1.94; 95% CI, 1.32 to 2.83) compared with patients that only received MTX.[277, 278] This finding contrasts with a large retrospective cohort study of 15,597 U.S. Medicare patients receiving adalimumab, etanercept, or infliximab;[222] compared with MTX use there was no increased risk of serious infection with these biologic DMARDs. Two additional good-rated cohort studies showed an increased risk of infection hospitalization.[223, 240] One retrospective cohort study using U.S. administrative claims data showed a slightly increased risk of hospitalized infection with adalimumab, anakinra, etanercept, and infliximab (RR, 1.21; 95% CI, 1.02 to 1.43).[223] Another retrospective cohort study of Tennessee Medicaid patients did not find a statistically significant increase in risk of hospitalization due to pneumonia (HR, 1.31; 95% CI, 0.78 to 2.19) or serious infection (HR, 1.65; 95% CI, 0.85 to 3.03) for patients treated with adalimumab, etanercept, or infliximab compared with MTX.[240]

In addition to bacterial pathogens, serious infections included cases of TB,[283] coccidiomycosis,[325] histoplasmosis,[286] listeriosis,[287] candida,[283] and herpes.[224, 225]

In a fair-rated cohort study of 13,739 patients with RA in the BSRBR the incidence of TB with oral DMARDs was compared with adalimumab, etanercept, and infliximab.[279] No cases of TB were observed among oral DMARD users and only 40 cases of TB were observed among the biologic DMARD users, so statistical analyses only compared biologic DMARDs. Compared with etanercept, the incidence rate ratio of TB was higher for infliximab (IRR, 3.1; 95% CI, 1.0 to 9.5) and adalimumab (IRR, 4.2; 95% CI, 1.4- to 12.4).

Six additional cohort studies determined the risk of TB or granulomatous infections during treatment with infliximab or etanercept.[219, 280-285] All studies reported a significant increase in risk attributable to biologic DMARDs relative to placebo. For example, in a fair-rated retrospective cohort study of 112,300 U.S. patients with RA, the rate ratio for developing TB was 1.5 with biologic DMARDs (95% CI, 1.1 to 1.9).[219] For the individual agents, the rate ratio was highest with infliximab (RR, 1.6; 95% CI, 1.0 to 2.6) compared with etanercept and anakinra (respectively, RR, 1.2; 95% CI, 0.9 to 1.8; and RR, 1.3; 95% CI, 0.8 to 2.1).

Other evidence regarding the risk of TB comes from Spanish, Swedish, and U.S. databases that collected data on patients treated with biologic DMARDs.[281, 282, 285] The U.S. study, using data from the National Data Bank of Rheumatic Diseases (NBI), reported an eightfold higher rate of TB in patients treated with infliximab than in patients in a historic control group who had been treated with synthetic DMARDs.[285] The analysis yielded rates of 6.2 cases per 100,000 person-years in the control group and 52.5 cases per 100,000 person-years in patients on infliximab. The other two studies were based on the Spanish BIOBADASER (Base de Datos de

Productos Biologicos de la Sociedad Espanola de Reumatologia)[282] and several Swedish databases.[281] Both studies analyzed data on infliximab and etanercept and indicated a substantially higher risk for TB in patients treated with etanercept or infliximab than in those on synthetic RA therapy. The Swedish study reported a fourfold increased risk of TB (RR, 4.0; 95% CI, 1.3 to 12) for patients on anti-TNF treatment compared with the risk for RA patients not exposed to etanercept or infliximab.[281] The incidence of TB in patients treated with infliximab was 145 per 100,000 (95% CI, 58 to 299) person years; in patients treated with etanercept, the incidence was 80 (95% CI, 16 to 232) per 100,000 person years.

Three studies based on spontaneously reported adverse events from the FDA AERS database provided similar results.[280, 283, 284] These studies reflecte reports of adverse events, but are subject to reporting and other biases. One analysis of AERS data focused on granulomatous infections in general. It indicated a higher rate among patients treated with infliximab (239 cases per 100,000 patients) than with etanercept (74 cases per 100,000 patients).[280] The rate of TB in this study was 144 cases per 100,000 patients for infliximab and 35 cases per 100,000 patients for etanercept. However, incidence rates must be compared cautiously because this study reported cases per treated patients and not per patient years.[280] Another AERS analysis reported histoplasmosis to be related to treatment with etanercept and infliximab.[286]

Two observational studies assessed the risk of herpes zoster infection with biologic DMARDs.[224, 225] A good-rated prospective cohort study of 5,040 patients with RA initiating treatment with adalimumab, etanercept, or infliximab reported a statistically nonsignificant but potentially clinically significant increase in the risk of herpes zoster infection (HR, 1.63; 95% CI, 0.97 to 2.74).[225] This risk was greatest among patients treated with adalimumab or infliximab (HR, 1.82; 95% CI, 1.03 to 3.15) in comparison with those treated with etanercept (HR, 1.36; 95% CI, 0.73 to 2.55). A fair-rated retrospective cohort study of patient in a U.S. claims database and patients from the UK General Practice Research Database found a risk of herpes zoster infection of similar magnitude (OR, 1.54; 95% CI, 1.04 to 2.29).[224]

One case-control study compared the risk of surgical site infections in patients taking anti-TNF drugs and patients taking oral DMARDs among patients with RA undergoing joint surgery.[327] In this relatively small study (N=128) the risk of infection was significantly greater among patients in the anti-TNF drug group (OR, 21.8; 95% CI, 1.2 to 386.1; *P*=0.036).

Infusion and injections site reactions. Infusion reactions (abatacept, infliximab, rituximab, tocilizumab) and injection site reactions (adalimumab, anakinra, certolizumab, etanercept, golimumab) were the more commonly and consistently reported adverse events. Most infusion reactions were nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. Studies reporting infusion or injection site reactions in patients treated with biologic DMARDs are presented in Table 53.

In clinical trials of infliximab for the treatment of RA or Crohn's disease, 17 percent of patients experienced infusion reactions; 0.5 percent were severe and resembled acute anaphylactic conditions or led to convulsions.[273] In these trials, however, less than 2 percent of patients discontinued because of infusion reactions.[273] A prospective cohort study of infliximab in a Canadian clinical care setting reported substantially higher rates of reactions than did the clinical trials.[329] Specifically, in the community study (113 patients with 1,183 infusions), 53 percent of patients experienced at least one infusion reaction during the course of the therapy (mean 15 months). Reactions with infliximab were reported more commonly than with other biologic DMARDs in an RCT comparing abatacept and infliximab,[66] and in a retrospective cohort study comparing adalimumab (injection site reaction), etanercept, and infliximab.[253] In the

Table 53. Infusion or injection site reactions in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Cohen et al., 2006[158] REFLEX Trial	RCT 520 24 weeks	Pts with RA with inadequate response to previous or current treatment with anti-TNF agents	RTX+MTX, MTX	Infusion reactions occurred in 23% of RTX+MTX pts vs. 18% in MTX alone	Fair
*Emery et al., 2006[161] DANCER trial	RCT 465 24 weeks	Pts with RA that failed prior treatment with at least 1 but not more than 5 DMARDs (other than MTX) and/or biologic response modifiers	RTX+MTX, MTX	Acute infusion reaction occurred more frequently in pts treated with RTX (23% and 32% in the 500-mg and 1,000-mg groups, respectively) vs. MTX alone (17%)	Fair
Fleischmann et al., 2003[259]	RCT 1,414 6 months	Pts with active RA despite MTX treatment	ANK	Higher rates of injection site reactions with ANK than placebo	Fair
Gartlehner et al., 2006[74]	Meta-analysis 5,248 NA	Patients who have failed MTX treatment; mean disease duration: varied	ADA, ANK, ETA,INF	Higher rates of injection site/infusion reactions for ANK than ADA and ETA (56% vs. 19% vs. 25%)	Good
Langer et al., 2003[320]	Postmarketing surveillance 454 6 months	Pts with RA, initiating ANK treatment	ANK	Lower rates of injection site reactions than in clinical trials	Fair
*Martin Du Pan et al., 2009[253]	Retrospective cohort 2,364 9 years	Pts with RA in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry treated with an anti-TNF agent	ADA, ETA, INF	Increased risk for injection site/infusion or systemic allergic reaction in INF vs. ETA and ADA (HR, 2.11;99%CI,1.23-3.62; *P*=0.018)	Fair
*Miyasaka et al., 2008[125] CHANGE study	RCT 352 24 weeks	Pts with RA that failed 1 DMARD, including MTX	ADA	Injection site reactions occurred more frequently in ADA pts vs. placebo (*P*<0.05); Placebo 2.3%; ADA 20 mg 31%; ADA 40 mg 30.8%; ADA 80 mg 33.3%	Fair
Schaible et al., 2000[273]	Retrospec-tive data analysis of clinical trials 913 12 weeks to 3 years	Pts with RA or Crohn's disease	INF	17% of pts on INF in clinical trials had acute infusion reactions	Fair
*Schiff et al., 2008[66]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA+MTX, INF+MTX, MTX	Acute infusional events occurred in 7.1% of those treated with ABA vs. 24.8% treated with INF.	Fair

Table 53. Infusion or injection site reactions in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Wasserman et al., 2004[329]	Prospective cohort study 113 15 months	Pts with RA starting INF treatment in a clinical care setting	INF	53% of pts on INF experienced at least one infusion reaction	Fair

* New study added since last review.
ABA = abatacept; ADA = adalimumab; ANK = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; INF = infliximab; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; TNF = tumor necrosis factor

randomized trial, 7.1 percent of those treated with abatacept and 24.8 percent of those treated with infliximab had an infusion reaction.[66] In the retrospective cohort study, the risk of infusion reaction (or systemic allergic reaction with adalimumab) was more than twofold greater with infliximab compared with injection site reactions with adalimumab and etanercept (HR, 2.11; 95% CI, 1.23 to 3.62; P=0.018).[253] While comparative data on infusion reactions were not available for rituximab and tocilizumab, two RCTs reported similar rates of infusion reactions; 23 percent[158] and 28 percent.[161]

Injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity, and they were the most common reason for discontinuation blamed on adverse events. A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1 to 27.9) for adalimumab, 22.4 percent (95% CI, 8.5 to 36.3) for etanercept, and 67.2 percent (95% CI, 38.7 to 95.7) for anakinra.[49] Injection site reactions for adalimumab were slightly higher than this estimate (31.7 percent) in an RCT of 352 patients with RA.[125] The substantially higher incidence of injection site reactions for anakinra than for adalimumab and etanercept is consistent with rates reported in the respective package inserts.[300, 330, 331] A German retrospective study based on postmarketing surveillance data, however, reported a lower incidence of injection site reaction for anakinra than was reported in clinical trials (20 percent).[320]

Interstitial lung disease. The risk of interstitial lung disease with biologic DMARDs was assessed by one fair-quality prospective cohort study conducted in 17,598 patients with RA in the NDB study (Table 54).[228] This study found that current treatment with etanercept and infliximab was not associated with hospitalization for interstitial lung disease. However, past treatment with etanercept (HR, 1.7; 95% CI, 1.0 to 3.0; P=0.056) and infliximab (HR, 2.1; 95% CI, 1.1 to 3.8; P=0.019) was associated with hospitalization for interstitial lung disease.

Table 54. Interstitial lung disease in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Wolfe et al., 2007[228]	Prospective cohort 17,598 Up to 3.5 years	Pts with RA in U.S. National Databank for Rheumatic Diseases	ETA, INF	Current treatment with ETA and INF not associated with hospitalization for interstitial lung disease. Past treatment with ETA and INF was associated with hospitalization for interstitial lung disease (HR, 1.7; 95% CI, 1.0 to 3.0; *P*=0.056; HR, 2.1; 95% CI, 1.1 to 3.8; *P*=0.019	Fair

* New study added since last review.
ETA = etanercept; HR = hazard ratio; INF = infliximab

Malignancies. The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with RA compared with the general population.[332] Data from controlled trials do not provide sufficient evidence concerning a further increase in their risk of cancer attributable to the use of either biologic DMARDs or a combination of biologic and synthetic DMARDs. Findings from retrospective observational studies are mixed (Table 55).

Table 55. Malignancies in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Askling et al., 2005[276]	Prospective cohort study 60,930 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, oral DMARDs	No increase in solid cancers for pts treated with anti-TNF drugs	Fair
Askling et al., 2005[292]	Prospective cohort study 53,067 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, oral DMARDs	No increase in lymphoma for pts treated with anti-TNF drugs	Fair
*Askling et al., 2009[295]	Prospective cohort 6,366 25,693 person-years	Pts with RA in Sweden	ADA, ETA, INF	Relative risk of first primary cancer in comparison to biologic-naïve patients: ADA (RR 1.32, 95% CI, 0.87 to 1.98); ETA (RR 0.78, 95% CI, 0.61 to 1.00); INF (RR 1.09, 95% CI, 0.91 to 1.30); *P*=0.034	Fair

Table 55. Malignancies in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Bongartz et al., 2006[271]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of malignancies for ADA and INF compared with placebo (0.8% vs. 0.2%; OR, 3.3; 95% CI, 1.2 to 9.1)	Fair
*Bongartz et al., 2009[294]	Meta-analysis 9 studies 3,316 patients At least 12 weeks	Pts with RA	ETA	Risk of maliginancy in ETA not statistically significantly higher than placebo: HR 1.84 (95% CI, 0.79 to 4.28)	Good
Brown et al., 2002[333]	Database analysis AERS 26 cases of lymphoma NA, AERS data	RA or CD pts treated with ETA and INF	INF, ETA	Median interval between initiation of therapy and lymphoma 8 weeks; some spontaneous remissions after discontinuation of therapy reported	Fair
Chakravarty et al., 2005[242]	Retrospective cohort study 15,789 NR	RA or osteoarthritis pts treated with ETA or INF	ETA, INF	Statistically significant association between anti-TNF (HR, 1.97; 95% CI, NR; *P*=0.001) and corticosteroid (HR, 1.28; 95% CI, NR; *P*=0.014) use and nonmelanoma skin cancer	Fair
Geborek et al., 2005[291]	Retrospective cohort study 1,557 5,551 pt-years	Pts with RA in daily clinical care in Sweden	ETA, INF	Higher risk of lymphoma for anti-TNF drugs than oral DMARDs	Fair
Lebwohl et al., 2005[334]	Postmarketing database review 1,442 3.7 years	Pts with RA treated with ETA	ETA	No increase in the incidence of cutaneous squamous cell carcinoma for ETA-treated pts	Fair
*Leombruno et al., 2009[255]	Meta-analysis 18 trials 8,808 patients Average 0.8 years	RA pts on anti-TNF therapy	ADA, ETA, INF	Anti-TNF treatment did not increase lymphoma (OR 1.26 95% CI, 0.52 to 3.06), nonmelanoma skin cancers (OR 1.27, 95% CI, 0.67 to 2.42), or noncutaneuous cancers plus melanomas (OR 1.31, 95% CI, 0.69 to 2.48)	Fair
*Pallavicini et al., 2010[296] LORHEN	Prospective cohort 1,114 Mean 23.32 months	RA pts that failed to respond to traditional DMARDs	ADA, ETA, INF	Similar cancer incidence rate as general population Hazard ratio of cancer risk compared with ETN: ADA (HR 1.66, 95% CI, 0.50 to 5.52, *P*=0.407); INF (HR 0.59, 95% CI, 0.17 to 2.09, *P*=0.412)	Fair

Table 55. Malignancies in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Setoguchi et al., 2006[293]	Retrospective cohort study 8,458 2,940 person-years (Biologic DMARD) to 30,300 person-years (MTX)	Pts with RA in daily clinical care in U.S. and Canada	ADA, ETA, INF	No increased risk of hematologic and overall malignancies for pts treated with anti-TNF drugs compared with those on oral DMARDs	Good
*Strangfeld et al., 2010[297] RABBIT	Prospective cohort 5,120 60 months	Pts with RA in Germany that failed at least one other DMARD therapy	ADA, ANK, ETA, INF, oral DMARDs	No statistically significant difference in the overall incidence of new or recurrent malignancies	Fair
*Wiens et al., 2010[183]	Meta-analysis 21 studies 6,503 patients 8 weeks to 3 years	Pts with RA with or without concomitant MTX	ADA, ETA, INF	Effect estimate of malignancies compared with placebo: ADA (0.55, 95% CI, 0.14 to 2.11, *P*=0.38), ETA (0.98, 95% CI, 0.32 to 3.02, *P*=0.97), INF (1.64, 95% CI, 0.30 to 8.89, *P*=0.57)	Fair
*Wolfe et al., 2007[335]	Prospective cohort 13,869 4. years (mean)	Pts with RA in U.S. NDB study	ADA, ANK, ETA, INF	Biologics were associated with an increased risk of nonmelanotic skin cancer (OR, 1.5; 95% CI, 1.2 to 1.8) and melanoma (OR, 2.3; 95% CI, 0.9 to 5.4). No other malignancy was associated with biologic use. The overall risk of any cancer was 1.0 (95% CI, 0.8 to 1.2).	Fair
Wolfe et al., 2004[289]	Prospective cohort study with external control 18,572 Up to 3 years	Pts with RA in daily clinical care in U.S.	INF, ETA	Pts with RA treated with INF or ETA are more likely to develop lymphoma than the general population	Fair
*Wolfe and Michaud, 2007[290] *Updates Wolfe 2004[289]	Prospective cohort 19,591 89,710 person-years	Pts with RA in U.S. NDB study	MTX, ADA, ETA, INF	Pts treated with any anti-TNFs did not have an increases risk for lymphoma compared with RA pts who had not received anti-TNFs.	Fair

* New study added since last review.
ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CD = Crohns disease; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HR = hazard ratio; INF = infliximab; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; TNF = tumor necrosis factor

Several cohort studies have assessed risk of lymphoma with anti-TNF drugs. An analysis of spontaneously reported cases of lymphoma associated with etanercept or infliximab suggested a

median time of 8 weeks from start of therapy to lymphoma diagnosis, and some cases spontaneously remitted after biologic DMARD discontinuation.[333] A large prospective cohort study followed 18,572 RA patients in a registry for up to 3 years.[289] The risk of lymphoma was higher for patients on anti-TNF therapies than for those on oral DMARDs, although not statistically significantly so. Confidence intervals for treatment groups overlapped and the results were insufficient to establish a causal relationship between RA treatments and lymphoma or to delineate differences in risks among treatments. The standardized incidence rate (SIR) in the overall cohort was 1.9 cases per 100,000. The SIR for patients not receiving MTX or any biologic agents was 1.0. The SIRs for patients on specific drugs were as follows: MTX, 1.7 (95% CI, 0.9 to 3.2); infliximab, 2.6 (95% CI, 1.4 to 4.5); and etanercept, 3.8 (95% CI, 1.9 to 7.5). An update of this analysis with additional patients and follow-up time confirmed that the risk of lymphoma was not increased among patients taking adalimumab, etanercept, and infliximab.[290]

Three community-based, retrospective cohort studies from Sweden, Canada, and the United States, however, did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on oral DMARDs.[291-293] The largest study included 4,160 patients treated with anti-TNF drugs.[292] Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6 to 2.1) for anti-TNF patients relative to patients on oral DMARDs.

Data from observartional studies and meta-analyses are also mixed regarding an increased risk for overall malignancies in patients treated with biologic DMARDs. Four meta-analyses have evaluated risk of malignancy with anti-TNF drugs.[183, 255, 271, 294] Effect size estimates were not statistically significant in three of these analyses, but one fair-rated meta-analysis of more than 5,000 RA patients from adalimumab and infliximab efficacy trials reported a pooled odds ratio for malignancies of 3.3 (95% CI, 1.2 to 9.1). The number needed to harm (NNH) was 154 (95% CI, 91 to 500) within a treatment period of 3 months to 12 months.

Five large cohort studies do not suggest a statistically significant increase in risk of malignancy.[276, 293, 295-297] For example, the largest of these two studies, based on data on more than 60,000 Swedish patients, found SIRs for solid cancers to be similar for RA patients treated with anti-TNF medications and those on conventional therapy using both a contemporary and a historic control group. In another Swedish analysis of 6,366 patients with RA during 25,693 person years of followup, the risk of first cancer did not differ for patients starting anti-TNF drug therapy and patients starting MTX (RR, 1.00; 95% CI, 0.86 to 1.15).[295] In a cohort of 8,458 patients with RA from the U.S. and Canada, no increase in risk of overall malignancies was observed for patients taking anti-TNF drugs relative to patients taking oral DMARDs.[293] In a German cohort of 5,120 patients with RA who had failed at least one other DMARD therapy (RABBIT), no statistically significant increase in the adjusted risk of developing malignancy was observed for anti-TNF drugs (HR, 0.7; 95% CI, 0.44 to 1.12; P=0.133) and anakinra (HR, 1.39; 95% CI, 0.56 to 3.48; P=0.48).[297] An Italian cohort from the Lombardi Rheumatology Network (LOHREN) registry reported an overall cancer risk for 1,114 RA patients treated with anti-TNF drugs to be similar to the general population, with no statistically significant differences observed among anti-TNF drugs.[296]

A clinical trial database review did not detect a higher incidence of squamous cell carcinoma in 1,442 RA patients (4,257 person-years) treated with etanercept (crude rate: 2.8 cases/1,000 patients) than for those on placebo;[334] the median follow-up time was only 3.7 years. A larger retrospective cohort study (N=15,789), however, reported a statistically significant association of a combination of anti-TNF and MTX treatment and nonmelanoma skin cancer (hazard ratio [HR]: 1.28; 95% CI, NR; P=0.014).[242] This finding also was observed in a large prospective

cohort study of 13,869 patients in the U.S. NDB study taking adalimumab, anakinra, etanercept, and infliximab.[335] These biologic DMARDs were associated with an increased risk of nonmelanotic skin cancer (OR, 1.5; 95% CI, 1.2 to 1.8) and melanoma (OR, 2.3; 95% CI, 0.9 to 5.4).

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity (Table 56). Reports based on data from the FDA's AERS indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[298, 299, 336] Similar cases have been seen in regulatory trials of adalimumab.[300] All neurologic events partially or completely resolved after discontinuation of treatment.

Table 56. Other specific adverse events in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
De Bandt et al., 2005[302]	Case series 22 cases with lupus syndrome	Pts with RA in daily clinical care in France	ETA, INF	Similar incidence of lupus syndrome between ETA and INF	Fair
Flendrie et al., 2005[304]	Prospective cohort study with historic control 578 911 person-years	Pts with RA starting anti-TNF therapy	ADA, ETA, INF	Higher rates of dermatological conditions in pts on anti-TNF drugs compared with DMARDs	Fair
*Harrison et al., 2009[305] BSRBR	Retrospective cohort study 12,706 1 to 2 years	Pts with severe RA from The British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF, oral DMARDs	Anti-TNF vs. oral DMARDs: IR 1.04 (95% CI, 0.67 to 1.54); Among anti-TNF: ADA had a significantly increased risk of psoriasis compared with those treated with ETA (IRR, 4.6; 95% CI, 1.7 to 12.1) and INF (IRR, 3.5; 95% CI, 1.3 to 9.3)	Fair
*Harrison et al., 2009[305] BSRBR	Retrospective cohort study 12,706 1 to 2 years	Pts with severe RA from The British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF, oral DMARDs	Anti-TNF vs. oral DMARDs: IR 1.04 (95% CI, 0.67 to 1.54); Among anti-TNF: ADA had a significantly increased risk of psoriasis compared with those treated with ETA (IRR, 4.6; 95% CI, 1.7 to 12.1) and INF (IRR, 3.5; 95% CI, 1.3 to 9.3)	Fair
*Kawakami et al., 2010[327]	Case-control 128 Post-surgery	Pts with RA that underwent joint surgery	ETN, INF, DMARDs	Increased risk of surgical site infection and deep vein thrombosis in anti-TNF group vs. oral DMARD group	Fair
*Maini et al., 2006[174] CHARISMA	RCT 359 20 weeks	Pts with RA despite MTX treatment	MTX, TCZ+MTX, TCZ	Liver enzymes (AST) increased with TOC use but was highest in TOC+MTX. No change in liver enzymes occurred with MTX alone	Fair

Table 56. Other specific adverse events in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Michaud and Wolfe, 2006[244]	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the NDB study	ADA, ETA, INF	Association (OR) of treatment with visits to physician for sinus problems: • ADA: 1.09 (95% CI, 0.79 to 1.51; *P*=0.600) • ETA: 1.21 (95% CI, 1.02 to 1.42; *P*=0.025) • INF: 1.00 (95% CI, 0.88 to 1.15; *P*=0.973)	Fair
Mohan et al., 2001[299]	Database analysis AERS 19 cases of demyelination NA, AERS data	Pts on anti-TNF therapy	ETA, INF	Discontinuation of therapy led to partial or complete resolution of all cases	Fair
Shin et al., 2006[336]	Database analysis AERS 15 cases of Guillain-Barre and Miller Fisher syndromes NA, AERS data	Pts on anti-TNF therapy	ADA, ETA, INF	Demyelination is a potential adverse event of anti-TNF therapy	Fair
*Sokolove et al., 2010[337] CORRONA	Prospective cohort 6861 Mean 17 months	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	ADA, ETA, INF, DMARDs	Adjusted odds ratio of elevated liver enzymes (ALT and/or AST>2xULN) compared with non-biologic DMARD users: ADA (OR, 1.72; 95% CI, 0.99 to 3.01); ETN (OR, 1.10; 95% CI, 0.64 to 1.88); INF (OR, 2.40; 95% CI, 1.53 to 3.76)	Fair

* New study added since last review.
ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; INF = infliximab; IR = incidence rate; IRR = incidence rate ratio; LEF = leflunomide; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; TNF = tumor necrosis factor

Similarly, reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases.[273, 301-303] Lupus-like syndromes have also been reported for adalimumab.[298] Development of antinuclear, antidouble-stranded DNA, or antihistone antibodies have also been reported in regulatory trials of other anti-TNF-α drugs.[300, 330]

The infliximab package insert reports that 34 percent of patients treated with infliximab and MTX experienced transient elevations of liver function parameters.[301] Severe liver injury, including acute liver failure, has been reported. One study, the Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) trial,[174] reported data on liver function tests. This trial compared MTX, tocilizumab plus MTX, and tocilizumab monotherapy over 20 weeks in 359 patients with RA. Both tocilizumab groups had elevated liver enzymes compared with MTX monotherapy. Liver enzymes were most elevated in the tocilizumab plus

MTX group. In a prospective cohort of 6,861 patients from the Consortium of Rheumatology Researchers of North America (CORRONA) registry, compared with patients receiving other nonbiologic DMARD treatments, liver enzymes were elevated for adalimumab- (OR, 1.72; 95% CI, 0.99 to 3.01) and infliximab-treated (OR, 2.40; 95% CI, 1.53 to 3.76) patients but not for etanercept-treated patients (OR, 1.10; 95% CI, 0.64 to 1.88).[337]

A prospective cohort study (N=578) indicated that patients on anti-TNF treatments developed dermatological conditions (skin infections, eczema, drug-related eruptions) statistically significantly more often than anti-TNF-naive patients over a median treatment time of 2.3 years (25 percent vs. 13 percent; $P<0.0005$).[304] Another retrospective cohort study of 12,076 patients with severe RA from the BSRBR failed to find an overall association of anti-TNF drugs with risk of psoriasis.[305] Among the three biologic DMARDs included, adalimumab had a significantly increased risk of psoriasis compared with those treated with etanercept (IRR, 4.6; 95% CI, 1.7 to 12.1) and infliximab (IRR, 3.5; 95% CI, 1.3 to 9.3).

One cross-sectional analysis of data from 7,243 patients in the prospective cohort of the NDB study assessed the relationship of treatment with adalimumab, etanercept, and infliximab with physician visits for sinus problems.[244] A small elevated risk was observed among patients treated with etanercept (OR, 1.21; 95% CI, 1.02 to 1.42). No statistically significant increased risk of sinus problems was observed with adalimumab (OR, 1.09; 95% CI, 0.79 to 1.51) or infliximab (OR, 1.00; 95% CI, 0.88 to 1.15).

Adherence. The published literature in this area frequently uses the terms *compliance* and *adherence* interchangeably. *Compliance* has traditionally been used to describe a patient's ability to take medications as prescribed. Some authors argue, however, that *adherence* better represents the more complex relationship among patients, providers, and medications; it is meant to reflect the fact that following a medication regimen is not necessarily a simple choice.[338] Given the lack of a clear definition, we use the term *adherence*. Table 57 summarizes studies for adherence.

Table 57. Studies assessing adherence in patients with rheumatoid arthritis

Author, Year	Study Type and Interventions	N	Results
Boers et al., 1997[95]	RCT MTX+SSZ+prednisolone vs. SSZ	155	Compliance satisfactory in 85%
Emery et al., 2000[105]	RCT LEF vs. MTX	999	Reason for withdrawal: noncompliance in the 1st year: LEF 11 (2%) vs. MTX 14 (3%) noncompliance in the 2nd year: LEF 6 (2%) vs. MTX 6 (2%)
Fleischmann et al., 2003[259]	RCT AKA vs. placebo	1,414	AKA vs. placebo: 100% adherent with use of study drug: 43.8% vs. 47.8% <70% adherent with use of study drug: 0.8% vs. 1.7% >40% missed no injections >90% received at least 90% of intended doses
Goekoop-Ruiterman et al., 2005[100]	RCT Four treatment strategies	508	24 (5%) were nonadherent

Table 57. Studies assessing adherence in patients with rheumatoid arthritis (continued)

Author, Year	Study Type and Interventions	N	Results
*Grijalva et al., 2007[339]	Retrospective cohort study Oral and Biologic DMARDs	6,018	SSZ, MTX+HCQ, MTX+INF, MTX+ETN, MTX+ADA, and ANK or ANK+MTX less adherent than MTX (*P*=0.014; *P*<0.001; *P*<0.001; *P*<0.001; *P*=0.001; *P*=0.008; respectively) LEF, INF, ETN, ADA more adherent than MTX (*P*<0.001; *P*<0.001; *P*<0.001; *P*=0.005; respectively)
Haagsma et al., 1997[58]	RCT SSZ+MTX vs. SSZ or MTX	105	Percentage of tablets taken>90% (pill count)
Harley et al., 2003[306]	Retrospective database analysis INF vs. ETN vs. MTX	2,662	INF more adherent than ETA or MTX (*P*<0.05)
*Hetland et al., 2010[73]	Prospective cohort ADA vs. ETA vs. INF	2,326	Drug adherence rates at 48 months: ADA, 52% (95% CI, 46 to 57); ETN, 56% (95% CI, 51 to 62); INF, 41% (95% CI, 37 to 44); *P*<0.0001
Hyrich et al., 2006[81]	Prospective observational study	2,711	Remained on treatment at 6 months: ETN 80% vs. INF 79% ETN subgroups (22% monotherapy, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy, vs. 22% DMARD co-therapy)
*Li et al., 2010[307]	Retrospective cohort ANK vs. ETA vs. INF	5,390	Adherence rates measured by PDC ≥0.8): ANK: 10.5% (*P*<0.05) ETA:32% INF:43%
*Kristensen et al., 2006[69]	Prospective cohort study ETN vs. INF	949	Withdrawals due to adverse events (*P*<0.001) and withdrawals due to lack of efficacy (*P*=0.018) more common for INF than for ETN
*Kristensen et al., 2006[251]	Prospective cohort study ETN vs. INF	1,161	INF less adherent than ETN for all subgroups (*P*<0.001). Adherence at 5 years 69% for INF+MTX vs. 89% for ETN+MTX (*P*<0.001).
Kremer et al., 2002[340]	RCT LEF+MTX vs. placebo+MTX	263	Overall, 98% adherent Adherence rates 80%-120% LEF, 87.7% placebo 90.2%
*Russell et al.,2007[116, 254]	RCT ABA+MTX vs. placebo+MTX	652	ABA+MTX adherence 89% MTX placebo adherence 74%
Strand et al., 1999[104]	RCT LEF vs. MTX vs. placebo	402	Nonadherence as the reason for withdrawal: LEF (1) MTX (1)

* New study added since last review.

ABA = abatacept; ADA = adalimumab; AKA = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HCQ = hydroxychloroquine; INF = infliximab; LEF = leflunomide; MTX = methotrexate; RCT = randomized controlled trial; SSZ = sulfasalazine

The majority of RCTs that reported adherence stated a rate between 85 percent and 100 percent. Seven published studies reported levels of adherence in RCTs.[58, 95, 100, 105, 116, 254, 259, 340] Most, however, contained only minimal information, and many did not stratify by treatment. Furthermore, they provided little or no information on the methods of assessment. For example, one study reported that adherence was satisfactory in 85 percent of patients, but the investigators did not describe their method of determining adherence.[95] Only four of the seven RCTs reported adherence rates for different treatment arms.[105, 116, 254, 259, 340] None of these studies noted a

significant difference in adherence (although differences in discontinuation rates were noted in many trials). To what extent results from these highly controlled efficacy trials can be extrapolated to effectiveness settings remains unclear.

A retrospective database analysis used a large U.S. health plan, which included commercial and Medicare insurance, to examine adherence levels in 2,662 patients being treated with infliximab, etanercept, or MTX from November 1999 to December 31, 2001.[306] The primary outcome measured was the number of drug administrations or prescriptions filled, divided by the expected number during a 365-day period. Their primary finding was that patients on infliximab were significantly more adherent than patients on etanercept or MTX. After controlling for baseline covariates (age, sex, baseline cost, insurance type, health plan region, history of therapy of RA, comorbidities, type of physician), 81 percent of the patients receiving infliximab were adherent compared with 68 percent of the etanercept and 64 percent of the MTX patients ($P<0.05$ for infliximab vs. both other drugs) over 1 year. This finding was supported by a retrospective cohort study of 5,390 patients taking anakinra, etanercept, or infliximab. In this study, adherence measured by the proportion of days covered was 43 percent for infliximab, but only 32 percent for etanercept and 10.5 percent for anakinra ($P<0.05$).[307] Another observational study reported similar adherence for etanercept and infliximab.[81] However, this is contradicted by three additional cohort studies.[69, 73, 251] A prospective cohort study of 1,161 patients taking etanercept or infliximab, where infliximab-treated patients were less adherent than etanercept-treated patients ($P<0.001$).[251] Adherence at 5 years was 69 percent for the infliximab group and 89 percent for the etanercept group. In an analysis of 949 patients derived from the same Swedish registry, withdrawals due to adverse events ($P<0.001$) and withdrawals due to lack of efficacy ($P=0.018$) were more common for infliximab than for etanercept.[69] In a prospective cohort study of 2,326 patients taking adalimumab, etanercept, or infliximab, drug adherenc rates at 48 months were 52 percent for adalimumab, 56 percent for etanercept, and 41 percent for infliximab ($P<0.0001$).[73]

A retrospective cohort study of 6,018 patients measured adherence with multiple oral DMARDs, biologic DMARDs, and combinations of DMARDs. Compared with patients on MTX monotherapy, patients taking monotherapy sulfasalazine or anakinra, and patients taking MTX plus hydroxychloroquine, adalimumab, anakinra, etanercept, and infliximab had lower adherence.[339] Patients on monotherapy leflunomide, adalimumab, etanercept, or infliximab had better adherence than patients on monotherapy MTX. However, these differences might also be capturing decrements in adherence related to measurement or to behavior with taking more than one treatment at the same time (since combination treatments had lower adherence).

Key Question 4: Benefits and Harms for Selected Populations

This key question (KQ) addressed the comparative benefits and harms of drug therapies for rheumatoid arthritis (RA) in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities. Early RA as a stage of disease and history of prior therapy were addressed under KQ 1; however, we present one study here that grouped subjects by early RA versus more advanced RA. We did not find studies that exclusively compared MTX-naive RA groups with those with RA who were MTX-experienced.

Overview

We focused on groups defined by stage of disease, demographics (age, sex, race, or ethnicity), concomitant therapies, and comorbidities (any comorbidity, cardiovascular disease,

osteoporosis, and renal disease). We included five good or fair quality studies: two RCTs, one subgroup analysis of multiple RCTs, one database analysis, and one systematic review met the inclusion criteria for this key question.

Stage of disease. One fair quality post-hoc analysis of two RCTs[341] compared those treated with MTX or etanercept or a combination of both in patients with moderate RA with those in a severe disease activity state. Generally, patients with moderate RA achieved significantly better DAS28 and HAQ results than those with severe RA; however, those with severe disease activity on etanercept or MTX monotherapies had greater change scores from baseline in DAS28.

Demographics. We found no studies that conducted comparisons by sex, race, or ethnicity, but we did include one fair systematic review that addressed age,[342] one pooled analysis of RCTs,[298] and a secondary database analysis of Medicare patients.[216]

One systematic review by the Rheumatoid Arthritis Clinical Trial Archive Group found an inverse relationship between age and major clinical improvement.[342] Of the three trials reviewed, the differences between the odds ratios was small.[342] One study directly compared the efficacy of etanercept in elderly RA patients (65 years of age or older) with younger RA patients (under 64 years of age and older than 18) and found no significant difference in functional status between age groups.[298] The secondary database analysis reported that in the elderly, the risk of cardiovascular events was higher in those who were treated with oral glucocorticoids or cyctotoxic immunosuppressant agents such as leflunomide, whereas biologic agents (abatacept, intanercept, infliximab, anakina) were found to have no beneficial or harmful effect.[216]

Concomitant therapies. We found no evidence from head-to-head comparisons, placebo-controlled trials, or observational studies on other treatment therapies. Differences based on comparisons of various combinations of RA medications are addressed in KQs 1 through 3. An analysis of data from one placebo-controlled trial involving RA patients receiving anakinra determined that the safety profiles did not differ in subjects receiving antihypertensive, antidiabetic, or statin medication treatments.[343]

Comorbidities. We identified two studies that addressed outcomes of RA patients with comorbidities. For RA patients with various high-risk conditions, one large placebo-controlled RCT of anakinra reported that there was no difference in serious adverse events or infections between the treated and placebo groups.[344] A systematic review of 11 MTX trials of RA patients determined that those with renal impairment were directly at greater risk for experiencing MTX toxicity, and the greater the renal impairment the greater the toxicity effects.[342]

We present detailed analyses below for the population groups noted above. Details about included studies are presented by subgroup analysis in Tables 64 to 68 (listed alphabetically within outcome sections).

Detailed Analysis

Stage of disease. A fair quality post-hoc analysis of TEMPO and ERA study data (Table 58)[341] looked at response to etanercept or MTX, or a combination of both, in regard to the patient's stage of RA—moderate (DAS20>3.2 and ≤5.1) or severe (DAS28>5.1). Although there were similarities between the two trial populations, the TEMPO subjects in this analysis had RA longer (6.6 vs. 1 mean years) and greater prior MTX use (43 percent vs. 0 percent) than the ERA group. Both analysis groups were primarily patients with severe RA (94 percent vs. 84.3 percent); however, the percentage of ERA patients with moderate RA was more than twice that in the TEMPO group (15.7 percent vs. 6 percent), making the TEMPO analysis group a more

severe population than the ERA group overall. The authors did not report any *P* values for differences between groups on baseline characteristics.

Table 58. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: By stage of disease

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Keystone et al., 2009[341]	Post-hoc analysis of two RCTs 1,091 12 months	Adults with moderate vs. severe RA treated with MTX, etanercept monotherapies or combinations	MTX (dose NR), ETN (25 mg twice weekly), MTX+ETN	Significant differences favored those with moderate RA in DAS28 and HAQ scores vs. those with severe stage, but greater gains from baseline scores for DAS28 were seen in the those with severe RA	Fair

ETN = etanercept; MTX = methotrexate; NR = not reported; RA = rheumatoid arthritis; RCT = randomized controlled trial

Investigators reported significant differences in DAS28 remission at 6 months in TEMPO patients with moderate RA treated with MTX or etanercept monotherapies or combination compared with those with severe RA. This significant trend continued for the MTX-only or MTX-etanercept combination groups at 12 months, but not for those treated with etanercept alone (MTX: P=0.0035; MTX plus etanercept: P=0.0006). In the ERA analysis, both those treated with MTX or etanercept monotherapies for moderate RA,achieved significant DAS28 improvements at both 6 months (MTX: P=0.0058; etanercept: P=0.0003) and 12 months (MTX: P=0.0094; etanercept: P<0.0001).[341]

A significant difference in low disease activity level was achieved by those with moderate RA in both trial groups at both 6 and 12 months in all treatment groups except those treated with etanercept monotherapy in the TEMPO study. Mean DAS28 scores were consistently lower in moderate RA groups in comparison with those with severe RA; however, mean changes in DAS28 scores at 12 months were significantly greater in those with severe RA (ERA trial: MTX only: 1.2 vs. 2.4, P<0.0001; etanercept only: 1.7 vs. 2.4 P<0.0110; TEMPO trial: MTX only: 1.6 vs. 2.6, P<0.0076; etanercept only: 1.5 vs. 2.7, P<0.0268; MTX plus etanercept 2.5 vs. 3.5, P<0.0069).[341]

Twelve-month changes in HAQ scores from baseline showed significant differences between moderate and severe disease activity in the MTX-only group from the TEMPO trial and the two monotherapies in the ERA trial (TEMPO trial: MTX only 0.29 vs. 0.68, P=0.0138; etanercept only 0.42 vs. 0.74, P=0.1329; MTX plus etanercept 0.74 vs. 1.00, P=0.0895; ERA trial: MTX only 0.44 vs. 0.77, P=0.0107; etanercept only 0.45 vs. 0.75, P=0.0070).[341]

In regard to radiographic changes, only the MTX monotherapy group in the TEMPO trial showed significant differences in median change of total sharp scores between moderate and severe RA patients (1.00 vs. 2.57, P=0.014).[341]

Demographics. We identified one study analyzing MTX use in the elderly and one database analysis of various agents of a Medicare population.[216, 342] Table 59 presents the studies of adults with RA that conducted comparisons by age groups.

Table 59. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: By age

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Rheumatoid Arthritis Clinical Trial Archive Group 1995[342]	Systematic review 496 ≥12 weeks	Adults with RA by age subgroups: under 60 years of age; 60 to 64 years; 65 to 69 years; and 70 years or above	MTX	Adjusted analysis demonstrated that as age increases, the odds ratio for major clinical improvement decreases; no effect found on toxicity	Fair
Solomon et al., 2006[216]	Nested case control database analysis (Medicare and PACE) 946 ≤24 months	Elderly adults with RA	MTX, ADA, ETN, INF, AKA, AZA, CSA, LEF, HCQ, SSZ, gold, and all oral glucocorticoid agents	Oral glucocorticoids and cytotoxic immunosuppressive agents increased risks for cardiovascular events, biologics neither increased risk or decreased risk	Fair

ADA = adalimumab; AERS = adverse events reporting system; AKA = anakinra; AZA = azathioprine; CHF = congestive heart failure; CSA = cyclosporine A; ETN = etanercept; HCQ = hydroxychloroquine; INF = infliximab; LEF = leflunomide; MTX = methotrexate; NA = not applicable; PACE = pharmaceutical assistance contract for the elderly; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; TNF = tumor necrosis factor

The Rheumatoid Arthritis Clinical Trial Archive Group 1995 review of 11 MTX trials for adults with RA evaluated the effects of age or renal impairment on adverse events or treatment efficacy.[342] Although the authors reported that the odds for major clinical improvement dropped slightly as age increases, among all clinical trial patients, age did not affect MTX efficacy or the rate of side effects. Using the group under age 60 as the referent, the odds of major clinical improvement for those 60 to 64 years of age was 1.4 (95% CI, 0.7 to 2.6), 1.0 (95% CI, 0.5 to 2.2) for those 65 to 69 years of age, and 0.7 (95% CI, 0.3 to 1.7) for those 70 years of age or older (*P*=NR).

A fair quality nested case control study investigating cardiovascular events in 946 RA patients was conducted using data from Medicare enrollees also receiving benefits from the state of Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program.[216] Index dates were established as the first cardiovascular event within patients who had a diagnosis of RA on at least two visits and a prescription of an immunosuppressant agent (MTX, adalimumab, etanercept, infliximab, anakinra, azathioprine, cyclosporine, leflunomide, gold, hydroxychloroquine, sulfasalazine, and all oral glucocorticoid agents) within 90 days of the index event. Using MTX as the reference group, oral glucocorticoids (monotherapy: OR, 1.5; 95% CI, 1.1 to 2.1; combinations: OR, 1.3; 95% CI, 0.8 to 2.0) and cytotoxic immunosuppressive agents: azathioprine, cyclosporine, and leflunomide (OR, 1.8; 95% CI, 1.1 to 3.0) were associated with an increased risk for cardiovascular events. Biologics (adalimumab, etanercept, infliximab), on the other hand, had no effect on risk for developing or preventing a cardiovascular event (monotherapy: OR, 1.0; 95% CI, 0.5 to 1.9; combination with MTX: OR 0.8; 95% CI, 0.3 to 2.0; combination with other immunosuppressive agents OR, 1.2; 95% CI, 0.7 to 2.2).[216]

Concomitant therapies. One placebo-controlled trial of 1,399 adults with active RA disease examined safety profiles of those treated with 100mg/day anakinra (Table 60). Investigators failed to find any differences in the adverse event profiles of the subjects taking or not taking

concomitant antihypertensive, antidiabetic, or statin pharmacotherapies. Even when the analysis compared those treated with anakinra with those on placebo, no differences emerged (*P*=NR).[343]

Table 60. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: By concomitant therapies

Study	Study Design N Duration	Study Population	Intervention	Outcomes	Quality Rating
Tesser et al., 2004[343]	RCT 1,399 6 months	Adults with RA taking or not taking antihypertensive, antidiabetic, or statin pharma-cotherapies	ANK, 100mg/day	No significant difference found in safety profiles	Fair

ANK = anakinra; RA = rheumatoid arthritis; RCT = randomized controlled trial

Comorbidities. Table 61 presents three studies identified as addressing comorbidities.

Table 61. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis by comorbidities

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Rheumatoid Arthritis Clinical Trial Archive Group, 1995[342]	Systematic review of 11 RCTs 454 NA	RA patients with impaired renal function treated with MTX	MTX	Severe toxicity (severe upper abdominal pain, renal failure, proteinurea, cytopenias and liver toxicity) and respiratory toxicity (cough, pneumonitis, dyspnea, wheezing) worse with greater renal impairment	Fair
Schiff et al., 2004[344]	RCT 951 6 months	RA patients with high-risk comorbid conditions	ANK, 100 mg/day	In patients with comorbid conditions, no differences were found between treatment groups in regard to incidence of serious adverse events or overall infectious events	Fair

ANK = anakinra; MTX = methotrexate; NA = not applicable; RA = rheumatoid arthritis; RCT = randomized controlled trial

Any comorbidity. We did not identify any study specifically designed to assess the comparative efficacy and risk of biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab) in RA patients with common comorbidities. A post-hoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with various comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, and central nervous system-related events).[344] Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

*Cardiovascular morbidity***.** No direct evidence exists on the comparative risk of biologic DMARDs in patients with both RA and cardiovascular disease.

Renal function. A systematic review of 11 RCTs of MTX use in 496 adults with RA concluded that toxicity worsened with greater renal impairment. Patients with high renal impairment had a fourfold risk (OR, 4.5; 95% CI, 0.9 to 22.6) for severe toxicity (severe upper

abdominal pain, renal failure, proteinurea, cytopenias, and liver toxicity) than those with no renal impairment. Slightly more (4 percent vs. 1 percent) had respiratory toxicity (cough, pneumonitis, dyspnea, wheezing). No effect was found between renal impairment and increased liver toxicity.[342] Baseline renal function was found to be a significant predictor of toxicity, with the lower creatinine clearances ending up with greater toxicity (P=0.027).[342]

Discussion

This report provides a comprehensive review of the comparative efficacy, effectiveness, and harms of members of the main classes of drugs used to treat adult patients with rheumatoid arthritis (RA). These include oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. The objective of our report was to evaluate the comparative efficacy, effectiveness, and harms of monotherapies, combination therapies, and different treatment strategies.

Table 62 summarizes our findings and the strength of evidence for three Key Questions (KQs) addressed by this report.

Table 62. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses **Low** No clinically significant difference for functional capacity **Low** Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide **Low**	No consistent differences in tolerability and discontinuation rates **Low** Mixed results for specific adverse events **Insufficient**
Leflunomide vs. sulfasalazine	Mixed ACR response rates **Insufficient** No differences in radiographic changes **Low** Greater improvement in functional capacity for leflunomide **Low**	No differences in tolerability and discontinuation rates **Low** Mixed results for specific adverse events **Insufficient**
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes* **Moderate** No differences for functional capacity* **Moderate**	No differences in tolerability; more patients stayed on MTX long-term **Low** Mixed results for specific adverse events **Insufficient**
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes **Moderate** No differences in functional capacity **Moderate**	Withdrawal rates attributable to adverse events higher with combination **Low** Insufficient evidence for specific adverse events **Insufficient**

Table 62. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity **Insufficient** Less radiographic progression In patients on DMARD plus prednisone **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints **Low** Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy **Moderate** No difference in quality of life **Low**	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment **Moderate** No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications **Low**
Biologic DMARD vs. Biologic DMARD		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. **Low**	Discontinuation rates and severe adverse events higher with infliximab **Low**
Biologic vs. biologic *(Mixed treatment comparisons)*	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX **Low** Less improvement in disease activity (ACR 50) for anakinra compared to etanercept and compared to adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab and tocilizumab did not reach statistical significance. **Low** Greater improvement in disease activity (ACR 50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab **Low**	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab and golimumab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. **Low** Risk of infusion reactions most common with infliximab **Low** Risk for injection site reactions apparently highest with anakinra **Low** Mixed results for specific adverse events **Insufficient**

Table 62. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARD vs. Oral DMARD		
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs **Moderate** No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX **Low**; **Insufficient** Faster improvement in quality of life with etanercept than MTX **Low**	No differences in adverse events in efficacy studies **Low** Insufficient evidence on differences in the risk for rare but severe adverse events **Insufficient**
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept **Low**	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy **Moderate**
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics **Moderate** In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group **Low** In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (**Moderate**) and quality of life (**Low**) with combination therapy In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life **Low**	No differences in adverse events in efficacy studies **Low** Insufficient evidence on differences in the risk for rare but severe adverse events **Insufficient**

Table 62. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy **Low**	No differences in adverse events in efficacy studies **Low** Insufficient evidence on differences in the risk for rare but severe adverse events **Insufficient**
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy **High** for clinical response and functional capacity, **Moderate** for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis **Low** Mixed evidence on differences in the risk for rare but severe adverse events **Insufficient**
Strategies in Early RA		
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks **Low** More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. **Low**	No differences in discontinuation rates **Moderate**
Three oral DMARDs plus prednisone vs. 1 oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less, less work disability **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints **Low**	No differences in discontinuation rates **Moderate**
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years **Low**	No differences in serious adverse events between groups **Low**

† at MTX doses ranging from 7.5-25 mg per week

ACR = American College of Rheumatology; DMARD = disease modifying antirheumatic drug; MTC = mixed treatment comparisons; MTX = methotrexate; RA = rheumatoid arthritis; vs. = versus

Key Findings

Existing comparative evidence permits us to draw some conclusions for monotherapies of oral and biologic DMARDs. Overall, the evidence supports similar efficacy and effectiveness for methotrexate (MTX) and sulfasalazine.[57-59] However, it is important to note that MTX dosing for two of these studies ranged in the lower part of the dosing range. The evidence is insufficient to draw conclusions about disease activity for sulfasalazine and leflunomide, but improvement in functional capacity was greater for patients on leflunomide in one study (low strength of evidence).[107, 200] All three drugs have similar discontinuation rates attributed to adverse events in short-term efficacy trials up to 2 years.[104, 105, 107, 345]

Although several biologic DMARDs are available, the head-to-head evidence remains very limited. Current evidence comparing biologic DMARDs is limited to one head-to-head randomized controlled trial (RCT), several observational studies, indirect analyses, and our mixed treatment comparisons (MTC) meta-analyses. Based on one RCT, abatacept lessens disease activity more than infliximab, but remission rates are not significantly different at 1 year (low strength of evidence).[66] Discontinuation rates and severe adverse events appear higher with infliximab; these results are also supported by observational studies.[158, 248, 250, 251]

Our MTC of RCTs of subjects with active RA despite MTX treatment suggest a higher odds of reaching the ACR 50 for etanercept compared to most other biologic DMARDs (low strength of evidence). Similarly, our indirect analyses from randomized trials indicate that patients taking certolizumab or etanercept are less likely to withdraw treatment than patients taking other biologic DMARDs. In contrast prior analyses found no differences among the set of anti-tumor necrosis factor (anti-TNF) drugs (namely, etanercept, infliximab, and adalimumab).[28, 74, 75, 179] The differences between our results and those of previous indirect analyses may be attributed to newer studies and drugs (certolizumab, golimumab, and tocilizumab) added to the analyses, which provide additional data. Further, unlike previous indirect analyses, our MTC meta-analysis uses methods that do not rely solely on placebo-controlled trials; it also allows the inclusion of data from head-to-head studies or those with active comparators, thus increasing statistical power. In addition, for efficacy, we limited our MTC inclusion criteria to studies enrolling patient populations who had an inadequate response to MTX and excluded studies with MTX-naïve populations, those with early RA, or those who had failed anti-TNF therapy.

Our MTC meta-analysis indicates that anakinra trended toward lower efficacy. Prior indirect comparisons consistently indicated that anakinra is less efficacious than biologics for patients with RA.[74, 75] Adjusted indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be verified, particularly the similarity of study populations.

The evidence comparing monotherapy using a biologic DMARD with monotherapy using an oral DMARD is mixed. Monotherapies of adalimumab in early RA[76] and etanercept in longstanding RA[77, 86] generally did not reveal a benefit relative to MTX monotherapy for response rates and had mixed results for functional capacity. There was faster improvement in quality of life for etanercept. Radiographic outcomes were also significantly better in patients on biologic DMARDs than on MTX. Whether such differences are clinically relevant and can alter the long-term progression of the disease remains unclear.

Although a substantial percentage of patients respond well to DMARD monotherapy,[76, 77, 86, 136, 138, 345] some patients do not achieve an acceptable treatment response. As the BeSt study (Dutch acronym for Behandel Strategieen, "treatment strategies"), a Dutch effectiveness trial assessing different treatment strategies for RA, has indicated, tight disease control and an

individualized treatment approach are paramount in achieving a satisfactory treatment response or remission.[100] Therefore, if dose escalation of a monotherapy does not achieve low levels of disease activity, combination therapies have to be taken into consideration. This is supported by multiple efficacy studies that indicate that combinations of biologic and oral DMARDs appear to be more efficacious than monotherapy of either drug in populations failing DMARD therapy.

The existing evidence supports combination strategies of up to three oral DMARDs, including corticosteroids, compared with strategies using one or two drugs. The data are limited, however, by the number of supporting studies for each drug combination. Moderate strength evidence from two efficacy trials reported higher proportions of patients meeting American College of Rheumatology (ACR) 20 criteria at 2 years for the combination of MTX plus sulfasalazine and hydroxychloroquine than for one or two drugs.[61, 62]

Combination therapy of biologic DMARDs with MTX achieved better results in clinical outcomes, functional capacity, and quality of life than monotherapy with biologic DMARDs in MTX-naïve subjects or those not recently on MTX.[76, 86, 87, 136, 138] Whether these results can be extrapolated to combinations of biologic DMARDs with other oral DMARDs is uncertain. In clinical practice, patients often receive biologic DMARDs as an add-on therapy to an existing regimen of various oral DMARDs.

Combinations of two biologic DMARDs did not yield an additional treatment benefit but rather led to substantially higher rates of serious adverse events than with biologic DMARD monotherapies (14.8 percent vs. 2.5 percent; *P*=NR [not reported]).[79, 80, 258]

The evidence is limited to draw firm conclusions about whether one combination strategy is better than another in early RA. Current evidence also suggests improved functional capacity[65, 95, 97, 202] and less radiographic progression[65, 95-98] for combination strategies with corticosteroids and one or more oral DMARDs compared with oral DMARD monotherapy. For most of these comparisons, the evidence is limited to a single study. One effectiveness trial for patients with early RA reported less radiographic progression over 12 months with either (1) combination therapy of MTX, sulfasalazine, and high-dose tapered prednisone or (2) MTX and infliximab versus (3) sequential DMARD therapy or (4) step-up combination therapy.[100] At 2 years,[102] results of this study reinforced the conclusion that patients on initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with MTX and infliximab had less radiographic progression. They also had more rapid improvement in disease activity functional capacity and quality of life, although the differences between groups were no longer present by 2 years. By 4 years, there was no difference in remission among the groups.[196]

Evidence of moderate strength suggests that studies of combinations of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had similar withdrawal rates attributable to adverse events. Studies of combinations including prednisone with one or more DMARDs had similar discontinuation rates between groups.

Similarly, patients on combinations of biologic and oral DMARDs were less likely than patients on oral DMARD monotherapy to withdraw from trials because of lack of efficacy. Combinations of biologic and oral DMARDs had similar rates of adverse events than monotherapies of either drugs However, because biologic DMARDs are relatively new medications, long-term data on safety are generally still missing. Especially rare but severe adverse events such as serious infections, lymphoma, autoimmunity, or congestive heart failure are of concern. One obvious difference among biologic DMARDs that might be clinically useful

for choosing a particular drug involves dosing and administration. Abatacept, infliximab, and rituximab require intravenous administration at different intervals and present the danger of rare but severe infusion reactions. Adalimumab, anakinra, and etanercept can be administered subcutaneously by the patient. Administration intervals differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, and etanercept once or twice per week. The route of administration is also the cause of the main differences in short-term tolerability. Anakinra appears to have a substantially higher rate of injection site reactions than anti-TNF drugs. Abatacept, infliximab, and rituximab carry the risk of severe infusion reactions that cannot occur in drugs administered subcutaneously. Fatal infusion reactions have been reported for infliximab and rituximab.[288, 301]

The existing evidence remains insufficient to draw firm conclusions on the best treatment regimen for patients with early RA. Studies conducted in patients with early aggressive RA suggested that an early start of a biologic DMARD can improve disease activity, radiographic findings, functional capacity, and quality of life compared to an oral DMARD. Because the studies were of limited duration, however, they do not allow conclusions on whether early initiation of a biologic regimen can improve the long-term prognosis of RA. Currently, clinical practice guidelines recommend that clinicians start biologic DMARDs if patients have suboptimal response to oral DMARDs or only if there is high disease activity. For those patients with longer disease duration, biologics are recommended.[23, 346]

Furthermore, we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups.

Applicability

A considerable limitation of our conclusions is that we have had to derive them primarily from efficacy trials that typically enroll a narrow spectrum of patients and are conducted in ideal settings. However, the direction and effect sizes of findings from effectiveness trials and observational studies were generally consistent with those from efficacy trials. Nonetheless, differences in the incidence of reported adverse events and discontinuation rates were obvious between clinical trials and population-based observational studies.

For example, clinical efficacy trials of infliximab reported infusion reactions, on average, in 17 percent of patients.[273] A prospective cohort study in a Canadian clinical care setting, however, reported substantially higher percentages.[329] Patients who were enrolled in efficacy trials usually suffered from more severe disease than the average patient in clinical practice.[347] For example, only a small proportion of consecutive patients with RA who were under the care of a private practice rheumatologist in Nashville, Tennessee, would have met eligibility criteria of the ERA (Early Rheumatoid Arthritis) trial;[77] only 31 percent of patients with early RA who had not taken MTX would have met the ERA criteria. The same pattern was true for the ATTRACT (anti-TNF trial in RA with concomitant therapy) study trials;[148, 347] only 5 percent of patients in a long-term RA database would have been eligible for this trial. Therefore, the applicability of results from efficacy trials to the average patient in community practice appears to be limited.

Additionally, some trials comparing MTX started with a lower dosing range than what is commonly given in practice.[57, 58, 110] This hinders evaluating some of the comparisons of MTX with other oral DMARDs. Otherwise, the dosing and frequencies of the included studies are directly applicable to community-based populations.

Conclusions

Despite the limitations of the available literature, this comprehensive review describes similar efficacy, functional capacity, and tolerability among oral DMARDs. Biologic DMARD comparisons are limited to mostly observational studies and findings from MTC meta-analyses. Our MTC meta-analysis,suggest some differences, such as etanercept having a higher probability of improvement in disease activity than most other biologic DMARDs, but are limited primarily to indirect evidence (Low SOE) and, therefore, should be interpreted with caution. The limited evidence precludes drawing firm conclusions about whether one combination strategy is better than another in early RA. Overall tolerability is similar among biologic and among oral DMARDs; however, several studies suggest that adverse events are more common with biologic DMARDs compared with oral DMARDs. Limited evidence does not suggest an increased risk of severe adverse events, including cardiovascular or cancer, with oral DMARDs. Most studies found no risk of cardiovascular events and malignancy with biologic DMARDs, except for cohort studies, which describe an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with oral DMARDs.

Clinical Relevance

Although the studies comparing oral DMARDs show therapeutic equivalence, the data are sparse and of lower strength, given the range of MTX dosing used in available trials. Vast clinical experience supports the use of MTX as the oral DMARD of choice unless there are contraindications. In addition, MTX is almost universally used as the anchor drug in studies of multidrug regimens. Data on the use of other oral DMARDs in combination with biologic therapy are sparse.

Data suggest that early institution of biologic therapy improves radiographic outcomes and should be considered in patients with poor prognostic features. Clearly, however, many patients can be effectively managed with oral DMARDs alone. There are few direct comparisons that can guide the selection of a specific biologic agent. Most agents have roughly equivalent efficacy using validated RA outcome measures (except anakinra, which is less effective). The apparent superiority of etanercept in MTCs is an unexpected finding and warrants further study.

Future Research

We have identified several areas that need further research to help clinicians and researchers arrive at stronger conclusions on the comparative efficacy, effectiveness, quality of life, and harms of medications for RA. Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) timing of initiation of therapies, and (3) applicability of combination strategies and biologic DMARD therapy in community practice.

Currently, evidence from systematic reviews, placebo-controlled trials, and observational studies does not allow us to draw any firm conclusions for the head-to-head comparisons between biologic DMARDs (i.e., those with greater than low strength of evidence). Although results of the MTC found some differences among biologics, the strength of evidence remains low, and head-to-head studies are needed to confirm or refute these results. Head-to-head RCTs are ideal to establish the comparative effectiveness and safety of biologic DMARDs. However, these types of trials would be costly and may be unrealistic. Although less rigorous, one initial approach could be to collect real data generated in clinical practice; for example, large databases

created from electronic medical records. This type of data would be more likely to reflect real practice.

Furthermore, we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups. Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases.

Timing of initiation of therapies needs to be addressed, including whether aggressive early treatment in RA influences the course and prognosis beneficially. Adequately powered, long-term RCTs must examine different treatment strategies with and without corticosteroids, oral DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in this population. These trials should be conducted over multiple years to guarantee that results provide a relevant assessment of the long-term prognosis of RA under different treatment strategies. Such trials would also provide insight about whether the long-term benefits of any combination of drugs outweigh the adverse effects.

Given that available long-term data indicate high discontinuation rates for drugs used to treat RA, having backup regimens is crucial. Additional well-conducted research is needed to assess the comparative efficacy and safety of oral DMARDs in patients who currently do not qualify for a treatment with a biologic DMARD. Also still unclear is whether newer oral DMARDs such as leflunomide have a better, long-term adverse events profile than older oral DMARDs such as MTX. Additionally, although combination strategies with oral DMARDs with or without corticosteroids appear more effective, further research examining *which* combination strategy is more effective would be beneficial for medical treatment decisionmaking.

Further studies need to be designed to mimic clinical decisionmaking. If patients are not doing well after 3 months of a therapy that takes less than 3 months to work, then the protocol needs to give them something different. Additionally, long-term outcomes are potentially more meaningful when protocols attempt to follow what would happen in real life. For example, radiographic progression becomes less meaningful if a clinician would have switched to a different drug due to lack of clinical effect earlier. Biologic DMARDs differ substantially in the route and frequency of administration, which can influence the choice of a biologic agent by patients and physicians. Establishing the comparative effectiveness and safety of biologic DMARDs, therefore, is helpful for balanced, informed decisionmaking.

The risk of rare but serious adverse events such as malignancies, serious infections, demyelinations, severe infusion reactions, or congestive heart failure must be established in well-conducted observational studies, such as large cohort or case-control studies. The balance of risks and benefits of biologic DMARDs can be determined reliably only if good long-term data on such harms are available.

In general, all future studies have to ensure applicability to patients seen in community practices. Future research has to establish the comparative effectiveness, health-related quality of life, and safety of all therapies, but especially biologic DMARDs, in settings that reflect daily clinical care and take into account factors such as varying adherence due to administration schedules, costs, and adverse events. The current evidence indicates that severity of disease and population characteristics may differ substantially between the highly selected populations enrolled in efficacy trials and those treated in daily clinical practice. Future trials must plan subgroup analyses in older patients or patients with comorbidities a priori.

References

1. Bolen J, Helmick CG, Sacks JJ, et al. Prevalence of self-reported arthritis or chronic joint symptoms among adults--United States, 2001. MMWR Morb Mortal Wkly Rep. 2002 Oct 25;51(42):948-50. PMID: 12437034.

2. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008 Jan;58(1):15-25. PMID: 18163481.

3. Bruce TO. Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. Curr Psychiatry Rep. 2008 Jun;10(3):258-64. PMID: 18652795.

4. Husted JA, Gladman DD, Farewell VT, et al. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum. 2001 Apr;45(2):151-8. PMID: 11324779.

5. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol. 2001 Aug;28(8):1842-6. PMID: 11508587.

6. Borman P, Toy GG, Babaoglu S, et al. A comparative evaluation of quality of life and life satisfaction in patients with psoriatic and rheumatoid arthritis. Clin Rheumatol. 2006 Apr 19PMID: 16622591.

7. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care. 2006 Apr;44(4):304-10. PMID: 16565630.

8. Mau W, Listing J, Huscher D, et al. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol. 2005 Apr;32(4):721-8. PMID: 15801031.

9. Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum. 2003 Oct;48(10):2750-62. PMID: 14558079.

10. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology (Oxford). 2006 Mar;45(3):325-31. PMID: 16287927.

11. Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis. 2006 Sep;65(9):1175-83. PMID: 16540552.

12. Ozminkowski RJ, Burton WN, Goetzel RZ, et al. The impact of rheumatoid arthritis on medical expenditures, absenteeism, and short-term disability benefits. J Occup Environ Med. 2006 Feb;48(2):135-48. PMID: 16474262.

13. . National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003. MMWR Morb Mortal Wkly Rep. 2007 Jan 12;56(1):4-7. PMID: 17218935.

14. Pugner KM, Scott DI, Holmes JW, et al. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum. 2000 Apr;29(5):305-20. PMID: 10805355.

15. Orozco G, Rueda B, Martin J. Genetic basis of rheumatoid arthritis. Biomed Pharmacother. 2006 Dec;60(10):656-62. PMID: 17055211.

16. Turesson C, Schaid DJ, Weyand CM, et al. The impact of HLA-DRB1 genes on extra-articular disease manifestations in rheumatoid arthritis. Arthritis Res Ther. 2005;7(6):R1386-93. PMID: 16277691.

17. Muller-Ladner U, Pap T, Gay RE, et al. Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheumatol. 2005 Dec;1(2):102-10. PMID: 16932639.

18. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001 Mar 22;344(12):907-16. PMID: 11259725.

19. Greiner A, Plischke H, Kellner H, et al. Association of anti-cyclic citrullinated peptide antibodies, anti-citrullin antibodies, and IgM and IgA rheumatoid factors with serological parameters of disease activity in rheumatoid arthritis. Ann N Y Acad Sci. 2005 Jun;1050:295-303. PMID: 16014545.

20. Liao KP, Batra KL, Chibnik L, et al. Anti-cyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis. Ann Rheum Dis. 2008 Nov;67(11):1557-61. PMID: 18234714.

21. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-24. PMID: 3358796.

22. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8. PMID: 20699241.

23. Saag KG, Gim GT, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care Res. 2008;59(6):762-84.

24. Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008 Jan 15;148(2):124-34. PMID: 18025440.

25. Chen YF, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006;10(42).

26. Donahue KE, Gartlehner G, Jonas DE, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis and psoriatic arthritis in adults. Comparative Effectiveness Review No. 11.(Prepared by RTI-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality; 2007. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

27. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Can Med Assoc J. 2009;181:787.

28. Wailoo A, Brennan A, Bansback N, et al. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program (prepared by University of Sheffeld under contract no: RFQ 01R000206). Agency for Healthcare Research and Quality. Technology Assessment. Rockville, MD: 2006.

29. National Institute for Health, Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. London: National Institute for Health and Clinical Excellence; 2007.

30. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.

31. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001.

32. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173. PMID: 14499048.

33. Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0. Rockville, MD: Agency for Healthcare Research and Quality; October 2007 (draft). http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf.

34. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

35. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105-24. PMID: 15449338.

36. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med. 1996 Dec 30;15(24):2733-49. PMID: 8981683.

37. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. Ann Intern Med. 1999 Jun 15;130(12):1005-13. PMID: 10383350.

38. Whitehead A. Meta-analysis of controlled clinical trials. Chichester, UK: John Wiley & Sons, Ltd.; 2002.

39. Stevens A. The BUGS Project. Cambridge, UK: Hosted by the MRC Biostatistics Unit. www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml Accessed on May 2, 2011.

40. Multi-Parameter Evidence Synthesis (MPES) Research Group. Mixed Treatment Comparisons. University of Bristol, Community-Based Medicine. www.bris.ac.uk/cobm/research/mpes/mtc.html. Accessed May 3, 2011.

41. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91. PMID: 9250266.

42. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003 Mar 1;326(7387):472. PMID: 12609941.

43. Sauriol L, Laporta M, Edwardes MD, et al. Meta-analysis comparing newer antipsychotic drugs for the treatment of schizophrenia: evaluating the indirect approach. Clin Ther. 2001 Jun;23(6):942-56. PMID: 11440294.

44. Felson DT, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.

45. van Tuyl LH, Vlad SC, Felson DT, et al. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum. 2009 May 15;61(5):704-10. PMID: 19405006.

46. Prevoo ML, van Gestel AM, van T. Hof MA, et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996 Nov;35(11):1101-5. PMID: 8948296.

47. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006 May;65(5):637-41. PMID: 16219709.

48. Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol. 1993 Mar;20(3):557-60. PMID: 8478873.

49. Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum. 2000 Jul;43(7):1478-87. PMID: 10902749.

50. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes. 2003;1:4. PMID: 12737635.

51. Ware JE, Snow KK, Kosinski M, et al. SF-36® Health Survey Manual and Interpretation Guide. Boston, MA: New England Medical Center, The Health Institute; 1993.

52. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum. 2001 Aug;45(4):384-91. PMID: 11501727.

53. Bruynesteyn K, van der Heijde D, Boers M, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum. 2002 Apr;46(4):913-20. PMID: 11953967.

54. Kirwan JR, Hallgren R, Mielants H, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis. 2004;63(6):688-95. PMID: 15140776.

55. Osiri M, Shea B, Robinson V, et al. Leflunomide for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2003(1):CD002047. PMID: 12535423.

56. Cohen S, Cannon G, Schiff M, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of leflunomide in the treatment of rheumatoid arthritis. Arthritis Rheum. 2001;44(9):1984-92. PMID: 11592358.

57. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis. 1999;58(4):220-5.

58. Haagsma CJ, van Riel PL, de Jong AJ, et al. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36(10):1082-8.

59. Capell H, Madhok R, Porter D, et al. Combination therapy with sulphasalazine and methotrexate is more effective than either drug alone in rheumatoid arthritis (ra) patients with a suboptimal response to sulphasalazine: Results from the double blind placebo controlled mascot study. Ann Rheum Dis. 2007 Feb;66(2):235-41.

60. Larsen A, Kvien TK, Schattenkirchner M, et al. Slowing of disease progression in rheumatoid arthritis patients during long-term treatment with leflunomide or sulfasalazine. Scand J Rheumatol. 2001;30(3):135-42.

61. O'Dell JR, Leff R, Paulsen G, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46(5):1164-70.

62. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996 May 16;334(20):1287-91. PMID: 8609945.

63. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007(1):CD006356. PMID: 17253590.

64. Choy EH, Smith CM, Farewell V, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis. 2008 May;67(5):656-63. PMID: 17768173.

65. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum. 2005;52(11):3360-70.

66. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008 Aug;67(8):1096-103. PMID: 18055472.

67. Geborek P, Crnkic M, Petersson IF, et al. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis. 2002 Sep;61(9):793-8. PMID: 12176803.

68. Weaver AL, Lautzenheiser RL, Schiff MH, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin. 2006 Jan;22(1):185-98. PMID: 16393444.

69. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum. 2006 Feb;54(2):600-6. PMID: 16447237.

70. Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol. 2007 Dec;34(12):2334-42. PMID: 17985409.

71. Kievit W, Adang EM, Fransen J, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis. 2008 Sep;67(9):1229-34. PMID: 18174220.

72. Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum. 2007 May;56(5):1417-23. PMID: 17469098.

73. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab results from eight years of surveillance of clinical practice in the Nationwide Danish DANBIO Registry. Arthritis Rheum. 2010;62(1):22-32.

74. Gartlehner G, Hansen RA, Jonas BL, et al. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408.

75. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess. 2004 May;8(18):iii-iv, ix-x, 1-105. PMID: 15130461.

76. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26-37. PMID: 16385520.

77. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000 Nov 30;343(22):1586-93. PMID: 11096165.

78. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther. 2006;8(3):R66. PMID: 16600016.

79. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9. PMID: 15146410.

80. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis. 2007 Feb;66(2):228-34. PMID: 16935912.

81. Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 May 30;54(6):1786-94. PMID: 16736520.

82. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43. PMID: 15529377.

83. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):716-22. PMID: 16508932.

84. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81. PMID: 15201414.

85. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357-62.

86. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81. PMID: 15001324.

87. van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Ann Rheum Dis. 2006 Feb 7;65(11):1478-83. PMID: 16464988.

88. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis. 2005 Sep;64(9):1274-9. PMID: 15708884.

89. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009 Dec;68(12):1870-7. PMID: 16935912.

90. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008 Aug 2;372(9636):375-82. PMID: 18635256.

91. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum. 2010 Mar;62(3):674-82. PMID: 20187135.

92. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83. PMID: 19644849.

93. Karanikolas G, Charalambopoulos D, Vaiopoulos G, et al. Adjunctive anakinra in patients with active rheumatoid arthritis despite methotrexate, or leflunomide, or cyclosporin-A monotherapy: a 48-week, comparative, prospective study. Rheumatology (Oxford). 2008 Sep;47(9):1384-8. PMID: 18603660.

94. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis. 2009 Jan;68(1):33-9. PMID: 18230627.

95. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18. PMID: 9251634.

96. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002 Feb;46(2):347-56. PMID: 11840436.

97. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of Combination Therapy With Single-Drug Therapy in Early Rheumatoid Arthritis: a Randomised Trial. Lancet. 1999;353(9164):1568-73.

98. Korpela M, Laasonen L, Hannonen P, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the Fin-Raco Study. Arthritis Rheum. 2004;50(7):2072-81.

99. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. 2009 Aug 8;374(9688):459-66. PMID: 19665644.

100. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90. PMID: 16258899.

101. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol. 2006 Nov-Dec;24(6 Suppl 43):S-77-82. PMID: 17083767.

102. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007;146(6):406-15. PMID: 2008225574.

103. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Jan 15;61(1):4-12. PMID: 19116965.

104. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med. 1999;159(21):2542-50.

105. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology (Oxford). 2000;39(6):655-65.

106. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9. PMID: 20447954.

107. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. Lancet. 1999;353(9149):259-66.

108. Smolen JS. Efficacy and safety of the new DMARD leflunomide: comparison to placebo and sulfasalazine in active rheumatoid arthritis. Scand J Rheumatol. 1999;112(Supplement):15-21.

109. Sharp JT, Strand V, Leung H, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum. 2000;43(3):495-505.

110. Schipper LG, Fransen J, Barrera P, et al. Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add? Rheumatology (Oxford). 2009 Oct;48(10):1247-53. PMID: 19638454.

111. Maillefert JF, Combe B, Goupille P, et al. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. Ann Rheum Dis. 2003;62(8):764-6.

112. BlueCross BlueShield Technology Evaluation Center (TEC). Special report: evidence on sequencing of conventional and biological disease-modifying anti-rheumatic drugs. 2003 2003;18(11).

113. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med. 2003 Nov 13;349(20):1907-15. PMID: 14614165.

114. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):2263-71. PMID: 16052582.

115. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 Apr;33(4):681-9. PMID: 16568505.

116. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis - a randomized trial. Ann Intern Med. 2006 Dec;144:865-76.

117. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23. PMID: 16162882.

118. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005(3):CD005113

119. van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003 Dec;62(12):1168-77. PMID: 14644854.

120. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11. PMID: 15146409.

121. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003 Dec;30(12):2563-71. PMID: 14719195.

122. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004 May;63(5):508-16. PMID: 15082480.

123. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45. PMID: 12528101.

124. Weinblatt ME, Keystone EC, Furst DE, et al. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis. 2006 Jun;65(6):753-9. PMID: 16308341.

125. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18(3):252-62. PMID: 18330677.

126. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: Systematic review and metaanalysis of efficacy and safety. BMC Musculoskeletal Disorders. 2008 April 17;9:52. PMID: 18419803.

127. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol. 2007;10(1):9-16.

128. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum. 1998 Dec;41(12):2196-204. PMID: 9870876.

129. Nuki G, Bresnihan B, Bear MB, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46. PMID: 12428223.

130. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum. 2000 May;43(5):1001-9. PMID: 10817552.

131. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24. PMID: 11920396.

132. Cohen SB, Woolley JM, Chan W. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol. 2003 Feb;30(2):225-31. PMID: 12563672.

133. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8. PMID: 15082469.

134. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev. 2009(1):CD005121. PMID: 19160248.

135. Jobanputra P, Barton P, Bryan S, et al. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110. PMID: 12387732.

136. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis. 2006 Mar;65(3):328-34. PMID: 16079172.

137. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis. 2005 Nov;64(11):1582-7. PMID: 15860509.

138. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006 Apr;54(4):1063-74. PMID: 16572441.

139. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Review. 2003(3):CD004525.

140. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86. PMID: 10075615.

141. Mathias SD, Colwell HH, Miller DP, et al. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther. 2000 Jan;22(1):128-39. PMID: 10688396.

142. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9. PMID: 9920948.

143. Lan JL, Chou SJ, Chen DY, et al. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004 Aug;103(8):618-23. PMID: 15340661.

144. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997 Jul 17;337(3):141-7. PMID: 9219699.

145. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis. 2009 Jul;68(7):1146-52. PMID: 18794178.

146. Blumenauer B, Judd M, Wells G, et al. Infliximab for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2002(3):CD003785.

147. Taylor P, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis Rheum. 2006;54(1):47-53.

148. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9. PMID: 10622295.

149. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004 Apr;50(4):1051-65. PMID: 15077287.

150. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum. 2005 Apr;52(4):1020-30. PMID: 15818697.

151. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602. PMID: 11096166.

152. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):149-55. PMID: 14722203.

153. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006 Jan;33(1):37-44. PMID: 16395748.

154. Kavanaugh A, St Clair EW, McCune WJ, et al. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol. 2000 Apr;27(4):841-50. PMID: 10782805.

155. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86. PMID: 16572442.

156. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR J Rheumatol. 2006;9(2):127-30. PMID: 2006338105.

157. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006 May;54(5):1390-400. PMID: 16649186.

158. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806. PMID: 2006485778.

159. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis. 2009 Feb;68(2):216-21. PMID: 18388156.

160. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008 Jun 15;59(6):785-93. PMID: 18512710.

161. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment - results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006 May 1;54(May):1390-400.

162. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010 Sep;69(9):1629-35. PMID: 20488885.

163. Finckh A, Ciurea A, Brulhart L, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis. 2010 Feb;69(2):387-93. PMID: 19416802.

164. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008 Mar 22;371(9617):987-97. PMID: 18358926.

165. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. PMID: 19015206.

166. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008 Apr;58(4):964-75. PMID: 18383539.

167. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. PMID: 19015207.

168. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008 Nov;58(11):3319-29. PMID: 18975346.

169. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. PMID: 19066176.

170. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21. PMID: 19560810.

171. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis. 2010(6):1129-35. PMID: CN-00748612.

172. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007 Sep;66(9):1162-7. PMID: 17485422.

173. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12-9. PMID: 18979150.

174. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006 Sep;54(9):2817-29. PMID: 16947782.

175. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008 Nov;67(11):1516-23. PMID: 18625622.

176. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80. PMID: 2008506176.

177. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jul 7(7)PMID: CD008331.

178. Kremer JL, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2010 Mar;63(3):609-21. PMID: 21360490.

179. Hochberg MC, Tracy JK, Hawkins-Holt M, et al. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 2003;62 Suppl 2:ii13-6.

180. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009(4)PMID: CD007848.

181. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv. PMID: 16014203.

182. Chen DY, Chou SJ, Hsieh TY, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. J Formos Med Assoc. 2009 Apr;108(4):310-9. PMID: 19369178.

183. Wiens A, Venson R, Correr CJ, et al. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. PMID: 20334454.

184. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Stat Med. 2007;26(6):1237-54.

185. Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. Pharmacotherapy. 2011 Jan;31(1):39-51. PMID: 21182357.

186. Bergman GJ, Hochberg MC, Boers M, et al. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum. 2010 Jun;39(6):425-41. PMID: 20223500.

187. Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH Therapeutic Review: Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis. Ottawa, ON: CADTH; 2010. www.cadth.ca/media/pdf/TR_RA_Clinical_and_Economic_Overview_e.pdf. Accessed December 1, 2010.

188. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun;46(6):1443-50. PMID: 12115173.

189. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1232-42. PMID: 15996057.

190. Hoff M, Kvien TK, Kalvesten J, et al. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis. 2009 Jul;68(7):1171-6. PMID: 18801760.

191. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis. 2009;68(7):1086-93.

192. Kavanaugh A, Klareskog L, van der Heijde D, et al. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis. 2008 Oct;67(10):1444-7. PMID: 18535115.

193. Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis. 2010 Jul;69(7):1298-304. PMID: 20421343.

194. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis. 2009 Jun;68(6):823-7. PMID: 18593759.

195. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2006;45(Dec):1558-65.

196. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Jun;68(6):914-21. PMID: 18662933.

197. Van Der Kooij SM, Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2008;67(2):266-9. PMID: 2008057728.

198. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics. 1999 Feb;15(2):141-55. PMID: 10351188.

199. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 1999 Sep;42(9):1870-8. PMID: 10513801.

200. Scott DL, Smolen JS, Kalden JR, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis. 2001;60(10):913-23.

201. Van Riel PLCM, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Ann Rheum Dis. 2008;67(8):1104-10. PMID: 2008355994.

202. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum. 2004;50(1):55-62.

203. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 04/01/;33(Apr):681-9.

204. Wells G, Li T, Maxwell L, et al. Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):260-5. PMID: 17846044.

205. Hassett AL, Li T, Buyske S, et al. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin. 2008 May;24(5):1443-53. PMID: 18402714.

206. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006 10/01/;45(Oct):1238-46.

207. Li T, Gignac M, Wells G, et al. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther. 2008 Apr;30(4):734-48. PMID: 18498922.

208. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol. 2008 Jan;35(1):20-30. PMID: 18050385.

209. Kavanaugh A, Smolen JS, Emery P, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1592-600. PMID: 19877104.

210. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010(1):CD008341. PMID: 20091667.

211. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care. 2002 Mar;8(3):231-40. PMID: 11915973.

212. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: The COMET trial. Ann Rheum Dis. 2010 Jan;69(1):222-5. PMID: 2010021141.

213. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. 1994. www.ich.org/LOB/media/MEDIA436.pdf.

214. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum. 2008 Aug 15;59(8):1090-6. PMID: 18668583.

215. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther. 2008;10(2):R30. PMID: 18325087.

216. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum. 2006 12/01/;54(Dec):3790-8.

217. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006 May;54(5):1435-9. PMID: 16645972.

218. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford). 2007 Jul;46(7):1157-60. PMID: 17478469.

219. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis. 2006 Sep 15;43(6):717-22. PMID: 16912945.

220. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002 Sep;46(9):2294-300. PMID: 12355476.

221. Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Aug 15;59(8):1074-81. PMID: 18668604.

222. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum. 2007 Jun;56(6):1754-64. PMID: 17530704.

223. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol. 2008 Mar;35(3):387-93. PMID: 18260176.

224. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum. 2007 Dec 15;57(8):1431-8. PMID: 18050184.

225. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009 Feb 18;301(7):737-44. PMID: 19224750.

226. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 Feb;69(2):380-6. PMID: 19359261.

227. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Oct 15;57(7):1151-7. PMID: 17907232.

228. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol. 2007 May-Jun;36(3):172-8. PMID: 17657669.

229. Cannon GW, Holden WL, Juhaeri J, et al. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol. 2004 Oct;31(10):1906-11. PMID: 15468352.

230. Maetzel A, Wong A, Strand V, et al. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford). 2000 Sep;39(9):975-81. PMID: 10986302.

231. O'Dell JR, Petersen K, Leff R, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):213-8. PMID: 16358366.

232. Schipper LG, Fransen J, Barrera P, et al. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology (Oxford). 2009 Jul;48(7):828-33. PMID: 19458163.

233. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol. 2008 Jun;35(6):979-85. PMID: 18412314.

234. Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum. 2006 Aug 15;55(4):531-6. PMID: 16874796.

235. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther. 2006;8(5):R151. PMID: 16984661.

236. Suissa S, Ernst P, Hudson M, et al. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med. 2004 Jul 15;117(2):87-92. PMID: 15234643.

237. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006 Feb;54(2):628-34. PMID: 16447241.

238. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum. 2009 Mar 15;61(3):300-4. PMID: 19248128.

239. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis. 2009 May 15;48(10):1364-71. PMID: 19368499.

240. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford). 2010;49:82-90.

241. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):692-701. PMID: 16508929.

242. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005 Nov;32(11):2130-5. PMID: 16265690.

243. Fuerst M, Mohl H, Baumgartel K, et al. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatol Int. 2006 Oct;26(12):1138-42. PMID: 16736164.

244. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol. 2006 Dec;33(12):2412-5. PMID: 17143978.

245. Karstila KL, Rantalaiho VM, Mustonen JT, et al. Renal safety of initial combination versus single DMARD therapy in patients with early rheumatoid arthritis: an 11-year experience from the FIN-RACo Trial. Clin Exp Rheumatol. 2010 Jan-Feb;28(1):73-8. PMID: 20346242.

246. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol. 2009 Jul-Aug;27(4):678-84. PMID: 19772806.

247. Flendrie M, Creemers MC, Welsing PM, et al. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii30-3. PMID: 14532145.

248. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol. 2006 Dec;33(12):2433-8. PMID: 17014004.

249. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis. 2007 Sep;66(9):1184-9. PMID: 17389656.

250. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007 Jan;56(1):13-20. PMID: 17195186.

251. Kristensen LE, Saxne T, Nilsson JA, et al. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther. 2006;8(6):R174. PMID: 17121678.

252. Marchesoni A, Zaccara E, Gorla R, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci. 2009 Sep;1173:837-46. PMID: 19758236.

253. Pan SM, Dehler S, Ciurea A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum. 2009 May 15;61(5):560-8. PMID: 19405000.

254. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis. 2007 Feb;66(2):189-94. PMID: 16984942.

255. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis. 2009 Jul;68(7):1136-45. PMID: 18753157.

256. Wiens A, Correr CJ, Pontarolo R, et al. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol. 2009 Oct;70(4):337-44. PMID: 19751268.

257. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis. 2007 Jun;66(6):732-9. PMID: 17329305.

258. Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006 Aug 31;54(9):2807-16. PMID: 16947384.

259. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34. PMID: 12687534.

260. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis. 2005 Feb;64(2):246-52. PMID: 15208177.

261. Moreland LW, Weinblatt ME, Keystone EC, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. J Rheumatol. 2006 May;33(5):854-61. PMID: 16541481.

262. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004 Mar 1;116(5):305-11. PMID: 14984815.

263. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford). 2007 Nov;46(11):1688-93. PMID: 17938138.

264. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum. 2008 Mar;58(3):667-77. PMID: 18311816.

265. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J. 2008 Aug;156(2):336-41. PMID: 18657665.

266. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8. PMID: 15996054.

267. Dixon WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2007;56(9):2905-12. PMID: 2007480319.

268. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jul 25;54(8):2368-76. PMID: 16868999.

269. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford, England). 2011 Jan;50(1):124-31. PMID: 20675706.

270. Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. J Rheumatol. 2010;37:928-31.

271. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. PMID: 16705109.

272. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009 Jan;68(1):25-32. PMID: 18203761.

273. Schaible TF. Long term safety of infliximab. Can J Gastroenterol. 2000 Sep;14(Suppl C):29C-32C. PMID: 11023558.

274. Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005 Nov;52(11):3403-12. PMID: 16255017.

275. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford). 2007 July 31, 2006;46(2):327-34.

276. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1421-6. PMID: 15829572.

277. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007 Apr;56(4):1125-33. PMID: 17393394.

278. Curtis JR, Xi J, Patkar N, et al. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007 Dec;56(12):4226-7. PMID: 18050253.

279. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010 Mar;69(3):522-8. PMID: 19854715.

280. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004 May 1;38(9):1261-5. PMID: 15127338.

281. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005 Jul;52(7):1986-92. PMID: 15986370.

282. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003 Aug;48(8):2122-7. PMID: 12905464.

283. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001 Oct 11;345(15):1098-104. PMID: 11596589.

284. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004 Aug 1;39(3):295-9. PMID: 15306993.

285. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum. 2004 Feb;50(2):372-9. PMID: 14872478.

286. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum. 2002 Oct;46(10):2565-70. PMID: 12384912.

287. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum. 2003 Feb;48(2):319-24. PMID: 12571839.

288. Anonymous. Rituxan (rituximab) package insert. Genentech, Inc. South San Francisco, CA. 2007.

289. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004 Jun;50(6):1740-51. PMID: 15188349.

290. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9. PMID: 17469100.

291. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703. PMID: 15695534.

292. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1414-20. PMID: 15843454.

293. Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64. PMID: 16947774.

294. Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. PMID: 19019889.

295. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009 Nov;60(11):3180-9. PMID: 19877027.

296. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev. 2010 Jan;9(3):175-80. PMID: 19647103.

297. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010;12(1):R5. PMID: 20064207.

298. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jul;65(7):889-94. PMID: 16439435.

299. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001 Dec;44(12):2862-9. PMID: 11762947.

300. Anonymous. Humira (adalimumab) package insert. Abbott Labs. North Chicago, IL. 2006.

301. Anonymous. Remicade (infliximab) package insert. Centocor, Inc. Malvern, PA. 2006.

302. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7(3):R545-51. PMID: 15899041.

303. Shakoor N, Michalska M, Harris CA, et al. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet. 2002 Feb 16;359(9306):579-80. PMID: 11867114.

304. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther. 2005;7(3):R666-76. PMID: 15899052.

305. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2009 Feb;68(2):209-15. PMID: 18385277.

306. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care. 2003 Oct;9(6 Suppl):S136-43. PMID: 14577718.

307. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. Value Health. 2010 Sep-Oct;13(6):805-12. PMID: 21054657.

308. Anonymous. Dexamethasone package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.

309. Anonymous. PredniSONE package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.

310. Anonymous. MethylPREDNIsolone package insert. Sandoz, Inc. Princeton, NJ. 2006.

311. Anonymous. Cortisone Acetate package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.

312. Anonymous. Cortef (hydrocortisone) package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.

313. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med. 1994 Feb;96(2):115-23. PMID: 8109596.

314. Anonymous. Methotrexate package insert. Mayne Pharma (USA) Inc. Paramus, NJ. 2005.

315. Anonymous. Azulfidine (sulfasalazine) package insert. Pharmacia & Upjohn Co. NY, NY. 2006.

316. Anonymous. Hydroxychloroquine package insert. Sandoz, Inc. Broomfield, CO. 2004.

317. Anonymous. Arava (leflunomide) package insert. Aventis Pharmaceuticals Inc. Kansas City, MO. 2005.

318. Svensson B, Ahlmen M, Forslind K. Treatment of early RA in clinical practice: a comparative study of two different DMARD/corticosteroid options. Clin Exp Rheumatol. 2003 May-Jun;21(3):327-32. PMID: 12846051.

319. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Aug;65(8):1006-12. PMID: 16396977.

320. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res. 2003;23(4):119-28. PMID: 15224501.

321. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11. PMID: 12755552.

322. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40. PMID: 12796126.

323. Coletta AP, Clark AL, Banarjee P, et al. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. Eur J Heart Fail. 2002 Aug;4(4):559-61. PMID: 12167397.

324. Food and Drug Administration. FDA alert on rituximab. 2006. www.fda.gov/cder/drug/infopage/rituximab/default.htm. Accessed March 25, 2007.

325. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004 Jun;50(6):1959-66. PMID: 15188373.

326. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007 Apr;34(4):689-95. PMID: 17117492.

327. Kawakami K, Ikari K, Kawamura K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of tumour necrosis factor-alpha blockers decreases complications? Rheumatology (Oxford). 2010;49:341-7.

328. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):415-26. PMID: 19505394.

329. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol. 2004 Oct;31(10):1912-7. PMID: 15468353.

330. Anonymous. Kineret (anakinra) package insert. Amgen, Inc. Thousand Oaks, CA. 2004.

331. Anonymous. Enbrel (etanercept) package insert. Immunex Corporation. Thousand Oaks, CA. 2006.

332. Baecklund E, Ekbom A, Sparen P, et al. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ. 1998 Jul 18;317(7152):180-1. PMID: 9665898.

333. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum. 2002 Dec;46(12):3151-8. PMID: 12483718.

334. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol. 2005 Jul;141(7):861-4. PMID: 16027301.

335. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis Rheum. 2007;56(9):2886-95. PMID: 2007480317.

336. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum. 2006 May;54(5):1429-34. PMID: 16645971.

337. Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis. 2010 Sep;69(9):1612-7. PMID: 20448284.

338. Miller LG, Hays RD. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. AIDS Read. 2000 Mar;10(3):177-85. PMID: 10758022.

339. Grijalva CG, Chung CP, Arbogast PG, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care. 2007 Oct;45(10 Supl 2):S66-76. PMID: 17909386.

340. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002;137(9):726-33.

341. Keystone E, Freundlich B, Schiff M, et al. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol. 2009 Mar;36(3):522-31. PMID: 19228659.

342. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol. 1995;22(2):218-23.

343. Tesser J, Fleischmann R, Dore R, et al. Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. J Rheumatol. 2004;31(4):649-54.

344. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum. 2004 Jun;50(6):1752-60. PMID: 15188350.

345. Osiri M, Shea B, Robinson V, et al. Leflunomide for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2002 Jun;30(6):1182-90. PMID: 12784387.

346. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford). 2005 Feb;44(2):157-63. PMID: 15637039.

347. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum. 2003 Feb;48(2):313-8. PMID: 12571838.

Appendix A. Search Strings

2007 Search

Search	Most Recent Queries	Result
#2	Search ("Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH])	82356
#3	Search ("Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]) Limits: All Adult: 19+ years, English, Publication Date from 1990, Humans	16462
#5	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	190820
#6	Search #3 AND #5	686
#7	Search #3 AND #5 Limits: Editorial, Letter, Practice Guideline	18
#8	Search #6 NOT #7	668
#18	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	28712
#28	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin"[Substance Name] OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	8701
#29	Search #3 AND #18	1365
#30	Search #3 AND #28	777
#31	Search #3 AND #18 Limits: Editorial, Letter, Practice Guideline	237
#32	Search #29 NOT #31	1128
#33	Search #3 AND #28 Limits: Editorial, Letter, Practice Guideline	178
#34	Search #30 NOT #33	599
#35	Search #8 OR #30 OR #34	1405

July 2009 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	85528
#2	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	239378
#3	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	31900
#4	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin"[Substance Name] OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	15567
#5	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1127
#6	Search "golimumab "[Substance Name]	12
#7	Search #2 OR #3 OR #4 OR #5 OR #6	283303
#8	Search #7 AND #1	11283
#9	Search #7 AND #1 Limits: Editorial, Letter, Practice Guideline	1368
#10	Search #8 NOT #9	9915
#11	Search #8 NOT #9 Limits: Humans, English, All Adult: 19+ years	4079
#12	Search Limits: Entrez Date from 2006/06/01, Humans, English, All Adult: 19+ years	498212
#13	Search #11 AND #12	1027

August 2009 Search (for Tocilizumab)

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	85692
#2	Search actemra	4
#4	Search "tocilizumab "[Substance Name]	103
#5	Search #2 OR #4	104
#6	Search #5 AND #1	75
#7	Search #5 AND #1 Limits: Editorial, Letter, Practice Guideline	8
#8	Search #6 NOT #7	67
#9	Search #6 NOT #7 Limits: Humans, English, All Adult: 19+ years	14
#10	Search #9 Limits: Entrez Date from 2006/06/01	14

March 2010 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	87507
#2	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	244454
#3	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	32512
#12	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	16979
#13	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1309
#14	Search actemra OR "tocilizumab"[Substance Name]	134
#15	Search "golimumab "[Substance Name]	32
#16	Search #2 OR #3 OR #12 OR #13 OR #14 OR #15	290354
#17	Search #16 AND #1	11855
#18	Search #17 Limits: Editorial, Letter, Practice Guideline	1450
#19	Search #17 NOT #18	10405
#20	Search #19 Limits: Humans, English, All Adult: 19+ years	4358
#21	Search "2009/05/01"[Entrez Date] : "3000"[Entrez Date] Limits: Humans, English, All Adult: 19+ years	89610
#22	Search #20 AND #21 Limits: Humans, English, All Adult: 19+ years Sort by: PublicationDate	176

August 2010 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	89162
#2	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	248455
#3	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	33034
#4	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	18212
#5	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1468
#6	Search actemra OR "tocilizumab"[Substance Name]	250
#7	Search "golimumab "[Substance Name]	47
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	296041
#9	Search #1 AND #8	12290
#10	Search #9 Limits: Editorial, Letter, Practice Guideline	1498
#11	Search #9 NOT #10	10792
#12	Search #11 Limits: Humans, English, All Adult: 19+ years	4578
#13	Search ((#12) AND "2010/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date] Sort by: Author	125

January 2011 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	90392
#2	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	251312
#3	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	33430
#4	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	19150
#5	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1583
#6	Search actemra OR "tocilizumab"[Substance Name]	305
#7	Search "golimumab "[Substance Name]	56
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	300191
#9	Search #1 AND #8	12597
#10	Search #9 Limits: Editorial, Letter, Practice Guideline	1540
#11	Search #9 NOT #10	11057
#12	Search #11 Limits: Humans, English, All Adult: 19+ years	4714
#13	Search ((#12) AND "2010/05/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date] Sort by: Author	116

Appendix B. Review and Abstraction Forms

Abstract Review Questions:		
Original research (no review articles, editorials, letters to the editor) published in English after 1990 in adult patients with rheumatoid or psoriatic arthritis AND is not a case report or case series?	Yes	
	No	
	Cannot determine	
	No, but article will be used for background	
Study includes one or more of the following pharmaceutical interventions (check all that apply):	Corticosteroids	
	Oral DMARDs including methotrexate, leflunomide, sulfasalazine, cyclosporine, hydroxychloroquine	
	Biologic DMARDs including anakinra, etanercept, infliximab, adalimumab, abatacept, certolizumab, golimumab, tocilizumab, rituximab	
	Cannot determine	
	Comparison is not of interest	
Study compares:	Two of the included drugs	
	Biological DMARD (TIM) versus placebo	
	One of the included drugs versus placebo but is of interest because of specific outcomes such as adverse events	
	Nothing of interest and article should not be included	
	Cannot determine	
Addresses one or more of the following key questions (check all that apply):	KQ1 For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission (reduce the incidence flare-ups?	
	KQ2- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?	
	KQ3 For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?	
	KQ4 What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?	
	Cannot determine by the title or abstract	
	None of the above	
Study design is one of the following:	RCT 3 months or longer	
	Meta-analysis or systematic review	
	Observational Study (N is greater or equal to 100) 3 months or longer	
	Case series	
	Case report	
	None of the above- so exclude	
	None of the above- but include	
	Cannot determine	

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Previewing at Level 2

Reviewer Comments (Add a Comment)

Refid: 2161, P. Efthimiou, A. Kontzias, C. M. Ward and N. S. Ogden, Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy?, *Nat Clin Pract Rheumatol*, 3(6), 2007, p. 328-35
State: Excluded, Level: 1

Save to finish later | Submit Data

1. **Should the article be *excluded* for any of the following reasons?**

- [ ] Study reported only in abstract
- [ ] Wrong outcome (i.e. pharmakinetic or intermediate outcomes)
- [ ] Wrong drug (not one of the following: corticosteroids, methotrexate, leflunomide, sulfasalazine, cyclosporine, hydroxychloroquine, anakinra, etanercept, infliximab, adalimumab, abatacept, certolizumab, golimumab, tocilizumab, rituximab)
- [ ] Wrong population (For example pediatric studies)
- [ ] Wrong publication type (e.g. letter or editorial)
- [ ] Wrong design (i.e. non--systematic meta-analysis or no comparision arm)
- [ ] RCT (n<100)
- [ ] Other? (Please explain!)
- [ ] Background article
- [ ] None of the above- should be included!

If the article has been excluded in the above question, the next two questions do not need to be answered.

2. **Which of the following key questions are addressed by the article**

- [ ] KQ1- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission (reduce the incidence flare-ups)?
- [ ] KQ2- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?
- [ ] KQ3- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?
- [ ] KQ4- What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?
- [ ] None of the above

3. **What is the study design?**

- ( ) RCT > or equal to 100
- ( ) Observational > or equal to 100
- ( ) Meta-analysis or systematic review (i.e. Cochrane Review)

○ None of the above, but it should be abstracted- please note why in the box!

○ None of the above, so exclude.

Clear Selection

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Reviewer Comments (Add a Comment)

Refid: 2161, P. Efthimiou, A. Kontzias, C. M. Ward and N. S. Ogden, Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy?, *Nat Clin Pract Rheumatol*, 3(6), 2007, p. 328-35
State: Excluded, Level: 1

Keywords:
Adrenal Cortex Hormones/therapeutic use

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Abstract:
Adult-onset Still's disease is a rare systemic inflammatory disease of unknown etiology, characterized by daily high, spiking fevers, evanescent rash, and arthritis. There is no single diagnostic test for adult-onset Still's disease; rather, the diagnosis is based on clinical criteria and necessitates the exclusion of infectious, neoplastic, and other 'autoimmune' diseases. Proinflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-18, interferon-gamma, tumor necrosis factor, and macrophage colony-stimulating factor are elevated in patients with adult-onset Still's disease and are thought to have a major role in the pathogenesis of the disease. Treatment consists of nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressants (methotrexate, gold, azathioprine, leflunomide, cyclosporin, and cyclophosphamide), intravenous immunoglobulin, and cytokine (tumor necrosis factor, IL-1 and IL-6) inhibitors. Recent advances in basic immunology have enhanced our ability to hinder the pathogenic mechanisms associated with adult-onset Still's disease and have led to a paradigm shift where targeted treatments have an increasingly important role.

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1. Original research (no review articles, editorials, letters to the editor) published in English after 1990 in adult patients with rheumatoid or psoriatic arthritis AND is not a case report or case series?

- ○ Yes
- ○ No
- ○ Cannot determine
- ○ No, but article will be used for background

Clear Selection

2. Study includes one or more of the following pharmaceutical interventions (check all that apply):

- ☐ Corticosteroids
- ☐ Oral DMARDs including methotrexate, leflunomide, sulfasalazine, cyclosporine, hydroxychloroquine
- ☐ Biologic DMARDs including anakinra, etanercept, infliximab, adalimumab, abatacept, certolizumab, golimumab, tocilizumab, rituximab
- ☐ Cannot determine
- ☐ Comparison is not of interest

3. Study compares-

- ○ Two of the included drugs
- ○ Biological DMARD (TIM) versus placebo
- ○ One of the included drugs versus placebo but is of interest because of specific outcome such as adverse events
- ○ Nothing of interest and article should not be included
- ○ Cannot determine

Clear Selection

4. Addresses one or more of the following key questions (check all that apply):

- ☐ KQ1 For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission (reduce the incidence flare-ups)?
- ☐ KQ2- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?
- ☐ KQ3 For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?
- ☐ KQ4 What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?
- ☐ Cannot determine by the title or abstract
- ☐ None of the above

5. Study design is one of the following:

- ☐ RCT 3 months or longer

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Previewing at Level 3

Reviewer Comments (Add a Comment)

Refid: 2161, P. Efthimiou, A. Kontzias, C. M. Ward and N. S. Ogden, Adult-onset Still's disease: can recent advances in our understa
State: Excluded, Level: 1

Save to finish later | Submit Data

1. Author, Year, Study name if applicable (i.e. BeST):

Enlarge Shrink

2. Country and setting:

If more than a couple of countries are included just call it multinational. Settings include primary care, hospitals, uni

3. Source of funding

- [ ] Pharmaceutical company or other commercial source- please list name.
- [ ] Government or non-profit organization- please list name.
- [ ] Not reported

4. Condition being treated:

- [ ] Rheumatoid arthritis
- [ ] Psoriatic arthritis
- [ ] Other? Please explain

5. **STUDY DESIGN**

- ( ) Controlled Trials
- ( ) Observational

Clear Selection

6. What is being compared?

- [ ] 1 Oral DMARD vs 1 Oral DMARD
- [ ] 1 Oral DMARD vs 1 BIOLOGIC
- [ ] 1 Oral DMARD vs 1 Corticosteroid
- [ ] 1 BIOLOGIC vs 1 BIOLOGIC
- [ ] 1 BIOLOGIC vs 1 Corticosteroid

- [ ] 1 BIOLOGIC vs Placebo
- [ ] Combination therapy vs Combination therapy
- [ ] SINGLE DRUG vs Combination therapy
- [ ] Strategy (Describe the strategy in detail for each arm in the 'Other' text box for numbers 8-12)

7. How many comparison arms does this study have?

- ( ) 2 ARMS
- ( ) 3 ARMS
- ( ) 4 ARMS
- ( ) 5 ARMS

Clear Selection

8. Check off the drug(s) studied for **ARM 1** and put dosage and frequency in the adjacent box

- [ ] Methylprednisolone
- [ ] Prednisone
- [ ] Prednisolone
- [ ] Methotrexate
- [ ] Leflunomide
- [ ] Sulfasalazine
- [ ] Hydroxychlorquine
- [ ] Etanercept
- [ ] Infliximab
- [ ] Adalimumab
- [ ] Anakinra
- [ ] Abatacept
- [ ] Rituximab
- [ ] Certolizumab
- [ ] Golimumab
- [ ] Tocilizumab
- [ ] Placebo
- [ ] Other (describe)

9. Check off the drug(s) studied for **ARM 2** and put dosage and frequency in the adjacent box

- [ ] Methylprednisolone
- [ ] Prednisone
- [ ] Prednisolone

- [ ] Methotrexate
- [ ] Leflunomide
- [ ] Sulfasalazine
- [ ] Hydroxychlorquine
- [ ] Etanercept
- [ ] Infliximab
- [ ] Adalimumab
- [ ] Anakinra
- [ ] Abatacept
- [ ] Rituximab
- [ ] Certolizumab
- [ ] Golimumab
- [ ] Tocilizumab
- [ ] Placebo
- [ ] Other (describe)

10. Check off the drug(s) studied for **ARM 3** and put dosage and frequency in the adjacent box

- [ ] Methylprednisolone
- [ ] Prednisone
- [ ] Prednisolone
- [ ] Methotrexate
- [ ] Leflunomide
- [ ] Sulfasalazine
- [ ] Hydroxychlorquine
- [ ] Etanercept
- [ ] Infliximab
- [ ] Adalimumab
- [ ] Anakinra
- [ ] Abatacept
- [ ] Rituximab
- [ ] Certolizumab

- [ ] Golimumab
- [ ] Tocilizumab
- [ ] Placebo
- [ ] Other (describe)

11. Check off the drug(s) studied for **ARM 4** and put dosage and frequency in the adjacent box

- [ ] Methylprednisolone
- [ ] Prednisone
- [ ] Prednisolone
- [ ] Methotrexate
- [ ] Leflunomide
- [ ] Sulfasalazine
- [ ] Hydroxychlorquine
- [ ] Etanercept
- [ ] Infliximab
- [ ] Adalimumab
- [ ] Anakinra
- [ ] Abatacept
- [ ] Rituximab
- [ ] Certolizumab
- [ ] Golimumab
- [ ] Tocilizumab
- [ ] Placebo
- [ ] Other (describe)

12. Check off the drug(s) studied for **ARM 5** and put dosage and frequency in the adjacent box

- [ ] Methylprednisolone
- [ ] Prednisone
- [ ] Prednisolone
- [ ] Methotrexate
- [ ] Leflunomide
- [ ] Sulfasalazine

- [ ] Hydroxychlorquine
- [ ] Etanercept
- [ ] Infliximab
- [ ] Adalimumab
- [ ] Anakinra
- [ ] Abatacept
- [ ] Rituximab
- [ ] Certolizumab
- [ ] Golimumab
- [ ] Tocilizumab
- [ ] Placebo
- [ ] Other (describe)

13. Research objective (*Please be brief and concise*):

Enlarge Shrink

14. Overall study n =

Enlarge Shrink

15. Duration of study:

Enlarge Shrink

16. Inclusion criteria (check all that apply and list additional criteria in the text box)

- [ ] MTX Naive
- [ ] Early RA
- [ ] Treatment resistant

Additional inclusion criteria

17.

Exclusion criteria

Enlarge Shrink

POPULATION CHARACTERISTICS

	ARM 1	ARM 2	
18. **Intervention/Treatment**			
19. # in group (n):			
20. Age (mean):			
21. Sex, female (%):			
22. Race, white (%):			
23. Race, black (%):			
24. Ethnicity, Latino (%):			
25. Disease duration (mean & SD):			
26. DMARD use (%):			
27. Corticosteroid use (%):			
28. MTX naive (%):			
29. Treatment resistant (%):			
30. Patients with early RA, three years or less, (%):			
31. Baseline DAS score:			
32. Tender joint count:			
33. Swollen joint count:			
34. Required treatment for latent TB:			
35. Other population characteristics?			

RESULTS: Outcome Measures and Health Outcomes
(Enter results for all time points and please specify units for all results)

	ARM 1	ARM 2	
36. ACR 20, %, (CI/SD/P value):			
37. ACR 50, %, (CI/SD/P value):			
38. ACR 70, %, (CI/SD/P value):			
39. PASI 20, %, (CI/SD/P value):			

40. PASI 50, %, (CI/SD/P value):

41. PASI 70, %, (CI/SD/P value):

42. HAQ, mean difference/absolute difference (CI/SD/P Value):

43. DAS, mean difference/absolute difference (CI/SD/P Value):

44. SF-36, mean difference/absolute difference (CI/SD/P Value):

45. PsARC, mean difference/absolute difference (CI/SD/P Value):

46. Radiographic measures, mean difference/absolute difference (CI/SD/P Value):

47. Quality of life scales (please name), mean difference/absolute difference (CI/SD/P Value):

48. Others, (please name); mean difference/absolute difference (CI/SD/P Value):

ATTRITION AND ADHERENCE

	ARM 1	ARM 2	
49. Overall attrition/withdrawal (n):			
50. Withdrawals due to adverse events (n):			
51. Withdrawals due to lack of efficacy (n):			
52. Adherent/compliant (n):			

53. Other attrition related comments?

Enlarge Shrink

RESULTS: Adverse Events, n

	ARM 1	ARM 2	
54. Overall adverse events reported (n):			
55. Death (n):			
56. Lymphoma or leukemia (n):			
57. Skin cancer (basal cell or squamous cell) (n):			
58. Other cancer (specify) (n):			
59. Cardiovascular events (specify) (n):			
60. Hepatotoxicity/elevated liver enzymes (n):			
61. Tuberculosis (n):			
62. Pneumonia (n):			
63. Upper respiratory infection (n):			
64. Urinary tract infection (n):			
65. Other infections (specify) (n):			
66. Fractures (n):			
67. Infusion/injection site reactions (n):			
68. Skin rash (n):			
69. Demyelenation or multiple sclerosis (n):			
70. Progressive multifocal leukoencephalopathy (n):			
71. Headache (n):			
72. Dizziness (n):			
73. Nausea or vomiting (n):			
74. Abdominal pain (n):			
75. GI bleed or ulcer (n):			
76. Bowel obstruction (n):			
77. Other GI symptoms (specify) (n):			
78. Other AEs 1 (n):			
79. Other AEs 2 (n):			
80. Other AEs 3 (n):			

81. Other AEs 4 (n):

82. Any other AEs:

Enlarge Shrink

83. Which Key Question(s) does this study address (check all that apply)?

- [ ] KQ1- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce disease activity, t
- [ ] KQ2- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capac
- [ ] KQ3- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adver
- [ ] KQ4- What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups

Quality Review for Controlled Trials

84. Randomization adequate?

- ○ Yes
- ○ No
- ○ Not randomized
- ○ Method not reported

Clear Selection

85. Allocation concealment adequate?

- ○ Yes
- ○ No
- ○ Not randomized
- ○ Method not reported

Clear Selection

86. Groups similar at baseline?

- ○ Yes
- ○ No (what are the differences)
- ○ Not reported
- ○ Not applicable

Clear Selection

87. Outcome assessors blinded?

- ○ Yes
- ○ No
- ○ Yes, but method not described
- ○ Not reported

Clear Selection

88. Care provider blinded?

- ○ Yes
- ○ No
- ○ Yes, but method not described
- ○ Not reported

Clear Selection

89. Patient blinded?

- ○ Yes
- ○ No
- ○ Yes, but method not described
- ○ Not reported

Clear Selection

90. Overall attrition high (≥ 20%)?

- ○ Yes (please state how high) [ ]
- ○ No

Clear Selection

91. Differential attrition high (≥ 15%)?

- ○ Yes (please state difference) [ ]
- ○ No

Clear Selection

92. Were the outcome measures valid and reliable?

- ○ Yes
- ○ No
- ○ Not reported

Clear Selection

93. Were the outcome measures equally applied?

- ○ Yes
- ○ No
- ○ Not reported

Clear Selection

94. Was the statistical analysis based on intention-to-treat (ITT)?

- ○ Yes
- ○ No
- ○ Cannot tell
- ○ Not applicable

Clear Selection

95. Were there any post-randomization exclusions?

- ○ Yes (how many?) [ ]
- ○ No
- ○ Cannot tell

Clear Selection

96. Quality rating for efficacy/effectiveness

- ☐ Good
- ☐ Fair
- ☐ Poor

If poor, why? [ ]

Quality Review for Observational Studies

97. Were both groups selected from the same source population?

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

98. Did both groups have the same risk of having the outcome of interest at baseline?

- Yes
- No
- Not reported

Clear Selection

99. Were subjects in both groups recruited over the same time period?

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

100. Were measurement methods adequate and equally applied to both groups?

- Yes
- No
- Not reported

Clear Selection

101. Was an attempt made to blind the outcome assessors?

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

102. Was the time of follow-up equal in both groups?

- Yes
- No
- Not reported

Clear Selection

103. Overall attrition high (≥ 20%)?

- Yes (please state how high)
- No

Clear Selection

104. Differential attrition high (≥ 15%)?

- Yes (please state difference)
- No

Clear Selection

105. Was confounding accounted for either through study design or statistical analysis?

- ○ Yes
- ○ No
- ○ Yes, but method not described
- ○ Not reported

Clear Selection

106. Did the statistical analysis adjust for different lengths of follow-up?

- ○ Yes
- ○ No
- ○ Yes, but method not described
- ○ Not reported

Clear Selection

107. Was the length of follow-up adequate to assess the outcome of interest?

- ○ Yes
- ○ No
- ○ Not reported

Clear Selection

108. Quality rating for observational studies

- ☐ Good
- ☐ Fair
- ☐ Poor

Why?

109. Any other quality related comments?

Enlarge Shrink

Quality Review for Adverse Events

110. Methods of adverse effects assessment

- ☐ Patient reported
- ☐ Physical exam at study visits
- ☐ Lab evaluations
- ☐ Standardized scale (e.g. WHO, UKU-SES)
- ☐ other (please specify)

111. Adverse events pre-specified and defined?

- ○ Yes
- ○ No

Clear Selection

112. Measurement techniques non-biased and adequately described?

- ○ Yes
- ○ No

Clear Selection

113. Quality rating adverse events assessment:

- ○ Good
- ○ Fair
- ○ Poor

Clear Selection

114. First abstraction done by:

- ○ Karen Crotty
- ○ Katrina Donahue
- ○ Rick Hansen
- ○ Dan Jonas
- ○ Linda Lux
- ○ Robert Roubey
- ○ Rachael Scheinman
- ○ Other (please write your name in the adjacent box):

Clear Selection

115. Second abstraction done by:

- ○ Karen Crotty
- ○ Katrina Donahue
- ○ Rick Hansen
- ○ Dan Jonas
- ○ Linda Lux
- ○ Robert Roubey
- ○ Rachael Scheinman
- ○ Other (please write your name in the adjacent box):

Clear Selection

116. Study is already included in systematic review/meta-analysis and does not need to be put in an evidence table

- ○ Yes
- ○ No

Clear Selection

Save to finish later | Submit Data

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Appendix C. Articles by Database Searched

Reference Source: PubMed

1. Juvenile and adult systemic-onset Still's disease. Lancet. 1990 Jul 14;336(8707):92.

2. Double blind controlled phase III multicenter clinical trial with interferon gamma in rheumatoid arthritis. German Lymphokine Study Group. Rheumatol Int. 1992;12(5):175-85.

3. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA Study. Am J Med. 1995 Feb;98(2):156-68.

4. Treatment methods. Nonsurgical treatment methods for diseases in multiple joints (polyarthritis). Scand J Rheumatol Suppl. 1999;110:7-14.

5. Etanercept and infliximab for rheumatoid arthritis. Drug Ther Bull. 2001 Jul;39(7):49-52.

6. One million U.S. adults may suffer from psoriatic arthritis. Dermatol Nurs. 2002 Jun;14(3):207-8.

7. Anakinra (Kineret) for rheumatoid arthritis. Med Lett Drugs Ther. 2002 Feb 18;44(1124):18-9.

8. Summaries for patients. Tumor necrosis factor antagonists and heart failure. Ann Intern Med. 2003 May 20;138(10):I48.

9. Is it true that vaccines may not be safe for people with rheumatoid arthritis (which I have)? Does that mean I shouldn't get a flu shot? Johns Hopkins Med Lett Health After 50. 2004 Oct;17(8):8.

10. Summaries for patients. Abatacept for people with active rheumatoid arthritis. Ann Intern Med. 2006 Jun 20;144(12):I18.

11. Rituximab and abatacept for rheumatoid arthritis. Drug Ther Bull. 2008 Aug;46(8):57-61.

12. The Chinese herbal remedy Tripterygium wilfordii Hook F in the treatment of rheumatoid arthritis. Ann Intern Med. 2009 Aug 18;151(4):I-36.

13. New drug information: Simponi. Jaapa. 2009 Aug;22(8):13.

14. Abarca J, Malone DC, Armstrong EP, et al. Longitudinal analysis of the use of etanercept versus infliximab determined from medical chart audit. J Manag Care Pharm. 2004 Nov-Dec;10(6):538-42.

15. Abe K, Mitsuka T, Kanamori S, et al. Gynecomastia associated with low-dose methotrexate therapy for rheumatoid arthritis. Mod Rheumatol. 2007;17(6):511-3.

16. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006 Jan;33(1):37-44.

17. Abedin M, Scheurich D, Reimold SC, et al. Acute coronary syndrome after infliximab infusion. Cardiol Rev. 2006 Jan-Feb;14(1):50-2.

18. Ablin JN, Boguslavski V, Aloush V, et al. Effect of anti-TNFalpha treatment on circulating endothelial progenitor cells (EPCs) in rheumatoid arthritis. Life Sci. 2006 Nov 17;79(25):2364-9.

19. Aboulafia DM, Bundow D, Wilske K, et al. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. Mayo Clin Proc. 2000 Oct;75(10):1093-8.

20. Abramovits W, Arrazola P, Gupta AK. Enbrel (etanercept). Skinmed. 2004 Nov-Dec;3(6):333-5.

21. Acero J, Navarro-Cuellar C, Menarguez J, et al. Naso-maxillary non-Hodgkin lymphoma

associated with methotrexate treatment in a patient with rheumatoid arthritis. J Oral Maxillofac Surg. 2006 Apr;64(4):708-11.

22. Adachi J, Cranney A, Goldsmith CH, et al. Intermittent cyclic therapy with etidronate in the prevention of corticosteroid induced bone loss. J Rheumatol. 1994 Oct;21(10):1922-6.

23. Adam DJ, Nawroz I, Petrie PW. Pyoderma gangrenosum severely affecting both hands. J Hand Surg [Br]. 1996 Dec;21(6):792-4.

24. Adebayo D, Popat R, Thjodleifsson B, et al. Granulomatous ileitis in a patient with ankylosing spondylitis. Nat Clin Pract Gastroenterol Hepatol. 2007 Jun;4(6):347-51.

25. Adhikesavan LG, Newman ED, Diehl MP, et al. American College of Rheumatology quality indicators for rheumatoid arthritis: benchmarking, variability, and opportunities to improve quality of care using the electronic health record. Arthritis Rheum. 2008 Dec 15;59(12):1705-12.

26. Adisen E, Karaca F, Gurer MA. When there is no single best biological agent: psoriasis and psoriatic arthritis in the same patient responding to two different biological agents. Clin Exp Dermatol. 2008 Mar;33(2):164-6.

27. Adzic TN, Stojsic JM, Radosavljevic-Asic GD, et al. Multinodular pulmonary amyloidosis in primary Sjogren's syndrome. Eur J Intern Med. 2008 Dec;19(8):e97-8.

28. Aeberli D, Oertle S, Mauron H, et al. Inhibition of the TNF-pathway: use of infliximab and etanercept as remission-inducing agents in cases of therapy-resistant chronic inflammatory disorders. Swiss Med Wkly. 2002 Jul 27;132(29-30):414-22.

29. Aeberli D, Seitz M, Juni P, et al. Increase of peripheral CXCR3 positive T lymphocytes upon treatment of RA patients with TNF-alpha inhibitors. Rheumatology (Oxford). 2005 Feb;44(2):172-5.

30. Aerts NE, Ebo DG, Bridts CH, et al. Flow cytometric analysis of phospho-p38 mitogen-activated kinase (MAPK): p38 MAPK does not mediate the effect of adalimumab on peripheral T cell cytokine production in rheumatoid arthritis. Cytokine. 2009 Sep;47(3):178-84.

31. Agarwal PK, Gallaghar M, Murphy E, et al. Endogenous endophthalmitis in a rheumatoid patient on tumor necrosis factor alpha blocker. Indian J Ophthalmol. 2007 May-Jun;55(3):230-2.

32. Agarwal S, Zaman T, Handa R. Retention rates of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. Singapore Med J 2009;50(7):686-92.

33. Agarwal SK, Maier AL, Chibnik LB, et al. Pattern of infliximab utilization in rheumatoid arthritis patients at an academic medical center. Arthritis Rheum. 2005 Dec 15;53(6):872-8.

34. Aggarwal A, Panda S, Misra R. Effect of etanercept on matrix metalloproteinases and angiogenic vascular endothelial growth factor: a time kinetic study. Ann Rheum Dis. 2004 Jul;63(7):891-2.

35. Aggarwal P, Naik S, Mishra KP, et al. Correlation between methotrexate efficacy & toxicity with C677T polymorphism of the methylenetetrahydrofolate gene in rheumatoid arthritis patients on folate supplementation. Indian J Med Res. 2006 Nov;124(5):521-6.

36. Agirbasli M, Inanc N, Baykan OA, et al. The effects of TNF alpha inhibition on plasma fibrinolytic balance in patients with chronic inflammatory rheumatical disorders. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):580-3.

37. Ahmadi-Simab K, Lamprecht P, Nolle B, et al. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. Ann Rheum Dis. 2005 Jul;64(7):1087-8.

38. Ahmed M, Luggen M, Herman JH, et al. Hypertrophic pachymeningitis in rheumatoid arthritis after adalimumab administration. J Rheumatol. 2006 Nov;33(11):2344-6.

39. Ahmed MM, Mubashir E, Wolf RE, et al. Impact of treatment with infliximab on anticyclic citrullinated peptide antibody and rheumatoid factor in patients with rheumatoid arthritis. South Med J. 2006 Nov;99(11):1209-15.

40. Aida S, Okawa-Takatsuji M, Aotsuka S, et al. Calcitonin inhibits production of immunoglobulins, rheumatoid factor and interleukin-1 by mononuclear cells from patients with rheumatoid arthritis. Ann Rheum Dis. 1994 Apr;53(4):247-9.

41. Akai M, Ohno T, Kamura S, et al. Epidural abscess following septic arthritis in a rheumatoid patient. A case report. Spine. 1990 Jun;15(6):603-5.

42. Akay OM, Korkmaz C, Gulbas Z. Development of acute inflammatory arthritis by granulocyte-macrophage colony-stimulating factor during autologous stem cell transplantation for cryoglobulinemia. Rheumatol Int. 2007 Oct;27(12):1167-9.

43. Akritidis N, Papadopoulos A, Pappas G. Long-term follow-up of patients with adult-onset Still's disease. Scand J Rheumatol. 2006 Sep-Oct;35(5):395-7.

44. Alarcon GS. Early rheumatoid arthritis: combination therapy of doxycycline plus methotrexate versus methotrexate monotherapy. Nat Clin Pract Rheumatol. 2006 Jun;2(6):296-7.

45. Al-Arfaj AS, Al-Saleh S. Adult-Onset Still's disease in Saudi Arabia. Clin Rheumatol. 2001;20(3):197-200.

46. Alegre-Sancho JJ, Juanola X, Narvaez FJ, et al. Septic arthiritis due to Prevotella bivia in a patient with rheumatoid arthritis. Joint Bone Spine. 2000;67(3):228-9.

47. Alessandri C, Bombardieri M, Papa N, et al. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. Ann Rheum Dis. 2004 Oct;63(10):1218-21.

48. Aletaha D, Funovits J, Keystone EC, et al. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum. 2007 Oct;56(10):3226-35.

49. Alex P, Szodoray P, Arthur E, et al. Influence of intraarticular corticosteroid administration on serum cytokines in rheumatoid arthritis. Clin Rheumatol. 2007 May;26(5):845-8.

50. Alex P, Szodoray P, Knowlton N, et al. Multiplex serum cytokine monitoring as a prognostic tool in rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):584-92.

51. Alexander D, Friedrich B, Abruzzese T, et al. The active form of leflunomide, HMR1726, facilitates TNF-alpha and IL-17 induced MMP-1 and MMP-3 expression. Cell Physiol Biochem. 2006;17(1-2):69-78.

52. Ali AA, Moatter T, Baig JA, et al. Polymorphism of HLA-DR and HLA-DQ in rheumatoid arthritis patients and clinical response to methotrexate--a hospital-based study. J Pak Med Assoc. 2006 Oct;56(10):452-6.

53. Alivernini S, Mazzotta D, Zoli A, et al. Leflunomide treatment in elderly patients with rheumatoid or psoriatic arthritis: retrospective analysis of safety and adherence to treatment. Drugs Aging. 2009;26(5):395-402.

54. Alkassab F. Overlap of systemic sclerosis and rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1593-4.

55. Allanore Y, Bremont C, Kahan A, et al. Transient hyperthyroidism in a patient with rheumatoid arthritis treated by etanercept. Clin Exp Rheumatol. 2001 May-Jun;19(3):356-7.

56. Allanore Y, Sellam J, Batteux F, et al. Induction of autoantibodies in refractory rheumatoid arthritis treated by infliximab. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):756-8.

57. Allantaz F, Chaussabel D, Stichweh D, et al. Blood leukocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade. J Exp Med. 2007 Sep 3;204(9):2131-44.

58. Almodovar R, Izquierdo M, Zarco P, et al. Pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):99-101.

59. Almodovar R, Zarco P, Quiros FJ, et al. Infliximab treatment efficacy in lymphoedema associated with ankylosing spondylitis. Rheumatology (Oxford). 2004 Nov;43(11):1456.

60. al-Mughales J, Blyth TH, Hunter JA, et al. The chemoattractant activity of rheumatoid synovial fluid for human lymphocytes is due to multiple cytokines. Clin Exp Immunol. 1996 Nov;106(2):230-6.

61. Alonso-Bartolome P, Martinez-Taboada VM, Blanco R, et al. Insufficiency fractures of the tibia and fibula. Semin Arthritis Rheum. 1999 Jun;28(6):413-20.

62. Alshekhlee A, Basiri K, Miles JD, et al. Chronic inflammatory demyelinating polyneuropathy associated with tumor necrosis factor-alpha antagonists. Muscle Nerve. 2010 May;41(5):723-7.

63. Alstergren P, Larsson PT, Kopp S. Successful treatment with multiple intra-articular injections of infliximab in a patient with psoriatic arthritis. Scand J Rheumatol. 2008 Mar-Apr;37(2):155-7.

64. Altintop L, Cakar B, Hokelek M, et al. Strongyloides stercoralis hyperinfection in a patient with rheumatoid arthritis and bronchial asthma: a case report. Ann Clin Microbiol Antimicrob. 2010;9:27.

65. Alvarez-Rodriguez L, Carrasco-Marin E, Lopez-Hoyos M, et al. Interleukin-1RN gene polymorphisms in elderly patients with rheumatic inflammatory chronic conditions: Association of IL-1RN*2/2 genotype with polymyalgia rheumatica. Hum Immunol. 2009 Jan;70(1):49-54.

66. Aman S, Hakala M, Silvennoinen J, et al. Low incidence of osteoporosis in a two year follow-up of early community based patients with rheumatoid arthritis. Scand J Rheumatol. 1998;27(3):188-93.

67. Amenomori M, Migita K, Miyashita T, et al. Cytomegalovirus-associated hemophagocytic syndrome in a patient with adult onset Still's disease. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):100-2.

68. Amichai B, Gat A, Grunwald MH. Cutaneous hyperpigmentation during therapy with hydroxychloroquine. J Clin Rheumatol. 2007 Apr;13(2):113.

69. Amital H, Aamar S, Rubinow A. Bilateral septic arthritis of the hip: does etanercept play a role? A case report. J Bone Joint Surg Am. 2003 Nov;85-A(11):2205-6.

70. Amital H, Arnson Y, Chodick G, et al. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology (Oxford). 2009 Sep;48(9):1107-10.

71. Anandacoomarasamy A, Kannangara S, Barnsley L. Cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis. Intern Med J. 2005 Oct;35(10):638-40.

72. Anandarajah AP, Schwarz EM, Totterman S, et al. The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. Ann Rheum Dis. 2008 Mar;67(3):296-301.

73. Ancuta C, Ancuta E, Miu S, et al. Adalimumab therapy in patients with active rheumatoid arthritis. Rev Med Chir Soc Med Nat Iasi. 2009 Jul-Sep;113(3):710-5.

74. Andonopoulos AP, Meimaris N, Daoussis D, et al. Intra-articular anti-tumor necrosis factor alpha antibody in recalcitrant arthritis of Behcet's disease. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S57-8.

75. Andres E, Limbach FX, Goichot B, et al. Silent thyroiditis associated with etanercept

in rheumatoid arthritis. Ann Rheum Dis. 2002 Jun;61(6):565.

76. Anelli MG, Torres DD, Manno C, et al. Improvement of renal function and disappearance of hepatitis B virus DNA in a patient with rheumatoid arthritis and renal amyloidosis following treatment with infliximab. Arthritis Rheum. 2005 Aug;52(8):2519-20.

77. Ang HT, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-alpha antagonists in patients with rheumatoid arthritis? J Rheumatol. 2003 Nov;30(11):2315-8.

78. Anis A, Zhang W, Emery P, et al. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford) 2009;48(10):1283-9.

79. Anolik JH, Ravikumar R, Barnard J, et al. Cutting edge: anti-tumor necrosis factor therapy in rheumatoid arthritis inhibits memory B lymphocytes via effects on lymphoid germinal centers and follicular dendritic cell networks. J Immunol. 2008 Jan 15;180(2):688-92.

80. Antolin J, Azahara M, Hernandez C, et al. Tuberculous peritonitis after treatment with adalimumab. Scand J Infect Dis. 2008;40(8):677-8.

81. Antoni C, Dechant C, Hanns-Martin Lorenz PD, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. Arthritis Rheum. 2002 Oct 15;47(5):506-12.

82. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005 Aug;64(8):1150-7.

83. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36.

84. Antoni CE, Kavanaugh A, van der Heijde D, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76.

85. Antoniou KM, Mamoulaki M, Malagari K, et al. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):23-8.

86. Antony T, Jose VM, Paul BJ, et al. Efficacy and safety of leflunomide alone and in combination with methotrexate in the treatment of refractory rheumatoid arthritis. Indian J Med Sci. 2006 Aug;60(8):318-26.

87. Aouba A, De Bandt M, Aslangul E, et al. Haemophagocytic syndrome in a rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford). 2003 Jun;42(6):800-2.

88. Aparicio AG, Munoz-Fernandez S, Bonilla G, et al. Report of an additional case of anti-tumor necrosis factor therapy and Listeria monocytogenes infection: comment on the letter by Gluck et al. Arthritis Rheum. 2003 Jun;48(6):1764-5; author reply 5-6.

89. Appel da Silva F, Appel da Silva MC, Romagna ES. Clinical images: Psoriatic arthritis mutilans. Arthritis Rheum. 2010 Jul;62(7):2159.

90. Appenzeller S, Castro GR, Costallat LT, et al. Adult-onset Still disease in southeast Brazil. J Clin Rheumatol. 2005 Apr;11(2):76-80.

91. Arabelovic S, Sam G, Dallal GE, et al. Preliminary evidence shows that folic acid fortification of the food supply is associated with higher methotrexate dosing in patients with rheumatoid arthritis. J Am Coll Nutr. 2007 Oct;26(5):453-5.

92. Aramaki T, Kawakami A, Iwamoto N, et al. Prediction of DAS28-CRP remission in patients with rheumatoid arthritis treated with tacrolimus at 6 months by baseline variables. Mod Rheumatol. 2009;19(6):652-6.

93. Ardalan MR, Shoja MM. Multiple myeloma presented as acute interstitial nephritis and rheumatoid arthritis-like polyarthritis. Am J Hematol. 2007 Apr;82(4):309-13.

94. Arend SM, Kuijper EJ, Allaart CF, et al. Cavitating pneumonia after treatment with infliximab and prednisone. Eur J Clin Microbiol Infect Dis. 2004 Aug;23(8):638-41.

95. Argyropoulou MI, Glatzouni A, Voulgari PV, et al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. Joint Bone Spine. 2005 Dec;72(6):557-61.

96. Arif S, Cox P, Afzali B, et al. Anti-TNFalpha therapy--killing two birds with one stone? Lancet 2010;375(9733):2278.

97. Arkachaisri T, Lehman TJ. Use of biologics in the treatment of childhood rheumatic diseases. Curr Rheumatol Rep. 2000 Aug;2(4):330-6.

98. Arman A, Yilmaz B, Coker A, et al. Interleukin-1 receptor antagonist (IL-1RN) and interleukin-1B gene polymorphisms in Turkish patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Nov-Dec;24(6):643-8.

99. Armstrong DJ, McCarron MT, Wright GD. Successful treatment of rheumatoid vasculitis-associated foot-drop with infliximab. J Rheumatol. 2005 Apr;32(4):759; author reply -60.

100. Arnold EL, Khanna D, Paulus H, et al. Acute injection site reaction to intraarticular etanercept administration. Arthritis Rheum. 2003 Jul;48(7):2078-9.

101. Arvidson NG, Larsen A, Aaseth J, et al. Short-term effects of the TNFalpha antagonist infliximab on the acute phase reaction and activities of daily life in patients with rheumatoid arthritis. Scand J Clin Lab Invest. 2007;67(3):337-42.

102. Asanuma Y, Chung CP, Oeser A, et al. Serum osteoprotegerin is increased and independently associated with coronary-artery atherosclerosis in patients with rheumatoid arthritis. Atherosclerosis. 2007 Dec;195(2):e135-41.

103. Asherson RA, Pascoe L. Adult onset Still's disease: response to Enbrel. Ann Rheum Dis. 2002 Sep;61(9):859-60; author reply 60.

104. Ashok D, Ayliffe WH, Kiely PD. Necrotizing scleritis associated with rheumatoid arthritis: long-term remission with high-dose infliximab therapy. Rheumatology (Oxford). 2005 Jul;44(7):950-1.

105. Ashok D, Dubey S, Tomlinson I. C-ANCA positive systemic vasculitis in a patient with rheumatoid arthritis treated with infliximab. Clin Rheumatol. 2008 Feb;27(2):261-4.

106. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005 Jul;52(7):1986-92.

107. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum 2009;60(11):3180-9.

108. Aslangul E, Perrot S, Durand E, et al. Successful etanercept treatment of constrictive pericarditis complicating rheumatoid arthritis. Rheumatology (Oxford). 2005 Dec;44(12):1581-3.

109. Aslanidis S, Pyrpasopoulou A, Douma S, et al. Is it safe to readminister tumor necrosis factor alpha antagonists following tuberculosis flare? Arthritis Rheum. 2008 Jan;58(1):327-8.

110. Aslanidis S, Vassiliadis T, Pyrpasopoulou A, et al. Inhibition of TNFalpha does not

induce viral reactivation in patients with chronic hepatitis C infection: two cases. Clin Rheumatol. 2007 Feb;26(2):261-4.

111. Asli B, Wechsler B, Lemaitre C. Inhibition of tumor necrosis factor alpha and ankylosing spondylitis. N Engl J Med. 2003 Jan 23;348(4):359-61; author reply -61.

112. Asplund MS, Hagberg H, Holmstrom M. Chemotherapy in severe nasal polyposis--a possible beneficial effect? A report of three cases. Rhinology. 2010 Sep;48(3):374-6.

113. Assimakopoulos SF, Michalopoulou S, Melachrinou M, et al. Primary Sjogren syndrome complicated by autoimmune hemolytic anemia and pure red cell aplasia. Am J Med Sci. 2007 Dec;334(6):493-6.

114. Assmann G, Pfreundschuh M, Voswinkel J. Rituximab in patients with rheumatoid arthritis and vasculitis-associated cutaneous ulcers. Clin Exp Rheumatol. 2010 Jan-Feb;28(1 Suppl 57):81-3.

115. Assous N, Gossec L, Dieude P, et al. Rituximab therapy in rheumatoid arthritis in daily practice. J Rheumatol. 2008 Jan;35(1):31-4.

116. Atchia, II, Kidd CE, Bell RW. Rheumatoid arthritis-associated necrotizing scleritis and peripheral ulcerative keratitis treated successfully with infliximab. J Clin Rheumatol. 2006 Dec;12(6):291-3.

117. Atteno M, Peluso R, Costa L, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. Clin Rheumatol 2010;29(4):399-403.

118. Atzeni F, Doria A, Ghirardello A, et al. Organ-specific autoantibodies in patients with rheumatoid arthritis treated with adalimumab: a prospective long-term follow-up. Autoimmunity. 2008 Feb;41(1):87-91.

119. Atzeni F, Sarzi-Puttini P, DePortu S, et al. In etanercept-treated psoriatic arthritis patients clinical improvement correlated with an increase of serum cortisol relative to other adrenal hormones. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):103-8.

120. Augustsson J, Eksborg S, Ernestam S, et al. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1462-6.

121. Augustsson J, Neovius M, Cullinane-Carli C, et al. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). Ann Rheum Dis 2010;69(1):126-31.

122. Avancini-Dobrovic V, Vrbanic TS, Kukuljan M, et al. Spontaneous serial fractures of metatarsal bones in female patient with rheumatoid arthritis on long-term steroid therapy. Coll Antropol. 2010 Sep;34(3):1123-6.

123. Avriel A, Zeller L, Flusser D, et al. Coexistence of psoriatic arthritis and systemic lupus erythematosus. Isr Med Assoc J. 2007 Jan;9(1):48-9.

124. Ayaz NA, Demirkaya E, Bilginer Y, et al. Preventing tuberculosis in children receiving anti-TNF treatment. Clin Rheumatol. 2010 Apr;29(4):389-92.

125. Aydin T, Karacan I, Demir SE, et al. Bone loss in males with ankylosing spondylitis: its relation to sex hormone levels. Clin Endocrinol (Oxf). 2005 Oct;63(4):467-9.

126. Aydintug AO, D'Cruz D, Cervera R, et al. Low dose methotrexate treatment in adult Still's disease. J Rheumatol. 1992 Mar;19(3):431-5.

127. Aydog E, Yesilli O, Sever A, et al. Dermatitis herpetiformis and rheumatoid arthritis. Saudi Med J. 2006 Jun;27(6):881-4.

128. Azuma T, Ishimaru H, Hatta K, et al. Improved response to infliximab after leukocytapheresis in a patent with

rheumatoid arthritis. Mod Rheumatol. 2007;17(3):253-5.

129. Babacan T, Onat AM, Pehlivan Y, et al. Successful treatment of refractory adult Still's disease and membranous glomerulonephritis with infliximab. Clin Rheumatol. 2010 Apr;29(4):423-6.

130. Bacquet-Deschryver H, Jouen F, Quillard M, et al. Impact of three anti-TNFalpha biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients. J Clin Immunol. 2008 Sep;28(5):445-55.

131. Bae SC, Corzillius M, Kuntz KM, et al. Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. Rheumatology (Oxford). 2003 Jan;42(1):46-53.

132. Baer AN, Dessypris EN, Krantz SB. The pathogenesis of anemia in rheumatoid arthritis: a clinical and laboratory analysis. Semin Arthritis Rheum. 1990 Feb;19(4):209-23.

133. Baeten D, De Keyser F, Veys EM, et al. Tumour necrosis factor alpha independent disease mechanisms in rheumatoid arthritis: a histopathological study on the effect of infliximab on rheumatoid nodules. Ann Rheum Dis. 2004 May;63(5):489-93.

134. Baeten D, Van Damme N, Van den Bosch F, et al. Impaired Th1 cytokine production in spondyloarthropathy is restored by anti-TNFalpha. Ann Rheum Dis. 2001 Aug;60(8):750-5.

135. Bagalas V, Kioumis I, Argyropoulou P, et al. Visceral leishmaniasis infection in a patient with rheumatoid arthritis treated with

etanercept. Clin Rheumatol. 2007 Aug;26(8):1344-5.

136. Baghai M, Osmon DR, Wolk DM, et al. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. Mayo Clin Proc. 2001 Jun;76(6):653-6.

137. Baig MA, Aksoy T, McClain D, et al. Calciphylaxis in a hemodialysis patient on corticosteroids and etanercept for psoriatic arthritis. J Clin Rheumatol. 2010 Mar;16(2):92-3.

138. Bakewell C, Dugowson C. Images in clinical medicine. Baker's cyst in a patient with rheumatoid arthritis. N Engl J Med. 2009 Sep 10;361(11):1098.

139. Bakland G, Nossent H. Acute myelogenous leukaemia following etanercept therapy. Rheumatology (Oxford). 2003 Jul;42(7):900-1.

140. Balandraud N, Guis S, Baptiste Meynard J, et al. Long-term treatment with methotrexate or tumor necrosis factor alpha inhibitors does not increase epstein-barr virus load in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Jun 15;57(5):762-7.

141. Balanescu A, Radu E, Nat R, et al. Early and late effect of infliximab on circulating dendritic cells phenotype in rheumatoid arthritis patients. Int J Clin Pharmacol Res. 2005;25(1):9-18.

142. Balbir-Gurman A, Guralnik L, Best LA, et al. Accelerated pulmonary nodulosis and sterile pleural effusion in a patient with psoriatic arthropathy during methotrexate therapy: a case report. J Clin Rheumatol. 2009 Feb;15(1):29-30.

143. Bambery P, Thomas RJ, Malhotra HS, et al. Adult onset Still's disease: clinical experience with 18 patients over 15 years in northern India. Ann Rheum Dis. 1992 Apr;51(4):529-32.

144. Bandelier C, Guerne PA, Genevay S, et al. Clinical experience with mycophenolate mofetil in systemic autoimmune conditions refractory to common immunosuppressive therapies. Swiss Med Wkly. 2009 Jan 24;139(3-4):41-6.

145. Bang LM, Keating GM. Adalimumab: a review of its use in rheumatoid arthritis. BioDrugs. 2004;18(2):121-39.

146. Bankhurst AD. Etanercept and methotrexate combination therapy. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S69-72.

147. Baraliakos X, Brandt J, Listing J, et al. Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. Arthritis Rheum. 2005 Dec 15;53(6):856-63.

148. Baraliakos X, Davis J, Tsuji W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum. 2005 Apr;52(4):1216-23.

149. Baraliakos X, Listing J, Rudwaleit M, et al. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. Ann Rheum Dis. 2005 Oct;64(10):1462-6.

150. Barber J, Sheeran T, Mulherin D. Anti-tumour necrosis factor treatment in a patient with anorexia nervosa and juvenile idiopathic arthritis. Ann Rheum Dis. 2003 May;62(5):490-1.

151. Bargagli E, Galeazzi M, Rottoli P. Infliximab treatment in a patient with rheumatoid arthritis and pulmonary fibrosis. Eur Respir J. 2004 Oct;24(4):708.

152. Barra L, Pope JE, Payne M. Real-world anti-tumor necrosis factor treatment in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: cost-effectiveness based on number needed to treat to improve health assessment questionnaire. J Rheumatol. 2009 Jul;36(7):1421-8.

153. Barrera P, Oyen WJ, Boerman OC, et al. Scintigraphic detection of tumour necrosis factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2003 Sep;62(9):825-8.

154. Barrera P, van der Laken CJ, Boerman OC, et al. Radiolabelled interleukin-1 receptor antagonist for detection of synovitis in patients with rheumatoid arthritis. Rheumatology (Oxford). 2000 Aug;39(8):870-4.

155. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007 Jul;66(7):921-6.

156. Barthel HR. Rapid remission of treatment-resistant ankylosing spondylitis with etanercept--a drug for refractory ankylosing spondylitis? Arthritis Rheum. 2001 Aug;45(4):404.

157. Bartke U, Venten I, Kreuter A, et al. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab. Br J Dermatol. 2004 Apr;150(4):784-6.

158. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology (Oxford). 2002 Oct;41(10):1126-32.

159. Barton A, Myerscough A, John S, et al. A single nucleotide polymorphism in exon 1 of cytotoxic T-lymphocyte-associated-4 (CTLA-4) is not associated with rheumatoid arthritis. Rheumatology (Oxford). 2000 Jan;39(1):63-6.

160. Barton P, Jobanputra P, Wilson J, et al. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess. 2004 Mar;8(11):iii, 1-91.

161. Bartram D, Sheeran T, Price T, et al. Anti-tumour necrosis factor therapy in the West Midlands. Rheumatology (Oxford). 2004 Mar;43(3):400; author reply -1.

162. Bas S, Gauthier BR, Spenato U, et al. CD14 is an acute-phase protein. J Immunol. 2004 Apr 1;172(7):4470-9.

163. Baskan BM, Sivas F, Alemdaroglu E, et al. Association of bone mineral density and vertebral deformity in patients with rheumatoid arthritis. Rheumatol Int. 2007 Apr;27(6):579-84.

164. Bassetti S, Wasmer S, Hasler P, et al. Staphylococcus aureus in patients with rheumatoid arthritis under conventional and anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2005 Nov;32(11):2125-9.

165. Bathon JM, Fleischmann RM, Van der Heijde D, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):234-43.

166. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000 Nov 30;343(22):1586-93.

167. Batsis JA, Phy MP. West Nile virus meningitis in a chronic immunosuppressed patient with rheumatoid arthritis. Clin Rheumatol. 2005 Sep;24(5):548-50.

168. Bauer AS, Blazar PE, Earp BE, et al. Mycobacterial hand infections occurring postoperatively in patients treated with tumor necrosis factor-alpha inhibitors for inflammatory arthritis: report of three cases. J Hand Surg Am. 2010 Jan;35(1):104-8.

169. Baumgartner SW, Fleischmann RM, Moreland LW, et al. Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability. J Rheumatol. 2004 Aug;31(8):1532-7.

170. Bayer M, Stepan J, Nemcova D, et al. Juvenile chronic arthritis--bone mineral density in relation to corticosteroid therapy. Acta Univ Carol [Med] (Praha). 1994;40(1-4):33-5.

171. Bejarano V, Quinn M, Conaghan PG, et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 2008;59(10):1467-74.

172. Bejot Y, Osseby GV, Ben Salem D, et al. Bilateral optic neuropathy revealing Sjogren's syndrome. Rev Neurol (Paris). 2008 Dec;164(12):1044-7.

173. Belknap R, Reves R, Burman W. Immune reconstitution to Mycobacterium tuberculosis after discontinuing infliximab. Int J Tuberc Lung Dis. 2005 Sep;9(9):1057-8.

174. Bellisai F, Giannitti C, Donvito A, et al. Combination therapy with cyclosporine A and anti-TNF-alpha agents in the treatment of rheumatoid arthritis and concomitant hepatitis C virus infection. Clin Rheumatol. 2007 Jul;26(7):1127-9.

175. Belostocki K, Pricop L, Redecha PB, et al. Infliximab treatment shifts the balance between stimulatory and inhibitory Fcgamma receptor type II isoforms on neutrophils in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Feb;58(2):384-8.

176. Bender NK, Heilig CE, Droll B, et al. Immunogenicity, efficacy and adverse events of adalimumab in RA patients. Rheumatol Int. 2007 Jan;27(3):269-74.

177. Ben-Horin S, Goldstein I, Koltakov A, et al. The effect of blockade of tumor necrosis factor alpha on VLA-1+ T-cells in rheumatoid arthritis patients. J Clin Immunol. 2007 Nov;27(6):580-8.

178. Benito-Garcia E, Heller JE, Chibnik LB, et al. Dietary caffeine intake does not affect methotrexate efficacy in patients with rheumatoid arthritis. J Rheumatol. 2006 Jul;33(7):1275-81.

179. Bennett AN, Peterson P, Zain A, et al. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. Rheumatology (Oxford). 2005 Aug;44(8):1026-31.

180. Bennett AN, Wong M, Zain A, et al. Adalimumab-induced asthma. Rheumatology (Oxford). 2005 Sep;44(9):1199-200.

181. Benucci M, Li GF, Del Rosso A, et al. Adalimumab (anti-TNF-alpha) therapy to improve the clinical course of adult-onset Still's disease: the first case report. Clin Exp Rheumatol. 2005 Sep-Oct;23(5):733.

182. Benucci M, Li Gobbi F, Fossi F, et al. Drug-induced lupus after treatment with infliximab in rheumatoid arthritis. J Clin Rheumatol. 2005 Feb;11(1):47-9.

183. Benucci M, Li Gobbi F, Saviola G, et al. Improved rheumatoid digital vasculitis in a patient treated with TNFalpha agent blocking (infliximab). Rheumatol Int. 2008 Oct;28(12):1253-5.

184. Benucci M, Manfredi M, Mecocci L. Effect of etanercept plus lamivudine in a patient with rheumatoid arthritis and viral hepatitis B. J Clin Rheumatol. 2008 Aug;14(4):245-6.

185. Benucci M, Saviola G, Baiardi P, et al. Anti-nucleosome antibodies as prediction factor of development of autoantibodies during therapy with three different TNFalpha blocking agents in rheumatoid arthritis. Clin Rheumatol. 2008 Jan;27(1):91-5.

186. Berard A, Solomon DH, Avorn J. Patterns of drug use in rheumatoid arthritis. J Rheumatol. 2000 Jul;27(7):1648-55.

187. Berg L, Lampa J, Rogberg S, et al. Increased peripheral T cell reactivity to microbial antigens and collagen type II in rheumatoid arthritis after treatment with soluble TNFalpha receptors. Ann Rheum Dis. 2001 Feb;60(2):133-9.

188. Berger A, Edelsberg J, Li TT, et al. Dose intensification with infliximab in patients with rheumatoid arthritis. Ann Pharmacother. 2005 Dec;39(12):2021-5.

189. Bergman J, Schjott J. Hepatitis caused by Lotus-f3? Basic Clin Pharmacol Toxicol. 2009 May;104(5):414-6.

190. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004 Jun;50(6):1959-66.

191. Berkun Y, Abou Atta I, Rubinow A, et al. 2756GG genotype of methionine synthase reductase gene is more prevalent in rheumatoid arthritis patients treated with methotrexate and is associated with methotrexate-induced nodulosis. J Rheumatol. 2007 Aug;34(8):1664-9.

192. Bernatsky S, Ehrmann Feldman D. Discontinuation of methotrexate therapy in older patients with newly diagnosed rheumatoid arthritis: analysis of administrative health databases in Quebec, Canada. Drugs Aging. 2008;25(10):879-84.

193. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46(7):1157-60.

194. Berookhim B, Fischer HD, Weinberg JM. Treatment of recalcitrant pemphigus vulgaris with the tumor necrosis factor alpha antagonist etanercept. Cutis. 2004 Oct;74(4):245-7.

195. Berthelot C, Cather J, Jones D, et al. Atypical CD8+ cutaneous T-cell lymphoma after immunomodulatory therapy. Clin Lymphoma Myeloma. 2006 Jan;6(4):329-32.

196. Berthelot JM, De Bandt M, Goupille P, et al. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. Joint Bone Spine. 2009 Jan;76(1):28-34.

197. Berthelot JM, Glemarec J, Maugars Y, et al. Lethal medium-vessel panarteritis mimicking deep sepsis following etanercept and minocycline therapy in a patient with severe rheumatoid arthritis. Rheumatology (Oxford). 2002 Jun;41(6):703-5.

198. Berthelot JM, Varin S, Cormier G, et al. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy. Joint Bone Spine. 2007 Mar;74(2):144-7.

199. Bertoli AM, Strusberg I, Baravalle M, et al. Rate and causes of infliximab discontinuation in patients with rheumatoid arthritis in a private clinical practice. J Clin Rheumatol. 2008 Dec;14(6):313-7.

200. Beuthien W, Mellinghoff HU, von Kempis J. Skin reaction to adalimumab. Arthritis Rheum. 2004 May;50(5):1690-2.

201. Beyeler C, Frey BM, Bird HA. Urinary 6 beta-hydroxycortisol excretion in rheumatoid arthritis. Br J Rheumatol. 1997 Jan;36(1):54-8.

202. Bhagat S, Ostor AJ. Diagnosing joint pain in the older people. Practitioner. 2010 Jan;254(1725):17-21, 2.

203. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int. 2004 May;25(5):331-5.

204. Bicer A, Tursen U, Cimen OB, et al. Prevalence of dermatophytosis in patients with rheumatoid arthritis. Rheumatol Int. 2003 Jan;23(1):37-40.

205. Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007 Mar;91(3):319-24.

206. Bilsborough W, Keen H, Taylor A, et al. Anti-tumour necrosis factor-alpha therapy over conventional therapy improves endothelial function in adults with rheumatoid arthritis. Rheumatol Int. 2006 Oct;26(12):1125-31.

207. Biro T, Griger Z, Kiss E, et al. Abnormal cell-specific expressions of certain protein kinase C isoenzymes in peripheral mononuclear cells of patients with systemic lupus erythematosus: effect of corticosteroid application. Scand J Immunol. 2004 Oct;60(4):421-8.

208. Biyikoglu B, Buduneli N, Kardesler L, et al. Evaluation of t-PA, PAI-2, IL-1beta and PGE(2) in gingival crevicular fluid of rheumatoid arthritis patients with periodontal disease. J Clin Periodontol. 2006 Sep;33(9):605-11.

209. Biyikoglu B, Buduneli N, Kardesler L, et al. Gingival crevicular fluid MMP-8 and -13 and TIMP-1 levels in patients with rheumatoid arthritis and inflammatory periodontal disease. J Periodontol. 2009 Aug;80(8):1307-14.

210. Blackman MR, Muniyappa R, Wilson M, et al. Diurnal secretion of growth hormone, cortisol, and dehydroepiandrosterone in pre- and perimenopausal women with active rheumatoid arthritis: a pilot case-control study. Arthritis Res Ther. 2007;9(4):R73.

211. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, et al. Successful therapy with danazol in refractory autoimmune thrombocytopenia associated with rheumatic diseases. Br J Rheumatol. 1997 Oct;36(10):1095-9.

212. Bleumink GS, ter Borg EJ, Ramselaar CG, et al. Etanercept-induced subacute cutaneous lupus erythematosus. Rheumatology (Oxford). 2001 Nov;40(11):1317-9.

213. Blom M, Kievit W, Fransen J, et al. The reason for discontinuation of the first tumor necrosis factor (TNF) blocking agent does not influence the effect of a second TNF blocking agent in patients with rheumatoid arthritis. J Rheumatol. 2009 Oct;36(10):2171-7.

214. Blom M, Kievit W, Kuper HH, et al. Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1335-41.

215. Blumberg SN, Fox DA. Rheumatoid arthritis: guidelines for emerging therapies. Am J Manag Care. 2001 Jun;7(6):617-26.

216. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol. 1994 May;33(5):461-3.

217. Boatright MD, Wang BW. Clinical infection with Strongyloides sterocoralis following etanercept use for rheumatoid arthritis. Arthritis Rheum. 2005 Apr;52(4):1336-7.

218. Bobbio-Pallavicini F, Alpini C, Caporali R, et al. Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. Arthritis Res Ther. 2004;6(3):R264-72.

219. Bobbio-Pallavicini F, Caporali R, Alpini C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. Ann Rheum Dis. 2007 Mar;66(3):302-7.

220. Bodur H, Ataman S, Akbulut L, et al. Characteristics and medical management of patients with rheumatoid arthritis and ankylosing spondylitis. Clin Rheumatol. 2008 Sep;27(9):1119-25.

221. Bodur H, Seckin U, Eser F, et al. Coexistence of familial Mediterranean fever and psoriasis in a patient with seronegative spondyloarthropathy. Rheumatol Int. 2008 Nov;29(1):107-10.

222. Boeger CA, Wittwer H, Schattenkirchner M, et al. Treatment of ankylosing spondylitis with infliximab. Ann Rheum Dis. 2001 Dec;60(12):1159-60.

223. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18.

224. Boesen M, Boesen L, Jensen KE, et al. Clinical outcome and imaging changes after intraarticular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and ultrasound-Doppler show no effect of IA injections in the wrist after 4 weeks. J Rheumatol. 2008 Apr;35(4):584-91.

225. Boesen M, Jensen KE, Torp-Pedersen S, et al. Intra-articular distribution pattern after ultrasound-guided injections in wrist joints of patients with rheumatoid arthritis. Eur J Radiol. 2009 Feb;69(2):331-8.

226. Boey O, Van Hooland S, Woestenburg A, et al. Methotrexate should not be used for patients with end-stage kidney disease. Acta Clin Belg. 2006 Jul-Aug;61(4):166-9.

227. Bogoch E, Ouellette G, Hastings D. Failure of internal fixation of displaced femoral neck fractures in rheumatoid patients. J Bone Joint Surg Br. 1991 Jan;73(1):7-10.

228. Bogoch ER, Ouellette G, Hastings DE. Intertrochanteric fractures of the femur in rheumatoid arthritis patients. Clin Orthop Relat Res. 1993 Sep(294):181-6.

229. Bohanec Grabar P, Grabnar I, Rozman B, et al. Investigation of the influence of CYP1A2 and CYP2C19 genetic polymorphism on 2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (A77 1726) pharmacokinetics in leflunomide-treated patients with rheumatoid arthritis. Drug Metab Dispos. 2009 Oct;37(10):2061-8.

230. Bohanec Grabar P, Logar D, Lestan B, et al. Genetic determinants of methotrexate toxicity in rheumatoid arthritis patients: a study of polymorphisms affecting methotrexate transport and folate metabolism. Eur J Clin Pharmacol. 2008 Nov;64(11):1057-68.

231. Bohanec Grabar P, Rozman B, Tomsic M, et al. Genetic polymorphism of CYP1A2 and the toxicity of leflunomide treatment in rheumatoid arthritis patients. Eur J Clin Pharmacol. 2008 Sep;64(9):871-6.

232. Bolla G, Disdier P, Harle JR, et al. Concurrent acute megaloblastic anaemia and pneumonitis: a severe side-effect of low-dose methotrexate therapy during rheumatoid arthritis. Clin Rheumatol. 1993 Dec;12(4):535-7.

233. Bollow M, Braun J, Taupitz M, et al. CT-guided intraarticular corticosteroid injection into the sacroiliac joints in patients with spondyloarthropathy: indication and follow-up with contrast-enhanced MRI. J Comput Assist Tomogr. 1996 Jul-Aug;20(4):512-21.

234. Bologna C, Jorgensen C, Sany J. Association of methotrexate and corticosteroids in the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1996 Jul-Aug;14(4):401-6.

235. Bolstad AI, Eiken HG, Rosenlund B, et al. Increased salivary gland tissue expression of Fas, Fas ligand, cytotoxic T lymphocyte-associated antigen 4, and programmed cell death 1 in primary Sjogren's syndrome. Arthritis Rheum. 2003 Jan;48(1):174-85.

236. Bombardieri S, Ruiz AA, Fardellone P, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology (Oxford). 2007 Jul;46(7):1191-9.

237. Bongartz T, Harle P, Friedrich S, et al. Successful treatment of psoriatic onycho-pachydermo periostitis (POPP) with adalimumab. Arthritis Rheum. 2005 Jan;52(1):280-2.

238. Bongiorno MR, Pistone G, Doukaki S, et al. Adalimumab for treatment of moderate to severe psoriasis and psoriatic arthritis. Dermatol Ther. 2008 Oct;21 Suppl 2:S15-20.

239. Book C, Karlsson M, Akesson K, et al. Disease activity and disability but probably not glucocorticoid treatment predicts loss in bone mineral density in women with early rheumatoid arthritis. Scand J Rheumatol. 2008 Jul-Aug;37(4):248-54.

240. Book C, Karlsson MK, Akesson K, et al. Early rheumatoid arthritis and body composition. Rheumatology (Oxford). 2009 Sep;48(9):1128-32.

241. Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. J Rheumatol. 2005 Mar;32(3):430-4.

242. Boonen A, van der Heijde D, Severens JL, et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. Ann Rheum Dis. 2006 Feb;65(2):201-8.

243. Borowski LC, Lopes RP, Gonzalez TP, et al. Is steroid resistance related to multidrug resistance-I (MDR-I) in rheumatoid arthritis? Int Immunopharmacol. 2007 Jun;7(6):836-44.

244. Borras-Blasco J, Gracia-Perez A, Nunez-Cornejo C, et al. Exacerbation of psoriatic skin lesions in a patient with psoriatic arthritis receiving adalimumab. J Clin Pharm Ther. 2008 Jun;33(3):321-5.

245. Borras-Blasco J, Gracia-Perez A, Rosique-Robles JD, et al. Urticaria due to etanercept in a patient with psoriatic arthritis. South Med J. 2009 Mar;102(3):304-5.

246. Borras-Blasco J, Nunez-Cornejo C, Gracia-Perez A, et al. Parapharyngeal abscess in a patient receiving etanercept. Ann Pharmacother. 2007 Feb;41(2):341-4.

247. Bos WH, Bartelds GM, Vis M, et al. Preferential decrease in IgG4 anti-citrullinated protein antibodies during treatment with tumour necrosis factor blocking agents in patients with rheumatoid arthritis. Ann Rheum Dis. 2009 Apr;68(4):558-63.

248. Bos WH, Bartelds GM, Wolbink GJ, et al. Differential response of the rheumatoid factor and anticitrullinated protein antibodies during adalimumab treatment in patients with rheumatoid arthritis. J Rheumatol. 2008 Oct;35(10):1972-7.

249. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004 Dec;1032:141-53.

250. Bosello S, Santoliquido A, Zoli A, et al. TNF-alpha blockade induces a reversible but transient effect on endothelial dysfunction in patients with long-standing severe rheumatoid arthritis. Clin Rheumatol. 2008 Jul;27(7):833-9.

251. Boss B, Neeck G, Engelhardt B, et al. Influence of corticosteroids on neutrophils, lymphocytes, their subsets, and T-cell activity markers in patients with active rheumatoid arthritis, compared to healthy controls. Ann N Y Acad Sci. 1999 Jun 22;876:198-200.

252. Bostrom EA, d'Elia HF, Dahlgren U, et al. Salivary resistin reflects local inflammation in Sjogren's syndrome. J Rheumatol. 2008 Oct;35(10):2005-11.

253. Botez SA, Herrmann DN. Prolonged remission of a demyelinating neuropathy in a patient with lymphoma and Sjogren's syndrome after Rituximab therapy. J Clin Neuromuscul Dis. 2010 Mar;11(3):127-31.

254. Bourgeois E, Caulier MT, Rose C, et al. Role of splenectomy in the treatment of myelodysplastic syndromes with peripheral thrombocytopenia: a report on six cases. Leukemia. 2001 Jun;15(6):950-3.

255. Boveri E, Castagnola C, Castello A, et al. Aberrant phenotype of plasmacytoid monocytes in acute myeloid leukemia. Am J Hematol. 2008 May;83(5):428-9.

256. Bowie VL, Snella KA, Gopalachar AS, et al. Listeria meningitis associated with infliximab. Ann Pharmacother. 2004 Jan;38(1):58-61.

257. Bozkurt FY, Berker E, Akkus S, et al. Relationship between interleukin-6 levels in gingival crevicular fluid and periodontal status in patients with rheumatoid arthritis and adult periodontitis. J Periodontol. 2000 Nov;71(11):1756-60.

258. Bramlage CP, Kaps C, Ungethum U, et al. Modulatory effects of inflammation and therapy on GDF-5 expression in rheumatoid arthritis synovium. Scand J Rheumatol. 2008 Nov-Dec;37(6):401-9.

259. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum. 2000 Jun;43(6):1346-52.

260. Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum. 2003 Jun;48(6):1667-75.

261. Brandt J, Listing J, Haibel H, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. Rheumatology (Oxford). 2005 Mar;44(3):342-8.

262. Brandt J, Listing J, Sieper J, et al. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. Ann Rheum Dis. 2004 Nov;63(11):1438-44.

263. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006;43(6):717-22.

264. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum 2009;61(3):300-4.

265. Braun J, Baraliakos X, Brandt J, et al. Persistent clinical response to the anti-TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. Rheumatology (Oxford). 2005 May;44(5):670-6.

266. Braun J, Baraliakos X, Golder W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum. 2003 Apr;48(4):1126-36.

267. Braun J, Bollow M, Seyrekbasan F, et al. Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: clinical outcome and followup by dynamic magnetic resonance imaging. J Rheumatol. 1996 Apr;23(4):659-64.

268. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. Arthritis Rheum. 2003 Aug;48(8):2224-33.

269. Braun J, Brandt J, Listing J, et al. Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. Ann Rheum Dis. 2005 Feb;64(2):229-34.

270. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.

271. Braun J, Kastner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral

administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008 Jan;58(1):73-81.

272. Braun J, Landewe R, Hermann KG, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum. 2006 May;54(5):1646-52.

273. Braun J, Sieper J, Breban M, et al. Anti-tumour necrosis factor alpha therapy for ankylosing spondylitis: international experience. Ann Rheum Dis. 2002 Dec;61 Suppl 3:iii51-60.

274. Braun J, van der Heijde D. Imaging and scoring in ankylosing spondylitis. Best Pract Res Clin Rheumatol. 2002 Sep;16(4):573-604.

275. Braun-Moscovici Y, Markovits D, Rozin A, et al. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. Isr Med Assoc J. 2008 Apr;10(4):277-81.

276. Bravo Vergel Y, Hawkins NS, Claxton K, et al. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35.

277. Breban M, Vignon E, Claudepierre P, et al. Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. Rheumatology (Oxford). 2002 Nov;41(11):1280-5.

278. Breedveld F, Agarwal S, Yin M, et al. Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. J Clin Pharmacol. 2007 Sep;47(9):1119-28.

279. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63(2):149-55.

280. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26-37.

281. Breglia MD, Carter JD. Atypical insufficiency fracture of the tibia associated with long-term bisphosphonate therapy. J Clin Rheumatol. 2010 Mar;16(2):76-8.

282. Bremner R, Simpson E, White CR, et al. Palisaded neutrophilic and granulomatous dermatitis: an unusual cutaneous manifestation of immune-mediated disorders. Semin Arthritis Rheum. 2004 Dec;34(3):610-6.

283. Brennan A, Bansback N, Nixon R, et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford). 2007 Aug;46(8):1345-54.

284. Brennan MT, Sankar V, Leakan RA, et al. Sex steroid hormones in primary Sjogren's syndrome. J Rheumatol. 2003 Jun;30(6):1267-71.

285. Bresnihan B. Treating early rheumatoid arthritis in the younger patient. J Rheumatol Suppl. 2001 Jun;62:4-9.

286. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41(12):2196-204.

287. Bresnihan B, Newmark R, Robbins S, et al. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.

288. Brocq O, Albert C, Roux C, et al. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy:

experience with 18 patients. Joint Bone Spine. 2004 Nov;71(6):601-3.

289. Brocq O, Roux CH, Albert C, et al. TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 2007;74(2):148-54.

290. Brooks H, Taylor HG, Nichol FE. The three week sulphasalazine syndrome. Clin Rheumatol. 1992 Dec;11(4):566-8.

291. Brophy RH, MacKenzie CR, Gamradt SC, et al. The diagnosis and management of psoriatic arthritis in a professional football player presenting with a knee effusion: a case report. Clin J Sport Med. 2008 Jul;18(4):369-71.

292. Broussais F, Kawashima M, Marotte H, et al. Chronic myeloid leukaemia and tuberculosis in a patient with rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2005 Mar;64(3):509-10.

293. Broussard JS, Jr. Derangement, osteoarthritis, and rheumatoid arthritis of the temporomandibular joint: implications, diagnosis, and management. Dent Clin North Am. 2005 Apr;49(2):327-42.

294. Brown A, Grubbs P, Mongey AB. Infection of total hip prosthesis by Mycobacterium tuberculosis and Mycobacterium chelonae in a patient with rheumatoid arthritis. Clin Rheumatol. 2008 Apr;27(4):543-5.

295. Brown ES, Frol A, Bobadilla L, et al. Effect of lamotrigine on mood and cognition in patients receiving chronic exogenous corticosteroids. Psychosomatics. 2003 May-Jun;44(3):204-8.

296. Brown ES, Woolston DJ, Frol AB. Amygdala volume in patients receiving chronic corticosteroid therapy. Biol Psychiatry. 2008 Apr 1;63(7):705-9.

297. Brown GT, Wright FV, Lang BA, et al. Clinical responsiveness of self-report functional assessment measures for children with juvenile idiopathic arthritis undergoing intraarticular corticosteroid injections. Arthritis Rheum. 2005 Dec 15;53(6):897-904.

298. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum. 2002 Dec;46(12):3151-8.

299. Bruckle W, Eisenhut C, Goebel FD. Cerebral involvement in adult onset Still's disease. Clin Rheumatol. 1992 Jun;11(2):276-9.

300. Brunasso AM, Massone C. Thrombocytopenia associated with the use of anti-tumor necrosis factor-alpha agents for psoriasis. J Am Acad Dermatol. 2009 May;60(5):781-5.

301. Bruns A, Nicaise-Roland P, Hayem G, et al. Prospective cohort study of effects of infliximab on rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antinuclear antibodies in patients with long-standing rheumatoid arthritis. Joint Bone Spine. 2009 May;76(3):248-53.

302. Bruns H, Meinken C, Schauenberg P, et al. Anti-TNF immunotherapy reduces CD8+ T cell-mediated antimicrobial activity against Mycobacterium tuberculosis in humans. J Clin Invest. 2009 May;119(5):1167-77.

303. Bruyn GA, Tate G, Caeiro F, et al. Everolimus in patients with rheumatoid arthritis receiving concomitant methotrexate: a 3-month, double-blind, randomised, placebo-controlled, parallel-group, proof-of-concept study. Ann Rheum Dis. 2008 Aug;67(8):1090-5.

304. Bryl E, Vallejo AN, Matteson EL, et al. Modulation of CD28 expression with anti-tumor necrosis factor alpha therapy in rheumatoid arthritis. Arthritis Rheum. 2005 Oct;52(10):2996-3003.

305. Buccoliero G, Lonero G, Romanelli C, et al. Varicella zoster virus encephalitis during treatment with anti-tumor necrosis factor-alpha agent in a psoriatic arthritis patient. New Microbiol. 2010 Jul;33(3):271-4.

306. Buccoliero R, Gambelli S, Sicurelli F, et al. Leukoencephalopathy as a rare complication of hepatitis C infection. Neurol Sci. 2006 Nov;27(5):360-3.

307. Buch MH, Bingham SJ, Bryer D, et al. Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. Rheumatology (Oxford). 2007 Jul;46(7):1153-6.

308. Buch MH, Bingham SJ, Seto Y, et al. Lack of response to anakinra in rheumatoid arthritis following failure of tumor necrosis factor alpha blockade. Arthritis Rheum. 2004 Mar;50(3):725-8.

309. Buch MH, Boyle DL, Rosengren S, et al. Mode of action of abatacept in rheumatoid arthritis patients having failed tumour necrosis factor blockade: a histological, gene expression and dynamic magnetic resonance imaging pilot study. Ann Rheum Dis. 2009 Jul;68(7):1220-7.

310. Buch MH, Conaghan PG, Quinn MA, et al. True infliximab resistance in rheumatoid arthritis: a role for lymphotoxin alpha? Ann Rheum Dis. 2004 Oct;63(10):1344-6.

311. Buch MH, Reece RJ, Quinn MA, et al. The value of synovial cytokine expression in predicting the clinical response to TNF antagonist therapy (infliximab). Rheumatology (Oxford). 2008 Oct;47(10):1469-75.

312. Buch MH, Seto Y, Bingham SJ, et al. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of nonresponse and subsequent response to etanercept. Arthritis Rheum. 2005 Jan;52(1):42-8.

313. Buchbinder R, Barber M, Heuzenroeder L, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 2008 Jun 15;59(6):794-9.

314. Buchs N, Silvestri T, di Giovine FS, et al. IL-4 VNTR gene polymorphism in chronic polyarthritis. The rare allele is associated with protection against destruction. Rheumatology (Oxford). 2000 Oct;39(10):1126-31.

315. Buckland GT, 3rd, Carlson JA, Meyer DR. Persistent periorbital and facial lymphedema associated with Group A beta-hemolytic streptococcal infection (erysipelas). Ophthal Plast Reconstr Surg. 2007 Mar-Apr;23(2):161-3.

316. Buckley LM, Leib ES, Cartularo KS, et al. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9.

317. Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1996 Dec 15;125(12):961-8.

318. Buckley LM, Leib ES, Cartularo KS, et al. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1997 Aug;24(8):1489-94.

319. Buda-Okreglak EM, Drabick JJ, Delaney NR. Proinflammatory syndrome mimicking acute rheumatoid arthritis in a patient with Waldenstrom's macroglobulinemia treated with rituximab. Ann Hematol. 2004 Feb;83(2):117-9.

320. Bunescu A, Seideman P, Lenkei R, et al. Enhanced Fcgamma receptor I, alphaMbeta2 integrin receptor expression by monocytes and neutrophils in rheumatoid arthritis: interaction with platelets. J Rheumatol. 2004 Dec;31(12):2347-55.

321. Burge DJ, Bookbinder SA, Kivitz AJ, et al. Pharmacokinetic and pharmacodynamic properties of TRU-015, a CD20-directed small modular immunopharmaceutical protein therapeutic, in patients with rheumatoid arthritis: a Phase I, open-label, dose-escalation clinical study. Clin Ther. 2008 Oct;30(10):1806-16.

322. Burgos RA, Hancke JL, Bertoglio JC, et al. Efficacy of an Andrographis paniculata composition for the relief of rheumatoid

arthritis symptoms: a prospective randomized placebo-controlled trial. Clin Rheumatol. 2009 Aug;28(8):931-46.

323. Burmester GR, Ferraccioli G, Flipo RM, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008 Jan 15;59(1):32-41.

324. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66(6):732-9.

325. Burnham JM, Shults J, Dubner SE, et al. Bone density, structure, and strength in juvenile idiopathic arthritis: importance of disease severity and muscle deficits. Arthritis Rheum. 2008 Aug;58(8):2518-27.

326. Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet. 2008 Jan 19;371(9608):205-14.

327. Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. Ann Rheum Dis. 2010 Jul;69(7):1275-80.

328. Caballol Pons N, Montala N, Valverde J, et al. Isolated cerebral vasculitis associated with rheumatoid arthritis. Joint Bone Spine. 2010 Jul;77(4):361-3.

329. Cairns AP, Duncan MK, Hinder AE, et al. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis. 2002 Nov;61(11):1031-2.

330. Cairns AP, Taggart AJ. Anti-tumour necrosis factor therapy for severe inflammatory arthritis: two years of experience in Northern Ireland. Ulster Med J. 2002 Nov;71(2):101-5.

331. Calabrese LH. Rheumatoid arthritis and primary care: the case for early diagnosis and treatment. J Am Osteopath Assoc. 1999 Jun;99(6):313-21.

332. Calin A, Dijkmans BA, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004 Dec;63(12):1594-600.

333. Callaly EL, FitzGerald O, Rogers S. Hydroxychloroquine-associated, photo-induced toxic epidermal necrolysis. Clin Exp Dermatol. 2008 Aug;33(5):572-4.

334. Cambridge G, Leandro MJ, Edwards JC, et al. Serologic changes following B lymphocyte depletion therapy for rheumatoid arthritis. Arthritis Rheum. 2003 Aug;48(8):2146-54.

335. Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis Rheum. 2006 Mar;54(3):723-32.

336. Campion GV, Lebsack ME, Lookabaugh J, et al. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1Ra Arthritis Study Group. Arthritis Rheum. 1996 Jul;39(7):1092-101.

337. Campione E, Mazzotta A, Paterno EJ, et al. Effect of calcipotriol on etanercept partial responder psoriasis vulgaris and psoriatic arthritis patients. Acta Derm Venereol. 2009;89(3):288-91.

338. Cankaya H, Alpoz E, Karabulut G, et al. Effects of hydroxychloroquine on salivary flow rates and oral complaints of Sjogren patients: a prospective sample study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Jul;110(1):62-7.

339. Cannon GW, Holden WL, Juhaeri J, et al. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol. 2004 Oct;31(10):1906-11.

340. Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol. 2008 Mar;35(3):421-4.

341. Cantarini L, Tinazzi I, Biasi D, et al. Sulfasalazine-induced immune thrombocytopenia. Postgrad Med J. 2007 Jun;83(980):e1.

342. Cantini F, Niccoli L, Benucci M, et al. Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. Arthritis Rheum. 2006 Oct 15;55(5):812-6.

343. Cantini F, Niccoli L, Nannini C, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology (Oxford) 2008;47(6):872-6.

344. Capell H. Longterm maintenance therapy with disease modifying antirheumatic drugs. J Rheumatol Suppl. 2002 Nov;66:38-43.

345. Capell HA, Madhok R, Hunter JA, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis. 2004 Jul;63(7):797-803.

346. Capell HA, Murphy EA, Hunter JA. Rheumatoid arthritis: workload and outcome over 10 years. Q J Med. 1991 Jun;79(290):461-76.

347. Caplan L, Wolfe F, Russell AS, et al. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol. 2007 Apr;34(4):696-705.

348. Capria A, De Nardo D, Baffetti FR, et al. Long-term anti-TNF-alpha treatments reverse the endothelial dysfunction in rheumatoid arthritis: the biological coherence between synovial and endothelial inflammation. Int J Immunopathol Pharmacol. 2010 Jan-Mar;23(1):255-62.

349. Capsoni F, Sarzi-Puttini P, Atzeni F, et al. Effect of adalimumab on neutrophil function in patients with rheumatoid arthritis. Arthritis Res Ther. 2005;7(2):R250-5.

350. Caramaschi P, Biasi D, Carletto A, et al. A case of adult onset Still's disease treated with infliximab. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):113.

351. Caramaschi P, Biasi D, Carletto A, et al. Orbital myositis in a rheumatoid arthritis patient during etanercept treatment. Clin Exp Rheumatol. 2003 Jan-Feb;21(1):136-7.

352. Caramaschi P, Ruzzenente O, Pieropan S, et al. Determination of ANA specificity using multiplexed fluorescent microsphere immunoassay in patients with ANA positivity at high titres after infliximab treatment: preliminary results. Rheumatol Int. 2007 May;27(7):649-54.

353. Caramella C, Avouac J, Sogni P, et al. Association between rheumatoid arthritis and primary biliary cirrhosis. Joint Bone Spine. 2007 May;74(3):279-81.

354. Cardillo C, Schinzari F, Mores N, et al. Intravascular tumor necrosis factor alpha blockade reverses endothelial dysfunction in rheumatoid arthritis. Clin Pharmacol Ther. 2006 Sep;80(3):275-81.

355. Carloni A, Piciucchi S, Giannakakis K, et al. Diffuse alveolar hemorrhage after leflunomide therapy in a patient with rheumatoid arthritis. J Thorac Imaging. 2008 Feb;23(1):57-9.

356. Carlson E, Rothfield N. Etanercept-induced lupus-like syndrome in a patient with rheumatoid arthritis. Arthritis Rheum. 2003 Apr;48(4):1165-6; author reply 6.

357. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005 Jun;52(6):1766-72.

358. Caroyer JM, Manto MU, Steinfeld SD. Severe sensory neuronopathy responsive to

infliximab in primary Sjogren's syndrome. Neurology. 2002 Oct 8;59(7):1113-4.

359. Carrasco R, Smith JA, Lovell D. Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. Paediatr Drugs. 2004;6(3):137-46.

360. Carreira PE, Gonzalez-Crespo MR, Ciruelo E, et al. Polymorphism of the interleukin-1 receptor antagonist gene: a factor in susceptibility to rheumatoid arthritis in a Spanish population. Arthritis Rheum. 2005 Oct;52(10):3015-9.

361. Carrera C, Mascaro JM, Jr., Moreno-Romero JA, et al. Pyoderma vegetans associated with severe psoriatic arthritis: good response to etanercept. Dermatology. 2007;214(1):77-81.

362. Carroll MB, Bond MI. Use of tumor necrosis factor-alpha inhibitors in patients with chronic hepatitis B infection. Semin Arthritis Rheum. 2008 Dec;38(3):208-17.

363. Carter JD, Gerard HC, Hudson AP. Psoriasiform lesions induced by tumour necrosis factor antagonists: a skin-deep medical conundrum. Ann Rheum Dis. 2008 Aug;67(8):1181-3.

364. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. J Rheumatol. 2006 May;33(5):1014-7.

365. Caselli RJ, Scheithauer BW, Bowles CA, et al. The treatable dementia of Sjogren's syndrome. Ann Neurol. 1991 Jul;30(1):98-101.

366. Caselli RJ, Scheithauer BW, O'Duffy JD, et al. Chronic inflammatory meningoencephalitis should not be mistaken for Alzheimer's disease. Mayo Clin Proc. 1993 Sep;68(9):846-53.

367. Cash JM, Crofford LJ, Gallucci WT, et al. Pituitary-adrenal axis responsiveness to ovine corticotropin releasing hormone in patients with rheumatoid arthritis treated with low dose prednisone. J Rheumatol. 1992 Nov;19(11):1692-6.

368. Casoli P, Tumiati B. Rheumatoid arthritis, corticosteroid therapy and Kaposi's sarcoma: a coincidence? A case and review of literature. Clin Rheumatol. 1992 Sep;11(3):432-5.

369. Caspi D, Elkayam O, Eisinger M, et al. Clinical significance of low titer anti-nuclear antibodies in early rheumatoid arthritis: implications on the presentation and long-term course of the disease. Rheumatol Int. 2001 Feb;20(2):43-7.

370. Cassano N, Galluccio A, De Simone C, et al. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. J Biol Regul Homeost Agents. 2008 Oct-Dec;22(4):233-7.

371. Cassano N, Loconsole F, Amoruso A, et al. Infliximab monotherapy for refractory psoriasis: preliminary results. Int J Immunopathol Pharmacol. 2004 Sep-Dec;17(3):373-80.

372. Castagnetta LA, Carruba G, Granata OM, et al. Increased estrogen formation and estrogen to androgen ratio in the synovial fluid of patients with rheumatoid arthritis. J Rheumatol. 2003 Dec;30(12):2597-605.

373. Castaneda O, Nair MG. Controlled trial of methotrexate versus CH-1504 in the treatment of rheumatoid arthritis. J Rheumatol. 2006 May;33(5):862-4.

374. Catananti C, Mastropaolo S, Calabrese C, et al. A case of normal-pressure hydrocephalus associated with rheumatoid arthritis. Aging Clin Exp Res. 2010 Apr;22(2):189-91.

375. Catley D, Kaell AT, Kirschbaum C, et al. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. Arthritis Care Res. 2000 Feb;13(1):51-61.

376. Catrina AI, af Klint E, Ernestam S, et al. Anti-tumor necrosis factor therapy increases synovial osteoprotegerin expression in rheumatoid arthritis. Arthritis Rheum. 2006 Jan;54(1):76-81.

377. Catrina AI, Lampa J, Ernestam S, et al. Anti-tumour necrosis factor (TNF)-alpha therapy (etanercept) down-regulates serum matrix metalloproteinase (MMP)-3 and MMP-1 in rheumatoid arthritis. Rheumatology (Oxford). 2002 May;41(5):484-9.

378. Catrina AI, Trollmo C, af Klint E, et al. Evidence that anti-tumor necrosis factor therapy with both etanercept and infliximab induces apoptosis in macrophages, but not lymphocytes, in rheumatoid arthritis joints: extended report. Arthritis Rheum. 2005 Jan;52(1):61-72.

379. Catrina AI, Ulfgren AK, Lindblad S, et al. Low levels of apoptosis and high FLIP expression in early rheumatoid arthritis synovium. Ann Rheum Dis. 2002 Oct;61(10):934-6.

380. Cattalini M, Maduskuie V, Fawcett PT, et al. Predicting duration of beneficial effect of joint injection among children with chronic arthritis by measuring biomarkers concentration in synovial fluid at the time of injection. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1153-60.

381. Cauli A, Yanni G, Panayi GS. Interleukin-1, interleukin-1 receptor antagonist and macrophage populations in rheumatoid arthritis synovial membrane. Br J Rheumatol. 1997 Sep;36(9):935-40.

382. Cauza E, Cauza K, Hanusch-Enserer U, et al. Intravenous anti TNF-alpha antibody therapy leads to elevated triglyceride and reduced HDL-cholesterol levels in patients with rheumatoid and psoriatic arthritis. Wien Klin Wochenschr. 2002 Dec 30;114(23-24):1004-7.

383. Cauza E, Hanusch-Enserer U, Frischmuth K, et al. Short-term infliximab therapy improves symptoms of psoriatic arthritis and decreases concentrations of cartilage oligomeric matrix protein. J Clin Pharm Ther. 2006 Apr;31(2):149-52.

384. Cauza E, Spak M, Cauza K, et al. Treatment of psoriatic arthritis and psoriasis vulgaris with the tumor necrosis factor inhibitor infliximab. Rheumatol Int. 2002 Nov;22(6):227-32.

385. Cavagna L, Caporali R, Epis O, et al. Infliximab in the treatment of adult Still's disease refractory to conventional therapy. Clin Exp Rheumatol. 2001 May-Jun;19(3):329-32.

386. Cavallasca JA, Caubet M, Helling CA, et al. Cryptogenic organizing pneumonia (COP), as presentation of rheumatoid arthritis. Rheumatol Int. 2008 Nov;29(1):99-101.

387. Cavazzana I, Bobbio-Pallavicini F, Franceschini F, et al. Anti-TNF-alpha treatment in rheumatoid arthritis with anti-Ro/SSA antibodies. Analysis of 17 cases among a cohort of 322 treated patients. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):676-83.

388. Cay HF, Gungor HA, Sezer I, et al. Adverse effect of TNF-alpha blocker? Demyelination in an ankylosing spondylitis patient: a case report. J Clin Pharm Ther. 2006 Dec;31(6):645-8.

389. Cefle A. Leflunomide and azathioprine combination in refractory adult-onset Still's disease. Ann Pharmacother. 2005 Apr;39(4):764-7.

390. Cepeda EJ, Williams FM, Ishimori ML, et al. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis. 2008 May;67(5):710-2.

391. Chakraborty PP, Achar A. Spontaneous bleeding in a patient of rheumatoid arthritis: a complication after accidental overdose of methotrexate. J Assoc Physicians India. 2007 Jul;55:501.

392. Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. J Rheumatol. 2003 Feb;30(2):241-6.

393. Chambers CD, Johnson DL, Robinson LK, et al. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum 2010;62(5):1494-503.

394. Chan AT, Cleeve V, Daymond TJ. Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis. Postgrad Med J. 2002 Jan;78(915):47-8.

395. Chan JL, Davis-Reed L, Kimball AB. Counter-regulatory balance: atopic dermatitis in patients undergoing infliximab infusion therapy. J Drugs Dermatol. 2004 May-Jun;3(3):315-8.

396. Chandra PA, Margulis Y, Schiff C. Rituximab is useful in the treatment of Felty's syndrome. Am J Ther. 2008 Jul-Aug;15(4):321-2.

397. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. J Rheumatol. 2008 Mar;35(3):469-71.

398. Chandran V, Siannis F, Rahman P, et al. Folate pathway enzyme gene polymorphisms and the efficacy and toxicity of methotrexate in psoriatic arthritis. J Rheumatol. 2010 Jul;37(7):1508-12.

399. Chang DM, Chang SY, Yeh MK, et al. The pharmacokinetics of interleukin-1 receptor antagonist in Chinese subjects with rheumatoid arthritis. Pharmacol Res. 2004 Sep;50(3):371-6.

400. Chang DM, Weinblatt ME, Schur PH. The effects of methotrexate on interleukin 1 in patients with rheumatoid arthritis. J Rheumatol. 1992 Nov;19(11):1678-82.

401. Chang HK, Park W, Ryu DS. Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. J Korean Med Sci. 2002 Apr;17(2):270-3.

402. Chang J, Girgis L. Clinical use of anti-TNF-alpha biological agents--a guide for GPs. Aust Fam Physician. 2007 Dec;36(12):1035-8.

403. Chang WH, Katz BJ, Warner JE, et al. A novel method for screening the multifocal electroretonogram in patients using hydroxychloroquine. Retina. 2008 Nov-Dec;28(10):1478-86.

404. Chantler IW, Davie MW, Evans SF, et al. Oral corticosteroid prescribing in women over 50, use of fracture prevention therapy, and bone densitometry service. Ann Rheum Dis. 2003 Apr;62(4):350-2.

405. Chapman PT, O'Donnell JL, Moller PW. Rheumatoid pleural effusion: response to intrapleural corticosteroid. J Rheumatol. 1992 Mar;19(3):478-80.

406. Charabaty S, Shanmugam V. A 65-year-old man with longstanding seropositive rheumatoid arthritis and lower extremity ulceration. Arthritis Rheum. 2009 Sep 15;61(9):1275-80.

407. Charles PJ, Smeenk RJ, De Jong J, et al. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum. 2000 Nov;43(11):2383-90.

408. Charles-Schoeman C, Watanabe J, Lee YY, et al. Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. Arthritis Rheum. 2009 Oct;60(10):2870-9.

409. Chatterjee S. Severe interstitial pneumonitis associated with infliximab therapy. Scand J Rheumatol. 2004;33(4):276-7.

410. Chatzikyriakidou A, Georgiou I, Voulgari PV, et al. Transcription regulatory polymorphism -43T>C in the 5'-flanking region of SLC19A1 gene could affect rheumatoid arthritis patient response to methotrexate therapy. Rheumatol Int. 2007 Sep;27(11):1057-61.

411. Chauhan A, Mikulik Z, Hackshaw KV. Multicentric reticulohistiocytosis with positive anticyclic citrullinated antibodies. J Natl Med Assoc. 2007 Jun;99(6):678-80.

412. Chaveiro MA, Vieira R, Cardoso J, et al. Cutaneous infection due to Scedosporium apiospermum in an immunosuppressed patient. J Eur Acad Dermatol Venereol. 2003 Jan;17(1):47-9.

413. Chavez-Lopez MA, Delgado-Villafana J, Gallaga A, et al. Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. Allergol Immunopathol (Madr). 2005 Sep-Oct;33(5):291-2.

414. Cheema GS, Quismorio FP, Jr. Pulmonary involvement in adult-onset Still's disease. Curr Opin Pulm Med. 1999 Sep;5(5):305-9.

415. Chen DY, Shen GH, Hsieh TY, et al. Effectiveness of the combination of a whole-blood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. Arthritis Rheum. 2008 Jun 15;59(6):800-6.

416. Chen HA, Lin KC, Chen CH, et al. The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jan;65(1):35-9.

417. Chen YC, Hsu SW. Tuberculous arthritis mimic arthritis of the Sjogren's syndrome: findings from sonography, computed tomography and magnetic resonance images. Eur J Radiol. 2001 Dec;40(3):232-5.

418. Chen YC, Yang WC, Yang AH, et al. Primary Sjogren's syndrome associated with Gitelman's syndrome presenting with muscular paralysis. Am J Kidney Dis. 2003 Sep;42(3):586-90.

419. Cheung KK, Chow KM, Szeto CC, et al. Fatal pancytopenia in a hemodialysis patient after treatment with low-dose methotrexate. J Clin Rheumatol. 2009 Jun;15(4):177-80.

420. Chevillotte-Maillard H, Ornetti P, Mistrih R, et al. Survival and safety of treatment with infliximab in the elderly population. Rheumatology (Oxford). 2005 May;44(5):695-6.

421. Chew AL, Bennett A, Smith CH, et al. Successful treatment of severe psoriasis and psoriatic arthritis with adalimumab. Br J Dermatol. 2004 Aug;151(2):492-6.

422. Chikanza IC, Petrou P, Kingsley G, et al. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis Rheum. 1992 Nov;35(11):1281-8.

423. Chikanza IC, Roux-Lombard P, Dayer JM, et al. Dysregulation of the in vivo production of interleukin-1 receptor antagonist in patients with rheumatoid arthritis. Pathogenetic implications. Arthritis Rheum. 1995 May;38(5):642-8.

424. Chikkamuniyappa S. Streptococcal toxic shock syndrome and sepsis manifesting in a patient with chronic rheumatoid arthritis. Dermatol Online J. 2004;10(1):7.

425. Chikura B, Sathi N, Lane S, et al. Variation of immunological response in methotrexate-induced pneumonitis. Rheumatology (Oxford). 2008 Nov;47(11):1647-50.

426. Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care. 2008 Mar;6(1):1-14.

427. Chim CS, Pang YY, Ooi GC, et al. EBV-associated synovial lymphoma in a chronically inflamed joint in rheumatoid arthritis receiving prolonged methotrexate treatment. Haematologica. 2006 Aug;91(8 Suppl):ECR31.

428. Chiou CF, Sherbourne CD, Cornelio I, et al. Revalidation of the original Cedars-Sinai health-related quality of life in rheumatoid arthritis questionnaire. J Rheumatol. 2006 Feb;33(2):256-62.

429. Cho I, Mori S, Imamura F, et al. Methotrexate pneumonia lacking dyspnea and radiographic interstitial patterns during treatment for early rheumatoid arthritis: bronchoalveolar lavage and transbronchial lung biopsy in a differential diagnosis. Mod Rheumatol. 2007;17(3):256-61.

430. Choi SW, Ahn JJ, Hwang YT, et al. A case of tuberculous arthritis following the use of etanercept. Korean J Intern Med. 2009 Dec;24(4):397-401.

431. Chomarat P, Vannier E, Dechanet J, et al. Balance of IL-1 receptor antagonist/IL-1 beta in rheumatoid synovium and its regulation by IL-4 and IL-10. J Immunol. 1995 Feb 1;154(3):1432-9.

432. Chopin F, Garnero P, le Henanff A, et al. Long-term effects of infliximab on bone and cartilage turnover markers in patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Mar;67(3):353-7.

433. Chopra A, Saluja M, Lagu-Joshi V, et al. Leflunomide (Arava) is a useful DMARD in Indian (Asian) patients: a clinic-based observational study of 1-year treatment. Clin Rheumatol 2008;27(8):1039-44.

434. Chou CT. The clinical application of etanercept in Chinese patients with rheumatic diseases. Mod Rheumatol. 2006;16(4):206-13.

435. Choy EH, Isenberg DA, Garrood T, et al. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. Arthritis Rheum. 2002 Dec;46(12):3143-50.

436. Choy EH, Smith CM, Farewell V, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 2008;67(5):656-63.

437. Chung CP, Oeser A, Solus JF, et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum. 2008 Jul;58(7):2105-12.

438. Chung CP, Russell AS, Segami MI, et al. The effect of low-dose prednisone on bone mineral density in Peruvian rheumatoid arthritis patients. Rheumatol Int. 2005 Mar;25(2):114-7.

439. Ciboddo G, Idone C. Treatment of renal amyloidosis in rheumatoid arthritis requires further investigation: comment on the case report by Elkayam et al. Arthritis Rheum. 2003 Nov;48(11):3299; author reply -300.

440. Cisternas M, Gutierrez M, Jacobelli S. Successful rechallenge with anti-tumor necrosis factor alpha for psoriatic arthritis after development of demyelinating nervous system disease during initial treatment: comment on the article by Mohan et al. Arthritis Rheum. 2002 Nov;46(11):3107-8; author reply 8-9.

441. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess. 2004 May;8(18):iii-iv, ix-x, 1-105.

442. Clarke LE, Junkins-Hopkins J, Seykora JT, et al. Methotrexate-associated lymphoproliferative disorder in a patient with rheumatoid arthritis presenting in the skin. J Am Acad Dermatol. 2007 Apr;56(4):686-90.

443. Cleland LG, Caughey GE, James MJ, et al. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. J Rheumatol. 2006 Oct;33(10):1973-9.

444. Clelland S, Hunek JR. Etanercept injection site reaction. Dermatol Nurs. 2005 Oct;17(5):375-.

445. Clementine RR, Lyman J, Zakem J, et al. Tumor necrosis factor-alpha antagonist-induced sarcoidosis. J Clin Rheumatol. 2010 Sep;16(6):274-9.

446. Clifford LJ, Rossiter JD. Peripheral visual field loss following treatment with etanercept. Br J Ophthalmol. 2004 Jun;88(6):842.

447. Clunie G, Voules S, Watts R. Dose reduction of etanercept--can we treat more patients using a fixed budget? Rheumatology (Oxford). 2003 Apr;42(4):600-1.

448. Coates LC, Cawkwell LS, Ng NW, et al. Sustained response to long-term biologics and switching in psoriatic arthritis: results from real life experience. Ann Rheum Dis. 2008 May;67(5):717-9.

449. Cobo Ibanez T, Yehia Tayel M, Balsa Criado A, et al. Safety and efficacy of leflunomide and infliximab versus methotrexate and infliximab combination therapy in rheumatoid arthritis. Rheumatology (Oxford). 2005 Nov;44(11):1467-8.

450. Coca A, Sanz I. B cell depletion in lupus and Sjogren's syndrome: an update. Curr Opin Rheumatol. 2009 Sep;21(5):483-8.

451. Cocito D, Bergamasco B, Tavella A, et al. Multifocal motor neuropathy during treatment with infliximab. J Peripher Nerv Syst. 2005 Dec;10(4):386-7.

452. Cohen CD, Horster S, Sander CA, et al. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. Ann Rheum Dis. 2003 Jul;62(7):684.

453. Cohen G, Courvoisier N, Cohen JD, et al. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):795-800.

454. Cohen J. Still looking for the cause of fever? Crit Care Resusc. 2006 Jun;8(2):155-6.

455. Cohen JD, Bournerias I, Buffard V, et al. Psoriasis induced by tumor necrosis factor-alpha antagonist therapy: a case series. J Rheumatol. 2007 Feb;34(2):380-5.

456. Cohen JD, Zaltni S, Kaiser MJ, et al. Secondary addition of methotrexate to partial responders to etanercept alone is effective in severe rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):209-10.

457. Cohen MD, Conn DL. Benefits of low-dose corticosteroids in rheumatoid arthritis. Bull Rheum Dis. 1997 Jun;46(4):4-7.

458. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.

459. Cohen SB, Cheng TT, Chindalore V, et al. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Feb;60(2):335-44.

460. Cohen SB, Dore RK, Lane NE, et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum. 2008 May;58(5):1299-309.

461. Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis 2010;69(6):1158-61.

462. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8.

463. Cohen SB, Strand V, Aguilar D, et al. Patient- versus physician-reported outcomes in rheumatoid arthritis patients treated with recombinant interleukin-1 receptor antagonist (anakinra) therapy. Rheumatology (Oxford). 2004 Jun;43(6):704-11.

464. Cohen SB, Woolley JM, Chan W. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol. 2003 Feb;30(2):225-31.

465. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007;27(4):369-73.

466. Cole JC, Li T, Lin P, et al. Treatment impact on estimated medical expenditure and job

loss likelihood in rheumatoid arthritis: re-examining quality of life outcomes from a randomized placebo-controlled clinical trial with abatacept. Rheumatology (Oxford). 2008 Jul;47(7):1044-50.

467. Coluccia D, Wolf OT, Kollias S, et al. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. J Neurosci. 2008 Mar 26;28(13):3474-8.

468. Colwell CW, Jr., Robinson CA, Stevenson DD, et al. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. Orthopedics. 1996 Nov;19(11):941-6.

469. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis 2009;68(7):1146-52.

470. Comby E, Tanaff P, Mariotte D, et al. Evolution of antinuclear antibodies and clinical patterns in patients with active rheumatoid arthritis with longterm infliximab therapy. J Rheumatol. 2006 Jan;33(1):24-30.

471. Conaghan PG, O'Connor P, McGonagle D, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum. 2003 Jan;48(1):64-71.

472. Constantinescu F, Goucher S, Weinstein A, et al. Racial disparities in treatment preferences for rheumatoid arthritis. Med Care. 2009 Mar;47(3):350-5.

473. Constantinou M, Jhanji V, Tao LW, et al. Clinical review of corneal ulcers resulting in evisceration and enucleation in elderly population. Graefes Arch Clin Exp Ophthalmol. 2009 Oct;247(10):1389-93.

474. Conti A, Sartorio A, Ferrero S, et al. Modifications of biochemical markers of bone and collagen turnover during corticosteroid therapy. J Endocrinol Invest. 1996 Feb;19(2):127-30.

475. Conti F, Ceccarelli F, Marocchi E, et al. Switching tumour necrosis factor alpha antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period. Ann Rheum Dis. 2007 Oct;66(10):1393-7.

476. Conti F, Priori R, Chimenti MS, et al. Successful treatment with intraarticular infliximab for resistant knee monarthritis in a patient with spondylarthropathy: a role for scintigraphy with 99mTc-infliximab. Arthritis Rheum. 2005 Apr;52(4):1224-6.

477. Contreras-Yanez I, Ponce De Leon S, Cabiedes J, et al. Inadequate therapy behavior is associated to disease flares in patients with rheumatoid arthritis who have achieved remission with disease-modifying antirheumatic drugs. Am J Med Sci. 2010 Oct;340(4):282-90.

478. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis. 1995 Jan;54(1):49-52.

479. Cordero-Coma M, Anzaar F, Sobrin L, et al. Systemic immunomodulatory therapy in severe dry eye secondary to inflammation. Ocul Immunol Inflamm. 2007 Mar-Apr;15(2):99-104.

480. Cordiali-Fei P, Trento E, D'Agosto G, et al. Effective therapy with anti-TNF-alpha in patients with psoriatic arthritis is associated with decreased levels of metalloproteinases and angiogenic cytokines in the sera and skin lesions. Ann N Y Acad Sci. 2007 Sep;1110:578-89.

481. Corrao S, Pistone G, Arnone S, et al. Safety of etanercept therapy in rheumatoid patients undergoing surgery: preliminary report. Clin Rheumatol. 2007 Sep;26(9):1513-5.

482. Corsi F, Previde P, Colombo F, et al. Two cases of intestinal perforation in patients on anti-rheumatic treatment with etanercept. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):113.

483. Cortet B, Flipo RM, Pigny P, et al. How useful are bone turnover markers in rheumatoid arthritis? Influence of disease

activity and corticosteroid therapy. Rev Rhum Engl Ed. 1997 Mar;64(3):153-9.

484. Cortet B, Guyot MH, Solau E, et al. Factors influencing bone loss in rheumatoid arthritis: a longitudinal study. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):683-90.

485. Cortot AB, Cottin V, Miossec P, et al. Improvement of refractory rheumatoid arthritis-associated constrictive bronchiolitis with etanercept. Respir Med. 2005 Apr;99(4):511-4.

486. Courtney PA, Alderdice J, Whitehead EM. Comment on methotrexate pneumonitis after initiation of infliximab therapy for rheumatoid arthritis. Arthritis Rheum. 2003 Aug 15;49(4):617; author reply -8.

487. Coury F, Ferraro-Peyret C, Le Cam S, et al. Peripheral blood lymphocytes from patients with rheumatoid arthritis are differentially sensitive to apoptosis induced by anti-tumour necrosis factor-alpha therapy. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):234-9.

488. Covelli M, Scioscia C, Iannone F, et al. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after discontinuation of infliximab. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):145-51.

489. Coyle CM, Weiss LM, Rhodes LV, 3rd, et al. Fatal myositis due to the microsporidian Brachiola algerae, a mosquito pathogen. N Engl J Med. 2004 Jul 1;351(1):42-7.

490. Cracchiolo A, 3rd, Severt R, Moreland J. Uncemented total hip arthroplasty in rheumatoid arthritis diseases. A two- to six-year follow-up study. Clin Orthop Relat Res. 1992 Apr(277):166-74.

491. Creamer P, Keen M, Zananiri F, et al. Quantitative magnetic resonance imaging of the knee: a method of measuring response to intra-articular treatments. Ann Rheum Dis. 1997 Jun;56(6):378-81.

492. Creemers MC, Franssen MJ, van de Putte LB, et al. Methotrexate in severe ankylosing spondylitis: an open study. J Rheumatol. 1995 Jun;22(6):1104-7.

493. Crellin AM, Shareef DS, Maher EJ. Opportunistic Listeria pericardial effusion. Postgrad Med J. 1990 Mar;66(773):203-4.

494. Crilly A, Maiden N, Capell HA, et al. Predictive value of interleukin 1 gene polymorphisms for surgery. Ann Rheum Dis. 2000 Sep;59(9):695-9.

495. Criswell LA, Lum RF, Turner KN, et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis Rheum. 2004 Sep;50(9):2750-6.

496. Crnkic M, Mansson B, Larsson L, et al. Serum cartilage oligomeric matrix protein (COMP) decreases in rheumatoid arthritis patients treated with infliximab or etanercept. Arthritis Res Ther. 2003;5(4):R181-5.

497. Croce A, Firuzi O, Altieri F, et al. Effect of infliximab on the glycosylation of IgG of patients with rheumatoid arthritis. J Clin Lab Anal. 2007;21(5):303-14.

498. Crofford LJ, Kalogeras KT, Mastorakos G, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. J Clin Endocrinol Metab. 1997 Apr;82(4):1279-83.

499. Crowson CS, Rahman MU, Matteson EL. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. J Rheumatol. 2009 Aug;36(8):1606-10.

500. Cruse LM, Valeriano J, Vasey FB, et al. Prevalence of evaluation and treatment of glucocorticoid-induced osteoporosis in men. J Clin Rheumatol. 2006 Oct;12(5):221-5.

501. Cuchacovich M, Catalan D, Wainstein E, et al. Basal anti-cyclic citrullinated peptide (anti-CCP) antibody levels and a decrease in anti-CCP titres are associated with clinical response to adalimumab in rheumatoid

arthritis. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1067-73.

502. Cuchacovich M, Ferreira L, Aliste M, et al. Tumour necrosis factor-alpha (TNF-alpha) levels and influence of -308 TNF-alpha promoter polymorphism on the responsiveness to infliximab in patients with rheumatoid arthritis. Scand J Rheumatol. 2004;33(4):228-32.

503. Cuchacovich M, Soto L, Edwardes M, et al. Tumour necrosis factor (TNF)alpha -308 G/G promoter polymorphism and TNFalpha levels correlate with a better response to adalimumab in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Nov-Dec;35(6):435-40.

504. Cuchacovich R, Espinoza CG, Virk Z, et al. Biologic therapy (TNF-alpha antagonists)-induced psoriasis: a cytokine imbalance between TNF-alpha and IFN-alpha? J Clin Rheumatol. 2008 Dec;14(6):353-6.

505. Cuchacovich R, Espinoza LR. Does TNF-alpha blockade play any role in cardiovascular risk among rheumatoid arthritis (RA) patients? Clin Rheumatol. 2009 Oct;28(10):1217-20.

506. Cui J, Saevarsdottir S, Thomson B, et al. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. Arthritis Rheum 2010;62(7):1849-61.

507. Culy CR, Keating GM. Etanercept: an updated review of its use in rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis. Drugs. 2002;62(17):2493-537.

508. Cunnane G, Madigan A, Murphy E, et al. The effects of treatment with interleukin-1 receptor antagonist on the inflamed synovial membrane in rheumatoid arthritis. Rheumatology (Oxford). 2001 Jan;40(1):62-9.

509. Cunnane G, Warnock M, Fye KH, et al. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Aug;47(4):445-9.

510. Curkendall S, Patel V, Gleeson M, et al. Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? Arthritis Rheum. 2008 Oct 15;59(10):1519-26.

511. Cursiefen C, Grunke M, Dechant C, et al. Multiple bilateral eyelid molluscum contagiosum lesions associated with TNFalpha-antibody and methotrexate therapy. Am J Ophthalmol. 2002 Aug;134(2):270-1.

512. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford) 2007;46(11):1688-93.

513. Curtis JR, Martin C, Saag KG, et al. Confirmation of administrative claims-identified opportunistic infections and other serious potential adverse events associated with tumor necrosis factor alpha antagonists and disease-modifying antirheumatic drugs. Arthritis Rheum. 2007 Mar 15;57(2):343-6.

514. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(4):1125-33.

515. Curtis JR, Xi J, Patkar N, et al. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(12):4226-7.

516. Cutolo M, Balleari E, Giusti M, et al. Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum. 1991 Jan;34(1):1-5.

517. Cutolo M, Bisso A, Sulli A, et al. Antiproliferative and antiinflammatory effects of methotrexate on cultured differentiating myeloid monocytic cells (THP-1) but not on synovial macrophages from patients with rheumatoid arthritis. J Rheumatol. 2000 Nov;27(11):2551-7.

518. Cutolo M, Foppiani L, Minuto F. Hypothalamic-pituitary-adrenal axis impairment in the pathogenesis of

rheumatoid arthritis and polymyalgia rheumatica. J Endocrinol Invest. 2002;25(10 Suppl):19-23.

519. Cutolo M, Foppiani L, Prete C, et al. Hypothalamic-pituitary-adrenocortical axis function in premenopausal women with rheumatoid arthritis not treated with glucocorticoids. J Rheumatol. 1999 Feb;26(2):282-8.

520. Cutolo M, Maestroni GJ, Otsa K, et al. Circadian melatonin and cortisol levels in rheumatoid arthritis patients in winter time: a north and south Europe comparison. Ann Rheum Dis. 2005 Feb;64(2):212-6.

521. Cutolo M, Villaggio B, Pizzorni C, et al. Inflammatory gene profile in early rheumatoid arthritis and modulation by leflunomide and prednisone treatment. Ann N Y Acad Sci. 2010 Apr;1193(1):15-21.

522. Cvetkovic JT, Wallberg-Jonsson S, Stegmayr B, et al. Susceptibility for and clinical manifestations of rheumatoid arthritis are associated with polymorphisms of the TNF-alpha, IL-1beta, and IL-1Ra genes. J Rheumatol. 2002 Feb;29(2):212-9.

523. Cypiene A, Laucevicius A, Venalis A, et al. Non-invasive assessment of arterial stiffness indices by applanation tonometry and pulse wave analysis in patients with rheumatoid arthritis treated with TNF-alpha blocker remicade (infliximab). Proc West Pharmacol Soc. 2007;50:119-22.

524. D'Acquisto F, Paschalidis N, Raza K, et al. Glucocorticoid treatment inhibits annexin-1 expression in rheumatoid arthritis CD4+ T cells. Rheumatology (Oxford). 2008 May;47(5):636-9.

525. Dagci H, Zeyrek F, Gerzile YK, et al. A case of myiasis in a patient with psoriasis from Turkey. Parasitol Int. 2008 Jun;57(2):239-41.

526. Dahlqvist SR, Engstrand S, Berglin E, et al. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. Scand J Rheumatol. 2006 Mar-Apr;35(2):107-11.

527. Dahlqvist SR, Olsson T. Interference with the cortisol axis by the microtubule antagonist, CPH82. Br J Rheumatol. 1993 Sep;32(9):804-6.

528. Dain L, Braun-Moscovici Y, Baum E, et al. Modification of neutrophil function by plasma of rheumatoid arthritis patients treated with infliximab. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):38-44.

529. Dalrymple JM, Stamp LK, O'Donnell JL, et al. Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Nov;58(11):3299-308.

530. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. Arthritis Rheum. 2009 May;60(5):1232-41.

531. Danko JR, Gilliland WR, Miller RS, et al. Disseminated Mycobacterium marinum infection in a patient with rheumatoid arthritis receiving infliximab therapy. Scand J Infect Dis. 2009;41(4):252-5.

532. Dans M, Hivnor C, van Voorhees AS. Psoriatic onychopachydermoperiostitis: improvement with etanercept. Br J Dermatol. 2005 Oct;153(4):858-9.

533. Darabi K, Jaiswal R, Hostetler S, et al. Infectious complications in patients with psoriasis and rheumatoid arthritis treated with antitumor necrosis factor agents and methotrexate. J Drugs Dermatol. 2009 Feb;8(2):175-8.

534. Darmawan J, Muirden KD, Valkenburg HA, et al. The epidemiology of rheumatoid arthritis in Indonesia. Br J Rheumatol. 1993 Jul;32(7):537-40.

535. Das P, Raghu P, Amit Kumar D, et al. Strongyloides hyperinfection in rheumatoid arthritis. Int J Surg Pathol. 2007 Oct;15(4):391-2.

536. Das SK, Pareek A, Mathur DS, et al. Efficacy and safety of hydroxychloroquine sulphate in rheumatoid arthritis: a

randomized, double-blind, placebo controlled clinical trial--an Indian experience. Curr Med Res Opin. 2007 Sep;23(9):2227-34.

537. Dascalu C, Mrejen-Shakin K, Bandagi S. Adalimumab-induced acute pneumonitis in a patient with rheumatoid arthritis. J Clin Rheumatol. 2010 Jun;16(4):172-4.

538. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjogren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008 Nov;67(11):1541-4.

539. Dauendorffer JN, Rivet J, Allard A, et al. Sezary syndrome in a patient receiving infliximab for ankylosing spondylitis. Br J Dermatol. 2007 Apr;156(4):742-3.

540. D'Auria F, Rovere-Querini P, Giazzon M, et al. Accumulation of plasma nucleosomes upon treatment with anti-tumour necrosis factor-alpha antibodies. J Intern Med. 2004 Mar;255(3):409-18.

541. Davaine AC, Saraux A, Prigent S, et al. Cutaneous events during treatment of chronic inflammatory joint disorders with anti-tumour necrosis factor alpha: a cross-sectional study. J Eur Acad Dermatol Venereol. 2008 Dec;22(12):1471-7.

542. Davey M, Buchbinder R. Glucocorticoids in early rheumatoid arthritis. Aust Fam Physician. 2008 Jan-Feb;37(1-2):31-2.

543. Davies K, Stiehm ER, Woo P, et al. Juvenile idiopathic polyarticular arthritis and IgA deficiency in the 22q11 deletion syndrome. J Rheumatol. 2001 Oct;28(10):2326-34.

544. Davis JC, Jr. The role of etanercept in ankylosing spondylitis. Clin Exp Rheumatol. 2002 Nov-Dec;20(6 Suppl 28):S111-5.

545. Davis JC, Jr., Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003 Nov;48(11):3230-6.

546. Davis JC, van der Heijde D, Dougados M, et al. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum. 2005 Aug 15;53(4):494-501.

547. Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis. 2005 Nov;64(11):1557-62.

548. Davis JC, Jr., Van der Heijde DM, Dougados M, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. J Rheumatol. 2005 Sep;32(9):1751-4.

549. Davis JM, 3rd, Maradit Kremers H, Crowson CS, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007 Mar;56(3):820-30.

550. Davis MC, Zautra AJ, Younger J, et al. Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. Brain Behav Immun. 2008 Jan;22(1):24-32.

551. Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. Lancet. 2002 Feb 16;359(9306):540-1.

552. Daza L, Martin-Jimenez R, De la Torre PX, et al. Improvement of ACTH response to insulin tolerance test in female patients with rheumatoid arthritis due to tumor necrosis factor inhibition. Eur J Endocrinol. 2007 Jul;157(1):47-51.

553. De A, Blotta HM, Mamoni RL, et al. Effects of dexamethasone on lymphocyte proliferation and cytokine production in rheumatoid arthritis. J Rheumatol. 2002 Jan;29(1):46-51.

554. De Bandt M, Kahn MF. Takayasu's arteritis associated with Still's disease in an adult. Clin Exp Rheumatol. 1991 Nov-Dec;9(6):639-40.

555. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7(3):R545-51.

556. De Bandt M, Vittecoq O, Descamps V, et al. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol. 2003 Feb;22(1):56-61.

557. De Benedetti F. Targeting interleukin-6 in pediatric rheumatic diseases. Curr Opin Rheumatol. 2009 Sep;21(5):533-7.

558. De Benedetti F, Pignatti P, Gerloni V, et al. Differences in synovial fluid cytokine levels between juvenile and adult rheumatoid arthritis. J Rheumatol. 1997 Jul;24(7):1403-9.

559. de' Clari F, Salani I, Safwan E, et al. Sudden death in a patient without heart failure after a single infusion of 200 mg infliximab: does TNF-alpha have protective effects on the failing heart, or does infliximab have direct harmful cardiovascular effects? Circulation. 2002 May 28;105(21):E183.

560. De Felice C, Mazzotta A, Esposito M, et al. High-dose initiation of etanercept in psoriatic arthritis and plaque psoriasis: efficacy, safety and impact on patients' quality of life. J Dermatolog Treat. 2006;17(6):355-8.

561. de Jong JW, van Altena R. Non-respiratory tuberculosis with Mycobacterium tuberculosis after penetrating lesions of the skin: five case histories. Int J Tuberc Lung Dis. 2000 Dec;4(12):1184-7.

562. de la Torre B, Hedman M, Nilsson E, et al. Relationship between blood and joint tissue DHEAS levels in rheumatoid arthritis and osteoarthritis. Clin Exp Rheumatol. 1993 Nov-Dec;11(6):597-601.

563. De Leonardis F, Govoni M, Lo Monaco A, et al. Visceral leishmaniasis and anti-TNF-alpha therapy: case report and review of the literature. Clin Exp Rheumatol. 2009 May-Jun;27(3):503-6.

564. De Miguel S, Jover JA, Vadillo C, et al. B cell activation in rheumatoid arthritis patients under infliximab treatment. Clin Exp Rheumatol. 2003 Nov-Dec;21(6):726-32.

565. de Nijs RN, Jacobs JW, Bijlsma JW, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology (Oxford). 2001 Dec;40(12):1375-83.

566. de Paz B, Alperi-Lopez M, Ballina-Garcia FJ, et al. Interleukin 10 and tumor necrosis factor-alpha genotypes in rheumatoid arthritis--association with clinical response to glucocorticoids. J Rheumatol. 2010 Mar;37(3):503-11.

567. De Rosa FG, Shaz D, Campagna AC, et al. Invasive pulmonary aspergillosis soon after therapy with infliximab, a tumor necrosis factor-alpha-neutralizing antibody: a possible healthcare-associated case? Infect Control Hosp Epidemiol. 2003 Jul;24(7):477-82.

568. De Rycke L, Baeten D, Foell D, et al. Differential expression and response to anti-TNFalpha treatment of infiltrating versus resident tissue macrophage subsets in autoimmune arthritis. J Pathol. 2005 May;206(1):17-27.

569. De Rycke L, Baeten D, Kruithof E, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. Arthritis Rheum. 2005 Jul;52(7):2192-201.

570. De Rycke L, Kruithof E, Van Damme N, et al. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum. 2003 Apr;48(4):1015-23.

571. De Rycke L, Vandooren B, Kruithof E, et al. Tumor necrosis factor alpha blockade treatment down-modulates the increased systemic and local expression of Toll-like receptor 2 and Toll-like receptor 4 in spondylarthropathy. Arthritis Rheum. 2005 Jul;52(7):2146-58.

572. De Rycke L, Verhelst X, Kruithof E, et al. Rheumatoid factor, but not anti-cyclic citrullinated peptide antibodies, is modulated by infliximab treatment in rheumatoid arthritis. Ann Rheum Dis. 2005 Feb;64(2):299-302.

573. de Seze J, Delalande S, Fauchais AL, et al. Myelopathies secondary to Sjogren's syndrome: treatment with monthly intravenous cyclophosphamide associated with corticosteroids. J Rheumatol. 2006 Apr;33(4):709-11.

574. De Stefano R, Frati E, Nargi F, et al. Comparison of combination therapies in the treatment of rheumatoid arthritis: leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. Clin Rheumatol 2010;29(5):517-24.

575. de Thurah A, Norgaard M, Johansen M, et al. Time to methotrexate treatment in patients with rheumatoid arthritis referred to hospital. Scand J Rheumatol. 2010;39(1):19-25.

576. de Thurah A, Norgaard M, Johansen MB, et al. Methotrexate compliance among patients with rheumatoid arthritis: the influence of disease activity, disease duration, and co-morbidity in a 10-year longitudinal study. Scand J Rheumatol. 2010 May;39(3):197-205.

577. De Vita S, Zaja F, Sacco S, et al. Efficacy of selective B cell blockade in the treatment of rheumatoid arthritis: evidence for a pathogenetic role of B cells. Arthritis Rheum. 2002 Aug;46(8):2029-33.

578. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum. 2008 May;58(5):1293-8.

579. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Wesoly J, et al. Ex vivo interleukin 1 receptor antagonist production on lipopolysaccharide stimulation is associated with rheumatoid arthritis and with joint damage. Ann Rheum Dis. 2007 Aug;66(8):1033-7.

580. de Winter S, van Buchem MA, Vermeer MH. Annular erythema of Sjogren's syndrome. Lancet. 2006 May 13;367(9522):1604.

581. Debiais S, Maillot F, Luca L, et al. Efficacy of anakinra in a case of refractory Still disease. J Clin Rheumatol. 2008 Dec;14(6):357-8.

582. Deighton CM, Watson MJ, Walker DJ. Sex hormones in postmenopausal HLA-identical rheumatoid arthritis discordant sibling pairs. J Rheumatol. 1992 Nov;19(11):1663-7.

583. Dekkers JC, Geenen R, Godaert GL, et al. Experimentally challenged reactivity of the hypothalamic pituitary adrenal axis in patients with recently diagnosed rheumatoid arthritis. J Rheumatol. 2001 Jul;28(7):1496-504.

584. del Porto F, Aloe L, Lagana B, et al. Nerve growth factor and brain-derived neurotrophic factor levels in patients with rheumatoid arthritis treated with TNF-alpha blockers. Ann N Y Acad Sci. 2006 Jun;1069:438-43.

585. Del Porto F, Lagana B, Lai S, et al. Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. Rheumatology (Oxford). 2007 Jul;46(7):1111-5.

586. Delabaye I, De Keyser F. 74-week follow-up of safety of infliximab in patients with refractory rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R121.

587. Delaunay C, Farrenq V, Marini-Portugal A, et al. Infliximab to etanercept switch in patients with spondyloarthropathies and psoriatic arthritis: preliminary data. J Rheumatol. 2005 Nov;32(11):2183-5.

588. Delmez JA, Dusso AS, Slatopolsky E, et al. Modulation of renal osteodystrophy by extrarenal production of calcitriol. Am J Nephrol. 1995;15(1):85-9.

589. Demir H, Kelestimur F, Tunc M, et al. Hypothalamo-pituitary-adrenal axis and growth hormone axis in patients with rheumatoid arthritis. Scand J Rheumatol. 1999;28(1):41-6.

590. den Broeder A, van de Putte L, Rau R, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol. 2002 Nov;29(11):2288-98.

591. den Broeder AA, Assmann KJ, van Riel PL, et al. Nephrotic syndrome as a complication of anti-TNFalpha in a patient with rheumatoid arthritis. Neth J Med. 2003 Apr;61(4):137-41.

592. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol 2007;34(4):689-95.

593. Den Broeder AA, Creemers MC, van Gestel AM, et al. Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-alpha. Rheumatology (Oxford). 2002 Jun;41(6):638-42.

594. den Broeder AA, Joosten LA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis. 2002 Apr;61(4):311-8.

595. den Broeder AA, Wanten GJ, Oyen WJ, et al. Neutrophil migration and production of reactive oxygen species during treatment with a fully human anti-tumor necrosis factor-alpha monoclonal antibody in patients with rheumatoid arthritis. J Rheumatol. 2003 Feb;30(2):232-7.

596. Denault A, Dimopoulos MA, Fitzcharles MA. Meningoencephalitis and peripheral neuropathy complicating adult Still's disease. J Rheumatol. 1990 May;17(5):698-700.

597. Deng A, Harvey V, Sina B, et al. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol. 2006 Feb;142(2):198-202.

598. Denis B, Lefort A, Flipo RM, et al. Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-alpha antagonist therapy: safe re-initiation of TNF-alpha blockers after appropriate anti-tuberculous treatment. Clin Microbiol Infect. 2008 Feb;14(2):183-6.

599. Deodhar A, Allen E, Daoud K, et al. Vasculitis secondary to staphylococcal Protein A immunoadsorption (Prosorba column) treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2002 Aug;32(1):3-9.

600. Dequeker J, Borghs H, Van Cleemput J, et al. Transplantation osteoporosis and corticosteroid-induced osteoporosis in autoimmune diseases: experience with alfacalcidol. Z Rheumatol. 2000;59 Suppl 1:53-7.

601. Dereure O, Guillot B, Jorgensen C, et al. Psoriatic lesions induced by antitumour necrosis factor-alpha treatment: two cases. Br J Dermatol. 2004 Aug;151(2):506-7.

602. Derot G, Marini-Portugal A, Maitre B, et al. Marked regression of pulmonary rheumatoid nodules under etanercept therapy. J Rheumatol. 2009 Feb;36(2):437-9.

603. Dervieux T, Greenstein N, Kremer J. Pharmacogenomic and metabolic biomarkers in the folate pathway and their association with methotrexate effects during dosage escalation in rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3095-103.

604. Desai D, Goldbach-Mansky R, Milner JD, et al. Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. Ann Pharmacother. 2009 May;43(5):967-72.

605. Despaux J, Manzoni P, Toussirot E, et al. Prospective study of the prevalence of bronchiectasis in rheumatoid arthritis using

high-resolution computed tomography. Rev Rhum Engl Ed. 1998 Jul-Sep;65(7-9):453-61.

606. Dessein PH, Joffe BI. Suppression of circulating interleukin-6 concentrations is associated with decreased endothelial activation in rheumatoid arthritis. Clin Exp Rheumatol. 2006 Mar-Apr;24(2):161-7.

607. Dessein PH, Joffe BI, Stanwix AE, et al. Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis. Arthritis Res. 2001;3(3):183-8.

608. Dessein PH, Woodiwiss AJ, Joffe BI, et al. Aminotransferases are associated with insulin resistance and atherosclerosis in rheumatoid arthritis. BMC Cardiovasc Disord. 2007;7:31.

609. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjogren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum. 2007 Mar 15;57(2):310-7.

610. Devos SA, Van Den Bossche N, De Vos M, et al. Adverse skin reactions to anti-TNF-alpha monoclonal antibody therapy. Dermatology. 2003;206(4):388-90.

611. Dhaille F, Viseux V, Caudron A, et al. Cutaneous sarcoidosis occurring during anti-TNF-alpha treatment: report of two cases. Dermatology. 2010;220(3):234-7.

612. di Comite G, Marinosci A, Di Matteo P, et al. Neuroendocrine modulation induced by selective blockade of TNF-alpha in rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:428-37.

613. Di Poi E, Perin A, Morassi MP, et al. Switching to etanercept in patients with rheumatoid arthritis with no response to infliximab. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):85-7.

614. Dichamp I, Bourgeois A, Dirand C, et al. Increased nuclear factor-kappaB activation in peripheral blood monocytes of patients with rheumatoid arthritis is mediated primarily by tumor necrosis factor-alpha. J Rheumatol. 2007 Oct;34(10):1976-83.

615. Dilek K, Ali I, Goksal K, et al. The effects of sulphasalazine on urinary excretion of the hydroxypyridinium crosslinks of collagen in patients with rheumatoid arthritis. Yonsei Med J. 2002 Aug;43(4):435-40.

616. Dilhuydy MS, Vatan R, Etienne G, et al. Prolonged efficacy of infliximab for refractory adult-onset Still's disease. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):121-2.

617. Dimakou K, Papaioannides D, Latsi P, et al. Disseminated tuberculosis complicating anti-TNF-alpha treatment. Int J Clin Pract. 2004 Nov;58(11):1052-5.

618. Diskin CJ, Stokes TJ, Dansby LM, et al. Removal of methotrexate by peritoneal dialysis and hemodialysis in a single patient with end-stage renal disease. Am J Med Sci. 2006 Sep;332(3):156-8.

619. Dockery KM, Sismanis A, Abedi E. Rheumatoid arthritis of the larynx: the importance of early diagnosis and corticosteroid therapy. South Med J. 1991 Jan;84(1):95-6.

620. Doggrell SA. Triamcinolone: new and old indications. Expert Opin Pharmacother. 2001 Jul;2(7):1177-86.

621. Doggrell SA. Is tocilizumab an option for the treatment of arthritis? Expert Opin Pharmacother. 2008 Aug;9(11):2009-13.

622. Dohn UM, Skjodt H, Hetland ML, et al. No erosive progression revealed by MRI in rheumatoid arthritis patients treated with etanercept, even in patients with persistent MRI and clinical signs of joint inflammation. Clin Rheumatol. 2007 Nov;26(11):1857-61.

623. Dombrecht EJ, Aerts NE, Schuerwegh AJ, et al. Influence of anti-tumor necrosis factor therapy (Adalimumab) on regulatory T cells and dendritic cells in rheumatoid arthritis. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):31-7.

624. Domiciano DS, de Carvalho JF, Macedo AR, et al. Central diabetes insipidus induced by tuberculosis in a rheumatoid arthritis patient. Acta Reumatol Port. 2010 Apr-Jun;35(2):232-5.

625. Domm A. A patient's reaction to infliximab. Ann Allergy Asthma Immunol. 2003 Mar;90(3):298-301.

626. Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008 Jan 15;148(2):124-34.

627. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002 Sep;46(9):2294-300.

628. Doran MF, Crowson CS, Pond GR, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002 Sep;46(9):2287-93.

629. Dore RK, Mathews S, Schechtman J, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):40-6.

630. Doria AS, Kiss MH, Sallum AM, et al. Correlation between osteochondral changes depicted by magnetic resonance imaging and disease progression. Rev Hosp Clin Fac Med Sao Paulo. 2001 Jul-Aug;56(4):107-14.

631. Doshi JA, Li P, Puig A. Impact of the Medicare Modernization Act of 2003 on utilization and spending for medicare part B-covered biologics in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010 Mar;62(3):354-61.

632. Douglas G, Bird K, Flume P, et al. Wegener's granulomatosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Sep;30(9):2064-9.

633. Doulton TW, Tucker B, Reardon J, et al. Antineutrophil cytoplasmic antibody-associated necrotizing crescentic glomerulonephritis in a patient receiving treatment with etanercept for severe rheumatoid arthritis. Clin Nephrol. 2004 Sep;62(3):234-8.

634. Drosos A. Methotrexate intolerance in elderly patients with rheumatoid arthritis: what are the alternatives? Drugs Aging. 2003;20(10):723-36.

635. Drouin J, Haraoui B. Predictors of clinical response and radiographic progression in patients with rheumatoid arthritis treated with methotrexate monotherapy. J Rheumatol. 2010 Jul;37(7):1405-10.

636. Drozdzik M, Rudas T, Pawlik A, et al. Reduced folate carrier-1 80G>A polymorphism affects methotrexate treatment outcome in rheumatoid arthritis. Pharmacogenomics J. 2007 Dec;7(6):404-7.

637. Drozdzik M, Rudas T, Pawlik A, et al. The effect of 3435C>T MDR1 gene polymorphism on rheumatoid arthritis treatment with disease-modifying antirheumatic drugs. Eur J Clin Pharmacol. 2006 Nov;62(11):933-7.

638. Drynda S, Kuhne C, Kekow J. Soluble tumour necrosis factor receptor treatment does not affect raised transforming growth factor beta levels in rheumatoid arthritis. Ann Rheum Dis. 2002 Mar;61(3):254-6.

639. Dubois T, Bisagni-Faure A, Coste J, et al. High levels of antibodies to annexins V and VI in patients with rheumatoid arthritis. J Rheumatol. 1995 Jul;22(7):1230-4.

640. Ducharme J, Pelletier C, Zacharias R. The safety of infliximab infusions in the community setting. Can J Gastroenterol 2010;24(5):307-11.

641. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33(12):2433-8.

642. Ducoulombier V, Solau E, Coquerelle P, et al. Long-term results of infliximab therapy in rheumatoid arthritis: experience acquired by the North-Pas-de-Calais hospital

network. Joint Bone Spine. 2007 Jan;74(1):56-9.

643. Duftner C, Dejaco C, Larcher H, et al. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic. Rheumatol Int. 2008 Nov;29(1):69-73.

644. Dumont-Berset M, Laffitte E, Gerber C, et al. Eczematous drug eruption after infliximab. Br J Dermatol. 2004 Dec;151(6):1272-3.

645. Dunne CA, Moran CJ, Thompson PW. The effect of regular intramuscular corticosteroid therapy on bone mineral density in rheumatoid patients. Scand J Rheumatol. 1995;24(1):48-9.

646. Durez P, Malghem J, Nzeusseu Toukap A, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis Rheum 2007;56(12):3919-27.

647. Durez P, Nzeusseu Toukap A, Lauwerys BR, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Ann Rheum Dis. 2004 Sep;63(9):1069-74.

648. Durez P, Van den Bosch F, Corluy L, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. Rheumatology (Oxford). 2005 Apr;44(4):465-8.

649. Dursun AB, Kalac N, Ozkan B, et al. Pulmonary tuberculosis in patients with rheumatoid arthritis (four case reports). Rheumatol Int. 2002 Jan;21(4):153-7.

650. Dweik M, Baethge BA, Duarte AG. Coccidioidomycosis pneumonia in a nonendemic area associated with infliximab. South Med J. 2007 May;100(5):517-8.

651. Eberhardt K, Rydgren L, Fex E, et al. D-penicillamine in early rheumatoid arthritis: experience from a 2-year double blind placebo controlled study. Clin Exp Rheumatol. 1996 Nov-Dec;14(6):625-31.

652. Eberhardt K, Sandqvist G, Geborek P. Hand function tests are important and sensitive tools for assessment of treatment response in patients with rheumatoid arthritis. Scand J Rheumatol. 2008 Mar-Apr;37(2):109-12.

653. Eberhardt R, Kruger K, Reiter W, et al. Long-term therapy with the new glucocorticosteroid deflazacort in rheumatoid arthritis. Double-blind controlled randomized 12-months study against prednisone. Arzneimittelforschung. 1994 May;44(5):642-7.

654. Eder L, Chandran V, Gladman DD. From ankylosis to pencil-in-cup deformity in psoriatic arthritis: a case report. Clin Exp Rheumatol. 2009 Jul-Aug;27(4):661-3.

655. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. Arthritis Rheum 2007;57(7):1151-7.

656. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81.

657. Edwards KR, Mowad CM, Tyler WB. Worsening injection site reactions with continued use of etanercept. J Drugs Dermatol. 2003 Apr;2(2):184-7.

658. Efde MN, Houtman PM, Spoorenberg JP, et al. Tonsillar tuberculosis in a rheumatoid arthritis patient receiving anti-TNFalpha (adalimumab) treatment. Neth J Med. 2005 Mar;63(3):112-4.

659. Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. Semin Arthritis Rheum. 2006 Dec;36(3):144-52.

660. Eggert M, Kluter A, Rusch D, et al. Expression analysis of the glucocorticoid receptor and the nuclear factor-kB subunit p50 in lymphocytes from patients with rheumatoid arthritis. J Rheumatol. 2002 Dec;29(12):2500-6.

661. Egnatios G, Warthan MM, Pariser R, et al. Pustular psoriasis following treatment of rheumatoid arthritis with TNF-alpha inhibitors. J Drugs Dermatol. 2008 Oct;7(10):975-7.

662. Eijsbouts AM, van den Hoogen FH, Laan RF, et al. Hypothalamic-pituitary-adrenal axis activity in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Sep-Oct;23(5):658-64.

663. Eklow C, Makrygiannakis D, Backdahl L, et al. Cellular distribution of the C-type II lectin dendritic cell immunoreceptor (DCIR) and its expression in the rheumatic joint: identification of a subpopulation of DCIR+ T cells. Ann Rheum Dis. 2008 Dec;67(12):1742-9.

664. Eklund KK, Leirisalo-Repo M, Ranta P, et al. Serum IL-1beta levels are associated with the presence of erosions in recent onset rheumatoid arthritis. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):684-9.

665. Eklund KK, Peltomaa R, Leirisalo-Repo M. Occurrence of pulmonary thromboembolism during infliximab therapy. Clin Exp Rheumatol. 2003 Sep-Oct;21(5):679.

666. El Maghraoui A, Do Santos Zounon AA, Jroundi I, et al. Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice. Osteoporos Int. 2005 Dec;16(12):1742-8.

667. Elkayam O, Burke M, Vardinon N, et al. Autoantibodies profile of rheumatoid arthritis patients during treatment with infliximab. Autoimmunity. 2005 Mar;38(2):155-60.

668. Elkayam O, Caspi D. Infliximab induced lupus in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2004 Jul-Aug;22(4):502-3.

669. Elkayam O, Caspi D, Reitblatt T, et al. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2004 Feb;33(4):283-8.

670. Elkayam O, Hawkins PN, Lachmann H, et al. Rapid and complete resolution of proteinuria due to renal amyloidosis in a patient with rheumatoid arthritis treated with infliximab. Arthritis Rheum. 2002 Oct;46(10):2571-3.

671. Elkayam O, Paran D, Flusser G, et al. Insufficiency fractures in rheumatic patients: misdiagnosis and underlying characteristics. Clin Exp Rheumatol. 2000 May-Jun;18(3):369-74.

672. Elkayam O, Yaron I, Shirazi I, et al. Serum levels of IL-10, IL-6, IL-1ra, and sIL-2R in patients with psoriatic arthritis. Rheumatol Int. 2000;19(3):101-5.

673. ElKayam O, Yaron M, Caspi D. From wheels to feet: a dramatic response of severe chronic psoriatic arthritis to etanercept. Ann Rheum Dis. 2000 Oct;59(10):839.

674. Ellerton ML. When parents and children disagree about care. Can Nurse. 2000 Aug;96(7):35-6.

675. Ellingsen T, Hornung N, Moller BK, et al. In active chronic rheumatoid arthritis, dipeptidyl peptidase IV density is increased on monocytes and CD4(+) T lymphocytes. Scand J Immunol. 2007 Oct;66(4):451-7.

676. Ellingsen T, Hornung N, Moller BK, et al. Differential effect of methotrexate on the increased CCR2 density on circulating CD4 T lymphocytes and monocytes in active chronic rheumatoid arthritis, with a down regulation only on monocytes in responders. Ann Rheum Dis. 2007 Feb;66(2):151-7.

677. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994 Oct 22;344(8930):1105-10.

678. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum 2010;62(3):674-82.

679. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372(9636):375-82.

680. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis 2010;69(9):1629-35.

681. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60(8):2272-83.

682. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67(11):1516-23.

683. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 Apr;33(4):681-9.

684. Emkey RD, Lindsay R, Lyssy J, et al. The systemic effect of intraarticular administration of corticosteroid on markers of bone formation and bone resorption in patients with rheumatoid arthritis. Arthritis Rheum. 1996 Feb;39(2):277-82.

685. Emlen W, Niebur J, Kadera R. Accelerated in vitro apoptosis of lymphocytes from patients with systemic lupus erythematosus. J Immunol. 1994 Apr 1;152(7):3685-92.

686. Engels EA, Cerhan JR, Linet MS, et al. Immune-related conditions and immune-modulating medications as risk factors for non-Hodgkin's lymphoma: a case-control study. Am J Epidemiol. 2005 Dec 15;162(12):1153-61.

687. Epler GR. Bronchiolitis obliterans organizing pneumonia. Semin Respir Infect. 1995 Jun;10(2):65-77.

688. Eriksson C, Engstrand S, Sundqvist KG, et al. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann Rheum Dis. 2005 Mar;64(3):403-7.

689. Eriksson C, Rantapaa-Dahlqvist S, Sundqvist KG. T-cell expression of CD91 - a marker of unresponsiveness to anti-TNF therapy in rheumatoid arthritis. APMIS. 2010 Nov;118(11):837-45.

690. Ernestam S, Hafstrom I, Werner S, et al. Increased DHEAS levels in patients with rheumatoid arthritis after treatment with tumor necrosis factor antagonists: evidence for improved adrenal function. J Rheumatol. 2007 Jul;34(7):1451-8.

691. Escalante A, Kaufman RL, Quismorio FP, Jr., et al. Cardiac compression in rheumatoid pericarditis. Semin Arthritis Rheum. 1990 Dec;20(3):148-63.

692. Esmailzadeh A, Yousefi P, Farhi D, et al. Predictive factors of eczema-like eruptions among patients without cutaneous psoriasis receiving infliximab: a cohort study of 92 patients. Dermatology. 2009;219(3):263-7.

693. Esser AC, Abril A, Fayne S, et al. Acute development of multiple keratoacanthomas

and squamous cell carcinomas after treatment with infliximab. J Am Acad Dermatol. 2004 May;50(5 Suppl):S75-7.

694. Estradas J, Pascual-Ramos V, Martinez B, et al. Autoimmune hepatitis with giant-cell transformation. Ann Hepatol. 2009 Jan-Mar;8(1):68-70.

695. Etemad L, Yu EB, Wanke LA. Dose adjustment over time of etanercept and infliximab in patients with rheumatoid arthritis. Manag Care Interface. 2005 Apr;18(4):21-7.

696. Ettefagh L, Nedorost S, Mirmirani P. Alopecia areata in a patient using infliximab: new insights into the role of tumor necrosis factor on human hair follicles. Arch Dermatol. 2004 Aug;140(8):1012.

697. Evans CH, Robbins PD, Ghivizzani SC, et al. Gene transfer to human joints: progress toward a gene therapy of arthritis. Proc Natl Acad Sci U S A. 2005 Jun 14;102(24):8698-703.

698. Eyigor S, Karapolat H, Kirazli Y. Efficacy of etanercept and complete decongestive physical therapy in bilateral lower-limb lymphoedema associated with rheumatoid arthritis: a case report. Adv Ther. 2008 Jan;25(1):23-8.

699. Fabre S, Dupuy AM, Dossat N, et al. Protein biochip array technology for cytokine profiling predicts etanercept responsiveness in rheumatoid arthritis. Clin Exp Immunol. 2008 Aug;153(2):188-95.

700. Fabre S, Gibert C, Lechiche C, et al. Visceral leishmaniasis infection in a rheumatoid arthritis patient treated with infliximab. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):891-2.

701. Fabre S, Gibert C, Lechiche C, et al. Primary cutaneous Nocardia otitidiscaviarum infection in a patient with rheumatoid arthritis treated with infliximab. J Rheumatol. 2005 Dec;32(12):2432-3.

702. Fabre S, Guisset C, Tatem L, et al. Protein biochip array technology to monitor rituximab in rheumatoid arthritis. Clin Exp Immunol. 2009 Mar;155(3):395-402.

703. Familian A, Voskuyl AE, van Mierlo GJ, et al. Infliximab treatment reduces complement activation in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Jul;64(7):1003-8.

704. Fantasia JE. Bisphosphonates--what the dentist needs to know: practical considerations. J Oral Maxillofac Surg. 2009 May;67(5 Suppl):53-60.

705. Fantini F, Gallazzi M, Gattinara M, et al. Monitoring bone mineralization in chronic rheumatic children on steroid treatment. Acta Univ Carol [Med] (Praha). 1994;40(1-4):17-22.

706. Fantini F, Gallazzi M, Gattinara M, et al. Monitoring osteopenia by dual-photon absorptiometry in chronically ill children treated with steroids. Acta Univ Carol [Med] (Praha). 1991;37(1-2):68-72.

707. Farah RE, Shay MD. Pulmonary sarcoidosis associated with etanercept therapy. Pharmacotherapy. 2007 Oct;27(10):1446-8.

708. Farahani P, Levine M, Gaebel K, et al. Clinical data gap between phase III clinical trials (pre-marketing) and phase IV (post-marketing) studies: evaluation of etanercept in rheumatoid arthritis. Can J Clin Pharmacol. 2005 Fall;12(3):e254-63.

709. Farahani P, Levine M, Gaebel K, et al. Community-based evaluation of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2006 Apr;33(4):665-70.

710. Farukhi FI, Bollinger K, Ruggieri P, et al. Infliximab-associated third nerve palsy. Arch Ophthalmol. 2006 Jul;124(7):1055-7.

711. Fautrel B, Borget C, Rozenberg S, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. J Rheumatol. 1999 Feb;26(2):373-8.

712. Fautrel B, Flipo RM, Saraux A. Eligibility of rheumatoid arthritis patients for anti-TNF-alpha therapy according to the 2005 recommendations of the French and British

Societies for Rheumatology. Rheumatology (Oxford). 2008 Nov;47(11):1698-703.

713. Fautrel B, Foltz V, Frances C, et al. Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: comment on the article by Pisetsky and the letter from Aringer et al. Arthritis Rheum. 2002 May;46(5):1408-9; author reply 9.

714. Fautrel B, Sibilia J, Mariette X, et al. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis. 2005 Feb;64(2):262-6.

715. Fautrel B, Woronoff-Lemsi MC, Ethgen M, et al. Impact of medical practices on the costs of management of rheumatoid arthritis by anti-TNFalpha biological therapy in France. Joint Bone Spine. 2005 Dec;72(6):550-6.

716. Favalli EG, Arreghini M, Arnoldi C, et al. Anti-tumor necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. Arthritis Rheum. 2004 Apr 15;51(2):301-2.

717. Favalli EG, Marchesoni A, Colombo GL, et al. Pattern of use, economic burden and vial optimization of infliximab for rheumatoid arthritis in Italy. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):45-51.

718. Favalli EG, Sinigaglia L, Varenna M, et al. Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. Lupus. 2002;11(11):753-5.

719. Favero M, Schiavon F, Riato L, et al. Rheumatoid arthritis is the major risk factor for septic arthritis in rheumatological settings. Autoimmun Rev. 2008 Oct;8(1):59-61.

720. Feijoo M, Tunez I, Tasset I, et al. Infliximab reduces myeloperoxidase concentration in chronic inflammatory joint diseases. Pharmacology. 2009;83(4):211-6.

721. Felder M, Ruegsegger P. Bone loss in patients with rheumatoid arthritis--effect of steroids measured by low dose quantitative computed tomography. Rheumatol Int. 1991;11(1):41-4.

722. Feldman SR, Gottlieb AB, Bala M, et al. Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. Br J Dermatol. 2008 Sep;159(3):704-10.

723. Feldstein AC, Elmer PJ, Nichols GA, et al. Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. Osteoporos Int. 2005 Dec;16(12):2168-74.

724. Feletar M, Brockbank JE, Schentag CT, et al. Treatment of refractory psoriatic arthritis with infliximab: a 12 month observational study of 16 patients. Ann Rheum Dis. 2004 Feb;63(2):156-61.

725. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis. 2005 Feb;64(2):246-52.

726. Fernandes M, Vemuganti GK, Rao GN. Bilateral periocular psoriasis: an initial manifestation of acute generalized pustular psoriasis with coexistent Sjogren's syndrome. Clin Experiment Ophthalmol. 2007 Nov;35(8):763-6.

727. Fernandes NF, Martin RR, Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. Am J Gastroenterol. 2000 Feb;95(2):532-5.

728. Fernandez-Castro M, Andreu JL, Munoz P, et al. Sepsis of a prosthetic joint and biological therapies. Rheumatology (Oxford). 2005 Aug;44(8):1076-7; author reply 5.

729. Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol 2007;34(12):2334-42.

730. Fernandez-Nebro A, Tomero E, Ortiz-Santamaria V, et al. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. Am J Med. 2005 May;118(5):552-6.

731. Ferraccioli G, Casatta L, Bartoli E. Increase of bone mineral density and anabolic variables in patients with rheumatoid arthritis resistant to methotrexate after cyclosporin A therapy. J Rheumatol. 1996 Sep;23(9):1539-42.

732. Ferraccioli G, Guerra P, Rizzi V, et al. Cyclosporin A increases somatomedin C insulin-like growth factor I levels in chronic rheumatic diseases. J Rheumatol. 1995 Jun;22(6):1060-4.

733. Ferraccioli G, Mecchia F, Di Poi E, et al. Anticardiolipin antibodies in rheumatoid patients treated with etanercept or conventional combination therapy: direct and indirect evidence for a possible association with infections. Ann Rheum Dis. 2002 Apr;61(4):358-61.

734. Ferraccioli G, Zoli A, Alivernini S, et al. Lupus anticoagulant and ischemic myocardial microangiopathy in rheumatoid arthritis. Nat Clin Pract Cardiovasc Med. 2006 Jun;3(6):339-43; quiz following 43.

735. Ferraccioli GF, Assaloni R, Di Poi E, et al. Rescue of combination therapy failures using infliximab, while maintaining the combination or monotherapy with methotrexate: results of an open trial. Rheumatology (Oxford). 2002 Oct;41(10):1109-12.

736. Ferri C, Ferraccioli G, Ferrari D, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008 Oct;35(10):1944-9.

737. Fidalgo A, Baptista J, Rocha Paris F, et al. Etanercept for psoriasis: two case reports. Int J Clin Pharmacol Res. 2005;25(4):159-63.

738. Fiedorczyk M, Klimiuk PA, Sierakowski S, et al. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with early rheumatoid arthritis. J Rheumatol. 2006 Aug;33(8):1523-9.

739. Fiehn C, Andrassy K. Case number 29: hitting three with one strike: rapid improvement of psoriatic arthritis, psoriatic erythroderma, and secondary renal amyloidosis by treatment with infliximab (Remicade). Ann Rheum Dis. 2004 Mar;63(3):232.

740. Fiehn C, Jacki S, Heilig B, et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. Rheumatol Int. 2007 Aug;27(10):975-9.

741. Figueiredo IT, Morel J, Sany J, et al. Maintenance and tolerability of infliximab in a cohort of 152 patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):18-23.

742. Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56(5):1417-23.

743. Finckh A, Ciurea A, Brulhart L, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69(2):387-93.

744. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis 2009;68(1):33-9.

745. Finckh A, Dudler J, Wermelinger F, et al. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. Joint Bone Spine. 2010 Jul;77(4):313-8.

746. Finckh A, Simard JF, Duryea J, et al. The effectiveness of anti-tumor necrosis factor therapy in preventing progressive

radiographic joint damage in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2006 Jan;54(1):54-9.

747. Finlay DG, Szauter K, Raju GS, et al. Tuberculous peritonitis. Am J Gastroenterol. 2005 Jul;100(7):1624-5.

748. Fiocco U, Ferro F, Vezzu M, et al. Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept. Ann Rheum Dis. 2005 Jun;64(6):899-905.

749. Firestein GS, Paine MM, Littman BH. Gene expression (collagenase, tissue inhibitor of metalloproteinases, complement, and HLA-DR) in rheumatoid arthritis and osteoarthritis synovium. Quantitative analysis and effect of intraarticular corticosteroids. Arthritis Rheum. 1991 Sep;34(9):1094-105.

750. Firth J, Helliwell P, Hale C, et al. The predictors of foot ulceration in patients with rheumatoid arthritis: a preliminary investigation. Clin Rheumatol. 2008 Nov;27(11):1423-8.

751. Fischer P. Resolution of treatment-related arthralgias and serologic findings with a switch of TNF antagonist therapies in a patient with psoriatic arthritis. J Clin Rheumatol. 2007 Oct;13(5):294-5.

752. Fiter J, Nolla JM, Navarro MA, et al. Weak androgen levels, glucocorticoid therapy, and bone mineral density in postmenopausal women with rheumatoid arthritis. Joint Bone Spine. 2000;67(3):199-203.

753. Fitzgerald AA, Leclercq SA, Yan A, et al. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum. 2005 Jun;52(6):1794-803.

754. Flaisler F, Hedon B, Sany J, et al. A study of ovarian function in rheumatoid arthritis. Rev Rhum Engl Ed. 1995 Oct;62(9):549-54.

755. Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86.

756. Fleischmann R, Baumgartner SW, Weisman MH, et al. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis 2006;65(3):379-84.

757. Fleischmann R, Stern R, Iqbal I. Anakinra: an inhibitor of IL-1 for the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2004 Aug;4(8):1333-44.

758. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11.

759. Fleischmann RM. Safety of anakinra, a recombinant interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis and comparison to anti-TNF-alpha agents. Clin Exp Rheumatol. 2002 Sep-Oct;20(5 Suppl 27):S35-41.

760. Fleischmann RM. Addressing the safety of anakinra in patients with rheumatoid arthritis. Rheumatology (Oxford). 2003 May;42 Suppl 2:ii29-35.

761. Fleischmann RM. Progressive multifocal leukoencephalopathy following rituximab treatment in a patient with rheumatoid arthritis. Arthritis Rheum. 2009 Nov;60(11):3225-8.

762. Fleischmann RM, Cohen SB, Moreland LW, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin. 2005 Aug;21(8):1181-90.

763. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34.

764. Flenaugh EL, Kolawole FO, Allen R. Dyspnea and dry cough in a patient with

rheumatoid arthritis. Am Fam Physician. 2007 Jan 1;75(1):103-5.

765. Flendrie M, Creemers MC, van Riel PL. Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns. Rheumatology (Oxford). 2007 Jan;46(1):146-9.

766. Flendrie M, Creemers MC, Welsing PM, et al. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii30-3.

767. Flendrie M, Creemers MC, Welsing PM, et al. The influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in patients with rheumatoid arthritis; a longitudinal observational study. Rheumatology (Oxford). 2005 Apr;44(4):472-8.

768. Foell D, Wittkowski H, Hammerschmidt I, et al. Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum. 2004 Apr;50(4):1286-95.

769. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis. 2006 Feb;65(2):191-4.

770. Fonollosa A, Segura A, Giralt J, et al. Tuberculous uveitis after treatment with etanercept. Graefes Arch Clin Exp Ophthalmol. 2007 Sep;245(9):1397-9.

771. Fonseca A, Wagner J, Yamaga LI, et al. (18) F-FDG PET imaging of rheumatoid articular and extraarticular synovitis. J Clin Rheumatol. 2008 Oct;14(5):307.

772. Fonseca JE, Canhao H, Tavares NJ, et al. Persistent low grade synovitis without erosive progression in magnetic resonance imaging of rheumatoid arthritis patients treated with infliximab over 1 year. Clin Rheumatol. 2009 Oct;28(10):1213-6.

773. Fonseca JE, Carvalho T, Cruz M, et al. Polymorphism at position -308 of the tumour necrosis factor alpha gene and rheumatoid arthritis pharmacogenetics. Ann Rheum Dis. 2005 May;64(5):793-4.

774. Font J, Ramos-Casals M, de la Red G, et al. Pure sensory neuropathy in primary Sjogren's syndrome. Longterm prospective followup and review of the literature. J Rheumatol. 2003 Jul;30(7):1552-7.

775. Foppiani L, Cutolo M, Sessarego P, et al. Desmopressin and low-dose ACTH test in rheumatoid arthritis. Eur J Endocrinol. 1998 Mar;138(3):294-301.

776. Forsblad d'Elia H, Pullerits R, Carlsten H, et al. Resistin in serum is associated with higher levels of IL-1Ra in post-menopausal women with rheumatoid arthritis. Rheumatology (Oxford). 2008 Jul;47(7):1082-7.

777. Forsblad-d'Elia H, Carlsten H, Labrie F, et al. Low serum levels of sex steroids are associated with disease characteristics in primary Sjogren's syndrome; supplementation with dehydroepiandrosterone restores the concentrations. J Clin Endocrinol Metab. 2009 Jun;94(6):2044-51.

778. Forslind K, Boonen A, Albertsson K, et al. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scand J Rheumatol. 2009 Nov-Dec;38(6):431-8.

779. Forslind K, Hafstrom I, Ahlmen M, et al. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis. 2007 Jan;66(1):46-52.

780. Forslund T, Hannonen P, Reitamo S, et al. Hypertension in cyclosporin A-treated patients is independent of circulating endothelin levels. J Intern Med. 1995 Jul;238(1):71-5.

781. Fortna RR, Gudjonsson JE, Seidel G, et al. Persistent pruritic papules and plaques: a characteristic histopathologic presentation seen in a subset of patients with adult-onset and juvenile Still's disease. J Cutan Pathol. 2010 Sep;37(9):932-7.

782. Fossaluzza V, De Vita S. Clinical differences between ANA/anti-ENA positive or negative primary Sjogren's syndrome. Clin Rheumatol. 1992 Sep;11(3):385-7.

783. Foster CS, Barrett F. Cataract development and cataract surgery in patients with juvenile rheumatoid arthritis-associated iridocyclitis. Ophthalmology. 1993 Jun;100(6):809-17.

784. Foster EN, Nguyen KK, Sheikh RA, et al. Crohn's disease associated with Sweet's syndrome and Sjogren's syndrome treated with infliximab. Clin Dev Immunol. 2005 Jun;12(2):145-9.

785. Fox RI, Stern M, Michelson P. Update in Sjogren syndrome. Curr Opin Rheumatol. 2000 Sep;12(5):391-8.

786. Fraenkel L, Bogardus ST, Concato J, et al. Patient preferences for treatment of rheumatoid arthritis. Ann Rheum Dis. 2004 Nov;63(11):1372-8.

787. Franchini S, Dagna L, Salvo F, et al. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum. 2010 Aug;62(8):2530-5.

788. Franck H, Gottwalt J. Peripheral bone density in patients with rheumatoid arthritis. Clin Rheumatol. 2009 Oct;28(10):1141-5.

789. Franklin CM. Clinical experience with soluble TNF p75 receptor in rheumatoid arthritis. Semin Arthritis Rheum. 1999 Dec;29(3):172-81.

790. Franklin J, Lunt M, Bunn D, et al. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. Ann Rheum Dis. 2007 Mar;66(3):308-12.

791. Fransen J, Moens HB, Speyer I, et al. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis. 2005 Sep;64(9):1294-8.

792. Fransen J, Stucki G, Twisk J, et al. Effectiveness of a measurement feedback system on outcome in rheumatoid arthritis: a controlled clinical trial. Ann Rheum Dis. 2003 Jul;62(7):624-9.

793. Fraser DA, Thoen J, Djoseland O, et al. Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients. Clin Exp Rheumatol. 2000 May-Jun;18(3):357-62.

794. Fraser DA, Thoen J, Selvaag AM, et al. A preliminary study of circadian serum cortisol concentrations in response to a 72-hour fast in rheumatoid arthritis patients not previously treated with corticosteroids. Clin Rheumatol. 2001;20(2):85-7.

795. Frediani B, Falsetti P, Baldi F, et al. Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. Bone. 2003 Oct;33(4):575-81.

796. Frediani B, Falsetti P, Bisogno S, et al. Effects of high dose methylprednisolone pulse therapy on bone mass and biochemical markers of bone metabolism in patients with active rheumatoid arthritis: a 12-month randomized prospective controlled study. J Rheumatol. 2004 Jun;31(6):1083-7.

797. Fries JF, Bruce B. Rates of serious gastrointestinal events from low dose use of acetylsalicylic acid, acetaminophen, and ibuprofen in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol. 2003 Oct;30(10):2226-33.

798. Fries JF, Miller SR, Spitz PW, et al. Identification of patients at risk for gastropathy associated with NSAID use. J Rheumatol Suppl. 1990 Feb;20:12-9.

799. Fries W, Giofre MR, Catanoso M, et al. Treatment of acute uveitis associated with Crohn's disease and sacroileitis with infliximab. Am J Gastroenterol. 2002 Feb;97(2):499-500.

800. Fu A, Bertouch JV, McNeil HP. Disseminated Salmonella typhimurium

infection secondary to infliximab treatment. Arthritis Rheum. 2004 Sep;50(9):3049.

801. Fucci JC, Nightengale ML. Primary esophageal histoplasmosis. Am J Gastroenterol. 1997 Mar;92(3):530-1.

802. Fuchs I, Avnon L, Freud T, et al. Repeated tuberculin skin testing following therapy with TNF-alpha inhibitors. Clin Rheumatol. 2009 Feb;28(2):167-72.

803. Fuerst M, Mohl H, Baumgartel K, et al. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatol Int 2006;26(12):1138-42.

804. Fujikawa S. Non-steroidal anti-inflammatory drugs and slow-acting anti-rheumatic drugs in juvenile rheumatoid arthritis. Acta Paediatr Jpn. 1993 Oct;35(5):447-53.

805. Fujita K, Tanaka E, Hatta K, et al. An autopsy case of Mycobacterium abscessus pulmonary infection complicated with rheumatoid arthritis. Intern Med. 2008;47(13):1273-6.

806. Fujita Y, Fujii T, Takeda N, et al. Successful treatment of primary Sjogren's syndrome with chronic natural killer lymphocytosis by high-dose prednisolone and indomethacin farnesil. Intern Med. 2007;46(5):251-4.

807. Fujiwara H, Nishimoto N, Hamano Y, et al. Masked early symptoms of pneumonia in patients with rheumatoid arthritis during tocilizumab treatment: a report of two cases. Mod Rheumatol. 2009;19(1):64-8.

808. Fukino K, Kawashima T, Suzuki M, et al. Methylenetetrahydrofolate reductase and reduced folate carrier-1 genotypes and methotrexate serum concentrations in patients with rheumatoid arthritis. J Toxicol Sci. 2007 Oct;32(4):449-52.

809. Fukuchi M, Mizushima Y, Hori T, et al. Cryptococcal pleural effusion in a patient with chronic renal failure receiving long-term corticosteroid therapy for rheumatoid arthritis. Intern Med. 1998 Jun;37(6):534-7.

810. Fulchiero GJ, Jr., Salvaggio H, Drabick JJ, et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. J Am Acad Dermatol. 2007 May;56(5 Suppl):S65-7.

811. Fumagalli M, Incorvaia C, Nitti F, et al. The assessment of quality of life as a measure of gold salts treatment efficacy in rheumatoid arthritis. Minerva Med. 2002 Jun;93(3):199-202.

812. Funahashi K, Koyano S, Miura T, et al. Efficacy of tocilizumab and evaluation of clinical remission as determined by CDAI and MMP-3 level. Mod Rheumatol. 2009;19(5):507-12.

813. Funovits J, Aletaha D, Bykerk V, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. Ann Rheum Dis. 2010 Sep;69(9):1589-95.

814. Furfaro N, Mease PJ. Nursing considerations for infusion therapy in rheumatoid arthritis versus malignancy. J Infus Nurs. 2008 Nov-Dec;31(6):350-60.

815. Furse RK, Rossetti RG, Seiler CM, et al. Oral administration of gammalinolenic acid, an unsaturated fatty acid with anti-inflammatory properties, modulates interleukin-1beta production by human monocytes. J Clin Immunol. 2002 Mar;22(2):83-91.

816. Furst DE. Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004 Dec;26(12):1960-75.

817. Furst DE, Gaylis N, Bray V, et al. Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. Ann Rheum Dis 2007;66(7):893-9.

818. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid

arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003 Dec;30(12):2563-71.

819. Furtado RN, Oliveira LM, Natour J. Polyarticular corticosteroid injection versus systemic administration in treatment of rheumatoid arthritis patients: a randomized controlled study. J Rheumatol. 2005 Sep;32(9):1691-8.

820. Furukawa K, Ohtani T, Furukawa F, et al. Infectious mononucleosis-like syndrome induced by salazosulfapyridine in a patient with rheumatoid arthritis. Mod Rheumatol. 2007;17(6):492-5.

821. Gadadhar H, Hawkins S, Huffstutter JE, et al. Cutaneous mucormycosis complicating methotrexate, prednisone, and infliximab therapy. J Clin Rheumatol. 2007 Dec;13(6):361-2.

822. Gadsby K, Deighton C. Characteristics and treatment responses of patients satisfying the BSR guidelines for anti-TNF in ankylosing spondylitis. Rheumatology (Oxford). 2007 Mar;46(3):439-41.

823. Gal I, Toth L, Szegedi L, et al. Gastric bleeding in a patient with rheumatoid arthritis complicated by immune thrombocytopenic purpura. Joint Bone Spine. 2008 May;75(3):350-2.

824. Galaria NA, Werth VP, Schumacher HR. Leukocytoclastic vasculitis due to etanercept. J Rheumatol. 2000 Aug;27(8):2041-4.

825. Galarraga B, Belch JJ, Pullar T, et al. Clinical improvement in rheumatoid arthritis is associated with healthier microvascular function in patients who respond to antirheumatic therapy. J Rheumatol. 2010 Mar;37(3):521-8.

826. Galarraga B, Khan F, Kumar P, et al. Etanercept improves inflammation-associated arterial stiffness in rheumatoid arthritis. Rheumatology (Oxford). 2009 Nov;48(11):1418-23.

827. Galindo M, Pablos JL, Gomez-Reino JJ. Internuclear ophthalmoplegia in systemic lupus erythematosus. Semin Arthritis Rheum. 1998 Dec;28(3):179-86.

828. Ganeshan A, Quen L, Smith D. Occurrence of vesicocolic fistula with a use of etanercept: a cautionary tale. J Clin Rheumatol. 2005 Oct;11(5):290-1.

829. Garcia-Gomez C, Nolla JM, Valverde J, et al. High HDL-cholesterol in women with rheumatoid arthritis on low-dose glucocorticoid therapy. Eur J Clin Invest. 2008 Sep;38(9):686-92.

830. Garcia-Porrua C, Gonzalez-Gay MA. Successful treatment of refractory mononeuritis multiplex secondary to rheumatoid arthritis with the anti-tumour necrosis factor alpha monoclonal antibody infliximab. Rheumatology (Oxford). 2002 Feb;41(2):234-5.

831. Garcia-Porrua C, Gonzalez-Gay MA, Quevedo V. Should anti-tumor necrosis factor-alpha be the first therapy for rheumatoid vasculitis? J Rheumatol. 2006 Feb;33(2):433; author reply -4.

832. Gardiner PV, Bell AL, Taggart AJ, et al. A potential pitfall in the use of the Disease Activity Score (DAS28) as the main response criterion in treatment guidelines for patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Mar;64(3):506-7.

833. Garfield BE, Krahl T, Appel S, et al. Regulation of p38 MAP kinase in CD4+ lymphocytes by infliximab therapy in patients with rheumatoid arthritis. Clin Immunol. 2005 Aug;116(2):101-7.

834. Garnero P, Gineyts E, Christgau S, et al. Association of baseline levels of urinary glucosyl-galactosyl-pyridinoline and type II collagen C-telopeptide with progression of joint destruction in patients with early rheumatoid arthritis. Arthritis Rheum. 2002 Jan;46(1):21-30.

835. Garnero P, Tabassi NC, Voorzanger-Rousselot N. Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with etanercept. J Rheumatol. 2008 Dec;35(12):2313-5.

836. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J of Clinical Epidemiology. 2006 Aug 4;59(10):1040-8.

837. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimensions of the spine in men with rheumatoid arthritis. Effects of low-dose corticosteroids. Arthritis Rheum. 1993 Feb;36(2):222-8.

838. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9.

839. Gaylis NB, Needell SD, Rudensky D. Comparison of in-office magnetic resonance imaging versus conventional radiography in detecting changes in erosions after one year of infliximab therapy in patients with rheumatoid arthritis. Mod Rheumatol. 2007;17(4):273-8.

840. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703.

841. Geborek P, Crnkic M, Petersson IF, et al. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis. 2002 Sep;61(9):793-8.

842. Geborek P, Mansson B, Wollheim FA, et al. Intraarticular corticosteroid injection into rheumatoid arthritis knees improves extensor muscles strength. Rheumatol Int. 1990;9(6):265-70.

843. Geenen R, Godaert GL, Heijnen CJ, et al. Experimentally induced stress in rheumatoid arthritis of recent onset: effects on peripheral blood lymphocytes. Clin Exp Rheumatol. 1998 Sep-Oct;16(5):553-9.

844. Gelinck LB, van der Bijl AE, Beyer WE, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis. 2008 May;67(5):713-6.

845. Genc H, Duyur Cakit B, Nacir B, et al. The effects of sulfasalazine treatment on enthesal abnormalities of inflammatory rheumatic diseases. Clin Rheumatol. 2007 Jul;26(7):1104-10.

846. Gengenbacher M, Sebald HJ, Villiger PM, et al. Infliximab inhibits bone resorption by circulating osteoclast precursor cells in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2008 May;67(5):620-4.

847. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1232-42.

848. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun;46(6):1443-50.

849. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23.

850. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9.

851. Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):547-54.

852. Genovese MC, Van den Bosch F, Roberson SA, et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the

treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum. 2010 Apr;62(4):929-39.

853. Geoghegan JM, Clark DI, Bainbridge LC, et al. Risk factors in carpal tunnel syndrome. J Hand Surg [Br]. 2004 Aug;29(4):315-20.

854. George D, Kadlubek P, Batra D, et al. Infliximab dose and charge escalation patterns in managed care. Manag Care Interface. 2004;Suppl A:5-8.

855. Georgescu C. Sulphasalazine therapy in rheumatoid arthritis. A two-year study and follow-up of clinical results. Rom J Intern Med. 1992 Apr-Jun;30(2):127-32.

856. Georgiadis AN, Papavasiliou EC, Lourida ES, et al. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment--a prospective, controlled study. Arthritis Res Ther. 2006;8(3):R82.

857. Georgiadis AN, Voulgari PV, Argyropoulou MI, et al. Early treatment reduces the cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients. Semin Arthritis Rheum. 2008 Aug;38(1):13-9.

858. Geraghty EM, Ristow B, Gordon SM, et al. Overwhelming parasitemia with Plasmodium falciparum infection in a patient receiving infliximab therapy for rheumatoid arthritis. Clin Infect Dis. 2007 May 15;44(10):e82-4.

859. Gergely P, Jr., Blazsek A, Danko K, et al. Detection of TT virus in patients with idiopathic inflammatory myopathies. Ann N Y Acad Sci. 2005 Jun;1050:304-13.

860. Gerlag DM, Boyle DL, Rosengren S, et al. Real-time quantitative PCR to detect changes in synovial gene expression in rheumatoid arthritis after corticosteroid treatment. Ann Rheum Dis. 2007 Apr;66(4):545-7.

861. Gerli R, Bertotto A, Agea E, et al. Basis for defective proliferation of peripheral blood T cells to anti-CD2 antibodies in primary Sjogren's syndrome. J Clin Invest. 1990 Dec;86(6):1870-7.

862. Gerli R, Lunardi C, Bocci EB, et al. Anti-tumor necrosis factor-alpha response in rheumatoid arthritis is associated with an increase in serum soluble CD30. J Rheumatol. 2008 Jan;35(1):14-9.

863. Gerli R, Schillaci G, Giordano A, et al. CD4+CD28- T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. Circulation. 2004 Jun 8;109(22):2744-8.

864. Gerloni V, Pontikaki I, Gattinara M, et al. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis. 2008 Aug;67(8):1145-52.

865. Germano V, Picchianti Diamanti A, Baccano G, et al. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis. 2005 Oct;64(10):1519-20.

866. Gerster JC, Dudler J. Cellulitis caused by Capnocytophaga cynodegmi associated with etanercept treatment in a patient with rheumatoid arthritis. Clin Rheumatol. 2004 Dec;23(6):570-1.

867. Geusens P, Dequeker J, Vanhoof J, et al. Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. Ann Rheum Dis. 1998 Dec;57(12):724-7.

868. Gevers G, Dequeker J, van Holsbeeck M, et al. A high dose (up to 200 mg) tolerance and efficacy study of intra-articular rimexolone (Org 6216) in rheumatoid synovitis of the knee. Clin Rheumatol. 1994 Mar;13(1):103-9.

869. Ghavami A, Genevay S, Fulpius T, et al. Etanercept in treatment of Felty's syndrome. Ann Rheum Dis. 2005 Jul;64(7):1090-1.

870. Giagounidis AA, Haase S, Germing U, et al. Autoimmune disorders in two patients with myelodysplastic syndrome and 5q deletion. Acta Haematol. 2005;113(2):146-9.

871. Gianella S, Schaer DJ, Schwarz U, et al. Retinal microangiopathy and rapidly fatal cerebral edema in a patient with adult-onset Still's disease and concurrent macrophage activation syndrome. Am J Hematol. 2008 May;83(5):424-7.

872. Giannelli G, Iannone F, Marinosci F, et al. Infliximab therapy does not modify MMP-2 and MMP-9 serum concentrations in chronic arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):867-72.

873. Giardina AR, Accardo-Palumbo A, Ciccia F, et al. Blocking TNF in vitro with infliximab determines the inhibition of expansion and interferon gamma production of Vgamma9/Vdelta2 T lymphocytes from patients with active rheumatoid arthritis. A role in the susceptibility to tuberculosis? Reumatismo. 2009 Jan-Mar;61(1):21-6.

874. Gibofsky A, Palmer WR, Goldman JA, et al. Real-world utilization of DMARDs and biologics in rheumatoid arthritis: the RADIUS (Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study) study. Curr Med Res Opin. 2006 Jan;22(1):169-83.

875. Gibson JN, Poyser NL, Morrison WL, et al. Muscle protein synthesis in patients with rheumatoid arthritis: effect of chronic corticosteroid therapy on prostaglandin F2 alpha availability. Eur J Clin Invest. 1991 Aug;21(4):406-12.

876. Gilbert ME, Savino PJ. Missing the bull's eye. Surv Ophthalmol. 2007 Jul-Aug;52(4):440-2.

877. Gilbert TD, Jr., Smith D, Ollendorf DA. Patterns of use, dosing, and economic impact of biologic agent use in patients with rheumatoid arthritis: a retrospective cohort study. BMC Musculoskelet Disord. 2004 Oct 14;5(1):36.

878. Gilboe IM, Kvien TK, Haugeberg G, et al. Bone mineral density in systemic lupus erythematosus: comparison with rheumatoid arthritis and healthy controls. Ann Rheum Dis. 2000 Feb;59(2):110-5.

879. Giles JT, Bartlett SJ, Gelber AC, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):333-7.

880. Giles JT, Fernandes V, Lima JA, et al. Myocardial dysfunction in rheumatoid arthritis: epidemiology and pathogenesis. Arthritis Res Ther. 2005;7(5):195-207.

881. Gill JB. Fat suppression imaging in epidural lipomatosis: case report. J Surg Orthop Adv. 2007 Fall;16(3):144-7.

882. Giltay EJ, Popp-Snijders C, van Schaardenburg D, et al. Serum testosterone levels are not elevated in patients with ankylosing spondylitis. J Rheumatol. 1998 Dec;25(12):2389-94.

883. Gladman DD, Mease PJ, Choy EH, et al. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther. 2010;12(3):R113.

884. Glass GE, Greig AV, Weir J, et al. Nasal tip necrosis--an unusual presentation of rheumatoid vasculitis. Clin Rheumatol. 2007 Nov;26(11):1943-5.

885. Gleissner C, Willershausen B, Kaesser U, et al. The role of risk factors for periodontal disease in patients with rheumatoid arthritis. Eur J Med Res. 1998 Aug 18;3(8):387-92.

886. Gluck T, Linde HJ, Scholmerich J, et al. Anti-tumor necrosis factor therapy and Listeria monocytogenes infection: report of two cases. Arthritis Rheum. 2002 Aug;46(8):2255-7; author reply 7.

887. Go RS, Li CY, Tefferi A, et al. Acquired pure red cell aplasia associated with lymphoproliferative disease of granular T lymphocytes. Blood. 2001 Jul 15;98(2):483-5.

888. Godaert GL, Hartkamp A, Geenen R, et al. Fatigue in daily life in patients with primary Sjogren's syndrome and systemic lupus

erythematosus. Ann N Y Acad Sci. 2002 Jun;966:320-6.

889. Godinho F, Godfrin B, El Mahou S, et al. Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis. Clin Exp Rheumatol. 2004 May-Jun;22(3):328-30.

890. Goeb V, Buch MH, Vital EM, et al. Costimulation blockade in rheumatic diseases: where we are? Curr Opin Rheumatol. 2009 May;21(3):244-50.

891. Goedkoop AY, Kraan MC, Picavet DI, et al. Deactivation of endothelium and reduction in angiogenesis in psoriatic skin and synovium by low dose infliximab therapy in combination with stable methotrexate therapy: a prospective single-centre study. Arthritis Res Ther. 2004;6(4):R326-34.

892. Goedkoop AY, Kraan MC, Teunissen MB, et al. Early effects of tumour necrosis factor alpha blockade on skin and synovial tissue in patients with active psoriasis and psoriatic arthritis. Ann Rheum Dis. 2004 Jul;63(7):769-73.

893. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis. 2007 Sep;66(9):1227-32.

894. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90.

895. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum. 2008 Feb;58(2 Suppl):S126-35.

896. Goerres GW, Forster A, Uebelhart D, et al. F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. Clin Nucl Med. 2006 Jul;31(7):386-90.

897. Goerttler E, Kutzner H, Peter HH, et al. Methotrexate-induced papular eruption in patients with rheumatic diseases: a distinctive adverse cutaneous reaction produced by methotrexate in patients with collagen vascular diseases. J Am Acad Dermatol. 1999 May;40(5 Pt 1):702-7.

898. Goksugur N, Yilmaz F. Medical image. Extensive oral ulcerations. N Z Med J. 2006;119(1242):U2236.

899. Golan TD, Keren D, Elias N, et al. Severe reversible cardiomyopathy associated with systemic vasculitis in primary Sjogren's syndrome. Lupus. 1997;6(6):505-8.

900. Golda N, Feldman M. Histoplasmosis clinically imitating cutaneous malignancy. J Cutan Pathol. 2008 Oct;35 Suppl 1:26-8.

901. Goldbach-Mansky R, Wilson M, Fleischmann R, et al. Comparison of Tripterygium wilfordii Hook F versus sulfasalazine in the treatment of rheumatoid arthritis: a randomized trial. Ann Intern Med. 2009 Aug 18;151(4):229-40, W49-51.

902. Goldberger C, Dulak J, Duftner C, et al. Vascular endothelial growth factor (VEGF) in ankylosing spondylitis--a pilot study. Wien Med Wochenschr. 2002;152(9-10):223-5.

903. Goldenberg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther. 1999 Jan;21(1):75-87; discussion 1-2.

904. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003 Aug;48(8):2122-7.

905. Gonnet-Gracia C, Barnetche T, Richez C, et al. Anti-nuclear antibodies, anti-DNA and C4 complement evolution in rheumatoid arthritis and ankylosing spondylitis treated

with TNF-alpha blockers. Clin Exp Rheumatol. 2008 May-Jun;26(3):401-7.

906. Gonzalez-Alvaro I, Ortiz AM, Tomero EG, et al. Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. Ann Rheum Dis. 2007 Dec;66(12):1675-8.

907. Gonzalez-Chavez JR, Berlingeri-Ramos AC, Sanchez Casiano MA. Puerto Rico psoriasis study group: efficacy and safety of etanercept. J Drugs Dermatol. 2005 Nov-Dec;4(6):735-9.

908. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, et al. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):83-6.

909. Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, et al. Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. Clin Exp Rheumatol. 2009 Mar-Apr;27(2):222-8.

910. Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, et al. Short-term effect of anti-TNF-alpha therapy on nitric oxide production in patients with severe rheumatoid arthritis. Clin Exp Rheumatol. 2009 May-Jun;27(3):452-8.

911. Gonzalez-Gay MA, Garcia-Unzueta MT, De Matias JM, et al. Influence of anti-TNF-alpha infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Jul-Aug;24(4):373-9.

912. Gonzalez-Gay MA, Garcia-Unzueta MT, Gonzalez-Juanatey C, et al. Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):311-6.

913. Gonzalez-Gay MA, Llorca J, Garcia-Unzueta MT, et al. High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):596-603.

914. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Garcia-Unzueta MT, et al. Visfatin is not associated with inflammation or metabolic syndrome in patients with severe rheumatoid arthritis undergoing anti-TNF-alpha therapy. Clin Exp Rheumatol. 2010 Jan-Feb;28(1):56-62.

915. Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, et al. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. Clin Exp Rheumatol. 2006 May-Jun;24(3):309-12.

916. Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, et al. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. Arthritis Rheum. 2008 Dec 15;59(12):1821-4.

917. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, et al. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. Arthritis Rheum. 2004 Jun 15;51(3):447-50.

918. Gonzalez-Lopez MA, Martinez-Taboada VM, Gonzalez-Vela MC, et al. Recall injection-site reactions associated with etanercept therapy: report of two new cases with immunohistochemical analysis. Clin Exp Dermatol. 2007 Nov;32(6):672-4.

919. Goossens PH, Heemskerk B, van Tongeren J, et al. Reliability and sensitivity to change of various measures of hand function in relation to treatment of synovitis of the metacarpophalangeal joint in rheumatoid arthritis. Rheumatology (Oxford). 2000 Aug;39(8):909-13.

920. Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med. 2002 May 2;346(18):1349-56.

921. Gosset P, Perez T, Lassalle P, et al. Increased TNF-alpha secretion by alveolar macrophages from patients with rheumatoid arthritis. Am Rev Respir Dis. 1991 Mar;143(3):593-7.

922. Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis. 2005 Jun;64(6):913-20.

923. Gottenberg JE, Miceli-Richard C, Ducot B, et al. Markers of B-lymphocyte activation are elevated in patients with early rheumatoid arthritis and correlated with disease activity in the ESPOIR cohort. Arthritis Res Ther. 2009;11(4):R114.

924. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010 Sep;62(9):2625-32.

925. Gottlieb AB, Kircik L, Eisen D, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. J Dermatolog Treat. 2006;17(6):343-52.

926. Gottlieb AB, Mease PJ, Mark Jackson J, et al. Clinical characteristics of psoriatic arthritis and psoriasis in dermatologists' offices. J Dermatolog Treat. 2006;17(5):279-87.

927. Gough A, Sheeran T, Arthur V, et al. Adverse interaction between intramuscular methylprednisolone and sulphasalazine in patients with early rheumatoid arthritis. A pilot study. Scand J Rheumatol. 1994;23(1):46-8.

928. Graf C, Cardoso G, Silva MB, et al. Intra ocular pressure in chronic users of oral glucocorticoids for rheumatoid arthritis. Acta Reumatol Port. 2006 Apr-Jun;31(2):151-5, 83.

929. Gran JT, Myklebust G. Toxicity of sulphasalazine in rheumatoid arthritis. Possible protective effect of rheumatoid factors and corticosteroids. Scand J Rheumatol. 1993;22(5):229-32.

930. Grange L, Nissen MJ, Garambois K, et al. Infliximab-induced cerebral thrombophlebitis. Rheumatology (Oxford). 2005 Feb;44(2):260-1.

931. Granjo E, Lima M, Correia T, et al. Cd8(+)/V beta 5.1(+) large granular lymphocyte leukemia associated with autoimmune cytopenias, rheumatoid arthritis and vascular mammary skin lesions: successful response to 2-deoxycoformycin. Hematol Oncol. 2002 Jun;20(2):87-93.

932. Grassi W, De Angelis R, Cervini C. Corticosteroid prescribing in rheumatoid arthritis and psoriatic arthritis. Clin Rheumatol. 1998;17(3):223-6.

933. Grassi W, Lamanna G, Farina A, et al. Synovitis of small joints: sonographic guided diagnostic and therapeutic approach. Ann Rheum Dis. 1999 Oct;58(10):595-7.

934. Gratacos J, Casado E, Real J, et al. Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. Ann Rheum Dis. 2007 Apr;66(4):493-7.

935. Gray RE, Doherty SM, Galloway J, et al. A double-blind study of deflazacort and prednisone in patients with chronic inflammatory disorders. Arthritis Rheum. 1991 Mar;34(3):287-95.

936. Greenberg JD, Kishimoto M, Strand V, et al. Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. Am J Med. 2008 Jun;121(6):532-8.

937. Greenwood MC, Hakim AJ, Doyle DV. A simple extension to the Rheumatoid Arthritis Quality of Life Questionnaire (RAQol) to explore individual patient concerns and monitor group outcome in clinical practice. Rheumatology (Oxford). 2006 Jan;45(1):61-5.

938. Grijalva CG, Chung CP, Arbogast PG, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45(10 Supl 2):S66-76.

939. Grijalva CG, Chung CP, Stein CM, et al. Changing patterns of medication use in patients with rheumatoid arthritis in a Medicaid population. Rheumatology (Oxford). 2008 Jul;47(7):1061-4.

940. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Adherence to disease-modifying antirheumatic drugs and the effects of exposure misclassification on the risk of hospital admission. Arthritis Care Res (Hoboken) 2010;62(5):730-4.

941. Grinblat B, Scheinberg M. Unexpected onset of psoriasis during infliximab treatment: comment on the article by Beuthien et al. Arthritis Rheum. 2005 Apr;52(4):1333-4; author reply 4.

942. Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: a review. Semin Arthritis Rheum. 2008 Feb;37(4):251-5.

943. Grisar J, Aletaha D, Steiner CW, et al. Endothelial progenitor cells in active rheumatoid arthritis: effects of tumour necrosis factor and glucocorticoid therapy. Ann Rheum Dis. 2007 Oct;66(10):1284-8.

944. Guarneri C, Polimeni G. Nicolau syndrome following etanercept administration. Am J Clin Dermatol. 2010;11 Suppl 1:51-2.

945. Guarneri C, Polimeni G, Nunnari G. Pityriasis rosea during etanercept therapy. Eur Rev Med Pharmacol Sci. 2009 Sep-Oct;13(5):383-7.

946. Guarnieri MV, Rosenberg L, Scheinberg MA. Intractable pain in a rheumatoid wrist. J Rheumatol. 2003 Dec;30(12):2718-9.

947. Gubinelli E, Angelo C, Pacifico V. A case of dystrophic epidermolysis bullosa improved with etanercept for concomitant psoriatic arthritis. Am J Clin Dermatol. 2010;11 Suppl 1:53-4.

948. Gudbjornsson B, Skogseid B, Oberg K, et al. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis. Effect of glucocorticoids. J Rheumatol. 1996 Apr;23(4):596-602.

949. Gudbrandsdottir S, Bliddal H, Petri A, et al. Plasma TNF binding capacity profiles during treatment with etanercept in rheumatoid arthritis. Scand J Rheumatol. 2004;33(6):385-8.

950. Guignard S, Dien G, Dougados M. Severe systemic inflammatory response syndrome in a patient with adult onset Still's disease treated with the anti-IL1 drug anakinra: a case report. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):758-9.

951. Guignard S, Gossec L, Bandinelli F, et al. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. Clin Exp Rheumatol 2008;26(3 Suppl 49):S23-9.

952. Guillot X, Solau-Gervais E, Coulon A, et al. Sjogren's syndrome with ANCA-associated crescentic extramembranous glomerulonephritis. Joint Bone Spine. 2009 Mar;76(2):188-9.

953. Guion TL, Sculco TP. Pasteurella multocida infection in total knee arthroplasty. Case report and literature review. J Arthroplasty. 1992 Jun;7(2):157-60.

954. Guis S, Balandraud N, Bouvenot J, et al. Influence of -308 A/G polymorphism in the tumor necrosis factor alpha gene on etanercept treatment in rheumatoid arthritis. Arthritis Rheum. 2007 Dec 15;57(8):1426-30.

955. Gul U, Gonul M, Kilic A, et al. Treatment of psoriatic arthritis with etanercept, methotrexate, and cyclosporin A. Clin Ther. 2006 Feb;28(2):251-4.

956. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Mar;68(3):330-6.

957. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, et al. Changes in bone

mineral density in patients with recent onset, active rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):823-8.

958. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, et al. Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1508-12.

959. Guler-Yuksel M, Klarenbeek NB, Goekoop-Ruiterman YP, et al. Accelerated hand bone mineral density loss is associated with progressive joint damage in hands and feet in recent-onset rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R96.

960. Gupta A, Bansal RK, Bambery P. Posterior scleritis related fundal mass in a patient with rheumatoid arthritis. Scand J Rheumatol. 1992;21(5):254-6.

961. Gupta N, Fox CM, Grisolano SW. Disseminated histoplasmosis with colonic ulcers in a patient receiving infliximab. Gastrointest Endosc. 2009 Sep;70(3):597-8.

962. Gutierrez MA, Garcia ME, Rodriguez JA, et al. Hypothalamic-pituitary-adrenal axis function in patients with active rheumatoid arthritis: a controlled study using insulin hypoglycemia stress test and prolactin stimulation. J Rheumatol. 1999 Feb;26(2):277-81.

963. Guzman-Clark JR, Fang MA, Sehl ME, et al. Barriers in the management of glucocorticoid-induced osteoporosis. Arthritis Rheum. 2007 Feb 15;57(1):140-6.

964. Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):888-9.

965. Habib GS, Haj S. Bone mineral density in patients with early rheumatoid arthritis treated with corticosteroids. Clin Rheumatol. 2005 Apr;24(2):129-33.

966. Hadi A, Hickling P, Brown M, et al. Scintigraphic evidence of effect of infliximab on disease activity in ankylosing spondylitis. Rheumatology (Oxford). 2002 Jan;41(1):114-6.

967. Hadj Kacem H, Kaddour N, Adyel FZ, et al. HLA-DQB1 CAR1/CAR2, TNFa IR2/IR4 and CTLA-4 polymorphisms in Tunisian patients with rheumatoid arthritis and Sjogren's syndrome. Rheumatology (Oxford). 2001 Dec;40(12):1370-4.

968. Haerden J, Coolen L, Dequeker J. The effect of D-penicillamine on lung function parameters (diffusion capacity) in rheumatoid arthritis. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):509-13.

969. Hafstrom I, Albertsson K, Boonen A, et al. Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open 2-year continuation study. Ann Rheum Dis. 2009 Apr;68(4):508-13.

970. Hafstrom I, Rohani M, Deneberg S, et al. Effects of low-dose prednisolone on endothelial function, atherosclerosis, and traditional risk factors for atherosclerosis in patients with rheumatoid arthritis--a randomized study. J Rheumatol. 2007 Sep;34(9):1810-6.

971. Hage CA, Wood KL, Winer-Muram HT, et al. Pulmonary cryptococcosis after initiation of anti-tumor necrosis factor-alpha therapy. Chest. 2003 Dec;124(6):2395-7.

972. Hagiwara K, Sato T, Takagi-Kobayashi S, et al. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. J Rheumatol. 2007 May;34(5):1151-4.

973. Hahtola PA, Jarvenpaa RE, Lounatmaa K, et al. Hard metal alveolitis accompanied by rheumatoid arthritis. Respiration. 2000;67(2):209-12.

974. Haibel H, Rudwaleit M, Brandt HC, et al. Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. Arthritis Rheum. 2006 Feb;54(2):678-81.

975. Haibel H, Rudwaleit M, Listing J, et al. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. Ann Rheum Dis. 2005 Feb;64(2):296-8.

976. Haigh RC, McCabe CS, Halligan PW, et al. Joint stiffness in a phantom limb: evidence of central nervous system involvement in rheumatoid arthritis. Rheumatology (Oxford). 2003 Jul;42(7):888-92.

977. Hall GM, Daniels M, Doyle DV, et al. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis Rheum. 1994 Oct;37(10):1499-505.

978. Hall GM, Peerbhoy D, Shenkin A, et al. Hip and knee arthroplasty: a comparison and the endocrine, metabolic and inflammatory responses. Clin Sci (Lond). 2000 Jan;98(1):71-9.

979. Hall GM, Perry LA, Spector TD. Depressed levels of dehydroepiandrosterone sulphate in postmenopausal women with rheumatoid arthritis but no relation with axial bone density. Ann Rheum Dis. 1993 Mar;52(3):211-4.

980. Hall GM, Spector TD, Delmas PD. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. Effects of corticosteroids and hormone replacement therapy. Arthritis Rheum. 1995 Jul;38(7):902-6.

981. Hall GM, Spector TD, Griffin AJ, et al. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum. 1993 Nov;36(11):1510-6.

982. Hall HA, Zimmermann B. Evolution of dermatomyositis during therapy with a tumor necrosis factor alpha inhibitor. Arthritis Rheum. 2006 Dec 15;55(6):982-4.

983. Hall J, Morand EF, Medbak S, et al. Abnormal hypothalamic-pituitary-adrenal axis function in rheumatoid arthritis. Effects of nonsteroidal antiinflammatory drugs and water immersion. Arthritis Rheum. 1994 Aug;37(8):1132-7.

984. Hall SJ, Hickling P. Failure of etanercept to control extra-articular manifestations of rheumatoid arthritis. J Clin Rheumatol. 2007 Feb;13(1):54.

985. Halpern MT, Cifaldi MA, Kvien TK. Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group. Ann Rheum Dis. 2009 Jun;68(6):930-7.

986. Halvorsen EH, Haavardsholm EA, Pollmann S, et al. Serum IgG antibodies to peptidylarginine deiminase 4 predict radiographic progression in patients with rheumatoid arthritis treated with tumour necrosis factor-alpha blocking agents. Ann Rheum Dis. 2009 Feb;68(2):249-52.

987. Hamada H, Kohno N, Yokoyama A, et al. KL-6 as a serologic indicator of Pneumocystis carinii pneumonia in immunocompromised hosts. Intern Med. 1998 Mar;37(3):307-10.

988. Hamadeh MA, Atkinson J, Smith LJ. Sulfasalazine-induced pulmonary disease. Chest. 1992 Apr;101(4):1033-7.

989. Hamalainen H, Arkela-Kautiainen M, Kautiainen H, et al. Bone mineral content in young adults with active or inactive juvenile idiopathic arthritis and in controls. Scand J Rheumatol. 2010 May;39(3):219-22.

990. Hamilton TK. Treatment of psoriatic arthritis and recalcitrant skin disease with combination therapy. J Drugs Dermatol. 2008 Nov;7(11):1089-93.

991. Hammer HB, Sveinsson M, Kongtorp AK, et al. A 78-joints ultrasonographic assessment is associated with clinical assessments and is highly responsive to improvement in a longitudinal study of patients with rheumatoid arthritis starting adalimumab treatment. Ann Rheum Dis. 2010 Jul;69(7):1349-51.

992. Hammoudeh M. Infliximab treatment in a patient with rheumatoid arthritis on haemodialysis. Rheumatology (Oxford). 2006 Mar;45(3):357-9.

993. Hammoudeh M. Recurrent postpartum episodic rheumatoid arthritis. J Clin Rheumatol. 2006 Aug;12(4):196-8.

994. Han C, Rahman MU, Doyle MK, et al. Association of anemia and physical disability among patients with rheumatoid arthritis. J Rheumatol. 2007 Nov;34(11):2177-82.

995. Han C, Smolen J, Kavanaugh A, et al. Comparison of employability outcomes among patients with early or long-standing rheumatoid arthritis. Arthritis Rheum. 2008 Apr 15;59(4):510-4.

996. Hanauer SB. Review article: safety of infliximab in clinical trials. Aliment Pharmacol Ther. 1999 Sep;13 Suppl 4:16-22; discussion 38.

997. Hanna B, Holdeman NR, Tang RA, et al. Retinal toxicity secondary to Plaquenil therapy. Optometry. 2008 Feb;79(2):90-4.

998. Hansel S, Lassig G, Pistrosch F, et al. Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity. Atherosclerosis. 2003 Sep;170(1):177-80.

999. Hansen IB, Ellingsen T, Hornung N, et al. Plasma level of CXC-chemokine CXCL12 is increased in rheumatoid arthritis and is independent of disease activity and methotrexate treatment. J Rheumatol. 2006 Sep;33(9):1754-9.

1000. Hansen KE, Cush J, Singhal A, et al. The safety and efficacy of leflunomide in combination with infliximab in rheumatoid arthritis. Arthritis Rheum. 2004 Apr 15;51(2):228-32.

1001. Hansen KE, Hildebrand JP, Genovese MC, et al. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol. 2004 Jun;31(6):1098-102.

1002. Hansen M, Florescu A, Stoltenberg M, et al. Bone loss in rheumatoid arthritis. Influence of disease activity, duration of the disease, functional capacity, and corticosteroid treatment. Scand J Rheumatol. 1996;25(6):367-76.

1003. Harada K, Akai Y, Koyama S, et al. A case of autoimmune hepatitis exacerbated by the administration of etanercept in the patient with rheumatoid arthritis. Clin Rheumatol. 2008 Aug;27(8):1063-6.

1004. Harada S, Mitsunobu F, Kodama F, et al. Giant cell arteritis associated with rheumatoid arthritis monitored by magnetic resonance angiography. Intern Med. 1999 Aug;38(8):675-8.

1005. Haraoui B, Cameron L, Ouellet M, et al. Anti-infliximab antibodies in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. J Rheumatol. 2006 Jan;33(1):31-6.

1006. Haraoui B, Keystone EC, Thorne JC, et al. Clinical outcomes of patients with rheumatoid arthritis after switching from infliximab to etanercept. J Rheumatol. 2004 Dec;31(12):2356-9.

1007. Harboe E, Tjensvoll AB, Vefring HK, et al. Fatigue in primary Sjogren's syndrome--a link to sickness behaviour in animals? Brain Behav Immun. 2009 Nov;23(8):1104-8.

1008. Harbuz MS, Korendowych E, Jessop DS, et al. Hypothalamo-pituitary-adrenal axis dysregulation in patients with rheumatoid arthritis after the dexamethasone/corticotrophin releasing factor test. J Endocrinol. 2003 Jul;178(1):55-60.

1009. Hardy R, Rabbitt EH, Filer A, et al. Local and systemic glucocorticoid metabolism in inflammatory arthritis. Ann Rheum Dis. 2008 Sep;67(9):1204-10.

1010. Hargreaves MR, Mowat AG, Benson MK. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports. Thorax. 1992 Aug;47(8):628-33.

1011. Harle P, Pongratz G, Weidler C, et al. Possible role of leptin in hypoandrogenicity

in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis. 2004 Jul;63(7):809-16.

1012. Harle P, Straub RH, Wiest R, et al. Increase of sympathetic outflow measured by neuropeptide Y and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with systemic lupus erythematosus and rheumatoid arthritis: another example of uncoupling of response systems. Ann Rheum Dis. 2006 Jan;65(1):51-6.

1013. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care. 2003 Oct;9(6 Suppl):S136-43.

1014. Harner KC, Jackson LW, Drabick JJ. Normalization of anticardiolipin antibodies following rituximab therapy for marginal zone lymphoma in a patient with Sjogren's syndrome. Rheumatology (Oxford). 2004 Oct;43(10):1309-10.

1015. Harney S, O'Shea FD, FitzGerald O. Peptostreptococcal pericarditis complicating anti-tumour necrosis factor alpha treatment in rheumatoid arthritis. Ann Rheum Dis. 2002 Jul;61(7):653-4.

1016. Haroon M, Bond U, Phelan M. Sinusitis: a possible link with adalimumab. Clin Rheumatol. 2008 Sep;27(9):1189-90.

1017. Haroon N, Srivastava R, Misra R, et al. A novel predictor of clinical response to methotrexate in patients with rheumatoid arthritis: a pilot study of in vitro T cell cytokine suppression. J Rheumatol. 2008 Jun;35(6):975-8.

1018. Harrison DJ, Huang X, Globe D. Dosing patterns and costs of tumor necrosis factor inhibitor use for rheumatoid arthritis. Am J Health Syst Pharm. 2010 Aug;67(15):1281-7.

1019. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009;68(2):209-15.

1020. Harrison MJ, Kim CA, Silverberg M, et al. Does age bias the aggressive treatment of elderly patients with rheumatoid arthritis? J Rheumatol. 2005 Jul;32(7):1243-8.

1021. Hartkamp A, Geenen R, Godaert GL, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjogren syndrome: a randomised controlled trial. Ann Rheum Dis. 2008 Jan;67(1):91-7.

1022. Hashiramoto A, Shiozawa K, Tanaka Y, et al. Prospective study of methotrexate treatment for rheumatoid arthritis treated legitimately according to the government recommended 8 mg/week dose. Mod Rheumatol. 2009;19(6):637-42.

1023. Hassell AB, Davis MJ, Fowler PD, et al. The relationship between serial measures of disease activity and outcome in rheumatoid arthritis. Q J Med. 1993 Sep;86(9):601-7.

1024. Hassett AL, Li T, Buyske S, et al. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin 2008;24(5):1443-53.

1025. Hassikou H, El Haouri M, Tabache F, et al. Leflunomide-induced toxic epidermal necrolysis in a patient with rheumatoid arthritis. Joint Bone Spine. 2008 Oct;75(5):597-9.

1026. Hatemi G, Melikoglu M, Fresko I, et al. Infliximab does not suppress the tuberculin skin test (purified protein derivative). J Rheumatol. 2007 Mar;34(3):474-80.

1027. Hau M, Kneitz C, Tony HP, et al. High resolution ultrasound detects a decrease in pannus vascularisation of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor alpha receptor (etanercept). Ann Rheum Dis. 2002 Jan;61(1):55-8.

1028. Haugeberg G, Orstavik RE, Uhlig T, et al. Clinical decision rules in rheumatoid

arthritis: do they identify patients at high risk for osteoporosis? Testing clinical criteria in a population based cohort of patients with rheumatoid arthritis recruited from the Oslo Rheumatoid Arthritis Register. Ann Rheum Dis. 2002 Dec;61(12):1085-9.

1029. Haugeberg G, Orstavik RE, Uhlig T, et al. Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. Arthritis Rheum. 2002 Jul;46(7):1720-8.

1030. Haugeberg G, Orstavik RE, Uhlig T, et al. Comparison of ultrasound and X-ray absorptiometry bone measurements in a case control study of female rheumatoid arthritis patients and randomly selected subjects in the population. Osteoporos Int. 2003 Jun;14(4):312-9.

1031. Haugeberg G, Uhlig T, Falch JA, et al. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. Arthritis Rheum. 2000 Mar;43(3):522-30.

1032. Haugen M, Lien G, Flato B, et al. Young adults with juvenile arthritis in remission attain normal peak bone mass at the lumbar spine and forearm. Arthritis Rheum. 2000 Jul;43(7):1504-10.

1033. Haugen MA, Lien G, Flato B, et al. Minor impact of juvenile arthritis on nutritional status in young adult patients. Arthritis Rheum. 2002 Dec 15;47(6):623-9.

1034. Hauselmann HJ, Caravatti M, Seifert B, et al. Can collagen type II sustain a methotrexate-induced therapeutic effect in patients with long-standing rheumatoid arthritis? A double-blind, randomized trial. Br J Rheumatol. 1998 Oct;37(10):1110-7.

1035. Havel J, Aboutalebi S, Doughty L, et al. Development of systemic lupus erythematosus in a patient with rheumatoid arthritis following treatment conversion of infliximab to adalimumab. J Drugs Dermatol. 2008 Aug;7(8):796-8.

1036. Havelka S, Vavrincova P, Stepan J. Metabolic bone status in young women with juvenile chronic arthritis. J Rheumatol Suppl. 1993 Apr;37:14-6.

1037. Havelka S, Vavrincova P, Stepan J, et al. Metabolic bone status in young women with JCA. Acta Univ Carol [Med] (Praha). 1994;40(1-4):65-7.

1038. Hawboldt J, Bader M. Intramuscular methotrexate-induced aseptic meningitis. Ann Pharmacother. 2007 Nov;41(11):1906-11.

1039. Hayashi H, Fujimaki C, Daimon T, et al. Genetic polymorphisms in folate pathway enzymes as a possible marker for predicting the outcome of methotrexate therapy in Japanese patients with rheumatoid arthritis. J Clin Pharm Ther. 2009 Jun;34(3):355-61.

1040. He Y, Lu A, Zha Y, et al. Differential effect on symptoms treated with traditional Chinese medicine and western combination therapy in RA patients. Complement Ther Med. 2008 Aug;16(4):206-11.

1041. He Y, Lu A, Zha Y, et al. Correlations between symptoms as assessed in traditional chinese medicine (TCM) and ACR20 efficacy response: a comparison study in 396 patients with rheumatoid arthritis treated with TCM or Western medicine. J Clin Rheumatol. 2007 Dec;13(6):317-21.

1042. Healy PJ, Groves C, Chandramohan M, et al. MRI changes in psoriatic dactylitis--extent of pathology, relationship to tenderness and correlation with clinical indices. Rheumatology (Oxford). 2008 Jan;47(1):92-5.

1043. Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? J Rheumatol. 2007 Jun;34(6):1302-6.

1044. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum. 2008 May 15;59(5):686-91.

1045. Hebbar M, Hebbar-Savean K, Hachulla E, et al. Participation of cryoglobulinaemia in the severe peripheral neuropathies of primary Sjogren's syndrome. Ann Med Interne (Paris). 1995;146(4):235-8.

1046. Hedman M, Nilsson E, de la Torre B. Low blood and synovial fluid levels of sulpho-conjugated steroids in rheumatoid arthritis. Clin Exp Rheumatol. 1992 Jan-Feb;10(1):25-30.

1047. Heiberg MS, Koldingsnes W, Mikkelsen K, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008 Feb 15;59(2):234-40.

1048. Heiberg MS, Nordvag BY, Mikkelsen K, et al. The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. Arthritis Rheum. 2005 Aug;52(8):2506-12.

1049. Heikkila R, Aho K, Heliovaara M, et al. Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. Ann Rheum Dis. 1998 May;57(5):281-5.

1050. Helliwell PS, Taylor WJ. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs -- comparison of drugs and adverse reactions. J Rheumatol. 2008 Mar;35(3):472-6.

1051. Henke PK, Sukheepod P, Proctor MC, et al. Clinical relevance of peripheral vascular occlusive disease in patients with rheumatoid arthritis and systemic lupus erythematosus. J Vasc Surg. 2003 Jul;38(1):111-5.

1052. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol. 2004 Oct;31(10):2055-61.

1053. Hepburn AL, Mason JC, Davies KA. Expression of Fcgamma and complement receptors on peripheral blood monocytes in systemic lupus erythematosus and rheumatoid arthritis. Rheumatology (Oxford). 2004 May;43(5):547-54.

1054. Herenius MM, Hoving JL, Sluiter JK, et al. Improvement of work ability, quality of life, and fatigue in patients with rheumatoid arthritis treated with adalimumab. J Occup Environ Med. 2010 Jun;52(6):618-21.

1055. Hermann J, Mueller T, Fahrleitner A, et al. Early onset and effective inhibition of bone resorption in patients with rheumatoid arthritis treated with the tumour necrosis factor alpha antibody infliximab. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):473-6.

1056. Herrera-Esparza R, Avalos-Diaz E. Infliximab treatment in a case of rheumatoid scleromalacia perforans. Reumatismo. 2009 Jul-Sep;61(3):212-5.

1057. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum. 2006 May;54(5):1401-9.

1058. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis. 2008 Jun;67(6):815-22.

1059. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Radiographic progression and remission rates in early rheumatoid arthritis - MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Ann Rheum Dis. 2010 Oct;69(10):1789-95.

1060. Heytman M, Ahern MJ, Smith MD, et al. The longterm effect of pulsed corticosteroids on the efficacy and toxicity

of chrysotherapy in rheumatoid arthritis. J Rheumatol. 1994 Mar;21(3):435-41.

1061. Hider SL, Thomson W, Mack LF, et al. Polymorphisms within the adenosine receptor 2a gene are associated with adverse events in RA patients treated with MTX. Rheumatology (Oxford). 2008 Aug;47(8):1156-9.

1062. Higashida J, Wun T, Schmidt S, et al. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2005 Nov;32(11):2109-15.

1063. High WA, Muldrow ME, Fitzpatrick JE. Cutaneous lupus erythematosus induced by infliximab. J Am Acad Dermatol. 2005 Apr;52(4):E5.

1064. Hilliquin P, Houbaba H, Aissa J, et al. Correlations between PAF-acether and tumor necrosis factor in rheumatoid arthritis. Influence of parenteral corticosteroids. Scand J Rheumatol. 1995;24(3):169-73.

1065. Hirabayashi Y, Shimizu H, Kobayashi N, et al. Leflunomide-induced pneumonitis in a patient with rheumatoid arthritis. Intern Med. 2006;45(10):689-91.

1066. Hirano D, Nagashima M, Ogawa R, et al. Serum levels of interleukin 6 and stress related substances indicate mental stress condition in patients with rheumatoid arthritis. J Rheumatol. 2001 Mar;28(3):490-5.

1067. Hirano Y, Kishimoto H, Hagino H, et al. The change of bone mineral density in secondary osteoporosis and vertebral fracture incidence. J Bone Miner Metab. 1999;17(2):119-24.

1068. Hirano Y, Kojima T, Kanayama Y, et al. Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis. Clin Rheumatol 2010;29(5):495-500.

1069. Hirayama T, Danks L, Sabokbar A, et al. Osteoclast formation and activity in the pathogenesis of osteoporosis in rheumatoid arthritis. Rheumatology (Oxford). 2002 Nov;41(11):1232-9.

1070. Hirche D, Rubbert A, Lunau L, et al. Successful treatment of refractory rheumatoid arthritis-associated leg ulcerations with adalimumab. Br J Dermatol. 2005 May;152(5):1062-4.

1071. Hirohata M, Yasukawa Y, Ishida C, et al. Reversible cortical lesions in primary Sjogren's syndrome presenting with meningoencephalitis as an initial manifestation. J Neurol Sci. 2005 May 15;232(1-2):111-3.

1072. Hirohata S, Yanagida T, Tomita T, et al. Differential influences of bucillamine and methotrexate on the generation of fibroblast-like cells from bone marrow CD34+ cells of rheumatoid arthritis patients. Int Immunopharmacol. 2009 Jan;9(1):86-90.

1073. Hirose W, Nishikawa K, Hirose M, et al. Response of early active rheumatoid arthritis to tumor necrosis factor inhibitors: evaluation by magnetic resonance imaging. Mod Rheumatol. 2009;19(1):20-6.

1074. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis 2007;66(9):1184-9.

1075. Ho YV, Briganti EM, Duan Y, et al. Polymorphism of the vitamin D receptor gene and corticosteroid-related osteoporosis. Osteoporos Int. 1999;9(2):134-8.

1076. Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. Curr Med Res Opin. 2008 Feb;24(2):469-80.

1077. Hoff M, Kvien TK, Kalvesten J, et al. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis 2009;68(7):1171-6.

1078. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton Neurosci. 2008 Dec 5;143(1-2):58-67.

1079. Homsi S, Alexandrescu DT, Milojkovic N, et al. Diffuse large B-cell lymphoma with lung involvement in a psoriatic arthritis patient treated with methotrexate. Dermatol Online J. 2010;16(5):1.

1080. Hong BK, Kumar C, Marottoli RA. "MAC" attack. Am J Med. 2009 Dec;122(12):1096-8.

1081. Hong S, Kim T, Chung SH, et al. Recurrence after topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren's syndrome. J Ocul Pharmacol Ther. 2007 Feb;23(1):78-82.

1082. Hooper DR, Tarnopolsky MA, Baker SK. Lewis-Sumner syndrome associated with infliximab therapy in rheumatoid arthritis. Muscle Nerve. 2008 Oct;38(4):1318-25.

1083. Hoppe E, Masson C, Audran M, et al. Whipple's disease diagnosed during biological treatment for joint disease. Joint Bone Spine. 2010 Jul;77(4):335-9.

1084. Hornung N, Ellingsen T, Attermann J, et al. Patients with rheumatoid arthritis treated with methotrexate (MTX): concentrations of steady-state erythrocyte MTX correlate to plasma concentrations and clinical efficacy. J Rheumatol. 2008 Sep;35(9):1709-15.

1085. Hosaka K, Ryu J, Saitoh S, et al. The combined effects of anti-TNFalpha antibody and IL-1 receptor antagonist in human rheumatoid arthritis synovial membrane. Cytokine. 2005 Dec 21;32(6):263-9.

1086. Hoshida Y, Xu JX, Fujita S, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007 Feb;34(2):322-31.

1087. Hoshida Y, Yamamoto S, Wada N, et al. Infliximab-associated lymphoproliferative disorders. Int J Hematol. 2005 May;81(4):356-7.

1088. Hot A, Toh ML, Coppere B, et al. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore). 2010 Jan;89(1):37-46.

1089. Housden MM, Bell G, Heycock CR, et al. How to reduce morbidity and mortality from chest infections in rheumatoid arthritis. Clin Med. 2010 Aug;10(4):326-9.

1090. Houtman PM. Septic monarthritis due to Pasteurella multocida after a cat scratch in a patient with rheumatoid arthritis. Neth J Med. 1990 Apr;36(3-4):207-8.

1091. Hrycaj P, Korczowska I, Lacki JK. Severe Parkinson's disease in rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford). 2003 May;42(5):702-3.

1092. Hrycaj P, Lacki JK. Treatment resistant ankylosing spondylitis with peripheral joint involvement - a case for infliximab? J Rheumatol. 2003 Jan;30(1):204-6; author reply 6.

1093. Hsieh TY, Lan JL, Chen DY. Primary Sjogren's syndrome with protein-losing gastroenteropathy: report of two cases. J Formos Med Assoc. 2002 Jul;101(7):519-22.

1094. Hsu CT, Lin YT, Yang YH, et al. Factors affecting clinical and therapeutic outcomes of patients with juvenile rheumatoid arthritis. Scand J Rheumatol. 2004;33(5):312-7.

1095. Hsu PC, Lan JL, Hsieh TY, et al. Methotrexate pneumonitis in a patient with rheumatoid arthritis. J Microbiol Immunol Infect. 2003 Jun;36(2):137-40.

1096. Hu D, Bao C, Chen S, et al. A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. Rheumatol Int. 2009 Jan;29(3):297-303.

1097. Hu S, Cohen D, Murphy G, et al. Interstitial granulomatous dermatitis in a patient with rheumatoid arthritis on etanercept. Cutis. 2008 Apr;81(4):336-8.

1098. Huang F, Zhu J, Zhang L, et al. Response to one infusion predicts subsequent improvement as well as the rate of relapse of ankylosing spondylitis infused with three pulses of infliximab. Clin Rheumatol. 2007 Jun;26(6):920-6.

1099. Huang X, Gu NY, Fox KM, et al. Comparison of methods for measuring dose escalation of the subcutaneous TNF antagonists for rheumatoid arthritis patients treated in routine clinical practice. Curr Med Res Opin. 2010 Jul;26(7):1637-45.

1100. Hubscher O, Re R, Iotti R. Pulmonary rheumatoid nodules in an etanercept-treated patient. Arthritis Rheum. 2003 Jul;48(7):2077-8.

1101. Hughes LB, Criswell LA, Beasley TM, et al. Genetic risk factors for infection in patients with early rheumatoid arthritis. Genes Immun. 2004 Dec;5(8):641-7.

1102. Hurlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002 Oct 22;106(17):2184-7.

1103. Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009 Jul;68(7):1119-24.

1104. Husni ME, Maier AL, Mease PJ, et al. Etanercept in the treatment of adult patients with Still's disease. Arthritis Rheum. 2002 May;46(5):1171-6.

1105. Hussar DA. New drugs: abatacept, sorafenib, and nelarabine. J Am Pharm Assoc (Wash DC). 2006 Mar-Apr;46(2):300-3.

1106. Hutas G. Golimumab, a fully human monoclonal antibody against TNFalpha. Curr Opin Mol Ther. 2008 Aug;10(4):393-406.

1107. Huwait H, Wang B, Shustik C, et al. Composite cutaneous lymphoma in a patient with rheumatoid arthritis treated with methotrexate. Am J Dermatopathol. 2010 Feb;32(1):65-70.

1108. Hyon JY, Lee YJ, Yun PY. Management of ocular surface inflammation in Sjogren syndrome. Cornea. 2007 Oct;26(9 Suppl 1):S13-5.

1109. Hyrich KL, Deighton C, Watson KD, et al. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford) 2009;48(10):1323-7.

1110. Hyrich KL, Lunt M, Dixon WG, et al. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008 Jul;47(7):1000-5.

1111. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007;56(1):13-20.

1112. Iagnocco A, Filippucci E, Perella C, et al. Clinical and ultrasonographic monitoring of response to adalimumab treatment in rheumatoid arthritis. J Rheumatol. 2008 Jan;35(1):35-40.

1113. Iagnocco A, Perella C, Naredo E, et al. Etanercept in the treatment of rheumatoid arthritis: clinical follow-up over one year by ultrasonography. Clin Rheumatol. 2008 Apr;27(4):491-6.

1114. Iannone F, Trotta F, Montecucco C, et al. Etanercept maintains the clinical benefit achieved by infliximab in patients with rheumatoid arthritis who discontinued infliximab because of side effects. Ann Rheum Dis. 2007 Feb;66(2):249-52.

1115. Ichikawa T, Kageyama Y, Kobayashi H, et al. Etanercept treatment reduces the serum levels of interleukin-15 and interferon-gamma inducible protein-10 in patients with

rheumatoid arthritis. Rheumatol Int. 2010 Apr;30(6):725-30.

1116. Ideguchi H, Ohno S, Ishigatsubo Y. Risk factors associated with the cumulative survival of low-dose methotrexate in 273 Japanese patients with rheumatoid arthritis. J Clin Rheumatol. 2007 Apr;13(2):73-8.

1117. Iglesias J, Sathiraju S, Marik PE. Severe systemic inflammatory response syndrome with shock and ARDS resulting from Still's disease: clinical response with high-dose pulse methylprednisolone therapy. Chest. 1999 Jun;115(6):1738-40.

1118. Iikuni N, Inoue E, Tanaka E, et al. Low disease activity state with corticosteroid may not represent 'true' low disease activity state in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008 Apr;47(4):519-21.

1119. Ikegawa S, Urano F, Suzuki S, et al. Three cases of pustulotic arthro-osteitis associated with episcleritis. J Am Acad Dermatol. 1999 Nov;41(5 Pt 2):845-6.

1120. Ikonomidis I, Lekakis JP, Nikolaou M, et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation. 2008 May 20;117(20):2662-9.

1121. Ikonomidis I, Tzortzis S, Lekakis J, et al. Lowering interleukin-1 activity with anakinra improves myocardial deformation in rheumatoid arthritis. Heart. 2009 Sep;95(18):1502-7.

1122. Ilias I, Mastorakos G, Mavrikakis M, et al. Thyroid disease associated with rheumatoid arthritis is not adequately screened with a sensitive chemiluminescence thyrotrophin assay. Acta Med Austriaca. 1999;26(1):26-8.

1123. Imaizumi K, Sugishita M, Usui M, et al. Pulmonary infectious complications associated with anti-TNFalpha therapy (infliximab) for rheumatoid arthritis. Intern Med. 2006;45(10):685-8.

1124. Imrich R, Rovensky J, Malis F, et al. Low levels of dehydroepiandrosterone sulphate in plasma, and reduced sympathoadrenal response to hypoglycaemia in premenopausal women with rheumatoid arthritis. Ann Rheum Dis. 2005 Feb;64(2):202-6.

1125. Imrich R, Rovensky J, Zlnay M, et al. Hypothalamic-pituitary-adrenal axis function in ankylosing spondylitis. Ann Rheum Dis. 2004 Jun;63(6):671-4.

1126. Imrich R, Vigas M, Rovensky J, et al. Adrenal plasma steroid relations in glucocorticoid-naive premenopausal rheumatoid arthritis patients during insulin-induced hypoglycemia test compared to matched normal control females. Endocr Regul. 2009 Apr;43(2):65-73.

1127. Imrich R, Vlcek M, Aldag JC, et al. An endocrinologist's view on relative adrenocortical insufficiency in rheumatoid arthritis. Ann N Y Acad Sci. 2010 Apr;1193(1):134-8.

1128. Inanc N, Direskeneli H. Serious infections under treatment with TNF-alpha antagonists compared to traditional DMARDs in patients with rheumatoid arthritis. Rheumatol Int. 2006 Nov;27(1):67-71.

1129. Infante R, Lahita RG. Rheumatoid arthritis. New disease-modifying and anti-inflammatory drugs. Geriatrics. 2000 Mar;55(3):30-2, 5-6, 9-40.

1130. Ingegnoli F, Fantini F, Favalli EG, et al. Inflammatory and prothrombotic biomarkers in patients with rheumatoid arthritis: effects of tumor necrosis factor-alpha blockade. J Autoimmun. 2008 Sep;31(2):175-9.

1131. Ingegnoli F, Fantini F, Griffini S, et al. Anti-tumor necrosis factor alpha therapy normalizes fibrinolysis impairment in patients with active rheumatoid arthritis. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):254-7.

1132. Ingegnoli F, Sciascera A, Galbiati V, et al. Bronchus-associated lymphoid tissue lymphoma in a patient with primary Sjogren's syndrome. Rheumatol Int. 2008 Dec;29(2):207-9.

1133. Inokuma S, Sato T, Sagawa A, et al. Proposals for leflunomide use to avoid lung injury in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18(5):442-6.

1134. Inoue K, Takano H, Yanagisawa R, et al. Effects of tumor necrosis factor-alpha inhibitors on lung lesions with rheumatoid arthritis. Chest. 2003 Jul;124(1):413-4; author reply 4.

1135. Inoue S, Hashiguchi M, Kawai S, et al. Erythrocyte methotrexate-polyglutamate assay using fluorescence polarization immunoassay technique: application to the monitoring of patients with rheumatoid arthritis. Yakugaku Zasshi. 2009 Aug;129(8):1001-5.

1136. Inoue S, Hashiguchi M, Takagi K, et al. Preliminary study to identify the predictive factors for the response to methotrexate therapy in patients with rheumatoid arthritis. Yakugaku Zasshi. 2009 Jul;129(7):843-9.

1137. Iobst W, Ingraham K. Sneddon-Wilkinson disease in a patient with rheumatoid arthritis. Arthritis Rheum. 2005 Dec;52(12):3771.

1138. Ippolito JA, Palmer L, Spector S, et al. Bronchiolitis obliterans organizing pneumonia and rheumatoid arthritis. Semin Arthritis Rheum. 1993 Aug;23(1):70-8.

1139. Irwin LR, Beckett R, Suman RK. Steroid injection for carpal tunnel syndrome. J Hand Surg [Br]. 1996 Jun;21(3):355-7.

1140. Ishiguro T, Takayanagi N, Kurashima K, et al. Development of sarcoidosis during etanercept therapy. Intern Med. 2008;47(11):1021-5.

1141. Ishii H, Nagashima M, Tanno M, et al. Does being easily moved to tears as a response to psychological stress reflect response to treatment and the general prognosis in patients with rheumatoid arthritis? Clin Exp Rheumatol. 2003 Sep-Oct;21(5):611-6.

1142. Ishikawa Y, Yukawa N, Ohmura K, et al. Etanercept-induced anti-Jo-1-antibody-positive polymyositis in a patient with rheumatoid arthritis: a case report and review of the literature. Clin Rheumatol. 2010 May;29(5):563-6.

1143. Itonaga I, Fujikawa Y, Sabokbar A, et al. Rheumatoid arthritis synovial macrophage-osteoclast differentiation is osteoprotegerin ligand-dependent. J Pathol. 2000 Sep;192(1):97-104.

1144. Iwamoto N, Kawakami A, Fujikawa K, et al. Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population. Mod Rheumatol 2009;19(5):488-92.

1145. Iwatani M, Inoue E, Nakamura T, et al. Efficacy profile of bucillamine in rheumatoid arthritis patients in a large observational cohort study, IORRA. Mod Rheumatol 2006;16(6):376-80.

1146. Iyer S, Yamauchi P, Lowe NJ. Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. Br J Dermatol. 2002 Jan;146(1):118-21.

1147. Izumi A. Varicella zoster virus infection in patients taking the TNF-alpha inhibitor, etanercept: coincidence or causal? Hawaii Med J. 2009 Dec;68(11):277-8.

1148. Izumi M, Eguchi K, Nakamura H, et al. Corticosteroid irrigation of parotid gland for treatment of xerostomia in patients with Sjogren's syndrome. Ann Rheum Dis. 1998 Aug;57(8):464-9.

1149. Jacobs JW, Geenen R, Evers AW, et al. Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis. Ann Rheum Dis. 2001 Jan;60(1):61-4.

1150. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8.

1151. James HM, Gillis D, Hissaria P, et al. Common polymorphisms in the folate pathway predict efficacy of combination

regimens containing methotrexate and sulfasalazine in early rheumatoid arthritis. J Rheumatol. 2008 Apr;35(4):562-71.

1152. Jamnitski A, Visman IM, Peters MJ, et al. Beneficial effect of 1-year etanercept treatment on the lipid profile in responding patients with rheumatoid arthritis: the ETRA study. Ann Rheum Dis. 2010 Nov;69(11):1929-33.

1153. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-alpha therapy-induced vasculitis: case series. J Rheumatol. 2003 Oct;30(10):2287-91.

1154. Jenkins EA, Walker-Bone KE, Wood A, et al. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. Scand J Rheumatol. 1999;28(3):152-6.

1155. Jenks KA, Stamp LK, O'Donnell JL, et al. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol. 2007 Nov;34(11):2201-3.

1156. Jeurissen ME, Boerbooms AM, van de Putte LB, et al. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial. Arthritis Rheum. 1991 Aug;34(8):961-72.

1157. Jia J, Wang Q, Zhang T, et al. Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases. J Tradit Chin Med. 2006 Mar;26(1):26-8.

1158. Jian X, Guo G, Ruan Y, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of two cases. Cutan Ocul Toxicol. 2008;27(1):5-9.

1159. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum. 2000 May;43(5):1001-9.

1160. Jimenez FG, Colmenero JD, Irigoyen MV. Reactivation of brucellosis after treatment with infliximab in a patient with rheumatoid arthritis. J Infect. 2005 May;50(4):370-1.

1161. Jin T, Bokarewa M, Amu S, et al. Impact of short-term therapies with biologics on prothrombotic biomarkers in rheumatoid arthritis. Clin Exp Rheumatol. 2009 May-Jun;27(3):491-4.

1162. Jinno S, Pulido S, Pien BC. First reported United States case of Legionella pneumophila serogroup 1 pneumonia in a patient receiving anti-tumor necrosis factor-alpha therapy. Hawaii Med J. 2009 Jun;68(5):109-12.

1163. Jo SJ, Park JY, Yoon HS, et al. Case of acrodermatitis continua accompanied by psoriatic arthritis. J Dermatol. 2006 Nov;33(11):787-91.

1164. Jobanputra P, Amarasena R, Maggs F, et al. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: A case series from a local surveillance of serious adverse events. BMC Musculoskelet Disord. 2008;9:48.

1165. Johns KR, Littlejohn GO. The safety and efficacy of cyclosporine (Neoral) in rheumatoid arthritis. J Rheumatol. 1999 Oct;26(10):2110-3.

1166. Johnsen AK, Schiff MH, Mease PJ, et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. J Rheumatol. 2006 Apr;33(4):659-64.

1167. Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, et al. Hypofunction of the stress axis in Sjogren's syndrome. J Rheumatol. 1998 Aug;25(8):1508-14.

1168. Jois RN, Masding A, Somerville M, et al. Rituximab therapy in patients with resistant rheumatoid arthritis: real-life experience. Rheumatology (Oxford). 2007 Jun;46(6):980-2.

1169. Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. Expert Rev Clin Immunol 2010;6(2):189-95.

1170. Jones SM, Bhalla AK. Osteoporosis in rheumatoid arthritis. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):557-62.

1171. Jonsdottir T, Forslid J, van Vollenhoven A, et al. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. Ann Rheum Dis. 2004 Sep;63(9):1075-8.

1172. Jorgensen C, Bressot N, Bologna C, et al. Dysregulation of the hypothalamo-pituitary axis in rheumatoid arthritis. J Rheumatol. 1995 Oct;22(10):1829-33.

1173. Josefina M, Ana CJ, Ariel V, et al. Development of pseudogout during etanercept treatment. J Clin Rheumatol. 2007 Jun;13(3):177.

1174. Josipovic B. Levels of dehydroepiandrosterone sulfate in female patients with early stage of rheumatoid arthritis. Ann N Y Acad Sci. 1999 Jun 22;876:145-7.

1175. Josipovic B. Adrenal secretion of cortisol in patients with short-lasting rheumatoid arthritis. Z Rheumatol. 2000;59 Suppl 2:II/136.

1176. Ju JH, Kim SI, Lee JH, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. Arthritis Rheum 2007;56(6):2094-6.

1177. Juillard-Condat B, Constantin A, Cambon-Thomsen A, et al. Impact of etanercept on the costs of rheumatoid arthritis (RA): results from a French observational study. Joint Bone Spine. 2008 Jan;75(1):25-8.

1178. Julkunen H. Hormone replacement therapy in women with rheumatic diseases. Scand J Rheumatol. 2000;29(3):146-53.

1179. Jung N, Hellmann M, Hoheisel R, et al. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). Clin Rheumatol. 2010 Oct;29(10):1169-73.

1180. Kaaja R, Julkunen H, Ammala P, et al. Congenital heart block: successful prophylactic treatment with intravenous gamma globulin and corticosteroid therapy. Am J Obstet Gynecol. 1991 Nov;165(5 Pt 1):1333-4.

1181. Kadar J, Petrovicz E. Adult-onset Still's disease. Best Pract Res Clin Rheumatol. 2004 Oct;18(5):663-76.

1182. Kadota J, Kusano S, Kawakami K, et al. Usual interstitial pneumonia associated with primary Sjogren's syndrome. Chest. 1995 Dec;108(6):1756-8.

1183. Kageyama Y, Kobayashi H, Kato N. Infliximab treatment reduces the serum levels of interleukin-23 in patients with rheumatoid arthritis. Mod Rheumatol. 2009;19(6):657-62.

1184. Kageyama Y, Kobayashi H, Kato N, et al. Etanercept reduces the serum levels of macrophage chemotactic protein-1 in patients with rheumatoid arthritis. Mod Rheumatol. 2009;19(4):372-8.

1185. Kageyama Y, Takahashi M, Ichikawa T, et al. Reduction of oxidative stress marker levels by anti-TNF-alpha antibody, infliximab, in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):73-80.

1186. Kageyama Y, Torikai E, Nagano A. Anti-tumor necrosis factor-alpha antibody treatment reduces serum CXCL16 levels in patients with rheumatoid arthritis. Rheumatol Int. 2007 Mar;27(5):467-72.

1187. Kahan A, Modder G, Menkes CJ, et al. 169Erbium-citrate synoviorthesis after failure of local corticosteroid injections to treat rheumatoid arthritis-affected finger joints. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):722-6.

1188. Kahn KL, MacLean CH, Liu H, et al. Application of explicit process of care measurement to rheumatoid arthritis: Moving from evidence to practice. Arthritis Rheum. 2006 Dec 15;55(6):884-91.

1189. Kahn P, Weiss M, Imundo LF, et al. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology. 2006 May;113(5):864 e1-2.

1190. Kaipiainen-Seppanen O, Leino M. Recurrent uveitis in a patient with juvenile spondyloarthropathy associated with tumour necrosis factor alpha inhibitors. Ann Rheum Dis. 2003 Jan;62(1):88-9.

1191. Kaiser J. Clinical trials. Gene transfer an unlikely contributor to patient's death. Science. 2007 Dec 7;318(5856):1535.

1192. Kaiser J. Gene therapy. Questions remain on cause of death in arthritis trial. Science. 2007 Sep 21;317(5845):1665.

1193. Kaiser MJ, Bozonnat MC, Jorgensen C, et al. Effect of etanercept on tenosynovitis and nodules in rheumatoid arthritis. Arthritis Rheum. 2002 Feb;46(2):559-60.

1194. Kaiser MJ, Sany J. Efficacy of infliximab (Remicade) in the treatment of spondyloarthropathies. two case reports. Joint Bone Spine. 2001 Dec;68(6):525-7.

1195. Kakkassery V, Mergler S, Pleyer U. Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment. Curr Eye Res. 2010 Aug;35(8):751-6.

1196. Kalden JR, Nusslein HG, Wollenhaupt J, et al. Combination treatment with infliximab and leflunomide in patients with active rheumatoid arthritis: safety and efficacy in an open-label clinical trial. Clin Exp Rheumatol. 2008 Sep-Oct;26(5):834-40.

1197. Kalla AA, Bewerunge L, Langley A, et al. Trabecular bone density in premenopausal rheumatoid arthritis patients. S Afr Med J. 2002 Jan;92(1):62-8.

1198. Kalla AA, Brown GM, Meyers OL. Nutritional status in rheumatoid arthritis. Effects of disease activity, corticosteroid therapy and functional impairment. S Afr Med J. 1992 Dec;82(6):411-4.

1199. Kalla AA, Meyers OL, Kotze TJ, et al. Corticosteroid therapy and bone mass--comparison of rheumatoid arthritis and systemic lupus erythematosus. S Afr Med J. 1994 Jul;84(7):404-9.

1200. Kalyoncu U, Karadag O, Akdogan A, et al. Pneumocystis carinii pneumonia in a rheumatoid arthritis patient treated with adalimumab. Scand J Infect Dis. 2007;39(5):475-8.

1201. Kamal KM, Madhavan SS, Hornsby JA, et al. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. Joint Bone Spine. 2006 Dec;73(6):718-24.

1202. Kamarashev J, Lor P, Forster A, et al. Generalised pustular psoriasis induced by cyclosporin a withdrawal responding to the tumour necrosis factor alpha inhibitor etanercept. Dermatology. 2002;205(2):213-6.

1203. Kameda H, Okuyama A, Tamaru J, et al. Lymphomatoid granulomatosis and diffuse alveolar damage associated with methotrexate therapy in a patient with rheumatoid arthritis. Clin Rheumatol. 2007 Sep;26(9):1585-9.

1204. Kameda T, Dobashi H, Kittaka K, et al. A case of rheumatoid arthritis complicated by demyelination in both cerebral cortex and spinal cord during etanercept therapy. Mod Rheumatol. 2008;18(4):399-402.

1205. Kamili QA, Menter A. Atypical presentation of histoplasmosis in a patient with psoriasis and psoriatic arthritis on infliximab therapy. J Drugs Dermatol. 2010 Jan;9(1):57-60.

1206. Kamper AM, Malbrain M, Zachee P, et al. Parvovirus infection causing red cell aplasia and leukopenia in rheumatoid arthritis. Clin Rheumatol. 1994 Mar;13(1):129-31.

1207. Kanakoudi-Tsakalidou F, Tzimouli V, Pratsidou-Gertsi P, et al. The significance of persistent newly developed autoantibodies in JIA patients under long-term anti-TNF treatment. Cytokine. 2008 Jun;42(3):293-7.

1208. Kanbe K, Inoue K, Inoue Y, et al. Histological analysis of synovium in cases of effect attenuation associated with infliximab therapy in rheumatoid arthritis. Clin Rheumatol. 2008 Jun;27(6):777-81.

1209. Kanbe K, Inoue K, Inoue Y, et al. Histological changes in bone marrow after treatment of infliximab for rheumatoid arthritis. Clin Rheumatol. 2008 Apr;27(4):497-501.

1210. Kaneko K, Nonomura Y, Watanabe K, et al. Infected abdominal aortic aneurysm caused by nontyphoid Salmonella in an immunocompromised patient with rheumatoid arthritis. J Infect Chemother. 2009 Oct;15(5):312-5.

1211. Kaneko Y, Suwa A, Ikeda Y, et al. Pneumocystis jiroveci pneumonia associated with low-dose methotrexate treatment for rheumatoid arthritis: report of two cases and review of the literature. Mod Rheumatol. 2006;16(1):36-8.

1212. Kanekura T, Terasaki K, Higashi Y, et al. Improvement of adult Still's disease with granulocyte and monocyte adsorption apheresis. Clin Exp Dermatol. 2004 Jul;29(4):410-2.

1213. Kang CP, Lee KW, Yoo DH, et al. The influence of a polymorphism at position -857 of the tumour necrosis factor alpha gene on clinical response to etanercept therapy in rheumatoid arthritis. Rheumatology (Oxford). 2005 Apr;44(4):547-52.

1214. Kang MJ, Kim MS, Choi EH, et al. Adenoviral pneumonia during etanercept treatment in a patient with rheumatoid arthritis. Korean J Intern Med. 2007 Mar;22(1):63-6.

1215. Kang MJ, Lee YH, Lee J. Etanercept-induced systemic lupus erythematosus in a patient with rheumatoid arthritis. J Korean Med Sci. 2006 Oct;21(5):946-9.

1216. Kanik KS, Chrousos GP, Schumacher HR, et al. Adrenocorticotropin, glucocorticoid, and androgen secretion in patients with new onset synovitis/rheumatoid arthritis: relations with indices of inflammation. J Clin Endocrinol Metab. 2000 Apr;85(4):1461-6.

1217. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int. 2005 Jun;16(6):581-9.

1218. Kao CD, Liao KK. A flow chart proposed for early diagnosis of cryptococcal infection as a cause of stroke. Acta Neurol Taiwan. 2009 Mar;18(1):30-3.

1219. Kapetanovic MC, Larsson L, Truedsson L, et al. Predictors of infusion reactions during infliximab treatment in patients with arthritis. Arthritis Res Ther. 2006;8(4):R131.

1220. Kapetanovic MC, Saxne T, Sjoholm A, et al. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology (Oxford). 2006 Jan;45(1):106-11.

1221. Kaplan MJ. Do tumor-necrosis-factor inhibitors prevent first cardiovascular events in patients with rheumatoid arthritis? Nat Clin Pract Rheumatol. 2005 Dec;1(2):74-5.

1222. Kaplan RM, Groessl EJ, Sengupta N, et al. Comparison of measured utility scores and imputed scores from the SF-36 in patients with rheumatoid arthritis. Med Care. 2005 Jan;43(1):79-87.

1223. Karabacakoglu A, Karakose S, Ozerbil OM, et al. Fluoroscopy-guided intraarticular corticosteroid injection into the sacroiliac joints in patients with ankylosing spondylitis. Acta Radiol. 2002 Jul;43(4):425-7.

1224. Karaca-Mandic P, Joyce GF, Goldman DP, et al. Cost sharing, family health care burden, and the use of specialty drugs for rheumatoid arthritis. Health Serv Res. 2010 Oct;45(5 Pt 1):1227-50.

1225. Karagiannis S, Papaioannou D, Goulas S, et al. Intestinal tuberculosis in a patient on infliximab treatment. Gastrointest Endosc. 2008 Jun;67(7):1178-9; discussion 9.

1226. Karanikolas G, Charalambopoulos D, Vaiopoulos G, et al. Adjunctive anakinra in patients with active rheumatoid arthritis despite methotrexate, or leflunomide, or cyclosporin-A monotherapy: a 48-week, comparative, prospective study. Rheumatology (Oxford) 2008;47(9):1384-8.

1227. Karie S, Gandjbakhch F, Janus N, et al. Kidney disease in RA patients: prevalence and implication on RA-related drugs management: the MATRIX study. Rheumatology (Oxford). 2008 Mar;47(3):350-4.

1228. Karlsson JA, Kristensen LE, Kapetanovic MC, et al. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford) 2008;47(4):507-13.

1229. Karstila KL, Rantalaiho VM, Mustonen JT, et al. Renal safety of initial combination versus single DMARD therapy in patients with early rheumatoid arthritis: an 11-year experience from the FIN-RACo Trial. Clin Exp Rheumatol 2010;28(1):73-8.

1230. Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. Ann Rheum Dis. 2006 Mar;65(3):405-7.

1231. Kasama T, Wakabayashi K, Odai T, et al. Effects of low-dose mizoribine pulse therapy in combination with methotrexate in rheumatoid arthritis patients with an insufficient response to methotrexate. Mod Rheumatol. 2009;19(4):395-400.

1232. Kasser UR, Gleissner C, Dehne F, et al. Risk for periodontal disease in patients with longstanding rheumatoid arthritis. Arthritis Rheum. 1997 Dec;40(12):2248-51.

1233. Kassimos D, Choy EH, Grossman AB, et al. Endogenous opioid tone in patients with rheumatoid arthritis. Br J Rheumatol. 1996 May;35(5):436-40.

1234. Kastanek L. Using anakinra for adult rheumatoid arthritis. Nurse Pract. 2002 Apr;27(4):62-5.

1235. Kastbom A, Bratt J, Ernestam S, et al. Fcgamma receptor type IIIA genotype and response to tumor necrosis factor alpha-blocking agents in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Feb;56(2):448-52.

1236. Kastrinaki MC, Sidiropoulos P, Roche S, et al. Functional, molecular and proteomic characterisation of bone marrow mesenchymal stem cells in rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):741-9.

1237. Kasukawa R, Shio K, Kanno Y, et al. Doppler ultrasound measurements of knee joint synovitis in rheumatoid arthritis patients treated with infliximab. Mod Rheumatol. 2007;17(5):376-9.

1238. Katayama K, Matsuno T. Effects of bisphosphonates on fracture incidence and bone metabolism in rheumatoid arthritis patients in general practice taking long-term corticosteroid therapy: a retrospective study. Clin Drug Investig. 2008;28(3):149-58.

1239. Katayama K, Matsuno T. Long-term efficacy of leflunomide on disease activity and inhibition of joint damage: retrospective comparison with methotrexate for Japanese rheumatoid arthritis patients. Mod Rheumatol. 2009;19(5):513-21.

1240. Katayama Y, Kohriyama K, Kirizuka K, et al. Sjogren's syndrome complicated with autoimmune hepatitis and antiphospholipid antibody syndrome. Intern Med. 2000 Jan;39(1):73-6.

1241. Katchamart W, Trudeau J, Phumethum V, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2010;4:CD008495.

1242. Kato T, Hoshi K, Sekijima Y, et al. Rheumatoid meningitis: an autopsy report and review of the literature. Clin Rheumatol. 2003 Dec;22(6):475-80.

1243. Kato T, Kiire A, Yamagata H, et al. Hypersensitivity reaction against influenza vaccine in a patient with rheumatoid arthritis

after the initiation of etanercept injections. Mod Rheumatol. 2006;16(5):327-9.

1244. Katoulis AC, Kanelleas A, Zambacos G, et al. Development of two primary malignant melanomas after treatment with adalimumab: a case report and review of the possible link between biological therapy with TNF-alpha antagonists and melanocytic proliferation. Dermatology. 2010 Aug;221(1):9-12.

1245. Katz JA, Antoni C, Keenan GF, et al. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol. 2004 Dec;99(12):2385-92.

1246. Katz P, Yelin E, Patel V, et al. Patient-reported outcomes following biologic therapy in a sample of adults with rheumatoid arthritis recruited from community-based rheumatologists. Arthritis Rheum. 2009 May 15;61(5):593-9.

1247. Kaufman I, Schwartz D, Caspi D, et al. Sjogren's syndrome - not just Sicca: renal involvement in Sjogren's syndrome. Scand J Rheumatol. 2008 May-Jun;37(3):213-8.

1248. Kaufman KR. Etanercept, anticytokines and mania. Int Clin Psychopharmacol. 2005 Jul;20(4):239-41.

1249. Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. Dig Dis Sci. 2007 Jun;52(6):1481-4.

1250. Kaur PP, Chan VC, Berney SN. Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. J Clin Rheumatol. 2007 Apr;13(2):79-80.

1251. Kaur PP, Chan VC, Berney SN. Histological evaluation of liver in two rheumatoid arthritis patients with chronic hepatitis B and C treated with TNF-alpha blockade: case reports. Clin Rheumatol. 2008 Aug;27(8):1069-71.

1252. Kaur PP, Derk CT, Chatterji M, et al. Septic arthritis caused by Actinobacillus ureae in a patient with rheumatoid arthritis receiving anti-tumor necrosis factor-alpha therapy. J Rheumatol. 2004 Aug;31(8):1663-5.

1253. Kaushik P, Cooper ES, Banda VR, et al. Bronchiolitis obliterans with organizing pneumonia in rheumatoid arthritis--a fatal case and short review of literature. Rheumatol Int. 2005 Jun;25(5):391-3.

1254. Kavalar R, Skok P, Kramberger KG. Phlegmonous gastritis in a patient with rheumatoid arthritis. Wien Klin Wochenschr. 2005 May;117(9-10):364-8.

1255. Kavanaugh A, Antoni C, Krueger GG, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis. 2006 Apr;65(4):471-7.

1256. Kavanaugh A, Klareskog L, van der Heijde D, et al. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis 2008;67(10):1444-7.

1257. Kavanaugh A, Lee SJ, Weng HH, et al. Patient-derived joint counts are a potential alternative for determining Disease Activity Score. J Rheumatol 2010;37(5):1035-41.

1258. Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60(4):976-86.

1259. Kavanaugh A, Rosengren S, Lee SJ, et al. Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: clinical and synovial biomarker results. Ann Rheum Dis. 2008 Mar;67(3):402-8.

1260. Kavanaugh A, Smolen JS, Emery P, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum 2009;61(11):1592-600.

1261. Kavanaugh A, St Clair EW, McCune WJ, et al. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol. 2000 Apr;27(4):841-50.

1262. Kawano M, Okada K, Muramoto H, et al. Simultaneous, clonally identical T cell expansion in tonsil and synovium in a patient with rheumatoid arthritis and chronic tonsillitis. Arthritis Rheum. 2003 Sep;48(9):2483-8.

1263. Kawano M, Seya T, Koni I, et al. Elevated serum levels of soluble membrane cofactor protein (CD46, MCP) in patients with systemic lupus erythematosus (SLE). Clin Exp Immunol. 1999 Jun;116(3):542-6.

1264. Kawashima M, Miossec P. Effect of treatment of rheumatoid arthritis with infliximab on IFN gamma, IL4, T-bet, and GATA-3 expression: link with improvement of systemic inflammation and disease activity. Ann Rheum Dis. 2005 Mar;64(3):415-8.

1265. Kawashima N, Shindo R, Kohno M. Primary Sjogren's syndrome with subcortical dementia. Intern Med. 1993 Jul;32(7):561-4.

1266. Kawashiri SY, Kawakami A, Iwamoto N, et al. Proinflammatory cytokines synergistically enhance the production of chemokine ligand 20 (CCL20) from rheumatoid fibroblast-like synovial cells in vitro and serum CCL20 is reduced in vivo by biologic disease-modifying antirheumatic drugs. J Rheumatol. 2009 Nov;36(11):2397-402.

1267. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58(4):964-75.

1268. Kay LJ, Holland TM, Platt PN. Stress fractures in rheumatoid arthritis: a case series and case-control study. Ann Rheum Dis. 2004 Dec;63(12):1690-2.

1269. Kaya S, Kaptanoglu E, Elden H, et al. Coexistence of familial Mediterranean fever and juvenile idiopathic arthritis with osteoporosis successfully treated with etanercept. Intern Med. 2010;49(6):619-22.

1270. Kazkaz L, Marotte H, Hamwi M, et al. Rheumatoid arthritis and genetic markers in Syrian and French populations: different effect of the shared epitope. Ann Rheum Dis. 2007 Feb;66(2):195-201.

1271. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001 Oct 11;345(15):1098-104.

1272. Kedzia A, Boldys A, Krysiak R, et al. Potential benefit of paracetamol administration in adult-onset Still's disease. Pol Arch Med Wewn. 2009 Sep;119(9):595-8.

1273. Kekow J, Welte T, Kellner U, et al. Development of rheumatoid nodules during anti-tumor necrosis factor alpha therapy with etanercept. Arthritis Rheum. 2002 Mar;46(3):843-4.

1274. Kelaidi C, Tulliez M, Lecoq-Lafon C, et al. Long-term remission of an EBV-positive B cell lymphoproliferative disorder associated with rheumatoid arthritis under methotrexate with anti-CD20 monoclonal antibody (Rituximab) monotherapy. Leukemia. 2002 Oct;16(10):2173-4.

1275. Kelesidis T, Salhotra A, Fleisher J, et al. Listeria endocarditis in a patient with psoriatic arthritis on infliximab: are biologic agents as treatment for inflammatory arthritis increasing the incidence of Listeria infections? J Infect. 2010 May;60(5):386-96.

1276. Kellner H, Bornholdt K, Hein G. Leflunomide in the treatment of patients with early rheumatoid arthritis--results of a prospective non-interventional study. Clin Rheumatol. 2010 Aug;29(8):913-20.

1277. Kelsey JL, Lamster IB. Influence of musculoskeletal conditions on oral health among older adults. Am J Public Health. 2008 Jul;98(7):1177-83.

1278. Kemp E, Nielsen H, Petersen LJ, et al. Newer immunomodulating drugs in rheumatoid arthritis may precipitate glomerulonephritis. Clin Nephrol. 2001 Jan;55(1):87-8.

1279. Kennedy JW, Wong LK, Kalantarian B, et al. An unusual presentation of methotrexate-induced B-cell lymphoma of the metacarpophalangeal joint: a case report and literature review. J Hand Surg Am. 2006 Sep;31(7):1193-6.

1280. Kent PD, Davis JM, 3rd, Davis MD, et al. Bullous skin lesions following infliximab infusion in a patient with rheumatoid arthritis. Arthritis Rheum. 2002 Aug;46(8):2257-8; author reply 9.

1281. Keren Z, Braun-Moscovici Y, Markovits D, et al. Depletion of B lymphocytes in rheumatoid arthritis patients modifies IL-8-anti-IL-8 autoantibody network. Clin Immunol. 2009 Oct;133(1):108-16.

1282. Kesteman T, Yombi JC, Gigi J, et al. Listeria infections associated with infliximab: case reports. Clin Rheumatol. 2007 Dec;26(12):2173-5.

1283. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2008;59(6):785-93.

1284. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis 2009;68(2):216-21.

1285. Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum. 2007 Dec;56(12):3896-908.

1286. Keystone E, Freundlich B, Schiff M, et al. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol 2009;36(3):522-31.

1287. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58(11):3319-29.

1288. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68(6):789-96.

1289. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11.

1290. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.

1291. Khan IH, Krishnan VV, Ziman M, et al. A comparison of multiplex suspension array large-panel kits for profiling cytokines and chemokines in rheumatoid arthritis patients. Cytometry B Clin Cytom. 2009 May;76(3):159-68.

1292. Khanna M, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. J Dermatolog Treat. 2003 Dec;14(4):229-32.

1293. Kho LK, Kermode AG. Leflunomide-induced peripheral neuropathy. J Clin Neurosci. 2007 Feb;14(2):179-81.

1294. Khosla P, Aroaa N, Jain S. Tubercular pyomyositis in a case of rheumatoid arthritis being treated with infliximab. Int J Rheum Dis. 2010 Feb 1;13(1):82-5.

1295. Kielhorn A, Porter D, Diamantopoulos A, et al. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin. 2008 Sep;24(9):2639-50.

1296. Kiely PD, Johnson DM. Infliximab and leflunomide combination therapy in rheumatoid arthritis: an open-label study. Rheumatology (Oxford). 2002 Jun;41(6):631-7.

1297. Kietz DA, Pepmueller PH, Moore TL. Clinical response to etanercept in polyarticular course juvenile rheumatoid arthritis. J Rheumatol. 2001 Feb;28(2):360-2.

1298. Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two year period. Ann Rheum Dis. 2002 Feb;61(2):171-3.

1299. Kievit W, Adang EM, Fransen J, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis 2008;67(9):1229-34.

1300. Kievit W, Fransen J, Oerlemans AJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8.

1301. Kim SK, Jun JB, El-Sohemy A, et al. Cost-effectiveness analysis of MTHFR polymorphism screening by polymerase chain reaction in Korean patients with rheumatoid arthritis receiving methotrexate. J Rheumatol. 2006 Jul;33(7):1266-74.

1302. Kim TH, Stone M, Payne U, et al. Cartilage biomarkers in ankylosing spondylitis: relationship to clinical variables and treatment response. Arthritis Rheum. 2005 Mar;52(3):885-91.

1303. Kimball AB, Jackson JM, Sobell JM, et al. Reductions in healthcare resource utilization in psoriatic arthritis patients receiving etanercept therapy: results from the educate trial. J Drugs Dermatol. 2007 Mar;6(3):299-306.

1304. Kimel M, Cifaldi M, Chen N, et al. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35(2):206-15.

1305. Kimura E, Oga S, Pereira RM. Comparative study of the pharmacokinetics of MTX in juvenile idiopathic arthritis patients receiving long-term MTX monotherapy or MTX plus chloroquine. J Clin Pharm Ther. 2007 Dec;32(6):579-84.

1306. Kimura Y, Fieldston E, Devries-Vandervlugt B, et al. High dose, alternate day corticosteroids for systemic onset juvenile rheumatoid arthritis. J Rheumatol. 2000 Aug;27(8):2018-24.

1307. Kimura Y, Pinho P, Walco G, et al. Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis. J Rheumatol. 2005 May;32(5):935-42.

1308. Kinder A, Stephens S, Mortimer N, et al. Severe herpes zoster after infliximab infusion. Postgrad Med J. 2004 Jan;80(939):26.

1309. Kinder AJ, Edwards J, Samanta A, et al. Pregnancy in a rheumatoid arthritis patient on infliximab and methotrexate. Rheumatology (Oxford). 2004 Sep;43(9):1195-6.

1310. Kinjo M, Setoguchi S, Solomon DH. Bone mineral density in older adult patients with rheumatoid arthritis: an analysis of NHANES III. J Rheumatol. 2007 Oct;34(10):1971-5.

1311. Kiortsis DN, Mavridis AK, Vasakos S, et al. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2005 May;64(5):765-6.

1312. Kiortsis DN, Mavridis AK, Vasakos S, et al. Effects of infliximab treatment on lipoprotein profile in patients with

rheumatoid arthritis and ankylosing spondylitis. J Rheumatol. 2006 May;33(5):921-3.

1313. Kirchgatterer A, Weber T, Hinterreiter M, et al. Haemorrhagic colitis due to Escherichia coli O103:H2 associated with infliximab therapy in a patient with rheumatoid arthritis. Rheumatology (Oxford). 2002 Mar;41(3):355-6.

1314. Kirino Y, Takeno M, Murakami S, et al. Tumor necrosis factor alpha acceleration of inflammatory responses by down-regulating heme oxygenase 1 in human peripheral monocytes. Arthritis Rheum. 2007 Feb;56(2):464-75.

1315. Kirshen C, Kanigsberg N. Alopecia areata following adalimumab. J Cutan Med Surg. 2009 Jan-Feb;13(1):48-50.

1316. Kirwan J. Early rheumatoid arthritis: combination therapy with disease-modifying antirheumatic drugs and low-dose glucocorticoids? Nat Clin Pract Rheumatol. 2006 Apr;2(4):182-3.

1317. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995 Jul 20;333(3):142-6.

1318. Klaasen R, Thurlings RM, Wijbrandts CA, et al. The relationship between synovial lymphocyte aggregates and the clinical response to infliximab in rheumatoid arthritis: a prospective study. Arthritis Rheum. 2009 Nov;60(11):3217-24.

1319. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81.

1320. Klein A, Buskila D, Gladman D, et al. Cortisol catabolism by lymphocytes of patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol. 1990 Jan;17(1):30-3.

1321. Klein R, Rosenbach M, Kim EJ, et al. Tumor necrosis factor inhibitor-associated dermatomyositis. Arch Dermatol. 2010 Jul;146(7):780-4.

1322. Klimiuk PA, Kita J, Chwiecko J, et al. The changes in serum chemokines following leflunomide therapy in patients with rheumatoid arthritis. Clin Rheumatol. 2009 Jan;28(1):17-21.

1323. Klimiuk PA, Sierakowski S, Domyslawska I, et al. Effect of repeated infliximab therapy on serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with rheumatoid arthritis. J Rheumatol. 2004 Feb;31(2):238-42.

1324. Klimiuk PA, Sierakowski S, Domyslawska I, et al. Regulation of serum chemokines following infliximab therapy in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):529-33.

1325. Klimiuk PA, Sierakowski S, Domyslawska I, et al. Effect of etanercept on serum levels of soluble cell adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and vascular endothelial growth factor in patients with rheumatoid arthritis. Scand J Rheumatol. 2009 Nov-Dec;38(6):439-44.

1326. Kneitz C, Suerbaum S, Beer M, et al. Exacerbation of Whipple's disease associated with infliximab treatment. Scand J Rheumatol. 2005 Mar-Apr;34(2):148-51.

1327. Kneitz C, Wilhelm M, Tony HP. Improvement of refractory rheumatoid arthritis after depletion of B cells. Scand J Rheumatol. 2004;33(2):82-6.

1328. Kobak S. Osteonecrosis and monoarticular rheumatoid arthritis treated with intra-articular adalimumab. Mod Rheumatol. 2008;18(3):290-2.

1329. Kobak S, Deveci H. Retinopathy due to antimalarial drugs in patients with connective tissue diseases: are they so innocent? A single center retrospective study. Int J Rheum Dis. 2010 Aug;13(3):e11-5.

1330. Kobayashi K, Okamoto Y, Inoue H, et al. Leukoencephalopathy with cognitive impairment following tocilizumab for the treatment of rheumatoid arthritis (RA). Intern Med. 2009;48(15):1307-9.

1331. Kobelt G, Andlin-Sobocki P, Brophy S, et al. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology (Oxford). 2004 Sep;43(9):1158-66.

1332. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis. 2004 Jan;63(1):4-10.

1333. Kobelt G, Jonsson L, Young A, et al. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology (Oxford). 2003 Feb;42(2):326-35.

1334. Kobelt G, Lindgren P, Singh A, et al. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis. 2005 Aug;64(8):1174-9.

1335. Kobelt G, Sobocki P, Sieper J, et al. Comparison of the cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in the United Kingdom based on two different clinical trials. Int J Technol Assess Health Care. 2007 Summer;23(3):368-75.

1336. Koch AE, Kunkel SL, Chensue SW, et al. Expression of interleukin-1 and interleukin-1 receptor antagonist by human rheumatoid synovial tissue macrophages. Clin Immunol Immunopathol. 1992 Oct;65(1):23-9.

1337. Kocharla L, Taylor J, Weiler T, et al. Monitoring methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol. 2009 Dec;36(12):2813-8.

1338. Koczan D, Drynda S, Hecker M, et al. Molecular discrimination of responders and nonresponders to anti-TNF alpha therapy in rheumatoid arthritis by etanercept. Arthritis Res Ther. 2008;10(3):R50.

1339. Koffeman EC, Genovese M, Amox D, et al. Epitope-specific immunotherapy of rheumatoid arthritis: clinical responsiveness occurs with immune deviation and relies on the expression of a cluster of molecules associated with T cell tolerance in a double-blind, placebo-controlled, pilot phase II trial. Arthritis Rheum. 2009 Nov;60(11):3207-16.

1340. Kogure T, Tatsumi T, Sato H, et al. Traditional herbal medicines (Kampo) for patients with rheumatoid arthritis receiving concomitant methotrexate: a preliminary study. Altern Ther Health Med. 2010 Jan-Feb;16(1):46-51.

1341. Koh ET. New disease modifying agents in adult rheumatoid arthritis. Ann Acad Med Singapore. 2001 Mar;30(2):170-3.

1342. Koh MS, Leng PH, Eng P, et al. An unusual cause of pulmonary haemorrhage in a patient with rheumatoid arthritis. Ann Acad Med Singapore. 2004 May;33(3):365-7.

1343. Kohno M, Tsutsumi A, Matsui H, et al. Interleukin-17 gene expression in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18(1):15-22.

1344. Koide R, Isoo A, Ishii K, et al. Rheumatoid leptomeningitis: rare complication of rheumatoid arthritis. Clin Rheumatol. 2009 Sep;28(9):1117-9.

1345. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009 May;36(5):898-906.

1346. Kojima M, Itoh H, Hirabayashi K, et al. Methtrexate-associated lymphoproliferative disorders. A clinicopathological study of 13 Japanese cases. Pathol Res Pract. 2006;202(9):679-85.

1347. Kokkinos A, Iliopoulos A, Greka P, et al. Successful treatment of refractory adult-onset Still's disease with infliximab. A prospective, non-comparative series of four patients. Clin Rheumatol. 2004 Feb;23(1):45-9.

1348. Kolokotronis A, Avramidou E, Zaraboukas T, et al. Oral tuberculosis associated with a treatment with anti-rheumatic drugs. J Oral Pathol Med. 2006 Feb;35(2):123-5.

1349. Komai N, Morita Y, Sakuta T, et al. Anti-tumor necrosis factor therapy increases serum adiponectin levels with the improvement of endothelial dysfunction in patients with rheumatoid arthritis. Mod Rheumatol. 2007;17(5):385-90.

1350. Komano Y, Harigai M, Koike R, et al. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum. 2009 Mar 15;61(3):305-12.

1351. Komatsuda A, Okamoto Y, Hatakeyama T, et al. Sulfasalazine-induced hypersensitivity syndrome and hemophagocytic syndrome associated with reactivation of Epstein-Barr virus. Clin Rheumatol. 2008 Mar;27(3):395-7.

1352. Komatsuda A, Wakui H, Nimura T, et al. Reversible infliximab-related lymphoproliferative disorder associated with Epstein-Barr virus in a patient with rheumatoid arthritis. Mod Rheumatol. 2008;18(3):315-8.

1353. Konai MS, Vilar Furtado RN, Dos Santos MF, et al. Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients: a randomized double-blind controlled study. Clin Exp Rheumatol. 2009 Mar-Apr;27(2):214-21.

1354. Kong XD, Xu D, Zhang W, et al. Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. Clin Rheumatol. 2010 Sep;29(9):1015-9.

1355. Kononoff A, Heiskanen J, Lumiaho J, et al. Intensifying treatment of rheumatoid arthritis with combinations of traditional disease-modifying anti-rheumatic drugs among patients with persistent disease did not reduce the need for large joint surgery. Scand J Rheumatol. 2007 Nov-Dec;36(6):424-7.

1356. Konttinen YT, Ramsay H, Hietanen J, et al. Otitis externa sicca/fibrotising external otitis (FEO) as a complication of Sjogren's syndrome. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):746-8.

1357. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. Drugs. 2008;68(3):319-37.

1358. Kopp S, Alstergren P, Ernestam S, et al. Interleukin-1beta influences the effect of infliximab on temporomandibular joint pain in rheumatoid arthritis. Scand J Rheumatol. 2006 May-Jun;35(3):182-8.

1359. Kopp S, Alstergren P, Ernestam S, et al. Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs. 2005;180(1):22-30.

1360. Korah S, Kuriakose T. Optical coherence tomography in a patient with chloroquine-induced maculopathy. Indian J Ophthalmol. 2008 Nov-Dec;56(6):511-3.

1361. Korczowska I, Olewicz-Gawlik A, Trefler J, et al. Does low-dose and short-term glucocorticoids treatment increase the risk of osteoporosis in rheumatoid arthritis female patients? Clin Rheumatol. 2008 May;27(5):565-72.

1362. Korkmaz C, Kasifoglu T, Yasar B. Acceleration of left-ventricular diastolic dysfunction and pulmonary hypertension after TNF-alpha blocker. Ann Pharmacother. 2005 Jun;39(6):1138-9.

1363. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care. 2002 Mar;8(3):231-40.

1364. Kotaniemi K, Penttila H. Intraocular lens implantation in patients with juvenile idiopathic arthritis-associated uveitis. Ophthalmic Res. 2006;38(6):318-23.

1365. Kotha P, McGreevy MJ, Kotha A, et al. Early deaths with thrombolytic therapy for acute myocardial infarction in corticosteroid-dependent rheumatoid arthritis. Clin Cardiol. 1998 Nov;21(11):853-6.

1366. Kothapalli R, Nyland SB, Kusmartseva I, et al. Constitutive production of proinflammatory cytokines RANTES, MIP-1beta and IL-18 characterizes LGL leukemia. Int J Oncol. 2005 Feb;26(2):529-35.

1367. Kotter I, Wacker A, Koch S, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum. 2007 Dec;37(3):189-97.

1368. Kovacs A, Szekeres E, Berek L, et al. Relationship between the occurrence of anti-SSA, anti-SSB autoantibodies and HLA class II alleles from the aspect of in vitro inhibitory effect of glucocorticosteroid on the antibody-dependent cellular cytotoxicity in patients with primary Sjogren's syndrome. Acta Microbiol Immunol Hung. 2000;47(4):421-31.

1369. Kozaci DL, Chernajovsky Y, Chikanza IC. The differential expression of corticosteroid receptor isoforms in corticosteroid-resistant and -sensitive patients with rheumatoid arthritis. Rheumatology (Oxford). 2007 Apr;46(4):579-85.

1370. Kozora E, Laudenslager M, Lemieux A, et al. Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. J Int Neuropsychol Soc. 2001 Sep;7(6):745-54.

1371. Kraetsch HG, Antoni C, Kalden JR, et al. Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii55-7.

1372. Kramer N, Chuzhin Y, Kaufman LD, et al. Methotrexate pneumonitis after initiation of infliximab therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Dec 15;47(6):670-1.

1373. Kreitzer T, Saoud A. Bacillary angiomatosis following the use of long-term methotrexate therapy: a case report. W V Med J. 2006 Jan-Feb;102(1):317-8.

1374. Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum 2010;62(4):917-28.

1375. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009 Jul;60(7):1895-905.

1376. Kremer JM, Genant HK, Moreland LW, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum. 2008 Apr;58(4):953-63.

1377. Kremer JM, Habros JS, Kolba KS, et al. Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a six-month, open-label study. Arthritis Rheum. 2003 Oct;48(10):2763-8.

1378. Kremer JM, Weinblatt ME, Bankhurst AD, et al. Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. Arthritis Rheum. 2003 Jun;48(6):1493-9.

1379. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003;349(20):1907-15.

1380. Kremers HM, Nicola P, Crowson CS, et al. Therapeutic strategies in rheumatoid arthritis over a 40-year period. J Rheumatol. 2004 Dec;31(12):2366-73.

1381. Kreuter A, Rose C, Zillikens D, et al. Bullous rheumatoid neutrophilic dermatosis.

J Am Acad Dermatol. 2005 May;52(5):916-8.

1382. Krishnamurthy R, Dincer HE, Whittemore D. Strongyloides stercoralis hyperinfection in a patient with rheumatoid arthritis after anti-TNF-alpha therapy. J Clin Rheumatol. 2007 Jun;13(3):150-2.

1383. Kriss TC, Kriss VM. Neck pain. Primary care work-up of acute and chronic symptoms. Geriatrics. 2000 Jan;55(1):47-8, 51-4, 7.

1384. Kristensen LE, Gulfe A, Saxne T, et al. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis 2008;67(3):364-9.

1385. Kristensen LE, Kapetanovic MC, Gulfe A, et al. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008 Apr;47(4):495-9.

1386. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum. 2006 Feb;54(2):600-6.

1387. Kristensen LE, Saxne T, Nilsson JA, et al. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8(6):R174.

1388. Kritikos K, Haritatos E, Tsigkos S, et al. An atypical presentation of visceral leishmaniasis infection in a patient with rheumatoid arthritis treated with infliximab. J Clin Rheumatol. 2010 Jan;16(1):38-9.

1389. Kroesen S, Widmer AF, Tyndall A, et al. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003 May;42(5):617-21.

1390. Kroger H, Honkanen R, Saarikoski S, et al. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis--a population based study. Ann Rheum Dis. 1994 Jan;53(1):18-23.

1391. Kroot EJ, van Gestel AM, Swinkels HL, et al. Chronic comorbidity in patients with early rheumatoid arthritis: a descriptive study. J Rheumatol. 2001 Jul;28(7):1511-7.

1392. Kruithof E, Baeten D, De Rycke L, et al. Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. Arthritis Res Ther. 2005;7(3):R569-80.

1393. Kruize AA, Hene RJ, van der Heide A, et al. Long-term followup of patients with Sjogren's syndrome. Arthritis Rheum. 1996 Feb;39(2):297-303.

1394. Kucharekova M, Winnepenninckx V, Frank J, et al. Generalized pustulosis induced by adalimumab in a patient with rheumatoid arthritis - a therapeutic challenge. Int J Dermatol. 2008 Nov;47 Suppl 1:25-8.

1395. Kucharz EJ, Gozdzik J, Kopec M, et al. A single infusion of infliximab increases the serum endostatin level in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):273-4.

1396. Kuek A, Hazleman BL, Gaston JH, et al. Successful treatment of refractory polyarticular juvenile idiopathic arthritis with rituximab. Rheumatology (Oxford). 2006 Nov;45(11):1448-9.

1397. Kumar D, Bouldin TW, Berger RG. A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab. Arthritis Rheum. 2010 Nov;62(11):3191-5.

1398. Kumar N, Sandroni P, Steensma DP, et al. Polyradiculopathy due to methotrexate-induced ebv-associated lymphoproliferative disorder. Neurology. 2008 Nov 11;71(20):1644-5.

1399. Kumar S, Gupta N, Jhamb R, et al. Celiac disease: association with adult-onset Still's

disease: apropos of a clinical case. Indian J Med Sci. 2007 Jul;61(7):414-7.

1400. Kumari R, Uppal SS. Prolonged remission in adult-onset Still's disease with etanercept. Clin Rheumatol. 2006 Feb;25(1):106-8.

1401. Kumeda Y, Inaba M, Goto H, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum. 2002 Jun;46(6):1489-97.

1402. Kumon Y, Kakigi A, Sugiura T. Clinical images: Otalgia, an unusual complication of Sjogren's syndrome. Arthritis Rheum. 2009 Aug;60(8):2542.

1403. Kurasawa M, Kotani K, Kurasawa G, et al. Adult-onset Still's disease in a patient over 80 years old successfully treated with low-dose methotrexate therapy. Age Ageing. 2007 Jan;36(1):104-6.

1404. Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis 2010;69(7):1298-304.

1405. Kurmann PT, Van Linthoudt D, So AK. Miller-Fisher syndrome in a patient with rheumatoid arthritis treated with adalimumab. Clin Rheumatol. 2009 Jan;28(1):93-4.

1406. Kuroda T, Otaki Y, Sato H, et al. A case of AA amyloidosis associated with rheumatoid arthritis effectively treated with Infliximab. Rheumatol Int. 2008 Sep;28(11):1155-9.

1407. Kuroda T, Wada Y, Kobayashi D, et al. Effective anti-TNF-alpha therapy can induce rapid resolution and sustained decrease of gastroduodenal mucosal amyloid deposits in reactive amyloidosis associated with rheumatoid arthritis. J Rheumatol. 2009 Nov;36(11):2409-15.

1408. Kurschat P, Rubbert A, Poswig A, et al. Treatment of psoriatic arthritis with etanercept. J Am Acad Dermatol. 2001 Jun;44(6):1052.

1409. Kurtais Y, Tur BS, Elhan AH, et al. Hypothalamic-pituitary-adrenal hormonal responses to exercise stress test in patients with rheumatoid arthritis compared to healthy controls. J Rheumatol. 2006 Aug;33(8):1530-7.

1410. Kuruvilla J, Leitch HA, Vickars LM, et al. Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. Eur J Haematol. 2003 Nov;71(5):396-8.

1411. Kur-Zalewska J, Swarowska-Knap J, Tlustochowicz W. Neurological disorders with demyelinating brain white matter lesions in a patient with rheumatoid arthritis treated with etanercept. Pol Arch Med Wewn. 2008 Apr;118(4):234-7.

1412. Kurzawski M, Pawlik A, Safranow K, et al. 677C>T and 1298A>C MTHFR polymorphisms affect methotrexate treatment outcome in rheumatoid arthritis. Pharmacogenomics. 2007 Nov;8(11):1551-9.

1413. Kusabe T, Waguri-Nagaya Y, Tanikawa T, et al. The inhibitory effect of disease-modifying anti-rheumatic drugs and steroids on gliostatin/platelet-derived endothelial cell growth factor production in human fibroblast-like synoviocytes. Rheumatol Int. 2005 Oct;25(8):625-30.

1414. Kuuliala A, Nissinen R, Kautiainen H, et al. Low circulating soluble interleukin 2 receptor level predicts rapid response in patients with refractory rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2006 Jan;65(1):26-9.

1415. Kuzmanova SI. Arthroscopic treatment of rheumatoid synovitis. Folia Med (Plovdiv). 2003;45(3):48-54.

1416. Kvalvik AG, Aadland HA, Hoyeraal HM, et al. Were the patterns of treatment for rheumatoid arthritis during 1977-1992 consistent with modern clinical guidelines? Scand J Rheumatol. 2001;30(2):61-8.

1417. Kvalvik AG, Lefsaker L, Dyvik S, et al. Anti-tumor necrosis factor-alpha therapy in the ordinary clinical setting: Three-year effectiveness in patients with rheumatoid

arthritis. Joint Bone Spine. 2007 Dec;74(6):606-11.

1418. Kvien TK, Haugeberg G, Uhlig T, et al. Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis. Ann Rheum Dis. 2000 Oct;59(10):805-11.

1419. Kwak JJ, Chang JE, Lee J, et al. Chronic eosinophilic pneumonia associated with an initiation of rheumatoid arthritis. Clin Rheumatol. 2003 Sep;22(3):240-3.

1420. Kwon HH, Baek SH, Park SH. Miliary tuberculosis and necrotizing tuberculous fasciitis--an unusual coexistence in a rheumatoid arthritis patient. Int J Rheum Dis. 2010 May;13(2):171-4.

1421. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.

1422. La Montagna G, Cacciapuoti F, Buono R, et al. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diab Vasc Dis Res. 2007 Jun;4(2):130-5.

1423. La Montagna G, Valentini G. Listeria monocytogenes meningitis in a patient receiving etanercept for Still's disease. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):121.

1424. Laas K, Peltomaa R, Kautiainen H, et al. Clinical impact of switching from infliximab to etanercept in patients with rheumatoid arthritis. Clin Rheumatol. 2008 Jul;27(7):927-32.

1425. Labbe P, Hardouin P. Epidemiology and optimal management of polymyalgia rheumatica. Drugs Aging. 1998 Aug;13(2):109-18.

1426. Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 2008;59(8):1074-81.

1427. Lacroix BD, Lovern MR, Stockis A, et al. A pharmacodynamic Markov mixed-effects model for determining the effect of exposure to certolizumab pegol on the ACR20 score in patients with rheumatoid arthritis. Clin Pharmacol Ther. 2009 Oct;86(4):387-95.

1428. Lafforgue P, Monjanel-Mouterde S, Durand A, et al. Is there an interaction between low doses of corticosteroids and methotrexate in patients with rheumatoid arthritis? A pharmacokinetic study in 33 patients. J Rheumatol. 1993 Feb;20(2):263-7.

1429. Lafforgue P, Toussirot E, Bille F, et al. Astasia-abasia revealing a primary Sjogren's syndrome. Clin Rheumatol. 1993 Jun;12(2):261-4.

1430. Lagana B, Picchianti Diamanti A, Ferlito C, et al. Imaging progression despite clinical remission in early rheumatoid arthritis patients after etanercept interruption. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):447-54.

1431. Lahiff C, Khiaron OB, Nolan N, et al. Pneumocystis carinii pneumonia in a patient on etanercept for psoriatic arthritis. Ir J Med Sci. 2007 Dec;176(4):309-11.

1432. Lahiri M, Teng GG. A case of refractory adult-onset Still's disease treated with anakinra. Int J Rheum Dis. 2010 Aug;13(3):e36-41.

1433. Lahners WJ, Hardten DR, Lindstrom RL. Peripheral keratitis following laser in situ keratomileusis. J Refract Surg. 2003 Nov-Dec;19(6):671-5.

1434. Lai TY, Ngai JW, Chan WM, et al. Visual field and multifocal electroretinography and their correlations in patients on hydroxychloroquine therapy. Doc Ophthalmol. 2006 May;112(3):177-87.

1435. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. Gastroenterology. 2002 Oct;123(4):1006-12.

1436. Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology. 2003 Feb;124(2):288-92.

1437. Laine M, Porola P, Udby L, et al. Low salivary dehydroepiandrosterone and androgen-regulated cysteine-rich secretory protein 3 levels in Sjogren's syndrome. Arthritis Rheum. 2007 Aug;56(8):2575-84.

1438. Lainez B, Fernandez-Real JM, Romero X, et al. Identification and characterization of a novel spliced variant that encodes human soluble tumor necrosis factor receptor 2. Int Immunol. 2004 Jan;16(1):169-77.

1439. Lakatos P, Nagy Z, Kiss L, et al. Prevention of corticosteroid-induced osteoporosis by alfacalcidol. Z Rheumatol. 2000;59 Suppl 1:48-52.

1440. Lam A, Toma W, Schlesinger N. Mycobacterium marinum arthritis mimicking rheumatoid arthritis. J Rheumatol. 2006 Apr;33(4):817-9.

1441. Lamazza L, Guerra F, Pezza M, et al. The use of etanercept as a non-surgical treatment for temporomandibular joint psoriatric arthritis: a case report. Aust Dent J. 2009 Jun;54(2):161-5.

1442. Lan JL, Chou SJ, Chen DY, et al. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004 Aug;103(8):618-23.

1443. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002 Feb;46(2):347-56.

1444. Lane NE, Pressman AR, Star VL, et al. Rheumatoid arthritis and bone mineral density in elderly women. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1995 Feb;10(2):257-63.

1445. Lange U, Boss B, Teichmann J, et al. Bone mineral density and biochemical markers of bone metabolism in late onset rheumatoid arthritis and polymyalgia rheumatica--a prospective study on the influence of glucocorticoid therapy. Z Rheumatol. 2000;59 Suppl 2:II/137-41.

1446. Lange U, Teichmann J, Muller-Ladner U, et al. Increase in bone mineral density of patients with rheumatoid arthritis treated with anti-TNF-alpha antibody: a prospective open-label pilot study. Rheumatology (Oxford). 2005 Dec;44(12):1546-8.

1447. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res. 2003;23(4):119-28.

1448. Lassoued S, Sire S, Farny M, et al. Pulmonary aspergillosis in a patient with rheumatoid arthritis treated by etanercept. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):267-8.

1449. Lassoued S, Zabraniecki L, Marin F, et al. Toxoplasmic chorioretinitis and antitumor necrosis factor treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2007 Feb;36(4):262-3.

1450. Laurberg TB, Frystyk J, Ellingsen T, et al. Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol. 2009 Sep;36(9):1885-91.

1451. Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B cell-activating factor of the TNF family (BAFF) after rituximab treatment: insights into a new regulating system of BAFF production. Ann Rheum Dis. 2007 May;66(5):700-3.

1452. Lazzerini PE, Acampa M, Hammoud M, et al. Arrhythmic risk during acute infusion of infliximab: a prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis. J Rheumatol. 2008 Oct;35(10):1958-65.

1453. Le Loet X, Nordstrom D, Rodriguez M, et al. Effect of anakinra on functional status in patients with active rheumatoid arthritis receiving concomitant therapy with traditional disease modifying antirheumatic drugs: evidence from the OMEGA Trial. J Rheumatol. 2008 Aug;35(8):1538-44.

1454. Leandro MJ, Cambridge G, Ehrenstein MR, et al. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Feb;54(2):613-20.

1455. Leandro MJ, Cooper N, Cambridge G, et al. Bone marrow B-lineage cells in patients with rheumatoid arthritis following rituximab therapy. Rheumatology (Oxford). 2007 Jan;46(1):29-36.

1456. Leandro MJ, Edwards JC, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. Ann Rheum Dis. 2002 Oct;61(10):883-8.

1457. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol. 2005 Jul;141(7):861-4.

1458. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford). 2005 Feb;44(2):157-63.

1459. Ledwich LJ, Clarke K. Screening and treatment of glucocorticoid-induced osteoporosis in rheumatoid arthritis patients in an urban multispecialty practice. J Clin Rheumatol. 2009 Mar;15(2):61-4.

1460. Lee CK, Lee EY, Cho YS, et al. Increased expression of glucocorticoid receptor beta messenger RNA in patients with ankylosing spondylitis. Korean J Intern Med. 2005 Jun;20(2):146-51.

1461. Lee EB, Shin KC, Lee YJ, et al. 188Re-tin-colloid as a new therapeutic agent for rheumatoid arthritis. Nucl Med Commun. 2003 Jun;24(6):689-96.

1462. Lee H, Kimko HC, Rogge M, et al. Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. Clin Pharmacol Ther. 2003 Apr;73(4):348-65.

1463. Lee HJ, Waller RD, Stebbings S, et al. The effects of an orally administered probiotic on sulfasalazine metabolism in individuals with rheumatoid arthritis: a preliminary study. Int J Rheum Dis. 2010 Feb 1;13(1):48-54.

1464. Lee J, Noh JW, Hwang JW, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. Clin Rheumatol. 2010 Oct;29(10):1149-54.

1465. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum. 2002 Oct;46(10):2565-70.

1466. Lee SS, Park YW, Park JJ, et al. Combination treatment with leflunomide and methotrexate for patients with active rheumatoid arthritis. Scand J Rheumatol. 2009 Jan-Feb;38(1):11-4.

1467. Lee YC, Cui J, Costenbader KH, et al. Investigation of candidate polymorphisms and disease activity in rheumatoid arthritis patients on methotrexate. Rheumatology (Oxford). 2009 Jun;48(6):613-7.

1468. Lee YH, Choi SJ, Ji JD, et al. No association of polymorphisms of the CTLA-4 exon 1(+49) and promoter(-318) genes with rheumatoid arthritis in the Korean population. Scand J Rheumatol. 2002;31(5):266-70.

1469. Lee YH, Kim HJ, Rho YH, et al. Interleukin-1 receptor antagonist gene polymorphism and rheumatoid arthritis. Rheumatol Int. 2004 May;24(3):133-6.

1470. Lehman TJ. Clinical trials for the treatment of systemic onset juvenile rheumatoid arthritis-juvenile idiopathic arthritis. Curr Rheumatol Rep. 2000 Aug;2(4):313-5.

1471. Lehnen M, Franckson T, Knab J, et al. Successful infliximab therapy of psoriasis vulgaris and psoriatic arthritis in a patient with cirrhosis. Br J Dermatol. 2005 Jul;153(1):212-4.

1472. Lehnen M, Franckson T, Korber A, et al. Etanercept therapy of psoriatic arthritis in a patient with liver cirrhosis. Acta Derm Venereol. 2005;85(4):351-2.

1473. Leitch R, Walker SE, Hillard AE. The rheumatoid knee before and after arthrocentesis and prednisolone injection: evaluation by Gd-enhanced MRI. Clin Rheumatol. 1996 Jul;15(4):358-66.

1474. Lems WF, Gerrits MI, Jacobs JW, et al. Changes in (markers of) bone metabolism during high dose corticosteroid pulse treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 1996 May;55(5):288-93.

1475. Lems WF, Jacobs JW, van den Brink HR, et al. Transient decrease in osteocalcin and markers of type 1 collagen turnover during high-dose corticosteroid pulse therapy in rheumatoid arthritis. Br J Rheumatol. 1993 Sep;32(9):787-9.

1476. Lems WF, Jahangier ZN, Jacobs JW, et al. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol. 1995 May-Jun;13(3):293-7.

1477. Lems WF, Jahangier ZN, Raymakers JA, et al. Methods to score vertebral deformities in patients with rheumatoid arthritis. Br J Rheumatol. 1997 Feb;36(2):220-4.

1478. Leonardou A, Giali S, Daoussis D, et al. Moraxella catarrhalis-induced septic arthritis of a prosthetic knee joint in a patient with rheumatoid arthritis treated with anakinra: comment on the article by Schiff et al. Arthritis Rheum. 2005 Apr;52(4):1337; author reply 8.

1479. Lequerre T, Gauthier-Jauneau AC, Bansard C, et al. Gene profiling in white blood cells predicts infliximab responsiveness in rheumatoid arthritis. Arthritis Res Ther. 2006;8(4):R105.

1480. Lequerre T, Jouen F, Brazier M, et al. Autoantibodies, metalloproteinases and bone markers in rheumatoid arthritis patients are unable to predict their responses to infliximab. Rheumatology (Oxford). 2007 Mar;46(3):446-53.

1481. Lequerre T, Quartier P, Rosellini D, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis. 2008 Mar;67(3):302-8.

1482. Lesnik A, Bolivar J, Morel J, et al. On the AJR viewbox. Pseudotumoral colonic tuberculosis complicating rheumatoid arthritis treated with a tumor necrosis factor antagonist. AJR Am J Roentgenol. 2006 Jun;186(6):1799-800.

1483. Levalampi T, Korpela M, Vuolteenaho K, et al. Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons for discontinuation of treatment. Scand J Rheumatol. 2008 Jan-Feb;37(1):6-12.

1484. Levy Y, Uziel Y, Zandman GG, et al. Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. Ann Rheum Dis. 2003 Dec;62(12):1221-3.

1485. Lewiecki EM. Denosumab for joints and bones. Curr Rheumatol Rep. 2009 Jul;11(3):196-201.

1486. Li Gobbi F, Benucci M, Del Rosso A. Pneumonitis caused by Legionella pneumoniae in a patient with rheumatoid arthritis treated with anti-TNF-alpha therapy (infliximab). J Clin Rheumatol. 2005 Apr;11(2):119-20.

1487. Li JY, Lai PH, Lam HC, et al. Hypertrophic cranial pachymeningitis and lymphocytic hypophysitis in Sjogren's syndrome. Neurology. 1999 Jan 15;52(2):420-3.

1488. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. Value Health 2010;13(6):805-12.

1489. Li St, Kaur PP, Berney SN. Effects of methotrexate use in a patient with rheumatoid arthritis and multiple sclerosis. J Clin Rheumatol. 2008 Aug;14(4):241-2.

1490. Li T, Gignac M, Wells G, et al. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther 2008;30(4):734-48.

1491. Lian EC, Tzakis AG, Andrews D. Response of factor V inhibitor to rituximab in a patient who received liver transplantation for primary biliary cirrhosis. Am J Hematol. 2004 Dec;77(4):363-5.

1492. Liberopoulos EN, Drosos AA, Elisaf MS. Exacerbation of tuberculosis enteritis after treatment with infliximab. Am J Med. 2002 Nov;113(7):615.

1493. Lieberman-Maran L, Orzano IM, Passero MA, et al. Bronchiectasis in rheumatoid arthritis: report of four cases and a review of the literature--implications for management with biologic response modifiers. Semin Arthritis Rheum. 2006 Jun;35(6):379-87.

1494. Lin YT, Tsai MJ, Wang LH, et al. Efficacy and safety of methotrexate therapy for juvenile rheumatoid arthritis. J Formos Med Assoc. 2000 Aug;99(8):623-9.

1495. Linardaki G, Katsarou O, Ioannidou P, et al. Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. J Rheumatol. 2007 Jun;34(6):1353-5.

1496. Lindberg J, af Klint E, Catrina AI, et al. Effect of infliximab on mRNA expression profiles in synovial tissue of rheumatoid arthritis patients. Arthritis Res Ther. 2006;8(6):R179.

1497. Lindberg J, Wijbrandts CA, van Baarsen LG, et al. The gene expression profile in the synovium as a predictor of the clinical response to infliximab treatment in rheumatoid arthritis. PLoS One. 2010;5(6):e11310.

1498. Linde L, Hetland ML, Ostergaard M. Drug survival and reasons for discontinuation of intramuscular methotrexate: a study of 212 consecutive patients switching from oral methotrexate. Scand J Rheumatol. 2006 Mar-Apr;35(2):102-6.

1499. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int J Technol Assess Health Care. 2009 Apr;25(2):181-9.

1500. Lindsay K, Fraser AD, Layton A, et al. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology (Oxford). 2009 May;48(5):569-72.

1501. Ling S, Lewanczuk RZ, Russell AS, et al. Influence of controlled rheumatoid arthritis on the action and disposition of verapamil: focus on infliximab. J Clin Pharmacol. 2009 Mar;49(3):301-11.

1502. Lingg GM, Soltesz I, Kessler S, et al. Insufficiency and stress fractures of the long bones occurring in patients with rheumatoid arthritis and other inflammatory diseases, with a contribution on the possibilities of computed tomography. Eur J Radiol. 1997 Dec;26(1):54-63.

1503. Liote H, Liote F, Lenique F, et al. Adult-onset Still's disease revealed by a pleuropericarditis. Eur Respir J. 1990 Oct;3(9):1064-6.

1504. Liou LB. Serum and in vitro production of IL-1 receptor antagonist correlate with C-reactive protein levels in newly diagnosed, untreated lupus patients. Clin Exp Rheumatol. 2001 Sep-Oct;19(5):515-23.

1505. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602.

1506. Lisbona MP, Maymo J, Perich J, et al. Rapid reduction in tenosynovitis of the wrist and

fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. Ann Rheum Dis 2010;69(6):1117-22.

1507. Lisbona MP, Maymo J, Perich J, et al. Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. J Rheumatol 2008;35(3):394-7.

1508. Listing J, Brandt J, Rudwaleit M, et al. Impact of anti-tumour necrosis factor alpha treatment on admissions to hospital and days of sick leave in patients with ankylosing spondylitis. Ann Rheum Dis. 2004 Dec;63(12):1670-2.

1509. Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005 Nov;52(11):3403-12.

1510. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum 2008;58(3):667-77.

1511. Liu FC, Chiang SY, Chang DM, et al. Purtscher's-like retinopathy as an initial presentation of adult-onset Still's disease: a case report and review of the literature. Clin Rheumatol. 2007 Jul;26(7):1204-6.

1512. Liu MF, Yang CY, Li JS, et al. Increased expression of down-regulatory CTLA-4 molecule on T lymphocytes from rheumatoid synovial compartment. Scand J Immunol. 1999 Jul;50(1):68-72.

1513. Li-Yu J, Clayburne GM, Sieck MS, et al. Calcium apatite crystals in synovial fluid rice bodies. Ann Rheum Dis. 2002 May;61(5):387-90.

1514. Ljung L, Olsson T, Engstrand S, et al. Interleukin-1 receptor antagonist is associated with both lipid metabolism and inflammation in rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):617-20.

1515. Lloyd ME, Davitt S, Hall JR. Bilateral tibia and fibula fractures in a patient with rheumatoid arthritis. Clin Rheumatol. 2001;20(4):270-2.

1516. Lodder MC, de Jong Z, Kostense PJ, et al. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis. 2004 Dec;63(12):1576-80.

1517. Lodder MC, Haugeberg G, Lems WF, et al. Radiographic damage associated with low bone mineral density and vertebral deformities in rheumatoid arthritis: the Oslo-Truro-Amsterdam (OSTRA) collaborative study. Arthritis Rheum. 2003 Apr 15;49(2):209-15.

1518. Lonardo A, Neri P, Mascia MT, et al. Hereditary hemochromatosis masquerading as rheumatoid arthritis. Ann Ital Med Int. 2001 Jan-Mar;16(1):46-9.

1519. Long JA, Husted JA, Gladman DD, et al. The relationship between patient satisfaction with health and clinical measures of function and disease status in patients with psoriatic arthritis. J Rheumatol. 2000 Apr;27(4):958-66.

1520. Loos T, Dekeyzer L, Struyf S, et al. TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: enhanced CXCL9 in autoimmune arthritis. Lab Invest. 2006 Sep;86(9):902-16.

1521. Lopes RV, Furtado RN, Parmigiani L, et al. Accuracy of intra-articular injections in peripheral joints performed blindly in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008 Dec;47(12):1792-4.

1522. Lopez-Hoyos M, Rodrigo E, Fernandez-Fresnedo G, et al. Lack of effect of rapamycin in anti-CCP antibody production in a rheumatoid arthritis kidney allograft recipient. Clin Exp Rheumatol. 2005 Jul-Aug;23(4):529-31.

1523. Lorenzi AR, Morgan TA, Anderson A, et al. Thymic function in juvenile idiopathic arthritis. Ann Rheum Dis. 2009 Jun;68(6):983-90.

1524. Lories RJ, Derese I, Luyten FP, et al. Activation of nuclear factor kappa B and mitogen activated protein kinases in psoriatic arthritis before and after etanercept treatment. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):96-102.

1525. Louis M, Rauch J, Armstrong M, et al. Induction of autoantibodies during prolonged treatment with infliximab. J Rheumatol. 2003 Dec;30(12):2557-62.

1526. Louthrenoo W, Kongtawelert P, Sivasomboon C, et al. Correlation between serum hyaluronan and disease activity and severity in Thai patients with rheumatoid arthritis. J Med Assoc Thai. 2001 May;84(5):622-7.

1527. Louthrenoo W, Zager EL, Freundlich B, et al. Intravenous corticosteroid therapy of cervical cord compression in rheumatoid arthritis. Clin Exp Rheumatol. 1992 Mar-Apr;10(2):173-5.

1528. Lozeron P, Denier C, Lacroix C, et al. Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-alpha-blocker therapy. Arch Neurol. 2009 Apr;66(4):490-7.

1529. Lu LJ, Bao CD, Dai M, et al. Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. Arthritis Rheum. 2009 Jul 15;61(7):979-87.

1530. Lubbe S, Tikly M, van der Merwe L, et al. Interleukin-1 receptor antagonist gene polymorphisms are associated with disease severity in Black South Africans with rheumatoid arthritis. Joint Bone Spine. 2008 Jul;75(4):422-5.

1531. Lubrano E, D'Angelo S, Parsons WJ, et al. Effects of a combination treatment of an intensive rehabilitation program and etanercept in patients with ankylosing spondylitis: a pilot study. J Rheumatol. 2006 Oct;33(10):2029-34.

1532. Luessenhop CP, Higgins LD, Brause BD, et al. Multiple prosthetic infections after total joint arthroplasty. Risk factor analysis. J Arthroplasty. 1996 Oct;11(7):862-8.

1533. Lun SW, Wong CK, Tam LS, et al. Decreased ex vivo production of TNF-alpha and IL-8 by peripheral blood cells of patients with rheumatoid arthritis after infliximab therapy. Int Immunopharmacol. 2007 Dec 15;7(13):1668-77.

1534. Lurati A, Pontikaki I, Teruzzi B, et al. A comparison of response criteria to evaluate therapeutic response in patients with juvenile idiopathic arthritis treated with methotrexate and/or anti-tumor necrosis factor alpha agents. Arthritis Rheum. 2006 May;54(5):1602-7.

1535. Luukkainen R, Hakala M, Sajanti E, et al. Predictive value of synovial fluid analysis in estimating the efficacy of intra-articular corticosteroid injections in patients with rheumatoid arthritis. Ann Rheum Dis. 1992 Jul;51(7):874-6.

1536. Luzi G, Lagana B, Salemi S, et al. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3.

1537. Lyman J, Serebro L. Efalizumab-induced inflammatory polyarthritis: what are the implications? South Med J. 2010 Apr;103(4):357-60.

1538. Lyngberg KK, Harreby M, Bentzen H, et al. Elderly rheumatoid arthritis patients on steroid treatment tolerate physical training without an increase in disease activity. Arch Phys Med Rehabil. 1994 Nov;75(11):1189-95.

1539. Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. Am J Ophthalmol. 2007 May;143(5):801-9.

1540. Ma Y, Lin BR, Lin B, et al. Pharmacokinetics of CTLA4Ig fusion protein in healthy volunteers and patients with rheumatoid arthritis. Acta Pharmacol Sin. 2009 Mar;30(3):364-71.

1541. Machado P, Santos A, Pereira C, et al. Increased prevalence of allergic sensitisation in rheumatoid arthritis patients treated with

anti-TNFalpha. Joint Bone Spine 2009;76(5):508-13.

1542. Macias I, Garcia-Perez S, Ruiz-Tudela M, et al. Modification of pro- and antiinflammatory cytokines and vascular-related molecules by tumor necrosis factor-a blockade in patients with rheumatoid arthritis. J Rheumatol. 2005 Nov;32(11):2102-8.

1543. Mackie GC, Pohlen JM. Methotrexate-induced pulmonary non-Hodgkin lymphoma. Clin Nucl Med. 2006 May;31(5):272-4.

1544. MacLean CH, Mojica WA, Morton SC, et al. Effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Evid Rep Technol Assess (Summ). 2004 Mar(89):1-4.

1545. Maenpaa HM, Soini I, Lehto MU, et al. Insufficiency fractures in patients with chronic inflammatory joint diseases. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):77-9.

1546. Magaro M, Tricerri A, Piane D, et al. Generalized osteoporosis in non-steroid treated rheumatoid arthritis. Rheumatol Int. 1991;11(2):73-6.

1547. Magliocco MA, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. J Am Acad Dermatol. 2004 Oct;51(4):580-4.

1548. Magnusson SE, Engstrom M, Jacob U, et al. High synovial expression of the inhibitory FcgammaRIIb in rheumatoid arthritis. Arthritis Res Ther. 2007;9(3):R51.

1549. Maillard H, Ornetti P, Grimault L, et al. Severe pyogenic infections in patients taking infliximab: a regional cohort study. Joint Bone Spine. 2005 Jul;72(4):330-4.

1550. Maimon N, Brunton J, Chan AK, et al. Fatal pulmonary Mycobacterium xenopi in a patient with rheumatoid arthritis receiving etanercept. Thorax. 2007 Aug;62(8):739-40.

1551. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.

1552. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998 Sep;41(9):1552-63.

1553. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004 Apr;50(4):1051-65.

1554. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006;54(9):2817-29.

1555. Mainman H, McClaren E, Heycock C, et al. When should we use parenteral methotrexate? Clin Rheumatol. 2010 Oct;29(10):1093-8.

1556. Maki-Petaja KM, Hall FC, Booth AD, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. Circulation. 2006 Sep 12;114(11):1185-92.

1557. Maksymowych WP. Ankylosing spondylitis. Not just another pain in the back. Can Fam Physician. 2004 Feb;50:257-62.

1558. Maksymowych WP, Blackburn WD, Jr., Tami JA, et al. A randomized, placebo controlled trial of an antisense oligodeoxynucleotide to intercellular adhesion molecule-1 in the treatment of severe rheumatoid arthritis. J Rheumatol. 2002 Mar;29(3):447-53.

1559. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum. 2005 Aug 15;53(4):502-9.

1560. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. Arthritis Rheum. 2005 Oct 15;53(5):703-9.

1561. Maksymowych WP, Jhangri GS, Lambert RG, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. J Rheumatol. 2002 May;29(5):959-65.

1562. Maksymowych WP, Poole AR, Hiebert L, et al. Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis. J Rheumatol. 2005 Oct;32(10):1911-7.

1563. Maksymowych WP, Reeve JP, Reveille JD, et al. High-throughput single-nucleotide polymorphism analysis of the IL1RN locus in patients with ankylosing spondylitis by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry. Arthritis Rheum. 2003 Jul;48(7):2011-8.

1564. Malaviya AN, Kapoor S, Garg S, et al. A new strategy of drug treatment in NSAID-unresponsive ankylosing spondylitis: combination of pamidronate and methylprednisolone monthly intravenous infusions on the background of a combination of disease modifying drugs sulfasalazine and methotrexate. J Assoc Physicians India. 2007 Mar;55:193-7.

1565. Malesci D, Tirri R, Buono R, et al. Leflunomide in psoriatic arthritis: a retrospective study of discontinuation rate in daily clinical practice compared with methotrexate. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):881-4.

1566. Malfait AM, Verbruggen G, Almqvist KF, et al. Coculture of human articular chondrocytes with peripheral blood mononuclear cells as a model to study cytokine-mediated interactions between inflammatory cells and target cells in the rheumatoid joint. In Vitro Cell Dev Biol Anim. 1994 Nov;30A(11):747-52.

1567. Malipeddi AS, Rajendran R, Kallarackal G. Disseminated tuberculosis after anti-TNFalpha treatment. Lancet. 2007 Jan 13;369(9556):162.

1568. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol 2008;35(6):979-85.

1569. Manadan AM, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):526.

1570. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol. 2007 Aug;34(8):1670-3.

1571. Manda G, Neagu M, Constantin C, et al. Patterns of peripheral cellular immune disorders in severe rheumatoid arthritis. Roum Arch Microbiol Immunol. 2005 Jan-Dec;64(1-4):17-26.

1572. Mang R, Stege H, Ruzicka T, et al. Response of severe psoriasis to infliximab. Dermatology. 2002;204(2):156-7.

1573. Mangat P, Whittle S, Cleland L, et al. Digital vasculitis: a late complication of anti-tumour necrosis factor alpha therapy. Clin Rheumatol. 2008 Dec;27(12):1593-5.

1574. Manger B, Rech J, Schett G. Use of methotrexate in adult-onset Still's disease. Clin Exp Rheumatol. 2010 Sep-Oct;28(5 Suppl 61):S168-71.

1575. Marchesoni A, Arreghini M, Panni B, et al. Life-threatening reversible bone marrow toxicity in a rheumatoid arthritis patient switched from leflunomide to infliximab.

Rheumatology (Oxford). 2003 Jan;42(1):193-4.

1576. Marchesoni A, Ceravolo GP, Battafarano N, et al. Cyclosporin A in the treatment of adult onset Still's disease. J Rheumatol. 1997 Aug;24(8):1582-7.

1577. Marchesoni A, Puttini PS, Gorla R, et al. Cyclosporine in addition to infliximab and methotrexate in refractory rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):916-7.

1578. Marchesoni A, Zaccara E, Gorla R, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 2009;1173837-46.

1579. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum. 2004 Apr;50(4):1270-6.

1580. Maripuri S, Grande JP, Osborn TG, et al. Renal involvement in primary Sjogren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009 Sep;4(9):1423-31.

1581. Markatseli TE, Kaltsonoudis ES, Voulgari PV, et al. Induction of psoriatic skin lesions in a patient with rheumatoid arthritis treated with rituximab. Clin Exp Rheumatol. 2009 Nov-Dec;27(6):996-8.

1582. Marotte H, Arnaud B, Diasparra J, et al. Association between the level of circulating bioactive tumor necrosis factor alpha and the tumor necrosis factor alpha gene polymorphism at -308 in patients with rheumatoid arthritis treated with a tumor necrosis factor alpha inhibitor. Arthritis Rheum. 2008 May;58(5):1258-63.

1583. Marotte H, Gineyts E, Miossec P, et al. Effects of infliximab therapy on biological markers of synovium activity and cartilage breakdown in patients with rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1197-200.

1584. Marotte H, Maslinski W, Miossec P. Circulating tumour necrosis factor-alpha bioactivity in rheumatoid arthritis patients treated with infliximab: link to clinical response. Arthritis Res Ther. 2005;7(1):R149-55.

1585. Marotte H, Pallot-Prades B, Grange L, et al. The shared epitope is a marker of severity associated with selection for, but not with response to, infliximab in a large rheumatoid arthritis population. Ann Rheum Dis. 2006 Mar;65(3):342-7.

1586. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. Ophthalmology. 1999 Apr;106(4):811-6.

1587. Marshall NJ, Wilson G, Lapworth K, et al. Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study. Rheumatology (Oxford). 2004 Aug;43(8):1034-8.

1588. Marti L, Golmia R, Golmia AP, et al. Alterations in cytokine profile and dendritic cells subsets in peripheral blood of rheumatoid arthritis patients before and after biologic therapy. Ann N Y Acad Sci. 2009 Sep;1173:334-42.

1589. Martin JA, Jarrett P. Rheumatoid papules treated with dapsone. Clin Exp Dermatol. 2004 Jul;29(4):387-9.

1590. Martin JC, Munro R, Campbell MK, et al. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol. 1997 Jan;36(1):43-9.

1591. Martin JM, Ricart JM, Alcacer J, et al. Adalimumab-induced lupus erythematosus. Lupus. 2008 Jul;17(7):676-8.

1592. Martin K, Bentaberry F, Dumoulin C, et al. Peripheral neuropathy associated with leflunomide: is there a risk patient profile? Pharmacoepidemiol Drug Saf. 2007 Jan;16(1):74-8.

1593. Martin Martin LS, Migliore A, Todino V, et al. Infliximab therapy in patients with secondary Sjogren's syndrome: functional evaluation. Clin Exp Rheumatol. 2003 May-Jun;21(3):412.

1594. Martin N, Innes JA, Lambert CM, et al. Hypersensitivity pneumonitis associated with leflunomide therapy. J Rheumatol. 2007 Sep;34(9):1934-7.

1595. Martinez A, Salido M, Bonilla G, et al. Association of the major histocompatibility complex with response to infliximab therapy in rheumatoid arthritis patients. Arthritis Rheum. 2004 Apr;50(4):1077-82.

1596. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol 2009;27(4):678-84.

1597. Maruani A, Wierzbicka E, Machet MC, et al. Reversal of multifocal cutaneous lymphoproliferative disease associated with Epstein-Barr virus after withdrawal of methotrexate therapy for rheumatoid arthritis. J Am Acad Dermatol. 2007 Nov;57(5 Suppl):S69-71.

1598. Marzo-Ortega H, McGonagle D, Jarrett S, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis. 2005 Nov;64(11):1568-75.

1599. Marzo-Ortega H, McGonagle D, O'Connor P, et al. Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. Arthritis Rheum. 2001 Sep;44(9):2112-7.

1600. Marzo-Ortega H, McGonagle D, Rhodes LA, et al. Efficacy of infliximab on MRI-determined bone oedema in psoriatic arthritis. Ann Rheum Dis. 2007 Jun;66(6):778-81.

1601. Marzo-Ortega H, Misbah S, Emery P. Minocycline induced autoimmune disease in rheumatoid arthritis: a missed diagnosis? J Rheumatol. 2001 Feb;28(2):377-8.

1602. Masera RG, Carignola R, Sartori ML, et al. Circadian abnormalities of natural killer cell activity in rheumatoid arthritis. Ann N Y Acad Sci. 1999 Jun 22;876:88-90.

1603. Masi AT, Aldag JC, Chatterton RT, et al. Adrenal androgen and glucocorticoid dissociation in premenopausal rheumatoid arthritis: a significant correlate or precursor to onset? Z Rheumatol. 2000;59 Suppl 2:II/54-61.

1604. Masi AT, Chatterton RT, Aldag JC, et al. Perspectives on the relationship of adrenal steroids to rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:1-12.

1605. Masiero S, Boniolo A, Wassermann L, et al. Effects of an educational-behavioral joint protection program on people with moderate to severe rheumatoid arthritis: a randomized controlled trial. Clin Rheumatol. 2007 Dec;26(12):2043-50.

1606. Massarotti EM. Medical aspects of rheumatoid arthritis. Diagnosis and treatment. Hand Clin. 1996 Aug;12(3):463-75.

1607. Mastroianni A, Minutilli E, Mussi A, et al. Cytokine profiles during infliximab monotherapy in psoriatic arthritis. Br J Dermatol. 2005 Sep;153(3):531-6.

1608. Masuda K, Mochida Y, Fujii J, et al. Primary cervical epidural malignant lymphoma with rheumatoid arthritis: a case report. Mod Rheumatol. 2007;17(3):239-42.

1609. Mateo L, Nolla JM, Bonnin MR, et al. Sex hormone status and bone mineral density in men with rheumatoid arthritis. J Rheumatol. 1995 Aug;22(8):1455-60.

1610. Mathias SD, Colwell HH, Miller DP, et al. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther. 2000 Jan;22(1):128-39.

1611. Mathieu S, Vellin JF, Poujol D, et al. Cat scratch disease during etanercept therapy. Joint Bone Spine. 2007 Mar;74(2):184-6.

1612. Matsuda M, Morita H, Ikeda S. Long-term follow-up of systemic reactive AA amyloidosis secondary to rheumatoid arthritis: successful treatment with intermediate-dose corticosteroid. Intern Med. 2002 May;41(5):403-7.

1613. Matsui T, Komiya A, Shimada K, et al. Neutrophil CD64 as a marker of infection in patients treated with tocilizumab. Mod Rheumatol. 2009;19(6):696-7.

1614. Matsui T, Kuga Y, Kaneko A, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis. 2007 Sep;66(9):1221-6.

1615. Matsui T, Ohsumi K, Ozawa N, et al. CD64 on neutrophils is a sensitive and specific marker for detection of infection in patients with rheumatoid arthritis. J Rheumatol. 2006 Dec;33(12):2416-24.

1616. Matsumoto K, Hukuda S, Nishioka J, et al. Rupture of the Achilles tendon in rheumatoid arthritis with histologic evidence of enthesitis. A case report. Clin Orthop Relat Res. 1992 Jul(280):235-40.

1617. Matsumoto T, Kaneko T, Seto M, et al. The membrane proteinase 3 expression on neutrophils was downregulated after treatment with infliximab in patients with rheumatoid arthritis. Clin Appl Thromb Hemost. 2008 Apr;14(2):186-92.

1618. Matsuo T, Koyama T, Morimoto N, et al. Retinal vasculitis as a complication of rheumatoid arthritis. Ophthalmologica. 1990;201(4):196-200.

1619. Matsushita I, Uzuki M, Matsuno H, et al. Rheumatoid nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. Mod Rheumatol. 2006;16(6):401-3.

1620. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36(6):1180-7.

1621. Matthews C, Fitzgerald O. Seropositive erosive rheumatoid arthritis (RA). Rheumatology (Oxford). 2006 Sep;45(9):1100.

1622. Maugars Y, Mathis C, Berthelot JM, et al. Assessment of the efficacy of sacroiliac corticosteroid injections in spondylarthropathies: a double-blind study. Br J Rheumatol. 1996 Aug;35(8):767-70.

1623. Mavragani CP, La DT, Stohl W, et al. Association of the response to tumor necrosis factor antagonists with plasma type I interferon activity and interferon-beta/alpha ratios in rheumatoid arthritis patients: a post hoc analysis of a predominantly Hispanic cohort. Arthritis Rheum. 2010 Feb;62(2):392-401.

1624. Mavropoulos JC, Cuchacovich M, Llanos C, et al. Anti-tumor necrosis factor-alpha therapy augments dipeptidyl peptidase IV activity and decreases autoantibodies to GRP78/BIP and phosphoglucose isomerase in patients with rheumatoid arthritis. J Rheumatol. 2005 Nov;32(11):2116-24.

1625. Maxwell JR, Potter C, Hyrich KL, et al. Association of the tumour necrosis factor-308 variant with differential response to anti-TNF agents in the treatment of rheumatoid arthritis. Hum Mol Genet. 2008 Nov 15;17(22):3532-8.

1626. Mayer DF, Matteson EL. Testicular involvement in rheumatoid vasculitis. Clin Exp Rheumatol. 2004;22(6 Suppl 36):S62-4.

1627. Mayer Y, Balbir-Gurman A, Machtei EE. Anti-tumor necrosis factor-alpha therapy and periodontal parameters in patients with rheumatoid arthritis. J Periodontol. 2009 Sep;80(9):1414-20.

1628. Mazokopakis E, Katsogridakis K, Koutsopoulos A, et al. Fatal methotrexate-induced pneumonitis in a psoriatic patient. Mil Med. 2004 Apr;169(4):298-300.

1629. Mazzotta A, Esposito M, Costanzo A, et al. Efficacy and safety of etanercept in psoriasis

after switching from other treatments: an observational study. Am J Clin Dermatol. 2009;10(5):319-24.

1630. Mazzotta A, Esposito M, Schipani C, et al. Long-term experience with etanercept in psoriatic arthritis patients: a 3-year observational study. J Dermatolog Treat. 2009;20(6):354-8.

1631. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology (Oxford). 2002 Jan;41(1):116-7.

1632. McCarthy CJ, Regan M, Coughlan RJ. Treatment of rheumatoid hand synovitis with a regional block technique. Ir J Med Sci. 1993 Apr;162(4):143-4.

1633. McCombe PA, Klestov AC, Tannenberg AE, et al. Sensorimotor peripheral neuropathy in rheumatoid arthritis. Clin Exp Neurol. 1991;28:146-53.

1634. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis 2009;48(10):1364-71.

1635. McGarry F, Neilly J, Anderson N, et al. A polymorphism within the interleukin 1 receptor antagonist (IL-1Ra) gene is associated with ankylosing spondylitis. Rheumatology (Oxford). 2001 Dec;40(12):1359-64.

1636. McGonagle D, Tan AL, Madden J, et al. Rituximab use in everyday clinical practice as a first-line biologic therapy for the treatment of DMARD-resistant rheumatoid arthritis. Rheumatology (Oxford). 2008 Jun;47(6):865-7.

1637. McMinn JR, Jr., Cohen S, Moore J, et al. Complete recovery from refractory immune thrombocytopenic purpura in three patients treated with etanercept. Am J Hematol. 2003 Jun;73(2):135-40.

1638. Mease PJ, Cohen S, Gaylis NB, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. J Rheumatol 2010;37(5):917-27.

1639. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52(10):3279-89.

1640. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.

1641. Mease PJ, Kivitz AJ, Burch FX, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. J Rheumatol 2006;33(4):712-21.

1642. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50(7):2264-72.

1643. Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9.

1644. Mease PJ, Reich K. Alefacept with methotrexate for treatment of psoriatic arthritis: open-label extension of a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 2009 Mar;60(3):402-11.

1645. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol 2008;35(1):20-30.

1646. Mease PJ, Ritchlin CT, Martin RW, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol. 2004 Jul;31(7):1356-61.

1647. Mease PJ, Woolley JM, Singh A, et al. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. J Rheumatol 2010;37(6):1221-7.

1648. Mehta BM, Hashkes PJ, Avery R, et al. A 21-year-old man with Still's disease with fever, rash, and pancytopenia. Arthritis Care Res (Hoboken). 2010 Apr;62(4):575-9.

1649. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjogren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010 Apr;62(4):960-8.

1650. Meirer R, Muller-Gerbl M, Huemer GM, et al. Quantitative assessment of periarticular osteopenia in patients with early rheumatoid arthritis: a preliminary report. Scand J Rheumatol. 2004;33(5):307-11.

1651. Melikoglu MA, Melikoglu M, Gurbuz U, et al. Hydroxychloroquine-induced hyperpigmentation: a case report. J Clin Pharm Ther. 2008 Dec;33(6):699-701.

1652. Menard O, Petit N, Gillet P, et al. Association of histologically proven rheumatoid arthritis with pulmonary sarcoidosis. Eur Respir J. 1995 Mar;8(3):472-3.

1653. Menninger H, Herborn G, Sander O, et al. A 36 month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. Br J Rheumatol. 1998 Oct;37(10):1060-8.

1654. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev 2009(1):CD005121.

1655. Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci 2007;1111343-57.

1656. Messina OD, Barreira JC, Zanchetta JR, et al. Effect of low doses of deflazacort vs prednisone on bone mineral content in premenopausal rheumatoid arthritis. J Rheumatol. 1992 Oct;19(10):1520-6.

1657. Meusch U, Rossol M, Baerwald C, et al. Outside-to-inside signaling through transmembrane tumor necrosis factor reverses pathologic interleukin-1beta production and deficient apoptosis of rheumatoid arthritis monocytes. Arthritis Rheum. 2009 Sep;60(9):2612-21.

1658. Miceli-Richard C, Comets E, Verstuyft C, et al. A single tumour necrosis factor haplotype influences the response to adalimumab in rheumatoid arthritis. Ann Rheum Dis. 2008 Apr;67(4):478-84.

1659. Michaelsson G, Kajermo U, Michaelsson A, et al. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct? Br J Dermatol. 2005 Dec;153(6):1243-4.

1660. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol 2006;33(12):2412-5.

1661. Michel BA, Bloch DA, Fries JF. Predictors of fractures in early rheumatoid arthritis. J Rheumatol. 1991 Jun;18(6):804-8.

1662. Michel BA, Bloch DA, Wolfe F, et al. Fractures in rheumatoid arthritis: an evaluation of associated risk factors. J Rheumatol. 1993 Oct;20(10):1666-9.

1663. Michel M, Duvoux C, Hezode C, et al. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. J Rheumatol. 2003 Jul;30(7):1624-5.

1664. Michel M, Habibi A, Godeau B, et al. Characteristics and outcome of connective tissue diseases in patients with sickle-cell disease: report of 30 cases. Semin Arthritis Rheum. 2008 Dec;38(3):228-40.

1665. Mielants H, Goemaere S, De Vos M, et al. Intestinal mucosal permeability in inflammatory rheumatic diseases. I. Role of antiinflammatory drugs. J Rheumatol. 1991 Mar;18(3):389-93.

1666. Mielke F, Schweigert M. Safe adalimumab therapy for rheumatoid arthritis in a patient with pre-existing multiple myeloma. Nat Clin Pract Rheumatol. 2008 Apr;4(4):218-21.

1667. Migliore A, Bizzi E, Massafra U, et al. Can Cyclosporine-A associated to methotrexate maintain remission induced by anti-TNF agents in rheumatoid arthritis patients? (Cynar pilot study). Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):783-90.

1668. Migliore A, Massafra U, Capuano A, et al. Combined use of teriparatide and TNFalpha blockade: safety. Aging Clin Exp Res. 2007 Jun;19(3 Suppl):18-20.

1669. Migliore A, Signore A, Capuano A, et al. Relevance of 99mTc-HYNIC-tir-octreotide scintigraphy in a patient affected by sarcoidosis with lung and joints involvement and secondary Sjogren's syndrome treated with infliximab: case report. Eur Rev Med Pharmacol Sci. 2008 Mar-Apr;12(2):127-30.

1670. Mikashima Y, Kawamura K, Miyawaki M, et al. Neglected spontaneous rupture of the Achilles tendon in elderly patients with rheumatoid arthritis. J Clin Rheumatol. 2010 Aug;16(5):221-4.

1671. Mikhail M, Weinberg JM, Smith BL. Successful treatment with etanercept of von Zumbusch pustular psoriasis in a patient with human immunodeficiency virus. Arch Dermatol. 2008 Apr;144(4):453-6.

1672. Miller KL, Sawitzke AD, Doane J. Abatacept and serious respiratory infections in patients with previous lung disease. Clin Rheumatol. 2008 Dec;27(12):1569-71.

1673. Miller-Blair DJ, Robbins DL. Rheumatoid arthritis: new science, new treatment. Geriatrics. 1993 Jun;48(6):28-31, 5-8.

1674. Mima T, Nishimoto N. Clinical value of blocking IL-6 receptor. Curr Opin Rheumatol. 2009 May;21(3):224-30.

1675. Min JK, Han NI, Kim JA, et al. A case of cholestatic autoimmune hepatitis and acute liver failure: an unusual hepatic manifestation of mixed connective tissue disease and Sjogren's syndrome. J Korean Med Sci. 2001 Aug;16(4):512-5.

1676. Mirone L, Altomonte L, D'Agostino P, et al. A study of serum androgen and cortisol levels in female patients with rheumatoid arthritis. Correlation with disease activity. Clin Rheumatol. 1996 Jan;15(1):15-9.

1677. Misery L, Perrot JL, Gentil-Perret A, et al. Dermatological complications of etanercept therapy for rheumatoid arthritis. Br J Dermatol. 2002 Feb;146(2):334-5.

1678. Mishra KK, Pandey HP. A study on physiological changes in essential hypertension and rheumatoid arthritis with reference to the levels of cortisol, blood glucose, triglycerides and cholesterol. Indian J Physiol Pharmacol. 1995 Jan;39(1):68-70.

1679. Mishra KK, Pandey HP. A study on physiological changes in certain psychosomatic disorders with reference to cortisol, blood glucose and lipid profile. Indian J Physiol Pharmacol. 1996 Apr;40(2):151-4.

1680. Mitamura M, Tada Y, Koarada S, et al. Cyclosporin A treatment for Japanese patients with severe adult-onset Still's disease. Mod Rheumatol. 2009;19(1):57-63.

1681. Mittendorf T, Dietz B, Sterz R, et al. Personal and economic burden of late-stage rheumatoid arthritis among patients treated with adalimumab: an evaluation from a patient's perspective. Rheumatology (Oxford). 2008 Feb;47(2):188-93.

1682. Mittendorf T, Dietz B, Sterz R, et al. Improvement and longterm maintenance of quality of life during treatment with adalimumab in severe rheumatoid arthritis. J Rheumatol. 2007 Dec;34(12):2343-50.

1683. Miyagawa Y, Nagata N, Nakanishi Y, et al. A case of steroid-responsive organizing pneumonia in a patient with rheumatoid arthritis showing migratory infiltration and normal glucose levels in pleural effusions. Br J Rheumatol. 1993 Sep;32(9):829-31.

1684. Miyamoto S, Kageyama Y, Ozeki T, et al. Bone mineral density after total joint

arthroplasty of lower extremities in rheumatoid arthritis patients. Arch Orthop Trauma Surg. 2001;121(3):127-30.

1685. Miyanishi K, Hara T, Hamada T, et al. Co-occurrence of subchondral insufficiency fracture of the femoral head and contralateral femoral neck fracture in a rheumatic patient receiving steroid treatment. Mod Rheumatol. 2008;18(6):619-22.

1686. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008;18(3):252-62.

1687. Miyazaki T, Fujimaki K, Shirasugi Y, et al. Remission of lymphoma after withdrawal of methotrexate in rheumatoid arthritis: relationship with type of latent Epstein-Barr virus infection. Am J Hematol. 2007 Dec;82(12):1106-9.

1688. Moccia F, Mazzarello GP, Morra L. Effect of corticosteroid treatment on hemopoiesis in vivo and in vitro in a patient with Felty's syndrome. Biomed Pharmacother. 1991;45(9):403-8.

1689. Mochizuki T, Momohara S, Ikari K, et al. Spontaneous multiple insufficiency fractures after pelvic abscess and sepsis in a rheumatoid arthritis patient treated with high-load corticosteroid therapy: a case report. Clin Rheumatol. 2007 Nov;26(11):1925-8.

1690. Mochizuki T, Momohara S, Ikari K, et al. The serum concentration of infliximab in cases of autologous blood donation for patients with rheumatoid arthritis. Mod Rheumatol. 2007;17(1):24-7.

1691. Mody GM, Meyers OL. Therapeutic requirements in rheumatoid arthritis. S Afr Med J. 1990 May 19;77(10):497-9.

1692. Moen K, Kvalvik AG, Hellem S, et al. The long-term effect of anti TNF-alpha treatment on temporomandibular joints, oral mucosa, and salivary flow in patients with active rheumatoid arthritis: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Oct;100(4):433-40.

1693. Mogosan C, Stoica V, Mihai C, et al. Rheumatoid arthritis: travelling biological era a Romanian X-ray population. J Med Life. 2009 Oct-Dec;2(4):414-25.

1694. Mohammad A, Kilcoyne A, Bond U, et al. Methotrexate information booklet study 2008. Clin Exp Rheumatol. 2009 Jul-Aug;27(4):649-50.

1695. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004 Aug 1;39(3):295-9.

1696. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001 Dec;44(12):2862-9.

1697. Mohyuddin T, Elyan M, Kushner I. Pericarditis: a rare complication of methotrexate therapy. Clin Rheumatol. 2007 Dec;26(12):2157-8.

1698. Mok CC, Lau CS, Wong RW. Clinical characteristics, treatment, and outcome of adult onset Still's disease in southern Chinese. J Rheumatol. 1998 Dec;25(12):2345-51.

1699. Mok MY, Lo Y, Leung PY, et al. Pregnancy outcome in patients with adult onset Still's disease. J Rheumatol. 2004 Nov;31(11):2307-9.

1700. Mok MY, Wong SY, Chan TM, et al. Necrotizing fasciitis in rheumatic diseases. Lupus. 2006;15(6):380-3.

1701. Molenaar ET, Bultink IE, Dijkmans BA, et al. Development of fatal tuberculosis in a patient with rheumatoid arthritis after three years of treatment with infliximab: comment on the article by Wolfe et al. Arthritis Rheum. 2005 Apr;52(4):1334-6.

1702. Moller B, Kukoc-Zivojnov N, Koyama N, et al. Prednisolone induces interleukin-18 expression in mononuclear blood and myeloid progenitor cells. Inflamm Res. 2002 Sep;51(9):457-63.

1703. Molloy E, Ramakrishnan S, Murphy E, et al. Morbidity and mortality in rheumatoid patients during treatment with adalimumab and infliximab. Rheumatology (Oxford). 2004 Apr;43(4):522-3.

1704. Momeni M, Mehta AP, Katz JD. Anti-tumor necrosis factor therapy is tolerated in an individual with homozygous complement C2 deficiency. J Clin Rheumatol. 2005 Jun;11(3):180-2.

1705. Montagna GL, Malesci D, Buono R, et al. Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005 Nov;64(11):1667.

1706. Montecucco C, Caporali R, Caprotti P, et al. Sex hormones and bone metabolism in postmenopausal rheumatoid arthritis treated with two different glucocorticoids. J Rheumatol. 1992 Dec;19(12):1895-900.

1707. Montero JA, Ruiz-Moreno JM, Rodriguez AE, et al. Endogenous endophthalmitis by Propionibacterium acnes associated with leflunomide and adalimumab therapy. Eur J Ophthalmol. 2006 Mar-Apr;16(2):343-5.

1708. Moore A, Phillips C, Hunsche E, et al. Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis patients in the UK. Pharmacoeconomics. 2004;22(10):643-60.

1709. Moore J, Ma D, Will R, et al. A phase II study of Rituximab in rheumatoid arthritis patients with recurrent disease following haematopoietic stem cell transplantation. Bone Marrow Transplant. 2004 Aug;34(3):241-7.

1710. Mor A, Bingham C, 3rd, Barisoni L, et al. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. J Rheumatol. 2005 Apr;32(4):740-3.

1711. Mor A, Bingham CO, 3rd, Kishimoto M, et al. Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic. Ann Rheum Dis. 2008 Apr;67(4):462-5.

1712. Morand EF, Jefferiss CM, Dixey J, et al. Impaired glucocorticoid induction of mononuclear leukocyte lipocortin-1 in rheumatoid arthritis. Arthritis Rheum. 1994 Feb;37(2):207-11.

1713. Moreland LW. Inhibitors of tumor necrosis factor: new treatment options for rheumatoid arthritis. Cleve Clin J Med. 1999 Jun;66(6):367-74.

1714. Moreland LW, Alten R, Van den Bosch F, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum. 2002 Jun;46(6):1470-9.

1715. Moreland LW, Bucy RP, Weinblatt ME, et al. Immune function in patients with rheumatoid arthritis treated with etanercept. Clin Immunol. 2002 Apr;103(1):13-21.

1716. Moreland LW, Cohen SB, Baumgartner SW, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2001 Jun;28(6):1238-44.

1717. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.

1718. Morelli S, Sgreccia A, Bernardo ML, et al. Primary aspergillosis of the larynx in a patient with Felty's syndrome. Clin Exp Rheumatol. 2000 Jul-Aug;18(4):523-4.

1719. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain. 2005 Nov;128(Pt 11):2518-34.

1720. Mori S. A relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximab-resistant cases and PK-based modified therapy. Mod Rheumatol. 2007;17(2):83-91.

1721. Mori S, Cho I, Ichiyasu H, et al. Asymptomatic carriage of Pneumocystis jiroveci in elderly patients with rheumatoid

arthritis in Japan: a possible association between colonization and development of Pneumocystis jiroveci pneumonia during low-dose MTX therapy. Mod Rheumatol. 2008;18(3):240-6.

1722. Mori S, Cho I, Sugimoto M. A followup study of asymptomatic carriers of Pneumocystis jiroveci during immunosuppressive therapy for rheumatoid arthritis. J Rheumatol. 2009 Aug;36(8):1600-5.

1723. Mori S, Ebihara K. A sudden onset of diabetic ketoacidosis and acute pancreatitis after introduction of mizoribine therapy in a patient with rheumatoid arthritis. Mod Rheumatol. 2008;18(6):634-8.

1724. Mori S, Imamura F, Kiyofuji C, et al. Pneumocystis jiroveci pneumonia in a patient with rheumatoid arthritis as a complication of treatment with infliximab, anti-tumor necrosis factor alpha neutralizing antibody. Mod Rheumatol. 2006;16(1):58-62.

1725. Mori S, Imamura F, Kiyofuji C, et al. Development of interstitial pneumonia in a rheumatoid arthritis patient treated with infliximab, an anti-tumor necrosis factor alpha-neutralizing antibody. Mod Rheumatol. 2006;16(4):251-5.

1726. Mori S, Koga Y, Imamura F, et al. Early rheumatoid arthritis in a patient with Sjogren's syndrome and pulmonary nodular amyloidosis: clinical implication of early limited use of infliximab. Mod Rheumatol. 2007;17(6):500-6.

1727. Mori S, Tomita Y, Horikawa T, et al. Delayed spinal infection after laminectomy in a patient with rheumatoid arthritis interruptedly exposed to anti-tumor necrosis factor alpha agents. Clin Rheumatol. 2008 Jul;27(7):937-9.

1728. Morita Y, Fukazawa T, Hirashima M, et al. The effect of methotrexate (MTX) on expression of signalling lymphocytic activation molecule (SLAM) in patients with rheumatoid arthritis (RA) and its role in the regulation of cytokine production. Scand J Rheumatol. 2006 Jul-Aug;35(4):268-72.

1729. Morita Y, Sasae Y, Sakuta T, et al. Efficacy of low-dose tacrolimus added to methotrexate in patients with rheumatoid arthritis in Japan: a retrospective study. Mod Rheumatol. 2008;18(4):379-84.

1730. Morozzi G, Fabbroni M, Bellisai F, et al. Low serum level of COMP, a cartilage turnover marker, predicts rapid and high ACR70 response to adalimumab therapy in rheumatoid arthritis. Clin Rheumatol. 2007 Aug;26(8):1335-8.

1731. Morrison E, Crosbie D, Capell HA. Attitude of rheumatoid arthritis patients to treatment with oral corticosteroids. Rheumatology (Oxford). 2003 Oct;42(10):1247-50.

1732. Moszyk DJ, Sulit DJ. Rheumatoid arthritis in a military aviator. Aviat Space Environ Med. 2007 Jan;78(1):63-6.

1733. Motivala SJ, Khanna D, FitzGerald J, et al. Stress activation of cellular markers of inflammation in rheumatoid arthritis: protective effects of tumor necrosis factor alpha antagonists. Arthritis Rheum. 2008 Feb;58(2):376-83.

1734. Mourao AF, Rustin M, Isenberg D. Exacerbation of psoriatic skin lesions in patients with psoriatic arthritis receiving anti-tumour necrosis factor-alpha therapy: description of 3 cases and review of the literature. Clin Exp Rheumatol. 2010 May-Jun;28(3):408-10.

1735. Mrabet D, Meddeb N, Ajlani H, et al. Cerebral vasculitis in a patient with rheumatoid arthritis. Joint Bone Spine. 2007 Mar;74(2):201-4.

1736. Mufti AH, Toye BW, McKendry RR, et al. Mycobacterium abscessus infection after use of tumor necrosis factor alpha inhibitor therapy: case report and review of infectious complications associated with tumor necrosis factor alpha inhibitor use. Diagn Microbiol Infect Dis. 2005 Nov;53(3):233-8.

1737. Mugnier B, Balandraud N, Darque A, et al. Polymorphism at position -308 of the tumor necrosis factor alpha gene influences outcome of infliximab therapy in rheumatoid arthritis. Arthritis Rheum. 2003 Jul;48(7):1849-52.

1738. Mulherin D, Sheeran TP. Clinical image: hidden costs of anti-tumor necrosis factor alpha therapy. Arthritis Rheum. 2003 Mar;48(3):868.

1739. Mullan RH, Bresnihan B. Disease-modifying anti-rheumatic drug therapy and structural damage in early rheumatoid arthritis. Clin Exp Rheumatol. 2003 Sep-Oct;21(5 Suppl 31):S158-64.

1740. Muller K, Zak M, Nielsen S, et al. Interleukin-1 receptor antagonist in neonates, children and adults, and in patients with pauci- and polyarticular onset juvenile chronic arthritis. Clin Exp Rheumatol. 1997 Jul-Aug;15(4):439-44.

1741. Muntinghe FL, de Filippi JP, Breedveld RW, et al. A young woman with fever and a pericardial effusion. Neth J Med. 2002 Nov;60(10):414-5.

1742. Murata K, Yasuda T, Ito H, et al. Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Mod Rheumatol. 2006;16(1):14-9.

1743. Murphy FT, Enzenauer RJ, Battafarano DF, et al. Etanercept-associated injection-site reactions. Arch Dermatol. 2000 Apr;136(4):556-7.

1744. Murphy NG. Current concepts in the management of rheumatoid arthritis. Del Med J. 1992 Apr;64(4):257-64.

1745. Murray RP, Bourne MH, Fitzgerald RH, Jr. Metachronous infections in patients who have had more than one total joint arthroplasty. J Bone Joint Surg Am. 1991 Dec;73(10):1469-74.

1746. Musial J, Undas A, Celinska-Lowenhoff M. Polymyositis associated with infliximab treatment for rheumatoid arthritis. Rheumatology (Oxford). 2003 Dec;42(12):1566-8.

1747. Muto S, Asano Y, Okazaki H, et al. Renal potassium wasting in distal renal tubular acidosis: role of aldosterone. Intern Med. 1992 Aug;31(8):1047-51.

1748. Mutsukura K, Nakamura H, Iwanaga N, et al. Successful treatment of a patient with primary Sjogren's syndrome complicated with pericarditis during pregnancy. Intern Med. 2007;46(14):1143-7.

1749. Muzaffer MA, Dayer JM, Feldman BM, et al. Differences in the profiles of circulating levels of soluble tumor necrosis factor receptors and interleukin 1 receptor antagonist reflect the heterogeneity of the subgroups of juvenile rheumatoid arthritis. J Rheumatol. 2002 May;29(5):1071-8.

1750. Myers WA, Najarian D, Gottlieb AB. New-onset, debilitating arthritis in psoriasis patients receiving efalizumab. J Dermatolog Treat. 2006;17(6):353-4.

1751. Mylona E, Golfinopoulou S, Samarkos M, et al. Acute hepatitis in adult Still's disease during corticosteroid treatment successfully treated with anakinra. Clin Rheumatol. 2008 May;27(5):659-61.

1752. Mylona E, Vadala C, Papadakos V, et al. Cutaneous polyarteritis nodosa in adult onset Still's disease. Eur J Dermatol. 2009 Nov-Dec;19(6):621-2.

1753. Nabae M, Inoue K, Ushiyama T, et al. Gene expressions of antiinflammatory mediators in THR retrieved interfacial membranes. Acta Orthop Scand. 1999 Apr;70(2):149-54.

1754. Nadarajah K, Pritchard C. Listeria monocytogenes septic arthritis in a patient treated with etanercept for rheumatoid arthritis. J Clin Rheumatol. 2005 Apr;11(2):120-2.

1755. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum 2008;59(8):1090-6.

1756. Nagasawa H, Kameda H, Sekiguchi N, et al. Normalisation of physical function by infliximab in patients with RA: factors associated with normal physical function. Clin Exp Rheumatol. 2010 May-Jun;28(3):365-72.

1757. Nagashima M, Matsuoka T, Saitoh K, et al. Treatment continuation rate in relation to efficacy and toxicity in long-term therapy with low-dose methotrexate, sulfasalazine, and bucillamine in 1,358 Japanese patients with rheumatoid arthritis. Clin Exp Rheumatol 2006;24(3):260-7.

1758. Nair B, Raval G, Mehta P. TNF-alpha inhibitor etanercept and hematologic malignancies: report of a case and review of the literature. Am J Hematol. 2007 Nov;82(11):1022-4.

1759. Nakahara H, Mima T, Yoshio-Hoshino N, et al. A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. Mod Rheumatol. 2009;19(1):69-72.

1760. Nakajima A, Inoue E, Tanaka E, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol. 2010;39(5):360-7.

1761. Nakamura T, Higashi S, Tomoda K, et al. Efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):518-22.

1762. Nakashima C, Tanioka M, Takahashi K, et al. Diffuse large B-cell lymphoma in a patient with rheumatoid arthritis treated with infliximab and methotrexate. Clin Exp Dermatol. 2008 Jul;33(4):437-9.

1763. Nakashima Y, Kondo M, Harada H, et al. Clinical evaluation of tocilizumab for patients with active rheumatoid arthritis refractory to anti-TNF biologics: tocilizumab in combination with methotrexate. Mod Rheumatol. 2010 Aug;20(4):343-52.

1764. Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. Am J Med. 2002 Jan;112(1):78.

1765. Nakou M, Katsikas G, Sidiropoulos P, et al. Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells correlates with clinical response. Arthritis Res Ther. 2009;11(4):R131.

1766. Nampei A, Hashimoto J, Koyanagi J, et al. Characteristics of fracture and related factors in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18(2):170-6.

1767. Nanke Y, Kotake S, Yonemoto K, et al. Cricoarytenoid arthritis with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 2001 Mar;28(3):624-6.

1768. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10(2):R30.

1769. Naredo E, Moller I, Cruz A, et al. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Aug;58(8):2248-56.

1770. Narushima M, Suzuki H, Kasai T, et al. Pulmonary nocardiosis in a patient treated with corticosteroid therapy. Respirology. 2002 Mar;7(1):87-9.

1771. Narvaez J, Montala N, Busquets-Perez N, et al. Collagenous colitis and spondylarthropathy. Arthritis Rheum. 2006 Jun 15;55(3):507-12.

1772. Nash P, Thaci D, Behrens F, et al. Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. Dermatology. 2006;212(3):238-49.

1773. Nast A, Reytan N, Rosumeck S, et al. Low prescription rate for systemic treatments in the management of severe psoriasis vulgaris and psoriatic arthritis in dermatological practices in Berlin and Brandenburg, Germany: results from a patient registry. J Eur Acad Dermatol Venereol. 2008 Nov;22(11):1337-42.

1774. Natsuga K, Sawamura D, Homma E, et al. Amicrobial pustulosis associated with IgA nephropathy and Sjogren's syndrome. J Am Acad Dermatol. 2007 Sep;57(3):523-6.

1775. Nawata M, Saito K, Nakayamada S, et al. Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. Mod Rheumatol. 2008;18(5):460-4.

1776. Ndongo S, Lekpa FK, Ka MM, et al. Presentation and severity of rheumatoid arthritis at diagnosis in Senegal. Rheumatology (Oxford). 2009 Sep;48(9):1111-3.

1777. Neeck G, Federlin K, Graef V, et al. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J Rheumatol. 1990 Jan;17(1):24-9.

1778. Neeman N, Aronson MD, Schulze JE, et al. Improving pregnancy counseling for women with rheumatoid arthritis taking methotrexate. Am J Med. 2009 Nov;122(11):998-1000.

1779. Neff K, Stack J, Harney S, et al. The use of abatacept in debilitating cavitating lung disease associated with rheumatoid arthritis, bronchocentric granulomatosis and aspergillosis. Thorax. 2010 Jun;65(6):545-6.

1780. Neidel J, Schulze M, Lindschau J. Association between degree of bone-erosion and synovial fluid-levels of tumor necrosis factor alpha in the knee-joints of patients with rheumatoid arthritis. Inflamm Res. 1995 May;44(5):217-21.

1781. Nemoto Y, Taniguchi A, Kamioka M, et al. Epstein-Barr virus-infected subcutaneous panniculitis-like T-cell lymphoma associated with methotrexate treatment. Int J Hematol. 2010 Sep;92(2):364-8.

1782. Nerome Y, Imanaka H, Nonaka Y, et al. A case of planned pregnancy with an interruption in infliximab administration in a 27-year-old female patient with rheumatoid-factor-positive polyarthritis juvenile idiopathic arthritis which improved after restarting infliximab and methotrexate. Mod Rheumatol. 2008;18(2):189-92.

1783. Nesheiwat JP, Dillon K, McGlothan K, et al. An elderly man with rheumatoid arthritis and dyspnea. Chest. 2009 Apr;135(4):1090-3.

1784. Netea MG, Radstake T, Joosten LA, et al. Salmonella septicemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: association with decreased interferon-gamma production and Toll-like receptor 4 expression. Arthritis Rheum. 2003 Jul;48(7):1853-7.

1785. Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. J Rheumatol Suppl. 1997 Feb;47:17-22.

1786. Newman DK, Isaacs JD, Watson PG, et al. Prevention of immune-mediated corneal graft destruction with the anti-lymphocyte monoclonal antibody, CAMPATH-1H. Eye. 1995;9 (Pt 5):564-9.

1787. Newton SM, Mackie SL, Martineau AR, et al. Reduction of chemokine secretion in response to mycobacteria in infliximab-treated patients. Clin Vaccine Immunol. 2008 Mar;15(3):506-12.

1788. Ng CM, Bruno R, Combs D, et al. Population pharmacokinetics of rituximab (anti-CD20 monoclonal antibody) in rheumatoid arthritis patients during a phase II clinical trial. J Clin Pharmacol. 2005 Jul;45(7):792-801.

1789. Niemela RK, Hakala M. Primary Sjogren's syndrome with severe central nervous system disease. Semin Arthritis Rheum. 1999 Aug;29(1):4-13.

1790. Niemela RK, Hakala M, Huikuri HV, et al. Comprehensive study of autonomic function in a population with primary Sjogren's syndrome. No evidence of autonomic involvement. J Rheumatol. 2003 Jan;30(1):74-9.

1791. Niewold TB, Gibofsky A. Concomitant interferon-alpha therapy and tumor necrosis factor alpha inhibition for rheumatoid arthritis and hepatitis C. Arthritis Rheum. 2006 Jul;54(7):2335-7.

1792. Niitsu N, Okamoto M, Nakamine H, et al. Clinicopathologic correlations of diffuse large B-cell lymphoma in rheumatoid arthritis patients treated with methotrexate. Cancer Sci. 2010 May;101(5):1309-13.

1793. Nikas SN, Alamanos Y, Voulgari PV, et al. Infliximab treatment in ankylosing spondylitis: an observational study. Ann Rheum Dis. 2005 Jun;64(6):940-2.

1794. Nikas SN, Temekonidis TI, Zikou AK, et al. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. Ann Rheum Dis. 2004 Jan;63(1):102-3.

1795. Nikas SN, Voulgari PV, Alamanos Y, et al. Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. Ann Rheum Dis. 2006 Feb;65(2):257-60.

1796. Nikas SN, Voulgari PV, Takalou IP, et al. Healing of psoriatic skin lesions, and improvement of psoriatic arthritis resistant to immunosuppressive drugs, after infliximab treatment. Ann Rheum Dis. 2005 Nov;64(11):1665-7.

1797. Nishida K, Okada Y, Nawata M, et al. Induction of hyperadiponectinemia following long-term treatment of patients with rheumatoid arthritis with infliximab (IFX), an anti-TNF-alpha antibody. Endocr J. 2008 Mar;55(1):213-6.

1798. Nishie W, Sawamura D, Iitoyo M, et al. Intravascular histiocytosis associated with rheumatoid arthritis. Dermatology. 2008;217(2):144-5.

1799. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007;66(9):1162-7.

1800. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19(1):12-9.

1801. Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008 Nov 15;112(10):3959-64.

1802. Nishimura H, Tachibana H, Makiura N, et al. Corticosteroid-responsive parkinsonism associated with primary Sjogren's syndrome. Clin Neurol Neurosurg. 1994 Nov;96(4):327-31.

1803. Nissinen R, Leirisalo-Repo M, Peltomaa R, et al. Cytokine and chemokine receptor profile of peripheral blood mononuclear cells during treatment with infliximab in patients with active rheumatoid arthritis. Ann Rheum Dis. 2004 Jun;63(6):681-7.

1804. Niwa Y, Iio A, Niwa G, et al. Serum albumin metabolism in rheumatic diseases: relationship to corticosteroids and peptic ulcer. J Clin Lab Immunol. 1990 Jan;31(1):11-6.

1805. Nizam S, Johnstone A, Green M, et al. Necrotising scleritis and connective tissue disease--three cases and a review. Clin Rheumatol. 2009 Mar;28(3):339-41.

1806. Noguera-Pons R, Borras-Blasco J, Romero-Crespo I, et al. Optic neuritis with concurrent etanercept and isoniazid therapy. Ann Pharmacother. 2005 Dec;39(12):2131-5.

1807. Nonaka T, Nishisaka F, Fukuda K, et al. Relationship between bone mineral density and urine level of NTx in rheumatoid arthritis. J Bone Miner Metab. 2005;23(4):314-7.

1808. Novak S, Cikes N. Infliximab-induced lupus or rheumatoid arthritis (RA) overlapping with systemic lupus erythematosus (SLE) unmasked by infliximab. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):268.

1809. Nozaki Y, Nagare Y, Hino S, et al. Therapeutic strategy and significance of serum rheumatoid factor in patients with rheumatoid arthritis during infliximab

treatment. Nihon Rinsho Meneki Gakkai Kaishi. 2010;33(3):135-41.

1810. Nozaki Y, Nagare Y, Kinoshita K, et al. Successful treatment using tacrolimus plus corticosteroid in a patient with RA associated with MDS. Rheumatol Int. 2008 Mar;28(5):487-90.

1811. Nuijten MJ, Engelfriet P, Duijn K, et al. A cost-cost study comparing etanercept with infliximab in rheumatoid arthritis. Pharmacoeconomics. 2001;19(10):1051-64.

1812. Nuki G, Bresnihan B, Bear MB, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46.

1813. Nunez-Cornejo C, Borras-Blasco J, Gracia-Perez A, et al. Septic shock and community-acquired pneumonia associated with etanercept therapy. Int J Clin Pharmacol Ther. 2008 Apr;46(4):193-7.

1814. Nyhall-Wahlin BM, Petersson IF, Nilsson JA, et al. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. Rheumatology (Oxford). 2009 Apr;48(4):416-20.

1815. Oberstein EM, Kromo O, Tozman EC. Type I reaction of Hansen's disease with exposure to adalimumab: a case report. Arthritis Rheum. 2008 Jul 15;59(7):1040-3.

1816. Ochi S, Harigai M, Mizoguchi F, et al. Leflunomide-related acute interstitial pneumonia in two patients with rheumatoid arthritis: autopsy findings with a mosaic pattern of acute and organizing diffuse alveolar damage. Mod Rheumatol. 2006;16(5):316-20.

1817. Ochi S, Taniguchi K, Nagashima M. Leflunomide-induced polymyositis in a patient with rheumatoid arthritis. Mod Rheumatol. 2009;19(4):443-6.

1818. Ochiai T, Washio H, Shiraiwa H, et al. Psoriatic onycho-pachydermo-periostitis successfully treated with low-dose methotrexate. Med Sci Monit. 2006 Apr;12(4):CS27-30.

1819. O'Connor PA, Eustace S, O'Byrne J. Spinal cord injury following osteoporotic vertebral fracture: case report. Spine. 2002 Sep 15;27(18):E413-5.

1820. Oda S, Fujinaga H, Takahashi K. Infectious myositis involving the piriformis in a patient with rheumatoid arthritis. Mod Rheumatol. 2006;16(4):260-3.

1821. O'Dell J. Conventional DMARD options for patients with a suboptimal response to methotrexate. J Rheumatol Suppl. 2001 Jun;62:21-6.

1822. O'Dell JR, Petersen K, Leff R, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):213-8.

1823. Odessey E, Cohn A, Beaman K, et al. Invasive mucormycosis of the maxillary sinus: extensive destruction with an indolent presentation. Surg Infect (Larchmt). 2008 Feb;9(1):91-8.

1824. Oei HB, Hooker RS, Cipher DJ, et al. High rates of stopping or switching biological medications in veterans with rheumatoid arthritis. Clin Exp Rheumatol 2009;27(6):926-34.

1825. Oelzner P, Schwabe A, Lehmann G, et al. Significance of risk factors for osteoporosis is dependent on gender and menopause in rheumatoid arthritis. Rheumatol Int. 2008 Sep;28(11):1143-50.

1826. Ogawa H, Itokazu M, Ito Y, et al. Quality of life evaluated by Short Form-8 in patients with rheumatoid arthritis who were receiving infusion of infliximab. Mod Rheumatol. 2009;19(1):27-32.

1827. Ogiwara Y, Mochizuki H, Morioka T, et al. A case with life-threatening interstitial pneumonia associated with bucillamine

treatment. Mod Rheumatol. 2008;18(5):522-5.

1828. Oguz FM, Oguz A, Uzunlulu M. The effect of infliximab treatment on insulin resistance in patients with rheumatoid arthritis. Acta Clin Belg. 2007 Jul-Aug;62(4):218-22.

1829. Oh J, Arkfeld DG, Horwitz DA. Development of Crohn's disease in a patient taking etanercept. J Rheumatol. 2005 Apr;32(4):752-3.

1830. Oh WM, Hwang IN, Son HH, et al. Rapid periapical bone destruction during endodontic treatment of a patient with rheumatoid arthritis. J Endod. 2008 Oct;34(10):1261-3.

1831. Ohshima S, Mima T, Sasai M, et al. Tumour necrosis factor alpha (TNF-alpha) interferes with Fas-mediated apoptotic cell death on rheumatoid arthritis (RA) synovial cells: a possible mechanism of rheumatoid synovial hyperplasia and a clinical benefit of anti-TNF-alpha therapy for RA. Cytokine. 2000 Mar;12(3):281-8.

1832. Ohsugi Y, Kishimoto T. The recombinant humanized anti-IL-6 receptor antibody tocilizumab, an innovative drug for the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2008 May;8(5):669-81.

1833. Oili KS, Niinisalo H, Korpilahde T, et al. Treatment of reactive arthritis with infliximab. Scand J Rheumatol. 2003;32(2):122-4.

1834. Okamoto H, Koizumi K, Kamitsuji S, et al. Beneficial action of statins in patients with rheumatoid arthritis in a large observational cohort. J Rheumatol. 2007 May;34(5):964-8.

1835. Okamoto O, Oishi M, Fujiwara S. Steroid-resistant adult-onset Still's disease which showed a quick response to methotrexate. J Dermatol. 2008 Feb;35(2):106-10.

1836. Okuda Y, Takasugi K. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. Arthritis Rheum. 2006 Sep;54(9):2997-3000.

1837. Okuda Y, Takasugi K, Oyama T, et al. Intractable diarrhoea associated with secondary amyloidosis in rheumatoid arthritis. Ann Rheum Dis. 1997 Sep;56(9):535-41.

1838. Olewicz-Gawlik A, Korczowska-Lacka I, Lacki JK, et al. Fucosylation of serum alpha1-acid glycoprotein in rheumatoid arthritis patients treated with infliximab. Clin Rheumatol. 2007 Oct;26(10):1679-84.

1839. Olive A, del Blanco J, Pons M, et al. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalan Group for the Study of RS3PE. J Rheumatol. 1997 Feb;24(2):333-6.

1840. Oliveira B, Arkfeld DG, Weitz IC, et al. Successful rituximab therapy of acquired factor VIII inhibitor in a patient with rheumatoid arthritis. J Clin Rheumatol. 2007 Apr;13(2):89-91.

1841. Olivieri I, de Portu S, Salvarani C, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology (Oxford). 2008 Nov;47(11):1664-70.

1842. Olivieri I, de Stefano G, Padula A, et al. Infliximab in a case of early adult-onset Still's disease. Clin Rheumatol. 2003 Oct;22(4-5):369-70.

1843. Olivieri I, Palazzi C, Peruz G, et al. Management issues with elderly-onset rheumatoid arthritis: an update. Drugs Aging. 2005;22(10):809-22.

1844. Ollendorf DA, Massarotti E, Birbara C, et al. Frequency, predictors, and economic impact of upward dose adjustment of infliximab in managed care patients with rheumatoid arthritis. J Manag Care Pharm. 2005 Jun;11(5):383-93.

1845. Ollendorf DA, Peterson AN, Doyle J, et al. Impact of leflunomide versus biologic agents on the costs of care for rheumatoid arthritis in a managed care population. Am J Manag Care. 2002 May;8(7 Suppl):S203-13.

1846. Omdal R, Gunnarsson R. The effect of interleukin-1 blockade on fatigue in rheumatoid arthritis--a pilot study. Rheumatol Int. 2005 Aug;25(6):481-4.

1847. Ongaro A, De Mattei M, Pellati A, et al. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading to anti-TNFalpha therapy in rheumatoid arthritis? Rheumatol Int. 2008 Jul;28(9):901-8.

1848. Onuma S, Yamaji K, Kempe K, et al. Investigation of the clinical effect of large volume leukocytapheresis on methotrexate-resistant rheumatoid arthritis. Ther Apher Dial. 2006 Oct;10(5):404-11.

1849. Ooi KG, Wingate R, Adler PA. Necrotising anterior scleritis in a late-onset rheumatoid arthritis (LORA) patient. Ocul Immunol Inflamm. 2007 Jan-Feb;15(1):33-6.

1850. Oren S, Mandelboim M, Braun-Moscovici Y, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis. 2008 Jul;67(7):937-41.

1851. Ornetti P, Solau E, Gaudin P, et al. Increase in methotrexate dose in patients with rheumatoid arthritis who have an inadequate response to infliximab. Ann Rheum Dis. 2005 Sep;64(9):1379-80.

1852. Orstavik RE, Haugeberg G, Mowinckel P, et al. Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. Arch Intern Med. 2004 Feb 23;164(4):420-5.

1853. Orstavik RE, Haugeberg G, Uhlig T, et al. Vertebral deformities in 229 female patients with rheumatoid arthritis: associations with clinical variables and bone mineral density. Arthritis Rheum. 2003 Jun 15;49(3):355-60.

1854. Orstavik RE, Haugeberg G, Uhlig T, et al. Incidence of vertebral deformities in 255 female rheumatoid arthritis patients measured by morphometric X-ray absorptiometry. Osteoporos Int. 2005 Jan;16(1):35-42.

1855. Orstavik RE, Haugeberg G, Uhlig T, et al. Quantitative ultrasound and bone mineral density: discriminatory ability in patients with rheumatoid arthritis and controls with and without vertebral deformities. Ann Rheum Dis. 2004 Aug;63(8):945-51.

1856. Ortiz-Santamaria V, Valls-Roc M, Sanmarti M, et al. Anti-TNF treatment in secondary amyloidosis. Rheumatology (Oxford). 2003 Nov;42(11):1425-6.

1857. Osawa H, Yamabe H, Seino S, et al. A case of Sjogren's syndrome associated with Sweet's syndrome. Clin Rheumatol. 1997 Jan;16(1):101-5.

1858. Ostanek L, Pawlik A, Brzosko I, et al. The urinary excretion of pyridinoline and deoxypyridinoline during rheumatoid arthritis therapy with infliximab. Clin Rheumatol. 2004 Jun;23(3):214-7.

1859. Ostensen M, Eigenmann GO. Etanercept in breast milk. J Rheumatol. 2004 May;31(5):1017-8.

1860. Ostensen M, Forger F. Management of RA medications in pregnant patients. Nat Rev Rheumatol. 2009 Jul;5(7):382-90.

1861. Ostensen M, Raio L. A woman with rheumatoid arthritis whose condition did not improve during pregnancy. Nat Clin Pract Rheumatol. 2005 Dec;1(2):111-4; quiz 1 p following 4.

1862. Ostergaard M, Duer A, Nielsen H, et al. Magnetic resonance imaging for accelerated assessment of drug effect and prediction of subsequent radiographic progression in rheumatoid arthritis: a study of patients receiving combined anakinra and methotrexate treatment. Ann Rheum Dis. 2005 Oct;64(10):1503-6.

1863. Ostor AJ, Crisp AJ, Somerville MF, et al. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. BMJ. 2004 Nov 27;329(7477):1266.

1864. Ostrov BE. Beneficial effect of etanercept on rheumatoid lymphedema. Arthritis Rheum. 2001 Jan;44(1):240-1.

1865. Ostuni P, Botsios C, Punzi L, et al. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. Ann Rheum Dis. 2003 Jul;62(7):686-7.

1866. O'Sullivan MM, Amos N, Bedwell A, et al. Complement-mediated inhibition of immune precipitation in rheumatoid vasculitis. Rheumatol Int. 1990;10(4):159-63.

1867. Otabe S, Muto S, Asano Y, et al. Selective hypoaldosteronism in a patient with Sjogren's syndrome: insensitivity to angiotensin II. Nephron. 1991;59(3):466-70.

1868. Otsuka T, Koyama T, Ohtani R, et al. Leflunomide-induced lung injury that developed after its withdrawal, coinciding with peripheral blood lymphocyte count decrease. Mod Rheumatol. 2008;18(1):96-9.

1869. Ott SJ, Baron A, Berghaus T, et al. Liver failure in adult Still's disease during corticosteroid treatment. Eur J Gastroenterol Hepatol. 2003 Jan;15(1):87-90.

1870. Ouedraogo DD, Palazzo E, Nlome-Nze M, et al. Predominant cervical involvement in patients with psoriatic arthritis: report of two cases. Joint Bone Spine. 2007 Mar;74(2):175-8.

1871. Owino BO, Oyoo GO, Otieno CF. Socio-demographic and clinical aspects of rheumatoid arthritis. East Afr Med J. 2009 May;86(5):204-11.

1872. Ozaki D, Shirai Y, Nakayama Y, et al. A case report of insufficiency fracture of the Fossa acetabuli in a patient with rheumatoid arthritis. J Nippon Med Sch. 2000 Aug;67(4):267-70.

1873. Ozgocmen S, Godekmerdan A, Ozkurt-Zengin F. Acute-phase response, clinical measures and disease activity in ankylosing spondylitis. Joint Bone Spine. 2007 May;74(3):249-53.

1874. Ozgocmen S, Ozdemir H, Kiris A, et al. Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial inflammation in clinical remission. South Med J. 2008 Mar;101(3):240-5.

1875. Pace J, Adami JZ, Mallia C, et al. Toxic epidermal necrolysis in a patient with psoriatic arthritis. Adv Exp Med Biol. 1999;455:557-60.

1876. Pachot A, Arnaud B, Marrote H, et al. Increased tumor necrosis factor-alpha mRNA expression in whole blood from patients with rheumatoid arthritis: reduction after infliximab treatment does not predict response. J Rheumatol. 2007 Nov;34(11):2158-61.

1877. Padyukov L, Lampa J, Heimburger M, et al. Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis. Ann Rheum Dis. 2003 Jun;62(6):526-9.

1878. Pagliano P, Attanasio V, Fusco U, et al. Does etanercept monotherapy enhance the risk of Listeria monocytogenes meningitis? Ann Rheum Dis. 2004 Apr;63(4):462-3.

1879. Paira S, Caliani L, Luraquiz N. Distal extremity swelling with pitting oedema in rheumatoid arthritis. Clin Rheumatol. 2001;20(1):76-9.

1880. Palanichamy A, Roll P, Theiss R, et al. Modulation of molecular imprints in the antigen-experienced B cell repertoire by rituximab. Arthritis Rheum. 2008 Dec;58(12):3665-74.

1881. Palazzi C, D'Amico E, Pennese E, et al. Purpura and serum mixed cryoglobulinemia in psoriatic arthritis. Rheumatol Int. 2006 Dec;27(2):187-9.

1882. Palkonyai E, Kolarz G, Kopp M, et al. Depressive symptoms in early rheumatoid arthritis: a comparative longitudinal study. Clin Rheumatol. 2007 May;26(5):753-8.

1883. Pallinti V, Ganesan N, Anbazhagan M, et al. Serum biochemical markers in rheumatoid arthritis. Indian J Biochem Biophys. 2009 Aug;46(4):342-4.

1884. Pallotta P, Cianchini G, Ruffelli M, et al. Infliximab-induced lupus-like reaction in a

patient with psoriatic arthritis. Rheumatology (Oxford). 2006 Jan;45(1):116-7.

1885. Palm S, Hinrichsen H, Barth J, et al. Modulation of lymphocyte subsets due to psychological stress in patients with rheumatoid arthritis. Eur J Clin Invest. 1992 Oct;22 Suppl 1:26-9.

1886. Pamuk ON, Harmandar F. A case of cervical spine meningioma following etanercept use in a patient with RA. Nat Rev Rheumatol. 2009 Aug;5(8):457-60.

1887. Pamuk ON, Harmandar F, Cakir N. The development of trigeminal neuralgia related to auricular chondritis in a patient with rheumatoid arthritis-relapsing polychondritis and its treatment with etanercept. Description of the first case. Clin Exp Rheumatol. 2009 Jan-Feb;27(1):128-9.

1888. Pan SM, Dehler S, Ciurea A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009;61(5):560-8.

1889. Panfilio CB, Hernandez-Cossio O, Hernandez-Fustes OJ. Orbital myositis and rheumatoid arthritis: case report. Arq Neuropsiquiatr. 2000 Mar;58(1):174-7.

1890. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):72-5.

1891. Panthakalam S, Bhatnagar D, Klimiuk P. The prevalence and management of hyperglycaemia in patients with rheumatoid arthritis on corticosteroid therapy. Scott Med J. 2004 Nov;49(4):139-41.

1892. Papadaki HA, Kritikos HD, Valatas V, et al. Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: improvement following anti-tumor necrosis factor-alpha antibody therapy. Blood. 2002 Jul 15;100(2):474-82.

1893. Papadopoulos IA, Katsimbri P, Alamanos Y, et al. Early rheumatoid arthritis patients: relationship of age. Rheumatol Int. 2003 Mar;23(2):70-4.

1894. Papageorgiou SG, Kontaxis T, Bonakis A, et al. Orofacial dystonia related to Sjogren's syndrome. Clin Rheumatol. 2007 Oct;26(10):1779-81.

1895. Papagoras CE, Argyropoulou MI, Voulgari PV, et al. A case of Brucella spondylitis in a patient with psoriatic arthritis receiving infliximab. Clin Exp Rheumatol. 2009 Jan-Feb;27(1):124-7.

1896. Papanikolaou IC, Sharma OP. A 47-year-old woman with rheumatoid arthritis and dyspnea on exertion. Chest. 2009 Dec;136(6):1694-7.

1897. Papoutsaki M, Chimenti MS, Costanzo A, et al. Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. J Am Acad Dermatol. 2007 Aug;57(2):269-75.

1898. Parambil JG, Myers JL, Lindell RM, et al. Interstitial lung disease in primary Sjogren syndrome. Chest. 2006 Nov;130(5):1489-95.

1899. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. Respirology. 2009 Apr;14(3):443-8.

1900. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest. 2007 Jul;132(1):214-20.

1901. Park JH, Seo GY, Lee JS, et al. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. J Rheumatol. 2009 Oct;36(10):2158-63.

1902. Park MC, Chung SJ, Park YB, et al. Relationship of serum TWEAK level to cytokine level, disease activity, and response to anti-TNF treatment in patients with

rheumatoid arthritis. Scand J Rheumatol. 2008 May-Jun;37(3):173-8.

1903. Park SH, Kim CG, Kim JY, et al. Spontaneous regression of EBV-associated diffuse lymphoproliferative disease in a patient with rheumatoid arthritis after discontinuation of etanercept treatment. Rheumatol Int. 2008 Mar;28(5):475-7.

1904. Park YB, Ahn CW, Choi HK, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. Arthritis Rheum. 2002 Jul;46(7):1714-9.

1905. Park YB, Choi HK, Kim MY, et al. Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. Am J Med. 2002 Aug 15;113(3):188-93.

1906. Park YB, Lee SK, Lee WK, et al. Lipid profiles in untreated patients with rheumatoid arthritis. J Rheumatol. 1999 Aug;26(8):1701-4.

1907. Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum. 2004 Oct 15;51(5):800-4.

1908. Parker A, Izmailova ES, Narang J, et al. Peripheral blood expression of nuclear factor-kappab-regulated genes is associated with rheumatoid arthritis disease activity and responds differentially to anti-tumor necrosis factor-alpha versus methotrexate. J Rheumatol. 2007 Sep;34(9):1817-22.

1909. Parker SR, Solomon AR, Lane JE. A report of Epstein-Barr virus-positive primary cutaneous natural killer-/T-cell lymphoma. J Am Acad Dermatol. 2008 Jul;59(1):157-61.

1910. Paroli MP, Bruscolini A, De Carlo L, et al. Ring keratopathy in a patient with psoriatic arthritis and ulcerative rectocolitis. Ocul Immunol Inflamm. 2007 Jan-Feb;15(1):51-6.

1911. Parra Ruiz J, Ortego Centeno N, Raya Alvarez E. Development of tuberculosis in a patient treated with infliximab who had received prophylactic therapy with isoniazid. J Rheumatol. 2003 Jul;30(7):1657-8.

1912. Pasek M, Duk M, Podbielska M, et al. Galactosylation of IgG from rheumatoid arthritis (RA) patients--changes during therapy. Glycoconj J. 2006 Nov;23(7-8):463-71.

1913. Patel A, Kesler B, Wise RA. Persistent pneumomediastinum in interstitial fibrosis associated with rheumatoid arthritis: treatment with high-concentration oxygen. Chest. 2000 Jun;117(6):1809-13.

1914. Patel NK, Salathe C, Vu C, et al. Esophagitis dissecans: a rare cause of odynophagia. Endoscopy. 2007 Feb;39 Suppl 1:E127.

1915. Paulus HE, Di Primeo D, Sanda M, et al. Progression of radiographic joint erosion during low dose corticosteroid treatment of rheumatoid arthritis. J Rheumatol. 2000 Jul;27(7):1632-7.

1916. Paulus HE, Di Primeo D, Sharp JT, et al. Patient retention and hand-wrist radiograph progression of rheumatoid arthritis during a 3-year prospective study that prohibited disease modifying antirheumatic drugs. J Rheumatol. 2004 Mar;31(3):470-81.

1917. Pavelka K, Gatterova J, Tegzova D, et al. Radiographic progression of rheumatoid arthritis in patients from the Czech National Registry receiving infliximab treatment. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):540-5.

1918. Pavletic SZ, Klassen LW, Pope R, et al. Treatment of relapse after autologous blood stem cell transplantation for severe rheumatoid arthritis. J Rheumatol Suppl. 2001 Oct;64:28-31.

1919. Pavlica L, Peric-Hajzler Z, Jovelic A, et al. Psoriatic arthritis: a retrospective study of 162 patients. Vojnosanit Pregl. 2005 Sep;62(9):613-20.

1920. Pawlik A, Herczynska M, Kurzawski M, et al. The effect of exon (19C>A) dihydroorotate dehydrogenase gene polymorphism on rheumatoid arthritis

treatment with leflunomide. Pharmacogenomics. 2009 Feb;10(2):303-9.

1921. Pawlik A, Herczynska M, Kurzawski M, et al. IL-1beta, IL-6, and TNF gene polymorphisms do not affect the treatment outcome of rheumatoid arthritis patients with leflunomide. Pharmacol Rep. 2009 Mar-Apr;61(2):281-7.

1922. Pawlik A, Ostanek L, Brzosko I, et al. Therapy with infliximab decreases the CD4+CD28- T cell compartment in peripheral blood in patients with rheumatoid arthritis. Rheumatol Int. 2004 Nov;24(6):351-4.

1923. Peddle L, Butt C, Snelgrove T, et al. Interleukin (IL) 1alpha, IL1beta, IL receptor antagonist, and IL10 polymorphisms in psoriatic arthritis. Ann Rheum Dis. 2005 Jul;64(7):1093-4.

1924. Pelivani N, Hassan AS, Braathen LR, et al. Alopecia areata universalis elicited during treatment with adalimumab. Dermatology. 2008;216(4):320-3.

1925. Penn SK, Kao AH, Schott LL, et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 2010 Jun;37(6):1136-42.

1926. Perdriger A, Mariette X, Kuntz JL, et al. Safety of infliximab used in combination with leflunomide or azathioprine in daily clinical practice. J Rheumatol. 2006 May;33(5):865-9.

1927. Perera LC, Tymms KE, Wilson BJ, et al. Etanercept in severe active rheumatoid arthritis: first Australian experience. Intern Med J. 2006 Oct;36(10):625-31.

1928. Perez-De-Lis M, Akasbi M, Siso A, et al. Cardiovascular risk factors in primary Sjogren's syndrome: a case-control study in 624 patients. Lupus. 2010;19(8):941-8.

1929. Perez-Ezquerra PR, de Barrio Fernandez M, de Castro Martinez FJ, et al. Delayed hypersensitivity to hydroxychloroquine manifested by two different types of cutaneous eruptions in the same patient. Allergol Immunopathol (Madr). 2006 Jul-Aug;34(4):174-5.

1930. Perez-Garcia C, Maymo J, Lisbona Perez MP, et al. Drug-induced systemic lupus erythematosus in ankylosing spondylitis associated with infliximab. Rheumatology (Oxford). 2006 Jan;45(1):114-6.

1931. Perez-Guijo VC, Cravo AR, Castro Mdel C, et al. Increased efficacy of infliximab associated with methotrexate in ankylosing spondylitis. Joint Bone Spine. 2007 May;74(3):254-8.

1932. Perhala RS, Wilke WS, Clough JD, et al. Local infectious complications following large joint replacement in rheumatoid arthritis patients treated with methotrexate versus those not treated with methotrexate. Arthritis Rheum. 1991 Feb;34(2):146-52.

1933. Peris P, Font J, Grau JM, et al. Calcitriol-mediated hypercalcaemia and increased interleukins in a patient with sarcoid myopathy. Clin Rheumatol. 1999;18(6):488-91.

1934. Perkins DJ, St Clair EW, Misukonis MA, et al. Reduction of NOS2 overexpression in rheumatoid arthritis patients treated with anti-tumor necrosis factor alpha monoclonal antibody (cA2). Arthritis Rheum. 1998 Dec;41(12):2205-10.

1935. Perlmutter A, Mittal A, Menter A. Tuberculosis and tumour necrosis factor-alpha inhibitor therapy: a report of three cases in patients with psoriasis. Comprehensive screening and therapeutic guidelines for clinicians. Br J Dermatol. 2009 Jan;160(1):8-15.

1936. Perotti LA, Peretti L, Lovino C, et al. Concentration of cortisol in the synovial fluid of patients with untreated rheumatoid arthritis. Relation to in vitro IL-8 production by synovial mononuclear cells. Ann N Y Acad Sci. 1999 Jun 22;876:255-8.

1937. Perry MG, Kirwan JR, Jessop DS, et al. Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. Ann Rheum Dis. 2009 Jan;68(1):63-8.

1938. Pers JO, Saraux A, Pierre R, et al. Anti-TNF-alpha immunotherapy is associated with increased gingival inflammation without clinical attachment loss in subjects with rheumatoid arthritis. J Periodontol. 2008 Sep;79(9):1645-51.

1939. Peters MJ, Vis M, van Halm VP, et al. Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. Ann Rheum Dis. 2007 Jul;66(7):958-61.

1940. Peterson JR, Hsu FC, Simkin PA, et al. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Ann Rheum Dis. 2003 Nov;62(11):1078-82.

1941. Peyrou J, Saxer-Sekulic N, Lerch R, et al. Fast progression of aortic stenosis in rheumatoid arthritis. Arch Cardiovasc Dis. 2009 Mar;102(3):251-2.

1942. Pfeil A, Lippold J, Eidner T, et al. Effects of leflunomide and methotrexate in rheumatoid arthritis detected by digital X-ray radiogrammetry and computer-aided joint space analysis. Rheumatol Int. 2009 Jan;29(3):287-95.

1943. Pflugfelder SC, Jones D, Ji Z, et al. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjogren's syndrome keratoconjunctivitis sicca. Curr Eye Res. 1999 Sep;19(3):201-11.

1944. Pham TN, Rahman P, Richardson VJ. Divergent effects of infliximab and anakinra therapies on macrophage phenotype from patients with refractory rheumatoid arthritis. Int J Immunopathol Pharmacol. 2010 Apr-Jun;23(2):491-501.

1945. Phillips K, Aliprantis A, Coblyn J. Strategies for the prevention and treatment of osteoporosis in patients with rheumatoid arthritis. Drugs Aging. 2006;23(10):773-9.

1946. Phillips K, Weinblatt M. Granulomatous lung disease occurring during etanercept treatment. Arthritis Rheum. 2005 Aug 15;53(4):618-20.

1947. Pickartz T, Pickartz H, Lochs H, et al. Overlap syndrome of autoimmune pancreatitis and cholangitis associated with secondary Sjogren's syndrome. Eur J Gastroenterol Hepatol. 2004 Nov;16(12):1295-9.

1948. Pijpe J, Meijer JM, Bootsma H, et al. Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjogren's syndrome. Arthritis Rheum. 2009 Nov;60(11):3251-6.

1949. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum. 2005 Sep;52(9):2740-50.

1950. Pijpe J, van Imhoff GW, Vissink A, et al. Changes in salivary gland immunohistology and function after rituximab monotherapy in a patient with Sjogren's syndrome and associated MALT lymphoma. Ann Rheum Dis. 2005 Jun;64(6):958-60.

1951. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken). 2010 Jul;62(7):1034-9.

1952. Pillemer SR, Brennan MT, Sankar V, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjogren's syndrome. Arthritis Rheum. 2004 Aug 15;51(4):601-4.

1953. Pincus T, Ferraccioli G, Sokka T, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology (Oxford). 2002 Dec;41(12):1346-56.

1954. Pincus T, Olsen NJ, Russell IJ, et al. Multicenter study of recombinant human erythropoietin in correction of anemia in rheumatoid arthritis. Am J Med. 1990 Aug;89(2):161-8.

1955. Pincus T, Swearingen CJ, Bergman M, et al. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index

without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol. 2008 Nov;35(11):2136-47.

1956. Pisitkun P, Pattarowas C, Siriwongpairat P, et al. Reappraisal of cervical spine subluxation in Thai patients with rheumatoid arthritis. Clin Rheumatol. 2004 Feb;23(1):14-8.

1957. Pitsillides AA, Will RK, Bayliss MT, et al. Circulating and synovial fluid hyaluronan levels. Effects of intraarticular corticosteroid on the concentration and the rate of turnover. Arthritis Rheum. 1994 Jul;37(7):1030-8.

1958. Pittoni V, Bombardieri M, Spinelli FR, et al. Anti-tumour necrosis factor (TNF) alpha treatment of rheumatoid arthritis (infliximab) selectively down regulates the production of interleukin (IL) 18 but not of IL12 and IL13. Ann Rheum Dis. 2002 Aug;61(8):723-5.

1959. Pizzuti P, Liote F, Cerf-Payrastre I, et al. Hypersensitivity to glucocorticoids: does it exist? Rev Rhum Engl Ed. 1996 Mar;63(3):223-6.

1960. Plant MJ, Borg AA, Dziedzic K, et al. Radiographic patterns and response to corticosteroid hip injection. Ann Rheum Dis. 1997 Aug;56(8):476-80.

1961. Podgorski MR, Goulding NJ, Hall ND, et al. Autoantibodies to lipocortin-1 are associated with impaired glucocorticoid responsiveness in rheumatoid arthritis. J Rheumatol. 1992 Nov;19(11):1668-71.

1962. Pollet SM, Vogt PJ, Leek JC. Serous peritonitis in adult Still's syndrome. J Rheumatol. 1990 Jan;17(1):98-101.

1963. Polzer K, Baeten D, Soleiman A, et al. Tumour necrosis factor blockade increases lymphangiogenesis in murine and human arthritic joints. Ann Rheum Dis. 2008 Nov;67(11):1610-6.

1964. Pomerantz RG, Mody E, Husni ME, et al. Follow-up of psoriatic arthritis mutilans patients treated with anti-TNF-alpha therapy. J Drugs Dermatol. 2009 Apr;8(4):406-12.

1965. Pool AJ, Whipp BJ, Skasick AJ, et al. Serum cortisol reduction and abnormal prolactin and CD4+/CD8+ T-cell response as a result of controlled exercise in patients with rheumatoid arthritis and systemic lupus erythematosus despite unaltered muscle energetics. Rheumatology (Oxford). 2004 Jan;43(1):43-8.

1966. Poor G, Strand V. Efficacy and safety of leflunomide 10 mg versus 20 mg once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. Rheumatology (Oxford). 2004 Jun;43(6):744-9.

1967. Popa C, Leandro MJ, Cambridge G, et al. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. Rheumatology (Oxford). 2007 Apr;46(4):626-30.

1968. Popa C, Netea MG, de Graaf J, et al. Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. J Rheumatol. 2009 Apr;36(4):724-30.

1969. Popa C, Netea MG, Radstake TR, et al. Markers of inflammation are negatively correlated with serum leptin in rheumatoid arthritis. Ann Rheum Dis. 2005 Aug;64(8):1195-8.

1970. Popa C, van den Hoogen FH, Radstake TR, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1503-7.

1971. Popa C, van Tits LJ, Barrera P, et al. Anti-inflammatory therapy with tumour necrosis factor alpha inhibitors improves high-density lipoprotein cholesterol antioxidative capacity in rheumatoid arthritis patients. Ann Rheum Dis. 2009 Jun;68(6):868-72.

1972. Pope RM, Kniker WT, Talal N, et al. Delayed type hypersensitivity in patients

with rheumatoid arthritis. J Rheumatol. 1993 Jan;20(1):17-20.

1973. Porola P, Laine M, Virtanen I, et al. Androgens and integrins in salivary glands in Sjogren's syndrome. J Rheumatol. 2010 Jun;37(6):1181-7.

1974. Porola P, Virkki L, Przybyla BD, et al. Androgen deficiency and defective intracrine processing of dehydroepiandrosterone in salivary glands in Sjogren's syndrome. J Rheumatol. 2008 Nov;35(11):2229-35.

1975. Portales P, Fabre S, Vincent T, et al. Peripheral blood T4 cell surface CCR5 density as a marker of activity in rheumatoid arthritis treated with anti-CD20 monoclonal antibody. Immunology. 2009 Sep;128(1 Suppl):e738-45.

1976. Porterfield LM. Why has this patient developed sepsis? Rn. 1999 Aug;62(8):89.

1977. Porterfield LM. Rheumatoid arthritis patient's respiratory distress. Rn. 2009 Jan;72(1):21.

1978. Posten W, Swan J. Recurrence of alopecia areata in a patient receiving etanercept injections. Arch Dermatol. 2005 Jun;141(6):759-60.

1979. Potter C, Cordell HJ, Barton A, et al. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signalling pathways. Ann Rheum Dis. 2010 Jul;69(7):1315-20.

1980. Potter C, Hyrich KL, Tracey A, et al. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. Ann Rheum Dis 2009;68(1):69-74.

1981. Pou MA, Diaz-Torne C, Vidal S, et al. Development of autoimmune diseases after vaccination. J Clin Rheumatol. 2008 Aug;14(4):243-4.

1982. Price-Forbes AN, Callaghan R, Allen ME, et al. A regional audit of the use of COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) in rheumatology clinics in the West Midlands, in relation to NICE guidelines. Rheumatology (Oxford). 2005 Jul;44(7):921-4.

1983. Priori R, Ceccarelli F, Barone F, et al. Clinical, biological and sonographic response to IL-1 blockade in adult-onset Still's disease. Clin Exp Rheumatol. 2008 Sep-Oct;26(5):933-7.

1984. Probst C, Pongratz G, Capellino S, et al. Cryptococcosis mimicking cutaneous cellulitis in a patient suffering from rheumatoid arthritis: a case report. BMC Infect Dis. 2010;10:239.

1985. Probst LE, Holland EJ. Intraocular lens implantation in patients with juvenile rheumatoid arthritis. Am J Ophthalmol. 1996 Aug;122(2):161-70.

1986. Proudman SM, Keen HI, Stamp LK, et al. Response-driven combination therapy with conventional disease-modifying antirheumatic drugs can achieve high response rates in early rheumatoid arthritis with minimal glucocorticoid and nonsteroidal anti-inflammatory drug use. Semin Arthritis Rheum. 2007 Oct;37(2):99-111.

1987. Provenzano G, Termini A, Le Moli C, et al. Efficacy of infliximab in psoriatic arthritis resistant to treatment with disease modifying antirheumatic drugs: an open pilot study. Ann Rheum Dis. 2003 Jul;62(7):680-1.

1988. Puechal X, Miceli-Richard C, Mejjad O, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):880-4.

1989. Pullerits R, Bokarewa M, Dahlberg L, et al. Synovial fluid expression of autoantibodies specific for RAGE relates to less erosive course of rheumatoid arthritis. Rheumatology (Oxford). 2007 Aug;46(8):1367-71.

1990. Pulsatelli L, Dolzani P, Silvestri T, et al. Synovial expression of vasoactive intestinal

peptide in polymyalgia rheumatica. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):562-6.

1991. Pun YL, Barraclough DR, Muirden KD. Leg ulcers in rheumatoid arthritis. Med J Aust. 1990 Nov 19;153(10):585-7.

1992. Puri PK, Lountzis NI, Tyler W, et al. Hydroxychloroquine-induced hyperpigmentation: the staining pattern. J Cutan Pathol. 2008 Dec;35(12):1134-7.

1993. Pyrpasopoulou A, Douma S, Triantafyllou A, et al. Response to rituximab and timeframe to relapse in rheumatoid arthritis patients: association with B-cell markers. Mol Diagn Ther. 2010 Feb 1;14(1):43-8.

1994. Quallich LG, Greenson J, Haftel HM, et al. Is it Crohn's disease? A severe systemic granulomatous reaction to sulfasalazine in patient with rheumatoid arthritis. BMC Gastroenterol. 2001;1:8.

1995. Quartier P, Taupin P, Bourdeaut F, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum. 2003 Apr;48(4):1093-101.

1996. Quartuccio L, De Re V, Fabris M, et al. Atypical lymphoproliferation progressing into B-cell lymphoma in rheumatoid arthritis treated with different biological agents: clinical course and molecular characterization. Haematologica. 2006 May;91(5):691-4.

1997. Quartuccio L, Maset M, De Vita S. Efficacy of abatacept in a refractory case of adult-onset Still's disease. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):265-7.

1998. Queiro R, Torre JC, Belzunegui J, et al. Clinical features and predictive factors in psoriatic arthritis-related uveitis. Semin Arthritis Rheum. 2002 Feb;31(4):264-70.

1999. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Jan;52(1):27-35.

2000. Rachapalli S, O'Daunt S. Septic arthritis due to Listeria monocytogenes in a patient receiving etanercept. Arthritis Rheum. 2005 Mar;52(3):987.

2001. Racunica T, Cassidy D, Cicuttini F, et al. Trouble with tumor necrosis factor alpha inhibitors, not just tuberculosis. Arthritis Care Res (Hoboken) 2010;62(6):770-4.

2002. Radikova Z, Rovensky J, Vlcek M, et al. Adrenocortical response to low-dose ACTH test in female patients with rheumatoid arthritis. Ann N Y Acad Sci. 2008 Dec;1148:562-6.

2003. Radovits BJ, Kievit W, Laan RF. Tumour necrosis factor-alpha antagonists in the management of rheumatoid arthritis in the elderly: a review of their efficacy and safety. Drugs Aging. 2009;26(8):647-64.

2004. Radstake TR, Fransen J, Toonen EJ, et al. Macrophage migration inhibitory factor polymorphisms do not predict therapeutic response to glucocorticoids or to tumour necrosis factor alpha-neutralising treatments in rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1525-30.

2005. Raghavendra S, Nair MD, Chemmanam T, et al. Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate. Eur J Neurol. 2007 Mar;14(3):309-14.

2006. Rahman MU, Strusberg I, Geusens P, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Sep;66(9):1233-8.

2007. Rahman N, Healy C, Flint SR, et al. Cautionary note: a possible association between oral squamous cell carcinoma and tumor necrosis factor antagonists; need for oral screening. J Clin Rheumatol. 2010 Jun;16(4):197-9.

2008. Rahmlow M, Shuster EA, Dominik J, et al. Leflunomide-associated progressive

multifocal leukoencephalopathy. Arch Neurol. 2008 Nov;65(11):1538-9.

2009. Rajagopala S, Singh N, Gupta K, et al. Pulmonary amyloidosis in Sjogren's syndrome: a case report and systematic review of the literature. Respirology. 2010 Jul;15(5):860-6.

2010. Rajakulendran S, Deighton C. Delayed multiple injection site reaction in a rheumatoid arthritis patient treated with etanercept. Rheumatology (Oxford). 2004 Dec;43(12):1588-9.

2011. Rajakulendran S, Deighton C. Adverse dermatological reactions in rheumatoid arthritis patients treated with etanercept, an anti-TNFalpha drug. Curr Drug Saf. 2006 Aug;1(3):259-64.

2012. Rajakulendran S, Gadsby K, Deighton C. Rheumatoid arthritis, alcohol, leflunomide and methotrexate. Can changes to the BSR guidelines for leflunomide and methotrexate on alcohol consumption be justified? Musculoskeletal Care. 2008 Dec;6(4):233-45.

2013. Rajaraman RT, Kimura Y, Li S, et al. Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology. 2006 Feb;113(2):308-14.

2014. Ramirez-Hernandez M, Marras C, Martinez-Escribano JA. Infliximab-induced vitiligo. Dermatology. 2005;210(1):79-80.

2015. Ramos-Casals M, Brito-Zeron P, Siso A, et al. High prevalence of serum metabolic alterations in primary Sjogren's syndrome: influence on clinical and immunological expression. J Rheumatol. 2007 Apr;34(4):754-61.

2016. Ramos-Casals M, Garcia-Hernandez FJ, de Ramon E, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol. 2010 Jul-Aug;28(4):468-76.

2017. Ramos-Casals M, Lopez-Guillermo A, Brito-Zeron P, et al. Treatment of B-cell lymphoma with rituximab in two patients with Sjogren's syndrome associated with hepatitis C virus infection. Lupus. 2004;13(12):969-71.

2018. Ranganathan P. Infliximab-induced scleredema in a patient with rheumatoid arthritis. J Clin Rheumatol. 2005 Dec;11(6):319-22.

2019. Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum. 2009 May;60(5):1222-31.

2020. Raterman HG, Hoving JL, Nurmohamed MT, et al. Work ability: a new outcome measure in rheumatoid arthritis? Scand J Rheumatol. 2010 Mar;39(2):127-31.

2021. Rau R, Sander O, van Riel P, et al. Intravenous human recombinant tumor necrosis factor receptor p55-Fc IgG1 fusion protein Ro 45-2081 (lenercept): a double blind, placebo controlled dose-finding study in rheumatoid arthritis. J Rheumatol. 2003 Apr;30(4):680-90.

2022. Rau R, Sander O, Wassenberg S. Erosion healing in rheumatoid arthritis after anakinra treatment. Ann Rheum Dis. 2003 Jul;62(7):671-3.

2023. Rau R, Simianer S, van Riel PL, et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol. 2004;33(3):145-53.

2024. Ravindran J, Shenker N, Bhalla AK, et al. Case report: Response in proteinuria due to AA amyloidosis but not Felty's syndrome in a patient with rheumatoid arthritis treated with TNF-alpha blockade. Rheumatology (Oxford). 2004 May;43(5):669-72.

2025. Raza N, Hameed A, Ali MK. Detection of subclinical joint involvement in psoriasis with bone scintigraphy and its response to oral methotrexate. Clin Exp Dermatol. 2008 Jan;33(1):70-3.

2026. Reddy AR, Backhouse OC. Does etanercept induce uveitis? Br J Ophthalmol. 2003 Jul;87(7):925.

2027. Reed A, Haugen M, Pachman LM, et al. Abnormalities in serum osteocalcin values in children with chronic rheumatic diseases. J Pediatr. 1990 Apr;116(4):574-80.

2028. Regula CG, Hennessy J, Clarke LE, et al. Interstitial granulomatous drug reaction to anakinra. J Am Acad Dermatol. 2008 Aug;59(2 Suppl 1):S25-7.

2029. Rehnberg M, Amu S, Tarkowski A, et al. Short- and long-term effects of anti-CD20 treatment on B cell ontogeny in bone marrow of patients with rheumatoid arthritis. Arthritis Res Ther. 2009;11(4):R123.

2030. Rehnberg M, Brisslert M, Amu S, et al. Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment. Arthritis Res Ther. 2010;12(3):R111.

2031. Reitman CA, Lidsky MD, Heggeness MH. Neurologic and morphologic features of dural ectasia in ankylosing spondylitis and rheumatoid arthritis: a case report. Am J Orthop. 2006 Nov;35(11):530-1.

2032. Rejon E, Gimenez MD, Mayordomo L, et al. Therapeutic efficacy and safety of multiple intravenous infusions of infliximab in refractory ankylosing spondylitis patients with axial involvement. Scand J Rheumatol. 2004;33(5):323-6.

2033. Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjogren's syndrome. J Rheumatol. 2008 Feb;35(2):278-84.

2034. Renato GM. B cell depletion in early rheumatoid arthritis: a new concept in therapeutics. Ann N Y Acad Sci. 2009 Sep;1173:729-35.

2035. Resmini E, Farkas C, Murillo B, et al. Body composition after endogenous (Cushing's syndrome) and exogenous (rheumatoid arthritis) exposure to glucocorticoids. Horm Metab Res. 2010 Jul;42(8):613-8.

2036. Ribbens C, Andre B, Marcelis S, et al. Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor-alpha treatment: pilot study. Radiology. 2003 Nov;229(2):562-9.

2037. Ribbens C, Martin y Porras M, Franchimont N, et al. Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. Ann Rheum Dis. 2002 Feb;61(2):161-6.

2038. Richards BL, Spies J, McGill N, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. Intern Med J. 2007 Feb;37(2):101-7.

2039. Richette P, Dieude P, Damiano J, et al. Sensory neuropathy revealing necrotizing vasculitis during infliximab therapy for rheumatoid arthritis. J Rheumatol. 2004 Oct;31(10):2079-81.

2040. Richette P, Francois M, Vicaut E, et al. A high interleukin 1 receptor antagonist/IL-1beta ratio occurs naturally in knee osteoarthritis. J Rheumatol. 2008 Aug;35(8):1650-4.

2041. Richez C, Blanco P, Lagueny A, et al. Neuropathy resembling CIDP in patients receiving tumor necrosis factor-alpha blockers. Neurology. 2005 Apr 26;64(8):1468-70.

2042. Richez C, Dumoulin C, Schaeverbeke T. Infliximab induced chilblain lupus in a patient with rheumatoid arthritis. J Rheumatol. 2005 Apr;32(4):760-1.

2043. Richter C, Wanke L, Steinmetz J, et al. Mononeuritis secondary to rheumatoid arthritis responds to etanercept. Rheumatology (Oxford). 2000 Dec;39(12):1436-7.

2044. Richter J, Benson V, Grobarova V, et al. CD161 receptor participates in both impairing NK cell cytotoxicity and the response to glycans and vimentin in patients with rheumatoid arthritis. Clin Immunol. 2010 Jul;136(1):139-47.

2045. Riepl B, Grassel S, Wiest R, et al. Tumor necrosis factor and norepinephrine lower the levels of human neutrophil peptides 1-3 secretion by mixed synovial tissue cultures in osteoarthritis and rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R110.

2046. Rihl M, Kruithof E, Barthel C, et al. Involvement of neurotrophins and their receptors in spondyloarthritis synovitis: relation to inflammation and response to treatment. Ann Rheum Dis. 2005 Nov;64(11):1542-9.

2047. Rihl M, Ulbricht K, Schmidt RE, et al. Treatment of sicca symptoms with hydroxychloroquine in patients with Sjogren's syndrome. Rheumatology (Oxford). 2009 Jul;48(7):796-9.

2048. Riise T, Jacobsen BK, Gran JT. Changes in therapy of rheumatoid arthritis during the period 1979 to 1996. Scand J Rheumatol. 2001;30(4):199-202.

2049. Rijkeboer A, Voskuyl A, Van Agtmael M. Fatal Salmonella enteritidis septicaemia in a rheumatoid arthritis patient treated with a TNF-alpha antagonist. Scand J Infect Dis. 2007;39(1):80-3.

2050. Rimar D, Rozenbaum M, Slobodin G, et al. Etanercept related pseudo-empyema in rheumatoid arthritis. Clin Rheumatol 2010;29(5):547-9.

2051. Rinaldi F, Provenzano G, Termini A, et al. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. Ann Rheum Dis. 2005 Sep;64(9):1375-6.

2052. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005 Sep 15;72(6):1037-47.

2053. Rivers JK, Podgorski MR, Goulding NJ, et al. The presence of autoantibody to recombinant lipocortin-I in patients with psoriasis and psoriatic arthritis. Br J Dermatol. 1990 Nov;123(5):569-72.

2054. Rizzo R, Rubini M, Govoni M, et al. HLA-G 14-bp polymorphism regulates the methotrexate response in rheumatoid arthritis. Pharmacogenet Genomics. 2006 Sep;16(9):615-23.

2055. Rodrigues K, Neves FS, Stoeterau KB, et al. Pulmonary amyloidosis in Sjogren's syndrome: a rare diagnosis for nodular lung lesions. Int J Rheum Dis. 2009 Dec;12(4):358-60.

2056. Rodriguez-Escalera C, Belzunegui J, Lopez-Dominguez L, et al. Multifocal motor neuropathy with conduction block in a patient with rheumatoid arthritis on infliximab therapy. Rheumatology (Oxford). 2005 Jan;44(1):132-3.

2057. Rodriguez-Padilla JA, Hedges TR, 3rd, Monson B, et al. High-speed ultra-high-resolution optical coherence tomography findings in hydroxychloroquine retinopathy. Arch Ophthalmol. 2007 Jun;125(6):775-80.

2058. Rokhsar C, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. J Am Acad Dermatol. 2006 Feb;54(2):361-2.

2059. Roll P, Dorner T, Tony HP. Anti-CD20 therapy in patients with rheumatoid arthritis: predictors of response and B cell subset regeneration after repeated treatment. Arthritis Rheum. 2008 Jun;58(6):1566-75.

2060. Roll P, Palanichamy A, Kneitz C, et al. Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. Arthritis Rheum. 2006 Aug;54(8):2377-86.

2061. Rooryck C, Barnetche T, Richez C, et al. Influence of FCGR3A-V212F and TNFRSF1B-M196R genotypes in patients with rheumatoid arthritis treated with infliximab therapy. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):340-2.

2062. Roos JC, Ostor AJ. Orbital cellulitis in a patient receiving infliximab for Ankylosing spondylitis. Am J Ophthalmol. 2006 Apr;141(4):767-9.

2063. Rosenvinge A, Krogh-Madsen R, Baslund B, et al. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha

therapy. Scand J Rheumatol. 2007 Mar-Apr;36(2):91-6.

2064. Rosmarin D, Bush M, Scheinman PL. Patch testing a patient with allergic contact hand dermatitis who is taking infliximab. J Am Acad Dermatol. 2008 Jul;59(1):145-7.

2065. Roth EB, Stenberg P, Book C, et al. Antibodies against transglutaminases, peptidylarginine deiminase and citrulline in rheumatoid arthritis--new pathways to epitope spreading. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):12-8.

2066. Roth S. Effects of Prosorba column apheresis in patients with chronic refractory rheumatoid arthritis. J Rheumatol. 2004 Nov;31(11):2131-5.

2067. Roubenoff R, Roubenoff RA, Ward LM, et al. Catabolic effects of high-dose corticosteroids persist despite therapeutic benefit in rheumatoid arthritis. Am J Clin Nutr. 1990 Dec;52(6):1113-7.

2068. Roux CH, Brocq O, Albert CBV, et al. Cutaneous vasculitis and glomerulonephritis in a patient taking the anti-TNF alpha agent etanercept for rheumatoid arthritis. Joint Bone Spine. 2004 Sep;71(5):444-5.

2069. Roux N, Flipo RM, Cortet B, et al. Pneumocystis carinii pneumonia in rheumatoid arthritis patients treated with methotrexate. A report of two cases. Rev Rhum Engl Ed. 1996 Jun;63(6):453-6.

2070. Roux-Lombard P, Eberhardt K, Saxne T, et al. Cytokines, metalloproteinases, their inhibitors and cartilage oligomeric matrix protein: relationship to radiological progression and inflammation in early rheumatoid arthritis. A prospective 5-year study. Rheumatology (Oxford). 2001 May;40(5):544-51.

2071. Rovensky J, Bakosova J, Koska J, et al. Somatotropic, lactotropic and adrenocortical responses to insulin-induced hypoglycemia in patients with rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:263-70.

2072. Rovensky J, Bakosova J, Payer J, et al. Increased demand for steroid therapy in hyperprolactinemic patients with rheumatoid arthritis. Int J Tissue React. 2001;23(4):145-9.

2073. Rovensky J, Imrich R, Koska J, et al. Cortisol elimination from plasma in premenopausal women with rheumatoid arthritis. Ann Rheum Dis. 2003 Jul;62(7):674-6.

2074. Rovensky J, Radikova Z, Imrich R, et al. Gonadal and adrenal steroid hormones in plasma and synovial fluid of patients with rheumatoid arthritis. Endocr Regul. 2004 Dec;38(4):143-9.

2075. Rovensky J, Simorova E, Radikova Z, et al. Comparison of hormone transfer to pleural and synovial exudates. Endocr Regul. 2006 Jun;40(2):29-36.

2076. Rovere Querini P, Vecellio M, Sabbadini MG, et al. Miliary tuberculosis after biological therapy for rheumatoid arthritis. Rheumatology (Oxford). 2002 Feb;41(2):231.

2077. Roy A, Mould DR, Wang XF, et al. Modeling and simulation of abatacept exposure and interleukin-6 response in support of recommended doses for rheumatoid arthritis. J Clin Pharmacol. 2007 Nov;47(11):1408-20.

2078. Roy DB, Conte ET, Cohen DJ. The treatment of pyoderma gangrenosum using etanercept. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S128-34.

2079. Rozenbaum M, Boulman N, Slobodin G, et al. Polyarthritis flare complicating rheumatoid arthritis infliximab therapy: a paradoxic adverse reaction. J Clin Rheumatol. 2006 Dec;12(6):269-71.

2080. Rozenbaum M, Rosner I, Portnoy E. Remission of Behcet's syndrome with TNFalpha blocking treatment. Ann Rheum Dis. 2002 Mar;61(3):283-4.

2081. Ruderman EM, Pope RM. The evolving clinical profile of abatacept (CTLA4-Ig): a novel co-stimulatory modulator for the treatment of rheumatoid arthritis. Arthritis Res Ther. 2005;7 Suppl 2:S21-5.

2082. Rudwaleit M, Baraliakos X, Listing J, et al. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. Ann Rheum Dis. 2005 Sep;64(9):1305-10.

2083. Rudwaleit M, Listing J, Brandt J, et al. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis. 2004 Jun;63(6):665-70.

2084. Rudwaleit M, Van den Bosch F, Kron M, et al. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. Arthritis Res Ther. 2010;12(3):R117.

2085. Ruppert M, De Clerck L, van Offel J, et al. Intestinal necrosis in a patient with rheumatoid arthritis receiving anti-TNF treatment. Acta Chir Belg. 2006 Mar-Apr;106(2):225-7.

2086. Russell A, Haraoui B, Keystone E, et al. Current and emerging therapies for rheumatoid arthritis, with a focus on infliximab: clinical impact on joint damage and cost of care in canada. Clin Ther. 2001 Nov;23(11):1824-38; discussion 791.

2087. Russell E, Zeihen M, Wergin S, et al. Patients receiving etanercept may develop antibodies that interfere with monoclonal antibody laboratory assays. Arthritis Rheum. 2000 Apr;43(4):944.

2088. Ruyssen-Witrand A, Gossec L, Salliot C, et al. Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. Clin Exp Rheumatol. 2007 May-Jun;25(3):430-6.

2089. Saad AA, Ashcroft DM, Watson KD, et al. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. Arthritis Care Res (Hoboken) 2010;62(3):345-53.

2090. Saad AA, Symmons DP, Noyce PR, et al. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90.

2091. Saadeh C, Saadeh C. Asthma remission in a patient with rheumatoid arthritis while on antiangiogenesis therapy during a rheumatoid arthritis trial demonstrated by forced oscillation and spirometry. J Asthma. 2007 May;44(4):281-3.

2092. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med. 1994 Feb;96(2):115-23.

2093. Saario R, Sonninen P, Mottonen T, et al. Bone mineral density of the lumbar spine in patients with advanced rheumatoid arthritis. Influence of functional capacity and corticosteroid use. Scand J Rheumatol. 1999;28(6):363-7.

2094. Saba NS, Kosseifi SG, Charaf EA, et al. Adalimumab-induced acute myelogenic leukemia. South Med J. 2008 Dec;101(12):1261-2.

2095. Saber TP, Ng CT, Renard G, et al. Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis Res Ther. 2010;12(3):R94.

2096. Saeki Y, Ohshima S, Ishida T, et al. Remission of the renal involvement in a patient with primary Sjogren's syndrome (SS) after pulse high-dose corticosteroid infusion therapy. Clin Rheumatol. 2001;20(3):225-8.

2097. Saeki Y, Ohshima S, Mima T, et al. Suboptimal clinical response to anti-tumor necrosis factor alpha (TNFalpha) antibody therapy in a patient with severe rheumatoid arthritis and lymphadenopathy. Scand J Rheumatol. 1998;27(4):303-5.

2098. Sahin M, Keskin M, Tunc SE, et al. Kaposi's sarcoma complicating rheumatoid arthritis treated with corticosteroid Kaposi's sarcoma and rheumatoid arthritis. Saudi Med J. 2007 Jul;28(7):1133-4.

2099. Saiki O, Takao R, Naruse Y, et al. Infliximab but not methotrexate induces extra-high levels of VLDL-triglyceride in patients with rheumatoid arthritis. J Rheumatol. 2007 Oct;34(10):1997-2004.

2100. Saint Marcoux B, De Bandt M. Vasculitides induced by TNFalpha antagonists: a study in 39 patients in France. Joint Bone Spine. 2006 Dec;73(6):710-3.

2101. Saito S, Momohara S, Taniguchi A, et al. The intra-articular efficacy of hyaluronate injections in the treatment of rheumatoid arthritis. Mod Rheumatol. 2009;19(6):643-51.

2102. Sakai K, Hamaguchi T, Yamada M. Multiple cranial nerve enhancement on MRI in primary Sjogren's syndrome. Intern Med. 2010;49(9):857-9.

2103. Sakai Y, Sakai S, Otsuka T, et al. Efficacy of high-throughput leukocytapheresis for rheumatoid arthritis with a reduced response to infliximab. Ther Apher Dial. 2009 Jun;13(3):179-85.

2104. Sakamoto O, Saita N, Ando M, et al. Two cases of Sjogren's syndrome with multiple bullae. Intern Med. 2002 Feb;41(2):124-8.

2105. Sakaura H, Hosono N, Mukai Y, et al. Paraparesis due to exacerbation of preexisting spinal pseudoarthrosis following infliximab therapy for advanced ankylosing spondylitis. Spine J. 2006 May-Jun;6(3):325-9.

2106. Sakellariou GT, Vounotrypidis P, Berberidis C. Infliximab treatment in two patients with psoriatic arthritis and secondary IgA nephropathy. Clin Rheumatol. 2007 Jul;26(7):1132-3.

2107. Salamon L, Salamon T, Morovic-Vergles J. Thrombotic microangiopathy in adult-onset Still's disease: case report and review of the literature. Wien Klin Wochenschr. 2009;121(17-18):583-8.

2108. Saleem B, Brown AK, Keen H, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. Arthritis Rheum 2009;60(7):1915-22.

2109. Saleem B, Mackie S, Quinn M, et al. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? Ann Rheum Dis. 2008 Aug;67(8):1178-80.

2110. Saleem G, Li SC, MacPherson BR, et al. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. Arthritis Rheum. 2001 Aug;44(8):1966-8.

2111. Salli A, Sahin N, Paksoy Y, et al. Treatment of periodontoid pannus with infliximab in a patient with rheumatoid arthritis. J Clin Rheumatol. 2009 Aug;15(5):250-1.

2112. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009;68(1):25-32.

2113. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009 Jul;68(7):1100-4.

2114. Salloum E, Cooper DL, Howe G, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. J Clin Oncol. 1996 Jun;14(6):1943-9.

2115. Salvarani C, Cantini F, Olivieri I, et al. Efficacy of infliximab in resistant psoriatic arthritis. Arthritis Rheum. 2003 Aug 15;49(4):541-5.

2116. Salvarani C, Cantini F, Olivieri I, et al. Distal extremity swelling with pitting edema in psoriatic arthritis: evidence of 2 pathological mechanisms. J Rheumatol. 1999 Aug;26(8):1831-4.

2117. Samanta J, Kendall J, Samanta A. Polyarthralgia. BMJ. 2003 Apr 19;326(7394):859.

2118. Sambrook P, Birmingham J, Champion D, et al. Postmenopausal bone loss in rheumatoid arthritis: effect of estrogens and androgens. J Rheumatol. 1992 Mar;19(3):357-61.

2119. Sanchez A, Maximiano C, Cantos B, et al. Neurological symptoms simulating cord compression in breast cancer patient. J Neurooncol. 2005 Apr;72(2):149-50.

2120. Sanchez G, Castro JS, Snih SA, et al. Durability of treatment with methotrexate in Venezuelan patients with rheumatoid arthritis. Rheumatol Int. 2007 Apr;27(6):531-6.

2121. Sandler C, Lindstedt KA, Joutsiniemi S, et al. Selective activation of mast cells in rheumatoid synovial tissue results in production of TNF-alpha, IL-1beta and IL-1Ra. Inflamm Res. 2007 Jun;56(6):230-9.

2122. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum. 2004 Jul;50(7):2240-5.

2123. Sanmarti R, Gomez-Centeno A, Ercilla G, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol. 2007 Jul;26(7):1111-8.

2124. Sano H, Arai K, Murai T, et al. Tight control is important in patients with rheumatoid arthritis treated with an anti-tumor necrosis factor biological agent: prospective study of 91 cases who used a biological agent for more than 1 year. Mod Rheumatol. 2009;19(4):390-4.

2125. Santiago-Casas Y, Gonzalez-Rivera TC, Castro-Santana LE, et al. Impact of age on clinical manifestations and outcome in Puerto Ricans with rheumatoid arthritis. Ethn Dis. 2010 Winter;20(1 Suppl 1):S1-191-5.

2126. Santos-Ocampo AS, Santos-Ocampo RS. Non-contrast computed tomography-guided intra-articular corticosteroid injections of severe bilateral hip arthritis in a patient with ankylosing spondylitis. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):239-40.

2127. Sany J, Bourgeois P, Saraux A, et al. Characteristics of patients with rheumatoid arthritis in France: a study of 1109 patients managed by hospital based rheumatologists. Ann Rheum Dis. 2004 Oct;63(10):1235-40.

2128. Sany J, Cohen JD, Combescure C, et al. Medico-economic evaluation of infliximab in rheumatoid arthritis--prospective French study of a cohort of 635 patients monitored for two years. Rheumatology (Oxford). 2009 Oct;48(10):1236-41.

2129. Sany J, Kaiser MJ, Jorgensen C, et al. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. Ann Rheum Dis. 2005 Nov;64(11):1647-9.

2130. Sanz I, Anolik J. Reconstitution of the adult B cell repertoire after treatment with rituximab. Arthritis Res Ther. 2005;7(5):175-6.

2131. Saraux A, Devauchelle-Pensec V, Engerran L, et al. Most rheumatologists are conservative in active rheumatoid arthritis despite methotrexate therapy: results of the PRISME survey. J Rheumatol. 2006 Jul;33(7):1258-65.

2132. Sari I, Akar S, Birlik M, et al. Anti-tumor necrosis factor-alpha-induced psoriasis. J Rheumatol. 2006 Jul;33(7):1411-4.

2133. Saruhan-Direskeneli G, Inanc M, Fresko I, et al. The role of HLA-DRB1 shared epitope alleles in predicting short-term response to leflunomide in rheumatoid arthritis. Rheumatology (Oxford). 2007 Dec;46(12):1842-4.

2134. Sarzi-Puttini P, Antivalle M, Marchesoni A, et al. Efficacy and safety of anti-TNF agents in the Lombardy rheumatoid arthritis network (LORHEN). Reumatismo. 2008 Oct-Dec;60(4):290-5.

2135. Sarzi-Puttini P, Atzeni F, Scholmerich J, et al. Anti-TNF antibody treatment improves glucocorticoid induced insulin-like growth factor 1 (IGF1) resistance without influencing myoglobin and IGF1 binding proteins 1 and 3. Ann Rheum Dis. 2006 Mar;65(3):301-5.

2136. Sato H, Kazama JJ, Wada Y, et al. Decreased levels of circulating alpha2-Heremans-Schmid glycoprotein/Fetuin-A (AHSG) in patients with rheumatoid arthritis. Intern Med. 2007;46(20):1685-91.

2137. Sato H, Sakai T, Sugaya T, et al. Tocilizumab dramatically ameliorated life-threatening diarrhea due to secondary amyloidosis associated with rheumatoid arthritis. Clin Rheumatol. 2009 Sep;28(9):1113-6.

2138. Sato M, Takeda A, Honzu H, et al. Adult Still's disease with Sjogren's syndrome successfully treated with intravenous pulse methylprednisolone and oral cyclophosphamide. Intern Med. 1993 Sep;32(9):730-2.

2139. Sato T, Inokuma S, Sagawa A, et al. Factors associated with fatal outcome of leflunomide-induced lung injury in Japanese patients with rheumatoid arthritis. Rheumatology (Oxford). 2009 Oct;48(10):1265-8.

2140. Satoh K, Yoshida N, Imaizumi K, et al. Reversible methotrexate-associated lymphoproliferative disorder resembling advanced gastric cancer in a patient with rheumatoid arthritis. Am J Med Sci. 2009 Oct;338(4):334-5.

2141. Saunders SA, Capell HA, Stirling A, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum 2008;58(5):1310-7.

2142. Saviola G, Abdi Ali L, Shams Eddin S, et al. Compared clinical efficacy and bone metabolic effects of low-dose deflazacort and methyl prednisolone in male inflammatory arthropathies: a 12-month open randomized pilot study. Rheumatology (Oxford). 2007 Jun;46(6):994-8.

2143. Saxne T, Larsson L, Geborek P. Results of anakinra treatment in rheumatoid arthritis patients previously treated with tumor necrosis factor alpha blockade: comment on the article by Buch et al. Arthritis Rheum. 2004 Sep;50(9):3049-50; author reply 50-1.

2144. Scali JJ, Visentini S, Salomon J, et al. Rapid and deep control of inflammation in rheumatoid arthritis with infliximab and its correlation with acute-phase reactants. Ann N Y Acad Sci. 2007 Sep;1110:389-401.

2145. Scarpa R, Peluso R, Atteno M, et al. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. Clin Rheumatol. 2008 Jul;27(7):823-6.

2146. Scarsi M, Ziglioli T, Airo P. Decreased circulating CD28-negative T cells in patients with rheumatoid arthritis treated with abatacept are correlated with clinical response. J Rheumatol. 2010 May;37(5):911-6.

2147. Schafer JA, Kjesbo NK, Gleason PP. Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis. J Manag Care Pharm. 2010 Jul-Aug;16(6):402-16.

2148. Schalk E, Krogel C, Scheinpflug K, et al. Lymphomatoid granulomatosis in a patient with rheumatoid arthritis receiving methotrexate: successful treatment with the anti-CD20 antibody mabthera. Onkologie. 2009 Jul;32(7):440-1.

2149. Schapira D, Militeanu D, Israel O, et al. Insufficiency fractures of the pubic ramus. Semin Arthritis Rheum. 1996 Jun;25(6):373-82.

2150. Scharf SL, Christophidis N. Second-line agents for rheumatoid arthritis. Med J Aust. 1995 Aug 21;163(4):215-8.

2151. Schatteman L, Gyselbrecht L, De Clercq L, et al. Treatment of refractory inflammatory monoarthritis in ankylosing spondylitis by intraarticular injection of infliximab. J Rheumatol. 2006 Jan;33(1):82-5.

2152. Scheinberg M, Guedes-Barbosa LS, Mangueira C, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken) 2010;62(6):896-8.

2153. Scheinberg M, Hamerschlak N, Kutner JM, et al. Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002-2004). Clin Exp Rheumatol. 2006 Jan-Feb;24(1):65-9.

2154. Scheinfeld N. Menorrhagia and severe menstrual pain related to the use of adalimumab in a psoriatic. J Dermatolog Treat. 2008;19(3):188-9.

2155. Scherak O, Popp W, Kolarz G, et al. Bronchoalveolar lavage and lung biopsy in rheumatoid arthritis. In vivo effects of disease modifying antirheumatic drugs. J Rheumatol. 1993 Jun;20(6):944-9.

2156. Schett G, Herak P, Graninger W, et al. Listeria-associated arthritis in a patient undergoing etanercept therapy: case report and review of the literature. J Clin Microbiol. 2005 May;43(5):2537-41.

2157. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67(8):1096-103.

2158. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum. 2004 Jun;50(6):1752-60.

2159. Schipper LG, Fransen J, Barrera P, et al. Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add? Rheumatology (Oxford) 2009;48(10):1247-53.

2160. Schipper LG, Fransen J, Barrera P, et al. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology (Oxford) 2009;48(7):828-33.

2161. Schirren CA, Zachoval R, Schirren CG, et al. A role for chronic hepatitis C virus infection in a patient with cutaneous vasculitis, cryoglobulinemia, and chronic liver disease. Effective therapy with interferon-alpha. Dig Dis Sci. 1995 Jun;40(6):1221-5.

2162. Schlaghecke R, Beuscher D, Kornely E, et al. Effects of glucocorticoids in rheumatoid arthritis. Diminished glucocorticoid receptors do not result in glucocorticoid resistance. Arthritis Rheum. 1994 Aug;37(8):1127-31.

2163. Schlaghecke R, Kornely E, Wollenhaupt J, et al. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum. 1992 Jul;35(7):740-4.

2164. Schmeling H, Horneff G. Infliximab in two patients with juvenile ankylosing spondylitis. Rheumatol Int. 2004 May;24(3):173-6.

2165. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology (Oxford). 2005 Aug;44(8):1008-11.

2166. Schmid L, Muller M, Treumann T, et al. Induction of complete and sustained remission of rheumatoid pachymeningitis by rituximab. Arthritis Rheum. 2009 Jun;60(6):1632-4.

2167. Schmidt M, Hartung R, Capellino S, et al. Estrone/17beta-estradiol conversion to, and tumor necrosis factor inhibition by, estrogen metabolites in synovial cells of patients with rheumatoid arthritis and patients with osteoarthritis. Arthritis Rheum. 2009 Oct;60(10):2913-22.

2168. Schmidt M, Weidler C, Naumann H, et al. Reduced capacity for the reactivation of glucocorticoids in rheumatoid arthritis synovial cells: possible role of the sympathetic nervous system? Arthritis Rheum. 2005 Jun;52(6):1711-20.

2169. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007;56(6):1754-64.

2170. Schneider SW, Staender S, Schluter B, et al. Infliximab-induced lupus erythematosus tumidus in a patient with rheumatoid arthritis. Arch Dermatol. 2006 Jan;142(1):115-6.

2171. Schoels M, Aletaha D, Funovits J, et al. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010 Aug;69(8):1441-7.

2172. Schoels M, Kapral T, Stamm T, et al. Step-up combination versus switching of non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a retrospective observational study. Ann Rheum Dis 2007;66(8):1059-65.

2173. Schotte H, Schluter B, Drynda S, et al. Interleukin 10 promoter microsatellite polymorphisms are associated with response to long term treatment with etanercept in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Apr;64(4):575-81.

2174. Schotte H, Schluter B, Willeke P, et al. Long-term treatment with etanercept significantly reduces the number of proinflammatory cytokine-secreting peripheral blood mononuclear cells in patients with rheumatoid arthritis. Rheumatology (Oxford). 2004 Aug;43(8):960-4.

2175. Schramm C, Schneider A, Marx A, et al. Adalimumab could suppress the activity of non alcoholic steatohepatitis (NASH). Z Gastroenterol. 2008 Dec;46(12):1369-71.

2176. Schuh A, Zeiler G, Holzwarth U, et al. Malignant fibrous histiocytoma at the site of a total hip arthroplasty. Clin Orthop Relat Res. 2004 Aug(425):218-22.

2177. Schumacher HR, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. Am J Med. 2005 Nov;118(11):1208-14.

2178. Schwartz JI, Agrawal NG, Wong PH, et al. Examination of the effect of increasing doses of etoricoxib on oral methotrexate pharmacokinetics in patients with rheumatoid arthritis. J Clin Pharmacol. 2009 Oct;49(10):1202-9.

2179. Schwetz BA. From the Food and Drug Administration. JAMA. 2002 Mar 6;287(9):1103.

2180. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med. 2006 Aug 17;355(7):704-12.

2181. Scrivo R, Conti F, Spinelli FR, et al. Switching between TNFalpha antagonists in rheumatoid arthritis: personal experience and review of the literature. Reumatismo. 2009 Apr-Jun;61(2):107-17.

2182. Scuderi F, Convertino R, Molino N, et al. Effect of pro-inflammatory/anti-inflammatory agents on cytokine secretion by peripheral blood mononuclear cells in rheumatoid arthritis and systemic lupus erythematosus. Autoimmunity. 2003 Mar;36(2):71-7.

2183. Seidl C, Donner H, Fischer B, et al. CTLA4 codon 17 dimorphism in patients with rheumatoid arthritis. Tissue Antigens. 1998 Jan;51(1):62-6.

2184. Seitz CS, Berens N, Brocker EB, et al. Leg ulceration in rheumatoid arthritis--an underreported multicausal complication with considerable morbidity: analysis of thirty-six patients and review of the literature. Dermatology. 2010;220(3):268-73.

2185. Seitz M, Loetscher P, Dewald B, et al. Production of interleukin-1 receptor antagonist, inflammatory chemotactic proteins, and prostaglandin E by rheumatoid and osteoarthritic synoviocytes--regulation by IFN-gamma and IL-4. J Immunol. 1994 Feb 15;152(4):2060-5.

2186. Seitz M, Zwicker M, Villiger PM. Pretreatment cytokine profiles of peripheral blood mononuclear cells and serum from patients with rheumatoid arthritis in different american college of rheumatology response groups to methotrexate. J Rheumatol. 2003 Jan;30(1):28-35.

2187. Sekigawa I, Yanagida M, Iwabuchi K, et al. Protein biomarker analysis by mass spectrometry in patients with rheumatoid arthritis receiving anti-tumor necrosis factor-alpha antibody therapy. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):261-7.

2188. Sekiguchi N, Kawauchi S, Furuya T, et al. Messenger ribonucleic acid expression profile in peripheral blood cells from RA patients following treatment with an anti-TNF-alpha monoclonal antibody, infliximab. Rheumatology (Oxford). 2008 Jun;47(6):780-8.

2189. Sekiya H, Horii T, Kariya Y, et al. Arthroscopic-assisted tibiotalocalcaneal arthrodesis using an intramedullary nail with fins: a case report. J Foot Ankle Surg. 2006 Jul-Aug;45(4):266-70.

2190. Sellam J, Bouvard B, Masson C, et al. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. Joint Bone Spine. 2007 Mar;74(2):197-200.

2191. Semmler M, Seeck U, Neustadt B, et al. No effects of adalimumab therapy on the activation of NF-kappaB in lymphocytes from patients with severe rheumatoid arthritis. Clin Rheumatol. 2007 Sep;26(9):1499-504.

2192. Sennels H, Sorensen S, Ostergaard M, et al. Circulating levels of osteopontin, osteoprotegerin, total soluble receptor activator of nuclear factor-kappa B ligand, and high-sensitivity C-reactive protein in patients with active rheumatoid arthritis randomized to etanercept alone or in combination with methotrexate. Scand J Rheumatol. 2008 Jul-Aug;37(4):241-7.

2193. Seong SS, Choi CB, Woo JH, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol. 2007 Apr;34(4):706-11.

2194. Serelis J, Kontogianni MD, Katsiougiannis S, et al. Effect of anti-TNF treatment on body composition and serum adiponectin levels of women with rheumatoid arthritis. Clin Rheumatol. 2008 Jun;27(6):795-7.

2195. Seriolo B, Ferretti V, Sulli A, et al. Serum prolactin concentrations in male patients with rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:258-62.

2196. Seriolo B, Paolino S, Sulli A, et al. Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:414-9.

2197. Seriolo B, Paolino S, Sulli A, et al. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:420-7.

2198. Seror P, Pluvinage P, d'Andre FL, et al. Frequency of sepsis after local corticosteroid injection (an inquiry on 1160000 injections in rheumatological private practice in France). Rheumatology (Oxford). 1999 Dec;38(12):1272-4.

2199. Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis. 2007 Mar;66(3):351-7.

2200. Serratrice J, Granel B, Disdier P, et al. Resolution with etanercept of nephrotic syndrome due to renal AA amyloidosis in adult Still's disease. Am J Med. 2003 Nov;115(7):589-90.

2201. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J 2008;156(2):336-41.

2202. Seton M. Giant cell arteritis in a patient taking etanercept and methotrexate. J Rheumatol. 2004 Jul;31(7):1467.

2203. Settas LD, Tsimirikas G, Vosvotekas G, et al. Reactivation of pulmonary tuberculosis in a patient with rheumatoid arthritis during treatment with IL-1 receptor antagonists (anakinra). J Clin Rheumatol. 2007 Aug;13(4):219-20.

2204. Settergren M, Tornvall P. Does TNF-alpha blockade cause plaque rupture? Atherosclerosis. 2004 Mar;173(1):149.

2205. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. Curr Dir Autoimmun. 2010;11:180-210.

2206. Sfikakis PP, Iliopoulos A, Elezoglou A, et al. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. Arthritis Rheum. 2005 Aug;52(8):2513-8.

2207. Shadick NA, Fanta CH, Weinblatt ME, et al. Bronchiectasis. A late feature of severe rheumatoid arthritis. Medicine (Baltimore). 1994 May;73(3):161-70.

2208. Shakiba K, Falcone T. Tumour necrosis factor-alpha blockers: potential limitations in the management of advanced endometriosis? A case report. Hum Reprod. 2006 Sep;21(9):2417-20.

2209. Shakoor N, Michalska M, Harris CA, et al. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet. 2002 Feb 16;359(9306):579-80.

2210. Shan SJ, Wu EI, Akpek EK. Sterile corneal melt after descemet stripping endothelial keratoplasty in patients with previously undiagnosed Sjogren syndrome. Arch Ophthalmol. 2009 Feb;127(2):219-20.

2211. Sharma A, Baethge BA, Acebes JC, et al. Arthroscopic lavage treatment in rheumatoid arthritis of the knee. J Rheumatol. 1996 Nov;23(11):1872-4.

2212. Sharma S, Das M, Kumar A, et al. Interaction of genes from influx-metabolism-efflux pathway and their influence on methotrexate efficacy in rheumatoid arthritis patients among Indians. Pharmacogenet Genomics. 2008 Dec;18(12):1041-9.

2213. Sharma S, Das M, Kumar A, et al. Purine biosynthetic pathway genes and methotrexate response in rheumatoid arthritis patients among north Indians. Pharmacogenet Genomics. 2009 Oct;19(10):823-8.

2214. Shastri V, Betkerur J, Kushalappa PA, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of five cases. Indian J Dermatol Venereol Leprol. 2006 Jul-Aug;72(4):286-9.

2215. Shawe D, Hesp R, Gumpel JM, et al. Physical activity as a determinant of bone conservation in the radial diaphysis in rheumatoid arthritis. Ann Rheum Dis. 1993 Aug;52(8):579-81.

2216. Shbeeb M, Uramoto KM, Gibson LE, et al. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol. 2000 May;27(5):1247-50.

2217. Shedd AD, Reddy SG, Meffert JJ, et al. Acute onset of rash and oligoarthritis. J Fam Pract. 2007 Oct;56(10):811-4.

2218. Shehan JM, Sarma DP. Mycobacterium mucogenicum: report of a skin infection associated with etanercept. Dermatol Online J. 2008;14(1):5.

2219. Shergy WJ, Isern RA, Cooley DA, et al. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. J Rheumatol. 2002 Apr;29(4):667-77.

2220. Sherrer Y. Abatacept in biologic-naive patients and TNF inadequate responders: clinical data in focus. Curr Med Res Opin. 2008 Aug;24(8):2283-94.

2221. Shibata S, Ubara Y, Sawa N, et al. Severe interstitial cystitis associated with Sjogren's syndrome. Intern Med. 2004 Mar;43(3):248-52.

2222. Shih WJ, Ghesani N, Hongming Z, et al. F-18 FDG positron emission tomography demonstrates resolution of non-Hodgkin's lymphoma of the parotid gland in a patient with Sjogren's syndrome: before and after anti-CD20 antibody rituximab therapy. Clin Nucl Med. 2002 Feb;27(2):142-3.

2223. Shimada K, Matsui T, Kawakami M, et al. Methotrexate-related lymphomatoid granulomatosis: a case report of spontaneous regression of large tumours in multiple organs after cessation of methotrexate therapy in rheumatoid arthritis. Scand J Rheumatol. 2007 Jan-Feb;36(1):64-7.

2224. Shimizu H, Miyashita N, Obase Y, et al. An asymptomatic case of pulmonary cryptococcosis with endobronchial polypoid lesions and bilateral infiltrative shadow. J Infect Chemother. 2008 Aug;14(4):315-8.

2225. Shimojima Y, Ishii W, Matsuda M, et al. Cytomegalovirus-induced infectious mononucleosis-like syndrome in a rheumatoid arthritis patient treated with methotrexate and infliximab. Intern Med. 2010;49(10):937-40.

2226. Shimoyama M, Ohtahara A, Fukui H, et al. Acute secondary gastrointestinal amyloidosis in a patient with rheumatoid arthritis. Am J Med Sci. 2003 Sep;326(3):145-7.

2227. Shimura C, Satoh T, Takayama K, et al. Methotrexate-related lymphoproliferative disorder with extensive vascular involvement in a patient with rheumatoid arthritis. J Am Acad Dermatol. 2009 Jul;61(1):126-9.

2228. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum. 2006 May;54(5):1429-34.

2229. Shin K, Lee JC, Choi HJ, et al. Radiation synovectomy using 188Re-tin colloid improves knee synovitis as shown by MRI in refractory rheumatoid arthritis. Nucl Med Commun. 2007 Apr;28(4):239-44.

2230. Shin SJ, Na KS, Jung SS, et al. Acute acalculous cholecystitis associated with systemic lupus erythematosus with Sjogren's syndrome. Korean J Intern Med. 2002 Mar;17(1):61-4.

2231. Shingu M, Fujikawa Y, Wada T, et al. Increased IL-1 receptor antagonist (IL-1ra) production and decreased IL-1 beta/IL-1ra ratio in mononuclear cells from rheumatoid arthritis patients. Br J Rheumatol. 1995 Jan;34(1):24-30.

2232. Shinoda K, Taki H, Hounoki H, et al. Severe autoimmune hemolytic anemia associated with IgM warm auto-antibodies in primary Sjogren's syndrome. Int J Rheum Dis. 2010 Feb 1;13(1):94-6.

2233. Shinozaki M, Inoue E, Nakajima A, et al. Elevation of serum matrix metalloproteinase-3 as a predictive marker for the long-term disability of rheumatoid arthritis patients in a prospective observational cohort IORRA. Mod Rheumatol. 2007;17(5):403-8.

2234. Shio K, Homma F, Kanno Y, et al. Doppler sonographic comparative study on usefulness of synovial vascularity between knee and metacarpophalangeal joints for evaluation of articular inflammation in patients with rheumatoid arthritis treated by infliximab. Mod Rheumatol. 2006;16(4):220-5.

2235. Shoda H, Inokuma S, Yajima N, et al. Higher maximal serum concentration of methotrexate predicts the incidence of adverse reactions in Japanese rheumatoid arthritis patients. Mod Rheumatol. 2007;17(4):311-6.

2236. Sholsberg J, Jackson R. Best evidence topic report. Intra-articular corticosteroid injections in acute rheumatoid monoarthritides. Emerg Med J. 2004 Mar;21(2):204.

2237. Shovman O, Anouk M, Vinnitsky N, et al. QuantiFERON-TB Gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study. Int J Tuberc Lung Dis. 2009 Nov;13(11):1427-32.

2238. Shrestha RK, Stoller JK, Honari G, et al. Pneumonia due to Cryptococcus neoformans in a patient receiving infliximab: possible zoonotic transmission from a pet cockatiel. Respir Care. 2004 Jun;49(6):606-8.

2239. Shrim A, Koren G. Tumour necrosis factor alpha and use of infliximab. Safety during pregnancy. Can Fam Physician. 2005 May;51:667-8.

2240. Sibbitt WL, Jr., Peisajovich A, Michael AA, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? J Rheumatol. 2009 Sep;36(9):1892-902.

2241. Sibilia J, Javier RM, Albert A, et al. Pancytopenia secondary to hemophagocytic syndrome in rheumatoid arthritis treated with methotrexate and sulfasalazine. J Rheumatol. 1998 Jun;25(6):1218-20.

2242. Sichletidis L, Settas L, Spyratos D, et al. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis. 2006 Oct;10(10):1127-32.

2243. Sicotte NL, Voskuhl RR. Onset of multiple sclerosis associated with anti-TNF therapy. Neurology. 2001 Nov 27;57(10):1885-8.

2244. Sidiropoulos P, Bertsias G, Kritikos HD, et al. Infliximab treatment for rheumatoid arthritis, with dose titration based on the Disease Activity Score: dose adjustments are common but not always sufficient to assure sustained benefit. Ann Rheum Dis. 2004 Feb;63(2):144-8.

2245. Sidiropoulos P, Kritikos HD, Siakka P, et al. Low dose of infliximab is inadequate in most patients with spondylarthropathies. Clin Exp Rheumatol. 2005 Jul-Aug;23(4):513-6.

2246. Sidiropoulos PI, Siakka P, Pagonidis K, et al. Sustained improvement of vascular endothelial function during anti-TNFalpha treatment in rheumatoid arthritis patients. Scand J Rheumatol. 2009 Jan-Feb;38(1):6-10.

2247. Sidiropoulos PI, Siakka P, Raptopoulou A, et al. An open label, single dose study to evaluate the safety, efficacy, and effects on CD25 expression of ciclosporin in patients with active rheumatoid arthritis despite treatment with methotrexate and infliximab. Ann Rheum Dis. 2006 Apr;65(4):538-41.

2248. Sieper J, Baraliakos X, Listing J, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. Rheumatology (Oxford). 2005 Dec;44(12):1525-30.

2249. Sills ES, Perloe M, Tucker MJ, et al. Successful ovulation induction, conception, and normal delivery after chronic therapy with etanercept: a recombinant fusion anti-cytokine treatment for rheumatoid arthritis. Am J Reprod Immunol. 2001 Nov;46(5):366-8.

2250. Simms R, Kipgen D, Dahill S, et al. ANCA-associated renal vasculitis following anti-tumor necrosis factor alpha therapy. Am J Kidney Dis. 2008 Mar;51(3):e11-4.

2251. Simsek I, Erdem H, Pay S, et al. Optic neuritis occurring with anti-tumour necrosis factor alpha therapy. Ann Rheum Dis. 2007 Sep;66(9):1255-8.

2252. Singh JA, Mahowald ML. Intra-articular botulinum toxin A as an adjunctive therapy for refractory joint pain in patients with rheumatoid arthritis receiving biologics: a report of two cases. Joint Bone Spine. 2009 Mar;76(2):190-4.

2253. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev 2010(1):CD008341.

2254. Singh JA, Pando JA, Tomaszewski J, et al. Quantitative analysis of immunohistologic features of very early rheumatoid synovitis in disease modifying antirheumatic drug- and corticosteroid-naive patients. J Rheumatol. 2004 Jul;31(7):1281-5.

2255. Singh P, Taylor SF, Murali R, et al. Disseminated mucormycosis and orbital ischaemia in combination immunosuppression with a tumour necrosis factor alpha inhibitor. Clin Experiment Ophthalmol. 2007 Apr;35(3):275-80.

2256. Singh R, Cuchacovich R, Huang W, et al. Infliximab treatment in a patient with rheumatoid arthritis on hemodialysis. J Rheumatol. 2002 Mar;29(3):636-7.

2257. Singh S, Samant R, Joshi VR. Adult onset Still's disease: a study of 14 cases. Clin Rheumatol. 2008 Jan;27(1):35-9.

2258. Sinha A, Patient C. Rheumatoid arthritis in pregnancy: successful outcome with anti-TNF agent (Etanercept). J Obstet Gynaecol. 2006 Oct;26(7):689-91.

2259. Sinigaglia L, Nervetti A, Mela Q, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol. 2000 Nov;27(11):2582-9.

2260. Sinsawaiwong S, Tiyapun N, Hirunpat C, et al. Simultaneous bilateral painful ophthalmoplegia and exudative retinal detachment in rheumatoid arthritis. J Med Assoc Thai. 1999 Nov;82(11):1170-3.

2261. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum. 2003 Feb;48(2):319-24.

2262. Sliwinska-Stanczyk P, Pazdur J, Ziolkowska M, et al. The effect of methylprednisolone on proliferation of PBMCs obtained from steroid-sensitive and steroid-resistant rheumatoid arthritis patients. Scand J Rheumatol. 2007 May-Jun;36(3):167-71.

2263. Slovis BS, Eyler AE. A 33-year-old man with pharyngitis, transient rash, and multiorgan system failure. Chest. 2007 Sep;132(3):1080-3.

2264. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst. 2006 Jan 4;98(1):51-60.

2265. Smeets TJ, Kraan MC, van Loon ME, et al. Tumor necrosis factor alpha blockade reduces the synovial cell infiltrate early after initiation of treatment, but apparently not by induction of apoptosis in synovial tissue. Arthritis Rheum. 2003 Aug;48(8):2155-62.

2266. Smith AP, Musacchio MJ, O'Toole JE. Spinal epidural abscess associated with infliximab treatment for psoriatic arthritis. Case report. J Neurosurg Spine. 2008 Sep;9(3):261-4.

2267. Smith D, Letendre S. Viral pneumonia as a serious complication of etanercept therapy. Ann Intern Med. 2002 Jan 15;136(2):174.

2268. Smith GR, Tymms KE, Falk M. Etanercept treatment of renal amyloidosis complicating rheumatoid arthritis. Intern Med J. 2004 Sep-Oct;34(9-10):570-2.

2269. Smith KJ, Skelton HG. Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor alpha receptor IgG1-Fc fusion complex therapy. J Am Acad Dermatol. 2001 Dec;45(6):953-6.

2270. Smith MD, Slavotinek J, Au V, et al. Successful treatment of rheumatoid arthritis is associated with a reduction in synovial membrane cytokines and cell adhesion molecule expression. Rheumatology (Oxford). 2001 Sep;40(9):965-77.

2271. Smith N, Ding T, Butt S, et al. The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice. Rheumatology (Oxford). 2008 Sep;47(9):1389-91.

2272. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57(8):1431-8.

2273. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35(3):387-93.

2274. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68(6):797-804.

2275. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371(9617):987-97.

2276. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52(4):1020-30.

2277. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):716-22.

2278. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68(6):823-7.

2279. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374(9685):210-21.

2280. Snowden JA, Biggs JC, Milliken ST, et al. A phase I/II dose escalation study of intensified cyclophosphamide and autologous blood stem cell rescue in severe, active rheumatoid arthritis. Arthritis Rheum. 1999 Nov;42(11):2286-92.

2281. Sobhani I, Brousse N, Vissuzaine C, et al. A diffuse T lymphocytic gastrointestinal mucosal infiltration associated with Sjogren's syndrome resulting in a watery diarrhea syndrome and responsive to immunosuppressive therapy. Am J Gastroenterol. 1998 Dec;93(12):2584-6.

2282. Soderlin MK, Lindroth Y, Jacobsson LT. Trends in medication and health-related quality of life in a population-based rheumatoid arthritis register in Malmo, Sweden. Rheumatology (Oxford) 2007;46(8):1355-8.

2283. Soh MC, Hart HH, Corkill M. Pericardial effusions with tamponade and visceral constriction in patients with rheumatoid arthritis on tumour necrosis factor (TNF)-inhibitor therapy. Int J Rheum Dis. 2009 Apr;12(1):74-7.

2284. Sokka T, Kautiainen H, Toloza S, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007 Nov;66(11):1491-6.

2285. Sokka T, Mottonen T, Hannonen P. Mortality in early "sawtooth" treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol. 1999;28(5):282-7.

2286. Sokka T, Pincus T. Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol. 2002 Dec;29(12):2521-4.

2287. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum. 2003 Feb;48(2):313-8.

2288. Sokka T, Pincus T. Ascendancy of weekly low-dose methotrexate in usual care of rheumatoid arthritis from 1980 to 2004 at two sites in Finland and the United States. Rheumatology (Oxford). 2008 Oct;47(10):1543-7.

2289. Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69(9):1612-7.

2290. Sokolovic S, Kasumagic S, Mackic-Durovic M, et al. The impact of Rituximab therapy on the chromosomes of patients with Rheumatoid arthritis. Bosn J Basic Med Sci. 2010 May;10(2):121-4.

2291. Solau-Gervais E, Legrand JL, Cortet B, et al. Magnetic resonance imaging of the hand for the diagnosis of rheumatoid arthritis in

the absence of anti-cyclic citrullinated peptide antibodies: a prospective study. J Rheumatol. 2006 Sep;33(9):1760-5.

2292. Soliotis F, Glover M, Jawad AS. Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):850-1.

2293. Solomon DH, Katz JN, Cabral D, et al. Osteoporosis management in patients with rheumatoid arthritis: Evidence for improvement. Arthritis Rheum. 2006 Dec 15;55(6):873-7.

2294. Solomon DH, Kuntz KM. Should postmenopausal women with rheumatoid arthritis who are starting corticosteroid treatment be screened for osteoporosis? A cost-effectiveness analysis. Arthritis Rheum. 2000 Sep;43(9):1967-75.

2295. Solomon DH, Stedman M, Licari A, et al. Agreement between patient report and medical record review for medications used for rheumatoid arthritis: the accuracy of self-reported medication information in patient registries. Arthritis Rheum. 2007 Mar 15;57(2):234-9.

2296. Somer BG, Tsai DE, Downs L, et al. Improvement in Sjogren's syndrome following therapy with rituximab for marginal zone lymphoma. Arthritis Rheum. 2003 Jun 15;49(3):394-8.

2297. Sommer WH, Ganiere V, Gachoud D, et al. Neurological and pulmonary adverse effects of subcutaneous methotrexate therapy. Scand J Rheumatol. 2008 Jul-Aug;37(4):306-9.

2298. Sorajja P, Poirier MK, Bundrick JB, et al. Autonomic failure and proximal skeletal myopathy in a patient with primary Sjogren syndrome. Mayo Clin Proc. 1999 Jul;74(7):695-7.

2299. Sordet C, Gottenberg JE, Hellmich B, et al. Lack of efficacy of rituximab in Felty's syndrome. Ann Rheum Dis. 2005 Feb;64(2):332-3.

2300. Sorensen LK, Havemose-Poulsen A, Bendtzen K, et al. Aggressive periodontitis and chronic arthritis: blood mononuclear cell gene expression and plasma protein levels of cytokines and cytokine inhibitors. J Periodontol. 2009 Feb;80(2):282-9.

2301. Soubrier M, Haik S, Hauw JJ, et al. Creutzfeldt-Jakob disease in a patient treated by etanercept for rheumatoid arthritis (RA): just a coincidence? Joint Bone Spine. 2010 Mar;77(2):174-5.

2302. Soubrier M, Jeannin G, Kemeny JL, et al. Organizing pneumonia after rituximab therapy: Two cases. Joint Bone Spine. 2008 May;75(3):362-5.

2303. Soubrier M, Jouanel P, Mathieu S, et al. Effects of anti-tumor necrosis factor therapy on lipid profile in patients with rheumatoid arthritis. Joint Bone Spine. 2008 Jan;75(1):22-4.

2304. Soubrier M, Mathieu S, Payet S, et al. Elderly-onset rheumatoid arthritis. Joint Bone Spine. 2010 Jul;77(4):290-6.

2305. Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford). 2009 Nov;48(11):1429-34.

2306. Sowter MC, Burgess NA, Woodsford PV, et al. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. Br J Anaesth. 1992 Jan;68(1):103-5.

2307. Spadaro A, Scrivo R, Riccieri V, et al. Effect of tumor necrosis factor alpha antagonists in a patient with rheumatoid arthritis and primary biliary cirrhosis. Joint Bone Spine. 2008 Jan;75(1):87-9.

2308. Spalding JR, Hay J. Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. Pharmacoeconomics. 2006;24(12):1221-32.

2309. Spanakis E, Sidiropoulos P, Papadakis J, et al. Modest but sustained increase of serum high density lipoprotein cholesterol levels in

patients with inflammatory arthritides treated with infliximab. J Rheumatol. 2006 Dec;33(12):2440-6.

2310. Sperling RI, Coblyn JS, Larkin JK, et al. Inhibition of leukotriene B4 synthesis in neutrophils from patients with rheumatoid arthritis by a single oral dose of methotrexate. Arthritis Rheum. 1990 Aug;33(8):1149-55.

2311. Sprekeler R, Lemmel EM, Obert HJ. Correlation of clinical and serological findings in patients with rheumatoid arthritis treated for one year with interferon-gamma. Z Rheumatol. 1990 Jan-Feb;49(1):1-7.

2312. Squirrell DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. Rheumatology (Oxford). 1999 Dec;38(12):1245-8.

2313. Sri JC, Tsai CL, Deng A, et al. Osteomyelitis occurring during infliximab treatment of severe psoriasis. J Drugs Dermatol. 2007 Feb;6(2):207-10.

2314. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1992 Dec;39(4):342-8.

2315. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43.

2316. Stafford L, Bleasel J, Giles A, et al. Androgen deficiency and bone mineral density in men with rheumatoid arthritis. J Rheumatol. 2000 Dec;27(12):2786-90.

2317. Stalenheim G, Gudbjornsson B. Anti-inflammatory drugs do not alleviate bronchial hyperreactivity in Sjogren's syndrome. Allergy. 1997 Apr;52(4):423-7.

2318. Stamp LK, O'Donnell JL, Chapman PT, et al. Determinants of red blood cell methotrexate polyglutamate concentrations in rheumatoid arthritis patients receiving long-term methotrexate treatment. Arthritis Rheum. 2009 Aug;60(8):2248-56.

2319. Stamp LK, O'Donnell JL, Chapman PT, et al. Methotrexate polyglutamate concentrations are not associated with disease control in rheumatoid arthritis patients receiving long-term methotrexate therapy. Arthritis Rheum. 2010 Feb;62(2):359-68.

2320. Stanescu D, Bodaghi B, Huong du LT, et al. Pseudotumor cerebri associated with Sjogren's syndrome. Graefes Arch Clin Exp Ophthalmol. 2003 Apr;241(4):339-42.

2321. Starmans-Kool MJ, Peeters HR, Houben HH. Pustular skin lesions in patients treated with infliximab: report of two cases. Rheumatol Int. 2005 Sep;25(7):550-2.

2322. Starosta MA, Brandwein SR. Clinical manifestations and treatment of rheumatoid pachymeningitis. Neurology. 2007 Mar 27;68(13):1079-80.

2323. Steens SC, Steup-Beekman GM, Bosma GP, et al. The effect of corticosteroid medication on quantitative MR parameters of the brain. AJNR Am J Neuroradiol. 2005 Nov-Dec;26(10):2475-80.

2324. Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjogren's syndrome: a pilot study. Arthritis Rheum. 2001 Oct;44(10):2371-5.

2325. Stepien KE, Han DP, Schell J, et al. Spectral-domain optical coherence tomography and adaptive optics may detect hydroxychloroquine retinal toxicity before symptomatic vision loss. Trans Am Ophthalmol Soc. 2009 Dec;107:28-33.

2326. Sterling LP. Rheumatoid arthritis: current concepts and management, Part 2. Am Pharm. 1990 Sep;NS30(9):49-54.

2327. Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol. 2004 Aug;31(8):1538-45.

2328. Sterry W, Ortonne JP, Kirkham B, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Bmj. 2010;340:c147.

2329. Stewart M, Malkovska V, Krishnan J, et al. Lymphoma in a patient with rheumatoid arthritis receiving methotrexate treatment: successful treatment with rituximab. Ann Rheum Dis. 2001 Sep;60(9):892-3.

2330. Stewart MW, Palmer DG, Knight RG. A self-report articular index measure of arthritic activity: investigations of reliability, validity and sensitivity. J Rheumatol. 1990 Aug;17(8):1011-5.

2331. Stock CJ, Ogilvie EM, Samuel JM, et al. Comprehensive association study of genetic variants in the IL-1 gene family in systemic juvenile idiopathic arthritis. Genes Immun. 2008 Jun;9(4):349-57.

2332. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. Nephrol Dial Transplant. 2005 Jul;20(7):1400-6.

2333. Stoll ML, Solomon DH, Batra KL, et al. TNFalpha inhibitors may improve asthma symptoms: a case series of 12 patients with rheumatoid arthritis and asthma. J Clin Rheumatol. 2009 Jun;15(4):198-200.

2334. Stone M, Salonen D, Lax M, et al. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. J Rheumatol. 2001 Jul;28(7):1605-14.

2335. Stone MA, Inman RD, Wright JG, et al. Validation exercise of the Ankylosing Spondylitis Assessment Study (ASAS) group response criteria in ankylosing spondylitis patients treated with biologics. Arthritis Rheum. 2004 Jun 15;51(3):316-20.

2336. Stone MA, Payne U, Pacheco-Tena C, et al. Cytokine correlates of clinical response patterns to infliximab treatment of ankylosing spondylitis. Ann Rheum Dis. 2004 Jan;63(1):84-7.

2337. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther 2010;12(1):R5.

2338. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. Jama 2009;301(7):737-44.

2339. Stranzl T, Wolf J, Leeb BF, et al. Expression of folylpolyglutamyl synthetase predicts poor response to methotrexate therapy in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2003 Jan-Feb;21(1):27-32.

2340. Stratigos AJ, Antoniou C, Stamathioudaki S, et al. Discoid lupus erythematosus-like eruption induced by infliximab. Clin Exp Dermatol. 2004 Mar;29(2):150-3.

2341. Straub RH, Gunzler C, Miller LE, et al. Anti-inflammatory cooperativity of corticosteroids and norepinephrine in rheumatoid arthritis synovial tissue in vivo and in vitro. Faseb J. 2002 Jul;16(9):993-1000.

2342. Straub RH, Harle P, Atzeni F, et al. Sex hormone concentrations in patients with rheumatoid arthritis are not normalized during 12 weeks of anti-tumor necrosis factor therapy. J Rheumatol. 2005 Jul;32(7):1253-8.

2343. Straub RH, Harle P, Yamana S, et al. Anti-interleukin-6 receptor antibody therapy favors adrenal androgen secretion in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2006 Jun;54(6):1778-85.

2344. Straub RH, Kittner JM, Heijnen C, et al. Infusion of epinephrine decreases serum levels of cortisol and 17-hydroxyprogesterone in patients with rheumatoid arthritis. J Rheumatol. 2002 Aug;29(8):1659-64.

2345. Straub RH, Paimela L, Peltomaa R, et al. Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. Arthritis Rheum. 2002 Mar;46(3):654-62.

2346. Straub RH, Pongratz G, Cutolo M, et al. Increased cortisol relative to adrenocorticotropic hormone predicts improvement during anti-tumor necrosis

factor therapy in rheumatoid arthritis. Arthritis Rheum. 2008 Apr;58(4):976-84.

2347. Straub RH, Pongratz G, Hirvonen H, et al. Acute cold stress in rheumatoid arthritis inadequately activates stress responses and induces an increase of interleukin 6. Ann Rheum Dis. 2009 Apr;68(4):572-8.

2348. Straub RH, Pongratz G, Scholmerich J, et al. Long-term anti-tumor necrosis factor antibody therapy in rheumatoid arthritis patients sensitizes the pituitary gland and favors adrenal androgen secretion. Arthritis Rheum. 2003 Jun;48(6):1504-12.

2349. Straub RH, Sarzi-Puttini P, Atzeni F, et al. Anti-tumour necrosis factor antibody treatment does not change serum levels of cortisol binding globulin in patients with rheumatoid arthritis but it increases androstenedione relative to cortisol. Ann Rheum Dis. 2005 Sep;64(9):1353-6.

2350. Straub RH, Weidler C, Demmel B, et al. Renal clearance and daily excretion of cortisol and adrenal androgens in patients with rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis. 2004 Aug;63(8):961-8.

2351. Strober B, Teller C, Yamauchi P, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322-30.

2352. Strober BE. Successful treatment of psoriasis and psoriatic arthritis with etanercept and methotrexate in a patient newly unresponsive to infliximab. Arch Dermatol. 2004 Mar;140(3):366.

2353. Strober BE, Clarke S. Etanercept for the treatment of psoriasis: combination therapy with other modalities. J Drugs Dermatol. 2004 May-Jun;3(3):270-2.

2354. Stucki G, Bruhlmann P, Stoll T, et al. Low serum creatine kinase activity is associated with muscle weakness in patients with rheumatoid arthritis. J Rheumatol. 1996 Apr;23(4):603-8.

2355. Studenski SA. Rheumatology, geriatrics, and a way forward. J Am Geriatr Soc. 2002 Oct;50(10):1737-8.

2356. Suarez-Almazor ME, Soskolne CL, Saunders LD, et al. Use of second line drugs for the treatment of rheumatoid arthritis in Edmonton, Alberta. Patterns of prescription and longterm effectiveness. J Rheumatol. 1995 May;22(5):836-43.

2357. Sugihara M, Tsutsumi A, Suzuki E, et al. Effects of infliximab therapy on gene expression levels of tumor necrosis factor alpha, tristetraprolin, T cell intracellular antigen 1, and Hu antigen R in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Jul;56(7):2160-9.

2358. Sugimori S, Watanabe T, Tabuchi M, et al. Evaluation of small bowel injury in patients with rheumatoid arthritis by capsule endoscopy: effects of anti-rheumatoid arthritis drugs. Digestion. 2008;78(4):208-13.

2359. Sugimoto T, Yasuda M, Sakaguchi M, et al. Acute interstitial nephritis associated with etanercept. Rheumatol Int. 2008 Oct;28(12):1283-4.

2360. Sugioka Y, Inui K, Koike T. Use of etanercept in a patient with rheumatoid arthritis on hemodialysis. Mod Rheumatol. 2008;18(3):293-5.

2361. Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55(4):531-6.

2362. Suissa S, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2008;21(1):234-8.

2363. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006 May;54(5):1435-9.

2364. Sulit DJ, Clarke JE. Psoriatic arthritis in a military aviator. Aviat Space Environ Med. 2005 Jul;76(7):684-8.

2365. Sulli A, Maestroni GJ, Villaggio B, et al. Melatonin serum levels in rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:276-83.

2366. Sulli A, Montecucco CM, Caporali R, et al. Glucocorticoid effects on adrenal steroids and cytokine responsiveness in polymyalgia rheumatica and elderly onset rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:307-14.

2367. Sundberg E, Grundtman C, Af Klint E, et al. Systemic TNF blockade does not modulate synovial expression of the pro-inflammatory mediator HMGB1 in rheumatoid arthritis patients--a prospective clinical study. Arthritis Res Ther. 2008;10(2):R33.

2368. Suresh R, Gupta S, Sathananthan R. Sulphasalazine induced three-week syndrome. J Clin Rheumatol. 2009 Sep;15(6):311-2.

2369. Suwannalai P, Auethavekiat P, Udomsubpayakul U, et al. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: a retrospective study a the university-based hospital. Int J Rheum Dis 2009;12(2):118-24.

2370. Suzuki K, Kimura Y, Aoki M, et al. Persistent plaques and linear pigmentation in adult-onset Still's disease. Dermatology. 2001;202(4):333-5.

2371. Suzuki K, Saito K, Tsujimura S, et al. Tacrolimus, a calcineurin inhibitor, overcomes treatment unresponsiveness mediated by P-glycoprotein on lymphocytes in refractory rheumatoid arthritis. J Rheumatol. 2010 Mar;37(3):512-20.

2372. Suzuki T, Tsutsumi A, Suzuki H, et al. Tristetraprolin (TTP) gene polymorphisms in patients with rheumatoid arthritis and healthy individuals. Mod Rheumatol. 2008;18(5):472-9.

2373. Suzuki Y, Inoue K, Chiba J, et al. Histological analysis of synovium by treatment of etanercept for rheumatoid arthritis. Int J Rheum Dis. 2009 Apr;12(1):7-13.

2374. Suzuki Y, Mizushima Y. Osteoporosis in rheumatoid arthritis. Osteoporos Int. 1997;7 Suppl 3:S217-22.

2375. Suzuki Y, Uehara R, Tajima C, et al. Elevation of serum hepatic aminotransferases during treatment of rheumatoid arthritis with low-dose methotrexate. Risk factors and response to folic acid. Scand J Rheumatol. 1999;28(5):273-81.

2376. Svenson M, Geborek P, Saxne T, et al. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatology (Oxford). 2007 Dec;46(12):1828-34.

2377. Svensson B, Ahlmen M, Forslind K. Treatment of early RA in clinical practice: a comparative study of two different DMARD/corticosteroid options. Clin Exp Rheumatol. 2003 May-Jun;21(3):327-32.

2378. Svensson B, Hafstrom I, Forslind K, et al. Increased expression of proto-oncogene survivin predicts Joint destruction and persistent disease activity in early rheumatoid arthritis. Ann Med. 2010;42(1):45-54.

2379. Svensson B, Schaufelberger C, Teleman A, et al. Remission and response to early treatment of RA assessed by the Disease Activity Score. BARFOT study group. Better Anti-rheumatic Farmacotherapy. Rheumatology (Oxford). 2000 Sep;39(9):1031-6.

2380. Swale VJ, Perrett CM, Denton CP, et al. Etanercept-induced systemic lupus erythematosus. Clin Exp Dermatol. 2003 Nov;28(6):604-7.

2381. Swaneveld FH, van Vugt RM, de Boer JP, et al. A 57-year-old man who developed arthritis during R-CHOP chemotherapy for non-Hodgkin lymphoma. Clin Rheumatol. 2008 Feb;27(2):249-51.

2382. Swanson DL, Barnes SA, Mengden Koon SJ, et al. Caffeine consumption and methotrexate dosing requirement in psoriasis and psoriatic arthritis. Int J Dermatol. 2007 Feb;46(2):157-9.

2383. Sweet DD, Isac G, Morrison B, et al. Purulent pericarditis in a patient with rheumatoid arthritis treated with etanercept and methotrexate. Cjem. 2007 Jan;9(1):40-2.

2384. Szeto T, Peterson J, Silva F. A case of tuberculous peritonitis in the United States in a patient with rheumatoid arthritis treated with adalimumab. J Clin Rheumatol. 2010 Apr;16(3):135-7.

2385. Szturmowicz M, Wilinska E, Paczek A, et al. Primary Sjogren's Syndrome with two extraglandular sites involvement - case report. Pneumonol Alergol Pol. 2010;78(6):445-50.

2386. Taban M, Dupps WJ, Mandell B, et al. Etanercept (enbrel)-associated inflammatory eye disease: case report and review of the literature. Ocul Immunol Inflamm. 2006 Jun;14(3):145-50.

2387. Tack CJ, Kleijwegt FS, Van Riel PL, et al. Development of type 1 diabetes in a patient treated with anti-TNF-alpha therapy for active rheumatoid arthritis. Diabetologia. 2009 Jul;52(7):1442-4.

2388. Tada Y, Fukuoka M, Mitamura M, et al. Nocardiosis in adult-onset Still's disease and vasculitis syndrome. Am J Med Sci. 2008 Jul;336(1):77-80.

2389. Tai TL, O'Rourke KP, McWeeney M, et al. Pneumocystis carinii pneumonia following a second infusion of infliximab. Rheumatology (Oxford). 2002 Aug;41(8):951-2.

2390. Taira T, Matsuyama W, Mitsuyama H, et al. Increased serum high mobility group box-1 level in Churg-Strauss syndrome. Clin Exp Immunol. 2007 May;148(2):241-7.

2391. Taiwo B, Lee C, Venkat D, et al. Can tumor necrosis factor alpha blockade predispose to severe babesiosis? Arthritis Rheum. 2007 Feb 15;57(1):179-81.

2392. Takahashi A, Takeda I, Kanno T, et al. CD8-positive T cell-induced liver damage was found in a patient with polymyositis. Intern Med. 2006;45(18):1059-63.

2393. Takahashi H, Shigehara K, Yamamoto M, et al. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. Rheumatol Int. 2007 Oct;27(12):1143-8.

2394. Takahashi H, Tezuka F, Fujita S, et al. Vascular changes in major and lingual minor salivary glands in primary Sjogren's syndrome. Anal Cell Pathol. 1995 Dec;9(4):243-56.

2395. Takahashi M, Mizutani H, Nakamura Y, et al. A case of multicentric reticulohistiocytosis, systemic sclerosis and Sjogren syndrome. J Dermatol. 1997 Aug;24(8):530-4.

2396. Takahashi T, Satoh M, Satoh H. Unilateral acute exacerbation of pulmonary fibrosis in association with Sjogren's syndrome. Intern Med. 1996 Oct;35(10):811-4.

2397. Takami A, Nakao S, Miyamori H, et al. Adult-onset Still's disease with submassive hepatic necrosis. Intern Med. 1995 Feb;34(2):89-91.

2398. Takasugi JE, Godwin JD. Lung abscess caused by Rhodococcus equi. J Thorac Imaging. 1991 Apr;6(2):72-4.

2399. Takatori R, Takahashi KA, Tokunaga D, et al. ABCB1 C3435T polymorphism influences methotrexate sensitivity in rheumatoid arthritis patients. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):546-54.

2400. Takeuchi T, Miyasaka N, Inoue K, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol 2009;19(5):478-87.

2401. Takeuchi T, Tatsuki Y, Nogami Y, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):189-94.

2402. Takeuchi T, Yamanaka H, Inoue E, et al. Retrospective clinical study on the notable

efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18(5):447-54.

2403. Talip F, Walker N, Khan W, et al. Treatment of Felty's syndrome with leflunomide. J Rheumatol. 2001 Apr;28(4):868-70.

2404. Tam LS, Griffith JF, Yu AB, et al. Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation. Clin Rheumatol. 2007 Jun;26(6):941-6.

2405. Tam LS, Tomlinson B, Chu TT, et al. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol. 2007 Sep;26(9):1495-8.

2406. Tam MM, Meehan CJ. Subcutaneous granuloma annulare in a patient with rheumatoid arthritis and diabetes mellitus. Australas J Dermatol. 1996 Nov;37(4):199-201.

2407. Tambo Y, Fujimura M, Yasui M, et al. Eosinophilic pneumonia (EP) associated with rheumatoid arthritis in which drug-induced eosinophilic pneumonia could be ruled out. Intern Med. 2008;47(6):527-31.

2408. Tamura S, Koreeda T, Nakano T, et al. A case of rheumatoid arthritis which developed after recovery from adult respiratory distress syndrome. Jpn J Med. 1990 Nov-Dec;29(6):611-5.

2409. Tan AL, Marzo-Ortega H, O'Connor P, et al. Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. Ann Rheum Dis. 2004 Sep;63(9):1041-5.

2410. Tan RJ, Gibbons LJ, Potter C, et al. Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. Ann Rheum Dis 2010;69(6):1029-35.

2411. Tanaka A, Shigematsu H, Kojima M, et al. Methotrexate-associated lymphoproliferative disorder arising in a patient with adult Still's disease. J Oral Maxillofac Surg. 2008 Jul;66(7):1492-5.

2412. Tanaka E, Inoue E, Kawaguchi Y, et al. Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. Mod Rheumatol. 2006;16(4):214-9.

2413. Tanaka N, Sakahashi H, Hirose K, et al. Volume of a wash and the other conditions for maximum therapeutic effect of arthroscopic lavage in rheumatoid knees. Clin Rheumatol. 2006 Feb;25(1):65-9.

2414. Tanaka Y, Takeuchi T, Inoue E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18(2):146-52.

2415. Tanaka Y, Takeuchi T, Mimori T, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis. 2010 Jul;69(7):1286-91.

2416. Tang B, Rahman M, Waters HC, et al. Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. Clin Ther. 2008 Jul;30(7):1375-84.

2417. Taniguchi A, Urano W, Tanaka E, et al. Validation of the associations between single nucleotide polymorphisms or haplotypes and responses to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a proposal for prospective pharmacogenomic study in clinical practice. Pharmacogenet Genomics. 2007 Jun;17(6):383-90.

2418. Tanno M, Nakajima A, Ishiwata T, et al. Effect of general anesthesia on the abnormal immune response in patients with

rheumatoid arthritis. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):727-32.

2419. Taraborelli M, Andreoli L, Archetti S, et al. Methylenetetrahydrofolate reductase polymorphisms and methotrexate: no association with response to therapy nor with drug-related adverse events in an Italian population of rheumatic patients. Clin Exp Rheumatol 2009;27(3):499-502.

2420. Targonska-Stepniak B, Majdan M, Dryglewska M. Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. Rheumatol Int. 2008 Apr;28(6):585-91.

2421. Tascioglu F, Oner C, Armagan O. The effect of low-dose methotrexate on bone mineral density in patients with early rheumatoid arthritis. Rheumatol Int. 2003 Sep;23(5):231-5.

2422. Tassiopoulos S, Benopoulou O, Mytilineou E, et al. Late onset of long-lasting fever as a sole complication of treatment with anti-TNFalpha. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):122-3.

2423. Tateiwa T, Shinmura K, Ko M, et al. Iliopectineal bursitis associated with rapid destruction of a rheumatoid hip joint. J Orthop Sci. 2009 Jul;14(4):455-8.

2424. Tauber T, Turetz J, Barash J, et al. Optic neuritis associated with etanercept therapy for juvenile arthritis. J Aapos. 2006 Feb;10(1):26-9.

2425. Taylor JC, Orkin R, Lanham J. Tuberculosis following therapy with infliximab may be refractory to antibiotic therapy. Rheumatology (Oxford). 2003 Jul;42(7):901-2.

2426. Taylor WJ, Rajapakse CN, Harris KA, et al. Inpatient treatment of rheumatoid arthritis with synacthen depot: a double blind placebo controlled trial with 6 month followup. J Rheumatol. 1999 Dec;26(12):2544-50.

2427. Tchetverikov I, Kraan MC, van El B, et al. Leflunomide and methotrexate reduce levels of activated matrix metalloproteinases in complexes with alpha2 macroglobulin in serum of rheumatoid arthritis patients. Ann Rheum Dis. 2008 Jan;67(1):128-30.

2428. Teh J, Stevens K, Williamson L, et al. Power Doppler ultrasound of rheumatoid synovitis: quantification of therapeutic response. Br J Radiol. 2003 Dec;76(912):875-9.

2429. Tektonidou MG, Skopouli FN. Visceral leishmaniasis in a patient with psoriatic arthritis treated with infliximab: reactivation of a latent infection? Clin Rheumatol. 2008 Apr;27(4):541-2.

2430. Temekonidis TI, Alamanos Y, Nikas SN, et al. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. Ann Rheum Dis. 2003 Dec;62(12):1218-20.

2431. Temekonidis TI, Georgiadis AN, Alamanos Y, et al. Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):822-5.

2432. ten Tusscher MP, Jacobs PJ, Busch MJ, et al. Bilateral anterior toxic optic neuropathy and the use of infliximab. BMJ. 2003 Mar 15;326(7389):579.

2433. Teng YK, Levarht EW, Hashemi M, et al. Immunohistochemical analysis as a means to predict responsiveness to rituximab treatment. Arthritis Rheum. 2007 Dec;56(12):3909-18.

2434. Teng YK, Levarht EW, Toes RE, et al. Residual inflammation after rituximab treatment is associated with sustained synovial plasma cell infiltration and enhanced B cell repopulation. Ann Rheum Dis. 2009 Jun;68(6):1011-6.

2435. Tengstrand B, Carlstrom K, Fellander-Tsai L, et al. Abnormal levels of serum dehydroepiandrosterone, estrone, and estradiol in men with rheumatoid arthritis: high correlation between serum estradiol and current degree of inflammation. J Rheumatol. 2003 Nov;30(11):2338-43.

2436. Tengstrand B, Hafstrom I. Bone mineral density in men with rheumatoid arthritis is associated with erosive disease and sulfasalazine treatment but not with sex hormones. J Rheumatol. 2002 Nov;29(11):2299-305.

2437. Tengstrand B, Larsson E, Klareskog L, et al. Randomized withdrawal of long-term prednisolone treatment in rheumatoid arthritis: effects on inflammation and bone mineral density. Scand J Rheumatol. 2007 Sep-Oct;36(5):351-8.

2438. Terrier B, Lacroix C, Guillevin L, et al. Diagnostic and prognostic relevance of neuromuscular biopsy in primary Sjogren's syndrome-related neuropathy. Arthritis Rheum. 2007 Dec 15;57(8):1520-9.

2439. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Spectral Doppler and resistive index. A promising tool in ultrasonographic evaluation of inflammation in rheumatoid arthritis. Acta Radiol. 2003 Nov;44(6):645-52.

2440. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Effects of treatment with etanercept (Enbrel, TNRF:Fc) on rheumatoid arthritis evaluated by Doppler ultrasonography. Ann Rheum Dis. 2003 Feb;62(2):178-81.

2441. Theodoridou A, Kartsios C, Yiannaki E, et al. Reversible T-large granular lymphocyte expansion and neutropenia associated with adalimumab therapy. Rheumatol Int. 2006 Dec;27(2):201-2.

2442. Thomaidis T, Schorn C, Flaig W, et al. Immunoadsorption with tryptophan columns: a therapeutic option for the treatment of rheumatoid arthritis with septic complications. J Clin Apher. 2009;24(1):37-41.

2443. Thomas JE, Taoka CR, Gibbs BT, et al. Fatal pulmonary Mycobacterium abscessus infection in a patient using etanercept. Hawaii Med J. 2006 Jan;65(1):12-5.

2444. Thomas JW, Pflugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. Cornea. 2005 Aug;24(6):742-4.

2445. Thomason RW, Craig FE, Banks PM, et al. Epstein-Barr virus and lymphoproliferation in methotrexate-treated rheumatoid arthritis. Mod Pathol. 1996 Mar;9(3):261-6.

2446. Thompson AE, Bashook PG. Rheumatologists' recommended patient information when prescribing methotrexate for rheumatoid arthritis. Clin Exp Rheumatol. 2010 Jul-Aug;28(4):539-45.

2447. Thonhofer R, Gaugg M, Kriessmayr M, et al. Spontaneous remission of marginal zone B cell lymphoma in a patient with seropositive rheumatoid arthritis after discontinuation of infliximab-methotrexate treatment. Ann Rheum Dis. 2005 Jul;64(7):1098-9.

2448. Thonhofer R, Soleiman A, Kriessmayr M, et al. Decrease of proteinuria in a patient with adult-onset Still's disease and glomerulonephritis after anti-TNFalpha therapy. Scand J Rheumatol. 2006 Nov-Dec;35(6):485-8.

2449. Thorne JE, Volpe NJ, Liu GT. Magnetic resonance imaging of acquired Brown syndrome in a patient with psoriasis. Am J Ophthalmol. 1999 Feb;127(2):233-5.

2450. Thorne JE, Woreta FA, Dunn JP, et al. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010 Jul;117(7):1436-41.

2451. Thumboo J, Uramoto K, Shbeeb MI, et al. Risk factors for the development of psoriatic arthritis: a population based nested case control study. J Rheumatol. 2002 Apr;29(4):757-62.

2452. Thurlings RM, Vos K, Gerlag DM, et al. Disease activity-guided rituximab therapy in rheumatoid arthritis: the effects of re-treatment in initial nonresponders versus initial responders. Arthritis Rheum. 2008 Dec;58(12):3657-64.

2453. Thurlings RM, Vos K, Wijbrandts CA, et al. Synovial tissue response to rituximab: mechanism of action and identification of biomarkers of response. Ann Rheum Dis. 2008 Jul;67(7):917-25.

2454. Tiderius CJ, Sandin J, Svensson J, et al. Knee cartilage quality assessed with dGEMRIC in rheumatoid arthritis patients before and after treatment with a TNF inhibitor. Acta Radiol. 2010 Nov;51(9):1034-7.

2455. Tikiz H, Arslan O, Pirildar T, et al. The effect of anti-tumor necrosis factor (TNF)-alpha therapy with etanercept on endothelial functions in patients with rheumatoid arthritis. Anadolu Kardiyol Derg. 2010 Apr;10(2):98-103.

2456. Tikly M, Zannettou N, Hopley M. A longitudinal study of rheumatoid arthritis in South Africans. MedGenMed. 2003 Feb 5;5(1):2.

2457. Tiliakos AN, Tiliakos NA. Ocular inflammatory disease in patients with RA taking etanercept: is discontinuation of etanercept necessary? J Rheumatol. 2003 Dec;30(12):2727.

2458. Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Investig. 2006;26(2):55-62.

2459. Todoerti M, Scire CA, Boffini N, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Ann N Y Acad Sci 2010;1193(1):139-45.

2460. Toh ML, Marotte H, Blond JL, et al. Overexpression of synoviolin in peripheral blood and synoviocytes from rheumatoid arthritis patients and continued elevation in nonresponders to infliximab treatment. Arthritis Rheum. 2006 Jul;54(7):2109-18.

2461. Tokayer A, Carsons SE, Chokshi B, et al. High levels of interleukin 13 in rheumatoid arthritis sera are modulated by tumor necrosis factor antagonist therapy: association with dendritic cell growth activity. J Rheumatol. 2002 Mar;29(3):454-61.

2462. Tokuda H, Sakai F, Yamada H, et al. Clinical and radiological features of Pneumocystis pneumonia in patients with rheumatoid arthritis, in comparison with methotrexate pneumonitis and Pneumocystis pneumonia in acquired immunodeficiency syndrome: a multicenter study. Intern Med. 2008;47(10):915-23.

2463. Tolusso B, Pietrapertosa D, Morelli A, et al. IL-1B and IL-1RN gene polymorphisms in rheumatoid arthritis: relationship with protein plasma levels and response to therapy. Pharmacogenomics. 2006 Jul;7(5):683-95.

2464. Toms TE, Panoulas VF, John H, et al. Methotrexate therapy associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60- more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther. 2009;11(4):R110.

2465. Tong D, Eather S, Manolios N. Psoriatic arthritis and chronic lymphoedema: treatment efficacy by adalimumab. Clin Rheumatol. 2009 Nov;28(11):1349-50.

2466. Toonen EJ, Coenen MJ, Kievit W, et al. The tumour necrosis factor receptor superfamily member 1b 676T>G polymorphism in relation to response to infliximab and adalimumab treatment and disease severity in rheumatoid arthritis. Ann Rheum Dis. 2008 Aug;67(8):1174-7.

2467. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010 Jul;59(1):40-9.

2468. Torikai E, Kageyama Y, Suzuki M, et al. The effect of infliximab on chemokines in patients with rheumatoid arthritis. Clin Rheumatol. 2007 Jul;26(7):1088-93.

2469. Torikai E, Kageyama Y, Takahashi M, et al. The effect of methotrexate on bone metabolism markers in patients with rheumatoid arthritis. Mod Rheumatol. 2006;16(6):350-4.

2470. Toritsuka Y, Nakamura N, Lee SB, et al. Osteoclastogenesis in iliac bone marrow of patients with rheumatoid arthritis. J Rheumatol. 1997 Sep;24(9):1690-6.

2471. Torrance GW, Tugwell P, Amorosi S, et al. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8.

2472. Torre-Cisneros J, Del Castillo M, Caston JJ, et al. Infliximab does not activate replication of lymphotropic herpesviruses in patients with refractory rheumatoid arthritis. Rheumatology (Oxford). 2005 Sep;44(9):1132-5.

2473. Torsteinsdottir I, Arvidson NG, Hallgren R, et al. Monocyte activation in rheumatoid arthritis (RA): increased integrin, Fc gamma and complement receptor expression and the effect of glucocorticoids. Clin Exp Immunol. 1999 Mar;115(3):554-60.

2474. Toubi E, Kessel A, Slobodin G, et al. Changes in macrophage function after rituximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Jun;66(6):818-20.

2475. Tourinho TF, Capp E, Brenol JC, et al. Physical activity prevents bone loss in premenopausal women with rheumatoid arthritis: a cohort study. Rheumatol Int. 2008 Aug;28(10):1001-7.

2476. Tournadre A, Ledoux-Eberst J, Poujol D, et al. Exacerbation of interstitial lung disease during etanercept therapy: Two cases. Joint Bone Spine. 2008 Mar;75(2):215-8.

2477. Toussirot E, Berthelot JM, Pertuiset E, et al. Pulmonary nodulosis and aseptic granulomatous lung disease occurring in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha-blocking agent: a case series. J Rheumatol. 2009 Nov;36(11):2421-7.

2478. Toussirot E, Nguyen NU, Dumoulin G, et al. Relationship between growth hormone-IGF-I-IGFBP-3 axis and serum leptin levels with bone mass and body composition in patients with rheumatoid arthritis. Rheumatology (Oxford). 2005 Jan;44(1):120-5.

2479. Toussirot E, Pertuiset E, Sordet C, et al. Safety of rituximab in rheumatoid arthritis patients with a history of severe or recurrent bacterial infection: observational study of 30 cases in everyday practice. Joint Bone Spine. 2010 Mar;77(2):142-5.

2480. Toussirot E, Wendling D. Bacillus calmette-guerin vaccination in a patient treated with infliximab. J Rheumatol. 2005 Dec;32(12):2500-1.

2481. Toy WC, Jasin HE. An unusual case of hypokalemic paralysis associated with primary Sjogren's syndrome. J Ark Med Soc. 2008 Jun;104(12):286-7.

2482. Toyoda T, Inokuchi S, Saito S, et al. Bone loss of the radius in rheumatoid arthritis. Comparison between 34 patients and 40 controls. Acta Orthop Scand. 1996 Jun;67(3):269-73.

2483. Toyokawa Y, Kingetsu I, Yasuda C, et al. Pancytopenia, including macrocytic anemia, associated with leflunomide in a rheumatoid arthritis patient. Mod Rheumatol. 2007;17(5):436-40.

2484. Toyozawa S, Yamamoto Y, Nishide T, et al. Case report: a case of pyoderma gangrenosum with intractable leg ulcers treated by allogeneic cultured dermal substitutes. Dermatol Online J. 2008;14(11):17.

2485. Traer EA, Williams MR, Keenan JN. Erysipelothrix rhusiopathiae infection of a total knee arthroplasty an occupational hazard. J Arthroplasty. 2008 Jun;23(4):609-11.

2486. Tresch S, Trueb RM, Kamarachev J, et al. Disseminated herpes zoster mimicking rheumatoid vasculitis in a rheumatoid arthritis patient on etanercept. Dermatology. 2009;219(4):347-9.

2487. Trethewey P. The role of tumor necrosis factor inhibitors in patients with RA. Jaapa. 2002 Sep;15(9):23-4, 7, 30 passim.

2488. True DG, Penmetcha M, Peckham SJ. Disseminated cryptococcal infection in rheumatoid arthritis treated with methotrexate and infliximab. J Rheumatol. 2002 Jul;29(7):1561-3.

2489. Tsai TC, Chen CY, Lin WT, et al. Sjogren's syndrome complicated with IgA nephropathy and leukocytoclastic vasculitis. Ren Fail. 2008;30(7):755-8.

2490. Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol. 2000 Mar;27(3):623-9.

2491. Tsubota K, Fujita H, Tadano K, et al. Abnormal expression and function of Fas ligand of lacrimal glands and peripheral blood in Sjogren's syndrome patients with enlarged exocrine glands. Clin Exp Immunol. 2002 Jul;129(1):177-82.

2492. Tsujimura S, Saito K, Nawata M, et al. Overcoming drug resistance induced by P-glycoprotein on lymphocytes in patients with refractory rheumatoid arthritis. Ann Rheum Dis. 2008 Mar;67(3):380-8.

2493. Tsukahara S, Momohara S, Ikari K, et al. Disturbances of the symphysis pubis in rheumatoid arthritis: report of two cases. Mod Rheumatol. 2007;17(4):344-7.

2494. Tsuzaka K, Itami Y, Takeuchi T, et al. ADAMTS5 is a biomarker for prediction of response to infliximab in patients with rheumatoid arthritis. J Rheumatol. 2010 Jul;37(7):1454-60.

2495. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94.

2496. Tudhope SJ, von Delwig A, Falconer J, et al. Profound invariant natural killer T-cell deficiency in inflammatory arthritis. Ann Rheum Dis. 2010 Oct;69(10):1873-9.

2497. Turesson C, Riesbeck K. Septicemia with Staphylococcus aureus, beta-hemolytic streptococci group B and G, and Escherichia coli in a patient with rheumatoid arthritis treated with a recombinant human interleukin 1 receptor antagonist (Anakinra). J Rheumatol. 2004 Sep;31(9):1876.

2498. Ueki Y, Sagawa A, Tanimura K, et al. A multicenter study of leukocytapheresis in rheumatoid arthritis. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):810-6.

2499. Umeda N, Ito S, Hayashi T, et al. A patient with rheumatoid arthritis who had a normal delivery under etanercept treatment. Intern Med. 2010;49(2):187-9.

2500. Uneda S, Sonoki T, Nakamura Y, et al. Rapid vanishing of tumors by withdrawal of methotrexate in Epstein-Barr virus-related B cell lymphoproliferative disorder. Intern Med. 2008;47(15):1445-6.

2501. Unger L, Kayser M, Nusslein HG. Successful treatment of severe rheumatoid vasculitis by infliximab. Ann Rheum Dis. 2003 Jun;62(6):587-8.

2502. Unlu E, Pamuk ON, Cakir N. Color and duplex Doppler sonography to detect sacroiliitis and spinal inflammation in ankylosing spondylitis. Can this method reveal response to anti-tumor necrosis factor therapy? J Rheumatol. 2007 Jan;34(1):110-6.

2503. Usui Y, Kimula Y, Miura H, et al. A case of bronchiolitis obliterans organizing pneumonia associated with primary Sjogren's syndrome who died of superimposed diffuse alveolar damage. Respiration. 1992;59(2):122-4.

2504. Uthman I, Bizri AR, Hajj Ali R, et al. Miliary tuberculosis presenting as tenosynovitis in a case of rheumatoid arthritis. J Infect. 1998 Sep;37(2):196-8.

2505. Uthman I, Husari A, Touma Z, et al. Fatal streptococcal toxic shock syndrome in a patient with rheumatoid arthritis treated with etanercept. Rheumatology (Oxford). 2005 Sep;44(9):1200-1.

2506. Uthman I, Vazquez-Abad D, Senecal JL. Distinctive features of idiopathic inflammatory myopathies in French Canadians. Semin Arthritis Rheum. 1996 Aug;26(1):447-58.

2507. Vaglio A, Palmisano A, Ferretti S, et al. Peripheral inflammatory arthritis in patients with chronic periaortitis: report of five cases and review of the literature. Rheumatology (Oxford). 2008 Mar;47(3):315-8.

2508. Vaidya B, Pearce SH, Charlton S, et al. An association between the CTLA4 exon 1 polymorphism and early rheumatoid arthritis with autoimmune endocrinopathies. Rheumatology (Oxford). 2002 Feb;41(2):180-3.

2509. Valentino R, Savastano S, Tommaselli AP, et al. Hormonal pattern in women affected by rheumatoid arthritis. J Endocrinol Invest. 1993 Sep;16(8):619-24.

2510. Valenzuela-Castano A, Garcia-Lopez A, Perez-Vilches D, et al. The predictive value of the HLA shared epitope for severity of radiological joint damage in patients with rheumatoid arthritis. A 10 year observational prospective study. J Rheumatol. 2000 Mar;27(3):571-4.

2511. Valleala H, Mandelin J, Laasonen L, et al. Effect of cyclical intermittent etidronate therapy on circulating osteoprotegerin levels in patients with rheumatoid arthritis. Eur J Endocrinol. 2003 May;148(5):527-30.

2512. Vallerskog T, Heimburger M, Gunnarsson I, et al. Differential effects on BAFF and APRIL levels in rituximab-treated patients with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Res Ther. 2006;8(6):R167.

2513. Valtysdottir ST, Wide L, Hallgren R. Low serum dehydroepiandrosterone sulfate in women with primary Sjogren's syndrome as an isolated sign of impaired HPA axis function. J Rheumatol. 2001 Jun;28(6):1259-65.

2514. Valtysdottir ST, Wide L, Hallgren R. Mental wellbeing and quality of sexual life in women with primary Sjogren's syndrome are related to circulating dehydroepiandrosterone sulphate. Ann Rheum Dis. 2003 Sep;62(9):875-9.

2515. van Baarsen LG, Wijbrandts CA, Rustenburg F, et al. Regulation of IFN response gene activity during infliximab treatment in rheumatoid arthritis is associated with clinical response to treatment. Arthritis Res Ther. 2010;12(1):R11.

2516. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004 May;63(5):508-16.

2517. van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003 Dec;62(12):1168-77.

2518. van den Bemt BJ, den Broeder AA, Snijders GF, et al. Sustained effect after lowering high-dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study. Ann Rheum Dis. 2008 Dec;67(12):1697-701.

2519. Van den Bosch F, Kruithof E, Baeten D, et al. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis. 2000 Jun;59(6):428-33.

2520. Van den Bosch F, Kruithof E, De Vos M, et al. Crohn's disease associated with spondyloarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms. Lancet. 2000 Nov 25;356(9244):1821-2.

2521. Van den Bosch F, Manger B, Goupille P, et al. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. Ann Rheum Dis. 2010 Feb;69(2):394-9.

2522. van den Brink HR, van Wijk MJ, Bijlsma JW. Influence of steroid hormones on proliferation of peripheral blood mononuclear cells in patients with

rheumatoid arthritis. Br J Rheumatol. 1992 Oct;31(10):663-7.

2523. van den Brink HR, van Wijk MJ, Geertzen RG, et al. Influence of corticosteroid pulse therapy on the serum levels of soluble interleukin 2 receptor, interleukin 6 and interleukin 8 in patients with rheumatoid arthritis. J Rheumatol. 1994 Mar;21(3):430-4.

2524. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Mar 15;61(3):291-9.

2525. van der Bijl AE, Breedveld FC, Antoni CE, et al. An open-label pilot study of the effectiveness of adalimumab in patients with rheumatoid arthritis and previous infliximab treatment: relationship to reasons for failure and anti-infliximab antibody status. Clin Rheumatol. 2008 Aug;27(8):1021-8.

2526. van der Bijl AE, Emmer BJ, Breedveld FC, et al. Advanced magnetic resonance imaging of the brain in patients treated with TNF-alpha blocking agents. Clin Exp Rheumatol. 2007 Mar-Apr;25(2):301-4.

2527. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2007 Jul;56(7):2129-34.

2528. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996 Apr 15;124(8):699-707.

2529. van der Heijde D, Burmester G, Melo-Gomes J, et al. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. Ann Rheum Dis. 2008 Feb;67(2):182-8.

2530. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005 Feb;52(2):582-91.

2531. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis. 2005 Nov;64(11):1582-7.

2532. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006 Apr;54(4):1063-74.

2533. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis. 2006 Mar;65(3):328-34.

2534. van der Heijde D, Landewe R, Klareskog L, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum. 2005 Jan;52(1):49-60.

2535. van der Helm-van Mil AH, le Cessie S, van Dongen H, et al. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum. 2007 Feb;56(2):433-40.

2536. van der Klooster JM, Bosman RJ, Oudemans-van Straaten HM, et al. Disseminated tuberculosis, pulmonary aspergillosis and cutaneous herpes simplex infection in a patient with infliximab and methotrexate. Intensive Care Med. 2003 Dec;29(12):2327-9.

2537. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Jan 15;61(1):4-12.

2538. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Limited efficacy of conventional DMARDs after

initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2007 Oct;66(10):1356-62.

2539. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009;68(6):914-21.

2540. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1153-8.

2541. van der Laken CJ, Lems WF, van Soesbergen RM, et al. Paraplegia in a patient receiving anti-tumor necrosis factor therapy for rheumatoid arthritis: comment on the article by Mohan et al. Arthritis Rheum. 2003 Jan;48(1):269-70.

2542. van der Laken CJ, Voskuyl AE, Roos JC, et al. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. Ann Rheum Dis. 2007 Feb;66(2):253-6.

2543. van der Pouw Kraan TC, Wijbrandts CA, van Baarsen LG, et al. Responsiveness to anti-tumour necrosis factor alpha therapy is related to pre-treatment tissue inflammation levels in rheumatoid arthritis patients. Ann Rheum Dis. 2008 Apr;67(4):563-6.

2544. van der Veen MJ, Bijlsma JW. Effects of different regimes of corticosteroid treatment on calcium and bone metabolism in rheumatoid arthritis. Clin Rheumatol. 1992 Sep;11(3):388-92.

2545. van der Veen MJ, Bijlsma JW. The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol. 1993 Dec;12(4):500-5.

2546. van der Veen MJ, Dekker JJ, Dinant HJ, et al. Fatal pulmonary fibrosis complicating low dose methotrexate therapy for rheumatoid arthritis. J Rheumatol. 1995 Sep;22(9):1766-8.

2547. Van Doornum S, McColl G, Wicks IP. Tumour necrosis factor antagonists improve disease activity but not arterial stiffness in rheumatoid arthritis. Rheumatology (Oxford). 2005 Nov;44(11):1428-32.

2548. van Ede A, den Broeder A, Wagenaar M, et al. Etanercept-related extensive pulmonary nodulosis in a patient with rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1590-2.

2549. van Eijk IC, Peters MJ, Nurmohamed MT, et al. Decrease of fructosamine levels during treatment with adalimumab in patients with both diabetes and rheumatoid arthritis. Eur J Endocrinol. 2007 Mar;156(3):291-3.

2550. van Everdingen AA, Huisman AM, Wenting MJ, et al. Down regulation of glucocorticoid receptors in early-diagnosed rheumatoid arthritis. Clin Exp Rheumatol. 2002 Jul-Aug;20(4):463-8.

2551. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8(5):R151.

2552. van Ingen J, Boeree M, Janssen M, et al. Pulmonary Mycobacterium szulgai infection and treatment in a patient receiving anti-tumor necrosis factor therapy. Nat Clin Pract Rheumatol. 2007 Jul;3(7):414-9.

2553. van Leeuwen MA, van der Heijde DM, van Rijswijk MH, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Rheumatol. 1994 Mar;21(3):425-9.

2554. van Leeuwen MA, van Rijswijk MH, van der Heijde DM, et al. The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. Br J Rheumatol. 1993 Jun;32 Suppl 3:9-13.

2555. van Lieshout AW, Fransen J, Flendrie M, et al. Circulating levels of the chemokine CCL18 but not CXCL16 are elevated and correlate with disease activity in rheumatoid arthritis. Ann Rheum Dis. 2007 Oct;66(10):1334-8.

2556. van Middendorp H, Geenen R, Sorbi MJ, et al. Neuroendocrine-immune relationships between emotion regulation and health in patients with rheumatoid arthritis. Rheumatology (Oxford). 2005 Jul;44(7):907-11.

2557. van Oosterhout M, Levarht EW, Sont JK, et al. Clinical efficacy of infliximab plus methotrexate in DMARD naive and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNF alpha and IL18 but not CXCL12. Ann Rheum Dis. 2005 Apr;64(4):537-43.

2558. van Roon EN, Hoekstra M, Tobi H, et al. Leflunomide in the treatment of rheumatoid arthritis. An analysis of predictors for treatment continuation. Br J Clin Pharmacol. 2005 Sep;60(3):319-25.

2559. van Roon EN, van den Bemt PM, Jansen TL, et al. An evidence-based assessment of the clinical significance of drug-drug interactions between disease-modifying antirheumatic drugs and non-antirheumatic drugs according to rheumatologists and pharmacists. Clin Ther. 2009 Aug;31(8):1737-46.

2560. van Roon JA, Hartgring SA, Wenting-van Wijk M, et al. Persistence of interleukin 7 activity and levels on tumour necrosis factor alpha blockade in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 May;66(5):664-9.

2561. van Staa TP, Geusens P, Bijlsma JW, et al. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3104-12.

2562. van Thiel RJ, van der Burg S, Groote AD, et al. Bronchiolitis obliterans organizing pneumonia and rheumatoid arthritis. Eur Respir J. 1991 Jul;4(7):905-11.

2563. Van Tilt I, Lories RJ, Westhovens R, et al. Unusual cervical spine involvement in psoriatic arthritis: a case series. Clin Rheumatol. 2009 Nov;28(11):1343-6.

2564. van Tuyl LH, Lems WF, Voskuyl AE, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis. 2008 Nov;67(11):1574-7.

2565. van Tuyl LH, Plass AM, Lems WF, et al. Facilitating the use of COBRA combination therapy in early rheumatoid arthritis: a pilot implementation study. J Rheumatol. 2009 Jul;36(7):1380-6.

2566. van Vollenhoven R, Harju A, Brannemark S, et al. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis. 2003 Dec;62(12):1195-8.

2567. van Vollenhoven RF, Cifaldi MA, Ray S, et al. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res (Hoboken) 2010;62(2):226-34.

2568. van Vollenhoven RF, Emery P, Bingham CO, 3rd, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol 2010;37(3):558-67.

2569. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374(9688):459-66.

2570. van Vollenhoven RF, Ernestam S, Harju A, et al. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically

more efficacious. Arthritis Res Ther. 2003;5(6):R347-51.

2571. van Vollenhoven RF, Houbiers JG, Buttgereit F, et al. The selective estrogen receptor alpha agonist Org 37663 induces estrogenic effects but lacks antirheumatic activity: a phase IIa trial investigating efficacy and safety of Org 37663 in postmenopausal female rheumatoid arthritis patients receiving stable background methotrexate or sulfasalazine. Arthritis Rheum. 2010 Feb;62(2):351-8.

2572. van Vollenhoven RF, Klareskog L. Infliximab dosage and infusion frequency in clinical practice: experiences in the Stockholm biologics registry STURE. Scand J Rheumatol. 2007 Nov-Dec;36(6):418-23.

2573. van Woerkom JM, Kruize AA, Geenen R, et al. Safety and efficacy of leflunomide in primary Sjogren's syndrome: a phase II pilot study. Ann Rheum Dis. 2007 Aug;66(8):1026-32.

2574. Vander Cruyssen B, Durez P, Westhovens R, et al. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. Arthritis Res Ther. 2010;12(3):R77.

2575. Vandergheynst F, Gosset J, van de Borne P, et al. Myopericarditis revealing adult-onset Still's disease. Acta Clin Belg. 2005 Sep-Oct;60(4):205-8.

2576. Vandooren B, Kruithof E, Yu DT, et al. Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and down-regulation by tumor necrosis factor alpha blockade in spondylarthropathy. Arthritis Rheum. 2004 Sep;50(9):2942-53.

2577. Varani K, Massara A, Vincenzi F, et al. Normalization of A2A and A3 adenosine receptor up-regulation in rheumatoid arthritis patients by treatment with anti-tumor necrosis factor alpha but not methotrexate. Arthritis Rheum. 2009 Oct;60(10):2880-91.

2578. Varatharajan N, Lim IG, Anandacoomarasamy A, et al. Methotrexate: long-term safety and efficacy in an Australian consultant rheumatology practice. Intern Med J. 2009 Apr;39(4):228-36.

2579. Vasques Godinho FM, Parreira Santos MJ, Canas da Silva J. Refractory adult onset Still's disease successfully treated with anakinra. Ann Rheum Dis. 2005 Apr;64(4):647-8.

2580. Vassallo R, Matteson E, Thomas CF, Jr. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumor necrosis factor-alpha inhibition. Chest. 2002 Sep;122(3):1093-6.

2581. Vassilopoulos D, Apostolopoulou A, Hadziyannis E, et al. Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis. 2010 Jul;69(7):1352-5.

2582. Vassilopoulos D, Sialevris K, Malahtari S, et al. Subacute thyroiditis presenting as fever of unknown origin in a patient with rheumatoid arthritis under etanercept treatment. J Clin Rheumatol. 2010 Mar;16(2):88-9.

2583. Vastesaeger N, Xu S, Aletaha D, et al. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford). 2009 Sep;48(9):1114-21.

2584. Vavricka SR, Wettstein T, Speich R, et al. Pulmonary granulomas after tumour necrosis factor alpha antagonist therapy. Thorax. 2003 Mar;58(3):278-9.

2585. Vazquez I, Graell E, Gratacos J, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clin Exp Rheumatol. 2007 Mar-Apr;25(2):231-8.

2586. Vazquez-Del Mercado M, Delgado-Rizo V, Munoz-Valle JF, et al. Expression of interleukin-1 beta, tumor necrosis factor alpha, interleukins-6, -10 and -4, and metalloproteases by freshly isolated mononuclear cells from early never-treated and non-acute treated rheumatoid arthritis patients. Clin Exp Rheumatol. 1999 Sep-Oct;17(5):575-83.

2587. Vena GA, Altomare G, Ayala F, et al. Incidence of psoriasis and association with comorbidities in Italy: a 5-year observational study from a national primary care database. Eur J Dermatol. 2010 Sep-Oct;20(5):593-8.

2588. Venarucci D, Catalini P, Scendoni P, et al. Evaluation of certain immunity parameters in rheumatoid arthritis, treated with cortisone. Panminerva Med. 1994 Dec;36(4):188-91.

2589. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. J Rheumatol. 2008 Sep;35(9):1745-53.

2590. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology (Oxford). 2008 Apr;47(4):535-41.

2591. Verbruggen LA, Versaen H, Rebmann V, et al. Soluble HLA-DR levels in serum are associated with therapy and genetic factors in rheumatoid arthritis. Hum Immunol. 2002 Sep;63(9):758-64.

2592. Vergara G, Silvestre JF, Betlloch I, et al. Cutaneous drug eruption to infliximab: report of 4 cases with an interface dermatitis pattern. Arch Dermatol. 2002 Sep;138(9):1258-9.

2593. Vergunst CE, Gerlag DM, von Moltke L, et al. MLN3897 plus methotrexate in patients with rheumatoid arthritis: safety, efficacy, pharmacokinetics, and pharmacodynamics of an oral CCR1 antagonist in a phase IIa, double-blind, placebo-controlled, randomized, proof-of-concept study. Arthritis Rheum. 2009 Dec;60(12):3572-81.

2594. Verhave JC, van Altena R, Wijnands MJ, et al. Tuberculous peritonitis during infliximab therapy. Neth J Med. 2008 Feb;66(2):77-80.

2595. Verhelst X, Orlent H, Colle I, et al. Subfulminant hepatitis B during treatment with adalimumab in a patient with rheumatoid arthritis and chronic hepatitis B. Eur J Gastroenterol Hepatol. 2010 Apr;22(4):494-9.

2596. Verhoef CM, van Roon JA, Vianen ME, et al. The immune suppressive effect of dexamethasone in rheumatoid arthritis is accompanied by upregulation of interleukin 10 and by differential changes in interferon gamma and interleukin 4 production. Ann Rheum Dis. 1999 Jan;58(1):49-54.

2597. Verhoeven AC, Boers M, te Koppele JM, et al. Bone turnover, joint damage and bone mineral density in early rheumatoid arthritis treated with combination therapy including high-dose prednisolone. Rheumatology (Oxford). 2001 Nov;40(11):1231-7.

2598. Verschueren K, Van Essche E, Verschueren P, et al. Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. Clin Rheumatol. 2007 Nov;26(11):1969-71.

2599. Verschueren P, Esselens G, Westhovens R. Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):59-64.

2600. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis. 2007 Nov;66(11):1443-9.

2601. Verwilghen J, Lovis R, De Boer M, et al. Expression of functional B7 and CTLA4 on rheumatoid synovial T cells. J Immunol. 1994 Aug 1;153(3):1378-85.

2602. Vidal F, Fontova R, Richart C. Severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med. 2003 Aug 5;139(3):W-W63.

2603. Vieira Serrao V, Martins A, Lopes MJ. Infliximab in recalcitrant generalized pustular arthropatic psoriasis. Eur J Dermatol. 2008 Jan-Feb;18(1):71-3.

2604. Vigna-Perez M, Abud-Mendoza C, Portillo-Salazar H, et al. Immune effects of therapy

with Adalimumab in patients with rheumatoid arthritis. Clin Exp Immunol. 2005 Aug;141(2):372-80.

2605. Vignes S, Le Moing V, Meekel P, et al. Acquired hemophilia: a rare complication of Sjogren's syndrome. Clin Exp Rheumatol. 1996 Sep-Oct;14(5):559-60.

2606. Viguier M, Richette P, Aubin F, et al. Onset of psoriatic arthritis in patients treated with efalizumab for moderate to severe psoriasis. Arthritis Rheum. 2008 Jun;58(6):1796-802.

2607. Vila AT, Puig L, Fernandez-Figueras MT, et al. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. Br J Dermatol. 2005 Aug;153(2):417-23.

2608. Vila LM, Molina MJ. Chronic anemia and thrombocytosis as the initial presentation of Still's disease in an elderly patient. Gerontology. 2007;53(5):289-92.

2609. Vine JE, Hymes SR, Warner NB, et al. Pustular psoriasis induced by hydroxychloroquine: a case report and review of the literature. J Dermatol. 1996 May;23(5):357-61.

2610. Vintimilla M, Joseph A, Ranganathan P. Acquired factor VIII inhibitor in Sjogren's syndrome. Arthritis Care Res (Hoboken). 2010 Jul;62(7):1047-50.

2611. Virkki LM, Konttinen YT, Peltomaa R, et al. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1059-66.

2612. Virkki LM, Porola P, Forsblad-d'Elia H, et al. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjogren's syndrome. Arthritis Care Res (Hoboken). 2010 Jan 15;62(1):118-24.

2613. Vis M, Bos WH, Wolbink G, et al. IgM-rheumatoid factor, anti-cyclic citrullinated peptide, and anti-citrullinated human fibrinogen antibodies decrease during treatment with the tumor necrosis factor blocker infliximab in patients with rheumatoid arthritis. J Rheumatol. 2008 Mar;35(3):425-8.

2614. Vis M, Nurmohamed MT, Wolbink G, et al. Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. J Rheumatol. 2005 Feb;32(2):252-5.

2615. Vis M, Voskuyl AE, Wolbink GJ, et al. Bone mineral density in patients with rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2005 Feb;64(2):336-7.

2616. Vis M, Wolbink GJ, Lodder MC, et al. Early changes in bone metabolism in rheumatoid arthritis patients treated with infliximab. Arthritis Rheum. 2003 Oct;48(10):2996-7.

2617. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis. 2010 Jul;69(7):1333-7.

2618. Visvanathan S, Wagner C, Rojas J, et al. E-selectin, interleukin 18, serum amyloid a, and matrix metalloproteinase 9 are associated with clinical response to golimumab plus methotrexate in patients with active rheumatoid arthritis despite methotrexate therapy. J Rheumatol. 2009 Jul;36(7):1371-9.

2619. Visvanathan S, Wagner C, Smolen J, et al. IgG and IgM anticardiolipin antibodies following treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2840-4.

2620. Vital EM, Dass S, Rawstron AC, et al. Management of nonresponse to rituximab in rheumatoid arthritis: predictors and outcome of re-treatment. Arthritis Rheum. 2010 May;62(5):1273-9.

2621. Vivarelli M, D'Urbano LE, Insalaco A, et al. Macrophage migration inhibitory factor (MIF) and oligoarticular juvenile idiopathic arthritis (o-JIA): association of MIF promoter polymorphisms with response to intra-articular glucocorticoids. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):775-81.

2622. Vlachaki E, Psathakis K, Tsintiris K, et al. Delayed response to anti-tuberculosis treatment in a patient on infliximab. Respir Med. 2005 May;99(5):648-52.

2623. Vlachoyiannopoulos PG, Kanellopoulos PG, Ioannidis JP, et al. Atherosclerosis in premenopausal women with antiphospholipid syndrome and systemic lupus erythematosus: a controlled study. Rheumatology (Oxford). 2003 May;42(5):645-51.

2624. Vogl D, Falk W, Dorner M, et al. Serum levels of pregnenolone and 17-hydroxypregnenolone in patients with rheumatoid arthritis and systemic lupus erythematosus: relation to other adrenal hormones. J Rheumatol. 2003 Feb;30(2):269-75.

2625. Volpe A, Caramaschi P, Carletto A, et al. Psoriasis onset during infliximab treatment: description of two cases. Rheumatol Int. 2006 Oct;26(12):1158-60.

2626. Vonkeman H, ten Napel C, Rasker H, et al. Disseminated primary varicella infection during infliximab treatment. J Rheumatol. 2004 Dec;31(12):2517-8.

2627. Voog U, Alstergren P, Eliasson S, et al. Progression of radiographic changes in the temporomandibular joints of patients with rheumatoid arthritis in relation to inflammatory markers and mediators in the blood. Acta Odontol Scand. 2004 Feb;62(1):7-13.

2628. Vordenbaumen S, Neuen-Jacob E, Richter J, et al. Inclusion body myositis in a patient with long standing rheumatoid arthritis treated with anti-TNFalpha and rituximab. Clin Rheumatol. 2010 May;29(5):555-8.

2629. Vos K, Thurlings RM, Wijbrandts CA, et al. Early effects of rituximab on the synovial cell infiltrate in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Mar;56(3):772-8.

2630. Voskuyl AE, Van de Laar MA, Moens HJ, et al. Extra-articular manifestations of rheumatoid arthritis: risk factors for serious gastrointestinal events. Ann Rheum Dis. 1993 Nov;52(11):771-5.

2631. Voskuyl AE, Zwinderman AH, Westedt ML, et al. Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study. Ann Rheum Dis. 1996 Mar;55(3):190-2.

2632. Voulgarelis M, Giannouli S, Anagnostou D, et al. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford). 2004 Aug;43(8):1050-3.

2633. Voulgari PV, Alamanos Y, Nikas SN, et al. Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med. 2005 May;118(5):515-20.

2634. Voulgari PV, Markatseli TE, Exarchou SA, et al. Granuloma annulare induced by anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):567-70.

2635. Voulgari PV, Venetsanopoulou AI, Exarchou SA, et al. Sustained clinical response and high infliximab survival in psoriatic arthritis patients: a 3-year long-term study. Semin Arthritis Rheum. 2008 Apr;37(5):293-8.

2636. Voutilainen M, Sokka T, Juhola M, et al. Nonsteroidal anti-inflammatory drug-associated upper gastrointestinal lesions in rheumatoid arthritis patients. Relationships to gastric histology, Helicobacter pylori infection, and other risk factors for peptic ulcer. Scand J Gastroenterol. 1998 Aug;33(8):811-6.

2637. Vrzogic P, Pasic A, Podobnik-Takac T. Psoriasis vulgaris and arthritis psoriatica gravis mutilans. Acta Dermatovenerol Croat. 2003;11(1):22-8.

2638. Vytasek R, Sedova L, Vilim V. Increased concentration of two different advanced glycation end-products detected by enzyme immunoassays with new monoclonal antibodies in sera of patients with rheumatoid arthritis. BMC Musculoskelet Disord. 2010;11:83.

2639. Wachi K, Prasertsuntarasai T, Kishimoto M, et al. T-cell lymphopenia associated with

infliximab and cyclophosphamide. Am J Med Sci. 2005 Jul;330(1):48-51.

2640. Wagner U, Pierer M, Wahle M, et al. Ex vivo homeostatic proliferation of CD4+ T cells in rheumatoid arthritis is dysregulated and driven by membrane-anchored TNFalpha. J Immunol. 2004 Aug 15;173(4):2825-33.

2641. Waguri-Nagaya Y, Kobayashi M, Goto H, et al. Septic arthritis of the right ankle caused by Staphylococcus aureus infection in a rheumatoid arthritis patient treated with etanercept. Mod Rheumatol. 2007;17(4):338-40.

2642. Wakabayashi H, Sudo A, Hasegawa M, et al. Retrospective clinical study of the efficacy of lower-dose methotrexate and infliximab therapy in patients with rheumatoid arthritis. Clin Rheumatol 2010;29(6):671-5.

2643. Wakefield RJ, Freeston JE, Hensor EM, et al. Delay in imaging versus clinical response: a rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. Arthritis Rheum. 2007 Dec 15;57(8):1564-7.

2644. Wall E, Walker-Bone K. Use of bisphosphonates and dual-energy X-ray absorptiometry scans in the prevention and treatment of glucocorticoid-induced osteoporosis in rheumatology. Qjm. 2008 Apr;101(4):317-23.

2645. Wallace DJ, Metzger AL, Stecher VJ, et al. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. Am J Med. 1990 Sep;89(3):322-6.

2646. Wallberg-Jonsson S, Johansson H, Ohman ML, et al. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol. 1999 Dec;26(12):2562-71.

2647. Wallberg-Jonsson S, Ohman M, Rantapaa-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid arthritis? Scand J Rheumatol. 2004;33(6):373-9.

2648. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol. 1997 Mar;24(3):445-51.

2649. Walsh CA, Fearon U, FitzGerald O, et al. Decreased CD20 expression in rheumatoid arthritis synovium following 8 weeks of rituximab therapy. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):656-8.

2650. Walsh CA, Minnock P, Slattery C, et al. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2007 Jul;46(7):1148-52.

2651. Walsh LJ, Wong CA, Pringle M, et al. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ. 1996 Aug 10;313(7053):344-6.

2652. Wang M, Tsai RT, Ou WC, et al. Treatment with cytotoxic immunosuppression agents increases urinary excretion of JCV in patients with autoimmune disease. J Med Virol. 2000 Dec;62(4):505-10.

2653. Wang SJ, Yang YH, Lin YT, et al. Attained adult height in juvenile rheumatoid arthritis with or without corticosteroid treatment. Clin Rheumatol. 2002 Sep;21(5):363-8.

2654. Ward MM, Fries JF. Trends in antirheumatic medication use among patients with rheumatoid arthritis, 1981-1996. J Rheumatol. 1998 Mar;25(3):408-16.

2655. Wardwell NR, Jr., Miller R, Ware LB. Pulmonary alveolar proteinosis associated with a disease-modifying antirheumatoid arthritis drug. Respirology. 2006 Sep;11(5):663-5.

2656. Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama. 2007 Jul 11;298(2):187-93.

2657. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol. 2004 Oct;31(10):1912-7.

2658. Wasserteil V, Bruce S, Sessoms SL, et al. Pyoderma gangrenosum treated with hyperbaric oxygen therapy. Int J Dermatol. 1992 Aug;31(8):594-6.

2659. Watanabe H, Suzuki R, Asano T, et al. A case of emphysematous pyelonephritis in a patient with rheumatoid arthritis taking corticosteroid and low-dose methotrexate. Int J Rheum Dis. 2010 May;13(2):180-3.

2660. Watanabe T, Tsuchida T, Furue M, et al. Annular erythema, dermatomyositis, and Sjogren's syndrome. Int J Dermatol. 1996 Apr;35(4):285-7.

2661. Watson DJ, Rhodes T, Cai B, et al. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med. 2002 May 27;162(10):1105-10.

2662. Weaver AL, Lautzenheiser RL, Schiff MH, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin. 2006 Jan;22(1):185-98.

2663. Weidler C, Struharova S, Schmidt M, et al. Tumor necrosis factor inhibits conversion of dehydroepiandrosterone sulfate (DHEAS) to DHEA in rheumatoid arthritis synovial cells: a prerequisite for local androgen deficiency. Arthritis Rheum. 2005 Jun;52(6):1721-9.

2664. Weinblatt ME, Abbott GF, Koreishi AF. Case records of the Massachusetts General Hospital. Case 13-2009. A 54-year-old woman with respiratory failure and a cavitary lesion in the lung. N Engl J Med. 2009 Apr 23;360(17):1770-9.

2665. Weinblatt ME, Kavanaugh A, Burgos-Vargas R, et al. Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-controlled trial. Arthritis Rheum. 2008 Nov;58(11):3309-18.

2666. Weinblatt ME, Kavanaugh A, Genovese MC, et al. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. N Engl J Med. 2010 Sep 30;363(14):1303-12.

2667. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45.

2668. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9.

2669. Weinblatt ME, Schiff MH, Ruderman EM, et al. Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study. Arthritis Rheum. 2008 Jul;58(7):1921-30.

2670. Weisman MH, Moreland LW, Furst DE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003 Jun;25(6):1700-21.

2671. Weisman MH, Paulus HE, Burch FX, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology (Oxford) 2007;46(7):1122-5.

2672. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr. 1998 Aug;133(2):266-8.

2673. Weitoft T, Forsberg C. Importance of immobilization after intraarticular glucocorticoid treatment for elbow synovitis: a randomized controlled study.

Arthritis Care Res (Hoboken). 2010 May;62(5):735-7.

2674. Weitoft T, Larsson A, Ronnblom L. Serum levels of sex steroid hormones and matrix metalloproteinases after intra-articular glucocorticoid treatment in female patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Mar;67(3):422-4.

2675. Weitoft T, Ronnblom L. Glucocorticoid resorption and influence on the hypothalamic-pituitary-adrenal axis after intra-articular treatment of the knee in resting and mobile patients. Ann Rheum Dis. 2006 Jul;65(7):955-7.

2676. Weitoft T, Uddenfeldt P. Importance of synovial fluid aspiration when injecting intra-articular corticosteroids. Ann Rheum Dis. 2000 Mar;59(3):233-5.

2677. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun;68(6):954-60.

2678. Wells G, Li T, Maxwell L, et al. Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis 2008;67(2):260-5.

2679. Wells G, Li T, Tugwell P. Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale. Ann Rheum Dis. 2010 Oct;69(10):1768-73.

2680. Wells GA, Boers M, Li T, et al. Investigating the validity of the minimal disease activity state for patients with rheumatoid arthritis treated with abatacept. J Rheumatol. 2009 Feb;36(2):260-5.

2681. Wendling D, Materne GE, Michel F, et al. Infliximab continuation rates in patients with rheumatoid arthritis in everyday practice. Joint Bone Spine. 2005 Jul;72(4):309-12.

2682. Wendling D, Streit G, Toussirot E, et al. Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. Joint Bone Spine. 2008 Oct;75(5):540-3.

2683. Wessels JA, de Vries-Bouwstra JK, Heijmans BT, et al. Efficacy and toxicity of methotrexate in early rheumatoid arthritis are associated with single-nucleotide polymorphisms in genes coding for folate pathway enzymes. Arthritis Rheum. 2006 Apr;54(4):1087-95.

2684. Wessels JA, Kooloos WM, De Jonge R, et al. Relationship between genetic variants in the adenosine pathway and outcome of methotrexate treatment in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2830-9.

2685. Wessels JA, van der Kooij SM, le Cessie S, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum. 2007 Jun;56(6):1765-75.

2686. West SG, Troutner JL, Baker MR, et al. Sacral insufficiency fractures in rheumatoid arthritis. Spine. 1994 Sep 15;19(18):2117-21.

2687. Westhovens R, Houssiau F, Joly J, et al. A phase I study assessing the safety, clinical response, and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in patients with rheumatoid arthritis. J Rheumatol. 2006 May;33(5):847-53.

2688. Westhovens R, Nijs J, Taelman V, et al. Body composition in rheumatoid arthritis. Br J Rheumatol. 1997 Apr;36(4):444-8.

2689. Weusten BL, Jacobs JW, Bijlsma JW. Corticosteroid pulse therapy in active rheumatoid arthritis. Semin Arthritis Rheum. 1993 Dec;23(3):183-92.

2690. Weycker D, Yu EB, Woolley JM, et al. Retrospective study of the costs of care during the first year of therapy with etanercept or infliximab among patients aged > or =65 years with rheumatoid arthritis. Clin Ther. 2005 May;27(5):646-56.

2691. White D, Fayez S, Doube A. Atherogenic lipid profiles in rheumatoid arthritis. N Z Med J. 2006;119(1240):U2125.

2692. White KL. Psoriasis and psoriatic arthritis, axial type. Dermatol Online J. 2001 Dec;7(2):12.

2693. Wiatrowski M, Furfaro N. Patient profiles in psoriatic disease: a case-based approach. Dermatol Nurs. 2007 Oct;Suppl:5-19; quiz 20-1.

2694. Wick MC, Ernestam S, Lindblad S, et al. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. Scand J Rheumatol. 2005 Sep-Oct;34(5):353-8.

2695. Wiens A, Correr CJ, Pontarolo R, et al. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol 2009;70(4):337-44.

2696. Wiens A, Venson R, Correr CJ, et al. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy 2010;30(4):339-53.

2697. Wijbrandts CA, Dijkgraaf MG, Kraan MC, et al. The clinical response to infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour necrosis factor alpha expression in the synovium. Ann Rheum Dis. 2008 Aug;67(8):1139-44.

2698. Wijbrandts CA, Klaasen R, Dijkgraaf MG, et al. Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss. Ann Rheum Dis. 2009 Mar;68(3):373-6.

2699. Wijbrandts CA, Remans PH, Klarenbeek PL, et al. Analysis of apoptosis in peripheral blood and synovial tissue very early after initiation of infliximab treatment in rheumatoid arthritis patients. Arthritis Rheum. 2008 Nov;58(11):3330-9.

2700. Wijngaarden S, van de Winkel JG, Bijlsma JW, et al. Treatment of rheumatoid arthritis patients with anti-TNF-alpha monoclonal antibody is accompanied by down-regulation of the activating Fcgamma receptor I on monocytes. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):89-95.

2701. Wikaningrum R, Highton J, Parker A, et al. Pathogenic mechanisms in the rheumatoid nodule: comparison of proinflammatory cytokine production and cell adhesion molecule expression in rheumatoid nodules and synovial membranes from the same patient. Arthritis Rheum. 1998 Oct;41(10):1783-97.

2702. Wiland P, Wiela-Hojenska A, Glowska A, et al. Renal function in rheumatoid arthritis patients treated with methotrexate and infliximab. Clin Exp Rheumatol. 2004 Jul-Aug;22(4):469-72.

2703. Wilder RL. Adrenal and gonadal steroid hormone deficiency in the pathogenesis of rheumatoid arthritis. J Rheumatol Suppl. 1996 Mar;44:10-2.

2704. Williams CS, Butler E, Roman GC. Treatment of myelopathy in Sjogren syndrome with a combination of prednisone and cyclophosphamide. Arch Neurol. 2001 May;58(5):815-9.

2705. Wilson ML, Sewell LD, Mowad CM. Primary cutaneous Cryptococcosis during therapy with methotrexate and adalimumab. J Drugs Dermatol. 2008 Jan;7(1):53-4.

2706. Winfield H, Lain E, Horn T, et al. Eosinophilic cellulitislike reaction to subcutaneous etanercept injection. Arch Dermatol. 2006 Feb;142(2):218-20.

2707. Wirnsberger RM, de Vries J, Wouters EF, et al. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. Neth J Med. 1998 Aug;53(2):53-60.

2708. Wislowska M, Jakubicz D. Preliminary evaluation in rheumatoid arthritis activity in patients treated with TNF-alpha blocker plus methotrexate versus methotrexate or leflunomide alone. Rheumatol Int. 2007 May;27(7):641-7.

2709. Wittkowski H, Foell D, af Klint E, et al. Effects of intra-articular corticosteroids and anti-TNF therapy on neutrophil activation in rheumatoid arthritis. Ann Rheum Dis. 2007 Aug;66(8):1020-5.

2710. Wolbink GJ, Voskuyl AE, Lems WF, et al. Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 May;64(5):704-7.

2711. Wolf J, Kapral T, Grisar J, et al. Glucocorticoid treatment in rheumatoid arthritis: low-dose therapy does not reduce responsiveness to higher doses. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):113-6.

2712. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006 Feb;54(2):628-34.

2713. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol 2007;36(3):172-8.

2714. Wolfe F, Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol. 2000 Jul;27(7):1668-73.

2715. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010 Jun;62(6):775-84.

2716. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004 Jun;50(6):1740-51.

2717. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004 Mar 1;116(5):305-11.

2718. Wolfe F, Michaud K. Assessment of pain in rheumatoid arthritis: minimal clinically significant difference, predictors, and the effect of anti-tumor necrosis factor therapy. J Rheumatol. 2007 Aug;34(8):1674-83.

2719. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56(5):1433-9.

2720. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum. 2004 Feb;50(2):372-9.

2721. Wolfe F, Michaud K, Li T. Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. J Rheumatol. 2006 Oct;33(10):1942-51.

2722. Wollina U, Hansel G, Koch A, et al. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008;9(1):1-14.

2723. Wollina U, Konrad H. Treatment of recalcitrant psoriatic arthritis with anti-tumor necrosis factor-alpha antibody. J Eur Acad Dermatol Venereol. 2002 Mar;16(2):127-9.

2724. Wondergem MJ, Voskuyl AE, van Agtmael MA. A case of legionellosis during treatment with a TNFalpha antagonist. Scand J Infect Dis. 2004;36(4):310-1.

2725. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54

weeks of infliximab for rheumatoid arthritis. Am J Med. 2002 Oct 1;113(5):400-8.

2726. Wong T, Majchrzak B, Bogoch E, et al. Therapeutic implications for interferon-alpha in arthritis: a pilot study. J Rheumatol. 2003 May;30(5):934-40.

2727. Wood KL, Hage CA, Knox KS, et al. Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. Am J Respir Crit Care Med. 2003 May 1;167(9):1279-82.

2728. Wooten MD, Reddy GV, Johnson RD. Atrial fibrillation occurring in a patient taking etanercept plus methotrexate for rheumatoid arthritis. Del Med J. 2000 Dec;72(12):517-9.

2729. Wright T, Cron RQ. Pediatric rheumatology for the adult rheumatologist II: uveitis in juvenile idiopathic arthritis. J Clin Rheumatol. 2007 Aug;13(4):205-10.

2730. Wu E, Chen L, Birnbaum H, et al. Cost of care for patients with rheumatoid arthritis receiving TNF-antagonist therapy using claims data. Curr Med Res Opin. 2007 Aug;23(8):1749-59.

2731. Wulffraat NM, Sanders LA, Kuis W. Autologous hemopoietic stem-cell transplantation for children with refractory autoimmune disease. Curr Rheumatol Rep. 2000 Aug;2(4):316-23.

2732. Wung PK, Pipeling MR, Wigley FM. "Still" ill? Am J Med. 2008 Jun;121(6):491-3.

2733. Xiao H, Xu J, Zhou X, et al. Associations between the genetic polymorphisms of MTHFR and outcomes of methotrexate treatment in rheumatoid arthritis. Clin Exp Rheumatol. 2010 Sep-Oct;28(5):728-33.

2734. Xu JX, Hoshida Y, Hongyo T, et al. Analysis of p53 and Bak gene mutations in lymphoproliferative disorders developing in rheumatoid arthritis. J Cancer Res Clin Oncol. 2007 Feb;133(2):125-33.

2735. Xu Z, Vu T, Lee H, et al. Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-alpha human monoclonal antibody, in patients with psoriatic arthritis. J Clin Pharmacol. 2009 Sep;49(9):1056-70.

2736. Yakushiji F, Kita M, Hiroi N, et al. Exacerbation of rheumatoid arthritis after removal of adrenal adenoma in Cushing's syndrome. Endocr J. 1995 Apr;42(2):219-23.

2737. Yam LY, Wong R. Bronchiolitis obliterans and rheumatoid arthritis. Report of a case in a Chinese patient on d-penicillamine and review of the literature. Ann Acad Med Singapore. 1993 May;22(3):365-8.

2738. Yamada H, Kato EH, Ebina Y, et al. Fetal treatment of congenital heart block ascribed to anti-SSA antibody: case reports with observation of cardiohemodynamics and review of the literature. Am J Reprod Immunol. 1999 Oct;42(4):226-32.

2739. Yamada S, Takagi H, Tsuchiya H, et al. Comparative studies on effect of risedronate and alfacalcidol against glucocorticoid-induced osteoporosis in rheumatoid arthritic patients. Yakugaku Zasshi. 2007 Sep;127(9):1491-6.

2740. Yamada T, Okuda Y, Takasugi K, et al. Relative serum amyloid A (SAA) values: the influence of SAA1 genotypes and corticosteroid treatment in Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2001 Feb;60(2):124-7.

2741. Yamamoto M, Takahashi H, Wakasugi H, et al. Leukoencephalopathy during administration of etanercept for refractory rheumatoid arthritis. Mod Rheumatol. 2007;17(1):72-4.

2742. Yamanaka H, Inoue E, Singh G, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol. 2007;17(4):283-9.

2743. Yamanaka H, Tanaka Y, Sekiguchi N, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan

(RECONFIRM). Mod Rheumatol. 2007;17(1):28-32.

2744. Yamauchi PS, Gindi V, Lowe NJ. The treatment of psoriasis and psoriatic arthritis with etanercept: practical considerations on monotherapy, combination therapy, and safety. Dermatol Clin. 2004 Oct;22(4):449-59, ix.

2745. Yamauchi PS, Turner L, Lowe NJ, et al. Treatment of recurrent Sweet's syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S122-6.

2746. Yamazawa K, Matsui H, Sekiya S. Gastric perforation induced by combination chemotherapy in a patient with long-term use of corticosteroids. Int J Gynaecol Obstet. 2002 Aug;78(2):165-6.

2747. Yamout B, El-Hajj T, Barada W, et al. Successful treatment of refractory neuroSjogren with Rituximab. Lupus. 2007;16(7):521-3.

2748. Yang C, Gu J, Rihl M, et al. Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. Arthritis Rheum. 2004 Oct 15;51(5):691-9.

2749. Yang DH, Chang DM, Lai JH, et al. Etanercept as a rescue agent in patient with adult onset Still's disease complicated with congestive heart failure. Rheumatol Int. 2008 Nov;29(1):95-8.

2750. Yasuda M, Yasuda D, Tomooka K, et al. Plasma concentration of human atrial natriuretic hormone in patients with connective tissue diseases. Clin Rheumatol. 1993 Jun;12(2):231-5.

2751. Yasunori K, Masaaki T, Tetsuyuki N, et al. Reduction of urinary levels of pyridinoline and deoxypyridinoline and serum levels of soluble receptor activator of NF-kappaB ligand by etanercept in patients with rheumatoid arthritis. Clin Rheumatol. 2008 Sep;27(9):1093-101.

2752. Yazdani C, McLaughlin T, Cummins G, et al. Comparison of rheumatoid arthritis care costs in patients starting therapy with leflunomide versus etanercept. Am J Manag Care. 2001 Sep;7(13 Suppl):S419-26.

2753. Yazdani-Biuki B, Stadlmaier E, Mulabecirovic A, et al. Blockade of tumour necrosis factor {alpha} significantly alters the serum level of IgG- and IgA-rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Aug;64(8):1224-6.

2754. Yazdani-Biuki B, Wohlfahrt K, Mulabecirovic A, et al. Long term treatment of psoriatic arthritis with infliximab. Ann Rheum Dis. 2004 Nov;63(11):1531-2; author reply 2.

2755. Yazici S, Yazici M, Erer B, et al. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. Platelets. 2010;21(2):122-5.

2756. Yazici Y, Erkan D. Do etanercept-naive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? Ann Rheum Dis. 2004 May;63(5):607-8; author reply 8.

2757. Yazici Y, Erkan D, Kulman I, et al. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". Ann Rheum Dis. 2002 Jul;61(7):638-40.

2758. Yazici Y, Erkan D, Lockshin MD. A preliminary study of etanercept in the treatment of severe, resistant psoriatic arthritis. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):732-4.

2759. Yazici Y, Erkan D, Lockshin MD. Etanercept in the treatment of severe, resistant psoriatic arthritis: continued efficacy and changing patterns of use after two years. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):115.

2760. Yazici Y, Krasnokutsky S, Barnes JP, et al. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. J Rheumatol. 2009 May;36(5):907-13.

2761. Yazici Y, McMorris BJ, Darkow T, et al. Patient and physician perception of the infusion process of the biologic agents abatacept, infliximab, and rituximab for the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2009 Nov-Dec;27(6):907-13.

2762. Yee CS, Filer A, Pace A, et al. The prevalence of patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an out-patient study. Rheumatology (Oxford). 2003 Jul;42(7):856-9.

2763. Yeh HM, Liu MF, Chang KK, et al. Adult-onset Still's disease complicated with hemophagocytic syndrome. J Formos Med Assoc. 2010 Jan;109(1):85-8.

2764. Yelin E, Trupin L, Katz P, et al. Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. Arthritis Rheum. 2003 Nov;48(11):3046-54.

2765. Yelin EH, Trupin LS, Katz PP. Impact of managed care on the use of biologic agents for rheumatoid arthritis. Arthritis Rheum. 2005 Jun 15;53(3):423-30.

2766. Yeo SW, Park SN. Immune-mediated sensorineural hearing loss in a patient with ankylosing spondylitis: a case report. Otolaryngol Head Neck Surg. 2001 Jul;125(1):113-4.

2767. Yigla M, Simsolo C, Goralnik L, et al. The problem of empyematous pleural effusion in rheumatoid arthritis: report of two cases and review of the literature. Clin Rheumatol. 2002 May;21(2):180-3.

2768. Yilmaz L, Ozoran K, Gunduz OH, et al. Alendronate in rheumatoid arthritis patients treated with methotrexate and glucocorticoids. Rheumatol Int. 2001 Feb;20(2):65-9.

2769. Yim K, Nazeer SH, Kiska D, et al. Recurrent Mycobacterium xenopi infection in a patient with rheumatoid arthritis receiving etanercept. Scand J Infect Dis. 2004;36(2):150-4.

2770. Yocum DE, Furst DE, Bensen WG, et al. Safety of tacrolimus in patients with rheumatoid arthritis: long-term experience. Rheumatology (Oxford). 2004 Aug;43(8):992-9.

2771. Yokoo H, Nakazato Y, Harigaya Y, et al. Massive myelinolytic leukoencephalopathy in a patient medicated with low-dose oral methotrexate for rheumatoid arthritis: an autopsy report. Acta Neuropathol. 2007 Oct;114(4):425-30.

2772. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008 Mar 22;371(9617):998-1006.

2773. Yokoyama E, Muto M. Adult variant of self-healing papular mucinosis in a patient with rheumatoid arthritis: predominant proliferation of dermal dendritic cells expressing CD34 or factor XIIIa in association with dermal deposition of mucin. J Dermatol. 2006 Jan;33(1):30-5.

2774. Yonezawa T, Tsuji H, Matsui H, et al. Subaxial lesions in rheumatoid arthritis. Radiographic factors suggestive of lower cervical myelopathy. Spine. 1995 Jan 15;20(2):208-15.

2775. Yoshida A, Morozumi K, Suganuma T, et al. Clinicopathological findings of bucillamine-induced nephrotic syndrome in patients with rheumatoid arthritis. Am J Nephrol. 1991;11(4):284-8.

2776. Yoshida K, Bandoh S, Fujita J, et al. Pyothorax caused by Nocardia otitidiscaviarum in a patient with rheumatoid vasculitis. Intern Med. 2004 Jul;43(7):615-9.

2777. Yoshida K, Yokoyama T, Toyokawa Y, et al. Cryofibrinogenemia associated with Sjogren's syndrome: a case of successful treatment with high-dose corticosteroid. Intern Med. 2007;46(13):1039-42.

2778. Yoshioka T, Tachihara A, Koyama T, et al. Rapid destruction of the hip joint associated with enlarged iliopsoas bursa in a patient

with refractory rheumatoid arthritis. J Nippon Med Sch. 2008 Aug;75(4):233-8.

2779. Yosipovitch G, Tang MB. Practical management of psoriasis in the elderly: epidemiology, clinical aspects, quality of life, patient education and treatment options. Drugs Aging. 2002;19(11):847-63.

2780. You CG, Yin YS, Xie XD, et al. Sex influences on the penetrance of IL-1beta and IL-1RN genotypes for rheumatoid arthritis in the Chinese population. J Int Med Res. 2007 May-Jun;35(3):323-8.

2781. You CR, Kim HR, Yoon CH, et al. Macrophage activation syndrome in juvenile rheumatoid arthritis successfully treated with cyclosporine A: a case report. J Korean Med Sci. 2006 Dec;21(6):1124-7.

2782. Youm JY, Woo JH, Kim TH, et al. Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms in Korean patients with adult-onset Still's disease. Scand J Rheumatol. 2007 Sep-Oct;36(5):390-3.

2783. Young MG, Rijhsinghani S. Leflunomide and acute hypocalcemia. Endocr Pract. 2007 Nov-Dec;13(7):805-7.

2784. Young PJ, Weeden S, Kirwan JR. The analysis of a bivariate multi-state Markov transition model for rheumatoid arthritis with an incomplete disease history. Stat Med. 1999 Jul 15;18(13):1677-90.

2785. Yount S, Sorensen MV, Cella D, et al. Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):838-46.

2786. Yousem SA, Dacic S. Pulmonary lymphohistiocytic reactions temporally related to etanercept therapy. Mod Pathol. 2005 May;18(5):651-5.

2787. Yu EN, Meniconi ME, Tufail F, et al. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflamm. 2005 Sep-Oct;13(5):353-60.

2788. Yu EN, Paredes I, Foster CS. Surgery for hypotony in patients with juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm. 2007 Jan-Feb;15(1):11-7.

2789. Yu X, Ma J, Tian J, et al. A controlled study of double filtration plasmapheresis in the treatment of active rheumatoid arthritis. J Clin Rheumatol. 2007 Aug;13(4):193-8.

2790. Yukawa E, Mori S, Ueda K, et al. Population pharmacokinetic investigation of low-dose methotrexate in rheumatoid arthritics Japanese patients. J Clin Pharm Ther. 2007 Dec;32(6):573-8.

2791. Yukawa S, Yamaoka K, Sawamukai N, et al. Involvement of mast cells in systemic sclerosis. Nihon Rinsho Meneki Gakkai Kaishi. 2010;33(2):81-6.

2792. Yukioka M, Komatsubara Y, Yukioka K, et al. Adrenocorticotropic hormone and dehydroepiandrosterone sulfate levels of rheumatoid arthritis patients treated with glucocorticoids. Mod Rheumatol. 2006;16(1):30-5.

2793. Yum HK, Kim ES, Ok KS, et al. Lymphocytic interstitial pneumonitis associated with Epstein-Barr virus in Systemic Lupus Erythematosus and Sjogren's Syndrome. Complete remission with corticosteriod and cyclophosphamide. Korean J Intern Med. 2002 Sep;17(3):198-203.

2794. Yun JE, Lee SW, Kim TH, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol. 2002 Mar-Apr;20(2):127-32.

2795. Zabinski SJ, Sculco TP, Dicarlo EF, et al. Osteonecrosis in the rheumatoid femoral head. J Rheumatol. 1998 Sep;25(9):1674-80.

2796. Zamarron C, Maceiras F, Gonzalez J, et al. Worsening of obstructive sleep apnoeas in a patient with rheumatoid arthritis treated with anti-tumor necrosis factor. Respir Med. 2004 Feb;98(2):123-5.

2797. Zamarron C, Maceiras F, Mera A, et al. Effect of the first infliximab infusion on sleep and alertness in patients with active rheumatoid arthritis. Ann Rheum Dis. 2004 Jan;63(1):88-90.

2798. Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjogren's syndrome: a pilot study. J Rheumatol. 2004 Jan;31(1):96-101.

2799. Zandbelt MM, van den Hoogen FH, de Wilde PC, et al. Reversibility of histological and immunohistological abnormalities in sublabial salivary gland biopsy specimens following treatment with corticosteroids in Sjogren's syndrome. Ann Rheum Dis. 2001 May;60(5):511-3.

2800. Zangrilli A, Papoutsaki M, Talamonti M, et al. Long-term efficacy of adalimumab in generalized pustular psoriasis. J Dermatolog Treat. 2008;19(3):185-7.

2801. Zautra AJ, Burleson MH, Matt KS, et al. Interpersonal stress, depression, and disease activity in rheumatoid arthritis and osteoarthritis patients. Health Psychol. 1994 Mar;13(2):139-48.

2802. Zeidler HK, Kvien TK, Hannonen P, et al. Progression of joint damage in early active severe rheumatoid arthritis during 18 months of treatment: comparison of low-dose cyclosporin and parenteral gold. Br J Rheumatol. 1998 Aug;37(8):874-82.

2803. Zhang LL, Wei W, Xiao F, et al. A randomized, double-blind, multicenter, controlled clinical trial of chicken type II collagen in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Jul 15;59(7):905-10.

2804. Zhang W, Bansback N, Guh D, et al. Short-term influence of adalimumab on work productivity outcomes in patients with rheumatoid arthritis. J Rheumatol. 2008 Sep;35(9):1729-36.

2805. Zhao B, Takami M, Miyamoto Y, et al. Characterization of synovial cell clones isolated from rheumatoid arthritis patients: possible involvement of TNF-alpha in reduction of osteoprotegerin in synovium. Cytokine. 2008 Jan;41(1):61-70.

2806. Zhou H. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. J Clin Pharmacol. 2005 May;45(5):490-7.

2807. Zhou H, Buckwalter M, Boni J, et al. Population-based pharmacokinetics of the soluble TNFr etanercept: a clinical study in 43 patients with ankylosing spondylitis compared with post hoc data from patients with rheumatoid arthritis. Int J Clin Pharmacol Ther. 2004 May;42(5):267-76.

2808. Zhou H, Mayer PR, Wajdula J, et al. Unaltered etanercept pharmacokinetics with concurrent methotrexate in patients with rheumatoid arthritis. J Clin Pharmacol. 2004 Nov;44(11):1235-43.

2809. Zhu G, Liu G, Liu Y, et al. Liver abnormalities in adult onset Still's disease: a retrospective study of 77 Chinese patients. J Clin Rheumatol. 2009 Sep;15(6):284-8.

2810. Ziakas PD, Giannouli S, Tzioufas AG, et al. Lymphoma development in a patient receiving anti-TNF therapy. Haematologica. 2003 Jul;88(7):ECR25.

2811. Zikou AK, Argyropoulou MI, Voulgari PV, et al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with adalimumab. J Rheumatol. 2006 Feb;33(2):219-23.

2812. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis. 2005 Sep;64(9):1274-9.

2813. Zink A, Listing J, Ziemer S, et al. Practice variation in the treatment of rheumatoid arthritis among German rheumatologists. J Rheumatol. 2001 Oct;28(10):2201-8.

2814. Zintzaras E, Dahabreh IJ, Giannouli S, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther. 2008 Nov;30(11):1939-55.

2815. Ziolkowska M, Kurowska M, Radzikowska A, et al. High levels of osteoprotegerin and soluble receptor activator of nuclear factor kappa B ligand in serum of rheumatoid arthritis patients and their normalization after anti-tumor necrosis factor alpha treatment. Arthritis Rheum. 2002 Jul;46(7):1744-53.

2816. Ziswiler HR, Aeberli D, Villiger PM, et al. High-resolution ultrasound confirms reduced synovial hyperplasia following rituximab treatment in rheumatoid arthritis. Rheumatology (Oxford). 2009 Aug;48(8):939-43.

2817. Zoli A, Ferlisi EM, Lizzio M, et al. Prolactin/cortisol ratio in rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:508-12.

2818. Zoli A, Lizzio MM, Ferlisi EM, et al. ACTH, cortisol and prolactin in active rheumatoid arthritis. Clin Rheumatol. 2002 Aug;21(4):289-93.

2819. Zoukos Y, Leonard JP, Thomaides T, et al. beta-Adrenergic receptor density and function of peripheral blood mononuclear cells are increased in multiple sclerosis: a regulatory role for cortisol and interleukin-1. Ann Neurol. 1992 Jun;31(6):657-62

Reference Source: International Pharmaceutical Abstracts

1. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. Rheumatology. 2006 01/01/;45(JUN):7-2.

2. Aggarwal R, Manadan AM, Poliyedath A, et al. Safety of Etanercept in Patients at High Risk for Mycobacterial Tuberculosis Infections. Journal of Rheumatology. 2009;36:914.

3. Alcorn N, Saunders S, Madhok R, et al. Benefit-Risk Assessment of Leflunomide An Appraisal of Leflunomide in Rheumatoid Arthritis 10 Years After Licensing. Drug Safety (New Zealand). 2009;32:1123.

4. Aletaha D, Funovits J, Breedveld FC, et al. Rheumatoid Arthritis Joint Progression in Sustained Remission Is Determined by Disease Activity Levels Preceding the Period of Radiographic Assessment. Arthritis and Rheumatism (USA) 2009;601242.

5. Anonymous. Atlizumab - Anti-IL-6 receptor antibody - Chugai, anti-interleukin-6 receptor antibody - Chugai, MRA - Chugai. BioDrugs. 2003;17:369-72.

6. Anonymous. Tocilizumab for rheumatoid arthritis. Drug and Therapeutics Bulletin (England). 2010;48:9.

7. Antoniu SA, Apr. Cytokine Antagonists for the Treatment of Asthma Progress to Date. BioDrugs (New Zealand) 2009;23241.

8. Asahina A, Ohshima N, Nakayama H, et al. Henoch-Schonlein purpura in a patient with rheumatoid arthritis receiving etanercept. European Journal of Dermatology (France). 2010;20:521-2.

9. Baggott JE, Morgan SL, Aug. Methotrexate Catabolism to 7-Hydroxymethotrexate in Rheumatoid Arthritis Alters Drug Efficacy and Retention and Is Reduced by Folic Acid Supplementation. Arthritis and Rheumatism (USA) 2009;602257.

10. Bansard C, Lequerre T, Daveau M, et al. Can rheumatoid arthritis responsiveness to methotrexate and biologics be predicted? Rheumatology 2009;481021.

11. Bansback NJ, Ara R, Barkham N, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology. 2006 08/01/;45(Aug):1029-38.

12. Bathon JM, Fleischmann RM, van der Heijde DM, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. Journal of Rheumatology. 2006 02/01/;33(Feb):234-43.

13. Bell S. Payers have biologic alternative for patients with moderate to severe rheumatoid arthritis who do not respond to other DMARD therapies. Biotechnology Healthcare. 2006 06/01/;3(Jun):24-8.

14. Benhamou M, Rincheval N, Roy C, et al. The Gap Between Practice and Guidelines in the Choice of First-line Disease Modifying Antirheumatic Drug in Early Rheumatoid Arthritis: Results from the ESPOIR Cohort. Journal of Rheumatology 2009;36934.

15. Bernatsky S, Habel Y, Rahme E. Observational Studies of Infections in Rheumatoid Arthritis: A Metaanalysis of Tumor Necrosis Factor Antagonists. Journal of Rheumatology 2010;37928-31.

16. Bingham CO, Ince A, Haraoui B, et al. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-week, open-label, observational study. Current Medical Research and Opinion (England) 2009;251131.

17. Borah BJ, Huang XY, Zarotsky V, et al. Trends in RA patients' adherence to subcutaneous anti-TNF therapies and costs. Current Medical Research and Opinion (England) 2009;251365.

18. Bours MJ, Peeters RH, Landewe RB, et al. Adenosine 5'-triphosphate infusions reduced disease activity and inflammation in a

patient with active rheumatoid arthritis. Rheumatology (Oxford). 2010;49:2223-5.

19. Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: Review of the Efficacy and Tolerability of a Recently Approved Tumor Necrosis Factor-alpha Inhibitor. Clinical Therapeutics (USA). 2010;32:1681-703.

20. Bruce SP. Recent Developments in the Treatment of Rheumatoid Arthritis. Journal of Pharmacy Practice. 2009;22:65-74.

21. Bullano MF, McNeeley BJ, Yu YF, et al. Comparison of costs associated with the use of etanercept, infliximab, and adamlimumab for the treatment of rheumatoid arthritis. Managed Care Interface (USA). 2006 09/01/;19(Sep):47-53.

22. Butterly SJ, Pillans P, Horn B, et al. Off-label use of rituximab in a tertiary Queensland hospital. Internal Medicine Journal. 2010;40:443-52.

23. Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment - Relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):723-32.

24. Campas-Moya C. Golimumab: A novel anti-INF-alpha human monoclonal antibody for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Drugs of Today (Spain). 2010;46:13-22.

25. Cannon CP, Curtis SP, Bolognese JA, et al. Clinical trial design and patient demographics of the multinational etoricoxib and diclofenac arthritis long-term (MEDAL) study program: Cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. American Heart Journal. 2006 02/01/;152(Feb):237-45.

26. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet, The (USA). 2006 01/01/;368(Jan):1771-81.

27. Cantaert T, van Baarsen LG, Wijbrandts CA, et al. Type I interferons have no major influence on humoral autoimmunity in rheumatoid arthritis. Rheumatology (Oxford). 2010;49:156.

28. Carazo JL, Santos LM, Martinez VO. Safety of etanercept in psoriasis - A critical review. Drug Safety (New Zealand). 2006 08/01/;29(Aug):675-85.

29. Cavill I, Auerbach M, Bailie GR, et al. Iron and the anaemia of chronic disease: a review and strategic recommendations. Current Medical Research and Opinion (England). 2006 04/01/;22(Apr):731-7.

30. Chung SJ, Kim JK, Park MC, et al. Reactivation of Hepatitis B Viral Infection in Inactive HBsAg Carriers Following Anti-Tumor Necrosis Factor-alpha Therapy. Journal of Rheumatology 2009;362416.

31. Coates LC, Helliwell PS. Validation of Minimal Disease Activity Criteria for Psoriatic Arthritis Using Interventional Trial Data. Arthritis Care and Research. 2010;62:965.

32. Cohen PR, May. Neutrophilic Dermatoses A Review of Current Treatment Options. American Journal of Clinical Dermatology (New Zealand) 2009;10301.

33. Cohen SB. Updates from B cell trials: Efficacy. Journal of Rheumatology. 2006 01/01/;33(MAY):12-7.

34. Cui J, Saevarsdottir S, Thomson B, et al. Rheumatoid Arthritis Risk Allele <it>PTPRC</it> Is Also Associated With Response to Anti-Tumor Necrosis Factor alpha Therapy. Arthritis and Rheumatism (USA). 2010;62:1849.

35. Curtis JR, Chen L, Harrold LR, et al. Physician Preference Motivates the Use of Anti-Tumor Necrosis Factor Therapy Independent of Clinical Disease Activity. Arthritis Care and Research. 2010;62:101-7.

36. Curtis SP, Ko AT, Bolognese JA, et al. Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective inhibitor etoricoxib. Current Medical Research and Opinion (England). 2006 12/01/;22(Dec):2365-74.

37. DaSilva V, Roux CH, Bernard E, et al. Neuromeningeal Tuberculosis in a Patient with Rheumatoid Arthritis Previously Exposed to Ineffective Etanercept Therapy and Revealed by Infliximab. Journal of Rheumatology. 2010;37:471-2.

38. De Rycke L, Baeten D, Kruithof E, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity - Biologic and clinical implications in autoimmune arthritis. Arthritis and Rheumatism (USA). 2005 07/01/;52(Jul):2192-201.

39. de Vlam K, Lories RJ. Efficacy, effectiveness and safety of etanercept in monotherapy for refractory psoriatic arthritis: a 26-week observational study. Rheumatology. 2006 03/01/;45(Mar):321-4.

40. de Vries-Bouwstra J, Le Cessie S, Allaart C, et al. Using predicted disease outcome to provide differentiated treatment of early rheumatoid arthritis. Journal of Rheumatology. 2006 09/01/;33(Sep):1747-53.

41. Deighton C, Hyrich K, Ding T, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology (Oxford). 2010;49:1197-9.

42. Dewan P, Jawad A, Goldsmith P, et al. Melanoma in patients with rheumatoid arthritis treated with antitumour necrosis factor: cause or coincidence? Report of two cases. British Journal of Dermatology (England) 2009;1611412.

43. Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. Journal of Managed Care Pharmacy (USA). 2006 07/01/;12(Jul):555-69.

44. Driessen RJ, de Jong EM, Salemink GW, et al. Analysis of 4-year Dutch reimbursement application data of biological therapies for psoriatic arthritis. Rheumatology (Oxford). 2010;49:588-91.

45. Duggan ST, Keam SJ, Jun. Certolizumab Pegol In Rheumatoid Arthritis. BioDrugs (New Zealand). 2009;23:407.

46. Eder L, Chandran V, Ueng J, et al. Predictors of response to intra-articular steroid injection in psoriatic arthritis. Rheumatology (Oxford). 2010;49:1367-73.

47. El Miedany Y, Youssef SS, El Gaafary M. Short-term outcome after anti-tumor necrosis factor-alpha therapy in rheumatoid arthritis: Do we need to revise our assessment criteria? Journal of Rheumatology. 2006;33(3):490-6.

48. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment - Results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis and Rheumatism (USA) 2006;54(May):1390-400.

49. Emery P, Genovese MC, van Vollenhoven R, et al. Less Radiographic Progression with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy Across the Spectrum of Clinical Response in Early Rheumatoid Arthritis. Journal of Rheumatology 2009;361429.

50. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. Journal of Rheumatology 2006;33(Apr):681-9.

51. Esposito M, Mazzotta A, de Felice C, et al. Treatment of erythrodermic psoriasis with etanercept. British Journal of Dermatology (England). 2006 01/01/;155(Jan):156-9.

52. Finckh A, Bansback N, Marra CA, et al. Treatment of Very Early Rheumatoid Arthritis With Symptomatic Therapy, Disease-Modifying Antirheumatic Drugs, or

Biologic Agents A Cost-Effectiveness Analysis. Annals of Internal Medicine (USA). 2009;151:612.

53. Fleurence R, Spackman E. Cost-effectiveness of biologic agents for treatment of autoimmune disorders: Structured review of the literature. Journal of Rheumatology. 2006 11/01/;33(Nov):2124-31.

54. Fouache D, Goeb V, Massy-Guillemant N, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology 2009;48761.

55. Frey N, Grange S, Woodworth T. Population Pharmacokinetic Analysis of Tocilizumab in Patients With Rheumatoid Arthritis. Journal of Clinical Pharmacology (USA). 2010;50:754-66.

56. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. Canadian Medical Association Journal (Canada). 2006 11/01/;174(Nov):1589-94.

57. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Jan):2451-65.

58. Garcia JJ, Lobato JP, Garrido SL, et al. Biological therapies in rheumatoid arthritis. Atencion Farmaceutica: European Journal of Clinical Pharmacy. 2008;10(98):100-11.

59. Garnero P, Thompson E, Woodworth T, et al. Rapid and Sustained Improvement in Bone and Cartilage Turnover Markers With the Anti-Interleukin-6 Receptor Inhibitor Tocilizumab Plus Methotrexate in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate Results From a Substudy of the Multicenter Double-Blind, Placebo-Controlled Trial of Tocilizumab in Inadequate Responders to Methotrexate Alone. Arthritis and Rheumatism (USA). 2010;62:33.

60. Gladman DD, Sampalis JS, Illouz O, et al. Responses to Adalimumab in Patients with Active Psoriatic Arthritis Who Have Not Adequately Responded to Prior Therapy: Effectiveness and Safety Results From an Open-label Study. Journal of Rheumatology. 2010;37:1898.

61. Gladman DD, Tom BD, Mease PJ, et al. Informing Response Criteria for Psoriatic Arthritis. I: Discrimination Models Based on Data from 3 Anti-Tumor Necrosis Factor Randomized Studies. Journal of Rheumatology. 2010;37:1892-7.

62. Gompels LL, Smith A, Charles PJ, et al. Single-blind randomized trial of combination antibiotic therapy in rheumatoid arthritis. Journal of Rheumatology. 2006 02/01/;33(Feb):224-7.

63. Gonzalez-Juanatey C, Llorca J, Garcia-Porrua C, et al. Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2006 01/01/;55(Jan):150-3.

64. Graudal N, Juergens G. Similar Effects of Disease-Modifying Antirheumatic Drugs, Glucocorticoids, and Biologic Agents on Radiographic Progression in Rheumatoid Arthritis Meta-Analysis of 70 Randomized Placebo-Controlled or Drug-Controlled Studies, Including 112 Comparisons. Arthritis and Rheumatism (USA). 2010;62:2852.

65. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford) 2010;4982-90.

66. Hallinen TA, Soini EJ, Eklund K, et al. Cost-utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. Rheumatology (Oxford). 2010;49:767-77.

67. Haringman JJ, Gerlag DM, Smeets TJ, et al. A randomized controlled trial with an anti-CCL2 (anti-monocyte chemotactic protein 1) monoclonal antibody in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 08/01/;54(Aug):2387-92.

68. Harris CL, Raisch DW, Abhyankar U, et al. GI risk factors and use of GI protective agents among patients receiving nonsteroidal antiinflammatory drugs. Annals of Pharmacotherapy (USA). 2006 11/01/;40(Nov):1924-31.

69. Hassan B, Maxwell JR, Hyrich KL, et al. Genotype at the sIL-6R A358C polymorphism does not influence response to anti-TNF therapy in patients with rheumatoid arthritis. Rheumatology (Oxford). 2010;49:43-7.

70. Hetland ML, Christensen IJ, Tarp U, et al. Direct Comparison of Treatment Responses, Remission Rates, and Drug Adherence in Patients With Rheumatoid Arthritis Treated With Adalimumab, Etanercept, or Infliximab Results From Eight Years of Surveillance of Clinical Practice in the Nationwide Danish DANBIO Registry. Arthritis and Rheumatism (USA) 2010;6222-32.

71. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis - An investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1401-9.

72. Hu CP, Xu ZH, Rahman MU, et al. A latent variable approach for modeling categorical endpoints among patients with rheumatoid arthritis treated with golimumab plus methotrexate. Journal of Pharmacokinetics and Pharmacodynamics (USA). 2010;37:309-21.

73. Hudson M, Suissa S. Avoiding Common Pitfalls in the Analysis of Observational Studies of New Treatments for Rheumatoid Arthritis. Arthritis Care and Research. 2010;62:805-10.

74. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45(Dec):1558-65.

75. Isenberg DA. B cell targeted therapies in autoimmune diseases. Journal of Rheumatology. 2006 01/01/;33(MAY):24-8.

76. Jacobs JW, van Everdingen AA, Verstappen SM, et al. Followup radiographic data on patients with rheumatoid arthritis who participated in a two-year trial of prednisone therapy or placebo. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1422-8.

77. Jarand J, Zochodne DW, Martin LO, et al. Neurological complications of infliximab. Journal of Rheumatology. 2006 05/01/;33(May):1018-20.

78. Jazayeri JA, Carroll GJ, Vernallis AB. Interleukin-6 subfamily cytokines and rheumatoid arthritis: Role of antagonists. International Immunopharmacology (USA). 2010;10:1-8.

79. Kavanaugh A. Anakinra (interleukin-1 receptor antagonist) has positive effects on function and quality of life in patients with rheumatoid arthritis. Advances in Therapy (USA). 2006 02/01/;23(Feb):208-17.

80. Kavanaugh AF. B cell targeted therapies: Safety considerations. Journal of Rheumatology. 2006 01/01/;33(MAY):18-23.

81. Kawai S, Hashimoto H, Kondo H, et al. Comparison of tacrolimus and mizoribine in a randomized, double-blind controlled study in patients with rheumatoid arthritis. Journal of Rheumatology. 2006 11/01/;33(Nov):2153-61.

82. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. Rheumatology. 2006 04/01/;45(Apr):441-4.

83. Kawakami K, Ikari K, Kawamura K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of

tumour necrosis factor-alpha blockers decreases complications? Rheumatology (Oxford) 2010;49341-7.

84. Kawashiri SY, Kawakami A, Iwamoto N, et al. Proinflammatory Cytokines Synergistically Enhance the Production of Chemokine Ligand 20 (CCL20) from Rheumatoid Fibroblast-like Synovial Cells <it>in vitro</it> and Serum CCL20 Is Reduced <it>in vivo</it> by Biologic Disease-modifying Antirheumatic Drugs. Journal of Rheumatology 2009;362397.

85. Kay LJ, Griffiths ID, Management BSRBR. UK consultant rheumatologists' access to biological agents and views on the BSR Biologics Register. Rheumatology. 2006 11/01/;45(Nov):1376-9.

86. Kivitz A, Cohen S, Dowd JE, et al. Clinical assessment of pain, tolerability, and preference of an autoinjection pen versus a prefilled syringe for patient self-administration of the fully human, monoclonal antibody adalimumab: The TOUCH trial. Clinical Therapeutics (USA). 2006 10/01/;28(Oct):1619-29.

87. Kling MC, Larian AA, Scordi-Bello I, et al. Fatal Influenza A(H1N1) Respiratory Tract Infection in a Patient Having Psoriasis Treated With Infliximab. Archives of Dermatology (USA). 2010;146:651-4.

88. Koeller MD, Aletaha D, Funovits J, et al. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology 2009;481575.

89. Korkina L, Trakhtman P, De Luca C, et al. EFFICACY AND SAFETY OF BIOLOGICALS AGAINST IMMUNE-MEDIATED DISEASES: DO BENEFITS OUTWEIGH RISKS? Drugs of Today (Spain). 2010;46:119-36.

90. Krathen MS, Gottlieb AB, Mease PJ. Pharmacologic Immunomodulation and Cutaneous Malignancy in Rheumatoid Arthritis, Psoriasis, and Psoriatic Arthritis. Journal of Rheumatology. 2010;37:2205-15.

91. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis - A randomized trial. Annals of Internal Medicine (USA) 2006;144(Dec):865-76.

92. Kuan WP, Tam LS, Wong CK, et al. CXCL 9 and CXCL 10 as Sensitive Markers of Disease Activity in Patients with Rheumatoid Arthritis. Journal of Rheumatology. 2010;37:257-64.

93. Landewe R, van der Heijde D, Klareskog L, et al. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate - Results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis and Rheumatism (USA). 2006 10/01/;54(Oct):3119-25.

94. Lee YH, Ji JD, Bae SC, et al. Associations Between Tumor Necrosis Factor-alpha (TNF-alpha) -308 and -238 G/A Polymorphisms and Shared Epitope Status and Responsiveness to TNF-alpha Blockers in Rheumatoid Arthritis: A Metaanalysis Update. Journal of Rheumatology. 2010;37:740-6.

95. Lee YH, Song GG. Associations between the C677T and A1298C Polymorphisms of <it>MTHFR</it> and the Efficacy and Toxicity of Methotrexate in Rheumatoid Arthritis A Meta-Analysis. Clinical Drug Investigation (New Zealand). 2010;30:101-8.

96. Lester SE, Proudman SM, Lee AT, et al. Treatment-induced stable, moderate reduction in blood cell counts correlate to disease control in early rheumatoid arthritis. Internal Medicine Journal. 2009;39:296.

97. Looney RJ. B cell-targeted therapy for rheumatoid arthritis - An update on the evidence. Drugs (New Zealand). 2006 05/01/;66(May):625-39.

98. Luman KL, Amireh H, Gonzalez ER. A medication utilization evaluation of abatacept: a retrospective study. ASHP Midyear Clinical Meeting. 2010;2009:119.

99. Luman KL, Amireh H, Gonzalez ER. A medication utilization evaluation of

infliximab: a retrospective study. ASHP Midyear Clinical Meeting. 2010;2009:120.

100. Luqmani R, Hennell S, Estrach C, et al. British society for rheumatology and british health professionals in rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology. 2006 09/01/;45(Sep):1167-9.

101. Ma MH, Kingsley GH, Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2010;49:91-8.

102. Madland TM, Bjoerkkjaer T, Brunborg LA, et al. Subjective improvement in patients with psoriatic arthritis after short-term oral treatment with seal oil. A pilot study with double blind comparison to soy oil. Journal of Rheumatology. 2006 02/01/;33(Feb):307-10.

103. Magnusson M, Brisslert M, Zendjanchi K, et al. Epstein-Barr virus in bone marrow of rheumatoid arthritis patients predicts response to rituximab treatment. Rheumatology (Oxford). 2010;49:1911-9.

104. Maignen F, Hauben M, Tsintis P. Modelling the Time to Onset of Adverse Reactions with Parametric Survival Distributions A Potential Approach to Signal Detection and Evaluation. Drug Safety (New Zealand). 2010;33:417-34.

105. Marra C. Rheumatoid arthritis: A primer for pharmacists. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Feb):S4-10.

106. McCluggage LK, Scholtz JM. Golimumab: A Tumor Necrosis Factor Alpha Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy (USA). 2010;44:135-44.

107. McDermott MF, Jun. RILONACEPT IN THE TREATMENT OF CHRONIC INFLAMMATORY DISORDERS. Drugs of Today (Spain) 2009;45423.

108. McLean-Tooke A, Aldridge C, Waugh S, et al. Methotrexate, rheumatoid arthritis and infection riskwhat is the evidence. Rheumatology. 2009;48:867.

109. Mease PJ, Gladman DD, Keystone EC, et al. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis - Results of a randomized, double-blind, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1638-45.

110. Michot C, Costes V, Gerard-Dran D, et al. Subcutaneous panniculitis-like T-cell lymphoma in a patient receiving etanercept for rheumatoid arthritis. British Journal of Dermatology (England) 2009;160889.

111. Montecucco C. Remission, a therapeutic goal in inflammatory arthropathies? Clinical data from adalimumab studies. Drugs (New Zealand). 2006 01/01/;66(Mar):1783-95.

112. Muhammad K, Roll P, Einsele H, et al. Delayed Acquisition of Somatic Hypermutations in Repopulated IgD+CD27+ Memory B Cell Receptors After Rituximab Treatment. Arthritis and Rheumatism (USA) 2009;602284.

113. Mulleman D, Lin DC, Ducourau E, et al. Trough Infliximab Concentrations Predict Efficacy and Sustained Control of Disease Activity in Rheumatoid Arthritis. Therapeutic Drug Monitoring (USA). 2010;32:232.

114. Nagashima T, Minota S. Subcutaneous calcification following injection of triamcinolone hexacetonide for plantar fasciitis. Rheumatology, Dec. 2008;47:1838-40.

115. Nakamura T, Higashi S, Tomoda K, et al. Significance of SAA1.3 allele genotype in Japanese patients with amyloidosis secondary to rheumatoid arthritis. Rheumatology. 2006 01/01/;45(Jan):43-9.

116. Nannini C, Cantini F, Niccoli L, et al. Single-Center Series and Systematic Review of Randomized Controlled Trials of Malignancies in Patients With Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis Receiving Anti-Tumor Necrosis

Factor alpha Therapy: Is There a Need for More Comprehensive Screening Procedures? Arthritis and Rheumatism-Arthritis Care and Research 2009;61801.

117. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. Journal of Rheumatology 2006;33(Jun):1075-81.

118. Odai T, Matsunawa M, Takahashi R, et al. Correlation of CX3CL1 and CX3CR1 Levels with Response to Infliximab Therapy in Patients with Rheumatoid Arthritis. Journal of Rheumatology 2009;361158.

119. Oldfield V, Dhillon S, Plosker GL. Tocilizumab A Review of its Use in the Management of Rheumatoid Arthritis. Drugs. 2009;69:609-32.

120. Paul-Pletzer K. Tocilizumab: Blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. Drugs of Today (Spain). 2006 09/01/;42(Sep):559-76.

121. Phung OJ, Coleman CI, Sep. Golimumab: A human anti-TNF-alpha monoclonal antibody for the treatment of autoimmune joint diseases. Formulary (USA) 2009;44264.

122. Pincus T, Chung C, Segurado OG, et al. An index of patient reported outcomes (PRO-Index) discriminates effectively between active and control treatment in 4 clinical trials of adalimumab in rheumatoid arthritis. Journal of Rheumatology. 2006 11/01/;33(Nov):2146-52.

123. Plushner SL. Tocilizumab: An Interleukin-6 Receptor Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy. 2008;42:1660-8.

124. Polinski JM, Mohr PE, Johnson L, et al. Impact of Medicare Part D on Access to and Cost Sharing for Specialty Biologic Medications for Beneficiaries With Rheumatoid Arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2009;61:745.

125. Prodanovich S, Ricotti C, Glick BP, et al. Etanercept: An Evolving Role in Psoriasis and Psoriatic Arthritis. American Journal of Clinical Dermatology (New Zealand). 2010;11:3-9.

126. Pucino F, Harbus PT, Goldbach-Mansky R. Use of biologics in rheumatoid arthritis: Where are we going? American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Feb):S19-S41.

127. Quartuccio L, Fabris M, Salvin S, et al. Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis. Rheumatology 2009;481557.

128. Rachapalli SM, Williams R, Walsh DA, et al. First-line DMARD choice in early rheumatoid arthritis-do prognostic factors play a role? Rheumatology (Oxford). 2010;49:1267-71.

129. Raghavendran RR, Peart F, Grindulis KA. Long-term tocilizumab therapy in a patient with rheumatoid arthritis and chronic hepatitis B. Rheumatology, Dec. 2008;47.

130. Ranganathan P, McLeod HL. Methotrexate pharmacogenetics - The first step toward individualized therapy in rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1366-77.

131. Raterman HG, Simsek S, Lems WF, et al. Rituximab and Thyroid Function. Archives of Internal Medicine (USA) 2009;1691073.

132. Reiff A, Lovell DJ, van Adelsberg J, et al. Evaluation of the comparative efficacy and tolerability of rofecoxib and naproxen in children and adolescents with juvenile rheumatoid arthritis: A 12-week randomized controlled clinical trial with a 52-week open-label extension. Journal of Rheumatology. 2006 05/01/;33(May):985-95.

133. Resman-Targoff BH. Medical therapy: Where are we now? American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Feb):S11-S8.

134. Ristic GG, Lepic T, Gilsic B, et al. Rheumatoid arthritis is an independent risk factor for increased carotid intima-media thickness: impact of anti-inflammatory treatment. Rheumatology (Oxford). 2010;49:1076.

135. Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. Journal of Rheumatology. 2006 07/01/;33(Jul):1435-8.

136. Robinson V, Boers M, Brooks P, et al. Patient-reported pain is central to OMERACT rheumatology core measurement sets. Drug Information Journal (USA). 2006 01/01/;40(Jan):111-6.

137. Roman-Blas JA, Castaneda S, Cutolo M, et al. Efficacy and Safety of a Selective Estrogen Receptor beta Agonist, ERB-041, in Patients With Rheumatoid Arthritis: A 12-Week, Randomized, Placebo-Controlled, Phase II Study. Arthritis Care and Research. 2010;62:1588-93.

138. Rongioletti F, Burlando M, Parodi A. Adverse Effects of Biological Agents in the Treatment of Psoriasis. American Journal of Clinical Dermatology (New Zealand). 2010;11:35-7.

139. Rottem M, Mader R. Successful Use of Etanercept in Acquired Angioedema in a Patient with Psoriatic Arthritis. Journal of Rheumatology. 2010;37:209.

140. Roux CH, Brocq O, Breuil V, et al. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology. 2006 10/01/;45(Oct):1294-7.

141. Saad AA, Ashcroft DM, Watson KD, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010;49697-705.

142. Saraux A, Gossec L, Goupille P, et al. Cost-effectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in France. Rheumatology (Oxford). 2010;49:733-40.

143. Schiff MH, Yu EB, Weinblatt ME, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients - Patient-reported outcomes from multiple controlled and open-label extension studies. Drugs and Aging (New Zealand). 2006 02/01/;23(Feb):167-78.

144. Schlesselman LS, Hussey AP. Tocilizumab - A humanized anti-IL-6 receptor monoclonal antibody for the treatment of rheumatoid arthritis. Formulary. 2008;43:272-9.

145. Scott DL. Pursuit of optimal outcomes in rheumatoid arthritis. PharmacoEconomics (New Zealand). 2004 02/01/;22(Feb):13-26.

146. Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor. American Journal of Health System Pharmacy. 2008;65:1413-8.

147. Shadick NA, Cook NR, Karlson EW, et al. C-reactive protein in the prediction of rheumatoid arthritis in women. Archives of Internal Medicine (USA). 2006 01/01/;166(Jan):2490-4.

148. Sheth NU, Hilas O, Charneski L. Abatacept: A novel agent for rheumatoid arthritis. Journal of Pharmacy Technology (USA). 2006 06/01/;22(Jun):336-41.

149. Siddigui MA, Scott LJ. Spotlight on infliximab in Crohn disease and rheumatoid arthritis. BioDrugs (New Zealand). 2006 01/01/;20(Jan):67-70.

150. Siegel JN, Zhen BG. Use of the American College of Rheumatology N (ACR-N) Index of improvement in rheumatoid arthritis - Argument in favor. Arthritis and Rheumatism (USA). 2005 06/01/;52(Jun):1637-41.

151. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative Effectiveness Without Head-to-Head Trials A Method for Matching-Adjusted Indirect Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept. PharmacoEconomics (New Zealand). 2010;28:935-45.

152. Sihvonen S, Korpela M, Mustonen J, et al. Mortality in patients with rheumatoid

arthritis treated with low-dose oral glucocorticoids. A population-based cohort study. Journal of Rheumatology. 2006 09/01/;33(Sep):1740-6.

153. Silverman GJ. Therapeutic B cell depletion and regeneration in rheumatoid arthritis - Emerging patterns and paradigms. Arthritis and Rheumatism (USA). 2006 08/01/;54(Aug):2356-67.

154. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Canadian Medical Association Journal (Canada) 2009;181787.

155. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement - A detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis and Rheumatism (USA). 2005 04/01/;52(Apr):1020-30.

156. Smolen JS, van der Heijde DM, St Clair EW, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab - Results from the ASPIRE trial. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):702-10.

157. Snyder RA. Psoriatic Arthritis: A Dermatologist's Perspective. American Journal of Clinical Dermatology (New Zealand). 2010;11:19-22.

158. Sobanko JF, Freeman AF, Palmore TN, et al. A Sri Lankan woman with rheumatoid arthritis and anesthetic plaques. Journal of the American Academy of Dermatology (USA) 2009;601018.

159. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA) 2006;54(Dec):3790-8.

160. Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy <it>vs</it> its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology. 2009;48:1429.

161. Stockl KM, Shin JS, Lew HC, et al. Outcomes of a Rheumatoid Arthritis Disease Therapy Management Program Focusing on Medication Adherence. Journal of Managed Care Pharmacy (USA). 2010;16:593-604.

162. Strand V, Cohen S, Crawford B, et al. Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. Rheumatology. 2004 05/01/;43(May):640-7.

163. Strand V, Singh JA. Newer Biological Agents in Rheumatoid Arthritis Impact on Health-Related Quality of Life and Productivity. Drugs (New Zealand). 2010;70:121-45.

164. Straub RH, Haerle P, Yamana S, et al. Anti-interleukin-6 receptor antibody therapy favors adrenal androgen secretion in patients with rheumatoid arthritis - A randomized, double-blind, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 06/01/;54(Jun):1778-85.

165. Stuhlmueller B, Haeupl T, Hernandez MM, et al. CD11c as a Transcriptional Biomarker to Predict Response to Anti-TNF Monotherapy With Adalimumab in Patients With Rheumatoid Arthritis. Clinical Pharmacology and Therapeutics (USA). 2010;87:311-21.

166. Sweet BV. Abatacept. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Jan):2065-77.

167. Takatori S, Kamata Y, Murosaki T, et al. Abrupt Development of Sarcoidosis with a Prodromal Increase in Plasma Osteopontin in a Patient with Rheumatoid Arthritis During Treatment with Etanercept. Journal of Rheumatology. 2010;37:210-2.

168. Taylor PC, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results

from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 01/01/;54(Jan):47-53.

169. Thayer S, Watson C, Song R, et al. Etanercept treatment patterns in managed-care patients with psoriasis or psoriatic arthritis. Journal of Medical Economics (England). 2010;13:228-35.

170. Tielemans MM, Eikendal T, Jansen JB, et al. Identification of NSAID Users at Risk for Gastrointestinal Complications A Systematic Review of Current Guidelines and Consensus Agreements. Drug Safety (New Zealand). 2010;33:443-53.

171. Torikai E, Kageyama Y, Takahashi M, et al. The effect of infliximab on bone metabolism markers in patients with rheumatoid arthritis. Rheumatology. 2006 06/01/;45(Jun):761-4.

172. Tran S, Hooker RS, Cipher DJ, et al. Patterns of Biologic Agent Use in Older Males with Inflammatory Diseases An Institution-Focused, Observational Post-Marketing Study. Drugs and Aging (New Zealand). 2009;26:607.

173. Tubach F, Ravaud P, Salmon-Ceron D, et al. Emergence of <it>Legionella pneumophila</it> pneumonia in patients receiving tumor necrosis factor-alpha antagonist. Clinical Infectious Diseases. 2006 10/01/;43(Oct):E95-100.

174. van Assen S, Holvast A, Benne CA, et al. Humoral Responses After Influenza Vaccination Are Severely Reduced in Patients With Rheumatoid Arthritis Treated With Rituximab. Arthritis and Rheumatism (USA). 2010;62:75-81.

175. van der Linden MP, van der Woude D, Ioan-Facsinay A, et al. Value of Anti-Modified Citrullinated Vimentin and Third-Generation Anti-Cyclic Citrullinated Peptide Compared With Second-Generation Anti-Cyclic Citrullinated Peptide and Rheumatoid Factor in Predicting Disease Outcome in Undifferentiated Arthritis and Rheumatoid Arthritis. Arthritis and Rheumatism (USA) 2009;602232.

176. Van Rijthoven AW, Bijlsma JW, Canninga-Van Dijk M, et al. Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level. Rheumatology. 2006 10/01/;45(Oct):1317-9.

177. Vanags D, Williams B, Johnson B, et al. Therapeutic efficacy and safety of chaperonin 10 in patients with rheumatoid arthritis: a double-blind randomised trial. Lancet, The (USA). 2006 01/01/;368(Apr):855-63.

178. Varani K, Massara A, Vincenzi F, et al. Normalization of A<INF>2A</INF> and A<INF>3</INF> Adenosine Receptor Up-Regulation in Rheumatoid Arthritis Patients by Treatment With Anti-Tumor Necrosis Factor alpha but Not Methotrexate. Arthritis and Rheumatism (USA) 2009;602880.

179. Vergles JM, Radic M, Kovacic J, et al. Successful Use of Adalimumab for Treating Rheumatoid Arthritis with Autoimmune Sensorineural Hearing Loss: Two Birds with One Stone. Journal of Rheumatology. 2010;37:1080.

180. Villa-Blanco JI, Calvo-Alen J, Sep. Elderly Onset Rheumatoid Arthritis Differential Diagnosis and Choice of First-Line and Subsequent Therapy. Drugs and Aging (New Zealand) 2009;26739.

181. Virkki LM, Sumathikutty BC, Aarnio M, et al. Biological Therapy for Psoriatic Arthritis in Clinical Practice: Outcomes Up to 2 Years. Journal of Rheumatology 2010;372362-8.

182. Watson DJ, Bolognese JA, Yu C, et al. Use of gastroprotective agents and discontinuations due to dyspepsia with the selective cyclooxygenase-2 inhibitor etoricoxib compared with non-selective NSAIDs. Current Medical Research and Opinion (England). 2004 12/01/;20(Dec):1899-908.

183. Weisman MH, Durez P, Hallegua D, et al. Reduction of inflammatory biomarker

response by abatacept in treatment of rheumatoid arthritis. Journal of Rheumatology. 2006 11/01/;33(Nov):2162-6.

184. Welsing PM, Severens JL, Hartman M, et al. The initial validation of a Markov model for the economic evaluation of (New) treatments for rheumatoid arthritis. PharmacoEconomics (New Zealand). 2006 10/01/;24(Oct):1011-20.

185. Weng HH, Ranganath VK, Khanna D, et al. Equivalent Responses to Disease-modifying Antirheumatic Drugs Initiated at Any Time During the First 15 Months After Symptom Onset in Patients with Seropositive Rheumatoid Arthritis. Journal of Rheumatology. 2010;37:550-7.

186. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology 2006;45(Oct):1238-46.

187. Westlake SL, Colebatch AN, Baird J, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford). 2010;49:295.

188. White DH, Chapman PT, O'Donnell JL, et al. Lack of association between elevated mean red cell volume and haematological toxicity in patients receiving long-term methotrexate for rheumatoid arthritis. Internal Medicine Journal. 2010;40:561-5.

189. Williams GW, Kivitz AJ, Brown MT, et al. A comparison of valdecoxib and naproxen in the treatment of rheumatoid arthritis symptoms. Clinical Therapeutics (USA). 2006 02/01/;28(Feb):204-21.

190. Wolbink GJ, Vis M, Lems W, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):711-5.

191. Yuan Y, Trivedi D, Maclean R, et al. Indirect cost-effectiveness analyses of abatacept and rituximab in patients with moderate-to-severe rheumatoid arthritis in the United States. Journal of Medical Economics (England) 2010;13(1):33-41.

192. Zaiac M. The Role of Biological Agents in the Treatment of Nail Psoriasis. American Journal of Clinical Dermatology (New Zealand). 2010;11:27.

193. Zandbelt MM, Houbiers JG, van den Hoogen FH, et al. Intranasal administration of recombinant human cartilage glycoprotein-39. A phase I escalating cohort study in patients with rheumatoid arthritis. Journal of Rheumatology. 2006 09/01/;33(Sep):1726-33.

194. Zhang XP, Huang Y, Navarro MT, et al. A Proof-of-Concept and Drug-Drug Interaction Study of Pamapimod, a Novel p38 MAP Kinase Inhibitor, With Methotrexate in Patients With Rheumatoid Arthritis. Journal of Clinical Pharmacology (USA). 2010;50:1031-8.

195. Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study - Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis and Rheumatism (USA). 2006 11/01/;54(Nov):3399-407.

Reference Source: Handsearches (e.g., Scopus)

1. Cochrane Collaboration guidelines.
2. The BUGS Project. Stevens A, Hosted by the MRC Biostatistics Unit, Cambridge, UK. Accessed on May 2, 2011. www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml
3. Sulfasalazine in early rheumatoid arthritis. The Australian Multicentre Clinical Trial Group. J Rheumatol. 1992 Nov;19(11):1672-7.
4. Screening for hydroxychloroquine retinopathy. 2006.
5. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003. MMWR Morb Mortal Wkly Rep 2007;56(1):4-7.
6. Chapter 9: Analysing data and undertaking meta-analyses. Cochrane Handbook of Systematic Reviews of Intervention Version 500 (Updated February 2008). 2008.
7. Rituxan (Rituximab) [Package Insert]. 2008.
8. Ã˜stensen M, Motta M. Therapy Insight: The use of antirheumatic drugs during nursing. Nature Clinical Practice Rheumatology. 2007;3(7):400-6.
9. Ã˜tensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Research and Therapy. 2006;8(3).
10. Abeles AM, Pillinger MH. The role of the synovial fibroblast in rheumatoid arthritis: Cartilage destruction and the regulation of matrix metalloproteinases. Bulletin of the NYU Hospital for Joint Diseases. 2006;64(1-2):20-4.
11. Ackermann C, Kavanaugh A. Economic burden of psoriatic arthritis. PharmacoEconomics 2008;26(2):121-9.
12. ACR. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46.
13. ACR. ACR Hotline: Update on safety issues concerning TNF inhibitors; available at http://www.rheumatology.org/publications/hotline/0506JAMATNF.asp. 2006.
14. Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0. [Draft posted Oct. 2007]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf 2007.
15. Agrawal S, Misra R, Aggarwal A. Autoantibodies in rheumatoid arthritis: Association with severity of disease in established RA. Clinical rheumatology. 2007;26(2):201-4.
16. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: A systematic review. Journal of Rheumatology. 2008;35(7):1354-8.
17. Aletaha D, Machold KP, Nell VPK, et al. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology. 2006;45(9):1133-9.
18. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7(4):R796-806.
19. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-8.
20. Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheumatic Disease Clinics of North America. 2006;32(1):9-44.
21. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with

initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol. 2006 Nov-Dec;24(6 Suppl 43):S-77-82.

22. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: Systematic review and metaanalysis of efficacy and safety. BMC Musculoskeletal Disorders 2008;9.

23. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. . Arthritis Rheum. 1996 May;39(5):723-31.

24. Anandarajah AP, Ritchlin CT. Pathogenesis of psoriatic arthritis. Curr Opin Rheumatol. 2004 Jul;16(4):338-43.

25. Ang DC, Paulus HE, Louie JS. Patient's ethnicity does not influence utilization of effective therapies in rheumatoid arthritis. J Rheumatol. 2006 May;33(5):870-8.

26. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45(4):384-91.

27. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001 2001.

28. Anonymous. Cortisone Acetate package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.

29. Anonymous. Cortef (hydrocortisone) package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.

30. Anonymous. Dexamethasone package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.

31. Anonymous. PredniSONE package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.

32. Anonymous. Kineret (anakinra) package insert. Amgen, Inc. Thousand Oaks, CA. 2004.

33. Anonymous. Hydroxychloroquine package insert. Sandoz, Inc. Broomfield, CO. 2004.

34. Anonymous. Orencia (abatacept) package insert. Bristol-Myers Squibb. Princeton, NJ. 2005.

35. Anonymous. Methotrexate package insert. Mayne Pharma (USA) Inc. Paramus, NJ. 2005.

36. Anonymous. Arava (leflunomide) package insert. Aventis Pharmaceuticals Inc. Kansas City, MO. 2005.

37. Anonymous. Remicade (infliximab) package insert. Centocor, Inc. Malvern, PA. 2006.

38. Anonymous. Humira (adalimumab) package insert. Abbott Labs. North Chicago, IL. 2006.

39. Anonymous. Enbrel (etanercept) package insert. Immunex Corporation. Thousand Oaks, CA. 2006.

40. Anonymous. MethylPREDNIsolone package insert. Sandoz, Inc. Princeton, NJ. 2006.

41. Anonymous. Azulfidine (sulfasalazine) package insert. Pharmacia & Upjohn Co. NY, NY. 2006.

42. Anonymous. Rituxan (rituximab) package insert. Genetech, Inc. South San Francisco, CA. 2007.

43. Arkfeld DG. The potential utility of B cell-directed biologic therapy in autoimmune diseases. Rheumatology international. 2008;28(3):205-15.

44. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of

rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-24.

45. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1421-6.

46. AteÅŸ A, Kinikli G, Turgay M, et al. Effects of rheumatoid factor isotypes on disease activity and severity in patients with rheumatoid arthritis: A comparative study. Clinical rheumatology. 2007;26(4):538-45.

47. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res. 2004 Dec 22;4(1):38.

48. Baecklund E, Ekbom A, Sparen P, et al. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. Bmj. 1998 Jul 18;317(7152):180-1.

49. Balk EM, Lau J, Bonis PA. Reading and critically appraising systematic reviews and meta-analyses: a short primer with a focus on hepatology. J Hepatol. 2005;43(4):729-36.

50. Bansback NJ, Ara R, Barkham N, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology (Oxford). 2006 Aug;45(8):1029-38.

51. Bendtzen K, Geborek P, Svenson M, et al. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum. 2006 Dec;54(12):3782-9.

52. Berends MAM, Snoek J, De Jong EMGJ, et al. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Alimentary Pharmacology and Therapeutics. 2006;24(5):805-11.

53. Berglin E, Johansson T, Sundin U, et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Annals of the rheumatic diseases. 2006;65(4):453-8.

54. Bergman GJ, Hochberg MC, Boers M, et al. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2010;39(6):425-41.

55. Berliner AR, Haas M, Choi MJ. Sarcoidosis: the nephrologist's perspective. Am J Kidney Dis. 2006 Nov;48(5):856-70.

56. Bermas BL. Use of immunosuppressive drugs in pregnancy and lactation. 2007.

57. Bliddal H, Terslev L, Qvistgaard E, et al. A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Sep-Oct;35(5):341-5.

58. BlueCross BlueShield Technology Evaluation Center (TEC). Special report: evidence on sequencing of conventional and biological disease-modifying anti-rheumatic drugs. 2003 2003;18(11).

59. Boers M. Add-on or step-up trials for new drug development in rheumatoid arthritis: a new standard? Arthritis Rheum. 2003 Jun;48(6):1481-3.

60. Boers M. Abatacept in rheumatoid arthritis: a new branch on the "biologics" tree. Ann Intern Med. 2006 Jun 20;144(12):933-5.

61. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology. 2008 Dec;135(6):1953-60.

62. Boini S, Fuillemin F. Review. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and

advantages. Ann Rheum Dis. 2001;60:817-27.

63. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis. 2001 Sep;60(9):817-27.

64. Bolen J, Helmick CG, Sacks JJ, et al. Prevalence of self-reported arthritis or chronic joint symptoms among adults--United States, 2001. MMWR Morb Mortal Wkly Rep. 2002 Oct 25;51(42):948-50.

65. Bologna C, Viu P, Picot MC, et al. Long-term follow-up of 453 rheumatoid arthritis patients treated with methotrexate: an open, retrospective, observational study. Br J Rheumatol. 1997 May;36(5):535-40.

66. Bond SJ, Farewell VT, Schentag CT, et al. Predictors for radiological damage in psoriatic arthritis: Results from a single centre. Ann Rheum Dis. 2006 Aug 17.

67. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85.

68. Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis 2009;68(7):1177-83.

69. Borman P, Toy GG, Babaoglu S, et al. A comparative evaluation of quality of life and life satisfaction in patients with psoriatic and rheumatoid arthritis. Clin Rheumatol. 2006 Apr 19.

70. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: A comparison of the performance of meta-analytical methods with rare events. Statistics in Medicine. 2007;26(1):53-77.

71. Braun J, McHugh N, Singh A, et al. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford). 2007 Jun;46(6):999-1004.

72. Braun J, Sieper J. Biological therapies in the spondyloarthritides--the current state. Rheumatology (Oxford). 2004 Sep;43(9):1072-84.

73. Bren L. The importance of patient-reported outcomes... it's all about the patients. FDA Consumer. 2006;40(6).

74. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. Journal of Clinical Investigation. 2008;118(11):3537-45.

75. Bruce SP, Boyce EG. Update on abatacept: A selective costimulation modulator for rheumatoid arthritis. Annals of Pharmacotherapy. 2007;41(7-8):1153-62.

76. Bruce TO. Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. Curr Psychiatry Rep 2008;10(3):258-64.

77. Bruynesteyn K, van der Heijde D, Boers M, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum. 2002 Apr;46(4):913-20.

78. Buch MH, Bingham SJ, Bejarano V, et al. Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept. Arthritis Rheum. 2007 Apr 15;57(3):448-53.

79. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91.

80. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91.

81. Bukhari MA, Wiles NJ, Lunt M, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis Rheum. 2003 Jan;48(1):46-53.

82. Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9.

83. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review: Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis. 2010.

84. Cannella AC, O'Dell JR. Early rheumatoid arthritis: pitfalls in diagnosis and review of recent clinical trials. Drugs. 2006;66(10):1319-37.

85. Capell H, Madhok R, Porter D, et al. Combination therapy with sulphasalazine and methotrexate is more effective than either drug alone in rheumatoid arthritis (ra) patients with a suboptimal response to sulphasalazine: Results from the double blind placebo controlled mascot study. Ann Rheum Dis. 2006 August 22, 2006:ard.2006.057133.

86. Carlin CS, Feldman SR, Krueger JG, et al. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004 Jun;50(6):859-66.

87. Carmona L, Descalzo MÃ, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Annals of the rheumatic diseases. 2007;66(7):880-5.

88. Carmona L, Hernandez-Garcia C, Vadillo C, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Jul;30(7):1436-9.

89. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. J Rheumatol. 2006 Jul;33(7):1452-6.

90. Cassell S, Tutuncu Z, Kremer J, et al. Psoriatic arthritis patients have different rates of adverse events than rheumatoid arthritis patients when treated with TNF inhihitors: analysis from CORRONA Database [Abstract 491]. Arthritis Rheum. 2005;52(Suppl 9):S211-S2.

91. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005 Nov;32(11):2130-5.

92. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003 Jun;98(6):1315-24.

93. Chen Y, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Heath Technology Assessment. 2006;10(42).

94. Chernoff MC, Wang M, Anderson JJ, et al. Problems and suggested solutions in creating an archive of clinical trials data to permit later meta-analysis: an example of methotrexate trials in rheumatoid arthritis. Control Clin Trials. 1995 Oct;16(5):342-55.

95. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001 Mar 22;344(12):907-16.

96. Chung CP, Thompson JL, Koch GG, et al. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Annals of the rheumatic diseases. 2006;65(12):1602-7.

97. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor

necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.

98. Coburn LA, Wise PE, Schwartz DA. The successful use of adalimumab to treat active Crohn's disease of an ileoanal pouch during pregnancy. Digestive Diseases and Sciences. 2006;51(11):2045-7.

99. Cohen JD, Dougados M, Goupille P, et al. Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis. Journal of Rheumatology. 2006;33(10):1936-41.

100. Coletta AP, Clark AL, Banarjee P, et al. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. Eur J Heart Fail. 2002 Aug;4(4):559-61.

101. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: A double-blind comparison. Annals of the rheumatic diseases. 2006;65(10):1357-62.

102. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Annals of the rheumatic diseases. 2007;66(1):34-45.

103. Connell L, McInnes IB. New cytokine targets in inflammatory rheumatic diseases. Best Practice and Research: Clinical Rheumatology. 2006;20(5):865-78.

104. Cope AP. T cells in rheumatoid arthritis. Arthritis Research and Therapy. 2008;10(SUPPL. 1).

105. Corbo M, Tay LK, Leon F, et al. A single dose of abatacept does not prevent the development of a positive immune response to tetanus and pneumococcal vacciness. Ann Rheum Dis. 2006;65(SUPPL. II):184.

106. Cvetkovic RS, Scott LJ. Adalimumab: a review of its use in adult patients with rheumatoid arthritis. BioDrugs. 2006;20(5):293-311.

107. Davis MJ, Dawes PT, Fowler PD, et al. Should disease-modifying agents be used in mild rheumatoid arthritis? Br J Rheumatol. 1991 Dec;30(6):451-4.

108. De Filippis L, Caliri A, Anghelone S, et al. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. Panminerva Med 2006;48(2):129-35.

109. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173.

110. Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. Pharmacotherapy 2011;31(1):39-51.

111. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69(3):522-8.

112. Dixon WG, Symmons DP, Lunt M, et al. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum 2007;56(9):2896-904.

113. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jul 25;54(8):2368-76.

114. Donahue KE, Gartlehner G, Jonas DE, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis and psoriatic

arthritis in adults. Comparative Effectiveness Review No. 11. (Prepared by RTI-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality; 2007.

115. Edmonds J, Saudan A, Lassere M, et al. Introduction to reading radiographs by the Scott modification of the Larsen method. J Rheumatol. 1999;26:740-2.

116. Efthimiou P, Kontzias A, Ward CM, et al. Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy? Nat Clin Pract Rheumatol. 2007 Jun;3(6):328-35.

117. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care (2nd edition). 2001 2001.

118. Emery P, Breedveld FC, Jubb RW, et al. Efficacy and safety of leflunomide vs. methotrexate in rheumatoid arthritis (RA): results of a double-blind, randomized, 2-year trial. Arthritis and Rheumatism. 1999;42(9 (Suppl)):S271.

119. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54(5):1390-400.

120. Feagan BG, Yan S, Bala M, et al. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol. 2003 Oct;98(10):2232-8.

121. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993 Jun;36(6):729-40.

122. Felson DT, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.

123. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38(6):727-35.

124. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis Rheum. 1990 Oct;33(10):1449-61.

125. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis. Arthritis Rheum. 1994 Oct;37(10):1487-91.

126. Fernandez-Espartero MC, Perez-Zafrilla B, Naranjo A, et al. Demyelinating Disease in Patients Treated with TNF Antagonists in Rheumatology: Data from BIOBADASER, a Pharmacovigilance Database, and a Systematic Review. Semin Arthritis Rheum 2010;40(4):330-7.

127. Finckh A, Liang MH, Van Herckenrode CM, et al. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: Ameta-analysis. Arthritis and rheumatism. 2006;55(6):86-172.

128. Finckh A, Simard JF, Gabay C, et al. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52.

129. Firestein GS. Etiology and pathogenesis of rheumatoid arthritis. Kelley's Testbook of Rheumatology 2005;7.

130. Fleischmann R, Iqbal I. Risk: benefit profile of etanercept in elderly patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis. Drugs Aging. 2007;24(3):239-54.

131. Fleischmann R, Iqbal I, Nandeshwar P, et al. Safety and efficacy of disease-modifying anti-rheumatic agents: focus on the benefits and risks of etanercept. Drug Saf. 2002;25(3):173-97.

132. Fleischmann RM, Baumgartner SW, Tindall EA, et al. Response to etanercept (Enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trial results. J Rheumatol. 2003 Apr;30(4):691-6.

133. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther. 2005;7(3):R666-76.

134. Food and Drug Administration. FDA alert on rituximab, available at: http://www.fda.gov/cder/drug/infopage/rituximab/default.htm. 2006.

135. Frankel EH, Strober BE, Crowley JJ, et al. Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. Cutis. 2007 Apr;79(4):322-6.

136. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am 2009;35(4):745-57, vii-viii.

137. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

138. Friedrich-Rust M, Ong M, Martens S, et al. Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis. Gastroenterology. 2008;134(4).

139. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.

140. Fries JF, Williams CA, Morfeld D, et al. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum. 1996 Apr;39(4):616-22.

141. Furst D, Luggen M, Thompson A, et al. Adding leflunomide to patients with active rheumatoid arthritis patients while receiving methotrexate improves physical function and health related quality of life. Arthritis and Rheumatism. 2000;43(Suppl):S344.

142. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Annals of the rheumatic diseases. 2007;66(SUPPL. 3).

143. Furst DE, Keystone EC, Kirkham B, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Annals of the rheumatic diseases. 2008;67(SUPPL. 3).

144. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford, England) 2011;50(1):124-31.

145. GalvaÃ± VG, Oltra MR, Rueda D, et al. Severe acute hepatitis related to hydroxychloroquine in a woman with mixed connective tissue disease. Clinical rheumatology. 2007;26(6):971-2.

146. Gartlehner G, Hansen R, Thieda P, et al. Drug Class Review on Targeted Immune Modulators, Final AHRQ-approved report December 2006, available at http://www.ohsu.edu/drugeffectiveness/reports/draft.cfm. 2006.

147. Gartlehner G, Hansen RA, Jonas BL, et al. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006.

148. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 2005;53(4):573.

149. Genant HK, Peterfy C, Westhovens R. Abatacept sustains inhibition of radiographic progression over 2 years in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from the long-term extension of the AIM trial. Ann Rheum Dis. 2006;65(SUPPL. II):57-8.

150. Genovese M, Kaine J, Lowenstein M. Ocrelizumab, a novel humanized anti-CD20 antibody: Week 72 results from a phase I/II clinical trial in patients with rheumatoid arthritis [abstract]. American College of Rheumatology Annual Meeting. 2007.

151. Genovese MC, Mease PJ, Thomson GT, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol 2007;34(5):1040-50.

152. Gilaberte Y, Coscojuela C, Vazquez C, et al. Perforating folliculitis associated with tumour necrosis factor-alpha inhibitors administered for rheumatoid arthritis. Br J Dermatol. 2007 Feb;156(2):368-71.

153. Gladman DD. Effectiveness of psoriatic arthritis therapies. Semin Arthritis Rheum. 2003 Aug;33(1):29-37.

154. Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 Suppl 2ii14-7.

155. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv.

156. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005;9(26):1-134, iii-iv.

157. Golding A, Haque UJ, Giles JT. Rheumatoid arthritis and reproduction. Rheum Dis Clin North Am. 2007 May;33(2):319-43, vi-vii.

158. Goldman JA, Xia HA, White B, et al. Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept. Ann Rheum Dis. 2006 Dec;65(12):1649-52.

159. Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC, et al. Development of sarcoidosis during etanercept therapy. Arthritis Rheum. 2006 Oct 15;55(5):817-20.

160. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. Ann Intern Med. 1999 Jun 15;130(12):1005-13.

161. Gottlieb AB, Boehncke WH, Darif M. Safety and efficacy of alefacept in elderly patients and other special populations. J Drugs Dermatol. 2005 Nov-Dec;4(6):718-24.

162. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis 2010;69(2):380-6.

163. Greiner A, Plischke H, Kellner H, et al. Association of Anti-Cyclic Citrullinated Peptide Antibodies, Anti-Citrullin Antibodies, and IgM and IgA Rheumatoid Factors with Serological Parameters of Disease Activity in Rheumatoid Arthritis. Ann N Y Acad Sci. 2005 Jun;1050:295-303.

164. Grismer LE, Gill SA, Harris MD. Liver biopsy in psoriatic arthritis to detect methotrexate hepatotoxicity. J Clin Rheumatol. 2001 Aug;7(4):224-7.

165. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest. 2006 Jan;129(1):174-81.

166. HÃ¤kkinen A, Kautiainen H, Hannonen P, et al. Muscle strength, pain, and disease activity explain individual subdimensions of the Health Assessment Questionnaire disability index, especially in women with rheumatoid arthritis. Annals of the rheumatic diseases. 2006;65(1):30-4.

167. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology (Oxford). 2006 Mar;45(3):325-31.

168. Han C, Robinson DW, Jr., Hackett MV, et al. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol. 2006 Nov;33(11):2167-72.

169. Hara M, Abe T, Sugawara S, et al. Efficacy and safety of iguratimod compared with placebo and salazosulfapyridine in active rheumatoid arthritis: a controlled, multicenter, double-blind, parallel-group study. Mod Rheumatol. 2007;17(1):1-9.

170. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35.

171. Hasan U. Tumour necrosis factor inhibitors--what we need to know. N Z Med J. 2006;119(1246):U2336.

172. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med 2001;33(5):350-7.

173. Heiberg MS, Kaufmann C, Rodevand E, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007 Aug;66(8):1038-42.

174. Heiberg MS, RÃ¸devand E, Mikkelsen K, et al. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: Results from a 6-month longitudinal, observational, multicentre study. Annals of the rheumatic diseases 2006;65(10):1379-83.

175. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41.

176. Helliwell PS, Ibrahim G. Ethnic differences in responses to disease modifying drugs. Rheumatology (Oxford). 2003 Oct;42(10):1197-201.

177. Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii3-8.

178. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58(1):15-25.

179. Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: A systematic review of scales in use. Arthritis Care and Research. 2007;57(3):429-39.

180. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med 1996;15(24):2733-49.

181. Hochberg MC, Tracy JK, Flores RH. "Stepping-up" from methotrexate: a systematic review of randomised placebo controlled trials in patients with rheumatoid arthritis with an incomplete response to methotrexate. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii51-4.

182. Hochberg MC, Tracy JK, Hawkins-Holt M, et al. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 2003;62 Suppl 2:ii13-6.

183. Huedo-Medina TB, SÃ¡nchez-Meca J, MarÃ-n-MartÃ-nez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I² Index? Psychological Methods. 2006;11(2):193-206.

184. Hurst NP, Kind P, Ruta D, et al. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997 May;36(5):551-9.

185. Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis. 2006 Sep;65(9):1175-83.

186. Husted JA, Gladman DD, Farewell VT, et al. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum. 2001 Apr;45(2):151-8.

187. Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab

or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 May 30;54(6):1786-94.

188. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A; available at http://www.ich.org/LOB/media/MEDIA436.pdf. 1994.

189. Jansen JP, Crawford B, Bergman G, et al. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health. 2008 Sep-Oct;11(5):956-64.

190. Javitz HS, Ward MM, Farber E, et al. The direct cost of care for psoriasis and psoriatic arthritis in the United States. J Am Acad Dermatol. 2002 Jun;46(6):850-60.

191. Jobanputra P, Barton P, Bryan S, et al. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110.

192. Kaine J, Kivitz A, Birbara C, et al. Effect of adalimumab (HumiraÂ®) on response to pneumococcal and influenza virus vaccines in patients with rheumatoid arthritis (RA). Ann Rheum Dis. 2006;65(SUPPL. II):304.

193. Kaine JL, Kivitz AJ, Birbara C, et al. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol. 2007 Feb;34(2):272-9.

194. Kapetanovic M, Saxne T, Nilsson J. Influenza vaccination as model for testing immune modulation of anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Ann Rheum Dis. 2006;65(SUPPL. II):184.

195. Katchamart W, Ortiz Z, Shea B, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis (an update systematic review and metaanalysis). Arthritis Rheum. 2008;58(SUPPL.).

196. Kavanaugh A, Antoni C, Mease P, et al. Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. J Rheumatol 2006;33(11):2254-9.

197. Kavanaugh A, Krueger GG, Beutler A, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007 Apr;66(4):498-505.

198. Kavanaugh AF, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. J Rheumatol. 2006 Jul;33(7):1417-21.

199. Kievit W, Fransen J, Kupper HH, et al. The drug survival of adalimumab compared to etanercept and infliximab in the treatment of patients with rheumatoid arthritis in daily clinical practice. Ann Rheum Dis. 2006 June 1, 2006;65(Suppl 2):325-.

200. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology 2007;10(1):9-16.

201. Kind P. The EuroQol instrument: An index of health-related quality of life. Quality of life and PharmacoEconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1996.

202. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007(1):CD006356.

203. Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes

in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43(7):1478-87.

204. Kremer J, Westhovens R, Luggen M. Long-term efficacy and safety of abatacept through 3 years of treatment in rheumatoid arthritis patients in the AIM and ATTAIN trials [abstract]. American College of Rheumatology Meeting.

205. Kremer JL, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The LITHE study. Arthritis Rheum 2010.

206. Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. Arthritis Rheum. 1997 May;40(5):984-5.

207. Kremer JM, Caldwell JR, Cannon GW, et al. The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on methotrexate treatment alone: a double-blind placebo-controlled study. Arthritis Rheum. 2000;43(Suppl 9):S224.

208. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):2263-71.

209. Kristensen LE, Christensen R, Bliddal H, et al. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: A systematic literature review. Scandinavian Journal of Rheumatology 2007;36(6):411-7.

210. Laivoranta-Nyman S, Mottonen T, Hannonen P, et al. Association of tumour necrosis factor a, b and c microsatellite polymorphisms with clinical disease activity and induction of remission in early rheumatoid arthritis. Clin Exp Rheumatol. 2006 Nov-Dec;24(6):636-42.

211. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006 May;65(5):637-41.

212. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001 Oct 15;111(6):446-51.

213. Larsen A. Radiological grading of rheumatoid arthritis. An interobserver study. Scand J Rheumatol. 1973;2(3):136-8.

214. Larsen A. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J Rheumatol. 1995;22:1974-5.

215. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh). 1977 Jul;18(4):481-91.

216. Lau J, Ioannidis JPA, Terrin N, et al. The case of the misleading funnel plot. British Medical Journal. 2006;333(7568):597-600.

217. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58(1):26-35.

218. Lee YH, Woo JH, Rho YH, et al. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatology international 2008;28(6):553-9.

219. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68(7):1136-45.

220. Lequerre T, Vittecoq O, Klemmer N, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol. 2006 Jul;33(7):1307-14.

221. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care 2006;44(4):304-10.

222. Liao KP, Batra KL, Chibnik L, et al. Anti-cyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis. Ann Rheum Dis 2008;67(11):1557-61.

223. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum. 2007 Oct;56(10):3248-52.

224. Lindqvist E, Saxne T, Geborek P, et al. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis. 2002 Dec;61(12):1055-9.

225. Lindsay K, Gough A. Psoriatic arthritis, methotrexate and the liver - Are rheumatologists putting their patients at risk? Rheumatology. 2008;47(7):939-41.

226. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther. 2006;8(3):R66.

227. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105-24.

228. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002 Aug 30;21(16):2313-24.

229. MÃ¤ki-PetÃ¤jÃ¤ KM, Booth AD, Hall FC, et al. Ezetimibe and Simvastatin Reduce Inflammation, Disease Activity, and Aortic Stiffness and Improve Endothelial Function in Rheumatoid Arthritis. Journal of the American College of Cardiology. 2007;50(9):852-8.

230. Mader R, Keystone E. Optimizing treatment with biologics. Journal of Rheumatology. 2007;34(SUPPL. 80):16-24.

231. Maetzel A, Wong A, Strand V, et al. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford). 2000 Sep;39(9):975-81.

232. Manadan AM, Mohan AK. Tuberculosis and etanercept treatment. Arthritis Rheum. 2002;46:S166.

233. Marcora SM, Chester KR, Mittal G, et al. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006 Dec;84(6):1463-72.

234. Markham T, Mathews C, Rogers S, et al. Downregulation of the inhibitor of apoptosis protein survivin in keratinocytes and endothelial cells in psoriasis skin following infliximab therapy. British Journal of Dermatology. 2006;155(6):1191-6.

235. Martin M, Kosinski M, Bjorner JB, et al. Item response theory methods can improve the measurement of physical function by combining the modified health assessment questionnaire and the SF-36 physical function scale. Qual Life Res. 2007 May;16(4):647-60.

236. Mau W, Listing J, Huscher D, et al. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol. 2005 Apr;32(4):721-8.

237. McHorney CA, Ware JE, Jr., Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994 Jan;32(1):40-66.

238. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health

Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247-63.

239. McHorney CA, Ware JE, Jr., Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992 May;30(5 Suppl):MS253-65.

240. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nature Reviews Immunology. 2007;7(6):429-42.

241. Mease P. Psoriatic arthritis update. Bulletin of the NYU Hospital for Joint Diseases. 2006;64(1-2):25-31.

242. Mease PJ, Antoni CE, Gladman DD, et al. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii49-54.

243. Mease PJ, Gladman DD, Keystone EC. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2006 May;54(5):1638-45.

244. Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum. 2003 Oct;48(10):2750-62.

245. Miller LG, Hays RD. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. AIDS Read. 2000 Mar;10(3):177-85.

246. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999 Nov 27;354(9193):1896-900.

247. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336-41.

248. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997 Jul 17;337(3):141-7.

249. Moreland LW, Cohen SB, Baumgartner S, et al. Long-term use of etanercept in patients with DMARD-refractory arthritis. Arthritis Rheum. 1992;42(Suppl 9):S401.

250. Moreland LW, Genovese MC, Sato R, et al. Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):287-93.

251. Moreland LW, Weinblatt ME, Keystone EC, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. J Rheumatol. 2006 May;33(5):854-61.

252. Moss ML, Sklair-Tavron L, Nudelman R. Drug Insight: Tumor necrosis factor-converting enzyme as a pharmaceutical target for rheumatoid arthritis. Nature Clinical Practice Rheumatology. 2008;4(6):300-9.

253. Mroczkowski PJ, Weinblatt ME, Kremer JM. Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S66-8.

254. Muller-Ladner U, Pap T, Gay RE, et al. Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheumatol. 2005 Dec;1(2):102-10.

255. Multi-Parameter Evidence Synthesis (MPES) Research Group. Available at: https://www.bris.ac.uk/cobm/research/mpes/mtc.html.

256. Munafo A, Priestley A, Nestorov I, et al. Safety, pharmacokinetics and pharmacodynamics of atacicept in healthy volunteers. European Journal of Clinical Pharmacology. 2007;63(7):647-56.

257. Munoz P, Giannella M, Valerio M, et al. Cryptococcal meningitis in a patient treated

with infliximab. Diagn Microbiol Infect Dis. 2007 Apr;57(4):443-6.

258. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69(6):976-86.

259. Nash P. Therapies for axial disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1431-4.

260. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-Î± therapy: Guidelines for clinical approach. Journal of Gastroenterology and Hepatology. 2006;21(9):1366-71.

261. Nishimoto N, Kishimoto T. Humanized antihuman IL-6 receptor antibody, tocilizumab. Handbook of experimental pharmacology. 2008(181):151-60.

262. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Statistics in Medicine. 2007;26(6):1237-54.

263. Norris SL, Atkins D. Challenges in using nonrandomized studies in systematic reviews of treatment interventions. Ann Intern Med. 2005 Jun 21;142(12 Pt 2):1112-9.

264. O'Dell J, Leff R, Paulsen G, et al. Methotrexate (M)-Hydroxychloroquine (H)-Sulfasalazine (S) versus M-H or M-S for rheumatoid arthritis (RA): results of a double-blind study. Arthritis Rheum. 1999;42(Suppl 9):S117.

265. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996 May 16;334(20):1287-91.

266. Ogrendik M. Levofloxacin treatment in patients with rheumatoid arthritis receiving methotrexate. South Med J. 2007 Feb;100(2):135-9.

267. Ohsugi Y. Recent advances in immunopathophysiology of interleukin-6: An innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. Biological and Pharmaceutical Bulletin. 2007;30(11):2001-6.

268. Ojeda-Uribe M, Gilliot C, Jung G, et al. Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. Journal of Perinatology. 2006;26(4):252-5.

269. Okada SK, Siegel JN. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. Jama. 2006 Nov 8;296(18):2201-2; author reply 3-4.

270. Olivieri I, Mantovani LG, D'Angelo S, et al. Psoriatic arthritis: pharmacoeconomic considerations. Curr Rheumatol Rep 2009;11(4):263-9.

271. Oren C, Mendelbaum M, Paran D. Vaccination against influenza in rheumatoid arthritis patients: The effect of rituximab on the humoral response. Arthritis Rheum 2006;54(SUPPL. 9).

272. Ornetti P, Chevillotte H, Zerrak A, et al. Anti-tumour necrosis factor-alpha therapy for rheumatoid and other inflammatory arthropathies: update on safety in older patients. Drugs Aging. 2006;23(11):855-60.

273. Orozco G, Rueda B, Martin J. Genetic basis of rheumatoid arthritis. Biomed Pharmacother. 2006 Dec;60(10):656-62.

274. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis. 2003 Jul;62(7):597-604.

275. Ostergaard M, Baslund B, Rigby W. Ofatumumab, a human CD20 monoclonal antibody, in the treatment of rheumatoid

arthritis: Early results from an ongoing, double-blind, randomized, placebo-controlled clinical trial [abstract]. American College of Rheumatology Annual Meeting. 2007.

276. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23.

277. Ozminkowski RJ, Burton WN, Goetzel RZ, et al. The impact of rheumatoid arthritis on medical expenditures, absenteeism, and short-term disability benefits. J Occup Environ Med. 2006 Feb;48(2):135-48.

278. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev 2010;9(3):175-80.

279. Papp KA, Caro I, Leung HM, et al. Efalizumab for the treatment of psoriatic arthritis. J Cutan Med Surg. 2007 Mar-Apr;11(2):57-66.

280. Pieringer H, Stuby U, Biesenbach G. Patients with Rheumatoid Arthritis Undergoing Surgery: How Should We Deal with Antirheumatic Treatment? Seminars in Arthritis and Rheumatism. 2007;36(5):278-86.

281. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol. 1992 Dec;19(12):1885-94.

282. Pincus T, O'Dell JR, Kremer JM. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. Ann Intern Med. 1999 Nov 16;131(10):768-74.

283. Pincus T, Yazici Y, Bergman M. A practical guide to scoring a Multi-Dimensional Health Assessment Questionnaire (MDHAQ) and Routine Assessment of Patient Index Data (RAPID) scores in 10-20 seconds for use in standard clinical care, without rulers, calculators, websites or computers. Best Practice and Research: Clinical Rheumatology. 2007;21(4):755-87.

284. Pinzani M, Vizzutti F, Arena U, et al. Technology Insight: Noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nature Clinical Practice Gastroenterology and Hepatology. 2008;5(2):95-106.

285. Popovic M, Stefanovic D, Pejnovic N, et al. Comparative study of the clinical efficacy of four DMARDs (leflunomide, methotrexate, cyclosporine, and levamisole) in patients with rheumatoid arthritis. Transplant Proc. 1998 Dec;30(8):4135-6.

286. Pouchot J. How can we improve the management of adult-onset Still's disease? Joint Bone Spine. 2007 Mar;74(2):117-9.

287. Prevoo ML, van Gestel AM, van THMA, et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996 Nov;35(11):1101-5.

288. Pugner KM, Scott DI, Holmes JW, et al. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum. 2000 Apr;29(5):305-20.

289. Quinn MA, Conaghan PG, O'Connor PJ. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: Results from a twelve-month ran-liver disease? Hepatology. 2006;43:352-61.

290. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 -- Status and Review. In: Spilker B, ed. Quality of Life and Pharmacoleconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven Publischers 1996:227-37.

291. Ranganath VK, Furst DE. Disease-modifying antirheumatic drug use in the

elderly rheumatoid arthritis patient. Rheum Dis Clin North Am. 2007 Feb;33(1):197-217.

292. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. Annals of the rheumatic diseases 2008;67(6):855-9.

293. Reddy SM, Bingham Iii CO. Outcome measures in psoriatic arthritis clinical trials. Curr Rheumatol Rep 2005;7(4):299-305.

294. Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. Br J Dermatol. 2006 Jun;154(6):1161-8.

295. Rioda WT, Adorni G. Infliximab treatment in psoriatic arthritis: our experience. Acta Biomed. 2006 Aug;77(2):95-102.

296. Ritchie DA, Boyle JA, McInnes JM, et al. Evaluation of a simple articular index for joint tenderness in rheumatoid arthritis. Ann Rheum Dis. 1969 Mar;28(2):196.

297. Ritchie DM, Boyle JA, McInnes JM, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med. 1968 Jul;37(147):393-406.

298. Ritchlin CT, Kavanaugh A, Gladman DD, et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis. 2009 Sep;68(9):1387-94.

299. Roux CH, Brocq O, Breuil V, et al. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-Î± therapy. Rheumatology. 2007;46(4):695-8.

300. Ruderman EM, Markenson J. Granulomatous infections and tumor necrosis factor antagonists therapy: update through June 2002. Arthritis Rheum. 2003;48(9):S241.

301. Saad AA, Ashcroft DM, Watson KD, et al. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther 2009;11(2):R52.

302. Saag KG, Gim GT, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care and Research. 2008;59(6):762-84.

303. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology. 2006 July 31, 2006:kel236.

304. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-Î± blocker therapy for rheumatic diseases in daily practice: A systematic retrospective study of 709 patients. Rheumatology 2007;46(2):327-34.

305. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics 1999;15(2):141-55.

306. Sauriol L, Laporta M, Edwardes MD, et al. Meta-analysis comparing newer antipsychotic drugs for the treatment of schizophrenia: evaluating the indirect approach. Clin Ther. 2001 Jun;23(6):942-56.

307. Sbeity ZH, Baydoun L, Schmidt S, et al. Visual field changes in methotrexate therapy. Case report and review of the literature. J Med Liban. 2006 Jul-Sep;54(3):164-7.

308. Schaible TF. Long term safety of infliximab. Can J Gastroenterol. 2000 Sep;14 Suppl C:29C-32C.

309. Schardt C, Adams MB, Owens T, et al. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Medical Informatics and Decision Making. 2007;7.

310. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jul;65(7):889-94.

311. Schuna AA. Rituximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2007;27(12 I):1702-10.

312. Scott DL, Coulton BL, Bacon PA, et al. Methods of X-ray assessment in rheumatoid arthritis: a re-evaluation. Br J Rheumatol. 1985 Feb;24(1):31-9.

313. Scott DL, Houssien DA, Laasonen L. Proposed modification to Larsen's scoring methods for hand and wrist radiographs. Br J Rheum. 1995;34:56.

314. Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64.

315. Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum. 1985 Dec;28(12):1326-35.

316. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7.

317. Smolen JS, Aletaha D, Keystone E. Superior efficacy of combination therapy for rheumatoid arthritis: fact or fiction? Arthritis Rheum. 2005 Oct;52(10):2975-83.

318. Smolen JS, Keystone EC, Emery P, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2007;66(2):143-50.

319. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-75.

320. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol. 2003 Jun;30(6):1138-46.

321. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol. 2001 Aug;28(8):1842-6.

322. Solomon DH. The comparative safety and effectiveness of TNF-alpha antagonists [corrected]. J Manag Care Pharm. 2007 Jan;13(1 Suppl):S7-18.

323. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. Bmj. 2003 Mar 1;326(7387):472.

324. Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1422-30.

325. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988 Jul;26(7):724-35.

326. Stewart AL, Ware JE. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992.

327. Strand. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: Evidence from randomized controlled trials (American Journal of Managed Care). American Journal of Managed Care. 2008;14(4):234.

328. Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2

years. Rheumatology (Oxford) 2006;45(12):1505-13.

329. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 1999 Sep;42(9):1870-8.

330. Szekanecz Z, Koch AE. Macrophages and their products in rheumatoid arthritis. Current Opinion in Rheumatology. 2007;19(3):289-95.

331. Tak PP, Thurlings RM, Rossier C, et al. Atacicept in patients with rheumatoid arthritis: Results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. Arthritis and rheumatism. 2008;58(1):61-72.

332. Tanaka Y. Biologics: current therapeutic strategies for rheumatoid arthritis. Nippon rinsho Japanese journal of clinical medicine. 2007;65(7):1179-84.

333. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.

334. Tilg H, Kaser A, Moschen AR. How to modulate inflammatory cytokines in liver diseases. Liver International. 2006;26(9):1029-39.

335. Todd DJ, Costenbader KH, Weinblatt ME. Abatacept in the treatment of rheumatoid arthritis. International Journal of Clinical Practice. 2007;61(3):494-500.

336. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. Pharmacology and Therapeutics. 2008;117(2):244-79.

337. Tugwell P, Wells G, Strand V, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis: sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 2000 Mar;43(3):506-14.

338. Turesson C, Schaid DJ, Weyand CM, et al. The impact of HLA-DRB1 genes on extra-articular disease manifestations in rheumatoid arthritis. Arthritis Res Ther. 2005;7(6):R1386-93.

339. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999 Mar;26(3):743-5.

340. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000 Jan;27(1):261-3.

341. van der Heijde D, Da Silva JC, Dougados M, et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. Ann Rheum Dis. 2006 Dec;65(12):1572-7.

342. van der Heijde D, Dankert T, Nieman F, et al. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford). 1999 Oct;38(10):941-7.

343. van der Heijde D, Kavanaugh A, Gladman DD, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum 2007;56(8):2698-707.

344. van der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56(12):3928-39.

345. van der Heijde DM. Overview of radiologic efficacy of new treatments. Rheum Dis Clin North Am. 2004 May;30(2):285-93, vi.

346. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 1992 Jan;35(1):26-34.

347. van Dongen H, van Aken J, Lard LR, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2007 May;56(5):1424-32.

348. van Gestel AM, Anderson JJ, van Riel PL, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. J Rheumatol 1999;26(3):705-11.

349. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39(1):34-40.

350. van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Ann Rheum Dis. 2006 Feb 7.

351. van Tuyl LH, Vlad SC, Felson DT, et al. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum 2009;61(5):704-10.

352. Verhoeven AC, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systematic review. Br J Rheumatol. 1998 Jun;37(6):612-9.

353. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Annals of the rheumatic diseases. 2009;68(7):1086-93.

354. Visvanathan S, Keenan GF, Baker DG, et al. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. J Rheumatol. 2007 May;34(5):952-7.

355. Visvanathan S, Marini JC, Smolen JS, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1465-74.

356. Wailoo A, Brennan A, Bansback N, et al. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program. AHRQ Technology Assessment Program. 2006.

357. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004 May 1;38(9):1261-5.

358. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes 2003;14.

359. Ware JE, Jr., Kosinski M, Bayliss MS, et al. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care. 1995 Apr;33(4 Suppl):AS264-79.

360. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.

361. Ware JE, Snow KK, Kosinski M, et al. SF-36® Health Survey Manual and Interpretation Guide. 1993.

362. Weinblatt ME, Bathon JM, Kremer JM, et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010.

363. Weinblatt ME, Keystone EC, Furst DE, et al. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis. 2006 Jun;65(6):753-9.

364. Weinblatt ME, Kremer JM, Coblyn JS, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum. 1999 Jul;42(7):1322-8.

365. Wells GA, Sultan SA, Chen L. Indirect evidence: Indirect treatment comparisons in meta-analysis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2009.

366. Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20(3):557-60.

367. Welton NJ, Caldwell DM, Adamopoulos E, et al. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol 2009;169(9):1158-65.

368. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006 Oct;45(10):1238-46.

369. Whitehead A. Meta-analysis of controlled clinical trials. Chichester, UK: John Wiley & Sons, Ltd.; 2002.

370. Willkens RF, Williams HJ, Ward JR, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27(4):376-81.

371. Wood AJ. Thrombotic thrombocytopenic purpura and clopidogrel--a need for new approaches to drug safety. N Engl J Med. 2000 Jun 15;342(24):1824-6.

372. Woolacott N, Bravo Vergel Y, Hawkins N, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):1-258.

373. Yamamoto M, Takahashi H, Ohara M, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. Mod Rheumatol. 2006;16(6):335-40.

374. Yamanaka H, Inoue E, Tanaka E, et al. Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: Evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). Modern Rheumatology. 2007;17(2):98-105.

375. Yelin E. Work disability in rheumatic diseases. Current Opinion in Rheumatology. 2007;19(2):91-6.

376. Young MS, Furfaro N. The rheumatology/dermatology collaboration. Dermatol Nurs. 2006 Oct;Suppl:10-22.

377. Zachariae H, Zachariae R, Blomqvist K, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol. 2002;82(2):108-13.

378. Zhao LK, Liao ZT, Li CH, et al. Evaluation of quality of life using ASQoL questionnaire in patients with ankylosing spondylitis in a Chinese population. Rheumatol Int. 2007 May;27(7):605-11.

379. Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 Nov;54(11):3399-407.

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Reference Source: EMBASE

1. Abrahamian H, Endler G, Exner M, et al. Association of low-grade inflammation with nephropathy in type 2 diabetic patients: role of elevated CRP-levels and 2 different gene-polymorphisms of proinflammatory cytokines. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2007(1):38-41.

2. Abrahamyan L, Beyene J, Feng J, et al. Response times follow lognormal or gamma distribution in arthritis patients. Journal of Clinical Epidemiology. 2010;63(12):1363-9.

3. Accardo S, Seriolo B, Samanta E, et al. Controlled-Release Naproxen in Rheumatoid Arthritis. CURR THER RES CLIN EXP. 1991;49I(6):936-42.

4. Adams J, Burridge J, Mullee M, et al. The clinical effectiveness of static resting splints in early rheumatoid arthritis: A randomized controlled trial. Rheumatology. 2008;47(10):1548-53.

5. Agnew-Blais JC, Coblyn JS, Katz JN, et al. Measuring quality of care for rheumatic diseases using an electronic medical record. Annals of the Rheumatic Diseases. 2009;68(5):680-4.

6. Aguilar-Chavez EA, Gamez-Nava JI, Lopez-Olivo MA, et al. Circulating leptin and bone mineral density in rheumatoid arthritis. Journal of Rheumatology. 2009;36(3):512-6.

7. Ahern MJ, Wetherall M, Leslie A, et al. A Comparison of Ketoprofen Sr and Sulindac in the Elderly With Rheumatoid Arthritis. Br J Clin Pract. 1992;46(4):229-33.

8. Alarcon G, Castaneda O, Nair M, et al. Controlled Trial of Methotrexate Versus 10-Deazaaminopterin in the Treatment of Rheumatoid Arthritis. Ann Rheum Dis. 1992;51(5):600-3.

9. Alarcon GS, Castaneda O, Ferrandiz M, et al. Efficacy and Safety of 10-Deazaaminopterin in the Treatment of Rheumatoid Arthritis. A One-Year Continuation, Double-Blind Study. Arthritis Rheum. 1992;35(11):1318-21.

10. Alarcon I, Moreland G, Jaffe L, et al. The Use of Methotrexate Perioperatively in Patients With Rheumatoid Arthritis Undergoing Major Joint Replacement Surgery: Will We Ever Have Consensus About Its Use? J Clin Rheumatol. 1996;2(1):6-8.

11. Albert DA, Huang G, Dubrow G, et al. Criteria for Improvement in Rheumatoid Arthritis: Alternatives to the American College of Rheumatology 20. J Rheumatol. 2004;31(5):856-66.

12. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis and Rheumatism. 2006;54(9):2784-92.

13. Ali ML, Alam MN, Haq SA, et al. Efficacy of Methotrexate in Rheumatoid Arthritis. Bangladesh Medical Research Council bulletin. 1997;23(3):72-6.

14. Allen ZA, Shanahan EM, Crotty M. Does suprascapular nerve block reduce shoulder pain following stroke: A double-blind randomised controlled trial with masked outcome assessment. BMC Neurology. 2010;10.

15. Almarzouqi M, Scarsbrook D, Klinkhoff A. Gold therapy in women planning pregnancy: Outcomes in one center. Journal of Rheumatology. 2007;34(9):1827-31.

16. Alten R, Doring G, Cutolo M, et al. Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. Journal of Rheumatology. 2010;37(10):2025-31.

17. Alten R, Gromnica-Ihle E, Pohl C, et al. Inhibition of Leukotriene B4-Induced Cd11b/Cd18 (Mac-1) Expression by Biil 284, a New Long Acting Ltb4 Receptor Antagonist, in Patients With Rheumatoid

Arthritis. Annals of the rheumatic diseases. 2004;63(2):170-6.

18. Alten RE, Zerbini C, Jeka S, et al. Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. 2010.

19. Anaya JM, Fabre D, Bressolle F, et al. Effect of Etodolac on Methotrexate Pharmacokinetics in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1994;21(2):293-8.

20. Anders HJ, Rihl M, Loch O, et al. Prediction of Creatinine Clearance From Serum Creatinine in Patients With Rheumatoid Arthritis: Comparison of Six Formulae and One Nomogram. Clinical rheumatology. 2000;19(1):26-9.

21. Andersen LS, Hansen EL, Knudsen JB, et al. Prospectively Measured Red Cell Folate Levels in Methotrexate Treated Patients With Rheumatoid Arthritis: Relation to Withdrawal and Side Effects. The Journal of rheumatology. 1997;24(5):830-7.

22. Anderson JJ, O'Neill A, Woodworth T, et al. Health Status Response of Rheumatoid Arthritis to Treatment With Dab486il-2. Arthritis care and research : the official journal of the Arthritis Health Professions Association. 1996;9(2):112-9.

23. Anderson KO, Bradley LA, Turner RA, et al. Pain Behavior of Rheumatoid Arthritis Patients Enrolled in Experimental Drug Trials. Arthritis care and research : the official journal of the Arthritis Health Professions Association. 1994;7(2):64-8.

24. Andrianakos A, Trontzas P, Christoyannis F, et al. Prevalence and management of rheumatoid arthritis in the general population of Greece - The ESORDIG study. Rheumatology. 2006;45(12):1549-54.

25. Antoni C, Kalden J. Combination Therapy of the Chimeric Monoclonal Anti-Tumor Necrosis Factor Alpha Antibody (Infliximab) With Methotrexate in Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6 Suppl 18):S73-7.

26. Appel H, Mertz A, Distler A, et al. The 19 Kda Protein of Yersinia Enterocolitica O:3 Is Recognized on the Cellular and Humoral Level by Patients With Yersinia Induced Reactive Arthritis. J Rheumatol 1999 Sep;26(9):1964-71. 1999;26(9):1964-71.

27. April P, Abeles M, Baraf H, et al. Does the Acetyl Group of Aspirin Contribute to the Antiinflammatory Efficacy of Salicylic Acid in the Treatment of Rheumatoid Arthritis? Seminars in arthritis and rheumatism. 1990;19(4 Suppl 2):20-8.

28. Arborelius MJ, Konttinen YT, Nordstrom DC, et al. Gly-X-Y Repeat Sequences in the Treatment of Active Rheumatoid Arthritis. Rheumatology international. 1999;18(4):129-35.

29. Arendt-Nielsen L, Drewes AM, Svendsen L, et al. Quantitative Assessment of Joint Pain Following Treatment of Rheumatoid Arthritis With Ibuprofen Cream. Scandinavian journal of rheumatology. 1994;23(6):334-7.

30. Arnold MH, O'Callaghan J, McCredie M, et al. Comparative Controlled Trial of Low-Dose Weekly Methotrexate Versus Azathioprine in Rheumatoid Arthritis: 3-Year Prospective Study. British journal of rheumatology. 1990;29(2):120-5.

31. Arvidson NG, Gudbjornsson B, Larsson A, et al. The Timing of Glucocorticoid Administration in Rheumatoid Arthritis. Annals of the rheumatic diseases. 1997;56(1):27-31.

32. Aryaeian N, Shahram F, Djalali M, et al. Effect of conjugated linoleic acids, vitamin E and their combination on the clinical outcome of Iranian adults with active rheumatoid arthritis. International Journal of Rheumatic Diseases. 2009;12(1):20-8.

33. Asahina A, Nakagawa H, Etoh T, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: Efficacy and safety results from a Phase II/III randomized controlled study. Journal of Dermatology. 2010;37(4):299-310.

34. Assous N, Gossec L, Dougados M, et al. Efficacy of rituximab in patients with

rheumatoid arthritis refractory or with contra-indication to anti-tumor necrosis factor-alpha drugs in daily practice: An open label observational study [3]. Clinical and Experimental Rheumatology. 2007;25(3).

35. Astrauskiene D. Efficacy of Empirically Prescribed Amoxicillin and Amoxicillin + Clavulanic Acid in Children's Reactive Arthritis: a Randomised Trial. Clinical and experimental rheumatology. 2003;21(4):515-21.

36. Atkinson M, Khanna V, Menard H, et al. A Comparison of Tenoxicam and Piroxicam in the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 1992;19(4):538-42.

37. Atkinson MH, Buchanan WW, Fitzgerald AA, et al. A Comparison of Flurbiprofen and Naproxen in the Treatment of Rheumatoid Arthritis: a Canadian Multi-Centre Study. Current medical research and opinion. 1990;12(2):76-85.

38. Azuma T, Oishi M, Takei M, et al. Tacrolimus-related nocturnal myoclonus of the lower limbs in elderly patients with rheumatoid arthritis. Modern Rheumatology. 2007;17(3):247-50.

39. Bacon P, Luqmani RA, Bossingham DH, et al. A Comparison of Two Formulations of Indomethacin ('flexin Continus' Tablets and 'indocid' Capsules) in the Treatment of Rheumatoid Arthritis. Current medical research and opinion. 1990;12(2):128-34.

40. Baerwald C, Goebel KM, Krause A, et al. A randomized controlled trial of ciamexon versus placebo in the immunomodulatory treatment of rheumatoid arthritis. Arthritis Rheum. 1990 May;33(5):733-8.

41. Bagge E, Geijer M, Tarkowski A. Intra-Articular Administration of Polyclonal Immunoglobulin G in Rheumatoid Arthritis. A Double-Blind, Placebo-Controlled Pilot Study. Scandinavian journal of rheumatology. 1996;25(3):174-6.

42. Bahadori B, Uitz E, Thonhofer R, et al. (omega)-3 fatty acids infusions as adjuvant therapy in rheumatoid arthritis. Journal of Parenteral and Enteral Nutrition. 2010;34(2):151-5.

43. Bakker MF, Jacobs JWG, Welsing PMJ, et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Annals of the rheumatic diseases. 2010;69(10):1849-52.

44. Barnett ML, Kremer JM, St Clair EW, et al. Treatment of Rheumatoid Arthritis With Oral Type Ii Collagen. Results of a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1998;41(2):290-7.

45. Barrera P, Boerbooms AM, Demacker PN, et al. Circulating Soluble Tumor Necrosis Factor Receptors, Interleukin-2 Receptors, Tumor Necrosis Factor Alpha, and Interleukin-6 Levels in Rheumatoid Arthritis. Longitudinal Evaluation During Methotrexate and Azathioprine Therapy. Arthritis and rheumatism. 1994;33(11):1017-24.

46. Barrera P, Haagsma C, Boerbooms A, et al. Effect of Methotrexate Alone or in Combination With Sulphasalazine on the Production and Circulating Concentrations of Cytokines and Their Antagonists. Longitudinal Evaluation in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1995;34(8):747-55.

47. Barrera P, Joosten LA, den Broeder AA, et al. Effects of Treatment With a Fully Human Anti-Tumour Necrosis Factor Alpha Monoclonal Antibody on the Local and Systemic Homeostasis of Interleukin 1 and Tnfalpha in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2001;60(7):660-9.

48. Barrera P, van der Maas A, van Ede AE, et al. Drug Survival, Efficacy and Toxicity of Monotherapy With a Fully Human Anti-Tumour Necrosis Factor-a Antibody Compared With Methotrexate in Long-Standing Rheumatoid Arthritis. Rheumatology 2002;41(4):430-9.

49. Baslund B, Tvede N, Danneskiold-Samsoe B, et al. Targeting Interleukin-15 in Patients With Rheumatoid Arthritis: a Proof-of-Concept Study. Arthritis and rheumatism. 2005;52(9):2686-92.

50. Bateman J, Penfold R, Rigby SP. Comment on: Kidney disease in RA patients: Prevalence and implication on RA-related drugs management: The MATRIX study. Rheumatology. 2008;47(8).

51. Battistone MJ, Manaster BJ, Reda DJ, et al. The Prevalence of Sacroilitis in Psoriatic Arthritis: New Perspectives From a Large, Multicenter Cohort. A Department of Veterans Affairs Cooperative Study. Skeletal radiology. 1999;28(4):196-201.

52. Bazzani C, Filippini M, Caporali R, et al. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: Clinical outcomes. Autoimmunity Reviews 2009;8(3):260-5.

53. Beard AJ, Sleath B, Blalock SJ, et al. Predictors of rheumatoid arthritis patient-physician communication about medication costs during visits to rheumatologists. Arthritis Care and Research. 2010;62(5):632-9.

54. Bejarano V, Conaghan PG, Proudman SM, et al. Long-term efficacy and toxicity of ciclosporin A in combination with methotrexate in poor prognosis rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009;68(5):761-3.

55. Bejarano V, Conaghan PG, Quinn MA, et al. Benefits 8 years after a remission induction regime with an infliximab and methotrexate combination in early rheumatoid arthritis. Rheumatology. 2010;49(10):1971-4.

56. Benenson E, Timina O. Prospidine Versus Methotrexate Pulse in Highly Active Rheumatoid Arthritis: a Controlled 6-Month Clinical Trial. Clinical rheumatology. 1994;13(1):54-9.

57. Bengtsson A, Bengtsson M, Nilsson I, et al. Effects of Intravenous Regional Administration of Methylprednisolone Plus Mepivacaine in Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1998;27(4):277-80.

58. Benitha R, Tikly M. Functional disability and health-related quality of life in South Africans with rheumatoid arthritis and systemic lupus erythematosus. Clinical Rheumatology. 2007;26(1):24-9.

59. Bensen W, Weaver A, Espinoza L, et al. Efficacy and Safety of Valdecoxib in Treating the Signs and Symptoms of Rheumatoid Arthritis: a Randomized, Controlled Comparison With Placebo and Naproxen. Rheumatology (Oxford). 2002;41(9):1008-16.

60. Berliner MN, Giesecke T, Bornhovd KD. Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. Clinical Journal of Pain. 2007;23(6):530-4.

61. Bianchi L, Giunta A, Papoutsaki M, et al. Efficacy and safety of long-term infliximab therapy in moderate to severe psoriasis and psoriatic arthritis. Giornale Italiano di Dermatologia e Venereologia. 2006;141(1):73-8.

62. Bianchi Porro G, Montrone F, Lazzaroni M, et al. Clinical and Gastroscopic Evaluation of Amtolmetin Guacyl Versus Diclofenac in Patients With Rheumatoid Arthritis. Ital J Gastroenterol Hepatol. 1999;31(5):378-85.

63. Bingham ICO, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. 2010.

64. Bird H, Broggini M. Paroxetine Versus Amitriptyline for Treatment of Depression Associated With Rheumatoid Arthritis: a Randomized, Double Blind, Parallel Group Study. The Journal of rheumatology. 2000;27(12):2791-7.

65. Blackburn WDJ, Prupas HM, Silverfield JC, et al. Tenidap in Rheumatoid Arthritis. A 24-Week Double-Blind Comparison With Hydroxychloroquine-Plus-Piroxicam, and Piroxicam Alone. Arthritis and rheumatism. 1995;38(10):1447-56.

66. Bluhm GB, Sharp JT, Tilley BC, et al. Radiographic Results From the Minocycline in Rheumatoid Arthritis (Mira) Trial. The Journal of rheumatology. 1997;24(7):1295-302.

67. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000;343(21):1520-8.

68. Bombardier C, Peloso P, Goldsmith C. Salsalate, a Nonacetylated Salicylate, Is as Efficacious as Diclofenac in Patients With Rheumatoid Arthritis. Salsalate-Diclofenac Study Group. The Journal of rheumatology. 1995;22(4):617-24.

69. Bonilla E, Lee YY, Phillips PE, et al. Hypoglycaemia after initiation of treatment with etanercept in a patient with type 2 diabetes mellitus [5]. Annals of the Rheumatic Diseases. 2007;66(12).

70. Borg AA, Davis MJ, Fowler PD, et al. Rifampicin in Early Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1993;22(2):39-42.

71. Borg G, Allander E, Berg E, et al. Auranofin Treatment in Early Rheumatoid Arthritis May Postpone Early Retirement. Results From a 2-Year Double Blind Trial. The Journal of rheumatology. 1991;18(7):1015-20.

72. Borrs-Blasco J, Gracia-Prez A, Rosique-Robles JD, et al. Acceptability of switching adalimumab from a prefilled syringe to an autoinjection pen. Expert Opinion on Biological Therapy. 2010;10(3):301-7.

73. Bos WH, Dijkmans BAC, Boers M, et al. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: A randomised trial. Annals of the rheumatic diseases. 2010;69(3):571-4.

74. Bourikas LA, Sidiropoulos PI, Goulielmos GN, et al. Concomitant onset of Graves disease and rheumatoid arthritis after a serious life event [5]. Journal of Clinical Rheumatology. 2006;12(6):326-7.

75. Bradley JD, Dmitrienko AA, Kivitz AJ, et al. A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial of Ly333013, a Selective Inhibitor of Group Ii Secretory Phospholipase A2, in the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 2005;32(3):417-23.

76. Breedveld FC, Han C, Bala M, et al. Association Between Baseline Radiographic Damage and Improvement in Physical Function After Treatment of Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2005;64(1):52-5.

77. Bressolle F, Kinowski J, Morel J, et al. Folic Acid Alters Methotrexate Availability in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2000;27(9):2110-4.

78. Bridges Jr SL, Causey ZL, Burgos PI, et al. Radiographic severity of rheumatoid arthritis in African Americans: Results from a multicenter observational study. Arthritis Care and Research. 2010;62(5):624-31.

79. Brooks PJ, Spruill WJ, Parish RC, et al. Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients With Rheumatoid Arthritis. Arthritis & Rheumatism. 1990;33(1):91-4.

80. Buchanan WW, Kean WF, St-Jean J, et al. Clinical Evaluation of a Sustained Release Compared to a Standard Formulation of Tiaprofenic Acid (Surgam (R)) in Rheumatoid Arthritis: a Canadian Multicenter Study. J RHEUMATOL. 1991;18(7):1046-54.

81. Buckley L, Vacek P, Cooper S. Administration of Folinic Acid After Low Dose Methotrexate in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1990;17(9):1158-61.

82. Cacace E, Anedda C, Ruggiero V, et al. Etanercept in rheumatoid arthritis: Long term anti-inflammatory efficacy in clinical practice. European Journal of Inflammation. 2006;4(3):171-6.

83. Caldwell J. Comparison of the Efficacy, Safety, and Pharmacokinetic Profiles of Extended-Release Ketoprofen and Piroxicam in Patients With Rheumatoid Arthritis. Clinical therapeutics. 1994;16(2):222-35.

84. Calguneri M, Pay S, Caliskaner Z, et al. Combination Therapy Versus Monotherapy for the Treatment of Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6):699-704.

85. Camp NJ, Cox A, di Giovine FS, et al. Evidence of a Pharmacogenomic Response to Interleukin-L Receptor Antagonist in Rheumatoid Arthritis. Genes Immun. 2005;6(6):467-71.

86. Cannon GW, Reading JC, Ward JR, et al. Clinical and Laboratory Outcomes During the Treatment of Rheumatoid Arthritis With Methotrexate. Scandinavian journal of rheumatology. 1990;19(4):285-94.

87. Cantatore F, Acquista C, Pipitone V. Evaluation of Bone Turnover and Osteoclastic Cytokines in Early Rheumatoid Arthritis Treated With Alendronate. The Journal of rheumatology. 1999;41(3):247-51.

88. Capell H, Maiden N, Madhok R, et al. Intention-to-Treat Analysis of 200 Patients With Rheumatoid Arthritis 12 Years After Random Allocation to Either Sulfasalazine or Penicillamine. The Journal of rheumatology. 1998;25(10):1880-6.

89. Capell H, Marabani M, Madhok R, et al. Degree and Extent of Response to Sulphasalazine or Penicillamine Therapy for Rheumatoid Arthritis: Results From a Routine Clinical Environment Over a Two-Year Period. The Quarterly journal of medicine. 1990;75(276):335-44.

90. Caperton E, Heim Duthoy K, Matzke G, et al. Ceftriaxone Therapy of Chronic Inflammatory Arthritis. A Double-Blind Placebo Controlled Trial. Archives of internal medicine. 1990;150(8):1677-82.

91. Carmichael S, Beal J, Day R, et al. Combination Therapy With Methotrexate and Hydroxychloroquine for Rheumatoid Arthritis Increases Exposure to Methotrexate. The Journal of rheumatology. 2002;29(10):2077-83.

92. Carpenter M, West S, Vogelgesang S, et al. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics. 1996;19(3):207-10.

93. Carpentier N, Bertin P, Marquet P, et al. Is There an Optimal Time to Administer Methotrexate in the Treatment of Rheumatoid Arthritis? The Journal of rheumatology. 1998;25(7):1270-5.

94. Cavazzana I, Franceschini F, Quinzanini M, et al. Anti-Ro/SSA antibodies in rheumatoid arthritis: Clinical and immunologic associations. Clinical and Experimental Rheumatology. 2006;24(1):59-64.

95. Cazzola M, Antivalle M, Sarzi Puttini P, et al. Oral Type Ii Collagen in the Treatment of Rheumatoid Arthritis. A Six-Month Double Blind Placebo-Controlled Study. Clinical and experimental rheumatology. 2000;18(5):571-7.

96. Chan FKL, Hung LCT, Suen BY, et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. Gastroenterology. 2004;127(4):1038-43.

97. Chan G, Goh F, Hodgson T, et al. Outpatient follow-up for patients with rheumatoid arthritis in relation to New Zealand Rheumatology Association guidelines at Dunedin Hospital. New Zealand Medical Journal. 2008;121(1274):34-41.

98. Chandrashekara S, Syed M, Swapna R. Is three selected parameters adequate to monitor rheumatoid arthritis? Clinical Rheumatology. 2007;26(6):911-4.

99. Chard M, Crisp A. Astemizole, an H1 Antagonist, Has No Additional Therapeutic Effect in Rheumatoid Arthritis. The Journal of rheumatology. 1991;18(2):203-4.

100. Charles P, Elliott MJ, Davis D, et al. Regulation of Cytokines, Cytokine Inhibitors, and Acute-Phase Proteins

Following Anti-Tnf-Alpha Therapy in Rheumatoid Arthritis. Journal of immunology (Baltimore, Md : 1950). 1999;163(3):1521-8.

101. Chen DY, Chou SJ, Hsieh TY, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. 2009.

102. Chiang E, Selhub J, Bagley P, et al. Pyridoxine Supplementation Corrects Vitamin B6 Deficiency but Does Not Improve Inflammation in Patients With Rheumatoid Arthritis. Arthritis Res Ther. 2005;7(6):R1404-11.

103. Chijiwa T, Nishiya K, Hashimoto K. Serum Transferrin Receptor Levels in Patients With Rheumatoid Arthritis Are Correlated With Indicators for Anaemia. Clinical rheumatology. 2001;20(5):307-13.

104. Chong BF, Wong HK. Treatment of psoriasis with etanercept in a patient with a history of primary B-cell lymphoma. Clinical and Experimental Dermatology. 2009;34(5):e11-e3.

105. Choy EH, Kingsley GH, Khoshaba B, et al. A Two Year Randomised Controlled Trial of Intramuscular Depot Steroids in Patients With Established Rheumatoid Arthritis Who Have Shown an Incomplete Response to Disease Modifying Antirheumatic Drugs. Ann Rheum Dis. 2005;64(9):1288-93.

106. Choy EHS, Scott DL, Kingsley GH, et al. Treating Rheumatoid Arthritis Early With Disease Modifying Drugs Reduces Joint Damage: a Randomised Double Blind Trial of Sulphasalazine Vs Diclofenac Sodium. Clinical and experimental rheumatology. 2002;20(3):351-8.

107. Christensen AF, Lottenburger T, Lindegaard H, et al. Differential association of the N-propeptide of collagen IIA (PIIANP) and collagen II C-telopeptide (CTX-II) with synovitis and erosions in early and longstanding rheumatoid arthritis. Clinical and Experimental Rheumatology. 2009;27(2):307-14.

108. Ciconelli R, Ferraz M, Visioni R, et al. A Randomized Double-Blind Controlled Trial of Sulphasalazine Combined With Pulses of Methylprednisolone or Placebo in the Treatment of Rheumatoid Arthritis. British journal of rheumatology. 1996;35(2):150-4.

109. Claessen SJJ, Hazes JMW, Huisman MAM, et al. Use of risk stratification to target therapies in patients with recent onset arthritis; Design of a prospective randomized multicenter controlled trial. 2009.

110. Clark P, Casas E, Tugwell P, et al. Hydroxychloroquine Compared With Placebo in Rheumatoid Arthritis. A Randomized Controlled Trial. Annals of internal medicine. 1993;119(11):1067-71.

111. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of Sulfasalazine and Placebo in the Treatment of Psoriatic Arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis and rheumatism. 1996;39(12):2021-7.

112. Cohen G, Gossec L, Dougados M, et al. Radiological damage in patients with rheumatoid arthritis on sustained remission. Annals of the Rheumatic Diseases. 2007;66(3):358-63.

113. Cohen S, Cannon G, Schiff M, et al. Two-Year, Blinded, Randomized, Controlled Trial of Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis and rheumatism. 2001;44(9):1984-92.

114. Cohen S, Zwillich SH, Chow V, et al. Co-administration of the JAK inhibitor CP-690,550 and methotrexate is well tolerated in patients with rheumatoid arthritis without need for dose adjustment. British Journal of Clinical Pharmacology. 2010;69(2):143-51.

115. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety

at twenty-four weeks. Arthritis and Rheumatism 2006;54(9):2793-806.

116. Cojocaru L, Rusali A, Craiu E, et al. The efficacy and safety of simvastatin in patients with rheumatoid arthritis. Archives of the Balkan Medical Union. 2010;45(1):49-53.

117. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007(1):52-65.

118. Combe B, Goupille P, Kuntz J, et al. Sulphasalazine in Psoriatic Arthritis: a Randomized, Multicentre, Placebo-Controlled Study. British journal of rheumatology. 1996;35(7):664-8.

119. Combe B, Velicitat P, Garzon N, et al. Comparison of Intramuscular and Oral Meloxicam in Rheumatoid Arthritis Patients. Inflammation research : official journal of the European Histamine Research Society [et al]. 2001;50(Suppl 1):S10-6.

120. Cordero OJ, Salgado FJ, Mera-Varela A, et al. Serum Interleukin-12, Interleukin-15, Soluble Cd26, and Adenosine Deaminase in Patients With Rheumatoid Arthritis. Rheumatology international. 2001;21(2):69-74.

121. Corkill MM, Kirkham BW, Chikanza IC, et al. Intramuscular Depot Methylprednisolone Induction of Chrysotherapy in Rheumatoid Arthritis: a 24-Week Randomized Controlled Trial. British journal of rheumatology. 1990;29(4):274-9.

122. Corvetta A, Della B, Luchetti M, et al. Tenoxicam and Ketoprofen Level Monitoring With High Performance Liquid Chromatography in Patients Affected by Rheumatoid Arthritis. CLIN EXP RHEUMATOL. 1991;9(2):143-8.

123. Courvoisier N, Dougados M, Cantagrel A, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: A prospective study. Arthritis Research and Therapy. 2008;10(5).

124. Crowley B, Hamill J, Lyndon S, et al. Controlled-Release Indomethacin and Sustained-Release Diclofenac Sodium in the Treatment of Rheumatoid Arthritis: a Comparative Controlled Clinical Trial. Current medical research and opinion. 1990;12(3):143-50.

125. Cush J, Jasin H, Johnson R, et al. Relationship Between Clinical Efficacy and Laboratory Correlates of Inflammatory and Immunologic Activity in Rheumatoid Arthritis Patients Treated With Nonsteroidal Antiinflammatory Drugs. Arthritis and rheumatism. 1990;33(5):623-33.

126. Cush J, Lipsky P, Postlethwaite A, et al. Correlation of Serologic Indicators of Inflammation With Effectiveness of Nonsteroidal Antiinflammatory Drug Therapy in Rheumatoid Arthritis. Arthritis & Rheumatism. 1990;33(1):19-28.

127. Dalbeth N, Yeoman S, Dockerty JL, et al. A Randomised Placebo Controlled Trial of Delipidated, Deglycolipidated Mycobacterium Vaccae as Immunotherapy for Psoriatic Arthritis. Annals of the rheumatic diseases. 2004;63(6):790-4.

128. Danis V, Franic G, Rathjen D, et al. Circulating Cytokine Levels in Patients With Rheumatoid Arthritis: Results of a Double Blind Trial With Sulphasalazine. Annals of the rheumatic diseases. 1992;51(8):946-50.

129. Dawczynski C, Schubert R, Hein G, et al. Long-term moderate intervention with n-3 long-chain PUFA-supplemented dairy products: Effects on pathophysiological biomarkers in patients with rheumatoid arthritis. British Journal of Nutrition. 2009;101(10):1517-26.

130. de Boer IG, Peeters A, Ronday HK, et al. The usage of functional wrist orthoses in patients with rheumatoid arthritis. Disability and Rehabilitation. 2008;30(4):286-95.

131. De Graaf T, Van Ommen E, Van der Stelt M, et al. Effects of Low Dose Methotrexate Therapy on the Concentration and the Glycosylation of Alpha 1-Acid Glycoprotein in the Serum of Patients With Rheumatoid

Arthritis: a Longitudinal Study. The Journal of rheumatology. 1994;21(12):2209-16.

132. Deighton CM, George E, Kiely PDW, et al. Updating the British Society for Rheumatology guidelines for anti-tumour necrosis factor therapy in adult rheumatoid arthritis (again). Rheumatology. 2006;45(6):649-52.

133. Dennison W, Loeser R, Turner R, et al. A Double Blind Placebo Controlled Trial of Low Dose Clotrimazole in Rheumatoid Arthritis. The Journal of rheumatology. 1990;17(8):1003-7.

134. DeWitt EM, Glick HA, Albert DA, et al. Medicare coverage of tumor necrosis factor alpha inhibitors as an influence on physicians' prescribing behavior. Archives of Internal Medicine. 2006;166(1):57-63.

135. Di Munno O, Mazzantini M, Milani S, et al. Clinical Equivalence Between Deflazacort Oral Drops and Tablets in Active Rheumatoid Arthritis. Clinical rheumatology. 1999;18(2):140-4.

136. Dick W, Franchimont P, Veys E. Double-Blind Comparison of Etodolac and Piroxicam in the Treatment of Rheumatoid Arthritis. Clinical therapeutics. 1993;15(1):148-59.

137. Dimitrijevic M, Bartlett R. Leflunomide, a Novel Immunomodulating Drug, Inhibits Homotypic Adhesion of Peripheral Blood and Synovial Fluid Mononuclear Cells in Rheumatoid Arthritis. Inflammation research : official journal of the European Histamine Research Society [et al]. 1996;30(8):4132-3.

138. Dixon WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis and Rheumatism 2007;56(9):2905-12.

139. Dooley MA, Cush JJ, Lipsky PE, et al. The Effects of Nonsteroidal Antiinflammatory Drug Therapy in Early Rheumatoid Arthritis on Serum Levels of Soluble Interleukin 2 Receptor, Cd4, and Cd8. The Journal of rheumatology. 1993;20(11):1857-62.

140. Dore RK, Cohen SB, Lane NE, et al. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. Annals of the rheumatic diseases. 2010;69(5):872-5.

141. Dougados M, Combe B, Cantagrel A, et al. Combination Therapy in Early Rheumatoid Arthritis: a Randomised, Controlled, Double Blind 52 Week Clinical Trial of Sulphasalazine and Methotrexate Compared With the Single Components. Annals of the rheumatic diseases. 1999;58(4):220-5.

142. Drevlow BE, Lovis R, Haag MA, et al. Recombinant Human Interleukin-1 Receptor Type I in the Treatment of Patients With Active Rheumatoid Arthritis. Arthritis and rheumatism. 1996;39(2):257-65.

143. Drewes AM, Andreasen A, Jennum P, et al. Zopiclone as Night Medication in Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1998;27(3):180-7.

144. Drosos AA, Tsifetaki N, Tsiakou EK, et al. Influence of Methotrexate on Radiographic Progression in Rheumatoid Arthritis: a Sixty-Month Prospective Study. Clinical and experimental rheumatology. 1997;15(3):263-7.

145. Duffy T, Belton O, Bresnihan B, et al. Inhibition of PGE2 Production by Nimesulide Compared With Diclofenac in the Acutely Inflamed Joint of Patients With Arthritis. Drugs. 2003;63(Suppl 1):31-6.

146. Dugina JL, Petrov VI, Babayeva AR, et al. A Randomized, Open-Label, Comparative, 6-Month Trial of Oral Ultra-Low Doses of Antibodies to Tumor Necrosis Factor-Alpha and Diclofenac in Rheumatoid Arthritis. Int J Tissue React. 2005;27(1):15-21.

147. Dupuis LL, Koren G, Shore A, et al. Methotrexate-Nonsteroidal Antiinflammatory Drug Interaction in Children With Arthritis. Journal of Rheumatology. 1990;17(11):1469-73.

148. Eastell R, Devogelaer JP, Peel NF, et al. Prevention of Bone Loss With Risedronate in Glucocorticoid-Treated Rheumatoid Arthritis Patients. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2000;11(4):331-7.

149. Eder L, Chandran V, Schentag CT, et al. Time and predictors of response to tumour necrosis factor-(alpha) blockers in psoriatic arthritis: An analysis of a longitudinal observational cohort. Rheumatology. 2010;49(7):1361-6.

150. Edwards JCW, Leandro MJ, Cambridge G. B Lymphocyte Depletion in Rheumatoid Arthritis: Targeting of Cd20. Curr Dir Autoimmun. 2005;1422(8):175-92.

151. Eggelmeijer F, Papapoulos S, van Paassen H, et al. Clinical and Biochemical Response to Single Infusion of Pamidronate in Patients With Active Rheumatoid Arthritis: a Double Blind Placebo Controlled Study. The Journal of rheumatology. 1994;21(11):2016-20.

152. Eggelmeijer F, Papapoulos SE, van Paassen HC, et al. Increased Bone Mass With Pamidronate Treatment in Rheumatoid Arthritis. Results of a Three-Year Randomized, Double-Blind Trial. Arthritis and rheumatism. 1996;39(3):396-402.

153. Egsmose C, Lund B, Borg G, et al. Patients With Rheumatoid Arthritis Benefit From Early 2nd Line Therapy: 5 Year Followup of a Prospective Double Blind Placebo Controlled Study. The Journal of rheumatology. 1995;22(12):2208-13.

154. Egsmose C, TM H, Andersen LS, et al. Limited Effect of Sulphasalazine Treatment in Reactive Arthritis. A Randomised Double Blind Placebo Controlled Trial. Annals of the rheumatic diseases. 1997;56(1):32-6.

155. Eichler HG, Mavros P, Geling O, et al. Association Between Health-Related Quality of Life and Clinical Efficacy Endpoints in Rheumatoid Arthritis Patients After Four Weeks Treatment With Anti-Inflammatory Agents. International journal of clinical pharmacology and therapeutics. 2005;43(5):209-16.

156. Elewski B, Leonardi C, Gottlieb AB, et al. Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. The British journal of dermatology 2007(1):138-42.

157. Emery P. Disease Modification in Rheumatoid Arthritis With Leflunomide. Scandinavian journal of rheumatology Supplement. 1999;112(9):9-14.

158. Emery P, Breedveld FC, Lemmel EM, et al. A Comparison of the Efficacy and Safety of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(6):655-65.

159. Emery P, Clarke A, Williams P, et al. Nabumetone Compared With Naproxen in the Treatment of Rheumatoid Arthritis: a Multicenter, Double Blind, Randomized, Parallel Group Trial in Hospital Outpatients. The Journal of rheumatology Supplement. 1992;36:41-7.

160. Emery P, Durez P, Dougados M, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: A clinical and imaging study of abatacept (the ADJUST trial). Annals of the rheumatic diseases. 2010;69(3):510-6.

161. Emery P, Genovese MC, Fleischmann RM, et al. Efficacy of Golimumab, a human anti-TNF(alpha) antibody, by baseline CRP level in patients with rheumatoid arthritis: Results from three phase 3, randomized, double-blind, placebo-controlled studies. Rheumatology 2010;49i101.

162. Emery P, Zeidler H, Kvien TK, et al. Celecoxib Versus Diclofenac in Long-Term Management of Rheumatoid Arthritis: Randomised Double-Blind Comparison. Lancet. 2000;354(9196):2106-11.

163. Ergun T, Inanc N, Tuney D, et al. Skin manifestations of rheumatoid arthritis: A study of 215 Turkish patients. International

Journal of Dermatology. 2008;47(9):894-902.

164. Eriksson LO, Sturfelt G, Thysell H, et al. Effects of Sulindac and Naproxen on Prostaglandin Excretion in Patients With Impaired Renal Function and Rheumatoid Arthritis. The American journal of medicine. 1990;89(3):313-21.

165. Faarvang K, Egsmose C, Kryger P, et al. Hydroxychloroquine and Sulphasalazine Alone and in Combination in Rheumatoid Arthritis: a Randomised Double Blind Trial. Annals of the rheumatic diseases. 1993;52(10):711-5.

166. Fallatah HI, Akbar HO, Qari YA. Autoimmune hepatitis: Single-center experience of clinical presentation, response to treatment and prognosis in Saudi Arabia. Saudi Journal of Gastroenterology. 2010;16(2):95-9.

167. Farr M, Kitas G, Waterhouse L, et al. Sulphasalazine in Psoriatic Arthritis: a Double-Blind Placebo-Controlled Study. British journal of rheumatology. 1990;29(1):46-0.

168. Fernandez A, Quintana G, Rondon F, et al. Lupus arthropathy: A case series of patients with rhupus. Clinical Rheumatology. 2006;25(2):164-7.

169. Ferraz MB, Pinheiro GR, Helfenstein M, et al. Combination Therapy With Methotrexate and Chloroquine in Rheumatoid Arthritis. A Multicenter Randomized Placebo-Controlled Trial. Scandinavian journal of rheumatology. 1994;23(5):231-6.

170. Fleischmann R. Safety and efficacy of etanercept in the elderly. Aging Health. 2006;2(2):189-97.

171. Flicinski J, Brzosko M, Olewniczak S. Multiple haemangiomas in a psoriatic arthritis patient treated with cyclosporine [13]. Acta Dermato Venereologica. 2006;86(3):271-2.

172. Foell D, Kane D, Bresnihan B, et al. Expression of the Pro-Inflammatory Protein S100a12 (En-Rage) in Rheumatoid and Psoriatic Arthritis. Rheumatology (Oxford). 2003;42(11):1383-9.

173. Foell D, Wulffraat N, Wedderburn LR, et al. Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission a randomized clinical trial. JAMA - Journal of the American Medical Association. 2010;303(13):1266-73.

174. Franck H, Ittel T, Tasch O, et al. Osteocalcin in Patients With Rheumatoid Arthritis. A One-Year Followup Study. The Journal of rheumatology. 1994;21(7):1256-9.

175. Fransen J, Visser K, Van Dongen H, et al. Validity of the disease activity score in undifferentiated arthritis. Arthritis Care and Research. 2010;62(10):1392-8.

176. Fraser AD, van Kuijk AWR, Westhovens R, et al. A Randomised, Double Blind, Placebo Controlled, Multicentre Trial of Combination Therapy With Methotrexate Plus Ciclosporin in Patients With Active Psoriatic Arthritis. Ann Rheum Dis. 2005;64(6):859-64.

177. Fraser S, Hopkins R, Hunter J, et al. Sulphasalazine in the Management of Psoriatic Arthritis. British journal of rheumatology. 1993;32(10):923-5.

178. Friedman DM, Llanos C, Izmirly PM, et al. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis and rheumatism. 2010;62(4):1138-46.

179. Furst D, Erikson N, Clute L, et al. Adverse Experience With Methotrexate During 176 Weeks of a Longterm Prospective Trial in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1990;12:1628-35.

180. Furst D, Felson D, Thoren G, et al. Immunoadsorption for the Treatment of Rheumatoid Arthritis: Final Results of a Randomized Trial. Prosorba Trial Investigators. Ther Apher. 2002;6(1):99.

181. Furst DE, Kolba KS, Fleischmann R, et al. Dose Response and Safety Study of

Meloxicam up to 22.5 Mg Daily in Rheumatoid Arthritis: a 12 Week Multicenter, Double Blind, Dose Response Study Versus Placebo and Diclofenac. The Journal of rheumatology. 2002;29(3):436-46.

182. Furuya T, Kotake S, Inoue E, et al. Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: A prospective observational cohort study. Journal of Bone and Mineral Metabolism. 2008;26(5):499-505.

183. Furuya T, Kotake S, Inoue E, et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: A prospective 54-month observational study. Journal of Rheumatology. 2007;34(2):303-10.

184. Furuya Y, Ozeki T, Takayanagi R, et al. Theory based analysis of anti-inflammatory effect of infliximab on Crohn's disease. Drug metabolism and pharmacokinetics 2007(1):20-5.

185. Furuzawa-Carballeda J, Fenutria-Ausmequet R, Gil-Espinosa V, et al. Polymerized-type I collagen for the treatment of patients with rheumatoid arthritis. Effect of intramuscular administration in a double blind placebo-controlled clinical trial. Clinical and Experimental Rheumatology. 2006;24(5):514-20.

186. Garnero P, Thompson E, Woodworth T, et al. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. 2010.

187. Gasparyan AY, Stavropoulos-Kalinoglou A, Toms TE, et al. Association of mean platelet volume with hypertension in rheumatoid arthritis. Inflammation and Allergy - Drug Targets. 2010;9(1):45-50.

188. Genant HK. Interleukin-1 Receptor Antagonist Treatment of Rheumatoid Arthritis Patients: Radiologic Progression and Correlation of Genant/Sharp and Larsen Scoring Methods. Seminars in arthritis and rheumatism. 2001;30(5 Suppl 2):26-32.

189. Genant HK, Peterfy CG, Westhovens R, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: Results from the long-term extension of the AIM trial. Annals of the Rheumatic Diseases. 2007;67(8):1084-9.

190. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis and Rheumatism 2008;58(10):2968-80.

191. Genta MS, Kardes H, Gabay C. Clinical evaluation of a cohort of patients with rheumatoid arthritis treated with anti-TNF-alpha in the community. Joint Bone Spine. 2006;73(1):51-6.

192. Gerlag DM, Haringman JJ, Smeets TJM, et al. Effects of Oral Prednisolone on Biomarkers in Synovial Tissue and Clinical Improvement in Rheumatoid Arthritis. Arthritis and rheumatism. 2004;50(12):3783-91.

193. Gerlag DM, Hollis S, Layton M, et al. Preclinical and clinical investigation of a CCR5 antagonist, AZD5672, in patients with rheumatoid arthritis receiving methotrexate. Arthritis and rheumatism. 2010;62(11):3154-60.

194. Geusens P, Alten R, Rovensky J, et al. Efficacy, Safety and Tolerability of Lumiracoxib in Patients With Rheumatoid Arthritis. Int J Clin Pract. 2004;58(11):1033-41.

195. Geusens P, Truitt K, Sfikakis P, et al. A Placebo and Active Comparator-Controlled Trial of Rofecoxib for the Treatment of Rheumatoid Arthritis. Scandinavian journal of rheumatology. 2002;31(4):230-8.

196. Ghosh B, Halder S, Ghosh A, et al. Early rheumatoid arthritis: Clinical and therapeutic evaluation in a tertiary care centre in India. Indian Journal of Rheumatology 2008;3(2):48-51.

197. Giannini EH, Ilowite NT, Lovell DJ, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. 2009.

198. Gladman D, Blake R, Brubacher B, et al. Chloroquine Therapy in Psoriatic Arthritis. The Journal of rheumatology. 1992;19(11):1724-6.

199. Gladman DD, Mease PJ, Cifaldi MA, et al. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis 2007;66(2):163-8.

200. Gladman DD, Mease PJ, Ritchlin CT, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum. 2007 Feb;56(2):476-88.

201. Godfrey C, Sweeney K, Miller K, et al. The Population Pharmacokinetics of Long-Term Methotrexate in Rheumatoid Arthritis. British journal of clinical pharmacology. 1998;46(4):369-76.

202. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: A randomized trial. Annals of Internal Medicine 2007;146(6):406-15.

203. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Kerstens PJSM, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. 2010.

204. Gonzalez-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: Influence of new therapies and changes in management approach: Analysis of the EMECAR cohort. Arthritis Research and Therapy. 2008;10(6).

205. Goodnough L, Marcus R. The Erythropoietic Response to Erythropoietin in Patients With Rheumatoid Arthritis. The Journal of laboratory and clinical medicine. 1997;130(4):381-6.

206. Gossec L, van der Heijde D, Melian A, et al. Efficacy of Cyclo-Oxygenase-2 Inhibition by Etoricoxib and Naproxen on the Axial Manifestations of Ankylosing Spondylitis in the Presence of Peripheral Arthritis. Annals of the rheumatic diseases. 2005;64(1):1563-7.

207. Gøtzsche P, Johansen H. Meta-Analysis of Short-Term Low Dose Prednisolone Versus Placebo and Non-Steroidal Anti-Inflammatory Drugs in Rheumatoid Arthritis. British medical journal. 1998;316(7144):1606-7.

208. Gotzsche PC, Hansen M, Stoltenberg M, et al. Randomized, Placebo Controlled Tial of Withdrawal of Slow-Acting Antirheumatic Drugs and of Observer Bias in Rheumatoid Arthritis. Scandinavian Journal of Rheumatology. 1996;25(4):194-0.

209. Graell E, Vazquez I, Larrosa M, et al. Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: Prognostic factors after two years of follow-up. Clinical and Experimental Rheumatology. 2009;27(2):284-91.

210. Graham DY, White RH, Moreland LW, et al. Duodenal and Gastric Ulcer Prevention With Misoprostol in Arthritis Patients Taking Nsaids. Misoprostol Study Group. Annals of internal medicine. 1993;119(4):257-62.

211. Greenberg JD, Bingham ICO, Abramson SB, et al. Assessment of coxib utilization by rheumatologists for nonsteroidal antiinflammatory drug gastroprotection prior to the coxib market withdrawals. Arthritis Care and Research. 2006;55(4):543-50.

212. Greenwood MC, Rathi J, Hakim AJ, et al. Regression to the mean using the disease activity score in eligibility and response

criteria for prescribing TNF-alpha inhibitors in adults with rheumatoid arthritis. Rheumatology. 2007;46(7):1165-7.

213. Griffith SM, Fisher J, Clarke S, et al. Do Patients With Rheumatoid Arthritis Established on Methotrexate and Folic Acid 5 Mg Daily Need to Continue Folic Acid Supplements Long Term? Rheumatology (Oxford). 2000;39(10):1102-9.

214. Grigor C, Capell H, Stirling A, et al. Effect of a Treatment Strategy of Tight Control for Rheumatoid Arthritis (the Ticora Study): a Single-Blind Randomised Controlled Trial. Lancet. 2004;364(9430):263-9.

215. Gulec G, Yenilmez C, Ayranci U. Sulfasalazine plus chloroquine-induced mood disorder in a patient with rheumatoid arthritis. Iranian Journal of Medical Sciences. 2009;34(1):72-5.

216. Guler-Yuksel M, Allaart CF, Watt I, et al. Treatment with TNF-(alpha) inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. Osteoarthritis and Cartilage. 2010;18(10):1256-62.

217. Gupta AK, Grober JS, Hamilton TA, et al. Sulfasalazine Therapy for Psoriatic Arthritis: a Double Blind, Placebo Controlled Trial. The Journal of rheumatology. 1996;22(5):894-8.

218. Haagsma C, Russel F, Vree T, et al. Combination of Methotrexate and Sulphasalazine in Patients With Rheumatoid Arthritis: Pharmacokinetic Analysis and Relationship to Clinical Response. British journal of clinical pharmacology. 1997;36(10):1082-8.

219. Haagsma C, van Riel P, de Jong A, et al. Combination of Sulphasalazine and Methotrexate Versus the Single Components in Early Rheumatoid Arthritis: a Randomized, Controlled, Double-Blind, 52 Week Clinical Trial. British journal of rheumatology. 1997;36(10):1082-8.

220. Haagsma C, van Riel P, van de Putte L. Combining Sulphasalazine and Methotrexate in Rheumatoid Arthritis: Early Clinical Impressions. British journal of rheumatology. 1995;34(Suppl 2):104-8.

221. Haagsma CJ, Blom HJ, van Riel PL, et al. Influence of Sulphasalazine, Methotrexate, and the Combination of Both on Plasma Homocysteine Concentrations in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1999;58(2):79-84.

222. Haagsma CJ, van Riel PL, de Rooij DJ, et al. Combination of Methotrexate and Sulphasalazine Vs Methotrexate Alone: a Randomized Open Clinical Trial in Rheumatoid Arthritis Patients Resistant to Sulphasalazine Therapy. British journal of rheumatology. 1994;33(11):1049-55.

223. Haar D, Solvkjaer M, Unger B, et al. A Double-Blind Comparative Study of Hydroxychloroquine and Dapsone, Alone and in Combination, in Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1993;22(3):113-8.

224. Hafstrem I, Albertsson K, Boonen A, et al. Remission achieved after 2 years treatment with low-dose prednisolone in addition to diseasemodifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: An open 2-year continuation study. 2009.

225. Hakala M, Risteli J, Aman S, et al. Combination drug strategy in recent-onset rheumatoid arthritis suppresses collagen I degradation and is associated with retardation of radiological progression. Scandinavian Journal of Rheumatology. 2008;37(2):90-3.

226. Hamalainen H, Kaarela K, Kroger H, et al. Changes in bone mineral density in premenopausal women with rheumatoid arthritis during a two-year follow-up. Joint Bone Spine. 2007;74(5):482-7.

227. Hamilton J, McInnes I, Thomson E, et al. Comparative Study of Intramuscular Gold and Methotrexate in a Rheumatoid Arthritis Population From a Socially Deprived Area. Annals of the rheumatic diseases. 2001;60(6):566-72.

228. Hamilton R, Kremer J. Why Intramuscular Methotrexate May Be More Efficacious Than Oral Dosing in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1997;36(1):86-90.

229. Hamilton S, Campbell N, Kara M, et al. The Effect of Ingestion of Ferrous Sulfate on the Absorption of Oral Methotrexate in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2003;30(9):1948-50.

230. Hannequin JR. Efficacy of Arthrotec in the Treatment of Rheumatoid Arthritis. Scandinavian journal of rheumatology Supplement. 1992;96:7-14.

231. Hannonen P, Mottonen T, Hakola M, et al. Sulfasalazine in Early Rheumatoid Arthritis. A 48-Week Double-Blind, Prospective, Placebo-Controlled Study. Arthritis and rheumatism. 1993;36(11):1501-9.

232. Hansen M, Podenphant J, Florescu A, et al. A Randomised Trial of Differentiated Prednisolone Treatment in Active Rheumatoid Arthritis. Clinical Benefits and Skeletal Side Effects. Annals of the rheumatic diseases. 1999;58(11):713-8.

233. Hansen TM, Kryger P, Elling H, et al. Double Blind Placebo Controlled Trial of Pulse Treatment With Methylprednisolone Combined With Disease Modifying Drugs in Rheumatoid Arthritis. British medical journal. 1990;301(6749):268-70.

234. Hanyuda M, Kasama T, Isozaki T, et al. Activated Leucocytes Express and Secrete Macrophage Inflammatory Protein-1alpha Upon Interaction With Synovial Fibroblasts of Rheumatoid Arthritis Via a Beta2-Integrin/Icam-1 Mechanism. Rheumatology (Oxford). 2003;42(11):1390-7.

235. Haringman J, Kraan M, Smeets TJ, et al. Chemokine Blockade and Chronic Inflammatory Disease: Proof of Concept in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2003;62(8):715-21.

236. Hartmann SN, Rordorf CM, Milosavljev S, et al. Lumiracoxib Does Not Affect Methotrexate Pharmacokinetics in Rheumatoid Arthritis Patients. The Annals of pharmacotherapy. 2004;38(10):1582-7.

237. Hasegawa J, Nagashima M, Yamamoto M, et al. Bone Resorption and Inflammatory Inhibition Efficacy of Intermittent Cyclical Etidronate Therapy in Rheumatoid Arthritis. The Journal of rheumatology. 2004;38(10):1582-7.

238. Hatakka K, Martio J, Korpela M, et al. Effects of Probiotic Therapy on the Activity and Activation of Mild Rheumatoid Arthritis--a Pilot Study. Scandinavian journal of rheumatology. 2003;32(4):211-5.

239. Haugeberg G, Green MJ, Quinn MA, et al. Hand bone loss in early undifferentiated arthritis: Evaluating bone mineral density loss before the development of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2006;65(6):736-40.

240. Haugeberg G, Strand A, Kvien T, et al. Reduced Loss of Hand Bone Density With Prednisolone in Early Rheumatoid Arthritis: Results From a Randomized Placebo-Controlled Trial. Archives of internal medicine. 2005;165(11):1293-7.

241. Hazes JM, Taylor P, Strand V, et al. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. Rheumatology. 2010;49(10):1900-10.

242. Hemmings F, Farhan M, Rowland J, et al. Tolerability and Pharmacokinetics of the Collagenase-Selective Inhibitor Trocade in Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2001;40(5):537-43.

243. Henriksson K, Uribe A, Sandstedt B, et al. Helicobacter Pylori Infection, Abo Blood Group, and Effect of Misoprostol on Gastroduodenal Mucosa in Nsaid-Treated Patients With Rheumatoid Arthritis. Digestive diseases and sciences. 1993;38(9):1688-96.

244. Hepburn T, Totoritis M, Davis C. Antibody-Mediated Stripping of Cd4 From Lymphocyte Cell Surface in Patients With

Rheumatoid Arthritis. Rheumatology (Oxford). 2003;42(1):54-61.

245. Hernandez-Cruz B, Ariza-Ariza R, Cardiel-Rios MH. Cost of the standard rheumatology care in active rheumatoid arthritis patients seen in a tertiary care center in Mexico City. Reumatologia Clinica. 2006;2(3):124-30.

246. Herrick A, Grennan D, Griffen K, et al. Lack of Interaction Between Flucloxacillin and Methotrexate in Patients With Rheumatoid Arthritis. British journal of clinical pharmacology. 1996;41(3):223-7.

247. Hetland ML, Ejbjerg B, Horslev-Petersen K, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). 2009.

248. Hetland ML, Lindegaard HM, Hansen A, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Annals of the Rheumatic Diseases. 2008;67(7):1023-6.

249. Heurkens A, Westedt M, Breedveld F. Prednisone Plus Azathioprine Treatment in Patients With Rheumatoid Arthritis Complicated by Vasculitis. Archives of internal medicine. 1991;151(11):2249-54.

250. Hewlett S, Mitchell K, Haynes J, et al. Patient-Initiated Hospital Follow-up for Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(9):990-7.

251. Hickling P, Jacoby R, Kirwan J. Joint Destruction After Glucocorticoids Are Withdrawn in Early Rheumatoid Arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. British journal of rheumatology. 1994;21(3):435-41.

252. Hidaka T, Suzuki K, Kawakami M, et al. Dynamic Changes in Cytokine Levels in Serum and Synovial Fluid Following Filtration Leukocytapheresis Therapy in Patients With Rheumatoid Arthritis. J Clin Apher. 2001;16(2):74-81.

253. Hidaka T, Suzuki K, Matsuki Y, et al. Changes in Cd4+ T Lymphocyte Subsets in Circulating Blood and Synovial Fluid Following Filtration Leukocytapheresis Therapy in Patients With Rheumatoid Arthritis. Ther Apher. 1999;3(2):178-85.

254. Hilliquin P, Chermat Izard V, Menkes CJ. A Double Blind, Placebo Controlled Study of a Platelet Activating Factor Antagonist in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1998;25(8):1502-7.

255. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients With Rheumatoid Arthritis. Journal of Rheumatology. 2004;31(4):645-8.

256. Hoekstra M, van Ede A, Haagsma C, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2003;62(5):423-6.

257. Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Annals of internal medicine 2007(9):621-30.

258. Holm B, Jacobsen S, Skjodt H, et al. Keitel functional test for patients with rheumatoid arthritis: Translation, reliability, validity, and responsiveness. Physical Therapy. 2008;88(5):664-78.

259. Hor BTY, Vasoo S, Koh ET. The use of anti-tumour necrosis factor-alpha therapies for rheumatoid arthritis in Singapore. APLAR Journal of Rheumatology. 2006;9(2):157-60.

260. Horng MS. Early rheumatoid arthritis: Is there a best treatment? Journal of Clinical Outcomes Management. 2007;14(5):233-4.

261. Huang F, Wang L, Zhang J, et al. Risk of tuberculosis in a Chinese registry of rheumatoid arthritis and ankylosing

spondylitis for tumour necrosis factor-alpha antagonists. APLAR Journal of Rheumatology. 2006;9(2):170-4.

262. Huang SC, Wei JCC, Wu DJ, et al. Vitamin B6 supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. European Journal of Clinical Nutrition. 2010;64(9):1007-13.

263. Huffstutter J, Craig WD, Schimizzi G, et al. A multicenter, randomized, open study to evaluate the impact of an electronic data capture system on the care of patients with rheumatoid arthritis. Current Medical Research and Opinion. 2007;23(8):1967-79.

264. Hughes RA, Carr AJ, Carr M, et al. Improving patient safety: Reducing medication errors through use of acceptable, accessible medicines packaging. Pharmaceutical Journal. 2008;280(7484):22-5.

265. Huisman AM, Siewertsz van Everdingen AA, Wenting MJG, et al. Glucocorticoid Receptor up-Regulation in Early Rheumatoid Arthritis Treated With Low Dose Prednisone or Placebo. Clinical and experimental rheumatology. 2003;21(2):217-20.

266. Hunter J, Parnham M, Balaguer X. Aceclofenac in Rheumatoid Arthritis: a Useful and Novel Anti-Inflammatory. Clinical rheumatology. 1996;15(4):329-34.

267. Hurowitz EJ, Gould JS, Fleisig GS, et al. Outcome analysis of agility total ankle replacement with prior adjunctive procedures: Two to six year followup. Foot and Ankle International. 2007;28(3):308-12.

268. Huskisson EC. Four Commonly Prescribed Non-Steroidal Anti-Inflammatory Drugs for Rheumatoid Arthritis. European journal of rheumatology and inflammation. 1991;11(2):8-12.

269. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007(3):863-73; quiz 1165-6.

270. Iagnocco A, Cerioni A, Coari G, et al. Intra-articular methotrexate in the treatment of rheumatoid arthritis and psoriatic arthritis: A clinical and sonographic study. Clinical Rheumatology. 2006;25(2):159-63.

271. Ichikawa Y, Saito T, Yamanaka H, et al. Clinical activity after 12 weeks of treatment with nonbiologics in early rheumatoid arthritis may predict articular destruction 2 years later. Journal of Rheumatology. 2010;37(4):723-9.

272. Iglehart IWr, Sutton JD, Bender JC, et al. Intravenous Pulsed Steroids in Rheumatoid Arthritis: a Comparative Dose Study. The Journal of rheumatology. 1990;17(2):159-62.

273. Ince A, Yazici Y, Hamuryudan V, et al. The Frequency and Clinical Characteristics of Methotrexate (Mtx) Oral Toxicity in Rheumatoid Arthritis (Ra): a Masked and Controlled Study. Clinical rheumatology. 1996;15(5):491-4.

274. Iqbal M, Baig J, Ali A, et al. The Effects of Non-Steroidal Anti-Inflammatory Drugs on the Disposition of Methotrexate in Patients With Rheumatoid Arthritis. Biopharmaceutics & drug disposition. 1998;19(3):163-7.

275. Ishikawa H, Murasawa A, Nakazono K, et al. The patient-based outcome of upper-extremity surgeries using the DASH questionnaire and the effect of disease activity of the patients with rheumatoid arthritis. Clinical Rheumatology. 2008;27(8):967-73.

276. Islam M, Alam M, Haq S, et al. Efficacy of Sulphasalazine Plus Methotrexate in Rheumatoid Arthritis. Bangladesh Medical Research Council bulletin. 2000;26(1):1-7.

277. Isozaki T, Sato M, Takahashi R, et al. Effects of low-dose tacrolimus therapy in combination with methotrexate in patients with methotrexate-refractory rheumatoid arthritis. 2010;229-34.

278. Izumi Y, Tominaga M, Iwanaga N, et al. Twenty-four-week follow-up examination of a leukocytapheresis therapy in rheumatoid

arthritis. Modern Rheumatology. 2006;16(1):20-3.

279. Jacobs J, Rasker J, van Riel P, et al. Rheumajecta and Vasolastine in the Treatment of Rheumatoid Arthritis--the Results of a Placebo-Controlled, Double-Blind Trial of a Complementary Treatment. Scandinavian journal of rheumatology. 1991;20(6):434-40.

280. Jahangier ZN, Jacobs JWG, Lafeber FPJG, et al. Is Radiation Synovectomy for Arthritis of the Knee More Effective Than Intraarticular Treatment With Glucocorticoids? Results of an Eighteen-Month, Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. Arthritis and rheumatism. 2005;52(11):3391-402.

281. Jakez Ocampo J, Richaud Patin Y, Simon J, et al. Weekly Dose of Leflunomide for the Treatment of Refractory Rheumatoid Arthritis: an Open Pilot Comparative Study. Joint, bone, spine : revue du rhumatisme. 2004;51(1):147-8.

282. Jakob A, Porstmann R, Rompel R. Skin ulceration after leflunomide treatment in two patients with rheumatoid arthritis. [German, English]. JDDG Journal of the German Society of Dermatology. 2006;4(4):324-7.

283. Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. 2009.

284. Jaswal S, Mehta H, Sood A, et al. Antioxidant Status in Rheumatoid Arthritis and Role of Antioxidant Therapy. 338. 2003;1-2:international journal of clinical chemistry.

285. Jelinek G, Will R, Dusci L, et al. Intravenous Regional Administration of Methylprednisolone in Rheumatoid Arthritis. Rheumatology international. 1991;11(4-5):147-50.

286. Jenks K, Stebbings S, Burton J, et al. Probiotic therapy for the treatment of spondyloarthritis: A randomized controlled trial. Journal of Rheumatology. 2010;37(10):2118-25.

287. Jessop JD, O'Sullivan MM, Lewis PA, et al. A Long-Term Five-Year Randomized Controlled Trial of Hydroxychloroquine, Sodium Aurothiomalate, Auranofin and Penicillamine in the Treatment of Patients With Rheumatoid Arthritis. British journal of rheumatology. 1998;37(9):992-1002.

288. Jeurissen ME, Boerbooms AM, van de Putte LB, et al. Influence of Methotrexate and Azathioprine on Radiologic Progression in Rheumatoid Arthritis. A Randomized, Double-Blind Study. Annals of internal medicine. 1991;114(12):999-1004.

289. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. 2010.

290. Joyce D, Will R, Hoffman D, et al. Exacerbation of Rheumatoid Arthritis in Patients Treated With Methotrexate After Administration of Folinic Acid. Annals of the rheumatic diseases. 1991;50(12):913-4.

291. Kafediska I, Spasovski D, Gruev T, et al. Association between Sharp's radiographic index and acute phase reactants in rheumatoid arthritis. Journal of Medical Biochemistry. 2008;27(4):447-53.

292. Kageyama Y, Sano M, Ishihara C, et al. Flexor tendon ruptures in both small fingers of a patient with rheumatoid arthritis [2]. Journal of Clinical Rheumatology. 2006;12(2):103-4.

293. Kahn KL, MacLean CH, Wong AL, et al. Assessment of American College of Rheumatology quality criteria for rheumatoid arthritis in a pre-quality criteria patient cohort. Arthritis Care and Research. 2007;57(5):707-15.

294. Kalden JR, Schattenkirchner M, Sorensen H, et al. The Efficacy and Safety of Leflunomide in Patients With Active Rheumatoid Arthritis: a Five-Year Followup Study. Arthritis and rheumatism. 2003;48(6):1513-20.

295. Kalden JR, Scott DL, Smolen JS, et al. Improved Functional Ability in Patients With Rheumatoid Arthritis - Longterm Treatment With Leflunomide Versus Sulfasalazine. Journal of Rheumatology. 2001;28(9):1983-91.

296. Kalden Nemeth D, Grebmeier J, Antoni C, et al. Nmr Monitoring of Rheumatoid Arthritis Patients Receiving Anti-Tnf-Alpha Monoclonal Antibody Therapy. Rheumatology international. 1997;16(6):249-55.

297. Kaltwasser J, Nash P, Gladman D, et al. Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis: a Multinational, Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Arthritis and rheumatism. 2004;50(6):1393-50.

298. Kamel M, Serafi T. Fucose Concentrations in Sera From Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1995;13(2):243-6.

299. Kanbe K, Inoue K. Efficacy of arthroscopic synovectomy for the effect attenuation cases of infliximab in rheumatoid arthritis. Clinical Rheumatology. 2006;25(6):877-81.

300. Kanik K, Yarboro C, Naparstek Y, et al. Failure of Low-Dose Intravenous Immunoglobulin Therapy to Suppress Disease Activity in Patients With Treatment-Refractory Rheumatoid Arthritis. Arthritis and rheumatism. 1997;82(4):1279-83.

301. Karim A, Tolbert D, Hunt T, et al. Celecoxib, a Specific Cox-2 Inhibitor, Has No Significant Effect on Methotrexate Pharmacokinetics in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1999;26(12):2539-43.

302. Kavanaugh A, Genovese M, Baughman J, et al. Allele and Antigen-Specific Treatment of Rheumatoid Arthritis: a Double Blind, Placebo Controlled Phase 1 Trial. The Journal of rheumatology. 2003;30(3):449-54.

303. Kavanaugh A, Menter A, Mendelsohn A, et al. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: A randomized, placebo-controlled, phase II trial. Current Medical Research and Opinion. 2010;26(10):2385-92.

304. Kawai S, Uchida E, Kondo M, et al. Efficacy and safety of ketoprofen patch in patients with rheumatoid arthritis: A randomized, double-blind, placebo-controlled study. Journal of Clinical Pharmacology. 2010;50(10):1171-9.

305. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: The COMET trial. 2010.

306. Kerstens P, Boerbooms A, Jeurissen M, et al. Radiological and Clinical Results of Longterm Treatment of Rheumatoid Arthritis With Methotrexate and Azathioprine. The Journal of rheumatology. 2000;27(5):1148-55.

307. Kerstens P, Boerbooms A, Jeurissen M, et al. Accelerated Nodulosis During Low Dose Methotrexate Therapy for Rheumatoid Arthritis. An Analysis of Ten Cases. The Journal of rheumatology. 1992;19(6):867-71.

308. Kerstens P, Boerbooms A, Jeurissen M, et al. Antiperinuclear Factor and Disease Activity in Rheumatoid Arthritis. Longitudinal Evaluation During Methotrexate and Azathioprine Therapy. The Journal of rheumatology. 1994;21(12):2190-4.

309. Keystone E, Haraoui B, Bykerk V. Role of Adalimumab in the Treatment of Early Rheumatoid Arthritis. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S198-9.

310. Khan S, Otter S, Springett K. The effects of reflexology on foot pain and quality of life in a patient with rheumatoid arthritis: A case report. Foot. 2006;16(2):112-6.

311. Kiely P, Williams R, Walsh D, et al. Contemporary patterns of care and disease activity outcome in early rheumatoid

arthritis: The ERAN cohort. Rheumatology. 2009;48(1):57-60.

312. Kim H, Song Y. A Comparison Between Bucillamine and D-Penicillamine in the Treatment of Rheumatoid Arthritis. Rheumatology international. 1997;17(1):5-9.

313. Kimball AB, Bensimon AG, Guerin A, et al. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. American Journal of Clinical Dermatology 2011;12(1):51-62.

314. Kirkham B, Corkill M, Davison S, et al. Response to Glucocorticoid Treatment in Rheumatoid Arthritis: in Vitro Cell Mediated Immune Assay Predicts in Vivo Responses. The Journal of rheumatology. 1991;18(6):821-5.

315. Kirkham B, Davison S, Corkill M, et al. Serial Soluble Interleukin 2 Receptor Levels in Rheumatoid Arthritis: Differences in Response to Glucocorticoid Treatment and Chrysotherapy. The Journal of rheumatology. 1993;20(6):935-9.

316. Kirkham B, Navarro F, Corkill M, et al. In Vivo Analysis of Disease Modifying Drug Therapy Activity in Rheumatoid Arthritis by Sequential Immunohistological Analysis of Synovial Membrane Interleukin 1 Beta. The Journal of rheumatology. 1994;21(9):1615-9.

317. Kirwan J, Byron M, Watt I. The Relationship Between Soft Tissue Swelling, Joint Space Narrowing and Erosive Damage in Hand X-Rays of Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2001;40(3):688-95.

318. Kirwan JR, Hallgren R, Mielants H, et al. A Randomised Placebo Controlled 12 Week Trial of Budesonide and Prednisolone in Rheumatoid Arthritis. Annals of the rheumatic diseases. 2004;63-6-688-95.

319. Kloppenburg M, Breedveld F, Terwiel J, et al. Minocycline in Active Rheumatoid Arthritis. A Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1994;37(5):629-36.

320. Kloppenburg M, Dijkmans B, Verweij C, et al. Inflammatory and Immunological Parameters of Disease Activity in Rheumatoid Arthritis Patients Treated With Minocycline. Immunopharmacology. 1996;31(2-3):163-9.

321. Knijff Dutmer E, Kalsbeek Batenburg E, Koerts J, et al. Platelet Function Is Inhibited by Non-Selective Non-Steroidal Anti-Inflammatory Drugs but Not by Cyclo-Oxygenase-2-Selective Inhibitors in Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2002;41(4):458-61.

322. Knijff Dutmer E, Martens A, vd Laar M. Effects of Nabumetone Compared With Naproxen on Platelet Aggregation in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1999;58(4):257-9.

323. Knijff-Dutmer E, Drossaers-Bakker W, Verhoeven A, et al. Rheumatoid Factor Measured by Fluoroimmunoassay: a Responsive Measure of Rheumatoid Arthritis Disease Activity That Is Associated With Joint Damage. Annals of the rheumatic diseases. 2002;61(7):603-7.

324. Knudsen LS, Klarlund M, Skjodt H, et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome. Journal of Rheumatology. 2008;35(7):1277-87.

325. Kollerup G, Hansen M, Horslev Petersen K. Urinary Hydroxypyridinium Cross-Links of Collagen in Rheumatoid Arthritis. Relation to Disease Activity and Effects of Methylprednisolone. British journal of rheumatology. 1994;33(9):816-20.

326. Kondo H, Abe T, Hashimoto H, et al. Efficacy and Safety of Tacrolimus (Fk506) in Treatment of Rheumatoid Arthritis: a Randomized, Double Blind, Placebo Controlled Dose-Finding Study. The Journal of rheumatology. 2004;31(2):243-51.

327. Kopp S, Akerman S, Nilner M. Short-Term Effects of Intra-Articular Sodium Hyaluronate, Glucocorticoid, and Saline Injections on Rheumatoid Arthritis of the Temporomandibular Joint. Journal of

craniomandibular disorders : facial & oral pain. 1991;5(4):231-8.

328. Kornasoff D, Maisenbacher J, Bowdler J, et al. The Efficacy and Tolerability of Aceclofenac Compared to Indomethacin in Patients With Rheumatoid Arthritis. Rheumatology international. 1996;15(6):225-30.

329. Korpela M, Laasonen L, Hannonen P, et al. Retardation of Joint Damage in Patients With Early Rheumatoid Arthritis by Initial Aggressive Treatment With Disease-Modifying Antirheumatic Drugs: Five-Year Experience From the Fin-Raco Study. Arthritis and rheumatism. 2004;50(7):2072-81.

330. Korthals-de Bos I, Van Tulder M, Boers M, et al. Indirect and Total Costs of Early Rheumatoid Arthritis: a Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate, and Sulfasalazine With Sulfasalazine Alone. The Journal of rheumatology. 2004;31(9):1709-16.

331. Kraan MC, de Koster BM, Elferink JG, et al. Inhibition of Neutrophil Migration Soon After Initiation of Treatment With Leflunomide or Methotrexate in Patients With Rheumatoid Arthritis: Findings in a Prospective, Randomized, Double-Blind Clinical Trial in Fifteen Patients. Arthritis and rheumatism. 2000;43(7):1488-95.

332. Kraan MC, Reece RJ, Barg EC, et al. Modulation of Inflammation and Metalloproteinase Expression in Synovial Tissue by Leflunomide and Methotrexate in Patients With Active Rheumatoid Arthritis. Findings in a Prospective, Randomized, Double-Blind, Parallel-Design Clinical Trial in Thirty-Nine Patients at Two Centers. Arthritis and rheumatism. 2000;43(8):1820-30.

333. Kraan MC, Smeets TJM, van Loon MJ, et al. Differential Effects of Leflunomide and Methotrexate on Cytokine Production in Rheumatoid Arthritis. Annals of the rheumatic diseases. 2004;63(9):1056-61.

334. Kremer J, Genovese M, Cannon GW, et al. Combination Leflunomide and Methotrexate (Mtx) Therapy for Patients With Active Rheumatoid Arthritis Failing Mtx Monotherapy: Open-Label Extension of a Randomized, Double-Blind, Placebo Controlled Trial. The Journal of rheumatology. 2004;31(8):1521-31.

335. Kremer JM, Davies JM, Rynes RI, et al. Every-Other-Week Methotrexate in Patients With Rheumatoid Arthritis. A Double-Blind, Placebo-Controlled Prospective Study. Arthritis and rheumatism. 1995;38(5):601-7.

336. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant Leflunomide Therapy in Patients With Active Rheumatoid Arthritis Despite Stable Doses of Methotrexate. A Randomized, Double-Blind, Placebo-Controlled Trial. Annals of internal medicine. 2002;137(9):726-33.

337. Kristensen LE, Geborek P, Saxne T. Dose escalation of infliximab therapy in arthritis patients is related to diagnosis and concomitant methotrexate treatment: Observational results from the South Swedish Arthritis Treatment Group register. Rheumatology. 2009;48(3):243-5.

338. Krug H, Broadwell L, Berry M, et al. Tolerability and Efficacy of Nabumetone and Naproxen in the Treatment of Rheumatoid Arthritis. Clinical therapeutics. 2000;22(1):40-52.

339. Kumar K, Gordon C, Toescu V, et al. Beliefs about medicines in patients with rheumatoid arthritis and systemic lupus erythematosus: A comparison between patients of South Asian and White British origin. Rheumatology. 2008;47(5):690-7.

340. Kurowski M, Menninger H, Pauli E. The Efficacy and Relative Bioavailability of Diclofenac Resinate in Rheumatoid Arthritis Patients. International journal of clinical pharmacology and therapeutics. 1994;32(8):433-40.

341. Kuuliala A, Leirisalo-Repo M, Mottonen T, et al. Serum Soluble Interleukin-2 Receptor Predicts Early Remission in Patients With Recent-Onset Rheumatoid Arthritis Treated With a Single Disease-Modifying Antirheumatic Drug. Clinical and

experimental rheumatology. 2005;23(2):243-6.

342. Kvien TK, Gaston JSH, Bardin T, et al. Three Month Treatment of Reactive Arthritis With Azithromycin: a EULAR Double Blind, Placebo Controlled Study. Annals of the rheumatic diseases. 2004;63(9):1113-9.

343. Laan RF, van Riel PL, van de Putte LB, et al. Low-Dose Prednisone Induces Rapid Reversible Axial Bone Loss in Patients With Rheumatoid Arthritis. A Randomized, Controlled Study. Annals of internal medicine. 1993;119(10):963-8.

344. Laas K, Peltomaa R, Puolakka K, et al. Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. Clinical and Experimental Rheumatology 2009;27(2):315-20.

345. Laasila K, Laasonen L, Leirisalo RM. Antibiotic Treatment and Long Term Prognosis of Reactive Arthritis. Annals of the rheumatic diseases. 2003;62(7):655-8.

346. Lacki J, Leszczynski P, Mackiewicz S. Intravenous Cyclophosphamide Combined With Methylprednisolone in the Treatment of Severe Refractory Rheumatoid Arthritis: the Effect on Lymphocytes. Journal of investigational allergology & clinical immunology : official organ of the International Association of Asthmology (INTERASMA) and Sociedad Latinoamericana de Alergia e Inmunología. 1996;6(4):232-6.

347. Lacki J, Mackiewicz S, Wiktorowicz K. Lymphocyte Phenotype Studies of Rheumatoid Arthritis Patients Treated With Methotrexate. Archivum immunologiae et therapiae experimentalis. 1994;42(4):287-90.

348. Lacki J, Samborski W, Mackiewicz S. Interleukin-10 and Interleukin-6 in Lupus Erythematosus and Rheumatoid Arthritis, Correlations With Acute Phase Proteins. Clinical rheumatology. 1997;16(3):275-8.

349. Lacki JK, Schochat T, Sobieska M, et al. Immunological Studies in Patients With Rheumatoid Arthritis Treated With Methotrexate or Cyclophosphamide. Zeitschrift für Rheumatologie. 1994;53(2):76-82.

350. Laharie D, Seneschal J, Schaeverbeke T, et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: A case-control study. Journal of Hepatology. 2010;53(6):1035-40.

351. Laine L, Connors L, Griffin MR, et al. Prescription rates of protective co-therapy for NSAID users at high GI risk and results of attempts to improve adherence to guidelines. 2009.

352. Laine L, Curtis SP, Cryer B, et al. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet. 2007;369(9560):465-73.

353. Laine L, Curtis SP, Cryer B, et al. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients. Alimentary Pharmacology and Therapeutics. 2010;32(10):1240-8.

354. Laine L, Goldkind L, Curtis SP, et al. How common is diclofenac-associated liver injury? Analysis of 17,289 arthritis patients in a long-term prospective clinical trial. American Journal of Gastroenterology. 2009;104(2):356-62.

355. Lambert CM, Sandhu S, Lochhead A, et al. Dose Escalation of Parenteral Methotrexate in Active Rheumatoid Arthritis That Has Been Unresponsive to Conventional Doses of Methotrexate: a Randomized, Controlled Trial. Arthritis and rheumatism. 2004;50(2):364-71.

356. Landewe R, Geusens P, van der Heijde D, et al. Arthritis Instantaneously Causes Collagen Type I and Type Ii Degradation in Patients With Early Rheumatoid Arthritis: a

Longitudinal Analysis. Ann Rheum Dis. 2006;65(1):40-4.

357. Lard LR, Boers M, Verhoeven A, et al. Early and Aggressive Treatment of Rheumatoid Arthritis Patients Affects the Association of Hla Class Ii Antigens With Progression of Joint Damage. Arthritis and rheumatism. 2002;46(4):899-905.

358. Larsen A, Kvien TK, Schattenkirchner M, et al. Slowing of Disease Progression in Rheumatoid Arthritis Patients During Long-Term Treatment With Leflunomide or Sulfasalazine. Scandinavian journal of rheumatology. 2001;30(3):135-42.

359. Larsen CM, Faulenbach M, Vaag A, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. The New England journal of medicine 2007(15):1517-26.

360. Lauhio A, Leirisalo Repo M, Lahdevirta J, et al. Double-Blind, Placebo-Controlled Study of Three-Month Treatment With Lymecycline in Reactive Arthritis, With Special Reference to Chlamydia Arthritis. Arthritis and rheumatism. 1991;34(1):6-14.

361. Le Gallez P, Bird H, Wright V. A Comparison of Choline Magnesium Trisalicylate and Acetylsalicylic Acid in Patients With Rheumatoid Arthritis. Current medical research and opinion. 1990;12(2):71-5.

362. Lee EY, Lee EB, Park BJ, et al. Tramadol 37.5-mg/acetaminophen 325-mg combination tablets added to regular therapy for rheumatoid arthritis pain: A 1-Week, randomized, double-blind, placebo-controlled trial. Clinical Therapeutics. 2006;28(12):2052-60.

363. Lee KKC, You JHS, Ho JTS, et al. Economic Analysis of Celecoxib Versus Diclofenac Plus Omeprazole for the Treatment of Arthritis in Patients at Risk of Ulcer Disease. Alimentary pharmacology & therapeutics. 2003;18(2):217-22.

364. Lee VWY, Chan CW, Chan LH, et al. The direct medical cost of rheumatoid arthritis in Hong Kong. Journal of Medical Economics. 2007;10(4):443-53.

365. Lehman A, Esdaile J, Klinkhoff A, et al. A 48-Week, Randomized, Double-Blind, Double-Observer, Placebo-Controlled Multicenter Trial of Combination Methotrexate and Intramuscular Gold Therapy in Rheumatoid Arthritis: Results of the Metgo Study. Arthritis Rheum. 2005;52(5):1360-70.

366. Lemmel EM. Comparison of Pyritinol and Auranofin in the Treatment of Rheumatoid Arthritis. British Journal of Rheumatology. 1993;32(5):375-82.

367. Lemmel EM, Bolten W, Burgos-Vargas R, et al. Efficacy and Safety of Meloxicam in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1997;24(2):282-90.

368. Lerndal T, Svensson B. A Clinical Study of Cph 82 Vs Methotrexate in Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(3):316-20.

369. Levalampi T, Korpela M, Vuolteenaho K, et al. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: Adverse events and other reasons leading to discontinuation of the treatment. Rheumatology International. 2008;28(3):261-9.

370. Leventhal L, Boyce E, Zurier R. Treatment of Rheumatoid Arthritis With Gammalinolenic Acid. Annals of internal medicine. 1993;119(9):867-73.

371. Levi S, Goodlad RA, Lee CY, et al. Effects of Nonsteroidal Anti-Inflammatory Drugs and Misoprostol on Gastroduodenal Epithelial Proliferation in Arthritis. Gastroenterology. 1992;102(5):1609-11.

372. Lewandowski B, Bernacka K, Kucharewicz B, et al. Assessment of Beta-2-Microglobulin Concentration in Serum and Urine in Rheumatoid Arthritis. Roczniki Akademii Medycznej w Białymstoku (1995). 1996;41(2):482-91.

373. Li LC, Maetzel A, Davis AM, et al. Primary therapist model for patients referred for rheumatoid arthritis rehabilitation: A cost-

effectiveness analysis. Arthritis Care and Research. 2006;55(3):402-10.

374. Li T, Wells G, Westhovens R, et al. Validation of a simple activity participation measure for rheumatoid arthritis clinical trials. Rheumatology. 2009;48(2):170-5.

375. Lightfoot R. Comparison of the Efficacy and Safety of Etodolac and Piroxicam in Patients With Rheumatoid Arthritis. Etodolac Study 326 Rheumatoid Arthritis Investigators Group. The Journal of rheumatology Supplement. 1997;47:10-6.

376. Lin Q, Gu JR, Li TW, et al. Value of the peripheral blood B-cells subsets in patients with ankylosing spondylitis. 2009.

377. Lin Q, Lin Z, Gu J, et al. Abnormal high-expression of CD154 on T lymphocytes of ankylosing spondylitis patients is down-regulated by etanercept treatment. 2010.

378. Lipsky P, Isakson P. Outcome of Specific Cox-2 Inhibition in Rheumatoid Arthritis. The Journal of rheumatology Supplement. 1997;49:9-14.

379. Lisse JR. Clinical Efficacy and Safety of Naprelan Versus Naprosyn in the Treatment of Rheumatoid Arthritis. The American journal of orthopedics. 1996;25(9 Suppl):21-9.

380. Litinsky I, Paran D, Levartovsky D, et al. The effects of leflunomide on clinical parameters and serum levels of IL-6, IL-10, MMP-1 and MMP-3 in patients with resistant rheumatoid arthritis. Cytokine. 2006;33(2):106-10.

381. Littman B, Drury C, Zimmerer R, et al. Rheumatoid Arthritis Treated With Tenidap and Piroxicam. Clinical Associations With Cytokine Modulation by Tenidap. Arthritis and rheumatism. 1995;38(1):29-37.

382. Liu C, Batliwalla F, Li W, et al. Genome-wide association scan identifies candidate polymorphisms associated with differential response to anti-TNF treatment in rheumatoid arthritis. Molecular Medicine. 2008;14(9-10):575-81.

383. Lonauer G, Tisscher J, Lim H, et al. Double-Blind Comparison of Etodolac and Diclofenac in Patients With Rheumatoid Arthritis. Current medical research and opinion. 1993;13(2):70-7.

384. Lopez-Gonzalez R, Hernandez-Garcia C, Abasolo L, et al. Differences between rheumatology attending physicians and training residents in the management of rheumatoid arthritis in Spain. Scandinavian Journal of Rheumatology. 2008;37(6):419-26.

385. Lopez-Mendez A, Daniel WW, Reading JC, et al. Radiographic Assessment of Disease Progression in Rheumatoid Arthritis Patients Enrolled in the Cooperative Systematic Studies of the Rheumatic Diseases Program Randomized Clinical Trial of Methotrexate, Auranofin, or a Combination of the Two. Arthritis and rheumatism. 1993;36(10):1364-9.

386. Louly PG, Medeiros-Souza P, Santos-Neto L. N-of-1 double-blind, randomized controlled trial of tramadol to treat chronic cough. 2009.

387. Lu C, Zha Q, Chang A, et al. Pattern differentiation in traditional chinese medicine can help define specific indications for biomedical therapy in the treatment of rheumatoid arthritis. 2009.

388. Luis M, Pacheco-Tena C, Cazarin-Barrientos J, et al. Comparison of Two Schedules for Administering Oral Low-Dose Methotrexate (Weekly Versus Every-Other-Week) in Patients With Rheumatoid Arthritis in Remission: a Twenty-Four Week, Single Blind, Randomized Study. Arthritis and rheumatism. 1999;42(10):2160-5.

389. Maccagno A, Di Giorgio E, Roldan E, et al. Double Blind Radiological Assessment of Continuous Oral Pamidronic Acid in Patients With Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1994;23(4):211-4.

390. Machold K, Neumann K, Smolen J. Recombinant Human Interferon Gamma in the Treatment of Rheumatoid Arthritis: Double Blind Placebo Controlled Study.

Annals of the rheumatic diseases. 1992;51(9):1039-43.

391. Machold KP, Landewe R, Smolen JS, et al. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. Annals of the rheumatic diseases. 2010;69(3):495-502.

392. Maetzel A, Strand V, Tugwell P, et al. Economic Comparison of Leflunomide and Methotrexate in Patients With Rheumatoid Arthritis: an Evaluation Based on a 1-Year Randomised Controlled Trial. PharmacoEconomics. 2002;20(1):61-70.

393. Maillefert JF, Combe B, Goupille P, et al. Long Term Structural Effects of Combination Therapy in Patients With Early Rheumatoid Arthritis: Five Year Follow up of a Prospective Double Blind Controlled Study. Annals of the rheumatic diseases. 2003;62(8):764-6.

394. Maksymowych WP, Salonen D, Inman RD, et al. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: A randomized placebo-controlled study. Journal of Rheumatology. 2010;37(8):1728-34.

395. Manorot M, Rojanasathien N, Louthrenoo W, et al. Comparative Studies of Quality and Bioavailability of Methotrexate in Thai Patients With Rheumatoid Arthritis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 1998;81(12):978-85.

396. Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-TNF: Results of the 3-year prospective French RATIO registry. Annals of the rheumatic diseases 2010;69(2):400-8.

397. Marshall D, Hunter J, Capell H. Double Blind, Placebo Controlled Study of Metronidazole as a Disease Modifying Agent in the Treatment of Rheumatoid Arthritis. Annals of the rheumatic diseases. 1992;51(6):758-60.

398. Martens H, Sheets P, Tenover J, et al. Decreased Testosterone Levels in Men With Rheumatoid Arthritis: Effect of Low Dose Prednisone Therapy. The Journal of rheumatology. 1994;21(8):1427=31.

399. Martin Mola E, Gijon Banos J, Ansoleaga J. Aceclofenac in Comparison to Ketoprofen in the Treatment of Rheumatoid Arthritis. Rheumatology international. 1995;15(3):111-6.

400. Matsumoto AK, Melian A, Mandel DR, et al. A Randomized, Controlled, Clinical Trial of Etoricoxib in the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 2002;29(8):1623-30.

401. Matsuno H, Yudoh K, Kondo M, et al. Biochemical Effect of Intra-Articular Injections of High Molecular Weight Hyaluronate in Rheumatoid Arthritis Patients. Inflammation research : official journal of the European Histamine Research Society [et al]. 1999;48(3):154-9.

402. Matteson EL, Yocum DE, St Clair EW, et al. Treatment of Active Refractory Rheumatoid Arthritis With Humanized Monoclonal Antibody Campath-1h Administered by Daily Subcutaneous Injection. Arthritis and rheumatism. 1995;38(9):1187-93.

403. Mayo P, Skeith K, Russell A, et al. Decreased Dromotropic Response to Verapamil Despite Pronounced Increased Drug Concentration in Rheumatoid Arthritis. British journal of clinical pharmacology. 2000;50(6):605-13.

404. Mazzantini M, Di Munno O, Metelli M, et al. Single Infusion of Neridronate (6-Amino-1-Hydroxyhexylidene-1,1-Bisphosphonate) in Patients With Active Rheumatoid Arthritis: Effects on Disease Activity and Bone Resorption Markers. Aging Clin Exp Res. 2002;14(3):197-201.

405. McCarey DW, McInnes IB, Madhok R, et al. Trial of Atorvastatin in Rheumatoid Arthritis (Tara): Double-Blind, Randomised Placebo-Controlled Trial. Lancet. 2004;262(9426):2015-21.

406. Mcgee B, Small RE, Singh R, et al. B Lymphocytic Clonal Expansion in Rheumatoid Arthritis. The Journal of rheumatology. 1996;23(1):36-43.

407. McInnes I, Porter D, Murphy E, et al. Low Dose Desensitisation Does Not Reduce the Toxicity of Sulphasalazine in Rheumatoid Arthritis. Annals of the rheumatic diseases. 1996;55(5):328-30.

408. McKendry R, Kraag G, Seigel S, et al. Therapeutic Value of Colchicine in the Treatment of Patients With Psoriatic Arthritis. Annals of the rheumatic diseases. 1993;52(11):826-8.

409. McKendry RJ. Azathioprine and Methotrexate as Combination Chemotherapy in Rheumatoid Arthritis. The Journal of rheumatology Supplement. 1990;25:28-33.

410. McLachlan A, Tett S, Cutler D, et al. Disposition of the Enantiomers of Hydroxychloroquine in Patients With Rheumatoid Arthritis Following Multiple Doses of the Racemate. British journal of clinical pharmacology. 1993;36(1):78-81.

411. McLachlan A, Tett S, Cutler D, et al. Bioavailability of Hydroxychloroquine Tablets in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1994;33(3):235-9.

412. Mease PJ. Cytokine Blockers in Psoriatic Arthritis. Annals of the rheumatic diseases. 2001;60(Suppl 3):iii37-40.

413. Mease PJ, Hobbs K, Chalmers A, et al. Local delivery of a recombinant adenoassociated vector containing a tumour necrosis factor alpha antagonist gene in inflammatory arthritis: A phase 1 dose-escalation safety and tolerability study. 2009.

414. Mease PJ, Signorovitch J, Yu AP, et al. Impact of adalimumab on symptoms of psoriatic arthritis in patients with moderate to severe psoriasis: A pooled analysis of randomized clinical trials. Dermatology. 2010;220(1):1-7.

415. Mease PJ, Wei N, Fudman EJ, et al. Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumor necrosis factor antagonist gene: Results of a phase 1/2 study. Journal of Rheumatology. 2010;37(4):692-703.

416. Mehta S, Dasarathy S, Tandon R, et al. A Prospective Randomized Study of the Injurious Effects of Aspirin and Naproxen on the Gastroduodenal Mucosa in Patients With Rheumatoid Arthritis. The American journal of gastroenterology. 1992;87(8):996-1000.

417. Meineke I, Turck D. Population Pharmacokinetic Analysis of Meloxicam in Rheumatoid Arthritis Patients. British journal of clinical pharmacology. 2003;55(1):32-8.

418. Melikterminas E, Ranganath V, Furst DE. Treatment of the elderly rheumatoid arthritis patient. Future Rheumatology. 2008;3(3):235-8.

419. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007 Jan;56(1):31 e1-15.

420. Merkel PA, Dooley MA, Dawson DV, et al. Interleukin-2 Receptor Levels in Sera of Patients With Rheumatoid Arthritis Treated With Sulfasalazine, Parenteral Gold, or Placebo. The Journal of rheumatology. 1996;23(11):1856-61.

421. Michaels R, Reading J, Beezhold D, et al. Serum Phospholipase A2 Activity in Patients With Rheumatoid Arthritis Before and After Treatment With Methotrexate, Auranofin, or Combination of the Two. Journal of Rheumatology. 1996;23(2):226-9.

422. Mierau M, Schoels M, Gonda G, et al. Assessing remission in clinical practice. Rheumatology. 2007;46(6):975-9.

423. Miese FR, Ostendorf B, Wittsack HJ, et al. Metacarpophalangeal joints in rheumatoid arthritis: Delayed gadolinium-enhanced MR

imaging of cartilage - A feasibility study. Radiology. 2010;257(2):441-7.

424. Miyake K, Kusunoki M, Shinji Y, et al. Bisphosphonate increases risk of gastroduodenal ulcer in rheumatoid arthritis patients on long-term nonsteroidal antiinflammatory drug therapy. Journal of Gastroenterology. 2009;44(2):113-20.

425. Miyake K, Ueki N, Suzuki K, et al. Preventive Therapy for Non-Steroidal Anti-Inflammatory Drug-Induced Ulcers in Japanese Patients With Rheumatoid Arthritis: the Current Situation and a Prospective Controlled-Study of the Preventive Effects of Lansoprazole or Famotidine. Alimentary pharmacology & therapeutics. 2005;21(Suppl 2):67-72.

426. Miyamoto S, Kageyama Y, Ozeki T, et al. Effects of Glucocorticoids on Bone Mineral Density in Rheumatoid Arthritis Patients. A Longitudinal Study. Archives of orthopaedic and trauma surgery. 1999;199(1-2):18-21.

427. Mladenovic V, Domljan Z, Rozman B, et al. Safety and Effectiveness of Leflunomide in the Treatment of Patients With Active Rheumatoid Arthritis. Results of a Randomized, Placebo-Controlled, Phase Ii Study. Arthritis and rheumatism. 1995;38(11):1595-603.

428. Montrone F, Petrillo M, Caruso I, et al. A Comparison of Severe Gastric Damage as a Result of Pirprofen and Naproxen Treatment in Rheumatoid Arthritis: a Controlled Endoscopic Study. Journal of internal medicine. 1994;236(2):153-9.

429. Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. Journal of the American Academy of Dermatology 2007(4):598-603.

430. Moreland L, R G, King K, et al. Results of a Phase-I/II Randomized, Masked, Placebo-Controlled Trial of Recombinant Human Interleukin-11 (Rhil-11) in the Treatment of Subjects With Active Rheumatoid Arthritis. Arthritis Res. 2001;3(4):247-52.

431. Moreland LW. Disease modifiers: Making the right therapeutic choices for our patients. Journal of Rheumatology. 2007;34(SUPPL. 79):21-6.

432. Moreland LW, Pratt PW, Mayes MD, et al. Double-Blind, Placebo-Controlled Multicenter Trial Using Chimeric Monoclonal Anti-Cd4 Antibody, Cm-T412, in Rheumatoid Arthritis Patients Receiving Concomitant Methotrexate. Arthritis and rheumatism. 1995;38(11):1581-8.

433. Morgan AW, Hale G, Rebello PRUB, et al. A pilot study of combination anti-cytokine and anti-lymphocyte biological therapy in rheumatoid arthritis. Qjm. 2008;101(4):299-306.

434. Morris V, Cruwys S, Kidd B. Characterisation of Capsaicin-Induced Mechanical Hyperalgesia as a Marker for Altered Nociceptive Processing in Patients With Rheumatoid Arthritis. Pain. 1997;71(2):179-86.

435. Mottonen T, Hannonen P, Korpela M, et al. Delay to Institution of Therapy and Induction of Remission Using Single-Drug or Combination-Disease-Modifying Antirheumatic Drug Therapy in Early Rheumatoid Arthritis. Arthritis Rheum. 2002;46(4):894-8.

436. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of Combination Therapy With Single-Drug Therapy in Early Rheumatoid Arthritis: a Randomised Trial. Lancet. 1999;353(9164):1568-73.

437. Mould DR, Davis CB, Minthorn EA, et al. A Population Pharmacokinetic-Pharmacodynamic Analysis of Single Doses of Clenoliximab in Patients With Rheumatoid Arthritis. Clinical pharmacology and therapeutics. 1999;66(3):246-57.

438. Muller Fassbender HR. A 6-Month Randomized Dose Range Study of Om-8980 in Rheumatoid Arthritis. Br J Rheumatol. 1993;32(8):746-50.

439. Muller-Ladner U, Rockwitz K, Brandt-Jurgens J, et al. Tolerability and patient/physician satisfaction with

subcutaneously administered methotrexate provided in two formulations of different drug concentrations in patients with rheumatoid arthritis. Open Rheumatology Journal. 2010;4:15-22.

440. Mur E, Hartig F, Eibl G, et al. Randomized Double Blind Trial of an Extract From the Pentacyclic Alkaloid-Chemotype of Uncaria Tomentosa for the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 2002;29(4):678-81.

441. Nagafuchi H, Suzuki N, Kaneko A, et al. Prolactin Locally Produced by Synovium Infiltrating T Lymphocytes Induces Excessive Synovial Cell Functions in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1999;26(9):1890-900.

442. Nair R, Saag KG. The use of low-dose glucocorticoids for the treatment of early rheumatoid arthritis: What can we learn about bone effects of glucocorticoids from randomized controlled trials? Current Rheumatology Reports. 2006;8(1):47-8.

443. Nakamura H, Ueki Y, Sakito S, et al. Clinical Effects of Actarit in Rheumatoid Arthritis: Improvement of Early Disease Activity Mediated by Reduction of Serum Concentrations of Nitric Oxide. Clinical and experimental rheumatology. 2000;18(4):455-50.

444. Naredo E, Collado P, Cruz A, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: Predictive value in disease activity and radiologic progression. Arthritis Care and Research. 2007;57(1):116-24.

445. Nehring AK, Dua U, Mollee P, et al. Epstein-Barr virus T-cell immunity despite rituximab. British journal of haematology 2007(4):628-32.

446. Nieto-Colonia AM, Santos WS, Keusseyan SP, et al. Antibodies to citrullinated peptides are not associated with the rate of joint destruction in patients with a well-established diagnosis of rheumatoid arthritis. Brazilian Journal of Medical and Biological Research. 2008;41(3):188-92.

447. Nikolaisen C, Figenschau Y, Nossent JC. Anemia in early rheumatoid arthritis is associated with interleukin 6-mediated bone marrow suppression, but has no effect on disease course or mortality. Journal of Rheumatology. 2008;35(3):380-6.

448. Nisar M, Carlisle L, Amos R. Methotrexate and Sulphasalazine as Combination Therapy in Rheumatoid Arthritis. British journal of rheumatology. 1994;33(7):651-4.

449. Nishimoto N, Miyasaka N, Yamamoto K, et al. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): Evidence of safety and efficacy in a 5-year extension study. 2009.

450. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of Rheumatoid Arthritis With Humanized Anti-Interleukin-6 Receptor Antibody: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2004;50(6):1761-9.

451. Nived O, Sturfelt G, Eckernas S, et al. A Comparison of 6 Months' Compliance of Patients With Rheumatoid Arthritis Treated With Tenoxicam and Naproxen. Use of Patient Computer Data to Assess Response to Treatment. The Journal of rheumatology. 1994;21(8):1537-41.

452. Nobunaga M, Yasuda M. Comparison of Clinical Effects of Bucillamine Between Additive Combination and Single Administration Study in Rheumatoid Arthritis. Agents and actions Supplements. 1993;44:105-9.

453. Nomura T, Kodama K, Nishimura M, et al. Animation as a useful tool for assessing functional status in psoriatic arthritis. Journal of Dermatological Science. 2006;44(3):172-4.

454. Nourmohammadi I, Athari-Nikazm S, Vafa MR, et al. Effects of antioxidant supplementations on oxidative stress in rheumatoid arthritis patients. Journal of Biological Sciences. 2010;10(1):63-6.

455. Numo R. Multicentre Double-Blind Study of the Efficacy, Safety and Tolerance of

Pirazolac Compared With Sulindac in Patients With Rheumatoid Arthritis. Drugs under experimental and clinical research. 1990;16(1):17-27.

456. Nunez M, Nunez E, Yoldi C, et al. Health-related quality of life in rheumatoid arthritis: Therapeutic education plus pharmacological treatment versus pharmacological treatment only. Rheumatology International. 2006;26(8):752-7.

457. Ochi T, Hakomori S, Fujimoto M, et al. Therapeutic Effect of Intradermal Injections With Difucosyl Lactosamine (Dimeric Lex) on Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1993;20(12):2038-45.

458. O'Connor K, Burke R, Riminton S. Hospital supply of off-label immunomodulatory drugs. 2009.

459. O'Dell JR, Blakely KW, Mallek JA, et al. Treatment of Early Seropositive Rheumatoid Arthritis: a Two-Year, Double-Blind Comparison of Minocycline and Hydroxychloroquine. Arthritis and rheumatism. 2001;44(10):2235-41.

460. O'Dell JR, Leff R, Paulsen G, et al. Treatment of Rheumatoid Arthritis With Methotrexate and Hydroxychloroquine, Methotrexate and Sulfasalazine, or a Combination of the Three Medications: Results of a Two-Year, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2002;46(5):1164-70.

461. O'Dell JR, Paulsen G, Haire CE, et al. Treatment of Early Seropositive Rheumatoid Arthritis With Minocycline: Four-Year Followup of a Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1999;42(8):1691-5.

462. Odio C, Ramirez T, Arias G, et al. Double Blind, Randomized, Placebo-Controlled Study of Dexamethasone Therapy for Hematogenous Septic Arthritis in Children. The Pediatric infectious disease journal. 2003;22(10):883-8.

463. Ogrendik M. Treatment of rheumatoid arthritis with ornidazole: A randomized, double-blind, placebo-controlled study. Rheumatology International. 2006;26(12):1132-7.

464. Ollendorf DA, Klingman D, Hazard E, et al. Differences in annual medication costs and rates of dosage increase between tumor necrosis factor-antagonist therapies for rheumatoid arthritis in a managed care population. Clinical Therapeutics. 2009;31(4):825-35.

465. Olsen N, Teal G, Brooks R. Igm-Rheumatoid Factor and Responses to Second-Line Drugs in Rheumatoid Arthritis. Agents and actions. 1991;34(1-2):124-9.

466. Olsen NJ, Brooks RH, Cush JJ, et al. A Double-Blind, Placebo-Controlled Study of Anti-Cd5 Immunoconjugate in Patients With Rheumatoid Arthritis. Arthritis and rheumatism. 1996;39(7):1102-8.

467. Osiri M, Deesomchok U, Tugwell P. Disease activity and functional changes of RA patients receiving different DMARDs in clinical practice. Clinical Rheumatology 2006;25(5):721-7.

468. Osterhaus JT, Purcaru O, Richard L. Discriminant validity, responsiveness and reliability of the rheumatoid arthritis-specific Work Productivity Survey (WPS-RA). 2009.

469. Paleolog E, Young S, Stark A, et al. Modulation of Angiogenic Vascular Endothelial Growth Factor by Tumor Necrosis Factor Alpha and Interleukin-1 in Rheumatoid Arthritis. Arthritis and rheumatism. 1998;41(7):1258-65.

470. Paleolog EM, Hunt M, Elliott MJ, et al. Deactivation of Vascular Endothelium by Monoclonal Anti-Tumor Necrosis Factor Alpha Antibody in Rheumatoid Arthritis. Arthritis and rheumatism. 1996;39(7):1082-91.

471. Palosaari K, Vuotila J, Takalo R, et al. Bone oedema predicts erosive progression on wrist MRI in early RA - A 2-yr observational MRI and NC scintigraphy study. Rheumatology. 2006;45(12):1542-8.

472. Pandya S, Aggarwal A, Misra R. Methotrexate Twice Weekly Vs Once Weekly in Rheumatoid Arthritis: a Pilot Double-Blind, Controlled Study. Rheumatology international. 2002;22(1):1-4.

473. Panicheeva S, Ngsriwongse S, Mokkhavesa C, et al. Original Versus Generic Piroxicams, Their Cost-Effective Evaluation in Rheumatoid Arthritis (Ra) Patients. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 1992;75(2):104-9.

474. Park JY, Kim KA, Lee YH, et al. Pharmacokinetic comparison and bioequivalence of two leflunomide formulations in humans: A single dose, randomized, open-label, two-way crossover study. International Journal of Clinical Pharmacology and Therapeutics. 2010;48(4):291-5.

475. Pascual-Ramos V, Contreras-Yanez I, Villa AR, et al. Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: Associated factors and relationship with disease activity and with disability. Arthritis Research and Therapy. 2009;11(1).

476. Pasero G, Marcolongo R, Serni U, et al. A Multi-Centre, Double-Blind Comparative Study of the Efficacy and Safety of Aceclofenac and Diclofenac in the Treatment of Rheumatoid Arthritis. Current medical research and opinion. 1995;13(6):305-15.

477. Paul BJ, Thachil EJ, Jayachandran NV, et al. Clinical efficacy and adverse effects of weekly single dose leflunomide in refractory rheumatoid arthritis. Indian Journal of Rheumatology. 2007;2(1):3-7.

478. Paulus H, Egger M, Ward J, et al. Analysis of Improvement in Individual Rheumatoid Arthritis Patients Treated With Disease-Modifying Antirheumatic Drugs, Based on the Findings in Patients Treated With Placebo. The Cooperative Systematic Studies of Rheumatic Diseases Group. Arthritis and rheumatism. 1990;33(4):477-84.

479. Pavelka K, Jarosova K, Suchy D, et al. Increasing the infliximab dose in rheumatoid arthritis patients: A randomised, double blind study failed to confirm its efficacy. 2009.

480. Pavelka K, Recker D, Verburg K. Valdecoxib Is as Effective as Diclofenac in the Management of Rheumatoid Arthritis With a Lower Incidence of Gastroduodenal Ulcers: Results of a 26-Week Trial. Rheumatology (Oxford). 2003;42(10):1207-15.

481. Pease C, Pope JE, Thorne C, et al. Canadian variation by province in rheumatoid arthritis initiating anti-tumor necrosis factor therapy: Results from the optimization of adalimumab trial. Journal of Rheumatology. 2010;37(12):2469-74.

482. Peeters HR, Jongen-Lavrencic M, Bakker CH, et al. Recombinant Human Erythropoietin Improves Health-Related Quality of Life in Patients With Rheumatoid Arthritis and Anaemia of Chronic Disease; Utility Measures Correlate Strongly With Disease Activity Measures. Rheumatology international. 1999;18(5-6):201-6.

483. Peeters HR, Jongen-Lavrencic M, Vreugdenhil G, et al. Effect of Recombinant Human Erythropoietin on Anaemia and Disease Activity in Patients With Rheumatoid Arthritis and Anaemia of Chronic Disease: a Randomised Placebo Controlled Double Blind 52 Weeks Clinical Trial. Annals of the rheumatic diseases. 1996;55(10):739-44.

484. Peltomaa R, Paimela L, Helve T, et al. Comparison of Intramuscular Gold and Sulphasalazine in the Treatment of Early Rheumatoid Arthritis. A One Year Prospective Study. Scandinavian journal of rheumatology. 1995;24(6):330-5.

485. Pentek M, Kobelt G, Czirjak L, et al. Costs of rheumatoid arthritis in Hungary. Journal of Rheumatology. 2007;34(6):1437-9.

486. Peretz A, Siderova V, Neve J. Selenium Supplementation in Rheumatoid Arthritis Investigated in a Double Blind, Placebo-Controlled Trial. Scandinavian journal of rheumatology. 2001;30(4):208-12.

487. Perez Ruiz F, Alonso Ruiz A, Ansoleaga J. Comparative Study of the Efficacy and Safety of Aceclofenac and Tenoxicam in Rheumatoid Arthritis. Clinical rheumatology. 1996;15(5):473-7.

488. Pettersson T, Soderblom T, Nyberg P, et al. Pleural Fluid Soluble Interleukin 2 Receptor in Rheumatoid Arthritis and Systemic Lupus Erythematosus. The Journal of rheumatology. 1994;21(10):1820-4.

489. Pincus T, Swearingen CJ, Luta G, et al. Efficacy of prednisone 1-4 mg/day in patients with rheumatoid arthritis: A randomised, double-blind, placebo controlled withdrawal clinical trial. 2009.

490. Pisoni L, Murgo A, Paresce E, et al. Effectiveness and safety of leflunomide in the clinical practice. A different experience [1]. Clinical and Experimental Rheumatology. 2007;25(1).

491. Plant M, O'Sullivan MM, Lewis P, et al. What Factors Influence Functional Ability in Patients With Rheumatoid Arthritis. Do They Alter Over Time? Rheumatology (Oxford). 2005;44(9):1181-5.

492. Plant MJ, Williams AL, O'Sullivan MM, et al. Relationship Between Time-Integrated C-Reactive Protein Levels and Radiologic Progression in Patients With Rheumatoid Arthritis. Arthritis and rheumatism. 2000;43(7):1473-7.

493. Podas T, Nightingale JMD, Oldham R, et al. Is rheumatoid arthritis a disease that starts in the intestine? A pilot study comparing an elemental diet with oral prednisolone. Postgraduate Medical Journal. 2007;83(976):128-31.

494. Polisson RP, Dooley MA, Dawson DV, et al. Interleukin-2 Receptor Levels in the Sera of Rheumatoid Arthritis Patients Treated With Methotrexate. Arthritis and rheumatism. 1994;37(1):50-6.

495. Popp W, Rauscher H, Ritschka L, et al. Prediction of Interstitial Lung Involvement in Rheumatoid Arthritis; the Value of Clinical Data, Chest Roentgenogram, Lung Function, and Serologic Parameters. CHEST. 1992;102(2):391-4.

496. Porter D, Capell H. The 'natural' History of Active Rheumatoid Arthritis Over 3-6 Months--an Analysis of Patients Enrolled Into Trials of Potential Disease-Modifying Anti-Rheumatic Drugs, and Treated With Placebo. British journal of rheumatology. 1993;32(6):423-8.

497. Porter D, Madhok R, Hunter J, et al. Prospective Trial Comparing the Use of Sulphasalazine and Auranofin as Second Line Drugs in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1992;52(6):416-4.

498. Porter D, McInnes I, Hunter J, et al. Outcome of second line therapy in rheumatoid arthritis. Annals of the rheumatic diseases. 1994;53(12):812-5.

499. Prins AMA, Vos K, Franssen EJF. Instability of topical ciclosporin emulsion for nail psoriasis [4]. Dermatology. 2007;215(4):362-3.

500. Prochorec-Sobieszek M, Chelstowska M, Rymkiewicz G, et al. Biclonal T-cell receptor gammadelta+ large granular lymphocyte leukemia associated with rheumatoid arthritis. Leukemia and Lymphoma. 2008;49(4):828-31.

501. Pullerits R, D'Elia HF, Tarkowski A, et al. The decrease of soluble RAGE levels in rheumatoid arthritis patients following hormone replacement therapy is associated with increased bone mineral density and diminished bone/cartilage turnover: A randomized controlled trial. 2009.

502. Puolakka K, Kautiainen H, Mottonen T, et al. Early Suppression of Disease Activity Is Essential for Maintenance of Work Capacity in Patients With Recent-Onset Rheumatoid Arthritis: Five-Year Experience From the Fin-Raco Trial. Arthritis and rheumatism. 2005;52(1):36-41.

503. Puolakka K, Kautiainen H, Mottonen T, et al. Use of the Stanford Health Assessment Questionnaire in estimation of long-term productivity costs in patients with recent-onset rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2009;38(2):96-103.

504. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of Initial Aggressive Drug Treatment With a Combination of Disease-Modifying Antirheumatic Drugs on the Development of Work Disability in Early Rheumatoid Arthritis: a Five-Year Randomized Followup Trial. Arthritis and rheumatism. 2004;50(1):55-62.

505. Puri S, Bery A, Sekhon JS, et al. Prescription practices of general physicians in the treatment of rheumatoid arthritis. Indian Journal of Rheumatology. 2008;3(2):86-7.

506. Rao U, Naidu M, Kumar T, et al. Comparison of Phenytoin With Auranofin and Chloroquine in Rheumatoid Arthritis--a Double Blind Study. The Journal of rheumatology. 1995;22(7):1235-40.

507. Raspe H, Deck R, Mattussek S. The Outcome of Traditional or Comprehensive Outpatient Care for Rheumatoid Arthritis (Ra). Results of an Open, Non-Randomized, 2-Year Prospective Study. Zeitschrift für Rheumatologie. 1992;51(Suppl 1):61-6.

508. Rau R, Herborn G, Karger T, et al. A Double-Blind Comparison of Parenteral Methotrexate and Parenteral Gold in the Treatment of Early Erosive Rheumatoid Arthritis: an Interim Report on 102 Patients After 12 Months. Seminars in arthritis and rheumatism. 1991;21(2 Suppl 1):13-30.

509. Rau R, Herborn G, Menninger H, et al. Comparison of Intramuscular Methotrexate and Gold Sodium Thiomalate in the Treatment of Early Erosive Rheumatoid Arthritis: 12 Month Data of a Double-Blind Parallel Study of 174 Patients. British journal of rheumatology. 2997;36(3):345-52.

510. Rau R, Herborn G, Menninger H, et al. Progression in Early Erosive Rheumatoid Arthritis: 12 Month Results From a Randomized Controlled Trial Comparing Methotrexate and Gold Sodium Thiomalate. British journal of rheumatology. 1998;37(11):1220-6.

511. Rau R, Wassenberg S, Zeidler H. Low Dose Prednisolone Therapy (LDPT) Retards Radiographically Detectable Destruction in Early Rheumatoid Arthritis--Preliminary Results of a Multicenter, Randomized, Parallel, Double Blind Study. Zeitschrift für Rheumatologie. 2000;59(Supple 2):II/90-6.

512. Reece RJ, Kraan MC, Radjenovic A, et al. Comparative Assessment of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis, by Dynamic Enhanced Magnetic Resonance Imaging. Arthritis and rheumatism. 2002;46(2):366-72.

513. Reginster J, Distel M, Bluhmki E. A Double-Blind, Three-Week Study to Compare the Efficacy and Safety of Meloxicam 7.5 Mg and Meloxicam 15 Mg in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1996;35(Suppl 1):17-21.

514. Rell Bakalarska M, Filipowicz Sosnowska A, Garwolinska H, et al. Assessment of the Results of Combined Treatment With Cyclophosphamide and Prednisone or Methotrexate and Prednisone in Patients With Rheumatoid Arthritis With Concomitant Vasculitis. Reumatologia. 1998;36(1):15-22.

515. Rheumatoid Arthritis Clinical Trial Archive Group. The Effect of Age and Renal Function on the Efficacy and Toxicity of Methotrexate in Rheumatoid Arthritis. . J Rheumatol. 1995;22(2):218-23.

516. Rigopoulos D, Gregoriou S, Lazaridou E, et al. Treatment of nail psoriasis with adalimumab: An open label unblinded study: ORIGINAL ARTICLE. Journal of the European Academy of Dermatology and Venereology. 2010;24(5):530-4.

517. Robak T, Gladalska A, Stepien H. The Tumour Necrosis Factor Family of Receptors/Ligands in the Serum of Patients With Rheumatoid Arthritis. European cytokine network. 1998;9(2):145-54.

518. Robinson AJ, Taylor DH, Wright GD. Infliximab therapy reduces periodontoid rheumatoid pannus formation [5]. Rheumatology. 2008;47(2):225-6.

519. Rodriguez de la Serna A, Geli Ferrer C, Diaz Lopez C, et al. Comparative Double-

Blind Study of Droxicam (New Nsaid) Versus Indomethacin in Rheumatoid Arthritis. European journal of rheumatology and inflammation. 1991;11(4):35-44.

520. Rozman B. Clinical Experience With Leflunomide in Rheumatoid Arthritis. The Journal of rheumatology. 1998;52(Suppl):27-32.

521. Rubbert-Roth A, Tak PP, Zerbini C, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: Results of a Phase III randomized study (MIRROR). Rheumatology. 2010;49(9):1683-93.

522. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis. 2007 Feb;66(2):189-94.

523. Sacerdote P, Carrabba M, Galante A, et al. Plasma and Synovial Fluid Interleukin-1, Interleukin-6 and Substance P Concentrations in Rheumatoid Arthritis Patients: Effect of the Nonsteroidal Anti Inflammatory Drugs Indomethacin, Diclofenac and Naproxen. Inflammation research : official journal of the European Histamine Research Society [et al]. 1995;44(11):486-90.

524. Salaffi F, Filippucci E, Carotti M, et al. Inter-observer agreement of standard joint counts in early rheumatoid arthritis: A comparison with grey scale ultrasonography - A preliminary study. Rheumatology. 2008;47(1):54-8.

525. Salemi S, Picchianti-Diamanti A, Germano V, et al. Influenza vaccine administration in rheumatoid arthritis patients under treatment with TNF(alpha) blockers: Safety and immunogenicity. Clinical Immunology. 2010;134(2):113-20.

526. Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. Annals of internal medicine 2007(9):631-9.

527. Sanchez Andrada S, Rodriguez Valverde V. A Double-Blind Randomised Controlled Trial of Droxicam Versus Indomethacin in Rheumatoid Arthritis. European journal of rheumatology and inflammation. 1991;11(4):35-44.

528. Sander O, Rau R. Treatment of Refractory Rheumatoid Arthritis With a Tumor Necrosis Factor Alpha Receptor Fusion Protein (Tnfr 55-Igg1) - a Monocentric Observation in 80 Patients. Zeitschrift fur Rheumatologie. 1998;57(5):307-11.

529. Sands BE, Kozarek R, Spainhour J, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflammatory bowel diseases 2007(1):2-11.

530. Sany J, Anaya JM, Canovas F, et al. Influence of Methotrexate on the Frequency of Postoperative Infectious Complications in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1993;20(7):1129-32.

531. Sarzi Puttini P, Santandrea S, Boccassini L, et al. The Role of Nsaids in Psoriatic Arthritis: Evidence From a Controlled Study With Nimesulide. Clinical and experimental rheumatology. 2001;19(1 Suppl 22):S17-20.

532. Sasso E, Merrill C, Furst T. Immunoglobulin Binding Properties of the Prosorba Immunadsorption Column in Treatment of Rheumatoid Arthritis. Ther Apher. 2001;5(2):84-91.

533. Saul P, Korlipara K. Acemetacin and Indomethacin in the Treatment of Rheumatoid Arthritis: a Double-Blind Comparative Study in General Practice. Current medical research and opinion. 1991;12(5):332-41.

534. Savolainen E, Kautiainen H, Koivula MK, et al. Change of diagnoses and outcome of patients with early inflammatory joint diseases during a mean 13-month follow-up. Scandinavian Journal of Rheumatology. 2007;36(3):194-7.

535. Schattenkirchner M. Double-Blind Comparison of Etodolac and Piroxicam in

Patients With Rheumatoid Arthritis. Curr Med Res Opin. 1991;12(8):497-506.

536. Scheel AK, Hermann KGA, Ohrndorf S, et al. Prospective 7 year follow up imaging study comparing radiography, ultrasonography, and magnetic resonance imaging in rheumatoid arthritis finger joints. Annals of the Rheumatic Diseases. 2006;65(5):595-600.

537. Schiff MH. Role of Interleukin 1 and Interleukin 1 Receptor Antagonist in the Mediation of Rheumatoid Arthritis. Ann Rheum Dis. 2000;59(Suppl 1):i103-8.

538. Schirmer M, Mur E, Pfeiffer K, et al. The Safety Profile of Low-Dose Cladribine in Refractory Rheumatoid Arthritis. A Pilot Trial. Scandinavian journal of rheumatology. 1997;26(5):376-9.

539. Schlumpf U, Hofmann P. Comparison of Medium- and High-Dose Methylprednisolone Pulse Therapy in Rheumatoid Arthritis. Zeitschrift fur Rheumatologie. 1990;49(3):160-4.

540. Schmajuk G, Schneeweiss S, Katz JN, et al. Treatment of older adult patients diagnosed with rheumatoid arthritis: Improved but not optimal. Arthritis Care and Research. 2007;57(6):928-34.

541. Schnabel A, Herlyn K, Burchardi C, et al. Long-Term Tolerability of Methotrexate at Doses Exceeding 15 Mg Per Week in Rheumatoid Arthritis. Rheumatology international. 1996;15(5):195-200.

542. Schnabel A, Reinhold K, Willmann V, et al. Side Effects and Efficacy of 15 Mg and 25 Mg Methotrexate Per Week in Rheumatoid Arthritis. Z RHEUMATOL. 1994;53(3):142-9.

543. Schnabel A, Reinhold Keller E, Willmann V, et al. Tolerability of Methotrexate Starting With 15 or 25 Mg/Week for Rheumatoid Arthritis. Rheumatology international. 1994;14(1):33-8.

544. Schnitzer TJ, Truitt K, Fleischmann R, et al. The Safety Profile, Tolerability, and Effective Dose Range of Rofecoxib in the Treatment of Rheumatoid Arthritis. Clinical Therapeutics. 1999;21(10):1688-702.

545. Schrohenloher R, Koopman W, Woodworth T, et al. Suppression of in Vitro IgM Rheumatoid Factor Production by Diphtheria Toxin Interleukin 2 Recombinant Fusion Protein (Dab 486il-2) in Patients With Refractory Rheumatoid Arthritis. The Journal of rheumatology. 1996;23(11):1845-8.

546. Schuerwegh AJ, van Offel JF, Bridts CH, et al. Influence of Longterm Therapy With Methotrexate and Low Dose Corticosteroids on Type 1 and Type 2 Cytokine Production in Cd4+ and Cd8+ T Lymphocytes of Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2001;28(8):1793-9.

547. Schuerwegh AJ, Van Offel JF, Stevens WJ, et al. Influence of Therapy With Chimeric Monoclonal Tumour Necrosis Factor-Alpha Antibodies on Intracellular Cytokine Profiles of T Lymphocytes and Monocytes in Rheumatoid Arthritis Patients. Rheumatology (Oxford). 2003;42(4):541-8.

548. Schwartz JI, Agrawal NG, Wong PH, et al. Lack of Pharmacokinetic Interaction Between Rofecoxib and Methotrexate in Rheumatoid Arthritis Patients. Journal of clinical pharmacology. 2001;41(10):1120-30.

549. Scott BL, Ramakrishnan A, Fosdal M, et al. Anti-thymocyte globulin plus etanercept as therapy for myelodysplastic syndromes (MDS): A phase II study. British Journal of Haematology. 2010;149(5):706-10.

550. Scott DL. Leflunomide Improves Quality of Life in Rheumatoid Arthritis. Scandinavian journal of rheumatology Supplement. 1999;112:23-9.

551. Scott DL, Smolen JS, Kalden JR, et al. Treatment of Active Rheumatoid Arthritis With Leflunomide: Two Year Follow up of a Double Blind, Placebo Controlled Trial Versus Sulfasalazine. Annals of the rheumatic diseases. 2001;60(10):913-23.

552. Seideman P. Additive Effect of Combined Naproxen and Paracetamol in Rheumatoid

Arthritis. British journal of rheumatology. 1993;32(12):1077-82.

553. Seideman P. Better Effect of Methotrexate on C-Reactive Protein During Daily Compared to Weekly Treatment in Rheumatoid Arthritis. Clinical rheumatology. 1993;12(2):347-9.

554. Seideman P, Beck O, Eksborg S, et al. The Pharmacokinetics of Methotrexate and Its 7-Hydroxy Metabolite in Patients With Rheumatoid Arthritis. British journal of clinical pharmacology. 1993;35(4):409-12.

555. Seppala E, Nissila M, Isomaki H, et al. Effects of Non-Steroidal Anti-Inflammatory Drugs and Prednisolone on Synovial Fluid White Cells, Prostaglandin E2, Leukotriene B4 and Cyclic Amp in Patients With Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1990;19(1):71-5.

556. Sharif M, Salisbury C, Taylor D, et al. Changes in Biochemical Markers of Joint Tissue Metabolism in a Randomized Controlled Trial of Glucocorticoid in Early Rheumatoid Arthritis. Arthritis and rheumatism. 1998;41(7):1203-9.

557. Sharp JT, Strand V, Leung H, et al. Treatment With Leflunomide Slows Radiographic Progression of Rheumatoid Arthritis: Results From Three Randomized Controlled Trials of Leflunomide in Patients With Active Rheumatoid Arthritis. Arthritis and rheumatism. 2000;43(3):495-505.

558. Shashikumar NS, Shivamurthy MC, Chandrashekara S. Evaluation of efficacy of combination of methotrexate and hydroxychloroquine with leflunomide in active rheumatoid arthritis. Indian Journal of Pharmacology 2010;42(6):358-61.

559. Sheeran T, Roobottom C, Wanklyn P, et al. The Effect of Bed Rest and Intra-Articular Steroids on the Acute Phase Response in Rheumatoid Arthritis. Clinical and experimental rheumatology. 1993;11(1):49-52.

560. Sheldon P. Ileum-Targeted Steroid Therapy in Rheumatoid Arthritis: Double-Blind, Placebo-Controlled Trial of Controlled-Release Budesonide. Rheumatology international. 2003;23(4):154-8.

561. Shi W, Wang Y, Li L, et al. Safety and Efficacy of Oral Nonsteroidal Anti-Inflammatory Drugs in Patients With Rheumatoid Arthritis: a Six-Month Randomised Study. Clinical Drug Investigation. 2004;24(2):89-101.

562. Shikiar R, Heffernan M, Langley RG, et al. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. The Journal of dermatological treatment 2007(1):25-31.

563. Shiokawa Y, Shichikawa K, Nobunaga M, et al. Clinical Study of a New Anti-Rheumatic Drug, Ms-932 on Rheumatoid Arthritis: Double-Blind Comparative Study With Placebo. Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines). 1991;7(Suppl 2):113-47.

564. Shiozawa S, Shiozawa K, Kita M, et al. A Preliminary Study on the Effect of Alpha-Interferon Treatment on the Joint Inflammation and Serum Calcium in Rheumatoid Arthritis. British journal of rheumatology. 1992;31(6):405-8.

565. Shiroky J, Neville C, Skelton J. High Dose Intravenous Methotrexate for Refractory Rheumatoid Arthritis. The Journal of rheumatology. 1992;19(2):247-51.

566. Shiroky JB, Neville C, Esdaile JM, et al. Low-Dose Methotrexate With Leucovorin (Folinic Acid) in the Management of Rheumatoid Arthritis. Results of a Multicenter Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1993;36(6):795-803.

567. Siddiqui AK, Huberfeld SI, Weidenheim KM, et al. Hydroxychloroquine-induced toxic myopathy causing respiratory failure. Chest. 2007;131(2):588-90.

568. Sieper J, Fendler C, Laitko S, et al. No Benefit of Long-Term Ciprofloxacin Treatment in Patients With Reactive Arthritis and Undifferentiated Oligoarthritis: a Three-Month, Multicenter, Double-Blind,

Randomized, Placebo-Controlled Study. Arthritis and rheumatism. 1999;42(7):1386-96.

569. Sigidin Y, Loukina G, Skurkovich B, et al. Randomized, Double-Blind Trial of Anti-Interferon-Gamma Antibodies in Rheumatoid Arthritis. Scandinavian journal of rheumatology. 2001;30(4):203-7.

570. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol Reduces Serious Gastrointestinal Complications in Patients With Rheumatoid Arthritis Receiving Nonsteroidal Anti-Inflammatory Drugs. A Randomized, Double-Blind, Placebo-Controlled Trial. Annals of internal medicine. 1995;123(4):241-9.

571. Simon F, Parola P, Grandadam M, et al. Chikungunya infection: An emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. Medicine. 2007;86(3):123-37.

572. Simon L, Robinson D, Basch C. Naproxen Levels in Plasma and Synovial Fluid of Patients With Rheumatoid Arthritis. CLIN THER. 1991;13(Suppl A):35-43.

573. Simon LS, Weaver AL, Graham DY, et al. Anti-Inflammatory and Upper Gastrointestinal Effects of Celecoxib in Rheumatoid Arthritis: a Randomized Controlled Trial. JAMA. 1999;282(20):1921-8.

574. Slaughter JR, Parker JC, Martens MP, et al. Clinical Outcomes Following a Trial of Sertraline in Rheumatoid Arthritis. Psychosomatics. 2002;43(1):36-41.

575. Smieja M, MacPherson DW, Kean W, et al. Randomised, Blinded, Placebo Controlled Trial of Doxycycline for Chronic Seronegative Arthritis. Annals of the rheumatic diseases. 2001;60(12):1088-94.

576. Smith AM, Sperling JW, O'Driscoll SW, et al. Arthroscopic shoulder synovectomy in patients with rheumatoid arthritis. Arthroscopy Journal of Arthroscopic and Related Surgery. 2006;22(1):50-6.

577. Smith DM, Johnson JA, Loeser R, et al. Evaluation of Tenidap (Cp-66,248) on Human Neutrophil Arachidonic Acid Metabolism, Chemotactic Potential and Clinical Efficacy in the Treatment of Rheumatoid Arthritis. Agents and actions. 1990;31(1-2):102-9.

578. Smolen J, Emery P. Efficacy and Safety of Leflunomide in Active Rheumatoid Arthritis. Rheumatology. 2000;39(Suppl 1):48-56.

579. Smolen JS. Efficacy and Safety of the New Dmard Leflunomide: Comparison to Placebo and Sulfasalazine in Active Rheumatoid Arthritis. Scandinavian journal of rheumatology Supplement. 1999;112:15-21.

580. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and Safety of Leflunomide Compared With Placebo and Sulphasalazine in Active Rheumatoid Arthritis: a Double-Blind, Randomised, Multicentre Trial. Lancet. 1999;353(9149):259-66.

581. Snowden JA, Biggs JC, Milliken ST, et al. A Randomised, Blinded, Placebo-Controlled, Dose Escalation Study of the Tolerability and Efficacy of Filgrastim for Haemopoietic Stem Cell Mobilisation in Patients With Severe Active Rheumatoid Arthritis. Bone marrow transplantation. 1998;22(11):1035-41.

582. Soderlin MK, Geborek P. Changing pattern in the prescription of biological treatment in rheumatoid arthritis. A 7-year follow-up of 1839 patients in southern Sweden. Annals of the Rheumatic Diseases. 2008;67(1):37-42.

583. Song YW, Lee EY, Koh EM, et al. Assessment of comparative pain relief and tolerability of SKI306X compared with celecoxib in patients with rheumatoid arthritis: A 6-week, multicenter, randomized, double-blind, double-dummy, phase III, noninferiority clinical trial. Clinical Therapeutics. 2007;29(5):862-73.

584. Spalding SJ, Kent CK, Boudreau R, et al. Three-dimensional and thermal surface imaging produces reliable measures of joint shape and temperature: A potential tool for

quantifying arthritis. Arthritis Research and Therapy. 2008;10(1).

585. Sreekanth V, Handa R, Wali J, et al. Doxycycline in the Treatment of Rheumatoid Arthritis--a Pilot Study. The Journal of the Association of Physicians of India. 2000;48(8):804-7.

586. St Clair EW, Cohen SB, Lee ML, et al. Treatment of Rheumatoid Arthritis With a Dr4/1 Peptide. The Journal of rheumatology. 2000;27(8):1855-63.

587. St Clair EW, Wagner CL, Fasanmade AA, et al. The Relationship of Serum Infliximab Concentrations to Clinical Improvement in Rheumatoid Arthritis: Results From Attract, a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2002;46(6):1451-9.

588. Steen KSS, Nurmohamed MT, Visman I, et al. Decreasing incidence of symptomatic gastrointestinal ulcers and ulcer complications in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2008;67(2):256-9.

589. Stenberg VI, Fiechtner JJ, Rice JR, et al. Endocrine Control of Inflammation: Rheumatoid Arthritis Double-Blind, Crossover Clinical Trial. International journal of clinical pharmacology research. 1992;12(1):11-8.

590. Stewart C, Fleming R, Arkin C, et al. Coadministration of Naproxen and Low-Dose Methotrexate in Patients With Rheumatoid Arthritis. Clinical Pharmacology & Therapeutics. 1990;47(4):540-6.

591. Stichenwirth M, Riedl E, Pehamberger H, et al. Pyoderma Gangrenosum in a patient with seronegative rheumatoid arthritis during therapy with adalimumab: Toxic effects of adalimumab or failure of adalimumab to prevent the onset of this phenomenon? Archives of Dermatology. 2008;144(6):817-8.

592. Stoch SA, Saag KG, Greenwald M, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: A 12-month randomized, placebo-controlled clinical trial. 2009.

593. Strand V, Cohen S, Schiff M, et al. Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Placebo and Methotrexate. Archives of Internal Medicine. 1999;159(21):2542-50.

594. Stubenrauch K, Wessels U, Birnboeck H, et al. Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clinical Therapeutics. 2010;32(9):1597-609.

595. Suarez Almazor M, Russell A. Parenteral Methotrexate or Gold for Rheumatoid Arthritis: a Follow up. Clinical & Experimental Rheumatology. 1990;8(2):163-6.

596. Subbanna PKT, Chandy SJ, Danda D, et al. Correlation between serum methotrexate concentrations and disease remission status in rheumatoid arthritis patients on triple disease-modifying antirheumatic drug therapy [1]. Indian Journal of Pharmacology. 2007;39(2):117-8.

597. Sugiura F, Kojima T, Oguchi T, et al. A case of peripheral neuropathy and skin ulcer in a patient with rheumatoid arthritis after a single infusion of tocilizumab. Modern Rheumatology. 2009;19(2):199-203.

598. Sundal E, Bertelletti D. Thymopentin Treatment of Rheumatoid Arthritis. Progress in drug research Fortschritte der Arzneimittelforschung Progrès des recherches pharmaceutiques. 1994;44(10):1145-9.

599. Suzuki A, Yamada R, Ohtake-Yamanaka M, et al. Anti-Citrullinated Collagen Type I Antibody Is a Target of Autoimmunity in Rheumatoid Arthritis. Biochemical and biophysical research communications. 2005;333(2):418-26.

600. Svensson B, Boonen A, Albertsson K, et al. Low-Dose Prednisolone in Addition to the Initial Disease-Modifying Antirheumatic

Drug in Patients With Early Active Rheumatoid Arthritis Reduces Joint Destruction and Increases the Remission Rate: a Two-Year Randomized Trial. Arthritis and rheumatism. 2005;52(11):3360-70.

601. Symmons D, Tricker K, Harrison M, et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs - Results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. Rheumatology. 2006;45(5):558-65.

602. Symmons D, Tricker K, Roberts C, et al. The British Rheumatoid Outcome Study Group (Brosg) Randomised Controlled Trial to Compare the Effectiveness and Cost-Effectiveness of Aggressive Versus Symptomatic Therapy in Established Rheumatoid Arthritis. Health Technol Assess. 2005;9(34):iii-iv, ix-x, 1-78.

603. Szmyrka-Kaczmarek M, Nowak B, Swierkot J, et al. Antinuclear antibodies and anti-cyclic citrullinated peptide antibodies in patients treated with adalimumab. Central European Journal of Immunology. 2008;33(3):120-6.

604. Taha AS, McLaughlin S, Holland PJ, et al. Effect on Gastric and Duodenal Mucosal Prostaglandins of Repeated Intake of Therapeutic Doses of Naproxen and Etodolac in Rheumatoid Arthritis. Annals of the rheumatic diseases. 1990;49(6):354-8.

605. Tak PP, Taylor PC, Breedveld FC, et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis. Arthritis and rheumatism. 1996;39(7):1077-81.

606. Tak PP, van der Lubbe PA, Cauli A, et al. Reduction of Synovial Inflammation After Anti-Cd4 Monoclonal Antibody Treatment in Early Rheumatoid Arthritis. Arthritis and rheumatism. 1995;38(10):1457-65.

607. Takada K, Danning C, Kuroiwa T, et al. Lymphocyte Depletion With Fludarabine in Patients With Psoriatic Arthritis: Clinical and Immunological Effects. Annals of the rheumatic diseases. 2003;62(11):1112-5.

608. Takahashi M, Suzuki M, Kushida K, et al. Relationship Between Pentosidine Levels in Serum and Urine and Activity in Rheumatoid Arthritis. British journal of rheumatology. 1997;36(6):637-42.

609. Tanno M, Nakamura I, Kobayashi S, et al. New-onset demyelination induced by infliximab therapy in two rheumatoid arthritis patients. Clinical Rheumatology. 2006;25(6):929-33.

610. Taukumova L, Mouravjoy Y, Gribakin S. Mucocutaneous Side Effects and Continuation of Aurotherapy in Patients With Rheumatoid Arthritis. Advances in experimental medicine and biology. 1999;455:367-73.

611. Taylor P, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and rheumatism. 2006 2006;54(1):47-53.

612. Taylor PC, Steuer A, Gruber J, et al. Comparison of Ultrasonographic Assessment of Synovitis and Joint Vascularity With Radiographic Evaluation in a Randomized, Placebo-Controlled Study of Infliximab Therapy in Early Rheumatoid Arthritis. Arthritis and rheumatism. 2004;50(4):1107-16.

613. Tebib J, Mariette X, Bourgeois P, et al. Masitinib in the treatment of active rheumatoid arthritis: Results of a multicentre, open-label, dose-ranging, phase 2a study. 2009.

614. Tebib JG, Manil LM, Modder G, et al. Better Results With Rhenium-186 Radiosynoviorthesis Than With Cortivazol in Rheumatoid Arthritis (Ra): a Two-Year Follow-up Randomized Controlled Multicentre Study. Clinical and experimental rheumatology. 2004;22(5):609-16.

615. Tegelberg A, Kopp S. A 3-Year Follow-up of Temporomandibular Disorders in Rheumatoid Arthritis and Ankylosing Spondylitis. Acta odontologica Scandinavica. 1996;54(1):14-8.

616. Teir J, Koduri G, Meadows A, et al. An audit of recording cardiovascular risk factors in patients with rheumatoid arthritis and systemic lupus erythematosus in centres in East Anglia and the South East. Rheumatology. 2008;47(8):1252-4.

617. ten Klooster PM, Drossaers-Bakker KW, Taal E, et al. Can we assess baseline pain and global health retrospectively? Clinical and Experimental Rheumatology. 2007;25(2):176-81.

618. Ten Klooster PM, Veehof MM, Taal E, et al. Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. Annals of the Rheumatic Diseases. 2007;66(11):1485-90.

619. ten Wolde S, Breedveld FC, Hermans J, et al. Randomised Placebo-Controlled Study of Stopping Second-Line Drugs in Rheumatoid Arthritis. Lancet. 1996;347(8998):347-52.

620. Tenembaum SN. Therapy of multiple sclerosis in children and adolescents. Clinical Neurology and Neurosurgery. 2010;112(7):633-40.

621. Tesser J, Fleischmann R, Dore R, et al. Concomitant Medication Use in a Large, International, Multicenter, Placebo Controlled Trial of Anakinra, a Recombinant Interleukin 1 Receptor Antagonist, in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2004;31(4):649-54.

622. Tett S, Cutler D, Beck C, et al. Concentration-Effect Relationship of Hydroxychloroquine in Patients With Rheumatoid Arthritis--a Prospective, Dose Ranging Study. The Journal of rheumatology. 2000;27(7):1656-60.

623. The Australian Multicentre Clinical Trial Group. Sulfasalazine in Early Rheumatoid Arthritis. J Rheumatol. 1992 7;19(11):1672.

624. Thurlings RM, Boumans M, Tekstra J, et al. Relationship between the type I interferon signature and the response to rituximab in rheumatoid arthritis patients. Arthritis Care and Research. 2010;62(12):3607-14.

625. Tikiz C, Utuk O, Pirildar T, et al. Effects of Angiotensin-Converting Enzyme Inhibition and Statin Treatment on Inflammatory Markers and Endothelial Functions in Patients With Longterm Rheumatoid Arthritis. The Journal of rheumatology. 2005;32(11):2095-101.

626. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in Rheumatoid Arthritis. A 48-Week, Double-Blind, Placebo-Controlled Trial. Mira Trial Group. Annals of internal medicine. 1995;122(2):81-9.

627. Torsteinsdottir I, Groth T, U L. Production and Elimination of Hyaluronan in Rheumatoid Arthritis Patients: Estimation With a Loading Test. Seminars in arthritis and rheumatism. 1999;28(4):268-79.

628. Toussirot E, Pertuiset E, Kantelip B, et al. Sarcoidosis occuring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: Report of two cases. Clinical and Experimental Rheumatology. 2008;26(3):471-5.

629. Tracy T, Worster T, Bradley J, et al. Methotrexate Disposition Following Concomitant Administration of Ketoprofen, Piroxicam and Flurbiprofen in Patients With Rheumatoid Arthritis. British journal of clinical pharmacology. 1994;37(5):453-6.

630. Tugwell P, Bombardier C, Buchanan WW, et al. Methotrexate in Rheumatoid Arthritis. Impact on Quality of Life Assessed by Traditional Standard-Item and Individualized Patient Preference Health Status Questionnaires. Archives of internal medicine. 1990;150(1):59-62.

631. Turiel M, Tomasoni L, Sitia S, et al. Effects of long-term disease-modifying antirheumatic drugs on endothelial function in patients with early rheumatoid arthritis. Cardiovascular Therapeutics. 2010;28(5):e53-e64.

632. Tutuncu Z, Kavanaugh A. Treatment of elderly rheumatoid arthritis. Future Rheumatology. 2007;2(3):313-9.

633. Uddenfeldt P, Leden I, Rubin B. A Double-Blind Comparison of Oral Ketoprofen 'controlled Release' and Indomethacin Suppository in the Treatment of Rheumatoid Arthritis With Special Regard to Morning Stiffness and Pain on Awakening. Current medical research and opinion. 1993;13(3):127-32.

634. Uutela T, Hannonen P, Kautianen H, et al. Positive treatment response improves the health-ralated quality of life of patients with early rheumatiod arthritis. Clinical and Experimental Rheumatology. 2009;27(1):108-11.

635. Valleala H, Laasonen L, Koivula M-K, et al. Two Year Randomized Controlled Trial of Etidronate in Rheumatoid Arthritis: Changes in Serum Aminoterminal Telopeptides Correlate With Radiographic Progression of Disease. The Journal of rheumatology. 2003;30(3):468-73.

636. Valleala H, Laitinen K, Pylkkanen L, et al. Clinical and Biochemical Response to Single Infusion of Clodronate in Active Rheumatoid Arthritis - Double Blind Placebo Controlled Study. Inflammation Research. 2001;50(12):598-601.

637. Van Aken J, Van Dongen H, Le Cessie S, et al. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: An observational cohort study. Annals of the Rheumatic Diseases. 2006;65(1):20-5.

638. van Berlo WTM, van de Wiel HBM, Taal E, et al. Sexual functioning of people with rheumatoid arthritis: A multicenter study. Clinical Rheumatology. 2007;26(1):30-8.

639. Van Den Bemt BJF, Van Den Hoogen FHJ, Benraad B, et al. Adherence rates and associations with nonadherence in patients with rheumatoid arthritis using disease modifying antirheumatic drugs. 2009.

640. Van Der Bijl AE, Teng YKO, Van Oosterhout M, et al. Efficacy of intraarticular infliximab in patients with chronic or recurrent gonarthritis: A clinical randomized trial. 2009.

641. Van Der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-Year results of PREMIER. Journal of Rheumatology. 2010;37(11):2237-46.

642. Van Der Kooij SM, Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Annals of the Rheumatic Diseases 2008;67(2):266-9.

643. van der Lubbe PA, Dijkmans BA, Markusse HM, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Cd4 Monoclonal Antibody Therapy in Early Rheumatoid Arthritis. Arthritis and rheumatism. 1995;38(8):1097-106.

644. van der Lubbe PA, Reiter C, Breedveld FC, et al. Chimeric Cd4 Monoclonal Antibody Cm-T412 as a Therapeutic Approach to Rheumatoid Arthritis. Arthritis and rheumatism. 1993;36(10):1375-9.

645. van der Lubbe PA, Reiter C, Miltenburg AM, et al. Treatment of Rheumatoid Arthritis With a Chimeric Cd4 Monoclonal Antibody (Cm-T412): Immunopharmacological Aspects and Mechanisms of Action. Scandinavian journal of immunology. 1994;39(3):286-94.

646. van der Veen M, Bijlsma J. The Effect of Methylprednisolone Pulse Therapy on Methotrexate Treatment of Rheumatoid Arthritis. Clinical rheumatology. 1993;12(4):74-6.

647. van Ede AE, Laan RFJM, Blom HJ, et al. Homocysteine and Folate Status in Methotrexate-Treated Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2002;41(6):658-65.

648. Van Eijk Y, Boonen A, Schulpen G, et al. Safety and patient satisfaction of infliximab administration in an extramural setting

supervised by a rheumatology specialist nurse. Annals of the Rheumatic Diseases. 2006;65(2).

649. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, et al. Low-Dose Prednisone Therapy for Patients With Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Annals of internal medicine. 2002;136(1):1-12.

650. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JWG, et al. Low-Dose Glucocorticoids in Early Rheumatoid Arthritis: Discordant Effects on Bone Mineral Density and Fractures? Clinical and experimental rheumatology. 2003;21(2):155-60.

651. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JWG, et al. The Clinical Effect of Glucocorticoids in Patients With Rheumatoid Arthritis May Be Masked by Decreased Use of Additional Therapies. Arthritis and rheumatism. 2004;51(2):217-20.

652. van Holten J, Pavelka K, Vencovsky J, et al. A Multicentre, Randomised, Double Blind, Placebo Controlled Phase Ii Study of Subcutaneous Interferon Beta-1a in the Treatment of Patients With Active Rheumatoid Arthritis. Ann Rheum Dis. 2005;64(1):64-9.

653. van Jaarsveld CH, Jacobs JW, van der Veen MJ, et al. Aggressive Treatment in Early Rheumatoid Arthritis: a Randomised Controlled Trial. Annals of the Rheumatic Diseases. 2000;59(6):468-77.

654. van Jaarsveld CH, Jahangier ZN, Jacobs JW, et al. Toxicity of Anti-Rheumatic Drugs in a Randomized Clinical Trial of Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(12):1374-82.

655. Van Kuijk AWR, Gerlag DM, Vos K, et al. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: Effects of adalimumab treatment on synovial tissue. 2009.

656. Van Offel JF, Schuerwegh AJ, Bridts CH, et al. Influence of Cyclic Intravenous Pamidronate on Proinflammatory Monocytic Cytokine Profiles and Bone Density in Rheumatoid Arthritis Treated With Low Dose Prednisolone and Methotrexate. Clinical and experimental rheumatology. 2001;19(1):13-20.

657. Van Riel PLCM, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Annals of the Rheumatic Diseases 2008;67(8):1104-10.

658. van Roon J, Wijngaarden S, Lafeber FPJG, et al. Interleukin 10 Treatment of Patients With Rheumatoid Arthritis Enhances Fc Gamma Receptor Expression on Monocytes and Responsiveness to Immune Complex Stimulation. The Journal of rheumatology. 2003;30(4):648-51.

659. van Roon JA, van Roy JL, Gmelig-Meyling FH, et al. Prevention and Reversal of Cartilage Degradation in Rheumatoid Arthritis by Interleukin-10 and Interleukin-4. Arthritis and rheumatism. 1996;39(5):829-35.

660. van Schaardenburg D, Valkema R, Dijkmans BA, et al. Prednisone Treatment of Elderly-Onset Rheumatoid Arthritis. Disease Activity and Bone Mass in Comparison With Chloroquine Treatment. Arthritis and rheumatism. 1995;38(3):334-42.

661. Verdickt W, Moran C, Hantzschel H, et al. A Double-Blind Comparison of the Gastroduodenal Safety and Efficacy of Diclofenac and a Fixed Dose Combination of Diclofenac and Misoprostol in the Treatment of Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1992;21(2):85-91.

662. Verhoef J, Toussaint PJ, Zwetsloot-Schonk JHM, et al. Effectiveness of the introduction of an international classification of functioning, disability and health-based rehabilitation tool in multidisciplinary team care in patients with rheumatoid arthritis.

Arthritis Care and Research. 2007;57(2):240-8.

663. Verhoeven AC, Bibo JC, Boers M, et al. Cost-Effectiveness and Cost-Utility of Combination Therapy in Early Rheumatoid Arthritis: Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine With Sulphasalazine Alone. British journal of rheumatology. 1998;37(10):1102-9.

664. Verstappen S, Jacobs J, Bijlsma JW. The Utrecht Experience With Different Treatment Strategies in Early Rheumatoid Arthritis. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S165-8.

665. Verstappen S, van Albada Kuipers G, Bijlsma J, et al. A Good Response to Early Dmard Treatment of Patients With Rheumatoid Arthritis in the First Year Predicts Remission During Follow up. Ann Rheum Dis. 2005;64(1):38-43.

666. Verstappen SMM, Jacobs JWG, Bijlsma JWJ, et al. Five-Year Followup of Rheumatoid Arthritis Patients After Early Treatment With Disease-Modifying Antirheumatic Drugs Versus Treatment According to the Pyramid Approach in the First Year. Arthritis and rheumatism. 2003;48(7):1797-807.

667. Verstappen SMM, McCoy MJ, Roberts C, et al. Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: Results of the STIVEA trial. Annals of the rheumatic diseases. 2010;69(3):503-9.

668. Veys E, Menkes C, Emery P. A Randomized, Double-Blind Study Comparing Twenty-Four-Week Treatment With Recombinant Interferon-Gamma Versus Placebo in the Treatment of Rheumatoid Arthritis. Arthritis and rheumatism. 1997;40(1):62-8.

669. Vis M, Havaardsholm EA, Haugeberg G, et al. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkappaB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2006;65(11):1495-9.

670. Vischer TL. Follow-up With Om-8980 After a Double-Blind Study of Om-8980 and Auranofin in Rheumatoid Arthritis. Clinical rheumatology. 1990;9(3):356-61.

671. Vlak T, Eldar R. Disability in Rheumatoid Arthritis After Monotherapy With Dmards. International Journal Rehabilitation Research. 2003;26(3):207-12.

672. von Scheele B, Pena B, Wong J, et al. Economic Evaluation of Oral Valdecoxib Versus Diclofenac in the Treatment of Patients With Rheumatoid Arthritis in a Randomized Clinical Trial. Rheumatology (Oxford). 2003;42(Suppl 3):iii53-9.

673. Wailoo AJ, Bansback N, Brennan A, et al. Biologie drugs for rheumatoid arthritis in the medicare program: A cost-effectiveness analysis. Arthritis and Rheumatism. 2008;58(4):939-46.

674. Wakefield D, McCluskey P, Verma M, et al. Ciprofloxacin Treatment Does Not Influence Course or Relapse Rate of Reactive Arthritis and Anterior Uveitis. Arthritis and rheumatism. 1999;42(9):1894-7.

675. Walitt B, Pettinger M, Weinstein A, et al. Effects of postmenopausal hormone therapy on rheumatoid arthritis: The women's health initiative randomized controlled trials. Arthritis Care and Research. 2008;59(3):302-10.

676. Walsh JK, Muehlbach MJ, Lauter SA, et al. Effects of Triazolam on Sleep, Daytime Sleepiness, and Morning Stiffness in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1996;23(2):245-52.

677. Wassenberg S, Rau R, Steinfeld P, et al. Very Low-Dose Prednisolone in Early Rheumatoid Arthritis Retards Radiographic Progression Over Two Years: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2005;52(11):3371-80.

678. Weinblatt M, Maier A, Coblyn J. Low Dose Leucovorin Does Not Interfere With the Efficacy of Methotrexate in Rheumatoid Arthritis: an 8 Week Randomized Placebo Controlled Trial. The Journal of rheumatology. 1993;20(6):950-2.

679. Weinblatt M, Maier A, Fraser P, et al. Longterm Prospective Study of Methotrexate in Rheumatoid Arthritis: Conclusion After 132 Months of Therapy. The Journal of rheumatology. 1988;25(2):238-42.

680. Weinblatt M, Polisson R, Blotner SD, et al. The Effects of Drug Therapy on Radiographic Progression of Rheumatoid Arthritis. Results of a 36-Week Randomized Trial Comparing Methotrexate and Auranofin. Arthritis and rheumatism. 1993;36(5):613-9.

681. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Annals of the rheumatic diseases 2007(2):228-34.

682. Weinblatt ME, Kaplan H, Germain BF, et al. Methotrexate in Rheumatoid Arthritis. A Five-Year Prospective Multicenter Study. Arthritis and rheumatism. 1994;37(10):1492-8.

683. Weinblatt ME, Kaplan H, Germain BF, et al. Low-Dose Methotrexate Compared With Auranofin in Adult Rheumatoid Arthritis. A Thirty-Six-Week, Double-Blind Trial. Arthritis and rheumatism. 1990;33(3):330-8.

684. Weinblatt ME, Kaplan H, Germain BF, et al. Methotrexate in Rheumatoid Arthritis: Effects on Disease Activity in a Multicenter Prospective Study. The Journal of rheumatology. 1991;18(3):334-8.

685. Weinblatt ME, Kremer JM, Coblyn JS, et al. Zileuton, a 5-Lipoxygenase Inhibitor in Rheumatoid Arthritis. The Journal of rheumatology. 1992;19(10):1537-41.

686. Weinblatt ME, Maddison PJ, Bulpitt KJ, et al. Campath-1h, a Humanized Monoclonal Antibody, in Refractory Rheumatoid Arthritis. An Intravenous Dose-Escalation Study. Arthritis and rheumatism. 1995;38(11):1589-94.

687. Weinblatt ME, Weissman BN, Holdsworth DE, et al. Long-Term Prospective Study of Methotrexate in the Treatment of Rheumatoid Arthritis. 84-Month Update. Arthritis and rheumatism. 1992;35(2):129-37.

688. Weitoft T, Larsson A, Saxne T, et al. Changes of Cartilage and Bone Markers After Intra-Articular Glucocorticoid Treatment With and Without Postinjection Rest in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2005;64(12):1750-3.

689. Wendling D, Racadot E, Wijdenes J, et al. A Randomized, Double Blind, Placebo Controlled Multicenter Trial of Murine Anti-Cd4 Monoclonal Antibody Therapy in Rheumatoid Arthritis. The Journal of rheumatology. 1998;25(8):1457-61.

690. Wendling D, Wijdenes J, Racadot E, et al. Therapeutic use of monoclonal anti-CD4 antibody in rheumatoid arthritis. J Rheumatol. 1991 Mar;18(3):325-7.

691. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. 2009.

692. Westhovens R, Verwilghen J, Dequeker J. Total Lymphoid Irradiation in Rheumatoid Arthritis. A Ten-Year Followup. Arthritis and rheumatism. 1997;40(3):426-9.

693. Whitehead J, Thomas P. A Sequential Trial of Pain Killers in Arthritis: Issues of Multiple Comparisons With Control and of Interval-Censored Survival Data. Journal of Biopharmaceutical Statistics. 1997;7(3):333-53.

694. Wijnands M, van Riel P, van 't Hof M, et al. Longterm Treatment With Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis: a Prospective Drug Survival Study. The Journal of rheumatology. 1991;18(2):184-7.

695. Williams HJ, Ward JR, Reading JC, et al. Comparison of Auranofin, Methotrexate, and the Combination of Both in the Treatment of Rheumatoid Arthritis. A Controlled Clinical Trial. Arthritis and rheumatism. 1992;35(3):259-69.

696. Willich SN, Rossnagel K, Roll S, et al. Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial. 2010.

697. Willkens R, Sharp J, Stablein D, et al. Comparison of Azathioprine, Methotrexate, and the Combination of the Two in the Treatment of Rheumatoid Arthritis. A Forty-Eight-Week Controlled Clinical Trial With Radiologic Outcome Assessment. Arthritis and rheumatism. 1995;38(12):1799-806.

698. Willkens R, Stablein D. Combination Treatment of Rheumatoid Arthritis Using Azathioprine and Methotrexate: a 48 Week Controlled Clinical Trial. The Journal of rheumatology Supplement. 1996;44:64-8.

699. Willkens RF, Urowitz MB, Stablein DM, et al. Comparison of Azathioprine, Methotrexate, and the Combination of Both in the Treatment of Rheumatoid Arthritis. A Controlled Clinical Trial. Arthritis and rheumatism. 1992;35(8):849-56.

700. Wojtulewski JA, Schattenkirchner M, Barcelo P, et al. A Six-Month Double-Blind Trial to Compare the Efficacy and Safety of Meloxicam 7.5 Mg Daily and Naproxen 750 Mg Daily in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1996;35(Suppl 1):22-8.

701. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis and Rheumatism 2007;56(9):2886-95.

702. Wong M, Oakley SP, Young L, et al. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. 2009.

703. Wood Nd AMDSHSMGRSS. Cartilage Protective Agent (Cpa) Ro 32-3555, a New Matrix Metalloproteinase Inhibitor for the Treatment of Rheumatoid Arthritis. Agents and Actions Supplements. 1998;36(8):1087-8.

704. Woodworth TG. Early Clinical Studies of Il-2 Fusion Toxin in Patients With Severe Rheumatoid Arthritis and Recent Onset Insulin-Dependent Diabetes Mellitus. Clinical and experimental rheumatology. 1993;11(Suppl 8):S177-80.

705. Wu E, Chen L, Birnbaum H, et al. Retrospective claims data analysis of dosage adjustment patterns of TNF antagonists among patients with rheumatoid arthritis. Current Medical Research and Opinion. 2008;24(8):2229-40.

706. Wylie G, Appelboom T, Bolten W, et al. A Comparative Study of Tenidap, a Cytokine-Modulating Anti-Rheumatic Drug, and Diclofenac in Rheumatoid Arthritis: a 24-Week Analysis of a 1-Year Clinical Trial. British journal of rheumatology. 1995;34(6):554-63.

707. Yang ZX, Li ZB, Sun ZC, et al. Correlations between serum macrophage migration inhibitory factor and active rheumatoid arthritis. Journal of Clinical Rehabilitative Tissue Engineering Research. 2008;12(37):7390-3.

708. Yasuda M, Sakai K, Oribe M, et al. Efficacy of Additive Dmard Therapy in Patients With Rheumatoid Arthritis. Double Blind Controlled Trial Using Bucillamine and Placebo With Maintenance Doses of Gold Sodium Thiomalate. J Rheumatol. 1994;21(1):33-50.

709. Yocum D, Furst D, Kaine JL, et al. Efficacy and Safety of Tacrolimus in Patients With Rheumatoid Arthritis: a Double-Blind Trial. Arthritis Rheum. 2003;48(12):3328-37.

710. Yxfeldt A, Wallberg-Jonsson S, Hultdin J, et al. Homocysteine in Patients With Rheumatoid Arthritis in Relation to Inflammation and B-Vitamin Treatment. Scand J Rheumatol. 2003;32(4):205-10.

711. Zanette SdA, Born IG, Brenol JCT, et al. A pilot study of acupuncture as adjunctive treatment of rheumatoid arthritis. Clinical Rheumatology. 2008;27(5):627-35.

712. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China. APLAR Journal of Rheumatology 2006;9(2):127-30.

713. Zhao S, Fiechtner JI, Tindall E, et al. Evaluation of Health-Related Quality of Life of Rheumatoid Arthritis Patients Treated With Celecoxib. Arthritis care and research : the official journal of the Arthritis Health Professions Association. 2000;13(2):112-21.

714. Zhou X, Zhou Z, Jin M, et al. Clinical Study of Qingluo Tongbi Granules in Treating 63 Patients With Rheumatoid Arthritis of the Type of Yin-Deficiency and Heat in Collaterals. J Tradit Chin Med. 2004;24(2):83-7.

715. Ziebland S, Fitzpatrick R, Jenkinson C, et al. Comparison of Two Approaches to Measuring Change in Health Status in Rheumatoid Arthritis: the Health Assessment Questionnaire (Haq) and Modified Haq. Annals of the rheumatic diseases. 1992;51(11):1202-5.

716. Zoppi M, Peretti G, Boccard E. Placebo-Controlled Study of the Analgesic Efficacy of an Effervescent Formulation of 500 Mg Paracetamol in Arthritis of the Knee or the Hip. European Journal of Pain. 1995;16(1-2):42-8.

717. Zuo X, Duan L, Cao Z, et al. A Clinical Study on Rheumatoid Arthritis Treated by Cu.zn-Sod. Bulletin of Hunan Medical University. 1995;20(3):275-7.

Reference Source: Dossiers

1. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1414-20.

2. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):692-701.

3. Bernstein LE, Berry J, Kim S, et al. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med. 2006 Apr 24;166(8):902-8.

4. Breedveld FC, Kalden JR. Appropriate and effective management of rheumatoid arthritis. Ann Rheum Dis. 2004 Jun;63(6):627-33.

5. Brodszky V, Pentek M, Gulacsi L. Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR50 response after 24 weeks of treatment. Scand J Rheumatol. 2008 Sep-Oct;37(5):399-400.

6. Cardiel MH. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. Rheumatology (Oxford). 2006 Jun;45 Suppl 2:ii7-ii22.

7. Cella D, Yount S, Sorensen M, et al. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):811-9.

8. Combe BG, Codreanu C, Fiocco U, et al. Double-blind comparison of Etanercept and Sulphasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving Sulphasalazine. Ann Rheum Dis. 2006 Apr 10.

9. Emery P. Role of adalimumab, a novel TNF antagonist in advancing rheumatoid arthritis control. Drugs Today (Barc). 2003;39 Suppl B:17-23.

10. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Aug;65(8):1006-12.

11. Hashimoto J, Garnero P, van der Heijde D, et al. Humanized anti-interleukin-6-receptor antibody (tocilizumab) monotherapy is more effective in slowing radiographic

progression in patients with rheumatoid arthritis at high baseline risk for structural damage evaluated with levels of biomarkers, radiography, and BMI: data from the SAMURAI study. Mod Rheumatol. 2010 Jun 24.

12. Haugeberg G, Conaghan PG, Quinn M, et al. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2009 Dec;68(12):1898-901.

13. Jones G, Crotty M, Brooks P. Psoriatic arthritis: a quantitative overview of therapeutic options. The Psoriatic Arthritis Meta-Analysis Study Group. Br J Rheumatol. 1997 Jan;36(1):95-9.

14. Kavanaugh A, Antoni CE, Gladman D, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43.

15. Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. Ann Rheum Dis. 1999 November 1, 1999;58(90001):70i-2.

16. Kempeni J. Update on D2E7: a fully human anti-tumour necrosis factor alpha monoclonal antibody. Ann Rheum Dis. 2000 November 1, 2000;59(90001):44i-5.

17. Keystone EC. Appropriate and effective rheumatoid arthritis control: role of TNF antagonists. Drugs Today (Barc). 2003;39 Suppl B:9-15.

18. Klareskog L, Gaubitz M, Rodriguez-Valverde V, et al. A Long-Term, Open-Label Trial of the Safety and Efficacy of Etanercept (ENBREL(R)) In Patients With Rheumatoid Arthritis Not Treated With Other DMARDs (3-year Interim Report). Ann Rheum Dis. 2006 Mar 15.

19. Machold KP, Smolen JS. Adalimumab - a new TNF-alpha antibody for treatment of inflammatory joint disease. Expert Opin Biol Ther. 2003 Apr;3(2):351-60.

20. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. Expert Opin Biol Ther 2005;5(11):1491-504.

21. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol 2009;22(2):415-26.

22. Parekh K, Ching D, Rahman MU, et al. Onset of Wegener's granulomatosis during therapy with golimumab for rheumatoid arthritis: a rare adverse event? Rheumatology (Oxford). 2010 Sep;49(9):1785-7.

23. Pavelka K. Adalimumab in the treatment of rheumatoid arthritis. Aging Health. 2006;2(4):533-45.

24. Rau R. Adalimumab (a fully human anti-tumour necrosis factor {alpha} monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis. 2002 November 1, 2002;61(90002):70ii-3.

25. Rigopoulos D, Gregoriou S, Stratigos A, et al. Evaluation of the efficacy and safety of infliximab on psoriatic nails: an unblinded, nonrandomized, open-label study. Br J Dermatol. 2008 Aug;159(2):453-6.

26. Salfeld JG. Use of new biotechnology to design rational drugs against newly defined targets. Best Pract Res Clin Rheumatol. 2004 Feb;18(1):81-95.

27. Saliu OY, Sofer C, Stein DS, et al. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. J Infect Dis. 2006 Aug 15;194(4):486-92.

28. Santora LC, Kaymakcalan Z, Sakorafas P, et al. Characterization of noncovalent complexes of recombinant human monoclonal antibody and antigen using cation exchange, size exclusion chromatography, and BIAcore. Anal Biochem. 2001 Dec 15;299(2):119-29.

29. Simpson D, Scott LJ. Adalimumab : in psoriatic arthritis. Drugs. 2006;66(11):1487-96.

30. Smolen JS. Objectives and strategies for rheumatoid arthritis therapy: yesterday vs. today. Drugs Today (Barc). 2003;39 Suppl B:3-8.

31. Suissa S, Ernst P, Hudson M, et al. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med. 2004 Jul 15;117(2):87-92.

32. van de Putte L, Nichol MB. Adalimumab for Rheumatoid Arthritis: Considerations for Reimbursement by Third-Party Payors Disease Management & Health Outcomes. 2004;12(1):1-8.

33. Voulgari PV, Venetsanopoulou AI, Epagelis EK, et al. Infliximab in refractory psoriatic arthritis with severe psoriasis: a 2-year experience. Ann Rheum Dis. 2007 Feb;66(2):270-1.

34. Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006 Aug 31;54(9):2807-16.

35. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86.

36. Yazici Y, Adler NM, Yazici H. Most tumour necrosis factor inhibitor trials in rheumatology are undeservedly called 'efficacy and safety' trials: a survey of power considerations. Rheumatology (Oxford). 2008 Jul;47(7):1054-7.

Reference Source: The Cochrane Library

1. Aerts NE, Ebo DG, Bridts CH, et al. T cell signal transducer and activator of transcription (STAT) 4 and 6 are affected by adalimumab therapy in rheumatoid arthritis. Clinical and experimental rheumatology 2010(2):208-14.

2. Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2007(3).

3. Alfadhli A, McDonald J, Feagan B. Methotrexate for Induction of Remission in Refractory Crohn's Disease. The Cochrane Database of Systematic Reviews. 2004;2004(4).

4. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the Treatment of Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2003;2003(3).

5. Blumenauer B, Judd M, Wells G, et al. Infliximab for the Treatment of Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2002;2002(3).

6. Bongartz T. Tocilizumab for rheumatoid and juvenile idiopathic arthritis. Lancet. 2008(9617):961-3.

7. Bravo Vergel Y, Palmer S, Erhorn S, et al. Adalimumab for the treatment of moderate to severe psoriatic arthritis. Health Technology Assessment. 2010.

8. Burls A, Clark WK, Jobanputra P. Anakinra for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).

9. Chen J, Liu C. Methotrexate for Ankylosing Spondylitis. The Cochrane Database of Systematic Reviews. 2003;2003(3).

10. Chen J, Liu C. Sulfasalazine for Ankylosing Spondylitis. The Cochrane Database of Systematic Reviews. 2005;2005(2).

11. Chen J, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database of Systematic Reviews 2006(4).

12. Christensen AF, Hørslev-Petersen K, Christgau S, et al. Uncoupling of collagen II metabolism in newly diagnosed, untreated rheumatoid arthritis is linked to inflammation and antibodies against cyclic citrullinated peptides. The Journal of rheumatology 2010(6):1113-20.

13. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis (Brief record). Health Technology Assessment. 2004(18):1-118.

14. Clarke R, Derry S, Moore RA, et al. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009(2).

15. Coombs JH, Bloom BJ, Breedveld FC, et al. Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. Annals of the rheumatic diseases 2010(2):413-6.

16. Criswell L, Saag K, Sems KM, et al. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. 1998.

17. Criswell L, Saag KG, Sems KM, et al. Moderate-Term, Low-Dose Corticosteroids for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(3).

18. de Courten B, Barber Melissa N, Johnston Renea V, et al. Hypolipidemic and antihypertensive drugs for prevention of cardiovascular complications in patients with rheumatoid arthritis. Cochrane Database of Systematic Reviews 2008(3).

19. Deodhar A, Dore RK, Mandel D, et al. Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients. Arthritis care & research 2010(4):569-74.

20. Derry S, Barden J, McQuay Henry J, et al. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2008(4).

21. Egan M, Brosseau L, Farmer M, et al. Splints and Orthosis for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2001;2001(4).

22. Englbrecht M, Wang Y, Ronneberger M, et al. Measuring joint involvement in polyarticular psoriatic arthritis: an introduction of alternatives. Arthritis care & research 2010(7):977-83.

23. Flint Wagner HG, Lisse J, Lohman TG, et al. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2009;15(4):165-71.

24. Garner S, Fidan D, Frankish R, et al. Celecoxib for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2002;2002(4).

25. Garner S, Fidan DD, Frankish RR, et al. Rofecoxib for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).

26. Garner Sarah E, Fidan D, Frankish Ruth R, et al. Rofecoxib for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2005(1).

27. Gøtzsche P, Johansen H. Short-Term Low-Dose Corticosteroids Vs Placebo and Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).

28. Hashimoto J, Garnero P, van der Heijde D, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Modern rheumatology / the Japan Rheumatism Association. 2009;19(3):273-82.

29. Health Technology A. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation (Project record). Health Technology Assessment. 2010.

30. Health Technology A. The clinical and cost effectiveness of etanercept, infliximab and adalimumab - psoriatic arthritis (guidance review 104 and 125) (Project record). Health Technology Assessment. 2010.

31. Homer D, Nightingale P, Jobanputra P. Providing patients with information about disease-modifying anti-rheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction. Musculoskeletal care. 2009;7(2):78-92.

32. Jones G, Crotty M, Brooks P. Interventions for Treating Psoriatic Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(3).

33. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Annals of the rheumatic diseases 2010(6):1129-35.

34. Kirwan J, Shea B, Boers M. Glucocorticoids for Slowing Radiological Progression in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).

35. Klarenbeek NB, van der Kooij SM, Huizinga TJ, et al. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Annals of the rheumatic diseases. 2010(7):1342-5.

36. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2006(3).

37. Lekander I, Borgstrom F, Svarvar P, et al. Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. International Journal of Technology Assessment in Health Care. 2010;26(1):54-61.

38. Li L, Judd M, Pencharz JN. Comprehensive Physiotherapy for Rheumatoid Arthritis. Li L, Judd M, Pencharz JN Comprehensive physiotherapy for rheumatoid arthritis The Cochrane Database of Systematic Reviews: Protocols 2004 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 101002/14651858CD004802: John Wiley & Sons, Ltd. 2004;2004(2).

39. Lin JF, Chen JM, Liu C. A systematic review of methotrexate for ankylosing spondylitis (Brief record). Chinese Journal of Evidence-Based Medicine 2007(4):260-6.

40. Little C, Parsons T. Herbal Therapy for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).

41. Little Christine V, Parsons T, Logan S. Herbal therapy for treating osteoarthritis. 2000. Available at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002947/frame.html

42. Lopez-Olivo Maria A, Amezaga M, McGahan L, et al. Rituximab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2008(4).

43. Lu D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. Cochrane Database of Systematic Reviews 2010(3).

44. Lukas C, van der Heijde D, Fatenajad S, et al. Repair of erosions occurs almost exclusively in damaged joints without swelling. Annals of the rheumatic diseases 2010(5):851-5.

45. Lv D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. 2009. Available at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD008088/frame.html

46. Lv D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. Cochrane Database of Systematic Reviews 2010(3).

47. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2008(3).

48. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2009(4).

49. Navarro Sarabia F, Ariza Ariza R, Hernandez Cruz B, et al. Adalimumab for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(3).

50. Osiri M, Shea B, Robinson V, et al. Leflunomide for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews 2002;2002(3).

51. Osiri M, Shea B, Welch V, et al. Leflunomide for the treatment of rheumatoid arthritis. 2002.

52. Ramiro S, Radner H, van der Heijde D, et al. Combination therapy for pain management in inflammatory arthritis. Cochrane Database of Systematic Reviews 2010(12).

53. Rooney T, Roux-Lombard P, Veale DJ, et al. Synovial tissue and serum biomarkers of disease activity, therapeutic response and radiographic progression: analysis of a proof-of-concept randomised clinical trial of cytokine blockade. Annals of the rheumatic diseases 2010(4):706-14.

54. Ruiz Garcia V, Burls A, Cabello López Juan CL, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database of Systematic Reviews. 2009(1).

55. Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Annals of the rheumatic diseases. 2009;68(11):1708-14.

56. Sharp JT, Tsuji W, Ory P, et al. Denosumab prevents metacarpal shaft cortical bone loss in patients with erosive rheumatoid arthritis. Arthritis care & research 2010(4):537-44.

57. Singh Jasvinder A, Beg S, Lopez Olivo Maria A. Tocilizumab for rheumatoid arthritis. 2010.

58. Singh Jasvinder A, Beg S, Lopez-Olivo Maria A. Tocilizumab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2010(7).

59. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2009(2).

60. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2009(4).

61. Smolen JS, Aletaha D, Grisar JC, et al. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. Annals of the rheumatic diseases 2010(6):1058-64.

62. Smolen JS, van der Heijde DM, Aletaha D, et al. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Annals of the rheumatic diseases. 2009;68(10):1535-40.

63. Suarez Almazor M, Belseck E, Shea BJ, et al. Antimalarials for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).

64. Suarez Almazor M, Belseck E, Shea BJ, et al. Methotrexate for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).

65. Suarez Almazor M, Belseck E, Shea BJ, et al. Sulfasalazine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).

66. Suarez Almazor M, Belseck E, Spooner C. Penicillamine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).

67. Suarez Almazor M, Spooner C, Belseck E. Azathioprine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).

68. Suarez Almazor M, Spooner CH, Belseck E, et al. Auranofin Versus Placebo in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(2).

69. Suarez-Almazor Maria E, Belseck E, Shea B, et al. Sulfasalazine for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews. 1998(2).

70. Suarez-Almazor Maria E, Belseck E, Shea B, et al. Cyclophosphamide for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews 2000(4).

71. Tirunagari Shravan K, Derry S, Moore RA, et al. Single dose oral etodolac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009(3).

72. Towheed T, Hochberg Marc C, Shea B, et al. Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. Cochrane Database of Systematic Reviews 2006(1).

73. van der Heijde D, Burmester G, Melo Gomes J, et al. Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. Annals of the rheumatic diseases 2009;68(7):1113-8.

74. van Tuyl LH, Boers M, Lems WF, et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Annals of the rheumatic diseases. 2010(5):807-12.

75. Verstappen SM, Bakker MF, Heurkens AH, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. Annals of the rheumatic diseases 2010(6):1044-8.

76. Vidal L, Gafter-Gvili A, Leibovici L, et al. Rituximab as maintenance therapy for patients with follicular lymphoma. Cochrane Database of Systematic Reviews 2007(2).

77. Wallen Margaret M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2006(1).

78. Westhovens R, Kremer JM, Moreland LW, et al. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. The Journal of rheumatology. 2009;36(4):736-42.

79. Wienecke T, Gøtzsche P. Paracetamol Versus Nonsteroidal Anti-Inflammatory Drugs for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2004;2004(1).

Appendix D. Excluded Studies

Excluded Studies

Wrong Language

1. Garcia JJ, Lobato JP, Garrido SL, Fernandez ME, Eyaralar JR. Biological therapies in rheumatoid arthritis. Atencion Farmaceutica: European Journal of Clinical Pharmacy. 2008;10(98):100-11.
2. Rau R, Wassenberg S, Zeidler H. Low Dose Prednisolone Therapy (LDPT) Retards Radiographically Detectable Destruction in Early Rheumatoid Arthritis--Preliminary Results of a Multicenter, Randomized, Parallel, Double Blind Study. Zeitschrift für Rheumatologie. 2000;59(Supple 2):II/90-6.
3. Sander O, Rau R. Treatment of Refractory Rheumatoid Arthritis With a Tumor Necrosis Factor Alpha Receptor Fusion Protein (Tnfr 55-Igg1) - a Monocentric Observation in 80 Patients. Zeitschrift fur Rheumatologie. 1998;57(5):307-11.
4. Schnabel A, Reinhold K, Willmann V, Dihlmann W, Gross W. Side Effects and Efficacy of 15 Mg and 25 Mg Methotrexate Per Week in Rheumatoid Arthritis. Z RHEUMATOL. 1994;53(3):142-9.

Wrong Outcome

1. Aletaha D, Funovits J, Breedveld FC, Sharp J, Smolen JS, et al., et al. Rheumatoid Arthritis Joint Progression in Sustained Remission Is Determined by Disease Activity Levels Preceding the Period of Radiographic Assessment. *Arthritis and Rheumatism (USA)* 2009:1242.
2. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum. 2007 Oct;56(10):3226-35.
3. Ang DC, Paulus HE, Louie JS. Patient's ethnicity does not influence utilization of effective therapies in rheumatoid arthritis. J Rheumatol. 2006 May;33(5):870-8.
4. Aslanidis S, Pyrpasopoulou A, Douma S, Petidis K. Is it safe to readminister tumor necrosis factor alpha antagonists following tuberculosis flare? Arthritis Rheum. 2008 Jan;58(1):327-8.
5. Bacquet-Deschryver H, Jouen F, Quillard M, Menard JF, Goeb V, Lequerre T, et al. Impact of three anti-TNFalpha biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients. J Clin Immunol. 2008 Sep;28(5):445-55.
6. Baskan BM, Sivas F, Alemdaroglu E, Duran S, Ozoran K. Association of bone mineral density and vertebral deformity in patients with rheumatoid arthritis. Rheumatol Int. 2007 Apr;27(6):579-84.
7. Baslund B, Tvede N, Danneskiold-Samsoe B, Larsson P, Panayi G, Petersen J, et al. Targeting Interleukin-15 in Patients With Rheumatoid Arthritis: a Proof-of-Concept Study. Arthritis and rheumatism. 2005;52(9):2686-92.
8. Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum. 2006 Dec;54(12):3782-9.
9. Bingham ICO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. 2010.
10. Bobbio-Pallavicini F, Caporali R, Alpini C, Avalle S, Epis OM, Klersy C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. Ann Rheum Dis. 2007 Mar;66(3):302-7.
11. Breedveld F, Agarwal S, Yin M, Ren S, Li NF, Shaw TM, et al. Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. J Clin Pharmacol. 2007 Sep;47(9):1119-28.
12. Breedveld FC, Han C, Bala M, van der Heijde D, Baker D, Kavanaugh AF, et al. Association Between Baseline Radiographic Damage and Improvement in Physical Function After Treatment of Patients With

Rheumatoid Arthritis. Annals of the rheumatic diseases. 2005;64(1):52-5.
13. Buch MH, Seto Y, Bingham SJ, Bejarano V, Bryer D, White J, et al. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of nonresponse and subsequent response to etanercept. Arthritis Rheum. 2005 Jan;52(1):42-8.
14. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1997 Aug;24(8):1489-94.
15. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Jul;30(7):1436-9.
16. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. J Rheumatol. 2006 Jul;33(7):1452-6.
17. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):811-9.
18. Chung CP, Russell AS, Segami MI, Ugarte CA. The effect of low-dose prednisone on bone mineral density in Peruvian rheumatoid arthritis patients. Rheumatol Int. 2005 Mar;25(2):114-7.
19. Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Annals of the rheumatic diseases. 2006;65(12):1602-7.
20. Coates LC, Helliwell PS. Validation of Minimal Disease Activity Criteria for Psoriatic Arthritis Using Interventional Trial Data. Arthritis Care and Research. 2010;62:965.
21. Colwell CW, Jr., Robinson CA, Stevenson DD, Vint VC, Morris BA. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. Orthopedics. 1996 Nov;19(11):941-6.
22. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis. 1995 Jan;54(1):49-52.
23. Criswell LA, Lum RF, Turner KN, Woehl B, Zhu Y, Wang J, et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis Rheum. 2004 Sep;50(9):2750-6.
24. Cui J, Saevarsdottir S, Thomson B, Padyukov L, van der Helm-van Mil AH, Nititham J, et al. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. *Arthritis Rheum*. 2010/03/24 ed 2010:1849-61.
25. Cunnane G, Madigan A, Murphy E, FitzGerald O, Bresnihan B. The effects of treatment with interleukin-1 receptor antagonist on the inflamed synovial membrane in rheumatoid arthritis. Rheumatology (Oxford). 2001 Jan;40(1):62-9.
26. Curkendall S, Patel V, Gleeson M, Campbell RS, Zagari M, Dubois R. Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? Arthritis Rheum. 2008 Oct 15;59(10):1519-26.
27. Cypiene A, Laucevicius A, Venalis A, Ryliskyte L, Dadoniene J, Petrulioniene Z, et al. Non-invasive assessment of arterial stiffness indices by applanation tonometry and pulse wave analysis in patients with rheumatoid arthritis treated with TNF-alpha blocker remicade (infliximab). Proc West Pharmacol Soc. 2007;50:119-22.
28. Dahlqvist SR, Engstrand S, Berglin E, Johnson O. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. Scand J Rheumatol. 2006 Mar-Apr;35(2):107-11.
29. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum. 2008 May;58(5):1293-8.
30. Dervieux T, Greenstein N, Kremer J. Pharmacogenomic and metabolic biomarkers in the folate pathway and their association with methotrexate effects during

dosage escalation in rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3095-103.
31. di Comite G, Marinosci A, Di Matteo P, Manfredi A, Rovere-Querini P, Baldissera E, et al. Neuroendocrine modulation induced by selective blockade of TNF-alpha in rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:428-37.
32. Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. Journal of Managed Care Pharmacy (USA). 2006 07/01/;12(Jul):555-69.
33. Eklund KK, Leirisalo-Repo M, Ranta P, Maki T, Kautiainen H, Hannonen P, et al. Serum IL-1beta levels are associated with the presence of erosions in recent onset rheumatoid arthritis. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):684-9.
34. Ernestam S, Hafstrom I, Werner S, Carlstrom K, Tengstrand B. Increased DHEAS levels in patients with rheumatoid arthritis after treatment with tumor necrosis factor antagonists: evidence for improved adrenal function. J Rheumatol. 2007 Jul;34(7):1451-8.
35. Felder M, Ruegsegger P. Bone loss in patients with rheumatoid arthritis--effect of steroids measured by low dose quantitative computed tomography. Rheumatol Int. 1991;11(1):41-4.
36. Finckh A, Bansback N, Marra CA, Anis AH, Liang MH, et al., et al. Treatment of Very Early Rheumatoid Arthritis With Symptomatic Therapy, Disease-Modifying Antirheumatic Drugs, or Biologic Agents A Cost-Effectiveness Analysis. Annals of Internal Medicine (USA). 2009;151:612.
37. Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52.
38. Frey N, Grange S, Woodworth T. Population Pharmacokinetic Analysis of Tocilizumab in Patients With Rheumatoid Arthritis. Journal of Clinical Pharmacology (USA). 2010;50:754-66.
39. Garnero P, Tabassi NC, Voorzanger-Rousselot N. Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with etanercept. J Rheumatol. 2008 Dec;35(12):2313-5.
40. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. 2010.
41. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and Sustained Improvement in Bone and Cartilage Turnover Markers With the Anti-Interleukin-6 Receptor Inhibitor Tocilizumab Plus Methotrexate in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate Results From a Substudy of the Multicenter Double-Blind, Placebo-Controlled Trial of Tocilizumab in Inadequate Responders to Methotrexate Alone. Arthritis and Rheumatism (USA). 2010;62:33.
42. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimensions of the spine in men with rheumatoid arthritis. Effects of low-dose corticosteroids. Arthritis Rheum. 1993 Feb;36(2):222-8.
43. Genant HK. Interleukin-1 Receptor Antagonist Treatment of Rheumatoid Arthritis Patients: Radiologic Progression and Correlation of Genant/Sharp and Larsen Scoring Methods. Seminars in arthritis and rheumatism. 2001;30(5 Suppl 2):26-32.
44. Georgiadis AN, Papavasiliou EC, Lourida ES, Alamanos Y, Kostara C, Tselepis AD, et al. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment--a prospective, controlled study. Arthritis Res Ther. 2006;8(3):R82.
45. Gibofsky A, Palmer WR, Goldman JA, Lautzenheiser RL, Markenson JA, Weaver A, et al. Real-world utilization of DMARDs and biologics in rheumatoid arthritis: the RADIUS (Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study) study. Curr Med Res Opin. 2006 Jan;22(1):169-83.
46. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, Kerstens PJ, Grillet BA, de Jager MH, et al. Patient preferences for

treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis. 2007 Sep;66(9):1227-32.
47. Gonnet-Gracia C, Barnetche T, Richez C, Blanco P, Dehais J, Schaeverbeke T. Anti-nuclear antibodies, anti-DNA and C4 complement evolution in rheumatoid arthritis and ankylosing spondylitis treated with TNF-alpha blockers. Clin Exp Rheumatol. 2008 May-Jun;26(3):401-7.
48. Gonzalez-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: Influence of new therapies and changes in management approach: Analysis of the EMECAR cohort. Arthritis Research and Therapy. 2008;10(6).
49. Gonzalez-Juanatey C, Llorca J, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2006 01/01/;55(Jan):150-3.
50. Gotzsche PC, Hansen M, Stoltenberg M, Svendsen A, Beier J, Faarvang KL, et al. Randomized, Placebo Controlled Tial of Withdrawal of Slow-Acting Antirheumatic Drugs and of Observer Bias in Rheumatoid Arthritis. Scandinavian Journal of Rheumatology. 1996;25(4):194-0.
51. Grassi W, De Angelis R, Cervini C. Corticosteroid prescribing in rheumatoid arthritis and psoriatic arthritis. Clin Rheumatol. 1998;17(3):223-6.
52. Grijalva CG, Chung CP, Stein CM, Mitchel EF, Jr., Griffin MR. Changing patterns of medication use in patients with rheumatoid arthritis in a Medicaid population. Rheumatology (Oxford). 2008 Jul;47(7):1061-4.
53. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Groenendael JH, Mallee C, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Mar;68(3):330-6.
54. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Hulsmans HM, de Beus WM, et al. Changes in bone mineral density in patients with recent onset, active rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):823-8.
55. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Peeters AJ, et al. Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1508-12.
56. Haagsma CJ, Blom HJ, van Riel PL, van't Hof MA, Giesendorf BA, van Oppenraaij-Emmerzaal D, et al. Influence of Sulphasalazine, Methotrexate, and the Combination of Both on Plasma Homocysteine Concentrations in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1999;58(2):79-84.
57. Hafstrom I, Rohani M, Deneberg S, Wornert M, Jogestrand T, Frostegard J. Effects of low-dose prednisolone on endothelial function, atherosclerosis, and traditional risk factors for atherosclerosis in patients with rheumatoid arthritis--a randomized study. J Rheumatol. 2007 Sep;34(9):1810-6.
58. Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis Rheum. 1994 Oct;37(10):1499-505.
59. Hall GM, Spector TD, Delmas PD. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. Effects of corticosteroids and hormone replacement therapy. Arthritis Rheum. 1995 Jul;38(7):902-6.
60. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum. 1993 Nov;36(11):1510-6.
61. Halpern MT, Cifaldi MA, Kvien TK. Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group. Ann Rheum Dis. 2009 Jun;68(6):930-7.
62. Halvorsen EH, Haavardsholm EA, Pollmann S, Boonen A, van der Heijde D, Kvien TK, et al. Serum IgG antibodies to peptidylarginine deiminase 4 predict radiographic progression in patients with rheumatoid arthritis treated with tumour necrosis factor-alpha blocking agents. Ann Rheum Dis. 2009 Feb;68(2):249-52.
63. Hansen M, Florescu A, Stoltenberg M, Podenphant J, Pedersen-Zbinden B, Horslev-Petersen K, et al. Bone loss in rheumatoid arthritis. Influence of disease activity, duration of the disease, functional

capacity, and corticosteroid treatment. Scand J Rheumatol. 1996;25(6):367-76.
64. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Modern rheumatology / the Japan Rheumatism Association. 2009;19(3):273-82.
65. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S, et al. Humanized anti-interleukin-6-receptor antibody (tocilizumab) monotherapy is more effective in slowing radiographic progression in patients with rheumatoid arthritis at high baseline risk for structural damage evaluated with levels of biomarkers, radiography, and BMI: data from the SAMURAI study. Mod Rheumatol. 2010 Jun 24.
66. Hatemi G, Melikoglu M, Fresko I, Masatlioglu S, Tascilar K, Yazici H. Infliximab does not suppress the tuberculin skin test (purified protein derivative). J Rheumatol. 2007 Mar;34(3):474-80.
67. Haugeberg G, Orstavik RE, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. Arthritis Rheum. 2002 Jul;46(7):1720-8.
68. Haugeberg G, Strand A, Kvien T, Kirwan J. Reduced Loss of Hand Bone Density With Prednisolone in Early Rheumatoid Arthritis: Results From a Randomized Placebo-Controlled Trial. Archives of internal medicine. 2005;165(11):1293-7.
69. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41.
70. Hirano Y, Kojima T, Kanayama Y, Shioura T, Hayashi M, Kida D, et al. Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis. *Clin Rheumatol*. 2010/01/14 ed 2010:495-500.
71. Hornung N, Ellingsen T, Attermann J, Stengaard-Pedersen K, Poulsen JH. Patients with rheumatoid arthritis treated with methotrexate (MTX): concentrations of steady-state erythrocyte MTX correlate to plasma concentrations and clinical efficacy. J Rheumatol. 2008 Sep;35(9):1709-15.
72. Hu CP, Xu ZH, Rahman MU, Davis HM, Zhou HH. A latent variable approach for modeling categorical endpoints among patients with rheumatoid arthritis treated with golimumab plus methotrexate. Journal of Pharmacokinetics and Pharmacodynamics (USA). 2010;37:309-21.
73. Imrich R, Vigas M, Rovensky J, Aldag JC, Masi AT. Adrenal plasma steroid relations in glucocorticoid-naive premenopausal rheumatoid arthritis patients during insulin-induced hypoglycemia test compared to matched normal control females. Endocr Regul. 2009 Apr;43(2):65-73.
74. James HM, Gillis D, Hissaria P, Lester S, Somogyi AA, Cleland LG, et al. Common polymorphisms in the folate pathway predict efficacy of combination regimens containing methotrexate and sulfasalazine in early rheumatoid arthritis. J Rheumatol. 2008 Apr;35(4):562-71.
75. Jiang Y, Genant HK, Watt I, Cobby M, Bresnihan B, Aitchison R, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum. 2000 May;43(5):1001-9.
76. Jonsdottir T, Forslid J, van Vollenhoven A, Harju A, Brannemark S, Klareskog L, et al. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. Ann Rheum Dis. 2004 Sep;63(9):1075-8.
77. Josipovic B. Levels of dehydroepiandrosterone sulfate in female patients with early stage of rheumatoid arthritis. Ann N Y Acad Sci. 1999 Jun 22;876:145-7.
78. Kahn KL, MacLean CH, Liu H, Rubenstein LZ, Wong AL, Harker JO, et al. Application of explicit process of care measurement to rheumatoid arthritis: Moving from evidence to practice. Arthritis Rheum. 2006 Dec 15;55(6):884-91.
79. Kahn KL, MacLean CH, Wong AL, Rubenstein LZ, Liu H, Fitzpatrick DM, et al. Assessment of American College of Rheumatology quality criteria for rheumatoid arthritis in a pre-quality criteria patient cohort. Arthritis Care and Research. 2007;57(5):707-15.

80. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol. 2007 Feb;34(2):272-9.
81. Kalla AA, Meyers OL, Kotze TJ, Laubscher R. Corticosteroid therapy and bone mass--comparison of rheumatoid arthritis and systemic lupus erythematosus. S Afr Med J. 1994 Jul;84(7):404-9.
82. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8.
83. Klarenbeek NB, van der Kooij SM, Huizinga TJ, Goekoop-Ruiterman YP, Hulsmans HM, van Krugten MV, et al. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Annals of the rheumatic diseases. 2010(7):1342-5.
84. Klimiuk PA, Sierakowski S, Domyslawska I, Chwiecko J. Regulation of serum chemokines following infliximab therapy in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):529-33.
85. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis. 2004 Jan;63(1):4-10.
86. Kopp S, Alstergren P, Ernestam S, Nordahl S, Bratt J. Interleukin-1beta influences the effect of infliximab on temporomandibular joint pain in rheumatoid arthritis. Scand J Rheumatol. 2006 May-Jun;35(3):182-8.
87. Korczowska I, Olewicz-Gawlik A, Trefler J, Hrycaj P, Krzysztof Lacki J. Does low-dose and short-term glucocorticoids treatment increase the risk of osteoporosis in rheumatoid arthritis female patients? Clin Rheumatol. 2008 May;27(5):565-72.
88. Korthals-de Bos I, Van Tulder M, Boers M, Verhoeven AC, Ader HJ, Bibo J, et al. Indirect and Total Costs of Early Rheumatoid Arthritis: a Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate, and Sulfasalazine With Sulfasalazine Alone. The Journal of rheumatology. 2004;31(9):1709-16.
89. Kraan MC, Reece RJ, Barg EC, Smeets TJ, Farnell J, Rosenburg R, et al. Modulation of Inflammation and Metalloproteinase Expression in Synovial Tissue by Leflunomide and Methotrexate in Patients With Active Rheumatoid Arthritis. Findings in a Prospective, Randomized, Double-Blind, Parallel-Design Clinical Trial in Thirty-Nine Patients at Two Centers. Arthritis and rheumatism. 2000;43(8):1820-30.
90. Kristensen LE, Christensen R, Bliddal H, Geborek P, Danneskiold-SamsÃ¸e B, Saxne T. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: A systematic literature review. *Scandinavian Journal of Rheumatology* 2007:411-7.
91. Kroot EJ, van Gestel AM, Swinkels HL, Albers MM, van de Putte LB, van Riel PL. Chronic comorbidity in patients with early rheumatoid arthritis: a descriptive study. J Rheumatol. 2001 Jul;28(7):1511-7.
92. Kuuliala A, Leirisalo-Repo M, Mottonen T, Hannonen P, Nissila M, Kautiainen H, et al. Serum Soluble Interleukin-2 Receptor Predicts Early Remission in Patients With Recent-Onset Rheumatoid Arthritis Treated With a Single Disease-Modifying Antirheumatic Drug. Clinical and experimental rheumatology. 2005;23(2):243-6.
93. Lacroix BD, Lovern MR, Stockis A, Sargentini-Maier ML, Karlsson MO, Friberg LE. A pharmacodynamic Markov mixed-effects model for determining the effect of exposure to certolizumab pegol on the ACR20 score in patients with rheumatoid arthritis. Clin Pharmacol Ther. 2009 Oct;86(4):387-95.
94. Lau J, Ioannidis JPA, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. British Medical Journal. 2006;333(7568):597-600.
95. Lodder MC, de Jong Z, Kostense PJ, Molenaar ET, Staal K, Voskuyl AE, et al. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis. 2004 Dec;63(12):1576-80.

96. Macias I, Garcia-Perez S, Ruiz-Tudela M, Medina F, Chozas N, Giron-Gonzalez JA. Modification of pro- and antiinflammatory cytokines and vascular-related molecules by tumor necrosis factor-a blockade in patients with rheumatoid arthritis. J Rheumatol. 2005 Nov;32(11):2102-8.
97. Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Economic Comparison of Leflunomide and Methotrexate in Patients With Rheumatoid Arthritis: an Evaluation Based on a 1-Year Randomised Controlled Trial. PharmacoEconomics. 2002;20(1):61-70.
98. Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006 Dec;84(6):1463-72.
99. Marotte H, Pallot-Prades B, Grange L, Tebib J, Gaudin P, Alexandre C, et al. The shared epitope is a marker of severity associated with selection for, but not with response to, infliximab in a large rheumatoid arthritis population. Ann Rheum Dis. 2006 Mar;65(3):342-7.
100. Maxwell JR, Potter C, Hyrich KL, Barton A, Worthington J, Isaacs JD, et al. Association of the tumour necrosis factor-308 variant with differential response to anti-TNF agents in the treatment of rheumatoid arthritis. Hum Mol Genet. 2008 Nov 15;17(22):3532-8.
101. Mease PJ, Wei N, Fudman EJ, Kivitz AJ, Schechtman J, Trapp RG, et al. Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumor necrosis factor antagonist gene: Results of a phase 1/2 study. Journal of Rheumatology. 2010;37(4):692-703.
102. Ollendorf DA, Klingman D, Hazard E, Ray S. Differences in annual medication costs and rates of dosage increase between tumor necrosis factor-antagonist therapies for rheumatoid arthritis in a managed care population. Clinical Therapeutics. 2009;31(4):825-35.
103. Ollendorf DA, Peterson AN, Doyle J, Huse DM. Impact of leflunomide versus biologic agents on the costs of care for rheumatoid arthritis in a managed care population. Am J Manag Care. 2002 May;8(7 Suppl):S203-13.
104. Oren C, Mendelbaum M, Paran D. Vaccination against influenza in rheumatoid arthritis patients: The effect of rituximab on the humoral response. *Arthritis Rheum* 2006.
105. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol. 1992 Dec;19(12):1885-94.
106. Potter C, Hyrich KL, Tracey A, Lunt M, Plant D, Symmons DP, et al. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. *Ann Rheum Dis* 2009:69-74.
107. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Jan;52(1):27-35.
108. Rajakulendran S, Gadsby K, Deighton C. Rheumatoid arthritis, alcohol, leflunomide and methotrexate. Can changes to the BSR guidelines for leflunomide and methotrexate on alcohol consumption be justified? Musculoskeletal Care. 2008 Dec;6(4):233-45.
109. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology. 2006 10/01/;45(Oct):1294-7.
110. Saliu OY, Sofer C, Stein DS, Schwander SK, Wallis RS. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. J Infect Dis. 2006 Aug 15;194(4):486-92.
111. Sanmarti R, Gomez-Centeno A, Ercilla G, Larrosa M, Vinas O, Vazquez I, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol. 2007 Jul;26(7):1111-8.
112. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira

AC, et al. Yellow fever revaccination during infliximab therapy. *Arthritis Care Res (Hoboken)*. 2010/06/11 ed 2010:896-8.
113. Sennels H, Sorensen S, Ostergaard M, Knudsen L, Hansen M, Skjodt H, et al. Circulating levels of osteopontin, osteoprotegerin, total soluble receptor activator of nuclear factor-kappa B ligand, and high-sensitivity C-reactive protein in patients with active rheumatoid arthritis randomized to etanercept alone or in combination with methotrexate. Scand J Rheumatol. 2008 Jul-Aug;37(4):241-7.
114. Seriolo B, Paolino S, Sulli A, Fasciolo D, Cutolo M. Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:414-9.
115. Seriolo B, Paolino S, Sulli A, Ferretti V, Cutolo M. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:420-7.
116. Smolen JS, van der Heijde DM, Aletaha D, Xu S, Han J, Baker D, et al. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Annals of the rheumatic diseases. 2009;68(10):1535-40.
117. Soderlin MK, Geborek P. Changing pattern in the prescription of biological treatment in rheumatoid arthritis. A 7-year follow-up of 1839 patients in southern Sweden. Annals of the Rheumatic Diseases. 2008;67(1):37-42.
118. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007 Nov;66(11):1491-6.
119. Sokka T, Mottonen T, Hannonen P. Mortality in early "sawtooth" treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol. 1999;28(5):282-7.
120. Sokka T, Pincus T. Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol. 2002 Dec;29(12):2521-4.
121. Strand V, Cohen S, Crawford B, Smolen JS, Scott DL, et al. Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. Rheumatology. 2004 05/01/;43(May):640-7.
122. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322-30.
123. Stubenrauch K, Wessels U, Birnboeck H, Ramirez F, Jahreis A, Schleypen J. Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clinical Therapeutics. 2010;32(9):1597-609.
124. Suissa S, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2008;21(1):234-8.
125. Symmons D, Tricker K, Harrison M, Roberts C, Davis M, Dawes P, et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs - Results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. Rheumatology. 2006;45(5):558-65.
126. Tan RJ, Gibbons LJ, Potter C, Hyrich KL, Morgan AW, Wilson AG, et al. Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. *Ann Rheum Dis*. 2010/05/07 ed 2010:1029-35.
127. Tang B, Rahman M, Waters HC, Callegari P. Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. Clin Ther. 2008 Jul;30(7):1375-84.
128. Tascioglu F, Oner C, Armagan O. The effect of low-dose methotrexate on bone mineral density in patients with early rheumatoid arthritis. Rheumatol Int. 2003 Sep;23(5):231-5.
129. Tikly M, Zannettou N, Hopley M. A longitudinal study of rheumatoid arthritis in South Africans. MedGenMed. 2003 Feb 5;5(1):2.
130. Toms TE, Panoulas VF, John H, Douglas KM, Kitas GD. Methotrexate therapy

associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60- more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther. 2009;11(4):R110.
131. Torikai E, Kageyama Y, Takahashi M, Nagano A. The effect of methotrexate on bone metabolism markers in patients with rheumatoid arthritis. Mod Rheumatol. 2006;16(6):350-4.
132. Toubi E, Kessel A, Slobodin G, Boulman N, Pavlotzky E, Zisman D, et al. Changes in macrophage function after rituximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Jun;66(6):818-20.
133. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ten Wolde S, Han KH, van Krugten MV, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2007 Jul;56(7):2129-34.
134. van der Heijde D, Landewe R, Klareskog L, Rodriguez-Valverde V, Settas L, Pedersen R, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum. 2005 Jan;52(1):49-60.
135. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-Effectiveness and Cost-Utility of Combination Therapy in Early Rheumatoid Arthritis: Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine With Sulphasalazine Alone. British journal of rheumatology. 1998;37(10):1102-9.
136. Verhoeven AC, Boers M, te Koppele JM, van der Laan WH, Markusse HM, Geusens P, et al. Bone turnover, joint damage and bone mineral density in early rheumatoid arthritis treated with combination therapy including high-dose prednisolone. Rheumatology (Oxford). 2001 Nov;40(11):1231-7.
137. Visvanathan S, Marini JC, Smolen JS, Clair EW, Pritchard C, Shergy W, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1465-74.
138. Visvanathan S, Wagner C, Rojas J, Kay J, Dasgupta B, Matteson EL, et al. E-selectin, interleukin 18, serum amyloid a, and matrix metalloproteinase 9 are associated with clinical response to golimumab plus methotrexate in patients with active rheumatoid arthritis despite methotrexate therapy. J Rheumatol. 2009 Jul;36(7):1371-9.
139. Wallace DJ, Metzger AL, Stecher VJ, Turnbull BA, Kern PA. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. Am J Med. 1990 Sep;89(3):322-6.
140. Wells G, Li T, Tugwell P. Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale. Ann Rheum Dis. 2010 Oct;69(10):1768-73.
141. Wells GA, Boers M, Li T, Tugwell PS. Investigating the validity of the minimal disease activity state for patients with rheumatoid arthritis treated with abatacept. J Rheumatol. 2009 Feb;36(2):260-5.
142. Wells GA, Sultan SA, Chen L. Indirect evidence: Indirect treatment comparisons in meta-analysis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2009.
143. Weng HH, Ranganath VK, Khanna D, Oh M, Western Consortium P, et al. Equivalent Responses to Disease-modifying Antirheumatic Drugs Initiated at Any Time During the First 15 Months After Symptom Onset in Patients with Seropositive Rheumatoid Arthritis. Journal of Rheumatology. 2010;37:550-7.
144. Wolbink GJ, Vis M, Lems W, Voskuyl AE, Dijkmans B, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):711-5.
145. Wu E, Chen L, Birnbaum H, Yang E, Cifaldi M. Cost of care for patients with rheumatoid arthritis receiving TNF-antagonist therapy using claims data. Curr Med Res Opin. 2007 Aug;23(8):1749-59.
146. Wu E, Chen L, Birnbaum H, Yang E, Cifaldi M. Retrospective claims data analysis of dosage adjustment patterns of TNF antagonists among patients with rheumatoid arthritis. Current Medical Research and Opinion. 2008;24(8):2229-40.
147. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al.

Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol. 2007;17(4):283-9.
148. Yazici Y, Krasnokutsky S, Barnes JP, Hines PL, Wang J, Rosenblatt L. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. J Rheumatol. 2009 May;36(5):907-13.
149. Yee CS, Filer A, Pace A, Douglas K, Situnayake D, Rowe IF. The prevalence of patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an out-patient study. Rheumatology (Oxford). 2003 Jul;42(7):856-9.
150. Zink A, Strangfeld A, Schneider M, Herzer P, Listing J, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study - Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis and Rheumatism (USA). 2006 11/01/;54(Nov):3399-407.

Drug Not Included in the Report

1. Adams J, Burridge J, Mullee M, Hammond A, Cooper C. The clinical effectiveness of static resting splints in early rheumatoid arthritis: A randomized controlled trial. Rheumatology. 2008;47(10):1548-53.
2. Anderson JJ, O'Neill A, Woodworth T, Haddad J, Sewell KL, Moreland LW. Health Status Response of Rheumatoid Arthritis to Treatment With Dab486il-2. Arthritis care and research : the official journal of the Arthritis Health Professions Association. 1996;9(2):112-9.
3. Bae SC, Corzillius M, Kuntz KM, Liang MH. Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. Rheumatology (Oxford). 2003 Jan;42(1):46-53.
4. Bakker MF, Jacobs JWG, Welsing PMJ, Van Der Werf JH, Linn-Rasker SP, Van Der Veen MJ, et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Annals of the rheumatic diseases. 2010;69(10):1849-52.
5. Bejarano V, Conaghan PG, Proudman SM, Buch MH, Brown AK, Emery P. Long-term efficacy and toxicity of ciclosporin A in combination with methotrexate in poor prognosis rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009;68(5):761-3.
6. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol. 1994 May;33(5):461-3.
7. Capell H, Marabani M, Madhok R, Torley H, Hunter J. Degree and Extent of Response to Sulphasalazine or Penicillamine Therapy for Rheumatoid Arthritis: Results From a Routine Clinical Environment Over a Two-Year Period. The Quarterly journal of medicine. 1990;75(276):335-44.
8. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis. 2004 Jul;63(7):797-803.
9. Capell HA, Murphy EA, Hunter JA. Rheumatoid arthritis: workload and outcome over 10 years. Q J Med. 1991 Jun;79(290):461-76.
10. Choy EH, Kingsley GH, Khoshaba B, Pipitone N, Scott DL. A Two Year Randomised Controlled Trial of Intramuscular Depot Steroids in Patients With Established Rheumatoid Arthritis Who Have Shown an Incomplete Response to Disease Modifying Antirheumatic Drugs. Ann Rheum Dis. 2005;64(9):1288-93.
11. Choy EHS, Scott DL, Kingsley GH, Williams P, Wojtulewski J, Papasavvas G, et al. Treating Rheumatoid Arthritis Early With Disease Modifying Drugs Reduces Joint Damage: a Randomised Double Blind Trial of Sulphasalazine Vs Diclofenac Sodium. Clinical and experimental rheumatology. 2002;20(3):351-8.
12. Cohen SB, Cheng TT, Chindalore V, Damjanov N, Burgos-Vargas R, Delora P, et al. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid

arthritis. Arthritis Rheum. 2009 Feb;60(2):335-44.
13. Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum. 2008 May;58(5):1299-309.
14. Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum. 2003 Jan;48(1):64-71.
15. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. Arthritis Rheum. 2009 May;60(5):1232-41.
16. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002 Sep;46(9):2287-93.
17. Eberhardt R, Kruger K, Reiter W, Gross W, Zwingers T. Long-term therapy with the new glucocorticosteroid deflazacort in rheumatoid arthritis. Double-blind controlled randomized 12-months study against prednisone. Arzneimittelforschung. 1994 May;44(5):642-7.
18. Egsmose C, TM H, Andersen LS, Beier JM, Christensen L, Ejstrup L, et al. Limited Effect of Sulphasalazine Treatment in Reactive Arthritis. A Randomised Double Blind Placebo Controlled Trial. Annals of the rheumatic diseases. 1997;56(1):32-6.
19. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis. Arthritis Rheum. 1994 Oct;37(10):1487-91.
20. Ferraz MB, Pinheiro GR, Helfenstein M, Albuquerque E, Rezende C, Roimicher L, et al. Combination Therapy With Methotrexate and Chloroquine in Rheumatoid Arthritis. A Multicenter Randomized Placebo-Controlled Trial. Scandinavian journal of rheumatology. 1994;23(5):231-6.
21. Finckh A, Liang MH, Van Herckenrode CM, De Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: Ameta-analysis. Arthritis and rheumatism. 2006;55(6):86-172.
22. Fraser AD, van Kuijk AWR, Westhovens R, Karim Z, Wakefield R, Gerards AH, et al. A Randomised, Double Blind, Placebo Controlled, Multicentre Trial of Combination Therapy With Methotrexate Plus Ciclosporin in Patients With Active Psoriatic Arthritis. Ann Rheum Dis. 2005;64(6):859-64.
23. Furtado RN, Oliveira LM, Natour J. Polyarticular corticosteroid injection versus systemic administration in treatment of rheumatoid arthritis patients: a randomized controlled study. J Rheumatol. 2005 Sep;32(9):1691-8.
24. Gerlag DM, Hollis S, Layton M, Vencovsky J, Szekanecz Z, Braddock M, et al. Preclinical and clinical investigation of a CCR5 antagonist, AZD5672, in patients with rheumatoid arthritis receiving methotrexate. Arthritis and rheumatism. 2010;62(11):3154-60.
25. Gøtzsche P, Johansen H. Short-Term Low-Dose Corticosteroids Vs Placebo and Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
26. Gough A, Sheeran T, Arthur V, Panayi G, Emery P. Adverse interaction between intramuscular methylprednisolone and sulphasalazine in patients with early rheumatoid arthritis. A pilot study. Scand J Rheumatol. 1994;23(1):46-8.
27. Graell E, Vazquez I, Larrosa M, Rodriguez-Cros JR, Hernandez MV, Gratacos J, et al. Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: Prognostic factors after two years of follow-up. Clinical and Experimental Rheumatology. 2009;27(2):284-91.
28. Graudal N, Juergens G. Similar Effects of Disease-Modifying Antirheumatic Drugs, Glucocorticoids, and Biologic Agents on Radiographic Progression in Rheumatoid Arthritis Meta-Analysis of 70 Randomized Placebo-Controlled or Drug-Controlled Studies, Including 112 Comparisons. Arthritis and Rheumatism (USA). 2010;62:2852.
29. Gray RE, Doherty SM, Galloway J, Coulton L, de Broe M, Kanis JA. A double-blind

study of deflazacort and prednisone in patients with chronic inflammatory disorders. Arthritis Rheum. 1991 Mar;34(3):287-95.
30. Griffith SM, Fisher J, Clarke S, Montgomery B, Jones PW, Saklatvala J, et al. Do Patients With Rheumatoid Arthritis Established on Methotrexate and Folic Acid 5 Mg Daily Need to Continue Folic Acid Supplements Long Term? Rheumatology (Oxford). 2000;39(10):1102-9.
31. Hannonen P, Mottonen T, Hakola M, Oka M. Sulfasalazine in Early Rheumatoid Arthritis. A 48-Week Double-Blind, Prospective, Placebo-Controlled Study. Arthritis and rheumatism. 1993;36(11):1501-9.
32. Hetland ML, Stengaard-Pedersen K, Junker P, Horslev-Petersen K, Grp CS, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis - An investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1401-9.
33. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen T, Andersen LS, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum. 2006 May;54(5):1401-9.
34. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Hansen I, Andersen LS, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis. 2008 Jun;67(6):815-22.
35. Hetland ML, Stengaard-Pedersen K, Junker P, Ostergaard M, Ejbjerg BJ, Jacobsen S, et al. Radiographic progression and remission rates in early rheumatoid arthritis - MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Ann Rheum Dis. 2010 Oct;69(10):1789-95.
36. Hu D, Bao C, Chen S, Gu J, Li Z, Sun L, et al. A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. Rheumatol Int. 2009 Jan;29(3):297-303.
37. Ichikawa Y, Saito T, Yamanaka H, Akizuki M, Kondo H, Kobayashi S, et al. Clinical activity after 12 weeks of treatment with nonbiologics in early rheumatoid arthritis may predict articular destruction 2 years later. Journal of Rheumatology. 2010;37(4):723-9.
38. Jessop JD, O'Sullivan MM, Lewis PA, Williams LA, Camilleri JP, Plant MJ, et al. A Long-Term Five-Year Randomized Controlled Trial of Hydroxychloroquine, Sodium Aurothiomalate, Auranofin and Penicillamine in the Treatment of Patients With Rheumatoid Arthritis. British journal of rheumatology. 1998;37(9):992-1002.
39. Jeurissen ME, Boerbooms AM, van de Putte LB, Doesburg WH, Mulder J, Rasker JJ, et al. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial. Arthritis Rheum. 1991 Aug;34(8):961-72.
40. Johnsen AK, Schiff MH, Mease PJ, Moreland LW, Maier AL, Coblyn JS, et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. J Rheumatol. 2006 Apr;33(4):659-64.
41. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2010;4:CD008495.
42. Kavanaugh A, Menter A, Mendelsohn A, Shen YK, Lee S, Gottlieb AB. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: A randomized, placebo-controlled, phase II trial. Current Medical Research and Opinion. 2010;26(10):2385-92.
43. Kawai S, Hashimoto H, Kondo H, Murayama T, Abe T, et al. Comparison of tacrolimus and mizoribine in a randomized, double-blind controlled study in patients with rheumatoid arthritis. Journal of

Rheumatology. 2006 11/01/;33(Nov):2153-61.
44. Kirwan J, Byron M, Watt I. The Relationship Between Soft Tissue Swelling, Joint Space Narrowing and Erosive Damage in Hand X-Rays of Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2001;40(3):688-95.
45. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995 Jul 20;333(3):142-6.
46. Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2010/02/05 ed 2010:917-28.
47. Lambert CM, Sandhu S, Lochhead A, Hurst NP, McRorie E, Dhillon V. Dose Escalation of Parenteral Methotrexate in Active Rheumatoid Arthritis That Has Been Unresponsive to Conventional Doses of Methotrexate: a Randomized, Controlled Trial. Arthritis and rheumatism. 2004;50(2):364-71.
48. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001 Oct 15;111(6):446-51.
49. Lerndal T, Svensson B. A Clinical Study of Cph 82 Vs Methotrexate in Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(3):316-20.
50. Lu LJ, Bao CD, Dai M, Teng JL, Fan W, Du F, et al. Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. Arthritis Rheum. 2009 Jul 15;61(7):979-87.
51. Ma MH, Kingsley GH, Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2010;49:91-8.
52. Messina OD, Barreira JC, Zanchetta JR, Maldonado-Cocco JA, Bogado CE, Sebastian ON, et al. Effect of low doses of deflazacort vs prednisone on bone mineral content in premenopausal rheumatoid arthritis. J Rheumatol. 1992 Oct;19(10):1520-6.
53. Migliore A, Bizzi E, Massafra U, Vacca F, Martin Martin LS, Ferlito C, et al. Can Cyclosporine-A associated to methotrexate maintain remission induced by anti-TNF agents in rheumatoid arthritis patients? (Cynar pilot study). Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):783-90.
54. Mladenovic V, Domljan Z, Rozman B, Jajic I, Mihajlovic D, Dordevic J, et al. Safety and Effectiveness of Leflunomide in the Treatment of Patients With Active Rheumatoid Arthritis. Results of a Randomized, Placebo-Controlled, Phase Ii Study. Arthritis and rheumatism. 1995;38(11):1595-603.
55. Moreland L, R G, King K, Chase W, Weisman M, Greco T, et al. Results of a Phase-I/II Randomized, Masked, Placebo-Controlled Trial of Recombinant Human Interleukin-11 (Rhil-11) in the Treatment of Subjects With Active Rheumatoid Arthritis. Arthritis Res. 2001;3(4):247-52.
56. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of Rheumatoid Arthritis With Humanized Anti-Interleukin-6 Receptor Antibody: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2004;50(6):1761-9.
57. Paulus HE, Di Primeo D, Sanda M, Lynch JM, Schwartz BA, Sharp JT, et al. Progression of radiographic joint erosion during low dose corticosteroid treatment of rheumatoid arthritis. J Rheumatol. 2000 Jul;27(7):1632-7.
58. Peltomaa R, Paimela L, Helve T, Leirisalo-Repo M. Comparison of Intramuscular Gold and Sulphasalazine in the Treatment of Early Rheumatoid Arthritis. A One Year Prospective Study. Scandinavian journal of rheumatology. 1995;24(6):330-5.
59. Perdriger A, Mariette X, Kuntz JL, Brocq O, Kara-Terki R, Loet XL, et al. Safety of infliximab used in combination with leflunomide or azathioprine in daily clinical practice. J Rheumatol. 2006 May;33(5):865-9.
60. Plant M, O'Sullivan MM, Lewis P, Camilleri J, Coles E, Jessop J. What Factors Influence Functional Ability in Patients With Rheumatoid Arthritis. Do They Alter Over

Time? Rheumatology (Oxford). 2005;44(9):1181-5.
61. Porter D, McInnes I, Hunter J, Capell H. Outcome of second line therapy in rheumatoid arthritis. Annals of the rheumatic diseases. 1994;53(12):812-5.
62. Sany J, Kaiser MJ, Jorgensen C, Trape G. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. Ann Rheum Dis. 2005 Nov;64(11):1647-9.
63. Suarez Almazor M, Belseck E, Shea BJ, Homik J, Wells G, Tugwell P. Antimalarials for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
64. Suarez Almazor M, Belseck E, Shea BJ, Tugwell P, Wells G. Methotrexate for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).
65. Suarez Almazor M, Belseck E, Shea BJ, Tugwell P, Wells G. Sulfasalazine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).
66. Suarez Almazor M, Spooner C, Belseck E. Azathioprine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
67. Sugimori S, Watanabe T, Tabuchi M, Kameda N, Machida H, Okazaki H, et al. Evaluation of small bowel injury in patients with rheumatoid arthritis by capsule endoscopy: effects of anti-rheumatoid arthritis drugs. Digestion. 2008;78(4):208-13.
68. Tak PP, Thurlings RM, Rossier C, Nestorov I, Dimic A, Mircetic V, et al. Atacicept in patients with rheumatoid arthritis: Results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. Arthritis and rheumatism. 2008;58(1):61-72.
69. Tebib JG, Manil LM, Modder G, Verrier P, De Rycke Y, Bonmartin A, et al. Better Results With Rhenium-186 Radiosynoviorthesis Than With Cortivazol in Rheumatoid Arthritis (Ra): a Two-Year Follow-up Randomized Controlled Multicentre Study. Clinical and experimental rheumatology. 2004;22(5):609-16.
70. The Australian Multicentre Clinical Trial Group. Sulfasalazine in Early Rheumatoid Arthritis. J Rheumatol. 1992 7;19(11):1672.
71. Tsakonas E, Fitzgerald AA, Fitzcharles MA, Cividino A, Thorne JC, M'Seffar A, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol. 2000 Mar;27(3):623-9.
72. van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996 Apr 15;124(8):699-707.
73. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, Bijlsma JWJ. Low-Dose Prednisone Therapy for Patients With Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Annals of internal medicine. 2002;136(1):1-12.
74. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JWG, Bijlsma JWJ. Low-Dose Glucocorticoids in Early Rheumatoid Arthritis: Discordant Effects on Bone Mineral Density and Fractures? Clinical and experimental rheumatology. 2003;21(2):155-60.
75. van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM, et al. Aggressive Treatment in Early Rheumatoid Arthritis: a Randomised Controlled Trial. Annals of the Rheumatic Diseases. 2000;59(6):468-77.
76. van Jaarsveld CH, Jahangier ZN, Jacobs JW, Blaauw AA, van Albada-Kuipers GA, ter Borg EJ, et al. Toxicity of Anti-Rheumatic Drugs in a Randomized Clinical Trial of Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(12):1374-82.
77. van Schaardenburg D, Valkema R, Dijkmans BA, Papapoulos S, Zwinderman AH, Han KH, et al. Prednisone Treatment of Elderly-Onset Rheumatoid Arthritis. Disease Activity and Bone Mass in Comparison With Chloroquine Treatment. Arthritis and rheumatism. 1995;38(3):334-42.
78. Verhoeven AC, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systematic review. Br J Rheumatol. 1998 Jun;37(6):612-9.

79. Verstappen S, van Albada Kuipers G, Bijlsma J, Blaauw A, Schenk Y, Haanen H, et al. A Good Response to Early Dmard Treatment of Patients With Rheumatoid Arthritis in the First Year Predicts Remission During Follow up. Ann Rheum Dis. 2005;64(1):38-43.
80. Verstappen SMM, Jacobs JWG, Bijlsma JWJ, Heurkens AHM, van Booma-Frankfort C, Borg EJt, et al. Five-Year Followup of Rheumatoid Arthritis Patients After Early Treatment With Disease-Modifying Antirheumatic Drugs Versus Treatment According to the Pyramid Approach in the First Year. Arthritis and rheumatism. 2003;48(7):1797-807.
81. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol. 1997 Mar;24(3):445-51.
82. Wallen Margaret M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2006(1).
83. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very Low-Dose Prednisolone in Early Rheumatoid Arthritis Retards Radiographic Progression Over Two Years: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2005;52(11):3371-80.
84. Weinblatt ME, Kaplan H, Germain BF, Merriman RC, Solomon SD, Wall B, et al. Methotrexate in Rheumatoid Arthritis: Effects on Disease Activity in a Multicenter Prospective Study. The Journal of rheumatology. 1991;18(3):334-8.
85. Wolfe F, Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol. 2000 Jul;27(7):1668-73.
86. Wolfe F, Michaud K, Li T. Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. J Rheumatol. 2006 Oct;33(10):1942-51.
87. Zhang LL, Wei W, Xiao F, Xu JH, Bao CD, Ni LQ, et al. A randomized, double-blind, multicenter, controlled clinical trial of chicken type II collagen in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Jul 15;59(7):905-10.

Wrong Population

1. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005 Aug;64(8):1150-7.
2. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36.
3. Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol*. 2010/01/13 ed 2010:399-403.
4. Boss B, Neeck G, Engelhardt B, Riedel W. Influence of corticosteroids on neutrophils, lymphocytes, their subsets, and T-cell activity markers in patients with active rheumatoid arthritis, compared to healthy controls. Ann N Y Acad Sci. 1999 Jun 22;876:198-200.
5. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003 Jun;98(6):1315-24.
6. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.
7. Clegg DO, Reda DJ, Weisman MH, Cush JJ, Vasey FB, Schumacher HRJ, et al. Comparison of Sulfasalazine and Placebo in the Treatment of Psoriatic Arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis and rheumatism. 1996;39(12):2021-7.

8. Combe B, Goupille P, Kuntz J, Tebib J, Liote F, Bregeon C. Sulphasalazine in Psoriatic Arthritis: a Randomized, Multicentre, Placebo-Controlled Study. *British journal of rheumatology.* 1996:664-8.
9. Dass S, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, et al. Reduction of fatigue in Sjogren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008 Nov;67(11):1541-4.
10. Davaine AC, Saraux A, Prigent S, Kupfer-Bessaguet I, Roswag D, Plantin P, et al. Cutaneous events during treatment of chronic inflammatory joint disorders with anti-tumour necrosis factor alpha: a cross-sectional study. J Eur Acad Dermatol Venereol. 2008 Dec;22(12):1471-7.
11. Duftner C, Dejaco C, Larcher H, Schirmer M, Herold M. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic. Rheumatol Int. 2008 Nov;29(1):69-73.
12. Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol. 2003 Oct;98(10):2232-8.
13. Fernandez-Nebro A, Tomero E, Ortiz-Santamaria V, Castro MC, Olive A, de Haro M, et al. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. Am J Med. 2005 May;118(5):552-6.
14. Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. *Ann Rheum Dis* 2006:379-84.
15. Fouache D, Goeb V, Massy-Guillemant N, Avenel G, Vittecoq O, et al., et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. *Rheumatology* 2009:761.
16. Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. Ann Rheum Dis. 2007 Mar;66(3):308-12.
17. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007:1040-50.
18. Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. *Ann Rheum Dis* 2007:163-8.
19. Helliwell PS, Ibrahim G. Ethnic differences in responses to disease modifying drugs. Rheumatology (Oxford). 2003 Oct;42(10):1197-201.
20. Jones G, Crotty M, Brooks P. Interventions for Treating Psoriatic Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(3).
21. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. 2010.
22. Kaltwasser J, Nash P, Gladman D, Rosen C, Behrens F, Jones P, et al. Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis: a Multinational, Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Arthritis and rheumatism. 2004;50(6):1393-50.
23. Kavanaugh A, Antoni C, Krueger GG, Yan S, Bala M, Dooley LT, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis. 2006 Apr;65(4):471-7.
24. Kavanaugh A, Antoni C, Mease P, Gladman D, Yan S, Bala M, et al. Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. *J Rheumatol* 2006:2254-9.
25. Kavanaugh A, Antoni CE, Gladman D, Wassenberg S, Zhou B, Beutler A, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43.
26. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in

psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009:976-86.
27. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Ann Rheum Dis* 2008:364-9.
28. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. *Expert Opin Biol Ther* 2005:1491-504.
29. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005:3279-89.
30. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
31. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006:712-21.
32. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004:2264-72.
33. Mease PJ, Woolley JM, Singh A, Tsuji W, Dunn M, Chiou CF. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. *J Rheumatol*. 2010/04/17 ed 2010:1221-7.
34. Nannini C, Cantini F, Niccoli L, Cassara E, Lally EV, et al., et al. Single-Center Series and Systematic Review of Randomized Controlled Trials of Malignancies in Patients With Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis Receiving Anti-Tumor Necrosis Factor alpha Therapy: Is There a Need for More Comprehensive Screening Procedures? *Arthritis and Rheumatism-Arthritis Care and Research* 2009:801.
35. Nash P, Thaci D, Behrens F, Falk F, Kaltwasser JP. Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. Dermatology. 2006;212(3):238-49.
36. Puechal X, Miceli-Richard C, Mejjad O, Lafforgue P, Marcelli C, Solau-Gervais E, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):880-4.
37. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Annals of the rheumatic diseases* 2008:855-9.
38. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. *Arthritis Res Ther*. 2009/04/10 ed 2009:R52.
39. Saad AA, Ashcroft DM, Watson KD, Symmons DP, Bsrbr, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)* 2010:697-705.
40. Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. *Arthritis Care Res (Hoboken)*. 2010/04/15 ed 2010:345-53.
41. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-Î± blocker therapy for rheumatic diseases in daily practice: A systematic retrospective study of 709 patients. *Rheumatology* 2007:327-34.
42. Schafer JA, Kjesbo NK, Gleason PP. Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis. J Manag Care Pharm. 2010 Jul-Aug;16(6):402-16.
43. Sichletidis L, Settas L, Spyratos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis. 2006 Oct;10(10):1127-32.
44. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Mulani PM, et al. Comparative Effectiveness Without Head-to-Head Trials A Method for Matching-Adjusted Indirect

Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept. PharmacoEconomics (New Zealand). 2010;28:935-45.
45. Tran S, Hooker RS, Cipher DJ, Reimold A, Jul. Patterns of Biologic Agent Use in Older Males with Inflammatory Diseases An Institution-Focused, Observational Post-Marketing Study. Drugs and Aging (New Zealand). 2009;26:607.
46. van der Heijde D, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. *Arthritis Rheum* 2007:2698-707.
47. Virkki LM, Sumathikutty BC, Aarnio M, Valleala H, Nordstroem DC, et al. Biological Therapy for Psoriatic Arthritis in Clinical Practice: Outcomes Up to 2 Years. *Journal of Rheumatology* 2010:2362-8.
48. Wendling D, Streit G, Toussirot E, Prati C. Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. Joint Bone Spine. 2008 Oct;75(5):540-3.
49. Willkens RF, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum*. 1984/04/01 ed 1984:376-81.
50. Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):1-258.

Wrong Publication Type

1. Cochrane Collaboration guidelines.
2. Anakinra (Kineret) for rheumatoid arthritis. Med Lett Drugs Ther. 2002 Feb 18;44(1124):18-9.
3. Is it true that vaccines may not be safe for people with rheumatoid arthritis (which I have)? Does that mean I shouldn't get a flu shot? Johns Hopkins Med Lett Health After 50. 2004 Oct;17(8):8.
4. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. Rheumatology. 2006 01/01/;45(JUN):7-2.
5. Screening for hydroxychloroquine retinopathy. 2006.
6. Rituxan (Rituximab) [Package Insert]. 2008.
7. Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheumatic Disease Clinics of North America. 2006;32(1):9-44.
8. Anandacoomarasamy A, Kannangara S, Barnsley L. Cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis. Intern Med J. 2005 Oct;35(10):638-40.
9. Andres E, Limbach FX, Goichot B, Sibilia J. Silent thyroiditis associated with etanercept in rheumatoid arthritis. Ann Rheum Dis. 2002 Jun;61(6):565.
10. Arend SM, Kuijper EJ, Allaart CF, Muller WH, Van Dissel JT. Cavitating pneumonia after treatment with infliximab and prednisone. Eur J Clin Microbiol Infect Dis. 2004 Aug;23(8):638-41.
11. Armstrong DJ, McCarron MT, Wright GD. Successful treatment of rheumatoid vasculitis-associated foot-drop with infliximab. J Rheumatol. 2005 Apr;32(4):759; author reply -60.
12. Arnold EL, Khanna D, Paulus H, Goodman MP. Acute injection site reaction to intraarticular etanercept administration. Arthritis Rheum. 2003 Jul;48(7):2078-9.
13. Ashok D, Ayliffe WH, Kiely PD. Necrotizing scleritis associated with rheumatoid arthritis: long-term remission with high-dose infliximab therapy. Rheumatology (Oxford). 2005 Jul;44(7):950-1.
14. Asli B, Wechsler B, Lemaitre C. Inhibition of tumor necrosis factor alpha and ankylosing spondylitis. N Engl J Med. 2003 Jan 23;348(4):359-61; author reply -61.
15. Assous N, Gossec L, Dougados M, Kahan A, Allanore Y. Efficacy of rituximab in patients with rheumatoid arthritis refractory or with contra-indication to anti-tumor necrosis factor-alpha drugs in daily practice: An open label observational study [3]. Clinical and Experimental Rheumatology. 2007;25(3).
16. Bankhurst AD. Etanercept and methotrexate combination therapy. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S69-72.

17. Bartke U, Venten I, Kreuter A, Gubbay S, Altmeyer P, Brockmeyer NH. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab. Br J Dermatol. 2004 Apr;150(4):784-6.
18. Bennett AN, Wong M, Zain A, Panayi G, Kirkham B. Adalimumab-induced asthma. Rheumatology (Oxford). 2005 Sep;44(9):1199-200.
19. Bermas BL. Use of immunosuppressive drugs in pregnancy and lactation. 2007.
20. Bleumink GS, ter Borg EJ, Ramselaar CG, Ch Stricker BH. Etanercept-induced subacute cutaneous lupus erythematosus. Rheumatology (Oxford). 2001 Nov;40(11):1317-9.
21. Boatright MD, Wang BW. Clinical infection with Strongyloides sterocoralis following etanercept use for rheumatoid arthritis. Arthritis Rheum. 2005 Apr;52(4):1336-7.
22. Bravo Vergel Y, Palmer S, Erhorn S, Young V, Brent S, Dyker A, et al. Adalimumab for the treatment of moderate to severe psoriatic arthritis. Health Technology Assessment. 2010.
23. Brocq O, Albert C, Roux C, Gerard D, Breuil V, Ziegler LE. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients. Joint Bone Spine. 2004 Nov;71(6):601-3.
24. Brodszky V, Pentek M, Gulacsi L. Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR50 response after 24 weeks of treatment. Scand J Rheumatol. 2008 Sep-Oct;37(5):399-400.
25. Bruce SP, Boyce EG. Update on abatacept: A selective costimulation modulator for rheumatoid arthritis. Annals of Pharmacotherapy. 2007;41(7-8):1153-62.
26. Burls A, Clark WK, Jobanputra P. Anakinra for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
27. Chevillotte-Maillard H, Ornetti P, Mistrih R, Sidot C, Dupuis J, Dellas JA, et al. Survival and safety of treatment with infliximab in the elderly population. Rheumatology (Oxford). 2005 May;44(5):695-6.
28. Clelland S, Hunek JR. Etanercept injection site reaction. Dermatol Nurs. 2005 Oct;17(5):375-.
29. Clunie G, Voules S, Watts R. Dose reduction of etanercept--can we treat more patients using a fixed budget? Rheumatology (Oxford). 2003 Apr;42(4):600-1.
30. Cobo Ibanez T, Yehia Tayel M, Balsa Criado A, Hernandez Sanz A, Martin Mola E. Safety and efficacy of leflunomide and infliximab versus methotrexate and infliximab combination therapy in rheumatoid arthritis. Rheumatology (Oxford). 2005 Nov;44(11):1467-8.
31. Cocito D, Bergamasco B, Tavella A, Poglio F, Paolasso I, Costa P, et al. Multifocal motor neuropathy during treatment with infliximab. J Peripher Nerv Syst. 2005 Dec;10(4):386-7.
32. Cohen CD, Horster S, Sander CA, Bogner JR. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. Ann Rheum Dis. 2003 Jul;62(7):684.
33. Cohen JD, Zaltni S, Kaiser MJ, Bozonnat MC, Jorgensen C, Daures JP, et al. Secondary addition of methotrexate to partial responders to etanercept alone is effective in severe rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):209-10.
34. Cohen MD, Conn DL. Benefits of low-dose corticosteroids in rheumatoid arthritis. Bull Rheum Dis. 1997 Jun;46(4):4-7.
35. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Annals of the rheumatic diseases. 2007;66(1):34-45.
36. Cunnane G, Warnock M, Fye KH, Daikh DI. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Aug;47(4):445-9.
37. Das P, Raghu P, Amit Kumar D, Garg P. Strongyloides hyperinfection in rheumatoid arthritis. Int J Surg Pathol. 2007 Oct;15(4):391-2.
38. Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. Lancet. 2002 Feb 16;359(9306):540-1.
39. De Bandt M, Vittecoq O, Descamps V, Le Loet X, Meyer O. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol. 2003 Feb;22(1):56-61.
40. Deighton CM, George E, Kiely PDW, Ledingham J, Luqmani RA, Scott DGI. Updating the British Society for Rheumatology guidelines for anti-tumour

necrosis factor therapy in adult rheumatoid arthritis (again). Rheumatology. 2006;45(6):649-52.
41. Duggan ST, Keam SJ, Jun. Certolizumab Pegol In Rheumatoid Arthritis. BioDrugs (New Zealand). 2009;23:407.
42. Dumont-Berset M, Laffitte E, Gerber C, Dudler J, Panizzon RG. Eczematous drug eruption after infliximab. Br J Dermatol. 2004 Dec;151(6):1272-3.
43. Emery P. Disease Modification in Rheumatoid Arthritis With Leflunomide. Scandinavian journal of rheumatology Supplement. 1999;112(9):9-14.
44. Emery P, Genovese MC, Fleischmann RM, Matteson EL, Hsia EC, Xu S, et al. Efficacy of Golimumab, a human anti-TNF(alpha) antibody, by baseline CRP level in patients with rheumatoid arthritis: Results from three phase 3, randomized, double-blind, placebo-controlled studies. *Rheumatology* 2010:i101.
45. Favalli EG, Arreghini M, Arnoldi C, Panni B, Marchesoni A, Tosi S, et al. Anti-tumor necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. Arthritis Rheum. 2004 Apr 15;51(2):301-2.
46. Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86.
47. Franklin CM. Clinical experience with soluble TNF p75 receptor in rheumatoid arthritis. Semin Arthritis Rheum. 1999 Dec;29(3):172-81.
48. Furst DE. Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004 Dec;26(12):1960-75.
49. Furst DE, Keystone EC, Kirkham B, Fleischmann R, Mease P, Breedveld FC, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Annals of the rheumatic diseases. 2008;67(SUPPL. 3).
50. Gadadhar H, Hawkins S, Huffstutter JE, Panda M. Cutaneous mucormycosis complicating methotrexate, prednisone, and infliximab therapy. J Clin Rheumatol. 2007 Dec;13(6):361-2.
51. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum. 2008 Feb;58(2 Suppl):S126-35.
52. Goldenberg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther. 1999 Jan;21(1):75-87; discussion 1-2.
53. Golding A, Haque UJ, Giles JT. Rheumatoid arthritis and reproduction. Rheum Dis Clin North Am. 2007 May;33(2):319-43, vi-vii.
54. Gupta N, Fox CM, Grisolano SW. Disseminated histoplasmosis with colonic ulcers in a patient receiving infliximab. Gastrointest Endosc. 2009 Sep;70(3):597-8.
55. Health Technology A. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation (Project record). Health Technology Assessment. 2010.
56. Health Technology A. The clinical and cost effectiveness of etanercept, infliximab and adalimumab - psoriatic arthritis (guidance review 104 and 125) (Project record). Health Technology Assessment. 2010.
57. Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: A systematic review of scales in use. Arthritis Care and Research. 2007;57(3):429-39.
58. Hirche D, Rubbert A, Lunau L, Krieg T, Eming SA. Successful treatment of refractory rheumatoid arthritis-associated leg ulcerations with adalimumab. Br J Dermatol. 2005 May;152(5):1062-4.
59. Hong BK, Kumar C, Marottoli RA. "MAC" attack. Am J Med. 2009 Dec;122(12):1096-8.
60. Horng MS. Early rheumatoid arthritis: Is there a best treatment? Journal of Clinical Outcomes Management. 2007;14(5):233-4.
61. Hoshida Y, Yamamoto S, Wada N, Xu JX, Sasaki T, Aozasa K. Infliximab-associated lymphoproliferative disorders. Int J Hematol. 2005 May;81(4):356-7.
62. Hrycaj P, Korczowska I, Lacki JK. Severe Parkinson's disease in rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford). 2003 May;42(5):702-3.
63. Inoue K, Takano H, Yanagisawa R, Yoshikawa T. Effects of tumor necrosis factor-alpha inhibitors on lung lesions with rheumatoid arthritis. Chest. 2003 Jul;124(1):413-4; author reply 4.

64. Josefina M, Ana CJ, Ariel V, Silvio AA. Development of pseudogout during etanercept treatment. J Clin Rheumatol. 2007 Jun;13(3):177.
65. Ju JH, Kim SI, Lee JH, Lee SI, Yoo WH, Choe JY, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. *Arthritis Rheum* 2007:2094-6.
66. Kaiser MJ, Bozonnat MC, Jorgensen C, Daures JP, Sany J. Effect of etanercept on tenosynovitis and nodules in rheumatoid arthritis. Arthritis Rheum. 2002 Feb;46(2):559-60.
67. Kelaidi C, Tulliez M, Lecoq-Lafon C, Pham XV, Kahan A, Dreyfus F, et al. Long-term remission of an EBV-positive B cell lymphoproliferative disorder associated with rheumatoid arthritis under methotrexate with anti-CD20 monoclonal antibody (Rituximab) monotherapy. Leukemia. 2002 Oct;16(10):2173-4.
68. Kemp E, Nielsen H, Petersen LJ, Gam AN, Dahlager J, Horn T, et al. Newer immunomodulating drugs in rheumatoid arthritis may precipitate glomerulonephritis. Clin Nephrol. 2001 Jan;55(1):87-8.
69. Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. Ann Rheum Dis. 1999 November 1, 1999;58(90001):70i-2.
70. Kempeni J. Update on D2E7: a fully human anti-tumour necrosis factor alpha monoclonal antibody. Ann Rheum Dis. 2000 November 1, 2000;59(90001):44i-5.
71. Kirwan J. Early rheumatoid arthritis: combination therapy with disease-modifying antirheumatic drugs and low-dose glucocorticoids? Nat Clin Pract Rheumatol. 2006 Apr;2(4):182-3.
72. Kirwan J, Shea B, Boers M. Glucocorticoids for Slowing Radiological Progression in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
73. Korkmaz C, Kasifoglu T, Yasar B. Acceleration of left-ventricular diastolic dysfunction and pulmonary hypertension after TNF-alpha blocker. Ann Pharmacother. 2005 Jun;39(6):1138-9.
74. Kramer N, Chuzhin Y, Kaufman LD, Ritter JM, Rosenstein ED. Methotrexate pneumonitis after initiation of infliximab therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Dec 15;47(6):670-1.
75. Krathen MS, Gottlieb AB, Mease PJ. Pharmacologic Immunomodulation and Cutaneous Malignancy in Rheumatoid Arthritis, Psoriasis, and Psoriatic Arthritis. Journal of Rheumatology. 2010;37:2205-15.
76. Kremer J, Westhovens R, Luggen M. Long-term efficacy and safety of abatacept through 3 years of treatment in rheumatoid arthritis patients in the AIM and ATTAIN trials [abstract]. American College of Rheumatology Meeting.
77. Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. Arthritis Rheum. 1997 May;40(5):984-5.
78. Kreuter A, Rose C, Zillikens D, Altmeyer P. Bullous rheumatoid neutrophilic dermatosis. J Am Acad Dermatol. 2005 May;52(5):916-8.
79. Kucharz EJ, Gozdzik J, Kopec M, Kotulska A, Lewicki M, Pieczyrak R, et al. A single infusion of infliximab increases the serum endostatin level in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):273-4.
80. Kurschat P, Rubbert A, Poswig A, Scharffetter-Kochanek K, Krieg T, Hunzelmann N. Treatment of psoriatic arthritis with etanercept. J Am Acad Dermatol. 2001 Jun;44(6):1052.
81. Liberopoulos EN, Drosos AA, Elisaf MS. Exacerbation of tuberculosis enteritis after treatment with infliximab. Am J Med. 2002 Nov;113(7):615.
82. Lindsay K, Gough A. Psoriatic arthritis, methotrexate and the liver - Are rheumatologists putting their patients at risk? Rheumatology. 2008;47(7):939-41.
83. Looney RJ. B cell-targeted therapy for rheumatoid arthritis - An update on the evidence. Drugs (New Zealand). 2006 05/01/;66(May):625-39.
84. Luqmani R, Hennell S, Estrach C, Birrell F, Audit Working G, et al. British society for rheumatology and british health professionals in rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology. 2006 09/01/;45(Sep):1167-9.
85. Manadan AM, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):526.

86. Mang R, Stege H, Ruzicka T, Krutmann J. Response of severe psoriasis to infliximab. Dermatology. 2002;204(2):156-7.
87. Marchesoni A, Puttini PS, Gorla R, Caporali R, Arnoldi C, Atzeni F, et al. Cyclosporine in addition to infliximab and methotrexate in refractory rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):916-7.
88. Matsui T, Komiya A, Shimada K, Nakayama H, Tohma S. Neutrophil CD64 as a marker of infection in patients treated with tocilizumab. Mod Rheumatol. 2009;19(6):696-7.
89. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2008(3).
90. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology (Oxford). 2002 Jan;41(1):116-7.
91. Mease P. Psoriatic arthritis update. Bulletin of the NYU Hospital for Joint Diseases. 2006;64(1-2):25-31.
92. Mease PJ. Cytokine Blockers in Psoriatic Arthritis. Annals of the rheumatic diseases. 2001;60(Suppl 3):iii37-40.
93. Michaelsson G, Kajermo U, Michaelsson A, Hagforsen E. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct? Br J Dermatol. 2005 Dec;153(6):1243-4.
94. Misery L, Perrot JL, Gentil-Perret A, Pallot-Prades B, Cambazard F, Alexandre C. Dermatological complications of etanercept therapy for rheumatoid arthritis. Br J Dermatol. 2002 Feb;146(2):334-5.
95. Molloy E, Ramakrishnan S, Murphy E, Barry M. Morbidity and mortality in rheumatoid patients during treatment with adalimumab and infliximab. Rheumatology (Oxford). 2004 Apr;43(4):522-3.
96. Montagna GL, Malesci D, Buono R, Valentini G. Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005 Nov;64(11):1667.
97. Murphy FT, Enzenauer RJ, Battafarano DF, David-Bajar K. Etanercept-associated injection-site reactions. Arch Dermatol. 2000 Apr;136(4):556-7.
98. Musial J, Undas A, Celinska-Lowenhoff M. Polymyositis associated with infliximab treatment for rheumatoid arthritis. Rheumatology (Oxford). 2003 Dec;42(12):1566-8.
99. Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. Am J Med. 2002 Jan;112(1):78.
100. Nikas SN, Temekonidis TI, Zikou AK, Argyropoulou MI, Efremidis S, Drosos AA. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. Ann Rheum Dis. 2004 Jan;63(1):102-3.
101. Nikas SN, Voulgari PV, Takalou IP, Katsimbri P, Drosos AA. Healing of psoriatic skin lesions, and improvement of psoriatic arthritis resistant to immunosuppressive drugs, after infliximab treatment. Ann Rheum Dis. 2005 Nov;64(11):1665-7.
102. Novak S, Cikes N. Infliximab-induced lupus or rheumatoid arthritis (RA) overlapping with systemic lupus erythematosus (SLE) unmasked by infliximab. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):268.
103. Ornetti P, Solau E, Gaudin P, Sibilia J, Berthelot JM, Puechal X, et al. Increase in methotrexate dose in patients with rheumatoid arthritis who have an inadequate response to infliximab. Ann Rheum Dis. 2005 Sep;64(9):1379-80.
104. Ostor AJ, Crisp AJ, Somerville MF, Scott DG. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. BMJ. 2004 Nov 27;329(7477):1266.
105. Ostrov BE. Beneficial effect of etanercept on rheumatoid lymphedema. Arthritis Rheum. 2001 Jan;44(1):240-1.
106. Pagliano P, Attanasio V, Fusco U, Mohamed DA, Rossi M, Faella FS. Does etanercept monotherapy enhance the risk of Listeria monocytogenes meningitis? Ann Rheum Dis. 2004 Apr;63(4):462-3.
107. Parekh K, Ching D, Rahman MU, Stamp LK. Onset of Wegener's granulomatosis during therapy with golimumab for rheumatoid arthritis: a rare adverse event? Rheumatology (Oxford). 2010 Sep;49(9):1785-7.
108. Pisoni L, Murgo A, Paresce E, Zeni S, Fantini F. Effectiveness and safety of leflunomide in the clinical practice. A different experience [1]. Clinical and Experimental Rheumatology. 2007;25(1).
109. Popovic M, Stefanovic D, Pejnovic N, Popovic R, Glisic B, Obradovic S, et al. Comparative study of the clinical efficacy of

four DMARDs (leflunomide, methotrexate, cyclosporine, and levamisole) in patients with rheumatoid arthritis. Transplant Proc. 1998 Dec;30(8):4135-6.
110. Provenzano G, Termini A, Le Moli C, Rinaldi F. Efficacy of infliximab in psoriatic arthritis resistant to treatment with disease modifying antirheumatic drugs: an open pilot study. Ann Rheum Dis. 2003 Jul;62(7):680-1.
111. Racunica T, Cassidy D, Cicuttini F, Hall A. Trouble with tumor necrosis factor alpha inhibitors, not just tuberculosis. *Arthritis Care Res (Hoboken)*. 2010/06/11 ed 2010:770-4.
112. Radovits BJ, Kievit W, Laan RF. Tumour necrosis factor-alpha antagonists in the management of rheumatoid arthritis in the elderly: a review of their efficacy and safety. Drugs Aging. 2009;26(8):647-64.
113. Rahman N, Healy C, Flint SR, Stassen LF. Cautionary note: a possible association between oral squamous cell carcinoma and tumor necrosis factor antagonists; need for oral screening. J Clin Rheumatol. 2010 Jun;16(4):197-9.
114. Reddy AR, Backhouse OC. Does etanercept induce uveitis? Br J Ophthalmol. 2003 Jul;87(7):925.
115. Richter C, Wanke L, Steinmetz J, Reinhold-Keller E, Gross WL. Mononeuritis secondary to rheumatoid arthritis responds to etanercept. Rheumatology (Oxford). 2000 Dec;39(12):1436-7.
116. Rimar D, Rozenbaum M, Slobodin G, Boulman N, Rosner I. Etanercept related pseudo-empyema in rheumatoid arthritis. *Clin Rheumatol*. 2010/02/04 ed 2010:547-9.
117. Rinaldi F, Provenzano G, Termini A, Spinello M, La Seta F. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. Ann Rheum Dis. 2005 Sep;64(9):1375-6.
118. Robinson V, Boers M, Brooks P, Francis D, Wells GA, et al. Patient-reported pain is central to OMERACT rheumatology core measurement sets. Drug Information Journal (USA). 2006 01/01/;40(Jan):111-6.
119. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-Î± therapy. Rheumatology. 2007;46(4):695-8.
120. Rozman B. Clinical Experience With Leflunomide in Rheumatoid Arthritis. The Journal of rheumatology. 1998;52(Suppl):27-32.
121. Ruiz Garcia V, Burls A, Cabello López Juan CL, Fry- Smith Anne FS, Gálvez Muñoz José G, Jobanputra P, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database of Systematic Reviews. 2009(1).
122. Russell E, Zeihen M, Wergin S, Litton T. Patients receiving etanercept may develop antibodies that interfere with monoclonal antibody laboratory assays. Arthritis Rheum. 2000 Apr;43(4):944.
123. Salli A, Sahin N, Paksoy Y, Kucuksarac S, Ugurlu H. Treatment of periodontoid pannus with infliximab in a patient with rheumatoid arthritis. J Clin Rheumatol. 2009 Aug;15(5):250-1.
124. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med. 2006 Aug 17;355(7):704-12.
125. Sholsberg J, Jackson R. Best evidence topic report. Intra-articular corticosteroid injections in acute rheumatoid monoarthritides. Emerg Med J. 2004 Mar;21(2):204.
126. Simpson D, Scott LJ. Adalimumab : in psoriatic arthritis. Drugs. 2006;66(11):1487-96.
127. Singh Jasvinder A, Beg S, Lopez Olivo Maria A. Tocilizumab for rheumatoid arthritis. 2010.
128. Smith D, Letendre S. Viral pneumonia as a serious complication of etanercept therapy. Ann Intern Med. 2002 Jan 15;136(2):174.
129. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010:964-75.
130. Soliotis F, Glover M, Jawad AS. Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):850-1.
131. Strand. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: Evidence from randomized controlled trials (American Journal of Managed Care). American Journal of Managed Care. 2008;14(4):234.
132. Suresh R, Gupta S, Sathananthan R. Sulphasalazine induced three-week syndrome. J Clin Rheumatol. 2009 Sep;15(6):311-2.

133. Sweet BV. Abatacept. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Jan):2065-77.
134. Tack CJ, Kleijwegt FS, Van Riel PL, Roep BO. Development of type 1 diabetes in a patient treated with anti-TNF-alpha therapy for active rheumatoid arthritis. Diabetologia. 2009 Jul;52(7):1442-4.
135. Tateiwa T, Shinmura K, Ko M, Mibe J, Yamamoto K. Iliopectineal bursitis associated with rapid destruction of a rheumatoid hip joint. J Orthop Sci. 2009 Jul;14(4):455-8.
136. Van Rijthoven AW, Bijlsma JW, Canninga-Van Dijk M, Derksen RH, Van Roon JA. Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level. Rheumatology. 2006 10/01/;45(Oct):1317-9.
137. Vis M, Voskuyl AE, Wolbink GJ, Dijkmans BA, Lems WF. Bone mineral density in patients with rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2005 Feb;64(2):336-7.
138. Vis M, Wolbink GJ, Lodder MC, Kostense PJ, van de Stadt RJ, de Koning MH, et al. Early changes in bone metabolism in rheumatoid arthritis patients treated with infliximab. Arthritis Rheum. 2003 Oct;48(10):2996-7.
139. Voulgari PV, Venetsanopoulou AI, Epagelis EK, Alamanos Y, Takalou I, Drosos AA. Infliximab in refractory psoriatic arthritis with severe psoriasis: a 2-year experience. Ann Rheum Dis. 2007 Feb;66(2):270-1.
140. Yazici Y, Erkan D, Lockshin MD. Etanercept in the treatment of severe, resistant psoriatic arthritis: continued efficacy and changing patterns of use after two years. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):115.

Wrong Study Design

1. Summaries for patients. Tumor necrosis factor antagonists and heart failure. Ann Intern Med. 2003 May 20;138(10):I48.
2. Abramovits W, Arrazola P, Gupta AK. Enbrel (etanercept). Skinmed. 2004 Nov-Dec;3(6):333-5.
3. Agarwal S, Zaman T, Handa R. Retention rates of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. *Singapore Med J* 2009:686-92.
4. Aggarwal A, Panda S, Misra R. Effect of etanercept on matrix metalloproteinases and angiogenic vascular endothelial growth factor: a time kinetic study. Ann Rheum Dis. 2004 Jul;63(7):891-2.
5. Aggarwal R, Manadan AM, Poliyedath A, Sequeira W, Block JA, May. Safety of Etanercept in Patients at High Risk for Mycobacterial Tuberculosis Infections. Journal of Rheumatology. 2009;36:914.
6. Alcorn N, Saunders S, Madhok R, Dec. Benefit-Risk Assessment of Leflunomide An Appraisal of Leflunomide in Rheumatoid Arthritis 10 Years After Licensing. Drug Safety (New Zealand). 2009;32:1123.
7. Amichai B, Gat A, Grunwald MH. Cutaneous hyperpigmentation during therapy with hydroxychloroquine. J Clin Rheumatol. 2007 Apr;13(2):113.
8. Ang HT, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-alpha antagonists in patients with rheumatoid arthritis? J Rheumatol. 2003 Nov;30(11):2315-8.
9. Antoni C, Dechant C, Hanns-Martin Lorenz PD, Wendler J, Ogilvie A, Lueftl M, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. Arthritis Rheum. 2002 Oct 15;47(5):506-12.
10. Antoni C, Kalden J. Combination Therapy of the Chimeric Monoclonal Anti-Tumor Necrosis Factor Alpha Antibody (Infliximab) With Methotrexate in Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6 Suppl 18):S73-7.
11. Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76.
12. Argyropoulou MI, Glatzouni A, Voulgari PV, Xydis VG, Nikas SN, Efremidis SC, et

al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. Joint Bone Spine. 2005 Dec;72(6):557-61.
13. Arif S, Cox P, Afzali B, Lombardi G, Lechler RI, Peakman M, et al. Anti-TNFalpha therapy--killing two birds with one stone? *Lancet*. 2010/07/09 ed 2010:2278.
14. Augustsson J, Eksborg S, Ernestam S, Gullstrom E, van Vollenhoven R. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1462-6.
15. Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S, van Vollenhoven RF. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Ann Rheum Dis* 2010:126-31.
16. Bansback NJ, Ara R, Barkham N, Brennan A, Emery P, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology. 2006 08/01/;45(Aug):1029-38.
17. Barra L, Pope JE, Payne M. Real-world anti-tumor necrosis factor treatment in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: cost-effectiveness based on number needed to treat to improve health assessment questionnaire. J Rheumatol. 2009 Jul;36(7):1421-8.
18. Barrera P, van der Maas A, van Ede AE, Kiemeney BALM, Laan RFJM, van de Putte LBA, et al. Drug Survival, Efficacy and Toxicity of Monotherapy With a Fully Human Anti-Tumour Necrosis Factor-a Antibody Compared With Methotrexate in Long-Standing Rheumatoid Arthritis. *Rheumatology* 2002:430-9.
19. Bathon JM, Fleischmann RM, van der Heijde DM, Tesser JR, White B, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. Journal of Rheumatology. 2006 02/01/;33(Feb):234-43.
20. Baumgartner SW, Fleischmann RM, Moreland LW, Schiff MH, Markenson J, Whitmore JB. Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability. J Rheumatol. 2004 Aug;31(8):1532-7.
21. Berends MAM, Snoek J, De Jong EMGJ, Van De Kerkhof PCM, Van Oijen MGH, Van Krieken JH, et al. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Alimentary Pharmacology and Therapeutics. 2006;24(5):805-11.
22. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int. 2004 May;25(5):331-5.
23. Bingham CO, Ince A, Haraoui B, Keystone EC, Baumgartner S, et al., et al. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-week, open-label, observational study. *Current Medical Research and Opinion (England)* 2009:1131.
24. Bliddal H, Terslev L, Qvistgaard E, Konig M, Holm CC, Rogind H, et al. A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Sep-Oct;35(5):341-5.
25. Blom M, Kievit W, Fransen J, Kuper IH, den Broeder AA, De Gendt CM, et al. The reason for discontinuation of the first tumor necrosis factor (TNF) blocking agent does not influence the effect of a second TNF blocking agent in patients with rheumatoid arthritis. J Rheumatol. 2009 Oct;36(10):2171-7.
26. Blom M, Kievit W, Kuper HH, Jansen TL, Visser H, den Broeder AA, et al. Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1335-41.
27. Bodur H, Ataman S, Akbulut L, Evcik D, Kavuncu V, Kaya T, et al. Characteristics and medical management of patients with rheumatoid arthritis and ankylosing spondylitis. Clin Rheumatol. 2008 Sep;27(9):1119-25.
28. Boesen M, Boesen L, Jensen KE, Cimmino MA, Torp-Pedersen S, Terslev L, et al. Clinical outcome and imaging changes after intraarticular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and

ultrasound-Doppler show no effect of IA injections in the wrist after 4 weeks. J Rheumatol. 2008 Apr;35(4):584-91.
29. Bohanec Grabar P, Rozman B, Tomsic M, Suput D, Logar D, Dolzan V. Genetic polymorphism of CYP1A2 and the toxicity of leflunomide treatment in rheumatoid arthritis patients. Eur J Clin Pharmacol. 2008 Sep;64(9):871-6.
30. Bologna C, Jorgensen C, Sany J. Association of methotrexate and corticosteroids in the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1996 Jul-Aug;14(4):401-6.
31. Bombardieri S, Ruiz AA, Fardellone P, Geusens P, McKenna F, Unnebrink K, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology (Oxford). 2007 Jul;46(7):1191-9.
32. Bongartz T. Tocilizumab for rheumatoid and juvenile idiopathic arthritis. Lancet. 2008(9617):961-3.
33. Borah BJ, Huang XY, Zarotsky V, Globe D, Jun. Trends in RA patients' adherence to subcutaneous anti-TNF therapies and costs. *Current Medical Research and Opinion (England)* 2009:1365.
34. Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: Review of the Efficacy and Tolerability of a Recently Approved Tumor Necrosis Factor-alpha Inhibitor. Clinical Therapeutics (USA). 2010;32:1681-703.
35. Braun-Moscovici Y, Markovits D, Rozin A, Toledano K, Nahir AM, Balbir-Gurman A. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. Isr Med Assoc J. 2008 Apr;10(4):277-81.
36. Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.
37. Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, et al. TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. *Joint Bone Spine* 2007:148-54.
38. Buch MH, Bingham SJ, Bejarano V, Bryer D, White J, Reece R, et al. Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept. Arthritis Rheum. 2007 Apr 15;57(3):448-53.
39. Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 2008 Jun 15;59(6):794-9.
40. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9.
41. Bukhari MA, Wiles NJ, Lunt M, Harrison BJ, Scott DG, Symmons DP, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis Rheum. 2003 Jan;48(1):46-53.
42. Burmester GR, Ferraccioli G, Flipo RM, Monteagudo-Saez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008 Jan 15;59(1):32-41.
43. Cacace E, Anedda C, Ruggiero V, Fornasier D, Denotti A, Perpignano G. Etanercept in rheumatoid arthritis: Long term anti-inflammatory efficacy in clinical practice. European Journal of Inflammation. 2006;4(3):171-6.
44. Calguneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I, et al. Combination Therapy Versus Monotherapy for the Treatment of Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6):699-704.
45. Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1Ra Arthritis Study Group. Arthritis Rheum. 1996 Jul;39(7):1092-101.
46. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology (Oxford)* 2008:872-6.
47. Carmona L, Descalzo MÃ, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than

expected when treated with tumour necrosis factor antagonists. Annals of the rheumatic diseases. 2007;66(7):880-5.
48. Cassano N, Galluccio A, De Simone C, Loconsole F, Massimino SD, Plumari A, et al. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. J Biol Regul Homeost Agents. 2008 Oct-Dec;22(4):233-7.
49. Cauza E, Spak M, Cauza K, Hanusch-Enserer U, Dunky A, Wagner E. Treatment of psoriatic arthritis and psoriasis vulgaris with the tumor necrosis factor inhibitor infliximab. Rheumatol Int. 2002 Nov;22(6):227-32.
50. Chambers CD, Johnson DL, Robinson LK, Braddock SR, Xu R, Lopez-Jimenez J, et al. Birth outcomes in women who have taken leflunomide during pregnancy. *Arthritis Rheum*. 2010/02/05 ed 2010:1494-503.
51. Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. 2009.
52. Ciconelli R, Ferraz M, Visioni R, Oliveira L, Atra E. A Randomized Double-Blind Controlled Trial of Sulphasalazine Combined With Pulses of Methylprednisolone or Placebo in the Treatment of Rheumatoid Arthritis. British journal of rheumatology. 1996;35(2):150-4.
53. Cohen G, Courvoisier N, Cohen JD, Zaltni S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):795-800.
54. Cohen JD, Dougados M, Goupille P, Cantagrel A, Meyer O, Sibilia J, et al. Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis. Journal of Rheumatology. 2006;33(10):1936-41.
55. Cole JC, Li T, Lin P, MacLean R, Wallenstein GV. Treatment impact on estimated medical expenditure and job loss likelihood in rheumatoid arthritis: re-examining quality of life outcomes from a randomized placebo-controlled clinical trial with abatacept. Rheumatology (Oxford). 2008 Jul;47(7):1044-50.
56. Contreras-Yanez I, Ponce De Leon S, Cabiedes J, Rull-Gabayet M, Pascual-Ramos V. Inadequate therapy behavior is associated to disease flares in patients with rheumatoid arthritis who have achieved remission with disease-modifying antirheumatic drugs. Am J Med Sci. 2010 Oct;340(4):282-90.
57. Covelli M, Scioscia C, Iannone F, Lapadula G. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after discontinuation of infliximab. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):145-51.
58. Criswell L, Saag K, Sems KM, Welch V, Shea B, Wells George A, et al. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. 1998.
59. Cuchacovich M, Ferreira L, Aliste M, Soto L, Cuenca J, Cruzat A, et al. Tumour necrosis factor-alpha (TNF-alpha) levels and influence of -308 TNF-alpha promoter polymorphism on the responsiveness to infliximab in patients with rheumatoid arthritis. Scand J Rheumatol. 2004;33(4):228-32.
60. Curtis JR, Martin C, Saag KG, Patkar NM, Kramer J, Shatin D, et al. Confirmation of administrative claims-identified opportunistic infections and other serious potential adverse events associated with tumor necrosis factor alpha antagonists and disease-modifying antirheumatic drugs. Arthritis Rheum. 2007 Mar 15;57(2):343-6.
61. Davis JM, 3rd, Maradit Kremers H, Crowson CS, Nicola PJ, Ballman KV, Therneau TM, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007 Mar;56(3):820-30.
62. De Felice C, Mazzotta A, Esposito M, Bianchi L, Chimenti S. High-dose initiation of etanercept in psoriatic arthritis and plaque psoriasis: efficacy, safety and impact on patients' quality of life. J Dermatolog Treat. 2006;17(6):355-8.
63. De Filippis L, Caliri A, Anghelone S, Scibilia G, Lo Gullo R, Bagnato G. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. *Panminerva Med* 2006:129-35.

64. De Rycke L, Baeten D, Kruithof E, Van den Bosch F, De Keyser F, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity - Biologic and clinical implications in autoimmune arthritis. Arthritis and Rheumatism (USA). 2005 07/01/;52(Jul):2192-201.
65. De Rycke L, Baeten D, Kruithof E, Van den Bosch F, Veys EM, De Keyser F. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. Arthritis Rheum. 2005 Jul;52(7):2192-201.
66. del Porto F, Aloe L, Lagana B, Triaca V, Nofroni I, D'Amelio R. Nerve growth factor and brain-derived neurotrophic factor levels in patients with rheumatoid arthritis treated with TNF-alpha blockers. Ann N Y Acad Sci. 2006 Jun;1069:438-43.
67. Delabaye I, De Keyser F. 74-week follow-up of safety of infliximab in patients with refractory rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R121.
68. den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol. 2002 Nov;29(11):2288-98.
69. Dohn UM, Skjodt H, Hetland ML, Vestergaard A, Moller JM, Knudsen LS, et al. No erosive progression revealed by MRI in rheumatoid arthritis patients treated with etanercept, even in patients with persistent MRI and clinical signs of joint inflammation. Clin Rheumatol. 2007 Nov;26(11):1857-61.
70. Dore RK, Mathews S, Schechtman J, Surbeck W, Mandel D, Patel A, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):40-6.
71. Ducoulombier V, Solau E, Coquerelle P, Houvenagel E, Siame JL, Desprez X, et al. Long-term results of infliximab therapy in rheumatoid arthritis: experience acquired by the North-Pas-de-Calais hospital network. Joint Bone Spine. 2007 Jan;74(1):56-9.
72. Dunne CA, Moran CJ, Thompson PW. The effect of regular intramuscular corticosteroid therapy on bone mineral density in rheumatoid patients. Scand J Rheumatol. 1995;24(1):48-9.
73. Durez P, Malghem J, Nzeusseu Toukap A, Depresseux G, Lauwerys BR, Westhovens R, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis Rheum* 2007:3919-27.
74. Durez P, Nzeusseu Toukap A, Lauwerys BR, Manicourt DH, Verschueren P, Westhovens R, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Ann Rheum Dis. 2004 Sep;63(9):1069-74.
75. Durez P, Van den Bosch F, Corluy L, Veys EM, De Clerck L, Peretz A, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. Rheumatology (Oxford). 2005 Apr;44(4):465-8.
76. Eder L, Chandran V, Schentag CT, Shen H, Cook RJ, Gladman DD. Time and predictors of response to tumour necrosis factor-(alpha) blockers in psoriatic arthritis: An analysis of a longitudinal observational cohort. Rheumatology. 2010;49(7):1361-6.
77. Egnatios G, Warthan MM, Pariser R, Hood AF. Pustular psoriasis following treatment of rheumatoid arthritis with TNF-alpha inhibitors. J Drugs Dermatol. 2008 Oct;7(10):975-7.
78. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Sasso EH, et al., et al. Less Radiographic Progression with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy Across the Spectrum of Clinical Response in Early Rheumatoid Arthritis. *Journal of Rheumatology* 2009:1429.
79. Farahani P, Levine M, Gaebel K, Wang EC, Khalidi N. Community-based evaluation of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2006 Apr;33(4):665-70.
80. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of

two metaanalyses. Arthritis Rheum. 1990 Oct;33(10):1449-61.
81. Fernandez-Espartero MC, Perez-Zafrilla B, Naranjo A, Esteban C, Ortiz AM, Gomez-Reino JJ, et al. Demyelinating Disease in Patients Treated with TNF Antagonists in Rheumatology: Data from BIOBADASER, a Pharmacovigilance Database, and a Systematic Review. *Semin Arthritis Rheum* 2010:330-7.
82. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008 Oct;35(10):1944-9.
83. Fiehn C, Jacki S, Heilig B, Lampe M, Wiesmuller G, Richter C, et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. Rheumatol Int. 2007 Aug;27(10):975-9.
84. Finckh A, Simard JF, Duryea J, Liang MH, Huang J, Daneel S, et al. The effectiveness of anti-tumor necrosis factor therapy in preventing progressive radiographic joint damage in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2006 Jan;54(1):54-9.
85. Fischer P. Resolution of treatment-related arthralgias and serologic findings with a switch of TNF antagonist therapies in a patient with psoriatic arthritis. J Clin Rheumatol. 2007 Oct;13(5):294-5.
86. Fleischmann R. Safety and efficacy of etanercept in the elderly. Aging Health. 2006;2(2):189-97.
87. Fleischmann RM, Cohen SB, Moreland LW, Schiff M, Mease PJ, Smith DB, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin. 2005 Aug;21(8):1181-90.
88. Frankel EH, Strober BE, Crowley JJ, Fivenson DP, Woolley JM, Yu EB, et al. Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. Cutis. 2007 Apr;79(4):322-6.
89. Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum. 1996 Apr;39(4):616-22.
90. Furst D, Erikson N, Clute L, Koehnke R, Burmeister L, Kohler J. Adverse Experience With Methotrexate During 176 Weeks of a Longterm Prospective Trial in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1990;12:1628-35.
91. Furst DE, Gaylis N, Bray V, Olech E, Yocum D, Ritter J, et al. Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. *Ann Rheum Dis* 2007:893-9.
92. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Hara M, et al. Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: A prospective observational cohort study. Journal of Bone and Mineral Metabolism. 2008;26(5):499-505.
93. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Kobashigawa T, et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: A prospective 54-month observational study. Journal of Rheumatology. 2007;34(2):303-10.
94. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: Results from the long-term extension of the AIM trial. Annals of the Rheumatic Diseases. 2007;67(8):1084-9.
95. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23.
96. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):547-54.
97. George D, Kadlubek P, Batra D, Goldberg G. Infliximab dose and charge escalation patterns in managed care. Manag Care Interface. 2004;Suppl A:5-8.
98. Gibson JN, Poyser NL, Morrison WL, Scrimgeour CM, Rennie MJ. Muscle protein synthesis in patients with rheumatoid

arthritis: effect of chronic corticosteroid therapy on prostaglandin F2 alpha availability. Eur J Clin Invest. 1991 Aug;21(4):406-12.
99. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):333-7.
100. Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther. 2010;12(3):R113.
101. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum. 2007 Feb;56(2):476-88.
102. Gladman DD, Sampalis JS, Illouz O, Guerette B, Investigators AS. Responses to Adalimumab in Patients with Active Psoriatic Arthritis Who Have Not Adequately Responded to Prior Therapy: Effectiveness and Safety Results From an Open-label Study. Journal of Rheumatology. 2010;37:1898.
103. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Kerstens PJSM, Nielen MMJ, Vos K, Van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. 2010.
104. Goldman JA, Xia HA, White B, Paulus H. Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept. Ann Rheum Dis. 2006 Dec;65(12):1649-52.
105. Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC, Fernandez-Llaca H, Rodriguez-Valverde V. Development of sarcoidosis during etanercept therapy. Arthritis Rheum. 2006 Oct 15;55(5):817-20.
106. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010 Sep;62(9):2625-32.
107. Gottlieb AB, Kircik L, Eisen D, Jackson JM, Boh EE, Strober BE, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. J Dermatolog Treat. 2006;17(6):343-52.
108. Gran JT, Myklebust G. Toxicity of sulphasalazine in rheumatoid arthritis. Possible protective effect of rheumatoid factors and corticosteroids. Scand J Rheumatol. 1993;22(5):229-32.
109. Gratacos J, Casado E, Real J, Torre-Alonso JC. Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. Ann Rheum Dis. 2007 Apr;66(4):493-7.
110. Greenberg JD, Kishimoto M, Strand V, Cohen SB, Olenginski TP, Harrington T, et al. Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. Am J Med. 2008 Jun;121(6):532-8.
111. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a Treatment Strategy of Tight Control for Rheumatoid Arthritis (the Ticora Study): a Single-Blind Randomised Controlled Trial. Lancet. 2004;364(9430):263-9.
112. Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF, Jr., Griffin MR. Adherence to disease-modifying antirheumatic drugs and the effects of exposure misclassification on the risk of hospital admission. *Arthritis Care Res (Hoboken)*. 2010/03/02 ed 2010:730-4.
113. Haagsma C, van Riel P, van de Putte L. Combining Sulphasalazine and Methotrexate in Rheumatoid Arthritis: Early Clinical Impressions. British journal of rheumatology. 1995;34(Suppl 2):104-8.
114. Haagsma CJ, van Riel PL, de Rooij DJ, Vree TB, Russel FJ, van't Hof MA, et al. Combination of Methotrexate and Sulphasalazine Vs Methotrexate Alone: a Randomized Open Clinical Trial in Rheumatoid Arthritis Patients Resistant to Sulphasalazine Therapy. British journal of rheumatology. 1994;33(11):1049-55.
115. Hafstrom I, Albertsson K, Boonen A, van der Heijde D, Landewe R, Svensson B. Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open 2-year continuation study. Ann Rheum Dis. 2009 Apr;68(4):508-13.
116. Hall SJ, Hickling P. Failure of etanercept to control extra-articular manifestations of

rheumatoid arthritis. J Clin Rheumatol. 2007 Feb;13(1):54.
117. Hamilton TK. Treatment of psoriatic arthritis and recalcitrant skin disease with combination therapy. J Drugs Dermatol. 2008 Nov;7(11):1089-93.
118. Han C, Rahman MU, Doyle MK, Bathon JM, Smolen J, Kavanaugh A, et al. Association of anemia and physical disability among patients with rheumatoid arthritis. J Rheumatol. 2007 Nov;34(11):2177-82.
119. Han C, Smolen J, Kavanaugh A, St Clair EW, Baker D, Bala M. Comparison of employability outcomes among patients with early or long-standing rheumatoid arthritis. Arthritis Rheum. 2008 Apr 15;59(4):510-4.
120. Harrison MJ, Kim CA, Silverberg M, Paget SA. Does age bias the aggressive treatment of elderly patients with rheumatoid arthritis? J Rheumatol. 2005 Jul;32(7):1243-8.
121. Haugeberg G, Conaghan PG, Quinn M, Emery P. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2009 Dec;68(12):1898-901.
122. Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. Rheumatology. 2010;49(10):1900-10.
123. Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007 Aug;66(8):1038-42.
124. Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008 Feb 15;59(2):234-40.
125. Helliwell PS, Taylor WJ. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs -- comparison of drugs and adverse reactions. J Rheumatol. 2008 Mar;35(3):472-6.
126. Herenius MM, Hoving JL, Sluiter JK, Raterman HG, Lems WF, Dijkmans BA, et al. Improvement of work ability, quality of life, and fatigue in patients with rheumatoid arthritis treated with adalimumab. J Occup Environ Med. 2010 Jun;52(6):618-21.
127. Heytman M, Ahern MJ, Smith MD, Roberts-Thomson PJ. The longterm effect of pulsed corticosteroids on the efficacy and toxicity of chrysotherapy in rheumatoid arthritis. J Rheumatol. 1994 Mar;21(3):435-41.
128. Higashida J, Wun T, Schmidt S, Naguwa SM, Tuscano JM. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2005 Nov;32(11):2109-15.
129. Hirose W, Nishikawa K, Hirose M, Nanki T, Sugimoto H. Response of early active rheumatoid arthritis to tumor necrosis factor inhibitors: evaluation by magnetic resonance imaging. Mod Rheumatol. 2009;19(1):20-6.
130. Hoekstra M, van Ede A, Haagsma C, van de Laar M, Huizinga T, Kruijsen M, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2003;62(5):423-6.
131. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton Neurosci. 2008 Dec 5;143(1-2):58-67.
132. Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda J, Tomita Y, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007 Feb;34(2):322-31.
133. Huang F, Wang L, Zhang J, Deng X, Guo J, Zhang Y. Risk of tuberculosis in a Chinese registry of rheumatoid arthritis and ankylosing spondylitis for tumour necrosis factor-alpha antagonists. APLAR Journal of Rheumatology. 2006;9(2):170-4.
134. Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002 Oct 22;106(17):2184-7.

135. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009 Jul;68(7):1119-24.
136. Hyrich KL, Deighton C, Watson KD, Symmons DP, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. *Rheumatology (Oxford)* 2009:1323-7.
137. Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008 Jul;47(7):1000-5.
138. Inanc N, Direskeneli H. Serious infections under treatment with TNF-alpha antagonists compared to traditional DMARDs in patients with rheumatoid arthritis. Rheumatol Int. 2006 Nov;27(1):67-71.
139. Islam M, Alam M, Haq S, Moyenuzzaman M, Patwary M, Rahman M. Efficacy of Sulphasalazine Plus Methotrexate in Rheumatoid Arthritis. Bangladesh Medical Research Council bulletin. 2000;26(1):1-7.
140. Iwamoto N, Kawakami A, Fujikawa K, Aramaki T, Kawashiri SY, Tamai M, et al. Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population. *Mod Rheumatol* 2009:488-92.
141. Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. 2009.
142. Jenks KA, Stamp LK, O'Donnell JL, Savage RL, Chapman PT. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol. 2007 Nov;34(11):2201-3.
143. Jung N, Hellmann M, Hoheisel R, Lehmann C, Haase I, Perniok A, et al. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). Clin Rheumatol. 2010 Oct;29(10):1169-73.
144. Kalden JR, Schattenkirchner M, Sorensen H, Emery P, Deighton C, Rozman B, et al. The Efficacy and Safety of Leflunomide in Patients With Active Rheumatoid Arthritis: a Five-Year Followup Study. Arthritis and rheumatism. 2003;48(6):1513-20.
145. Kalden JR, Scott DL, Smolen JS, Schattenkirchner M, Rozman B, Williams BD, et al. Improved Functional Ability in Patients With Rheumatoid Arthritis - Longterm Treatment With Leflunomide Versus Sulfasalazine. Journal of Rheumatology. 2001;28(9):1983-91.
146. Kalden Nemeth D, Grebmeier J, Antoni C, Manger B, Wolf F, Kalden J. Nmr Monitoring of Rheumatoid Arthritis Patients Receiving Anti-Tnf-Alpha Monoclonal Antibody Therapy. Rheumatology international. 1997;16(6):249-55.
147. Kaplan MJ. Do tumor-necrosis-factor inhibitors prevent first cardiovascular events in patients with rheumatoid arthritis? Nat Clin Pract Rheumatol. 2005 Dec;1(2):74-5.
148. Kastbom A, Bratt J, Ernestam S, Lampa J, Padyukov L, Soderkvist P, et al. Fcgamma receptor type IIIA genotype and response to tumor necrosis factor alpha-blocking agents in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Feb;56(2):448-52.
149. Katz P, Yelin E, Patel V, Huang XY, Chiou CF. Patient-reported outcomes following biologic therapy in a sample of adults with rheumatoid arthritis recruited from community-based rheumatologists. Arthritis Rheum. 2009 May 15;61(5):593-9.
150. Kavanaugh A. Anakinra (interleukin-1 receptor antagonist) has positive effects on function and quality of life in patients with rheumatoid arthritis. Advances in Therapy (USA). 2006 02/01/;23(Feb):208-17.
151. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007 Apr;66(4):498-505.
152. Kavanaugh A, Lee SJ, Weng HH, Chon Y, Huang XY, Lin SL. Patient-derived joint counts are a potential alternative for determining Disease Activity Score. *J Rheumatol*. 2010/02/17 ed 2010:1035-41.
153. Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum. 2007 Dec;56(12):3896-908.
154. Keystone EC, Schiff MH, Kremer JM, Kafka S, Lovy M, DeVries T, et al. Once-weekly administration of 50 mg etanercept

in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.
155. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin. 2008 Sep;24(9):2639-50.
156. Kimball AB, Bensimon AG, Guerin A, Yu AP, Wu EQ, Okun MM, et al. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. *American Journal of Clinical Dermatology* 2011:51-62.
157. Kimball AB, Jackson JM, Sobell JM, Boh EE, Grekin S, Pharmd EB, et al. Reductions in healthcare resource utilization in psoriatic arthritis patients receiving etanercept therapy: results from the educate trial. J Drugs Dermatol. 2007 Mar;6(3):299-306.
158. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on lipoprotein profile in patients with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol. 2006 May;33(5):921-3.
159. Klareskog L, Gaubitz M, Rodriguez-Valverde V, Malaise M, Dougados M, Wajdula J. A Long-Term, Open-Label Trial of the Safety and Efficacy of Etanercept (ENBREL(R)) In Patients With Rheumatoid Arthritis Not Treated With Other DMARDs (3-year Interim Report). Ann Rheum Dis. 2006 Mar 15.
160. Koeller MD, Aletaha D, Funovits J, Pangan A, Smolen JS, et al., et al. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. *Rheumatology* 2009:1575.
161. Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009 May;36(5):898-906.
162. Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, et al. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum. 2009 Mar 15;61(3):305-12.
163. Kononoff A, Heiskanen J, Lumiaho J, Kautiainen H, Kaipiainen-Seppanen O. Intensifying treatment of rheumatoid arthritis with combinations of traditional disease-modifying anti-rheumatic drugs among patients with persistent disease did not reduce the need for large joint surgery. Scand J Rheumatol. 2007 Nov-Dec;36(6):424-7.
164. Kremer J, Genovese M, Cannon GW, Caldwell J, Cush J, Furst DE, et al. Combination Leflunomide and Methotrexate (Mtx) Therapy for Patients With Active Rheumatoid Arthritis Failing Mtx Monotherapy: Open-Label Extension of a Randomized, Double-Blind, Placebo Controlled Trial. The Journal of rheumatology. 2004;31(8):1521-31.
165. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum. 2008 Apr;58(4):953-63.
166. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008 Apr;47(4):495-9.
167. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003 May;42(5):617-21.
168. Kvalvik AG, Lefsaker L, Dyvik S, Brun JG. Anti-tumor necrosis factor-alpha therapy in the ordinary clinical setting: Three-year effectiveness in patients with rheumatoid arthritis. Joint Bone Spine. 2007 Dec;74(6):606-11.
169. Laas K, Peltomaa R, Puolakka K, Kautiainen H, Leirisalo-Repo M. Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. *Clinical and Experimental Rheumatology* 2009:315-20.
170. Laivoranta-Nyman S, Mottonen T, Hannonen P, Korpela M, Kautiainen H, Leirisalo-Repo M, et al. Association of

tumour necrosis factor a, b and c microsatellite polymorphisms with clinical disease activity and induction of remission in early rheumatoid arthritis. Clin Exp Rheumatol. 2006 Nov-Dec;24(6):636-42.
171. Landewe R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate - Results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis and Rheumatism (USA). 2006 10/01/;54(Oct):3119-25.
172. Lard LR, Boers M, Verhoeven A, Vos K, Visser H, Hazes JMW, et al. Early and Aggressive Treatment of Rheumatoid Arthritis Patients Affects the Association of Hla Class Ii Antigens With Progression of Joint Damage. Arthritis and rheumatism. 2002;46(4):899-905.
173. Lazzerini PE, Acampa M, Hammoud M, Maffei S, Capecchi PL, Selvi E, et al. Arrhythmic risk during acute infusion of infliximab: a prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis. J Rheumatol. 2008 Oct;35(10):1958-65.
174. Le Loet X, Nordstrom D, Rodriguez M, Rubbert A, Sarzi-Puttini P, Wouters JM, et al. Effect of anakinra on functional status in patients with active rheumatoid arthritis receiving concomitant therapy with traditional disease modifying antirheumatic drugs: evidence from the OMEGA Trial. J Rheumatol. 2008 Aug;35(8):1538-44.
175. Lekander I, Borgstrom F, Svarvar P, Ljung T, Carli C, van Vollenhoven RF. Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. International Journal of Technology Assessment in Health Care. 2010;26(1):54-61.
176. Lems WF, Jahangier ZN, Jacobs JW, Bijlsma JW. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol. 1995 May-Jun;13(3):293-7.
177. Lequerre T, Vittecoq O, Klemmer N, Goeb V, Pouplin S, Menard JF, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol. 2006 Jul;33(7):1307-14.
178. Lester SE, Proudman SM, Lee AT, Hall CA, Cleland LG, et al., et al. Treatment-induced stable, moderate reduction in blood cell counts correlate to disease control in early rheumatoid arthritis. Internal Medicine Journal. 2009;39:296.
179. Levalampi T, Korpela M, Vuolteenaho K, Moilanen E. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: Adverse events and other reasons leading to discontinuation of the treatment. Rheumatology International. 2008;28(3):261-9.
180. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int J Technol Assess Health Care. 2009 Apr;25(2):181-9.
181. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis. 2002 Dec;61(12):1055-9.
182. Lisbona MP, Maymo J, Perich J, Almirall M, Carbonell J. Rapid reduction in tenosynovitis of the wrist and fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. *Ann Rheum Dis*. 2010/05/08 ed 2010:1117-22.
183. Lisbona MP, Maymo J, Perich J, Almirall M, Perez-Garcia C, Carbonell J. Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. *J Rheumatol* 2008:394-7.
184. Luzi G, Lagana B, Salemi S, Di Rosa R. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3.
185. Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. Am J Ophthalmol. 2007 May;143(5):801-9.
186. Machado P, Santos A, Pereira C, Loureiro C, Silva J, Chieira C, et al. Increased prevalence of allergic sensitisation in rheumatoid arthritis patients treated with anti-TNFalpha. *Joint Bone Spine* 2009:508-13.

187. Maignen F, Hauben M, Tsintis P. Modelling the Time to Onset of Adverse Reactions with Parametric Survival Distributions A Potential Approach to Signal Detection and Evaluation. Drug Safety (New Zealand). 2010;33:417-34.
188. Malipeddi AS, Rajendran R, Kallarackal G. Disseminated tuberculosis after anti-TNFalpha treatment. Lancet. 2007 Jan 13;369(9556):162.
189. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol. 2007 Aug;34(8):1670-3.
190. Marotte H, Arnaud B, Diasparra J, Zrioual S, Miossec P. Association between the level of circulating bioactive tumor necrosis factor alpha and the tumor necrosis factor alpha gene polymorphism at -308 in patients with rheumatoid arthritis treated with a tumor necrosis factor alpha inhibitor. Arthritis Rheum. 2008 May;58(5):1258-63.
191. Martin N, Innes JA, Lambert CM, Turnbull CM, Wallace WA. Hypersensitivity pneumonitis associated with leflunomide therapy. J Rheumatol. 2007 Sep;34(9):1934-7.
192. Mastroianni A, Minutilli E, Mussi A, Bordignon V, Trento E, D'Agosto G, et al. Cytokine profiles during infliximab monotherapy in psoriatic arthritis. Br J Dermatol. 2005 Sep;153(3):531-6.
193. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd 2009.
194. Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol. 2009;10(5):319-24.
195. McCluggage LK, Scholtz JM. Golimumab: A Tumor Necrosis Factor Alpha Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy (USA). 2010;44:135-44.
196. McGonagle D, Tan AL, Madden J, Taylor L, Emery P. Rituximab use in everyday clinical practice as a first-line biologic therapy for the treatment of DMARD-resistant rheumatoid arthritis. Rheumatology (Oxford). 2008 Jun;47(6):865-7.
197. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L, Aug. Methotrexate, rheumatoid arthritis and infection riskwhat is the evidence. Rheumatology. 2009;48:867.
198. Mease PJ, Cohen S, Gaylis NB, Chubick A, Kaell AT, Greenwald M, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. *J Rheumatol*. 2010/03/03 ed 2010:917-27.
199. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9.
200. Mease PJ, Signorovitch J, Yu AP, Wu EQ, Gupta SR, Bao Y, et al. Impact of adalimumab on symptoms of psoriatic arthritis in patients with moderate to severe psoriasis: A pooled analysis of randomized clinical trials. Dermatology. 2010;220(1):1-7.
201. Mittendorf T, Dietz B, Sterz R, Kupper H, Cifaldi MA, von der Schulenburg JM. Improvement and longterm maintenance of quality of life during treatment with adalimumab in severe rheumatoid arthritis. J Rheumatol. 2007 Dec;34(12):2343-50.
202. Montecucco C, Caporali R, Caprotti P, Caprotti M, Notario A. Sex hormones and bone metabolism in postmenopausal rheumatoid arthritis treated with two different glucocorticoids. J Rheumatol. 1992 Dec;19(12):1895-900.
203. Moreland LW, Alten R, Van den Bosch F, Appelboom T, Leon M, Emery P, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum. 2002 Jun;46(6):1470-9.
204. Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2001 Jun;28(6):1238-44.
205. Moreland LW, Genovese MC, Sato R, Singh A. Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):287-93.

206. Mori S. A relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximab-resistant cases and PK-based modified therapy. Mod Rheumatol. 2007;17(2):83-91.
207. Mroczkowski PJ, Weinblatt ME, Kremer JM. Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S66-8.
208. Nagasawa H, Kameda H, Sekiguchi N, Amano K, Takeuchi T. Normalisation of physical function by infliximab in patients with RA: factors associated with normal physical function. Clin Exp Rheumatol. 2010 May-Jun;28(3):365-72.
209. Nawata M, Saito K, Nakayamada S, Tanaka Y. Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. Mod Rheumatol. 2008;18(5):460-4.
210. Niewold TB, Gibofsky A. Concomitant interferon-alpha therapy and tumor necrosis factor alpha inhibition for rheumatoid arthritis and hepatitis C. Arthritis Rheum. 2006 Jul;54(7):2335-7.
211. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): Evidence of safety and efficacy in a 5-year extension study. 2009.
212. Oei HB, Hooker RS, Cipher DJ, Reimold A. High rates of stopping or switching biological medications in veterans with rheumatoid arthritis. *Clin Exp Rheumatol*. 2010/02/13 ed 2009:926-34.
213. Oldfield V, Dhillon S, Plosker GL. Tocilizumab A Review of its Use in the Management of Rheumatoid Arthritis. Drugs. 2009;69:609-32.
214. Olivieri I, de Portu S, Salvarani C, Cauli A, Lubrano E, Spadaro A, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology (Oxford). 2008 Nov;47(11):1664-70.
215. Ongaro A, De Mattei M, Pellati A, Caruso A, Ferretti S, Masieri FF, et al. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading to anti-TNFalpha therapy in rheumatoid arthritis? Rheumatol Int. 2008 Jul;28(9):901-8.
216. Ostensen M, Forger F. Management of RA medications in pregnant patients. Nat Rev Rheumatol. 2009 Jul;5(7):382-90.
217. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, Kita MD, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):72-5.
218. Pavelka K, Jarosova K, Suchy D, Senolt L, Chroust K, Dusek L, et al. Increasing the infliximab dose in rheumatoid arthritis patients: A randomised, double blind study failed to confirm its efficacy. 2009.
219. Perera LC, Tymms KE, Wilson BJ, Shadbolt B, Brook AS, Dorai Raj AK, et al. Etanercept in severe active rheumatoid arthritis: first Australian experience. Intern Med J. 2006 Oct;36(10):625-31.
220. Pfeil A, Lippold J, Eidner T, Lehmann G, Oelzner P, Renz DM, et al. Effects of leflunomide and methotrexate in rheumatoid arthritis detected by digital X-ray radiogrammetry and computer-aided joint space analysis. Rheumatol Int. 2009 Jan;29(3):287-95.
221. Pisitkun P, Pattarowas C, Siriwongpairat P, Totemchokchyakarn K, Nantiruj K, Janwityanujit S. Reappraisal of cervical spine subluxation in Thai patients with rheumatoid arthritis. Clin Rheumatol. 2004 Feb;23(1):14-8.
222. Plushner SL. Tocilizumab: An Interleukin-6 Receptor Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy. 2008;42:1660-8.
223. Polinski JM, Mohr PE, Johnson L, Jun. Impact of Medicare Part D on Access to and Cost Sharing for Specialty Biologic Medications for Beneficiaries With Rheumatoid Arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2009;61:745.
224. Prochorec-Sobieszek M, Chelstowska M, Rymkiewicz G, Majewski M, Warzocha K, Maryniak R. Biclonal T-cell receptor gammadelta+ large granular lymphocyte leukemia associated with rheumatoid arthritis. Leukemia and Lymphoma. 2008;49(4):828-31.
225. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al.

Early Suppression of Disease Activity Is Essential for Maintenance of Work Capacity in Patients With Recent-Onset Rheumatoid Arthritis: Five-Year Experience From the Fin-Raco Trial. Arthritis and rheumatism. 2005;52(1):36-41.

226. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al. Use of the Stanford Health Assessment Questionnaire in estimation of long-term productivity costs in patients with recent-onset rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2009;38(2):96-103.

227. Quartuccio L, Fabris M, Salvin S, Atzeni F, De Vita S, et al., et al. Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis. *Rheumatology* 2009:1557.

228. Quinn MA, Conaghan PG, O'Connor PJ. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: Results from a twelve-month ran-liver disease? Hepatology. 2006;43:352-61.

229. Rahman MU, Strusberg I, Geusens P, Berman A, Yocum D, Baker D, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Sep;66(9):1233-8.

230. Ranganathan P, McLeod HL. Methotrexate pharmacogenetics - The first step toward individualized therapy in rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1366-77.

231. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Jarvenpaa S, Leirisalo-Repo M, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum. 2009 May;60(5):1222-31.

232. Rau R, Simianer S, van Riel PL, van de Putte LB, Kruger K, Schattenkirchner M, et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol. 2004;33(3):145-53.

233. Reece RJ, Kraan MC, Radjenovic A, Veale DJ, O'Connor PJ, Ridgway JP, et al. Comparative Assessment of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis, by Dynamic Enhanced Magnetic Resonance Imaging. Arthritis and rheumatism. 2002;46(2):366-72.

234. Richards BL, Spies J, McGill N, Richards GW, Vaile J, Bleasel JF, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. Intern Med J. 2007 Feb;37(2):101-7.

235. Rozenbaum M, Boulman N, Slobodin G, Ayubkhanov E, Rosner I. Polyarthritis flare complicating rheumatoid arthritis infliximab therapy: a paradoxic adverse reaction. J Clin Rheumatol. 2006 Dec;12(6):269-71.

236. Rubbert-Roth A, Tak PP, Zerbini C, Tremblay JL, Carreno L, Armstrong G, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: Results of a Phase III randomized study (MIRROR). Rheumatology. 2010;49(9):1683-93.

237. Rudwaleit M, Van den Bosch F, Kron M, Kary S, Kupper H. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. Arthritis Res Ther. 2010;12(3):R117.

238. Saag KG, Gim GT, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care and Research. 2008;59(6):762-84.

239. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum* 2009:1915-22.

240. Salvarani C, Cantini F, Olivieri I, Macchioni P, Padula A, Niccoli L, et al. Efficacy of infliximab in resistant psoriatic arthritis. Arthritis Rheum. 2003 Aug 15;49(4):541-5.

241. Sanchez G, Castro JS, Snih SA, Blanco LP, Esteva MH, Macgregor EG, et al. Durability of treatment with methotrexate in Venezuelan patients with rheumatoid

arthritis. Rheumatol Int. 2007 Apr;27(6):531-6.
242. Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. *Arthritis Rheum* 2008:1310-7.
243. Scali JJ, Visentini S, Salomon J, Sevilla D, Ju YC, Morales E, et al. Rapid and deep control of inflammation in rheumatoid arthritis with infliximab and its correlation with acute-phase reactants. Ann N Y Acad Sci. 2007 Sep;1110:389-401.
244. Schiff M, Pritchard C, Huffstutter JE, Rodriguez Valverde V, Durez P, Zhou X, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Annals of the rheumatic diseases. 2009;68(11):1708-14.
245. Schiff MH, Yu EB, Weinblatt ME, Moreland LW, Woolley JM, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients - Patient-reported outcomes from multiple controlled and open-label extension studies. Drugs and Aging (New Zealand). 2006 02/01/;23(Feb):167-78.
246. Schnabel A, Herlyn K, Burchardi C, Reinhold Keller E, Gross WL. Long-Term Tolerability of Methotrexate at Doses Exceeding 15 Mg Per Week in Rheumatoid Arthritis. Rheumatology international. 1996;15(5):195-200.
247. Schnabel A, Reinhold Keller E, Willmann V, Gross W. Tolerability of Methotrexate Starting With 15 or 25 Mg/Week for Rheumatoid Arthritis. Rheumatology international. 1994;14(1):33-8.
248. Scrivo R, Conti F, Spinelli FR, Truglia S, Magrini L, Di Franco M, et al. Switching between TNFalpha antagonists in rheumatoid arthritis: personal experience and review of the literature. Reumatismo. 2009 Apr-Jun;61(2):107-17.
249. Shashikumar NS, Shivamurthy MC, Chandrashekara S. Evaluation of efficacy of combination of methotrexate and hydroxychloroquine with leflunomide in active rheumatoid arthritis. *Indian Journal of Pharmacology* 2010:358-61.
250. Shedd AD, Reddy SG, Meffert JJ, Kraus EW, Usatine RP. Acute onset of rash and oligoarthritis. J Fam Pract. 2007 Oct;56(10):811-4.
251. Shergy WJ, Isern RA, Cooley DA, Harshbarger JL, Huffstutter JE, Hughes GM, et al. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. J Rheumatol. 2002 Apr;29(4):667-77.
252. Sheth NU, Hilas O, Charneski L. Abatacept: A novel agent for rheumatoid arthritis. Journal of Pharmacy Technology (USA). 2006 06/01/;22(Jun):336-41.
253. Singh Jasvinder A, Christensen R, Wells George A, Suarez-Almazor Maria E, Buchbinder R, Lopez-Olivo Maria A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2009(2).
254. Sinha A, Patient C. Rheumatoid arthritis in pregnancy: successful outcome with anti-TNF agent (Etanercept). J Obstet Gynaecol. 2006 Oct;26(7):689-91.
255. Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol. 2000 Nov;27(11):2582-9.
256. Smith N, Ding T, Butt S, Gadsby K, Deighton C. The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice. Rheumatology (Oxford). 2008 Sep;47(9):1389-91.
257. Smolen JS, Han C, Bala M, Maini RN, Grp AS, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement - A detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis and Rheumatism (USA). 2005 04/01/;52(Apr):1020-30.
258. Smolen JS, van der Heijde DM, St Clair EW, Emery P, Grp AS, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab - Results from the ASPIRE trial. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):702-10.

259. Soubrier M, Puechal X, Sibilia J, Mariette X, Dougados M, et al., et al. Evaluation of two strategies (initial methotrexate monotherapy <it>vs</it> its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology. 2009;48:1429.
260. Soubrier M, Puechal X, Sibilia J, Mariette X, Meyer O, Combe B, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford). 2009 Nov;48(11):1429-34.
261. Spalding JR, Hay J. Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. Pharmacoeconomics. 2006;24(12):1221-32.
262. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The Relationship of Serum Infliximab Concentrations to Clinical Improvement in Rheumatoid Arthritis: Results From Attract, a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2002;46(6):1451-9.
263. Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol. 2004 Aug;31(8):1538-45.
264. Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Bmj. 2010;340:c147.
265. Suarez-Almazor Maria E, Belseck E, Shea B, Tugwell P, Wells George A. Sulfasalazine for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews. 1998(2).
266. Suwannalai P, Auethavekiat P, Udomsubpayakul U, Janvitayanujit S. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: a retrospective study a the university-based hospital. *Int J Rheum Dis.* 2010/04/09 ed 2009:118-24.
267. Taiwo B, Lee C, Venkat D, Tambar S, Sutton SH. Can tumor necrosis factor alpha blockade predispose to severe babesiosis? Arthritis Rheum. 2007 Feb 15;57(1):179-81.
268. Takeuchi T, Miyasaka N, Inoue K, Abe T, Koike T. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. *Mod Rheumatol* 2009:478-87.
269. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):189-94.
270. Takeuchi T, Yamanaka H, Inoue E, Nagasawa H, Nawata M, Ikari K, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18(5):447-54.
271. Tam LS, Griffith JF, Yu AB, Li TK, Li EK. Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation. Clin Rheumatol. 2007 Jun;26(6):941-6.
272. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18(2):146-52.
273. Taniguchi A, Urano W, Tanaka E, Furihata S, Kamitsuji S, Inoue E, et al. Validation of the associations between single nucleotide polymorphisms or haplotypes and responses to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a proposal for prospective pharmacogenomic study in clinical practice. Pharmacogenet Genomics. 2007 Jun;17(6):383-90.
274. Taylor P, Steuer A, Gruber J, McClinton C, Cosgrove D, Blomley M, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and rheumatism. 2006 2006;54(1):47-53.
275. Taylor PC, Steuer A, Gruber J, McClinton C, Maini RN, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-

delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 01/01/;54(Jan):47-53.
276. Theodoridou A, Kartsios C, Yiannaki E, Markala D, Settas L. Reversible T-large granular lymphocyte expansion and neutropenia associated with adalimumab therapy. Rheumatol Int. 2006 Dec;27(2):201-2.
277. Thurlings RM, Vos K, Gerlag DM, Tak PP. Disease activity-guided rituximab therapy in rheumatoid arthritis: the effects of re-treatment in initial nonresponders versus initial responders. Arthritis Rheum. 2008 Dec;58(12):3657-64.
278. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010 Jul;59(1):40-9.
279. Torikai E, Kageyama Y, Suzuki M, Ichikawa T, Nagano A. The effect of infliximab on chemokines in patients with rheumatoid arthritis. Clin Rheumatol. 2007 Jul;26(7):1088-93.
280. Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8.
281. Tubach F, Ravaud P, Salmon-Ceron D, Petitpain N, Grp R, et al. Emergence of <it>Legionella pneumophila</it> pneumonia in patients receiving tumor necrosis factor-alpha antagonist. Clinical Infectious Diseases. 2006 10/01/;43(Oct):E95-100.
282. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94.
283. Tutuncu Z, Kavanaugh A. Treatment of elderly rheumatoid arthritis. Future Rheumatology. 2007;2(3):313-9.
284. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes JM, Kerstens PJ, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Mar 15;61(3):291-9.
285. Van Der Heijde D, Breedveld FC, Kavanaugh A, Keystone EC, Landewe R, Patra K, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-Year results of PREMIER. Journal of Rheumatology. 2010;37(11):2237-46.
286. van der Heijde D, Burmester G, Melo Gomes J, Codreanu C, Martin Mola E, Pedersen R, et al. Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. *Annals of the rheumatic diseases* 2009:1113-8.
287. van der Heijde D, Burmester G, Melo-Gomes J, Codreanu C, Mola EM, Pedersen R, et al. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. Ann Rheum Dis. 2008 Feb;67(2):182-8.
288. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, van Zeben D, Kerstens PJ, Gerards AH, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2007 Oct;66(10):1356-62.
289. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Zeben D, Kerstens PJ, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1153-8.
290. van der Veen MJ, Bijlsma JW. The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol. 1993 Dec;12(4):500-5.
291. Van Kuijk AWR, Gerlag DM, Vos K, Wolbink G, De Groot M, De Rie MA, et al. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: Effects of adalimumab treatment on synovial tissue. 2009.

292. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3104-12.
293. van Tuyl LH, Boers M, Lems WF, Landewé RB, Han H, van der Linden S, et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Annals of the rheumatic diseases. 2010(5):807-12.
294. van Vollenhoven RF, Emery P, Bingham CO, 3rd, Keystone EC, Fleischmann R, Furst DE, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol*. 2010/01/30 ed 2010:558-67.
295. van Vollenhoven RF, Ernestam S, Harju A, Bratt J, Klareskog L. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. Arthritis Res Ther. 2003;5(6):R347-51.
296. Vander Cruyssen B, Durez P, Westhovens R, De Keyser F. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. Arthritis Res Ther. 2010;12(3):R77.
297. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology (Oxford). 2008 Apr;47(4):535-41.
298. Verschueren P, Esselens G, Westhovens R. Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):59-64.
299. Verstappen S, Jacobs J, Bijlsma JW. The Utrecht Experience With Different Treatment Strategies in Early Rheumatoid Arthritis. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S165-8.
300. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis. 2007 Nov;66(11):1443-9.
301. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis. 2010 Jul;69(7):1333-7.
302. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Annals of the rheumatic diseases. 2009;68(7):1086-93.
303. Vlak T, Eldar R. Disability in Rheumatoid Arthritis After Monotherapy With Dmards. International Journal Rehabilitation Research. 2003;26(3):207-12.
304. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):567-70.
305. Wakabayashi H, Sudo A, Hasegawa M, Oka H, Uchida A, Nishioka K. Retrospective clinical study of the efficacy of lower-dose methotrexate and infliximab therapy in patients with rheumatoid arthritis. *Clin Rheumatol*. 2010/03/06 ed 2010:671-5.
306. Wakefield RJ, Freeston JE, Hensor EM, Bryer D, Quinn MA, Emery P. Delay in imaging versus clinical response: a rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. Arthritis Rheum. 2007 Dec 15;57(8):1564-7.
307. Wasko MC, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama. 2007 Jul 11;298(2):187-93.
308. Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2010.
309. Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, et al.

Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum. 1999 Jul;42(7):1322-8.
310. Weinblatt ME, Schiff MH, Ruderman EM, Bingham CO, 3rd, Li J, Louie J, et al. Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study. Arthritis Rheum. 2008 Jul;58(7):1921-30.
311. Weinblatt ME, Weissman BN, Holdsworth DE, Fraser PA, Maier AL, Falchuk KR, et al. Long-Term Prospective Study of Methotrexate in the Treatment of Rheumatoid Arthritis. 84-Month Update. Arthritis and rheumatism. 1992;35(2):129-37.
312. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003 Jun;25(6):1700-21.
313. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun;68(6):954-60.
314. Westhovens R, Cole JC, Li T, Martin M, Maclean R, Lin P, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006 Oct;45(10):1238-46.
315. Westhovens R, Houssiau F, Joly J, Everitt DE, Zhu Y, Sisco D, et al. A phase I study assessing the safety, clinical response, and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in patients with rheumatoid arthritis. J Rheumatol. 2006 May;33(5):847-53.
316. Westhovens R, Kremer JM, Moreland LW, Emery P, Russell AS, Li T, et al. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. The Journal of rheumatology. 2009;36(4):736-42.
317. Westlake SL, Colebatch AN, Baird J, Kiely P, Edwards CJ, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford). 2010;49:295.
318. White DH, Chapman PT, O'Donnell JL, James J, Stamp LK, et al. Lack of association between elevated mean red cell volume and haematological toxicity in patients receiving long-term methotrexate for rheumatoid arthritis. Internal Medicine Journal. 2010;40:561-5.
319. Wislowska M, Jakubicz D. Preliminary evaluation in rheumatoid arthritis activity in patients treated with TNF-alpha blocker plus methotrexate versus methotrexate or leflunomide alone. Rheumatol Int. 2007 May;27(7):641-7.
320. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008;9(1):1-14.
321. Yazici Y, Erkan D, Kulman I, Belostocki K, Harrison MJ. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". Ann Rheum Dis. 2002 Jul;61(7):638-40.
322. Yelin E, Trupin L, Katz P, Lubeck D, Rush S, Wanke L. Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. Arthritis Rheum. 2003 Nov;48(11):3046-54.
323. Yount S, Sorensen MV, Cella D, Sengupta N, Grober J, Chartash EK. Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):838-46.
324. Yuan Y, Trivedi D, Maclean R, Rosenblatt L. Indirect cost-effectiveness analyses of abatacept and rituximab in patients with

moderate-to-severe rheumatoid arthritis in the United States. *Journal of Medical Economics (England)* 2010:33-41.
325. Yun JE, Lee SW, Kim TH, Jun JB, Jung S, Bae SC, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol. 2002 Mar-Apr;20(2):127-32.
326. Zhang W, Bansback N, Guh D, Li X, Nosyk B, Marra CA, et al. Short-term influence of adalimumab on work productivity outcomes in patients with rheumatoid arthritis. J Rheumatol. 2008 Sep;35(9):1729-36.

Unable to Obtain Full Text

1. van der Veen M, Bijlsma J. The Effect of Methylprednisolone Pulse Therapy on Methotrexate Treatment of Rheumatoid Arthritis. Clinical rheumatology. 1993;12(4):74-6.

Appendix E. Evidence Tables

Index of Studies by Key Question

KQ1

RCTs and other studies found in Evidence Table 1

Allaart, 2006 – found under Goekoop-Ruiterman, 2005
Bathon, 2000
Boers, 1997
Breedveld, 2006
Capell, 2006
Choy, 2008
Cohen, 2001 – found under Strand 1999
Cohen, 2006
Combe, 2006
Dougados, 1999
Emery, 2000
Emery, 2006
Emery, 2008
Emery, 2008
Emery, 2009
Emery, 2010
Emery, 2010
Fernandez-Nebro, 2007
Finckh, 2007
Finckh, 2009
Fleischmann, 2009
Furst, 2003
Geborek, 2002
Genovese, 2002 – found under Bathon 2000
Genovese, 2004
Genovese, 2005 – found under Bathon 2000
Genovese, 2008
Goekoop-Ruiterman, 2005
Goekoop-Ruiterman, 2007 – found under Goekoop-Ruiterman 2005
Haagsma, 1997
Hetland, 2010
Hoff, 2009
Hyrich, 2006

Hyrich, 2006 [Change ET to say 2006] in 2003 file
Karanikola, 2008
Kavanaugh, 2008 – found under Klareskog 2004
Kay, 2008
Keystone, 2008
Keystone, 2008 – found under Cohen 2006
Keystone, 2009
Keystone, 2009 – found under Cohen 2006
Keystone, 2010
Kievit, 2008
Kim, 2007
Kirwan, 2004
Klareskog, 2004
Korpela, 2004 – found under Mottonen 1999
Kremer, 2006
Kremer, 2010
kristensen, 2006
Kristensen, 2007
Larsen, 2001 – found under Smolen 1999
Lee, 2008
Listing, 2006
Maillefert, 2003 – found under Dougados 1999
Maini, 2006
Miyasaka, 2008
Mottonen, 1999
Mottonen, 2002 – found under Mottonen 1999
Nishimoto, 2009
O'Dell, 1996
O'Dell, 2002
Osiri, 2002
Schiff, 2008
Schipper, 2009
Sharp, 2000 – found under Smolen 1999
Smolen, 1999
Smolen, 1999
Smolen, 2005 – found under Breedveld 2004
Smolen, 2006 – found under St. Clair 2004
Smolen, 2008
Smolen, 2009
Smolen, 2009
St. Clair, 2004

Strand, 1999
Svensson, 2005
van der Heijde, 2005 – found under Klareskog 2004
van der Heijde, 20062005 – found under Klareskog 2004
van der Heijde, 20062005 – found under Klareskog 2004
van der Kooij, 2008
van der Kooij, 2009 – found under Goekoop-Ruiterman 2005
van der Kooij, 2009 – found under Goekoop-Ruiterman 2005
van Riel, 2006
van Vollenhoven, 2009
Weaver, 2006
Weinblatt, 1999
Weinblatt, 2007
Westhovens, 2006
Westhovens, 2009
Zhang, 2006
Zink, 2005

Systematic Reviews and Meta-analyses found in Evidence Table 2

Alonso-Ruiz, 2008
Bergman, 2010
Clark, 2004
Devine, 2011
Gartlehner, 2006
Gaujoux-Viala, 2010
Hochberg, 2003
Kirwan, 2009
Kuriya, 2010
Nam, 2010
Osiri, 2002/9
Singh, 2009
Singh, 2009
Singh, 2010
Singh, 2010
Wailoo, 2006
Wiens, 2010

Does not have Schipper

KQ2

RCTs and other studies found in Evidence Table 1

Allaart, 2006 – found under Goekoop-Ruiterman 2005

Bathon, 2000
Boers, 1997
Breedveld, 2006
Capell, 2006
Choy, 2008
Cohen, 2001 – found under Strand 1999
Combe, 2006
Combe, 2009
Dougados, 1999
Emery, 2000
Emery, 2006
Emery, 2006
Emery, 2008
Emery, 2008
Emery, 2009
Emery, 2010
Fernandez-Nebro, 2007
Finckh, 2009
Genovese, 2002 – found under Bathon 2000
Genovese, 2005 – found under Bathon 2000
Goekoop-Ruiterman, 2005
Goekoop-Ruiterman, 2007 – found under Goekoop-Ruiterman 2005
Haagsma, 1997
Hassett, 2008
Kekow, 2010
Keystone, 2008 – found under Cohen 2006
Kievit, 2008
Kirwan, 2004
Klareskog, 2004
Korpela, 2004 – found under Mottonen 1999
Kosinski, 2002 – found under Bathon 2000
Kremer, 2010
Landewe, 2002 – found under Boers 1997
Li, 2008
Listing, 2006
Maillefert, 2003 – found under Dougados 1999
Mease, 2008
Mottonen, 1999
Nishimoto, 2009
Osiri, 2002
Puolakka, 1487 – found under Mottonen 1999
Schiff, 2008
Scott, 2000 – found under Smolen 1999
Smolen, 1999

Smolen, 2005 – found under Breedveld 1004
Smolen, 2006 – found under St. Clair 2004
St. Clair, 2004
Strand, 1999
Svensson, 2005
van der Heijde, 2005 – found under Klareskog 2004
van der Heijde, 2006 – found under Klareskog 2004
van der Heijde, 2006 – found under Klareskog 2004
van der Kooij, 2009 – found under Goekoop-Ruiterman 2005
van der Kooij, 2009 – found under Goekoop-Ruiterman 2005
van Riel, 2008
Weaver, 2006
Weinblatt, 2007
Wells, 2008 – found under Westhovens 2006
Westhovens, 2006
Westhovens, 2009

Systematic Reviews and Meta-analyses found in Evidence Table 2

Gaujoux-Viala, 2010
Mertens, 2009
Osiri, 2002/9
Singh, 2010
Singh, 2010

KQ3

RCTs and other studies found in Evidence Table 1

Allaart, 2006 – found under Goekoop-Ruiterman 2005
Askling, 2005
Askling, 2005
Askling, 2005
Askling, 2009
Baecklund, 2006
Bathon, 2000
Bergstrom, 2004
Bernatsky, 2007
Boers, 1997
Brassard, 2006
Brassard, 2009
Breedveld, 2006
Brown, 2002
Burmester
Cannon, 2004
Capell, 2006

Chakravarty, 2005
Choy, 2008
Chung, 2003
Cohen, 2001 – found under Strand 1999
Cohen, 2006
Combe, 2006
Combe, 2009
Curtis, 2007
Curtis, 2007
Curtis, 2007
DeBandt, 2005
den Broeder, 2007
Dixon, 2006
Dixon, 2007
Dixon, 2010
Doran, 2002
Dougados, 1999
Duclos, 2006
Edwards, 2007
Emery, 2000
Emery, 2006
Emery, 2008
Emery, 2008
Emery, 2009
Emery, 2010
Emery, 2010
Feltelius, 2005
Fernandez-Nebro, 2007
Fleischmann, 2003
Fleischmann, 2006 – found under Fleischmann 2003
Fleischmann, 2009
Flendrie, 2003
Flendrie, 2005
Fuerst, 2006
Furst, 2003
Galloway, 2011
Geborek, 2002
Geborek, 2005
Genovese, 2002 – found under Bathon 2000
Genovese, 2004
Genovese, 2005 – found under Bathon 2000
Genovese, 2008

Goekoop-Ruiterman, 2005

Goekoop-Ruiterman, 2007 – found under Goekoop-Ruiterman 2005

Gomez-Reino, 2003

Greenberg, 2010

Grijalva, 2007

Grijalva, 2010

Haagsma, 1997

Harley, 2003

Harrison, 2009

Hetland, 2010

Hjardem, 2007

Hyrich, 2006 [Change ET to say 2006] in 2003 file

Hyrich, 2007

Jacobsson, 2005

Karanikola, 2008

Karstila, 2010

Kawakami, 2010

Kay, 2008

Keane, 2001

Keystone, 2008

Keystone, 2009

Kim, 2007

Kirwan, 2004

Klareskog, 2004

Korpela, 2004 – found under Mottonen 1999

Kremer, 2002

Kremer, 2006

Kremer, 2010

kristensen, 2006

kristensen, 2006

Kwon, 2003

Lacaille, 2008

Langer, 2003

Lebwohl, 2005

Lee, 2002

Lee, 2008

Li, 2010

Listing, 2005

Listing, 2008

Maini, 2004 – found under Breedveld 2004

Malyshev, 2008

Marchesoni, 2009

McDonald, 2009
Michaud, 2006
Migliore, 2009
Miyasaka, 2008
Mohan, 2001
Mohan, 2004
Nadareishvili, 2008
Naranjo, 2008
Nishimoto, 2009
Nuki, 2002
O'Dell, 1996
O'Dell, 2002
O'Dell, 2006
Osiri, 2002
Pallavicini, 2010
Pan, 2009
Russell, 2007
Saag, 1994
Salliot, 2006
Schaible, 2000
Schiff, 2006
Schiff, 2008
Schipper, 2009
Schneeweiss, 2007
Setoguchi, 2006
Setoguchi, 2008
Shin, 2006
Slifman, 2003
Smitten, 2007
Smitten, 2008
Smolen, 1999
Smolen, 1999
Smolen, 2008
Smolen, 2009
Sokolove, 2010
Solomon, 2006
St. Clair, 2004
Strand, 1999
Strand, 2006
Strangfeld, 2009
Strangfeld, 2010
Suissa, 2004

Suissa, 2006
Suissa, 2006
Svensson, 2003
Svensson, 2005

van der Heijde, 2006 –f ound under Klareskog 2004

van der Heijde, 2006 – found under Klareskog 2004
van der Kooij, 2009 – found under Goekoop-Ruiterman 2005
van Halm, 2006
van Riel, 2006
van Vollenhoven, 2009
Wallis, 2004
Wasserman, 2004
Weinblatt, 1999
Weinblatt, 2006
Weinblatt, 2006
Weinblatt, 2007
Westhovens, 2006
Westhovens, 2009
Wolfe, 2004
Wolfe, 2004
Wolfe, 2004
Wolfe, 2006
Wolfe, 2007
Wolfe, 2007
Wolfe, 2007
Zhang, 2006
Zink, 2005

Systematic Reviews and Meta-analyses found in Evidence Table 2

Alonso-Ruiz, 2008
Bernatsky, 2010
Bongartz, 2006
Bongartz, 2009
Gartlehner, 2006
Leombruno, 2009
Maetzel, 2000
Martinez Lopez, 2009
Mertens, 2009
Osiri, 2002, 2009
Salliot, 2009
Schipper, 2009
Singh, 2009

Singh, 2009
Singh, 2010
Singh, 2010
Wiens, 2009
Wiens, 2010

KQ4

RCTs and other studies found in Evidence Table 1

Keystone, 2009
Schiff, 2004
Schiff, 2006 – found under Fleischmann 2003
Solomon, 2006
Tesser, 2004 – found under Fleischmann 2003

Systematic Reviews and Meta-analyses found in Evidence Table 2

Rheumatoid Arthritis Clinical Trial Archive Group, 1995

Abbreviations used in the evidence tables

ACR	American College of Rheumatology
ADA	adalimumab
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
AIMS	Arthritis Impact Measurement Scales
ANA	anakinra
ARA	American Rheumatism Association criteria (pre-1987)
AS	ankylosing spondylitis
ASHI	Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific Health Index)
AUC	area under the curve
BUD	budesonide
Ccs	corticosteroids
CFS	chronic fatigue syndrome
CHF	coronary heart failure
Cm	centimeters
Combo	combination therapy
CI	confidence interval
CHD	coronary heart disease
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CVD	cardiovascular disease
CXT	cyclophosamide
CYP	cyclosporine
Ds	days
DM	diabetes mellitus
DAS	Disease Activity Score
DMARD	disease modifying antirheumatic drug
D-HAQ	Dutch version of the Health Assessment Questionnaire (HAQ)
EQ-5D–	Quality of Life Questionnaire
ESR	erythrocyte sedimentation rate
ETA	etanercept
EULAR	European League against Rheumatism
EuroQol EQ-5D	European Quality of Life Questionnaire
EuroQOL VAS	European Quality of Life Visual Analogue Scale
GI	gastrointestinal
HAQ	Health Assessment Questionnaire

HAQ-DI	Disability Index of the Heath Assessment Questionnaire (HAQ)
HIV	Human immunodeficiency virus
HLA-DR4	Human immune-response, D-related antigen encoded by the D locus on chromosome 6
HR	hazard ratio
HRQOL	health related quality of life
ICD	International Classification of Diseases
INF	infliximab
ISRs	injection site reactions
ITT	intention to treat
JRA	juvenile rheumatoid arthritis
HCQ	hydroxychloroquine
JSN	joint space narrowing
LEF	leflunomide
MTX	methotrexate
Mg	milligrams
mSharp Scale	Modified Sharp Method for Scoring Radiographs
mos	months
MHAQ	Modified Health Assessment Questionnaire
NSAIDs	non-steroidal anti-inflammatory drugs
NSFHS	National Survey of Functional Health Status
NA	not applicable
NMSC	non-melanoma skin cancer
NR	not reported
NS	not significant
NYHA	New York Heart Association
OA	osteoarthritis
OR	odds ratio
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PASI	Psoriasis Area and Severity Index
PNL	prednisolone
PRED	prednisone
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Scale
Pt	patient
PY	person-year
QOL	quality of life
RCT	randomized controlled trial
RAI	Ritchie Articular Index
RA	rheumatoid arthritis
RDS	radiological damage score
RF	rheumatoid factor
RIT	rituximab
RR	risk ratio
SAEs	serious adverse events
SAARDs	slow-acting anti-rheumatic drugs
SCC	squamous cell carcinoma
SD	standard deviation
SF-36	Medical Outcomes Study Short Form 36 Health Survey
SJC	swollen joint count
SHS	Sharp/van der Heijde Method (SHS) for Scoring Radiographs
SIR	standardized incidence ratio
SLE	Systemic Lupus Erythematosus
SMR	standardized morbidity ratio
SSZ	sulfasalazine
SSTG	South Swedish Arthritis Treatment Group
TB	Tuberculosis
TIM	targeted immune modulator
TJC	tender joint count
TNF	tumor necrosis factor
Txt	treatment
URTI	upper respiratory tract infection
UTI	urinary tract infection

vs.	versus
yrs	years
w/	with
w/in	with in
w/o	with out

Evidence Table 1. Randomized controlled trials and observational studies

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling et al., 2005 [1] **Country, Setting:** Sweden; registries **Funding:** Swedish Cancer Society; AFA Insurance Company; Wyeth-Ayerst; Schering-Plough; Abbott Immunology; Bristol-Myers Squibb; King Gustav V; Österlund and Kock Foundations; Reumatikerför-bundet **Research Objective:** The risk of TB pts with RA **Study Design:** Retrospective cohort study **Overall N:** 36,115 w/ RA **Study Duration:** 467,770 PY	**Inclusion Criteria:** • Diagnosed with RA according to ACR criteria • RA inpatient btwn 1964 to 2001 **Exclusion Criteria:** • Psoriatic arthritis, SLE, or AS diagnosis	**Interventions, dose:** D1: RA inpatient D2: Early RA D3: TNF treated RA **N:** D1: 31,185 D2: 2430 D3: 2500 **Mean age, yrs:** D1: 0-39: 19.08%;40-59: 40.80%;60-79: 35.90%;80+: 4.22% D2: 0-39: 15.80%;40-59: 38.40%;60-79: 41.60%;80+: 4.20% D3: 0-39: 18.40%;40-59: 49.44%;60-79: 30.52%;80+: 1.64% **Sex, % female:** D1: 73.4 D2: 70.2 D3: 73.4 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: NA D2: 3.6 D3: 5.8 **HAQ:** D1: NA D2: 0.8 D3: 1.84 TB cases: D1: 27 D2: 2	1987 to 2001 • RA inpatient vs. General RR 3.9 (95% CI,3.1-5.0) • RA inpatient vs. General inpatient RR 1.6 (95% CI,1.3-1.9) 1999 to 2001 • RA inpatient vs. General were at increased risk of TB RR 2.0, (95% CI,1.2-3.4) • TNF treated RA had a 4-fold increased risk of TB RR 4.0, (95% CI,1.3-12) vs. RA inpatient	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling et al., 2005 [2] **Country, Setting:** Sweden, **Multicenter Funding:** Swedish Cancer Society; insurance company AFA; Wyeth Ayerst, Schering-Plough, Abbott, Bristol Myer Squibb; Swedish National Board of Health and Welfare **Research Objective:** Cancer pattern of contemporary pts with RA and risk of solid cancer after TNF **Study Design:** Retrospective cohort study **Overall N:** 60,930 **Study Duration:** NR	**Inclusion Criteria:** • Inpatient Register RA cohort: inpts > 16 yrs or age ever discharged with an RA diagnosis between January 1990 and December 31 2003 • Early RA cohort: pts diagnosed within 1 yr with RA from 1995 through 2003. • TNF antagonist cohort: pts with RA treated with ETA, INF, or ADA from a Swedish registry of pts treated with anti-TNF medications **Exclusion Criteria:** • Pregnant or lactating • Inpatient Register RA cohort • Pts discharged with SLE, AS, or PsA • Observed and expected cancers during the 1st yr of follow up	**Interventions, dose:** D1: Inpatient RA Cohort D2: Early Arthritis RA Cohort D3: TNF antagonist cohort **N:** NR **Mean age, yrs:** NR **Sex, % female:** D1: 71.4 D2: 69.9 D3: 74.8 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: NR D2: 3.5 D3: 5.5 **% age 45-74 yrs:** D1: 56.3 D2: 65.4 D3: 71.8	**Inpatient RA cohort:** Based on 3379 observed solid cancers, this cohort had minimally increased overall risk of solid cancer (SIR: 1.05, 95% CI,1.01 to 1.08) **Overall RR was 1.19 (95% CI,1.13 to 1.26, N:1311) among men and 0.97 (95% CI,0.93 to 1.02, N:2068) among women** GI cancer risk (SIR: 0.85, 95% CI,0.78 to 0.93); Lung cancers (SIR: 1.48, 95% CI,1.33 to 1.65); (SIR: 1.66, 95% CI,1.50 to 1.84); **Early Arthritis cohort:** 138 solid cancers (SIR: 1.1, 95% CI,0.9 to 1.3), women (SIR: 0.87, 95% CI,0.67 to 1.11, n:64) Men (SIR: 1.42, 95% CI,1.12 to 1.79, n:74) **TNF cohort** • 67 solid cancers observed (SIR: 0.9, 95% CI,0.7 to 1.2) **Women (SIR: 0.87, 95% CI,0.63 to 1.16, N:45) Men 1.06 (95% CI,0.67 to 1.61, N:22)** Risk of colorectal cancer	NA	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA: retrospective cohort **Quality Rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
				(SIR: 1.2 lung cancer (SIR: 1.8), breast cancer (SIR: 0.4), NMSC (SIR: 3.6)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling, 2005[3] **Country, Setting:** Sweden, Registry data **Funding:** AFA Insurance Company, Pharmas: Swedish National Board of Health and Welfare; Swedish Cancer Society **Research Objective:** Risks of hemapoetic malignancies, especially those with associtaed with TNF **Study Design:** Retrospective cohort study **Overall N:** Prevalent Cohort (inpatient): 53,067 **Study Duration:** 4 yrs	**Inclusion Criteria:** • Age: Prevalence: 16+ • Diagnosed with RA according to ACR criteria • Prevalence: 1987 **Exclusion Criteria:** • Prevalence: discharged with systemic lupus, AS, or PsA	**Interventions, dose:** D1: Prevalence D2: Incidence D3: TNF Antagonist **N:** D1: 53,067 D2: 3,703 D3: 4,160 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	See AEs	**Haematopoetic malignancnies:** D1: SIR: 1.7 (1.5-1.8) D2: SIR: 1.6 (0.9-2.6) D3: 2.1 (1.1-3.8)	**Overall Attrition Rate, %:** **ITT Analysis:** NA **Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Askling et al., 2009[4] Swedish Biologics Register **Country and setting** Sweden **Source of funding** Swedish Cancer Society; Stockholm County Council **Research objective** To assess the risk of cancer in RA patients treated with anti-TNF therapy **Study design** Observational **Overall N** 6366 (first time anti-TNF users) **Duration of study** 25,693 person-yrs	**Inclusion Criteria** • RA patients, older than 16 yrs • Starting treatment with TNF antagonists **Exclusion Criteria**	**Comparisons (dosage and frequency)** D1: ETN: dose NR D2: ADA: dose NR D3: INF: dose NR **Number in group** D1: 2287 D2: 937 D3: 3380 Overall: 6604 **Mean age (years)** D1: 54 D2: 55 D3: 55 Overall: 55 **Sex, % female** D1: 77 D2: 77 D3: 74 Overall: 75 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 10.7 D2: 11.9 D3: 10.1 Overall: 10.6 **TJC, mean** D1: 9.1 D2: 8.4 D3: 8.6 Overall: 8.7 **SJC, mean** D1: 9.8 D2: 9.1 D3: 9.4 Overall: 9.5 **Corticosteroid use, %** D1: 57 D2: 56 D3: 45 Overall: 51 **DMARD use, %:** D1: 64.3 D2: 76.9 D3: 90.7 Overall: 80 **MTX naïve, %:** D1: 44.3 D2: 31.9 D3: 12.9 Overall: 27 **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** NR **Serious adverse events:** NR **Malignancies:** Skin cancer (basal cell or squamous cell) (n): D1: 7 D2: 2 D3: 23 Overall: 32 Respiratory cancer: D1: 9 D2: 2 D3: 25 Overall: 36 GI cancer: D1: 8 D2: 4 D3: 19 Overall: 31 Reproductive cancer D1: 25 D2: 10 D3: 40 Overall: 75 Urogenital cancer: D1: 8 D2: 1 D3: 6 Overall: 15 Hematopoeietic cancer: D1: 8 D2: 4 D3: 16	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			Baseline DAS score D1: 5.6 D2: 5.4 D3: 5.5 Overall: 5.5 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	NR	Overall: 28 Other cancer: D1: 5 D2: 3 D3: 14 Overall: 22 **Respiratory events:** NR **Other infections:** NR **GI:** NR **Other:** Other AEs 1 (n): RR of first primary cancer compared to biologic naive patients: D1: 0.78 (0.61 to 1.00) D2: 1.09 (0.91 to 1.30) D3: 1.32 (0.87 to 1.98) Overall: 1.00 (0.86 to 1.15, *P*=0.034) Any other AEs: RR of first primary cancer in RA patients first starting anti-TNF therapy versus starting biologic-naive patients: 1.00 (0.87 to 1.17) RR of first primary cancer in RA patients first starting anti-TNF therapy versus starting MTX therapy: 0.99 (0.79 to 1.24) RR of first primary cancer in RA pts first	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					starting anti-TNF therapy versus starting DMARD combination therapy: 0.97 (0.69 to 1.36)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Baecklund et al 2006[5] **Country, Setting:** Sweden, inpatient **Funding:** Swedish Rheumatism Society; Lions Cancer Research Foundation of Uppsala; AFA InsuranceSwedish Cancer Society **Research Objective:** To investigate which RA pts are at highest risk of lymphoma, and whether antirheumatic txt is hazardous or protective **Study Design:** Cohort **Overall N:** 756 **Study Duration:** 1964 to 1995	**Inclusion Criteria:** • Age: ≥ 16 • RA and lymphoma • All pts receiving inpatient care in Sweden discharged with a diagnosis of RA (ICD) • Randomly selected as potential controls 3 individuals from underlying RA cohort • From potential controls, we included first of 3 whose medical record could be identified and who fulfilled ACR criteria for RA **Exclusion Criteria:** NR	**Interventions, dose:** NR MTX SSZ Other?: steroids **N:** 756 378 cases 378 controls **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Risk of developing lymphoma is increased in subset of RA with severe disease.(Cases vs. controls) Inflammatory activity • Low inflammatory activity: 94 (25%) vs. 278 (74%) OR 1 (referent) • Medium: 196 (52%) vs. 94 (25%) OR 7.7 (95% CI,4.8-12.3) • High: 86 (23%) vs. 4 (1%) OR 71.3 (95% CI,24.1-211.4) Functional class • I 34 (9) vs. 138 (37) OR 1 (referent) • II 185 (49) vs. 204 (54) OR 3.9 (95% CI,2.4-6.3) • III 105 (28) vs. 31 (8) OR 13.8 (95% CI,7.2-26.2) • IV 52 (14) vs. 3 (1) OR 67.5 (95% CI,18.9-239.8) • DMARD OR 0.9 (95% CI,0.6-1.2) • MTX crude OR 0.8 (95% CI,0.4-1.4); adjusted OR 0.7 (95% CI,0.3-1.6) • SSZ; crude OR 0.6 (95% CI,0.4-1.0); adjusted OR 0.6 (95% CI,0.3-1.1) • Oral steroids (adjusted OR 0.6 [95% CI,0.4-0.9]) and intraarticular steroids (adjusted OR 0.4 [95% CI,0.2-0.6]), calculated with adjustment for disease activity and DMARD use	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: Case contol study **Quality Rating:** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Txt Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon et al., 2000[6]; Genovese et al., 2002 [7]; Kosinski et al., 2002[8]; Genovese et al., 2005[9]; ERA **Country, Setting:** US, clinics **Funding:** Immunex **Research Objective:** To compare ETA and MTX in pts with early RA **Study Design:** RCT **Overall N:** 632 (468 extension) **Study Duration:** 12 mos (1 year open label extension; 2 more years, total of 5 yrs)	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: < 3 yrs • Positive serum test for RF or at least 3 bone erosions evident on radiographs of hands, wrists, or feet • At least 10 swollen joints and at least 12 tender or painful joints • ESR ≥ 28 mm per hour • Serum CRP concentration of at least 2.0 mg per deciliter • Morning stiffness that lasted at least 45 minutes • Stable doses of NSAIDS and PRE allowed **Exclusion Criteria:** • Prior txt with MTX • No other important concurrent illnesses	**Interventions, dose:** D1: MTX (19 mg/wk) D2: ETA (10 mg twice wkly) D3: ETA (25 mg twice wkly) **N:** D1: 49 D2: 50 D3: 51 **Mean age, yrs:** D1: 49 D2: 50 D3: 51 **Sex, % female:** D1: 75 D2: 75 D3: 74 **Race, % white:** D1: 88 D2: 84 D3: 86	**Mean disease duration, yrs:** D1: 12 mos D2: 11 mos D3: 12 mos **TJC, mean:** D1: 30 (16.1) D2: 31 (15.5) D3: 31 (15.8) **SJC, mean:** D1: 24 (11.9) D2: 24 (11.7) D3: 24 (11.9) **DMARD use, %:** NR **Corticosteroid use, %** D1: 41 D2: 42 D3: 39 **MTX naive, %:** D1: 100 D2: 100 D3: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** D1: 100 D2: 100 D3: 100 **Baseline DAS, mean:** NR	**First 12 weeks** Mean changes in SF-36, HAQ, and ASHI significantly better in with ETA vs. MTX ($P < 0.0001$) **16 to 52 weeks** No significant difference in SF-36, HAQ, and ASHI scores between groups **At 6 months** Significantly more pts on ETA (25 mg) than on MTX achieved ACR50 and ACR70 responses (data NR, $P < 0.05$) **At 12 months** **ACR 20 response rates, %:** D1: 65 D3: 72 ($P = 0.16$) **Mean increase in Sharp score** D1: 1.00 D3: 1.59 ($P = 0.11$) **Erosion score change** D1: 1.03 D3: 0.47 ($P = 0.002$) Despite improvement, QoL measures remained below general population ($P < 0.0001$); at start QoL measures were significantly below that of general population ($P < 0.0001$) **24 month open-label extension**: **ACR20,%** D1: 59	**At year 2** **SAEs:** 20.6 **Cardiovascular Events:** 1.8 MI **Malignancies:** 3% overall Total events: 18 Breast: 3 Prostate: 3 Colon: 3 Lung: 12 Malignant melanoma: l2 Leukemia: 1 Kidney: 1 Hodgkins: 1 Adenocarcinoma: 1 **URTI:** Pnuemonia 2 Overall SAE rate of 0.093 events per pt-year comparable to rate observed in first year of efficacy study, events per pt-year MTX: 0.109 ETA: 0.091	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Txt Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				D3: 72 (*P* = 0.005); **ACR50, %** D1: 49 D3: 42 **ACR 70,%** D1: 29 D2: 24 **HAQ improvement of at least 0.5 units, %:** D1: 55 D2: 37 (*P* < 0.001) **Total modified Sharp score change** D1: 1.3 D3: 3.2 *(P* = 0.001) **Erosion score change** D1: 0.7 D3: 1.9 *(P* = 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bergstrom, 2004[10] **Country, Setting:** US, 5 practices **Funding:** NR **Research Objective:** To assess if pts who were treated with TNF antagonists have a higher risk of developing coccidioido-mycosis **Study Design:** Retrospective cohort study **Overall N:** 985 **Study Duration:** 3 yrs	**Inclusion Criteria:** • Pts with RA, reactive arthritis, PsA, JRA • Other meds were allowed **Exclusion Criteria:** • NA	**Interventions, dose:** D1: INF D2: Other Anti-TNF alpha D3: control **N:** D1: 7 D2: 4 D3: 974 **Mean age, yrs:** D1: 64.8 D2: 64 D3: 57.8 **Sex, % female:** D1: 71 D2: 75 D3: 77 **Race, % white:** D1: 86 D2: 75 D3: NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** D1: 100 D2: 50 D3: 50	Pts treated with INF are at higher risk for developing symptomatic coccidioidomycosis 7 of 247 pts receiving INF and 4 of 738 pts receiving other therapies developed symptomatic coccidioidomycosis (relative risk 5.23, 95% confidence interval 1.54-17.71; *P* < 0.01)	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Bernatsky et al., 2007[11] **Country and setting** Canada (Province of Quebec), phDacy and hospital (discharge) databases **Source of funding** Not reported **Research objective** Assess risk of severe infections associated with use of traditional DMARDs and glucocorticoid agents **Study design** Cohort Study – Nested Analysis **Overall N** 23,733 (RA cohort) For each case of hospitalization for infection that occurred in cohort, they randomly selected 10 controls **Duration of study** January 1, 1980 and December 31, 2003 **Quality rating** Fair	**Inclusion Criteria** • Registered in phDacy claims database of Re´gie d'assurance maladie du Que´bec (RAMQ) and Ministry of Health's Maintenance et exploitation des donne´es pour l'e´tude de la cliente` le hospitalie`re (MEDECHO). • Diagnosis of RA using physician billing codes (ICD-9 code 714) • Were dispensed at least 1 DMARD after January 1, 1980. **Exclusion Criteria** • Record of a hospitalization for infection at any time prior to cohort entry date.	**Interventions, Dose** D1: • MTX: Dosage NR • LEF: Dosage NR • SSZ: Dosage NR • Hydroxychlorquine: Dosage NR • ETN: Dosage NR • IFX: Dosage NR • Glucocorticoids: Dosage NR D2: • MTX: Dosage NR • LEF: Dosage NR • SSZ: Dosage NR • Hydroxychlorquine: Dosage NR • ETN: Dosage NR • IFX: Dosage NR • Glucocorticoids: Dosage NR **Number in group** Overall: 23,733 **Mean age (years)** Overall: 61.7 **Sex, % female** Overall: 69.9 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** Overall: Drug exposures at cohort entry for RA subjects (n/%): • MTX 7044 (29.7) • Anti-malarial agent: 9415 (39.7) • Anti-TNF agents: 261 (1.1) • All other DMARDs: 6180 (26.0). **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population**	**ACR** NR **HAQ,** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** Overall adverse events reported, n: Overall: 1991 from entire RA cohort **Serious adverse events** NR **Malignancies** NR **Respiratory events** Pneumonia, n: Overall: 1,315 **Other infections** NR **GI** NR **Other** Any other AEs: • Entire RA cohort generated 156,520 person-yrs of follow-up time, for an average follow-up of 6.3 yrs. During this time, 1970 cases of serious infection occurred, for an incidence rate of 129.1 events per 10 000 person-years. Of these infections, most common event was pneumonia with 1315 cases, for an incidence rate of 83.4 per 10 000 person-years. There were only 21 cases of TB recorded. Risk for all infections requiring hospitalization appeared to be most elevated with

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			characteristics, %, (CI/SD/P value) Avera age at cohort entry • Overall: 61.7 yrs • % Female • Overall: 69.9. Average followup: Overall: 6.3 year follow up • After average of 6.3 yrs followup • Mean age, Cases: 71.0 yrs • Mean age, Controls: 71.5 yrs • % Male, Overall: 65.5 Average yearly number of physician visits: • Cases: 5.5 • Controls: 5.1 Events occurred at a mean time of 5.5 (S.D. 4.7) yrs after cohort entry.		current exposures to systemic glucocorticoid agents (RR: 2.6, 95% CI: 2.3 - 2.9) • Similar effects were seen with pneumonia as outcome (RR 2.1 (2.4-3.1). For MTX, there was a trend towards increased risk for all infections (RR 1.10 (0.98-1.2), and a moderate increased risk for pneumonia (RR: 1.2, 95% CI: 1.0 - 1.3). For HCQ (and chloroquine) RR 1.1 (0.94-1.2) • Anti-TNF 1.9 (0.7-5.3); and for other DMARDs 0.9 (0.8-1.05). Limiting sample to subjects aged 65 yrs and older, estimates were similar, but with suggestion of slightly more pronounced effects, noted particularly for MTX (adjusted RR: 1.3; 95% CI: 1.1-1.5).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997[12]; Landewe et al., 2002[13]; COBRA study **Country, Setting:** Netherlands and Belgium, multicenter **Funding:** Netherland **Research Objective:** Comparing efficacy and radiographic outcomes of combination of SSZ, MTX and PNL with SSZ alone **Study Design:** RCT **Overall N:** 155 (148) **Study Duration:** 56 wks; (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 69 • Diagnosed with RA according to ACR criteria • Duration of condition < 2 yrs • NSAID txt at least 3 mos, 6 or more active inflamed joints AND presence of 2 or more (9 or more tender joints, morning stiffness 45 min or more, EST of 28 or more in first hour **Exclusion Criteria:** • Pregnant or lactating: adequate contraception • Prior txt with: DMARDS except HCQ or steroids • Past TB • Impaired renal or hepatic system serious comorbidity surgery in past 3 mos • Unable to comply with protocol • Allergy to study med • Alcohol or substance abuse	**Interventions, dose:** D1: Combined txt (SSZ, MTX, PNL) D2: SSZ Only SSZ: 2g/d MTX: 7.5 mg/wk, weaned after 40 wks PNL: 60 mg/d wk 1 40 mg/d wk 2 25 mg/d wk 3 20 mg/d wk 4 15 mg/d wk 5 10 mg/d wk 6 then 7.5 mg/d until wk 28 then weaned off **N:** D1: 76 D2: 79 **Mean age, yrs:** NR **Sex, % female:** D1: 66% D2: 52% **Race, % white:** NR	**Mean disease duration, yrs:** D1: 4 mos D2: 4 mos **TJC, mean:** NR **SJC, mean:** NR **Antimalarial use (%):** D1: 21 D2: 24 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Erosions on hand or foot xrays, %:** D1: 74 D2: 79	**At week 28** **Mean pooled index** D1: - 1.4 (95% CI, 1.2-1.6) D2: - 0.8 (95% CI, 0.6-1.0) (*P* < 0.0001) **ACR20, %:** D1: 72 D2: 49 (*P* = 0.006) **ACR50, %:** D1: 49 D2: 27 (*P* = 0.007) **DAS median change:** D1: -2.1 (SD 1.2) D2: -1.3 (SD 1.2) (*P* < 0.0001) **HAQ mean change:** D1: -1.1 (SD 0.8) D2: -0.6 (SD 0.6) (*P* < 0.0001) **Sharp mean change**: D1: 1 D2: 4 (*P* < 0.001) **At week 56** **Mean pooled index:** D1: 1.1 (SD 0.8) D2: 0.9 (SD 0.8) (*P* = 0.20) **DAS median change:** D1: 1.4 (SD 1.2) D2: 1.3 (SD 1.4) (*P* = 0.78) **HAQ mean change:** D1: 0.8 (SD 0.8) D2: 0.6 (SD 0.7) (*P* < 0.06) **Sharp mean change:** D1: 2 D2: 6 (*P* < 0.004)	**Overall:** D1: 72.3 D2: 62.0 **SAEs:** D1: 2.6 D2: 7.6 **Infections:** D1: 15.8 D2: 7.6 **Cardiovascular Events:** D1: 7.9 D2: 5.1 **Hepatotoxicity:** D1: 2.6 D2: 0	**Overall Attrition Rate, %:** 3.2 **ITT Analysis:** Yes **Quality Rating:** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				At week 80 **Sharp mean change**: D1: 4 D2: 12 (*P* < 0.01) **Five yr follow up** **Sharp score mean change:** D1: 5.6 (95% CI, 4.3, 7.1) (*P* = 0.001) D2: 8.6 (95%CI, 6.2-11) (*P* = 0.001) **Time averaged DAS28, points/yr**: D1: -0.07 D2: -0.17		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Brassard et al., 2009[14] **Country and setting** Canada, hospital (inpatient) or outpatient setting **Source of funding** Mentions support by Canadian career award and institutes Not reported **Research objective** Determine risk of TB and assess whether this risk is associated with exposure to DMARDs **Study design** Cohort – Case / Control **Overall N** Cohort consisted of 24,282 patients with RA; 70.1% were women. mean (SD) subject age at time of cohort entry was 61.7 (14.6) years. **Duration of study** 1980-2003 for cohort and 1992-2003 for TB incidence rates **Quality rating** Fair: Confounding and potential bias in	**Inclusion Criteria** • Patients registered in provincial phDacy claims database, which covers residents age ≤ 65 years, those who receive social assistance, and those who do not have private drug insurance through their employer. • ≥ 1 occurrence of diagnosis of RA using physician billing code for RA (ICD-9 code 714) during inpatient or outpatient visit. • Cohort subjects further restricted to those who were dispensed ≥ 1 prescription for DMARD therapy. • Cohort entry was defined by date of first DMARD prescription after 1 year of eligibility in provincial health	**Interventions, Dose** D1: • MTX: dosage and frequency NR • LEF: dosage and frequency NR Other: • Corticosteroids: dosage and frequency NR • All DMARDs included MTX, HCQ, chloroquine, SSZ, azathioprine, LEF, cyclophosphamide, cyclosporine, gold compounds, minocycline, or penicillamine D2: • MTXDosage NR • LEF: dosage and frequency NR • Other: Corticosteroids: dosage and frequency NR **Number in group** D1: 50 D2: 1500 Overall: 1550 **Mean age (years)** D1: 65 D2: 67 *P* =.06 **Sex, % female** D1: 50 D2: 70	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: 18 D2: 8.1 *P* = 0.03 **DMARD use, %** D1: 72 D2: 45.6 *P* = 0.0004 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %** Other comorbid clinical conditions and risk factors:	**ACR** NR **HAQ,** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** Any other AEs: • RR of TB associated with any nonbiologic DMARD exposure in year prior to index date is 3.0 (95% CI 1.6-5.8). • Current use of corticosteroids was also significantly associated with occurrence of TB (adjusted RR 2.4, 95% CI 1.1-5.4). • There were 50 cases of TB identified during followup period. overall sex and age-standardized rate of TB in RA cohort for period 1992-2003 was 45.8 cases per 100,000 person-years of followup compared with

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
population characteristics (older population). Use of case definitions to validate diagnosis of TB and RA conditions.	insurance system. • TB as a primary hospitalization diagnosis (ICD-9 codes 010-018) or if TB was part of a medical claim. • Had at least 2 classes of usual first-line anti-TB medications prescribed (isoniazid, rifampin, pyrazinamide, or ethambutol) • Treatment lasted at least 6 months. **Exclusion Criteria** • TB cases that occurred before date of cohort entry were excluded from cohort.	*P* = 0.002 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	D1: 2.0 D2: 1.9 Overall: : *P* = 0.62 Diabetes: D1: 12.0 D2: 10.1 *P* = 0.67 Use of COX-2 inhibitors: D1: 8.0 D2: 5.7 *P* = 0.53 Use of NSAIDS: D1: 56.0 D2: 49.9 *P* = 0.39		4.2 cases per 100,000 person-years in general population of Quebec (SIR 10.9, 95% CI 7.9-15.0).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Brassard, P., et al.; 2006; Antirheumatic Drugs and Risk of TB[15] **Country and setting** Canada; Medical and phDaceutical claims data from PhDetrics Patient-Centric Database were reviewed. **Source of funding** Not reported **Research objective** Quantify rate of Mycobacterium TB and assess whether independent use of DMARDs is associated with risk of developing TB **Study design** Cohort Study with Nested Case / Control **Overall N** n: 112,300 patients from which a nested case-control was selected (386 cases, 38,600 controls) **Duration of study** September 1998 - December 31, 2003 **Quality rating**	**Inclusion Criteria** • Patients aged 18 years or older with 1 or more occurrence of a diagnosis of RA • Dispensed 1 or more prescriptions for any anti-RA drug during study period were inlcuded in cohort. • Cases were those patients who were diagnosed with TB during study period. • For each case, 100 controls were matched on date of cohort entry and confirmation that they were at risk for TB at time case occurred. **Exclusion Criteria** • Patients who had TB prior to cohort entry were excluded from being cases.	**Interventions, Dose** D1: • MTX: dosage and frequency NR • LEF: dosage and frequency NR • SSZ: dosage and frequency NR • HCQ: dosage and frequency NR • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ANK: dosage and frequency NR • Other: auronofin, cyclosporin, penacillamine, and cyclophosphamide: dosage and frequency NR D2: • MTX: dosage and frequency NR • LEF: dosage and frequency NR • SSZ: dosage and frequency NR • HCQ: dosage and frequency NR • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ANK: dosage and frequency NR • Other: auronofin, cyclosporin, penacillamine, and	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: 46.6 D2: 31.2 *P* =.001 **DMARD use, %** D1: biologic DMARDs 17.4%; Traditional DMARDs 50.8% D2: biologic DMARDs 11.8% *(P* = .008); Traditional DMARDs 44.1% *(P* = .008) **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population**	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference** NR	**Overall** Overall attrition/withdrawal, n: NA Overall adverse events reported, n: D1: 386 D2: 0 **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR Any other AEs: • Crude and Adjusted rate ratio (RR) of developing TB, according to antirheumatoid arthritis medications use (cases: 386, controls: 38,600) • Use of biologic DMARDs, crude RR: 1.5, adjusted RR: 1.5 (1.1 - 1.9); Infliximib, crude RR: 1.7, adjusted RR: 1.6 (1.0 - 2.6); ETN, crude RR: 1.4, adjusted RR: 1.2 (0.9 - 1.8); ANK, crude RR: 1.5, adjusted RR: 1.3 (0.8 -

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Fair		cyclophosphamide: dosage and frequency NR **Number in group** D1: 386 D2: 38,600 **Mean age (years)** D1: 54 D2: 56 *P* =.01 **Sex, % female** D1: 77.2 D2: 73.7 *P* =.12 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**characteristics, %, (CI/SD/P value)** D1: Diabetes 19.9%; Other comorbid condition (silicosis, chronic renal failure/hemodialysis, solid organ transplantation, and carcinoma) 3.8%; use of corticosteroids 46.6% D2: Diabetes 15% *(P* = .007)Other comorbid condition (silicosis, chronic renal failure/hemodialysis, solid organ transplantation, and carcinoma) 1.9% *(P* = .007); Use of corticosteroids 31.2% *(P* = 0.001)		2.1); • Use of traditional DMARDs, crude RR: 1.3, adjusted RR 1.2 (1.0 - 1.5); study inlcudes a subanalysis of corticosteroid use among cases; crude and adjusted rate ratio (RR) of developing tuberulosis associated with anti-rheumatoid arthritis medication use stratified by current use of corticosteroids (noncurrent users among cases: 313, current users among cases: 73); • For noncurrent users on any biologic DMARDs, crude RR: 1.8, adjusted RR: 1.7 (1.3 - 2.3); noncurrent users on IFX, crude RR: 2.0, adjusted RR: 1.8 (1.1 - 3.0); noncurrent users on ETN, crude RR: 1.5, adjusted RR: 1.3 (0.9 - 2.0); noncurrent users on ANK, crude RR: 1.7, adjusted RR: 1.7 (1.1 - 2.8) • For noncurrent users on traditional DMARDs, crude RR: 1.5, adjusted RR: 1.4 (1.1 - 1.8) • For current users also on any biologic DMARDs, crude RR: 0.7, adjusted RR: 0.7 (0.3 - 1.3); for current users also on IFX, crude RR: 0.9, adjusted

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					RR: 1.1 (0.3 - 3.6), for current users also on ETN, crude RR: 0.9, adjusted RR: 0.9 (0.4 - 2.0), for current users also on ANK rates were not estimable; for current users on traditional DMARDs crude RR: 0.6, adjusted RR: 0.6 (0.4 - 1.0).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Breedveld et al. 2004[17], Maini et al. 2004 [18] and Smolen et al. 2005 [19] **Country, Setting:** Multinational Multicenter **Funding:** Centocor **Research Objective:** To examine the impact of INF + MTX on the progression of structural damage in pts with early RA. Subanalyses of ATTRACT, early RA and in non-responders. **Study Design:** RCT **Overall N =** 428 and 61 of these had available radiographs **Study Duration:** 102 wks	**Inclusion Criteria:** Previous use of DMARDs: current MTX 6 or more swollen and tender joints ESR ≥ 28 mm/hour; CRP ≥ 2mg/dl **Exclusion Criteria:** NR	**Interventions (dose):** D1: All D2: Early RA D3: Responders placebo/INF D4: Nonresponders placebo/INF MTXINF: 3 mg/kg every 4 or 8 wks and 10 mg/kg every 4 or 8 wks Placebo **N =** D1: 428 D2: 82 D3: 15/176 D4: 73/164 **Mean age (yrs):** D1: 54 D2: 50 D3: 49.7/50.6 D4: 51.2/55.2 **Sex (% female):** D1: 78 D2: 79 D3: 67/77 D4: 82/77 **Race (% white):** NR	**Mean disease duration (yrs):** D1: 8.4 D2: 1.7 D3: 9.9/9.5 D4: 10.8/11.2 **TJC (mean):** D1: 31 D2: 30 D3: 32.5/32.5 D4: 30.4/32.5 **SJC (mean):** D1: 20 D2: 20 D3: 21.2/22.6 D4: 21.5/22.7 **DMARD use (%):** NR **Corticosteroid use (%)** NR **MTX naïve (%):** NR **Txt resistant (%):** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS (mean):** NR **Erosion score:** D1: 23.5 D2: 8.9	Early RA at 102 wks- • Erosion scores mean • Placebo + MTX 12.21 (13.32)vs. INF + MTX -0.49 (3.89) $P < 0.001$ JSN • Placebo + MTX 12.82 (15.73) vs. INF + MTX -0.05 (4.30) $P < 0.001$ • Responders vs. non-responders • Radiographic progression was much greater in pts receiving MTX + placebo than in pts receiving INF + MTX, (mean change in modified Sharp/van der Heijde score 6.0 in ACR20 responders and 7.2 in ACR20 nonresponders in the MTX + placebo-treated group, vs. 0.1 in ACR20 responders and 1.2 in ACR20 nonresponders in the INF + MTX-treated group ($P < 0.01$) • HAQ median change MTX 0.1 vs. all INF 0.4 $P \leq 0.006$ • SF-36 median change MTX 2.8 vs. all INF 6.4 $P \leq 0.011$	**SAEs:** D1: 33 D2: 33 D3: 23 D4: 29/32 **Serious Infections:** D1: 13 D2: 11 D3: 13 D4: 13/10 **Malignancies:** D1: 1 D2: 1 D3: 0 D4: 3/6	**Overall Attrition Rate (%):** 428 randomised, 259 entered 2nd yr and 216 completed. **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
			JSN score: D1: 28.3 D2: 10.0			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Breedveld et al., 2006[16] PREMIER study **Country, Setting:** Multinational (Europe, North America, Australia), multicenter (133) **Funding:** Abbott Laboratories **Research Objective:** To compare efficacy and safety of ADA + MTX vs. MTX or ADA in pts with early, aggressive RA (RA) who had not previously received MTX txt **Study Design:** RCT **Overall N:** 799 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: 3 yrs or less • MTX naive pts • > 8 swollen joints, > 10 tender joints, and an erythrocyte sedimentation rate of > 28 • Folic acid only other med allowed **Exclusion Criteria:** • Prior txt with: MTX, cyclophosphamide, cyclosporine, azathioprine	**Interventions, dose:** D1: MTX (20 mg/wk) D2: ADA (40 mg/biwkly) D3: ADA (40 mg/biwkly) + MTX (20 mg/wk) **N:** D1: 257 D2: 274 D3: 268 **Mean age, yrs:** D1: 52 D2: 52.1 D3: 51.9 **Sex, % female:** D1: 73.9 D2: 77.4 D3: 72 **Race, % white:** NR	**Mean disease duration, yrs:** D1: .8 D2: .7 D3: .7 **TJC, mean:** D1: 32.3 D2: 31.8 D3: 30.7 **SJC, mean:** D1: 22.1 D2: 21.8 D3: 21.1 **DMARD use, %:** NR **Corticosteroid use, %** D1: 35.4 D2: 36.5 D3: 35.8 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 6.3 D2: 6.4 D3: 6.3 **HAQ:** D1: 1.5 D2: 1.6 D3: 1.5 **Erosion score:** D1: 13.6 D2: 11.3 D3: 11.0	**At 6 months** **Radiographic progression; change in Sharp scores:** D1: 3.5 D2: 2.1 ($P < 0.001$) **At 1 yr** **Radiographic progression; change in Sharp scores:** D1: 5.7 D2: 3.0 ($P < 0.001$) **HAQ DI improvement, mean units +/- sd:** D1: -0.8 +/- 0.7 D2: -0.8 +/- 0.6 D3: -1.1 +/- 0.6 D2 vs. D1, P = NR D3 vs. D1: $P < 0.001$ D3 vs. D2: P = 0.002) **At 2 yrs** **ACR50 response, %:** D1: 43 D2: 37 D3: 59 D3 vs. D2 or D1: $P < 0.001$ D1 vs. D2: P= NS **Clinical remission, %:** D1: 25 D2: 25 D3: 49 (both $P < 0.001$) **Radiographic progression; change in Sharp scores:** D1: 10.4 D2: 5.5 ($P < 0.001$)	**SAEs:** D1: 18.5 D2: 21.1 D3: 15.9 **Infections:** D1: 123 D2: 110 D3: 119 **Serious Infections:** D1: 2.9 D2: 0.7 D3: 1.6 **Malignancies:** D1: 0.4 D2: 0.9 D3: 0.9 **Withdrawal because of adverse events:** D1: 7% D2: 10% D3: 12%	**Overall Attrition Rate, %:** 32% **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Withdrawal because of lack of efficacy, %: D1: 18 D2: 19 D3: 4.9 **HAQ DI improvement, mean units +/- sd:** D1: -0.9 +/- 0.6 D2: -0.9 +/- 0.7 D3: -1.0 +/- 0.7 D2 vs. D1, *P* = NR D3 vs. D1; *P* < 0.05 D3 vs. D2; *P* = 0.058 **% with HAQ DI score of zero:** D1: 19 D2: 19 D3: 33 D3 vs. D2, *P* < 0.001 D3 vs. D1: *P* < 0.001 **% with HAQ DI improvement of ≥ 0.22 units from baseline:** D1: 63 D2: 58 D3: 72 D3 vs. D2, *P* < 0.05 D3 vs. D1: *P* < 0.05		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Brown, 2002[20] **Country, Setting:** US, NA **Funding:** Authors are from FDA and National Cancer Institute **Research Objective:** Occurrence of lympho-proliferative disorders in pts treated with ETA and INF **Study Design:** Database analysis; AERS system **Overall N:** 26 cases **Study Duration:** NA	**Inclusion Criteria:** MedWatch reports submitted to FDA for biologic products ETA and INF. All reports citing neoplasms, benign or malignant, were reviewed. Any report with a keyword of lymphoma or mentioned lymphoma in text was investigated further. Cases reported to MedWatch through December 2000 comprise basis for current summary **Exclusion Criteria:** NA	**Interventions, dose:** D1: ETA (various) D2: INF (various) **N:** D1: 18 D2: 8 **Mean age, yrs:** D1: 64 D2: 62 **Sex, % female:** D1: 61.1 D2: 25.0 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** D1: 72.2 D2: 25	**ETA** 19 cases per 100,000 treated persons **INF** • 6.6 cases per 100,000 treated persons • In general, diffuse large B cell lymphoma (non-Hodgkin's) were most common form • (21 of 26 were non-Hodgkin's lymphomas) • Treated person rates of lymphomas in ETA and INF users is probably an underestimate based on underreporting, according to authors (Age adjusted rate of lymphomas in US from 1992-1998 18.3 per 100,000 people) • Median time to lymphoma diagnosis was 8 wks (range 2-52 wks) for ETA and 6 wks (range 2-44 wks) for INF	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Burmester, B. R. et al., 2007 ReAct[21] **Country and setting** Multinational, multicenter **Source of funding** NR **Research objective** Evaluate safety and effectiveness of ADA alone or in combination with standard DMARDs fortreatment of RA. **Study design** Open – label Observational **Overall N** 6610 **Duration of study** 12 weeks for main study, 5 years total **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant defined as treatment failure with at least one traditional DMARD • Men and women ≥ 18 years of age with active, adult-onset RA in accordance with1987 revised criteria ofACR • Disease duration ≥ 3 mos • DAS based on ESR and an evaluation of 28 joints (DAS28) of greater than or equal to 3.2. **Exclusion Criteria** • Current pregnancy or breast feeding • Any persistent or severe infection within 30 days of baseline • Previous treatment with other TNF antagonists up	**Interventions, dose** D1: ADA: 40 mg every other week D2: MTX LEF SSZ ADA: 40 mg every other week Antimalarials **Number in group** D1: 1731 D2: 4879 1 DMARD 4004 2 DMARDs 769 ≥ 3 DMARDs 106 MTX only 2794 LEF only 842 SSZ only 133 AM only 148 1 other DMARD 84 MTX+LEF 180 MTX+AM 269 MTX+SSZ 182 MTX+SSZ+AM 76 Overall: 6610 **Mean age, years (SD)** D1: 55 (13) D2: 55 (13) 1 DMARD 53 (13) 2 DMARDs 53 (13) ≥ 3 DMARDs 52 (12) MTX only 53 (13) LEF only 54 (12) SSZ only 56 (13) AM only 56 (12) 1 other DMARD 55 (13) MTX+LEF 53 (13) MTX+AM 52 (13)	**Mean disease duration, years (SD)** D1: 12 (9) D2: 10 (8) 1 DMARD 10 (8) 2 DMARDs 9 (7) ≥ 3 DMARDs 10 (9) MTX only 10 (8) LEF only 11 (9) SSZ only 11 (8) AM only 8 (7) 1 other DMARD 13 (9) MTX+LEF 10 (8) MTX+AM 8 (7) MTX+SSZ 9 (8) MTX+SSZ+AM 9, S **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 Overall: 100 **Tender Joint Count, mean** D1: 14 (7) D2: 13 (7) 1 DMARD 13 (7) 2 DMARDs 13 (7) ≥ 3 DMARDs 13 (7) MTX only 13 (7) LEF only 13 (7) SSZ only 14 (8) AM only 15 (7) 1 other DMARD 14 (7) MTX+LEF 13 (7) MTX+AM 14 (7) MTX+SSZ 13 (7) MTX+SSZ+AM	**ACR mean difference/ absolute difference** Response at 12 weeks with ADA+MTX as comparison group, OR (CI): ACR 20: D1: 0.52 (0.45-0.60), *P* < 0.0001 D2: LEF only 0.69 (0.58-0.82), *P* < 0.0001, SSZ only 0.61 (0.41-0.89), *P* = 0.0 ACR 50: D1: 0.61 (0.53-0.70), *P* < 0.0001 D2: LEF only 0.72 (0.61-0.86), *P* = 0.0002, SSZ only 0.76 (0.52-1.22), *P* = 0.1555, AM only 1.14 (0.81-1.63), *P* = 0.4503; 1 other DMARD 092 (0.57-1.48), *P* = 0.7280, MTX+LEF 0.70 (0.50-0.97), *P* = 0.0307, MTX+AM 0.94 (0.72-1.23), *P* = 0.6590, MTX+SSZ 1.0 (0.73-1.36), *P* = 0.9822, MTX+SSZ+AM 0.97 (0.59-1.57), *P* = 0.8849 ACR 70: D1: 0.74 (0.62-0.87), *P* = 0.0004 D2: LEF only 0.67 (0.54-0.84), *P* = 0.0006, SSZ only 0.76 (0.46-1.26), *P* = 0.2817, AM only 1.11 (0.73-1.68), *P* = 0.6397, 1 other DMARD 1.08 (0.61-1.94), *P* = 0.7871,	**Attrition/withdrawal** NR by arm **Serious adverse events, n** D1: 126 D2: 260

to 2 mos before enrollment • Treatment with alkylating agents • Total lymphoid irradiation, IV immunoglobulin or any investigational biologic agent • History of active arthritis other than RA • Any uncontrolled medical condition • History or signs of demyelinating disease • Active TB or histoplasmosis, malignancy (except for completely treated squamous or basal cell carcinoma)	MTX+SSZ 52 (13) **Sex, % female** D1: 82 D2: 80 1 DMARD 81 2 DMARDs 75 ≥ 3 DMARDs 76 MTX only 82 LEF only 82 SSZ only 81 AM only 83 1 other DMARD 79 MTX+LEF 79 MTX+AM 75 MTX+SSZ 70 MTX+SSZ+AM 78 Overall: 81 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Swollen Joint Count, mean** D1: 11 (6) D2: 10 (6) 1 DMARD 10 (6) 2 DMARDs 11 (6) ≥ 3 DMARDs 12 (7) MTX only 10 (6) LEF only 11 (6) SSZ only 11 (6) AM only 10 (6) 1 other DMARD 11 (5) MTX+LEF 11 (6) MTX+AM 10 (6) MTX+SSZ 11 (6) MTX+SSZ+AM **Corticosteroid use, %** D1: 70 D2: 72 1 DMARD 71 2 DMARDs 75 ≥ 3 DMARDs 67 MTX only 70 LEF only 73 SSZ only 63 AM only 78 1 other DMARD 81 MTX+LEF 81 MTX+AM 74 MTX+SSZ 69 MTX+SSZ+AM 66Overall: 71 **DMARD use, %** D1: Prior: 3.1 (2.1) D2: Prior: 2.9 (1.7) 1 DMARD 2.8 (1.7) 2 DMARDs 3.3 (1.5) ≥ 3 DMARDs 3.8 (1.2) MTX only 2.7 (1.7) LEF only 3.3 (1.7) SSZ only 3.1 (1.8) AM only 2.8 (1.8) 1 other DMARD 4.1 (2.1) MTX+LEF 3.5 (1.6)	MTX+LEF 0.72 (0.47-1.11), *P* = 0.1387, MTX+AM 0.89 (0.64-1.24), *P* = 0.4860, MTX+SSZ 0.99 (0.67-1.44), *P* = 0.9438, MTX+SSZ+AM 1.11 (0.62-2.0), *P* = 0.7208 **HAQ,** D1: Abs change from baseline to 12 weeks: -0.47 (0.63 D2: Abs change from baseline to 12 weeks: -0.56 (0.60, 1 DMARD -0.56 (0.60, 2 DMARDs -0.56 (0.60, ≥ 3 DMARDs -0.56 (0.57, MTX only -0.58 (0.60, LEF only -0.49 (0.59, AM only -0.72 (0.63, SSZ only -0.52 (0.62, 1 other DMARD -0.55 (0.55, MTX+LEF -0.54 (0.58, MTX+AM -0.63 (0.66, MTX+SSZ -0.55 (0.52, MTX+SSZ+AM -0.58 (0.59 Overall: Abs change from baseline to 12 weeks: -0.54 (6.1 **DAS (CI)** Abs change from baseline to 12 weeks: D1: -1.9 (1.4, DAS28<2.6 OR for achieving a response at week 12 (ADA+MTX as comparison group): 0.59 (0.49-0.71), *P* < 0.0001 D2: -2.2, SD 1.3; 1 DMARD -2.2, SD 1.3; 2 DMARDs -2.3, SD 1.3; ≥ 3 DMARDs

MTX naïve, %
NR

Baseline DAS score
D1: 6.2 (1.1)
D2: 6.0 (1.1)
1 DMARD 6.0 (1.1)
2 DMARDs 6.0 (1.1)
≥ 3 DMARDs 5.9 (1.1)
MTX only 6.0 (1.1)
LEF only 6.0 (1.1)
SSZ only 6.1 (1.1)
AM only 6.2 (1.0)
1 other DMARD 6.3 (1.0)
MTX+LEF 6.1 (1.0)
MTX+AM 6.0, S

Required treatment for latent TB
D1: NR
D2: NR
Overall: 835

Other population characteristics, %, (CI/SD/P value)
D1: HAQ DI: 1.73 (0.68)
D2: HAQ DI: 1.60 (0.68)
1 DMARD 1.61 (0.68)
2 DMARDs 1.55 (0.69)
≥ 3 DMARDs 1.68 (0.65)
MTX only 1.61 (0.68)
LEF only 1.58 (0.68)
SSZ only 1.70 (0.71)
AM only 1.62 (0.69)
1 other DMARD 1.87 (0.69)
MTX+LEF 1.55 (0.64)
MTX+AM 1.52 (0.70)
MTX+SSZ 1.57 (0.70)
MTX+SSZ+AM 1.669 (0.66)
Overall: HAQ DI: 1.64 (0.68)

-2.3, SD 1.3; MTX only -2.3, SD 1.3; LEF only -2.0, SD 1.3; AM only -2.4, SD 1.4; SSZ only -2.1, SD 1.3; 1 other DMARD -2.2, SD 1.2; MTX+LEF -2.2, SD 1.3; MTX+AM -2.4, SD 1.3; MTX+SSZ -2.4, SD 1.3; MTX+SSZ+AM -2.4, SD 1.3; DAS28<2.6 OR for achieving a response at week 12 (ADA+MTX as comparison group): LEF only 0.75 (0.6-0.93), P= 0.0103; SSZ only 1.51 (0.97-2.36), P= 0.0694; AM only 1.03 (0.65-1.62), P= 0.9107; 1 other DMARD 0.93 (0.48-1.81), P= 0.8365; MTX+LEF 0.82 (0.53-1.25), P= 0.3491; MTX+AM 0.97 (0.69-1.34), P= 0.8310; MTX+SSZ 1.01(0.68-1.48), P= 0.9729; MTX+SSZ+AM 1.61 (0.91-2.84), P= 0.1006

SF-36, mean difference/absolute difference
NR

Radiographic measures, mean difference/absolute difference
NR

Quality of life scales, mean difference/absolute difference
NR

Others, (please name)
Moderate EULAR OR for

			achieving a response at week 12 (ADA+MTX as comparison group): D1: 0.45 (0.38-0.53), *P* < 0.0001 D2: LEF only 0.68 (0.54-0.84), *P* = 0.0004, SSZ only 0.72 (0.44-1.16), *P* = 0.1756, AM only 0.81 (0.51-1.30), *P* = 0.3859, 1 other DMARD 0.79 (0.42-1.46), *P* = 0.4446, MTX+LEF 0.92 (0.59-1.45), *P* = 0.7183, MTX+AM 1.33 (0.87-2.03), *P* = 0.1922, MTX+SSZ 1.36 (0.82-2.24), *P* = 0.2366, MTX+SSZ+AM 2.89 (1.04-8.01), *P* = 0.0411 Good EULAR OR for achieving a response at week 12 (ADA+MTX as comparison group): D1: 0.53 (0.46-0.62), *P* < 0.0001 D2: LEF only 0.77 (0.64-0.93), *P* = 0.0058, SSZ only 0.95 (0.63-1.43), *P* = 0.8142, AM only 0.99 (0.67-1.44), *P* = 0.9420, 1 other DMARD 0.97 (0.57-1.65), *P* = 0.9157, MTX+LEF 0.72 (0.50-1.02), *P* = 0.0673, MTX+AM 0.99 (0.75-1.32), *P* = 0.9493, MTX+SSZ 0.94 (0.67-1.32), *P* = 0.7336, MTX+SSZ+AM 1.24 (0.74-2.09), *P* = 0.4180

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Cannon et al., 2004[22] **Country, Setting:** US, claims database **Funding:** Aventis Pharmaceuticals; Veterans Affairs **Research Objective:** The incidence of serious adverse events during txt of RA with DMARDs, focusing on LEF **Study Design:** Retrospective cohort study **Overall N:** 40594 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 18 and older • Diagnosed with RA according to ACR criteria: ICD 9 code (rx for LEF-surrogate marker), 90 d observation period prior to entry **Exclusion Criteria:** • Impaired renal or hepatic system: if on DMARD other than LEF-hepatic event 90 ds prior to entering cohort • unable to determine sex or date of birth	**Interventions, dose:** **NR** HCT MTX LEF SSZ ETA INF **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Rates of AE in LEF group, alone and combined with MTX, were lower than or comparable to AE rates seen with MTX and other agents. LEF monotherapy had lowest rate of hepatic events in DMARD monotherapy groups All AE rates: LEF monotherapy (94 events/1000 PY, 95%CI, 84.4-104.8), MTX monotherapy (145 events/1000 PY, 95%CI,136.3-154.3), other DMARD (143 events/1000 PY, 95%CI,137.4-150.3), no DMARD (383 events/1000 PY, 95%CI,365.8-399.6) (*P* < 0.001). LEF + MTX (42.8/1000 PY, 95%CI, 32.8-55.9), LEF + other DMARD (58.7/1000 PY, 95%CI, 52.0-66.2), DMARD + MTX (69.5/1000 PY, 95%CI, 65.0-74.3; *P* = 0.002)	**Overall (rate per 1000 PY adjusted for age, sex, and comorbidities):** D1: 94.1 D2: 145.0 D3: 143.7 D4: 42.8 **Hepatotoxicity (adjusted rate per 1000 PY):** D1: 4.1 D2: 6.9 D3: 4.2 D4: 4.6	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006[23] **Country, Setting:** Scotland, 8 NHS sites **Funding:** Wyeth and Pharmacia - drugs Arthritis Research Campaign **Research Objective:** If a combination of SSZ and MTX is superior to either alone in RA pts with supoptimal response to 6 mos of SSZ **Study Design:** RCT **Overall N:** 165 **Study Duration:** Phase I: 6 mos; Phase 2: 12 additional mos for those with DAS > 2.4 after 6 mos	**Inclusion Criteria:** • Age: 18 to 80 • Duration of condition: < 10 yrs • Active disease defined by DAS > 2.4 after 6 mos SSZ txt were eligble for phase II • NSAIDs and other medications were continued • Intra-articular or intramuscular corticosteroid was permitted but not within 1 mo of 6, 12, & 18 mo assessments **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: MTX or SSZ • Impaired renal or hepatic system: creatinine > 150 mmol/dl, ALT, aspertate aminotransferase > 80 IU/l, alkaline phosphatase > 700 IU/l, gamma GT x3 • Other: abnormal white cell count (< 4 x 10*9/l) • Pre-existing	**Interventions, dose:** D1: SSZ + MTX D2: SSZ + placebo D3: MTX + placebo Phase I MTX: 7.5 mg/w (3 x 2.5 mg) increasing by 2.5 mg/mo until max of 25 mg or toxicity SSZ: enteric coated 500 mg/d increased by 500 mg/wkly until 40 mg/kg per d to a max of 4g/d for initial 6 mos Placebo: Folic Acid 5 mg/wk given 3 days after MTX and MTX + placebo **N:** D1: 56 D2: 55 D3: 54 Overall: 687 **Mean age, yrs:** D1: 56 D2: 55 D3: 53 Overall: 55 **Sex, % female:** D1: 75 D2: 75 D3: 79 Overall: 77 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 1.9 D2: 1.6 D3: 1.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** All **Txt resistant, %:** All **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 3.63 D2: 3.67 D3: 3.5 **Sharp:** D1: 17.0 D2: 14.0 D3: 12.0	**Median change 18 mos:** **DAS:** D1: -0.67 D2: -0.30 D3: -0.26 (D1 vs. D2; *P* = 0.039) (D1 vs. D3; *P* = 0.023) (D2 vs. D3; *P* = 0.79) **HAQ:** D1: -0.50 D2: -0.25 D3: -2.00 (D1 vs. D2; *P* = 0.51) (D1 vs. D3; *P* = 0.57) (D2 vs. D3; *P* = 0.99) **SJC:** D1: -3.00 D2: -3.00 D3: -2.00 (D1 vs. D2; *P* = 0.94) (D1 vs. D3; *P* = 0.81) (D2 vs. D3; *P* = 0.74) **ACR20, % :** D1: 29 D2: 18 (OR 1.25 (95% CI, 0.56-2.79) ; *P* = 0.68) D3: 15 (OR 2.01 (95% CI, 0.85-4.76), *P* = 0.14) **ACR50, %:** D1: 11 D2: 6 (OR 1.43 (95% CI, 0.43-4.81), *P* = 0.76) D3: 7 (OR 1.79 (95% CI, 0.49-6.49), *P* = 0.53) **ACR70, %:** D1: 4	NR	**Overall Attrition Rate, %:** 28.5 • 687 pts entered phase I (6 mos) • At 6 mos, 165 were not eliglbe to enter phase II (discontinued SSZ because of side effects: 19%, did not attend: 3.6%, died: 0.4%) • Another 191 were not randomized because DAS score was < 2.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			D2: 2 (OR 1.50 (95% CI, 0.24-9.34), *P* = 1.00) D3: 2 (OR 3.00 (95% CI, 0.30-29.78), *P* = 0.62)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Chakravarty, 2005[24] **Country, Setting:** US, multicenter **Funding:** Bristol-Myers-Squibb **Research Objective:** Rates of NMSC (non-melanoma skin camcer) in a large cohort of pts with RA or OA and to evaluate the role of immunosuppressive medications on the development of NMSC **Study Design:** Retrospective cohort study **Overall N:** 15,789 (RA); 3,639 (OA) **Study Duration:** NR	**Inclusion Criteria:** • Participants in National Data Bank for Rheumatic Diseases (NDB) • Recruited from 908 US rheumatologists; pts who returned at least 2 questionnaires between January 1999 and January 2003 **Exclusion Criteria:** NR	**Interventions, dose:** D1: pts with RA **D2: pts with OA** PRE MTX LEF **TNF inhibitors** **N:** D1: 15789 D2: 3639 **Mean age, yrs:** D1: 62 D2: 67 **Sex, % female:** D1: 77 D2: 83 **Race, % white:** D1: 91 D2: 94	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Skin cancer before NDB:** D1: 3.8 D2: 5.8 **History of smoking:** D1: 56 D2: 46	A total of 738 pts with RA reported new cases of NMSC during followup within the NDB; crude incidence rate: 18.1 / 1000 PY (95% CI, 16.8 -19.4 / 1000 PY) After excluding prevalent cases of NMSC, incidence rate was 15.2 / 1000 PY (95% CI, 14.1 -16.5) Based on multivariate Cox proportional hazard analysis restricted to pts with RA Use of PNL was associated with an increased hazard ratio (HR) (HR: 1.28, *P* = 0.014) for development of NMSC No association found with use of LEF or MTX alone Use of any anti-TNF (ETA, INF, and ADA) alone showed a slightly increased risk An approximately 2-fold HR for development of NMSC was found among pts with RA using both MTX and any TNF inhibitor (HR 1.97, *P* = 0.001)	NA	**Overall Attrition Rate, %:** After initial assessment, ~ 8% of pts decline to participate each yr **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Choy et al., 2008[25] **Country and setting** England/Wales multicenter **Source of funding** Medical Research Council, UK **Research objective** Test hypothesis that combining MTX with glucocorticoids and/or ciclosporin in early RA reducesproportion of pts developing new erosions within 2 yrs **Study design** Controlled Trials **Overall N** 467 **Duration of study** 2 yrs **Quality rating** Good	**Inclusion Criteria** • Early RA • Active RA by ACR criteria of less than 24 mos with three offollowing: >3 swollen joints, >6 tender joints, >45 min morning stiffness • ESR >28 mm/h, informed consent and aged >18 years. **Exclusion Criteria** • Other inflammatory arthropathies (e.g., psoriatic arthritis) • Current oral glucocorticoids • Serious medical disorders (e.g., hepatic or cardiac failure) • Women of child-bearing potential without adequate contraceptive protection • Contraindications for trial drugs	**Interventions, dose** D1: MTX: open-label MTX 7.5 mg weekly, increasing incrementally to target dose of 15 mg/week D2: MTX: open-label MTX 7.5 mg weekly, increasing incrementally to target dose of 15 mg/week Ciclosporin: started 3 mos after MTX, initial dose 100 mg/day, increased gradually to target dose of 3 mg/kg daily D3: PNL: step-down PNL started with MTX, 60 mg/day initially, reduced to 7.5 mg at 6 weeks, 7.5 mg daily from 6 to 28 weeks, stopped by 34 weeks MTX: open-label MTX starting 7.5 mg weekly, increasing incrementally to target dose of 15 mg/week D4: PNL: same as in arm 3 MTX: same as in other arms	**Mean disease duration, years** D1: 2.7 mos (3.8) D2: 4.2 (5.7) D3: 5.1 (5.8) D4: 3.9 (5.2) **Patients with early RA, three years or less, %** D1: 100 D2: 100 D3: 100 D4: 100 **Treatment resistant, %** NR **Tender Joint Count, mean (CI)** D1: NR D2: NR D3: NR D4: NR Overall: 11.8 (11.1 - 12.5) **Swollen Joint Count, mean (CI)** D1: NR D2: NR D3: NR D4: NR Overall: 9.9 (9.3 - 10.4) **Corticosteroid use, %** NR **DMARD use, %** D1: 12 D2: 14 D3: 14 D4: 16 Overall: 14 **MTX naïve, %**	**ACR mean difference/ absolute difference** NR **HAQ, mean change, at 2 years (SD)** D1: -0.29 (0.07) D2: -0.20 (0.06) D3: -0.28 (0.07) D4: -0.50 (0.06) Overall: NR/ *P* = 0.02/*P* = 0.35/*P* = 0.01 **DAS, mean change, at 2 years (SE)** D1: -1.42 (0.17) D2: -1.34 (0.15) D3: -1.37 (0.15) D4: -1.67 (0.15) Overall: NR/*P* = 0.19/ *P* = 0.13/*P* = 0.06 **SF-36, mean change, at 2 years (SE)** D1: 5.8 (1.0) D2: 3.9 (1.1) D3: 3.5 (1.0) D4: 8.0 (1.2) Overall: NR/ *P* = 0.22/*P* = 0.46/*P* = 0.001 **Radiographic measures at 2 years** Cases with new erosions (primary outcome), %: D1: 34 (29) D2: 19 (17) D3: 19 (16) D4: 15 (13) Mean change in Larsen score (SE):	**Overall** Overall attrition/withdrawal, n: D1: 49 D2: 62 D3: 54 D4: 55 Overall: 220 Withdrawals due to adverse events, n: D1: 8 D2: 9 D3: 14 D4: 23 Overall: 71 Withdrawals due to lack of efficacy, n: D1: 13 D2: 8 D3: 10 D4: 7 Overall: 71 Other attrition: • n's for various arms reported as "exclusively withdrew for toxicity and lack of effect", but n: 71 totals for each reported intext. Withdrawals from toxicity: D1: 12 D2: 21 D3: 22 D4: 33 Withdrawals lack of effect: D1:19 D2: 17 D3: 13 D4: 15

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Cyclosporin: same as in arm 2 **Number in group** D1: 117 D2: 119 D3: 115 D4: 116 Overall: 467 **Mean age, years (SD)** D1: 54 D2: 53 D3: 54 D4: 55 Overall: NR **Sex, % female** D1: 67 D2: 65 D3: 66 D4: 67 Overall: 70 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	NR **Baseline mean DAS28 score, mean (SD)** D1: 5.8 (1.2) D2: 5.9 (1.3) D3: 5.8 (1.4) D4: 5.6 (1.3) **Required treatment for latent TB** NR **Erosive changes on X-ray, %:** D1: 32 D2: 37 D3: 30 D4: 34 **Median Larsen score (IQR):** D1: 7 (3, 15) D2: 8 (3, 23) D3: 6 (2, 20) D4: 5 (2, 14) **HAQ score, mean (SD):** D1: 1.5 (0.7) D2: 1.7 (0.7) D3: 1.6 (0.7) D4: 1.6 (0.7) **SF-36 PCS, median (IQR):** D1: 30 (9) D2: 29 (8) D3: 30 (10) D4: 30 (9)	D1: 7.41 (0.99) D2: 4.53 (0.88) D3: 4.70 (0.69) D4: 2.99 (0.51) Overall: 95% CI: NR (0.36, 0.96), *P* = 0.03/ (0.33,0.88), *P* = 0.01, *P* = 0.32/ (5.47,9.33), *P* = 0.003, *P* = 0.008, *P* = 0.45 **Quality of life scales, mean difference/absolute difference** NR	NNH for any adverse event leading to withdrawal was 20 (95% CI 8, 1280) with added ciclosporin and 14 (95% CI 6, 65) with added PNL. Estimated NNH for triple therapy, based only on data from patients receiving this therapy was 6 (95% CI 3,23). Overall adverse events reported, n: D1: 21 D2: 18 D3: 19 D4: 23 Overall: 81 **Serious adverse events** Death, n: D1: 1 D2: 1 D3: 1 D4: 2 Overall: 5 Myocardial infarctions, angina, strokes, n: D1: 1 D2: 2 D3: 2 D4: 4 Overall: 9 Hepatotoxicity/elevated liver enzymes n: D1: 5 D2: 23 D3: 4 D4: 35 Overall: 67

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Malignancies, n D1: 5 D2: 2 D3: 0 D4: 1 Overall: 8 **Respiratory events** Tuberculosis: NR Pneumonia n: D1: NR D2: NR D3: NR D4: NR Overall: 3 Upper respiratory infection, n: D1: 54 D2: 51 D3: 49 D4: 55 Overall: NR **Other infections** Upper GI, n: D1: 1 D2: 2 D3: 0 D4: 1 Overall: 4 **GI** Nausea or vomiting, n: D1: 15 D2: 31 D3: 20 D4: 10 Overall: 76 Abdominal pain, n: D1: 7 D2: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D3: 9 D4: 7 Overall: 26 GI bleed or ulcer, n: D1: 5 D2: 16 D3: 4 D4: 14 Overall: 39 **Other** Headache, n: D1: 6 D2: 17 D3: 10 D4: 15 Overall: 48 Dizziness, n: D1: 4 D2: 14 D3: 6 D4: 5 Overall: 29 Diarrhea , n: D1: 5 D2: 10 D3: 10 D4: 3 Overall: 28 Paraesthesia, n: D1: 3 D2: 5 D3: 8 D4: 11 Overall: 27 Cough, n: D1: 7 D2: 5 D3: 11

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D4: 4 Overall: 27 Elevated blood pressure, n: D1: 1 D2: 11 D3: 8 D4: 17 Overall: 37

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Chung, 2003[26] **Country, Setting:** US, University clinics (32 centers) **Funding:** Centocor **Research Objective:** To assess effectiveness and safety of INF in pts with moderate to severe congestive heart failure **Study Design:** RCT **Overall N:** 150 **Study Duration:** 28 wks	**Inclusion Criteria:** • Age: 18+ • Stable New York Heart Association (NYHA) class III or IV heart failure **Exclusion Criteria:** • Prior txt with txt within 3 mos of INF or other therapeutic agents that could interfere with actions of TNF (eg, ETA, pentoxifylline, thalidomide, or D2E7) • History of TB: had latent TB or had had TB within 3 yrs • NSAID other than aspirin; experienced a serious infection within 2 mos • Documented HIV infection	**Interventions, dose:** D1: placebo D2: INF 5mg/kg D3: INF 10mg/kg **N:** D1: 49 D2: 50 D3: 51 **Mean age, yrs:** D1: 60 D2: 62 D3: 62 **Sex, % female:** D1: 24 D2: 14 D3: 16 **Race, % white:** D1: 88 D2: 88 D3: 84	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% confidence interval 1.01 to 7.97; nominal *P* = 0.043 using log-rank test);Pts in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than pts in the placebo or 5 mg/kg INF groups	Overall: D1: 83.3 D2: 92.2 D3: 84 SAEs: D1: 29.2 D2: 23.5 D3: 44 Serious Infections: D1: 2.1 D2: 5.9 D3: 8 Dizziness: D1: 4.2 D2: 31.4 D3: 20	**Overall Attrition Rate, %:** NR **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Cohen et al., 2006, Trial[27] ; Keystone et al. , 2008[28]; Keystone et al., 2009[29] REFLEX **Country and setting** Mulitnational, multicenter **Source of funding** Hoffman-La Roche, Biogen Idee, and Genentech NIH grant **Research objective** Determine efficacy and safety of tx with RIT + MTX in pts with inadequate responses to anti-tumor necrosis factor therapies **Study design** Controlled Trials **Overall N** 520 517 received treatment and were analyzed as part of "safety population." 499 were analyzed as ITT population. (3 never received treatment, some	**Inclusion Criteria** • Treatment resistant • Had RA for at least 6 mos • Had active disease (8 or more tender joints, 8 or more swollen joints, a CRP level of 1.5 or more, or an erythrocyte sedimentation rate of 28 mm/hour or greater, and radiographic evidence of at least 1 joint with a definite erosion attributable to RA) • Had to be taking MTX (10 - 25 mg/week) for at least 12 weeks prior to screening with last 4 weeks at stable dose • Experienced an inadequate response to previous or current treatment with anti-TNF agents inflixumab,	**Interventions, dose** D1: • MethylPNL: 100 mg, 30 minutes before each infusion • PREDoral: 60 mg on days 2 - 7, 30 mg on days 8 – 14 • MTX: 10 - 25 mg/week orally or parenterally • Placebo • Folate: 5 or more mg/week D2: • MethylPNL: 100 mg, 30 minutes before each infusion • PRED oral: 60 mg on days 2 - 7, 30 mg on days 8 – 14 • MTX: 10 - 25 mg/week orally or parenterally • RIT: 2 infusions of 1,000 mg each • Folate: 5 or more mg/week **Number in group** D1: 201 D2: 298 **Mean age, years (SD)** D1: 52.8 (12.6) D2: 52.2 (12.2) Based on safety population **Sex, % female** D1: 81	**Mean disease duration, years** Note: These data are based on safety population, n: D1: 11.7 (7.7) D2: 12.1 (8.3) Overall: 517 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 **Tender Joint Count, mean, (SD)** 68 joints assessed D1: 33.0 (15.6) D2: 33.9 (15.1) **Swollen Joint Count, mean (SD)** 66 joints assessed D1: 22.9 (12.7) D2: 23.4 (11.8) **Corticosteroid use, n (%)** D1: 127 (61) D2: 200 (65) **Previous DMARD use, n (%)** D1: 2.4 (1.8) D2: 2.6 (1.8) **MTX naïve, %** NR **Baseline DAS28 score, mean (SD)** D1: 6.8 (1.0) D2: 6.9 (1.0)	**ACR** ACR 20: D1: 18 D2: 51 *P* = 0.0001 ACR 50: D1: 5 D2: 27 *P* = 0.0001 ACR 70: D1: 1 D2: 12 *P* = 0.0001 **HAQ** NR **DAS** D1: -0.4 D2: -1.9 *P* = 0.0001 **SF-36** NR **Radiographic measures** D1: N: 177 D2: N: 268 Total Genant-modified Sharp radiographic score, mean change from baseline (SD): D1: 1.2 (3.3) D2: 0.6 (1.9) No worsening of erosions, n (%): D1: 106 (60%) D2: 176 (66%) **Quality of life scales** NR	**Attrition/withdrawal** Overall, n: D1: 97 D2: 57 Withdrawals due to adverse events, n: D1: 2 D2: 8 Withdrawals due to lack of efficacy, n: Required rescue therapy D1: 80 D2: 1 Adherent/compliant, n: D1: 112 D2: 254 **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR **Other infections** NR **GI** NR **Other AEs** • For safety population (N: 517) • Any adverse event, n: 183 (88) • Severe adverse event, n: 49 (23) • Related adverse event, n: 77 (37)

were treated prior to randomization, and others were participants at a center where blinding of the assessor was potentially compromised). **Duration of study** Results presented are at 24 weeks REFLEX trial is a 2-year trial. **Quality rating** Fair	adalimuman, or ETN • Were intolerant to at least 1 administration of these agents. **Exclusion Criteria** • History of rheumatic autoimmune disease other than RA (except secondary Sjorgen's syndrome) • Significant systematic involvement secondary to RA • ACR functional class IV disease	D2: 81 Based on safety population **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Baseline characteristics are reported for safety population, N: 517 - Placebo group, N: 209) HAQ-D, mean score (SD): D1: 1.9 (0.5) D2: 1.9 (0.6) Total Genant-modified Sharp radiographic score D1: 47.9 (36.0) D2: 48.3 (34.9) Previous anti-TNF agents taken (no (%) of patients): Inflixumab D1: 169 (81) D2: 219 (71) ADA D1: 38 (18) D2: 71 (23) ETN D1: 104 (50) D2: 168 (55) Previous anti-TNF agents taken (mean (±SD)) D1: 1.5 (0.67) D2: 1.5 (0.67) Inadequate efficacy of anti-TNF agents (%) D1: 90 D2: 92	**EULAR** Moderate Response, %: D1: 20 D2: 50 Good Response, %: D1: 2 D2: 15 Low disease, %: D1: 2 D2: 15 Remission, %: D1: 0 D2: 9	• Serious adverse event, n: 21 (10) • Death, n: 0 (0)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006[30] **Country, Setting:** Europe, multicenter **Funding:** Wyeth **Research Objective:** To compare efficacy and safety of ETA and SSZ, alone and in combination, in pts with active RA despite SSZ txt **Study Design:** RCT **Overall N:** 260 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • Diagnosed according to ACR criteria; • Functional class of: I-III • Previous use of DMARDs: 2 to 3g SSZ/d for ≥ 4, w/o toxicity • Duration of condition < 20 yrs • Stable doses of oral corticosteroids (10 mg/d of PRE or equivalent), one NSAID, simple analgesics with no anti-inflammatory action or daily doses of aspirin (300 mg) **Exclusion Criteria:** • Prior txt with: (1) ETA or other TNF antagonists or (2) received a DMARD other than SSZ within 3 mos. Or any biologic or cyclophosphamide within 6 mos, corticosteroids within 4 wks • Presence of relevant comorbidity, including active infections	**Interventions, dose:** D1: SSZ (2,2.5, or 3 g /d) + placebo D2: ETA (25 mg SC twice wkly) + placebo D3: ETA (25 mg SC twice wkly) + SSZ (2,2.5, or 3 g /d) **N:** D1: 50 D2: 103 D3: 101 Overall: 254 **Mean age, yrs:** D1: 53.3 D2: 51.3 D3: 50.6 Overall: 51.4 **Sex, % female:** D1: 82.0 D2: 78.6 D3: 80.2 Overall: 79.9 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 5.6 (sd 4.4) D2: 7.1 (sd 5.2) D3: 6.5 (sd 5.1) **TJC, mean:** D1: 14.0 D2: 14.7 D3: 14.1 **SJC, mean:** D1: 11.1 D2: 10.1 D3: 10.4 **DMARD use, %:** D1: 58.0 D2: 69.9 D3: 58.4 **Corticosteroid use, %** D1: 40.0 D2: 59.2 D3: 44.6 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.0 D2: 5.1 D3: 5.2	**At 24 weeks** **ACR20, %:** D1: 28.0 D2: 73.8 D3: 74.0 (*P* < 0.01) **ACR50, %:** D1: 14.0 D2: 46.6 D3: 52.0 (*P* < 0.01) **ACR70, %:** D1: 2.0 D2: 21.4 D3: 25.0 (*P* < 0.01) In groups receiving ETA, significant differences in ACR core components were observed by wk 2 compared with those receiving SSZ alone (*P* < 0.01) **DAS improvement, %:** D1: 19.6 D2: 48.2 D3: 49.7 (*P* < 0.01) **Mean HAQ improvement, %:** D1: 9.2 D2: 35.3 D3: 40.2 (*P* < 0.01) **Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical	**Infections:** D1: 13 D2: 47 D3: 31 **Infusion or injection reaction:** D1: 3 D2: 38 D3: 21 **Abdominal Pain:** D1: 0 D2: 7 D3: 8 **Headache:** D1: 4 D2: 5 D3: 15 **Nausea:** D1: 3 D2: 3 D3: 12 **URTI:** D1: 5 D2: 10 D3: 11	**Overall Attrition Rate, %:** 13 **ITT Analysis:** Yes **Quality Rating:** Fair

	advantage to use of ETA in combination with SSZ

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Combe et al., 2009[31]; add[30] from old report **Country and setting** Multinational, multicenter **Source of funding** Wyeth Research **Research objective** Determine efficacy and safety of ETN and ETN + SSZ versus SSZ **Study design** Controlled Trials **Overall N** 260 **Duration of study** 2 years **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant SSZ • 18 years or older • Disease duration of 20 years or less with active adult onset of RA • Previous use of DMARDs: 2 to 3g SSZ/d for ≥ 4, w/o toxicity • Stable doses of oral corticosteroids (10 mg/d of PRE or equivalent), one NSAID, simple analgesics with no anti-inflammatory action or daily doses of aspirin (300 mg) • Received stable dose of SFS for four mos or more before screening • Functional class of: I-III **Exclusion Criteria** • Prior txt with: (1) ETA or other TNF antagonists	**Interventions, dose** D1: • ETN: 25mg by sub-cutaneous injection twice daily • Placebo • Other: Patients in ETN discontinued SSZ D2: • SSZ: 2g, 2.5g or 3g daily • Placebo D3: • SSZ: 25mg by subcutaneous injection twice daily • ETN: 2g, 2.5g or 3g daily **Number in group** D1: 103 D2: 50 D3: 101 **Interventions, dose:** D1: SSZ (2,2.5, or 3 g /d) + placebo D2: ETA (25 mg SC twice wkly) + placebo D3: ETA (25 mg SC twice wkly) + SSZ (2,2.5, or 3 g /d) **N:** D1: 50 D2: 103 D3: 101 Overall: 254 **Mean age, yrs:**	**Mean disease duration, years** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** NR **Swollen Joint Count, mean** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score** NR **Required treatment for latent TB** NR	**ACR** At Week 2 ACR 20: D1: 67 D2: 77 D3: 34 *P* = 0.01 (ETA vs. SSZ) At Week 8 ACR 50: *P* = 0.01 At Week 12 ACR 70: *P* = 0.01 **HAQ achieved, by % patients** D1: 76 D2: 78 D3: 40 *P* = 0.01 (combination or ETN) **DAS mean change at 2 years** D1: 2.3 D2: -2.7 D3: -0.6 *P* = 0.05 for ETA vs. SFS **DAS, %: 2.4 at 2 years** D1: 45.6 D2: 4.0 D3: 57.0 DAS2.8 vs. 4.5 vs. 2.5 *P* = 0.01 **SF-36** NR **Radiographic measures, mean difference/absolute difference**	**Attrition/withdrawal** Overall, n: D1: 38 D2: 34 D3: 24 Overall: 96 Withdrawals due to adverse events, n (%): D1: 8 D2: 9 D3: 10 Overall: NR Withdrawals due to lack of efficacy, n (%): D1: 52 D2: 6 D3: 6 *P* = 0.001 **Overall adverse events reported, n:** D1: 166 D2: 53 D3: 140 Overall: 359 **Serious adverse events** Death, n: Overall: 2 23 patients receiving combination, 27 receiving ETN and 2 receiving SSZ had one or more serious adverse event (SAE). Non-infectious SAE were significantly greater in patients receiving ETN (20.8% for the combination and 20.4% for ETN alone)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	or (2) received a DMARD other than SSZ within 3 mos. Or any biologic or cyclophosphamide within 6 mos, corticosteroids within 4 wks • Presence of relevant comorbidity, including active infections	D1: 53.3 D2: 51.3 D3: 50.6 Overall: 51.4 **Sex, % female:** D1: 82.0 D2: 78.6 D3: 80.2 Overall: 79.9 . **Race, % white** Population described as predominantly white. **Race, % black** NR **Ethnicity, Latino** NR		NR **Quality of life scales** NR	compared with 4% for patients receiving SSZ (*P* = 0.01). **Malignancies** Lymphoma or leukemia, n: D1: 1 D2: 0 D3: 0 Overall: 1 Skin cancer (basal cell or squamous cell), n: D1: 1 D2: 0 D3: 0 Overall: 1 **Respiratory events** Tuberculosis: NR Pneumonitis, n: D1: 1 D2: 0 D3: 0 Overall: 1 Pharyngitis/laryngitis, n: D1: 24 D2: 2 D3: 10 *P* = 0.01 (combination vs. SFS) Sinusitis, n: D1: 12 D2: 0 D3: 3 **Other infections** Any treatment-emergent infection, n: D1: 76 D2: 21

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D3: 60 Bronchitis D1: 21 D2: 4 D3: 12 Gingival/dental infection: D1: 7 D2: 2 D3: 12 **GI** Nausea or vomiting, n: D1: 7 D2: 5 D3: 19 Overall: 31 Abdominal pain, n: D1: 14 D2: 1 D3: 12 Overall: 27 Dyspepsia, n: D1: 14 D2: 2 D3: 12 Overall: 28 Diarrhea, n: D1: 11 D2: 0 D3: 6 Overall: 17 **Other** Infusion/injection site reactions, n: D1: 34 D2: 2 D3: 2 Overall: 57

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Hemorrhage: D1: 9 D2: 3 D3: 14 Overall: 26 Skin rashes/miscellaneous skin infections, n: D1: 15/19 D2: 3/0 D3: 8/12 Overall: 31 Headache, n: D1: 11 D2: 4 D3: 25 Overall: 40 Back pain, n: D1: 9 D2: 5 D3: 20 Overall: 34 Parathesia , n: D1: 4 D2: 1 D3: 11 Overall: 16 Flu syndrome, n: D1: 18 D2: 2 D3: 12 Overall: 32 Leuccopenia, n: D1: 2 D2: 0 D3: 8 Overall: 10

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Curtis et al., 2007[32] **Country and setting** United States, Hospital and administrative claims data **Source of funding** Maryland Chapter of Arthritis Foundation, Agency for Healthcare Research and Quality and NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases **Research objective** Evaluate risk of serious bacterial infections associated with TNFα antagonists **Study design** Retrospective Cohort **Overall N** n: 5,326 (obtained and abstracted 187 records for analysis) **Duration of study** 67 months (May 1998 to December 2003), median follow up time 17 months; 3,894 person-years for RA patients	**Inclusion Criteria** • RA patients older than 18 years with 2 ICD9 codes for RA • Either received an infusion or filled a prescription for a TNFα antagonist or filled at least 3 prescriptions for MTX. **Exclusion Criteria** • Individuals with HIV, who had an organ transplant, diagnosed with a malignancy	**Interventions, Dose** D1: MTX, ETN, IFX, ADA, patients may have been using more than one biologic and/or other nonbiologic DMARDs or glucocorticoids in addition to a biologic D2: MTXOther (describe)patients may have been using other nonbiologic DMARDs or glucocorticoids in addition to MTX **Number in group** D1: 2393 D2: 2933 **Mean age (years)** D1: 50 D2: 55 *P* = 0.0001 **Sex, % female** D1: 73 D2: 73 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** D1: 100 (inferred) D2: NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: • Mean PRED equivalent dosage: None (referrent), 1,061 (44%) less than or equal to 5mg/day, 252	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** Overall attrition/withdrawal, n: D1: 17 records for individuals in exposed Dcould not be accessed, therefore they were not abstracted. number of exposed out of total number of records (217) identified to be abstracted is not given, so a percentage cannot be determined Withdrawals due to adverse events, n: NR Withdrawals due to lack of efficacy, n: NR Adherent/compliant, n: NR **Overall adverse events reported, n:** D1: 86 (total infections) D2: 82 (total infections) **Serious adverse events** Death, n: NR Cardiovascular events (specify), n: NR Hepatotoxicity/elevated liver enzymes, n: NR **Malignancies** Lymphoma or leukemia, n: NR Skin cancer (basal cell or squamous cell), n: NR Other cancer (specify), n: NR **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 25 D2: 23

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
receving TNFα antagonists and 4,846 person-years for RA patients receiving MTX. **Quality rating** Fair			(10%) • 5 - 10 mg/day, 348 (15%) • > 10 mg/day, 732 (31%) • Selected medical conditions and drug usage (only that those there were different between groups are abstracted, groups are similar with respect to other conditions investigated): • Severe RA (defined by claims for rheumatoid lung disease, rheumatoid carditis, inflammatory eye disease, or Felty's symdrome), 76 (3%) • Joint surgery or deformity, 64 (3%) • Coronary artery disease (inlcuding CABG, angioplasty), 285 (12%) • Number of comorbidities, • 0.7 ±1 • Anti TNFα use: IFX 792 (33%) • ETN 1,201 (50%) • ADA 118 (5%) • ≥ 1 anti TNFα 282 (12%) • MTX use 1,677 (70%); D2: • Mean PRED equivalent dosage: None (referrent), 1,290 (44%) less than or equal to 5mg/day, 294 (10%) • 5 - 10 mg/day, 418 (14%) • > 10 mg/day, 931 (32%) • Selected medical conditions (only those that		Upper respiratory infection, n: NR **Other infections** Urinary tract infection, n: kidney/UTI D1: 8 D2: 10 Other infections (specify), n: NR **GI** Nausea or vomiting, n:NR Abdominal pain, n: NR GI bleed or ulcer, n: NR Bowel obstruction, n: NR Other GI symptoms (specify), n: NR **Other AEs, n:** Cellulitis/soft tissue, n: D1: 23 D2: 17 Bacteremia/sepsis, n: D1: 7 D2: 8 Postoperative, n: D1: 7 D2: 5 Device associated, n: D1: 6 D2: 4 Septic Arthritis: D1: 4 D2: 4 Gastroenteritis: D1: 1 D2: 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			were different between groups are abstracted, groups are similar with respect to other conditions investigated): Severe RA (defined by claims for rheumatoid lung disease, rheumatoid carditis, inflammatory eye disease, or Felty's symdrome), 59 (2%) *(P* = 0.01) • Joint surgery or deformity, 37 (1%) *(P* = 0.001) • Coronary artery disease (inlcuding CABG, angioplasty), 43 (15%) *(P* <0.01) • Number of comorbidities, 0.9 ±1.2 *(P* = 0.0001). MTX use 2,933 (100%) *(P* = 0.0001)		Abdominal abscess: D1: 1 D2: 2 Osteomyelitis exposed: D1: 1 D2: 3 Bacterial sinusitis: D1: 3 D2: 0 Diverticulitis: D1: 0 D2: 0 Summary results: • 65 infections out of 2,393 exposed individuals (2.7%) • 58 infections among 2,933 unexposed individuals (2.0%) • In first 6 months after index date, there were 32 infections in exposed D(incidence of 2.9 infections per 100 person - years) compared with 19 infections in unexposed D(incidence rate of 1.4 infections per 100 person-years) • After mulitvariate adjustment, hazard ratios for "risk of hospitilization with a bacterial infection" for those receiving TNF-alpha antagonists was 1.94 (95% CI, 1.32 - 2.83) • Factors Associated hospitalization with a "definite" bacterial infection

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					(hazard ratio and 95% CI): Anti TNFα treatment crude HR: 1.39 (0.97 - 1.98), Adjusted HR: 1.94 (1.32 - 2.83) • Age (5 year increments)Crude HR: 1.22 (1.14 - 1.31), Adjusted HR: 1.14 (1.03 - 1.27) • Insurance Type, Medicare, Age: 65 years Crude HR: 2.82 (1.42 - 5.61), Adjusted HR: 2.88 (1.41 - 5.86), Age > 65 years Crude HR: 2.83 (1.89 - 4.22), Adjusted HR 1.88 (1.01 - 3.32) • Number of Face to Face physician visits Crude HR: 1.07 (1.05 - 1.10), Adjusted HR: 1.04 (1.01 - 1.07) • Prior Infection Crude HR: 1.98 (1.19 - 3.31), Adjusted HR: 1.46 (0.85 - 2.51) • Chronic Obstructive Pulmonary Disease Crude HR: 2.68 (1.71 - 4.18) • Adjusted HR: 1.90 (1.19 - 3.04) • Diabetes mellitus Crude HR: 2.60 (1.66 - 4.06), Adjusted HR: 1.75 (1.10 - 2.78) • Kidney Disease crude HR: 6.84 (3.01 - 15.5), Adjusted HR: 3.23 (1.35 - 7.73 • Decubitus Ulcer crude

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					HR: 6.35 (3.22 - 12.52), Adjusted HR: 3.05 (1.50 - 6.19) • Number of comorbidities crude HR: 1.50 (1.31 - 1.68), Adjusted HR: NS • Mean PRED equivalent doasage > 10 mg per day Crude HR: 1.92 (1.26 - 2.91), Adjusted HR 1.85 (1.21 - 2.85)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Curtis et al., 2007[33]; subanalysis of Curtis et al., 2007[32] **Country and setting** NR **Source of funding** Supported by Maryland Chapter of Arthritis Foundation, Agency for Healthcare Research and Quality (grant HS-10389), NIH (grant K24-AR-052361-01 from National Institute of Arthritis and Musculoskeletal and Skin Diseases and grant T32-AR **Research objective** Evaluate comparative effects of antibody-based and non-antibody-based TNFα antagonists on risk of hospitalization with a bacterial infection **Study design** Cohort Study **Overall N** 5195 **Duration of study** Greater than 6	**Inclusion Criteria** • At least 2 International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for RA (714.x, excluding 714.3), receiving either IFX, ADA, ETN or MTX without a TNFα antagonist • All patients exposed to TNFα antagonist were new users, defined as having at least 6 months of nonexposure to these drugs prior to first filled prescription. **Exclusion Criteria** • Patients who were exposed to multiple TNFα antagonists during same window of risk were excluded	**Interventions, Dose** D1: IFX: dose NR D2: ETN: dose NR D3: MTX **Number in group** D1: 850 D2: 1412 D3: 2933 Overall: 5195 **Mean age (years)** D1: 47.8 D2: 53.4 D3: 54.9 **Sex, % female** NR **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: Physician encounters in 6 months prior to therapy: 8.2 D2: Physician encounters in 6 months prior to therapy: 7.0	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** Overall attrition/withdrawal, n: NR Withdrawals due to adverse events, n: NR Withdrawals due to lack of efficacy, n: NR Adherent/compliant, n: NR Attrition information is not reported as they utilized person-years in their analyses. INF: 372 person-yrs, ETN: 602 person-yrs, MTX: 1197 person-yrs. **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** D1: Bacterial Infection:: 6 months, n: 16, IR/100 person-yrs: 4.30, 95% CI (2.46 - 6.98), adjusted IRR: 2.40, 95% CI (1.23-4.68); > 6 months, n: 10, IR/100 person-yrs: 1.61, 95% CI (0.77-2.97), adjusted IRR: 1.14, 95% CI (0.55-2.24); D2: Bacterial Infection:: 6

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
months (specific duration not provided); Person-years: IFX: 372, ETN: 602, MTX: 1197 **Quality rating** Fair	(within 90 days of most recent filled prescription for drug of interest).		D3: Physician encounters in 6 months prior to therapy: 6.9 Overall: NR		months, n: 12, IR/100 person-yrs: 1.99, 95% CI (1.03-3.48), adjusted IRR: 1.61, 95% CI (0.75-3.47); > 6 months, n: 19, IR/100 person-yrs: 1.34, 95% CI (0.81-2.10), adjusted IRR: 1.37, 95% CI (0.74-2.53) D3: Bacterial Infection:: 6 months, n: 20, IR/100 person-yrs: 1.67, 95% CI (1.02-2.58), adjusted IRR: referent; > 6 months, n: 34, IR/100 person-yrs: 1.55, 95% CI (1.11-2.22), adjusted IRR: referent Overall: Bacterial Infection:: 6 months, n: 48, > 6 months, n: 63, IR/100 person-yrs: NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Curtis et al., 2007[34] Country and setting USA Source of funding FDA CBER Award #223-02-1420 Task Order #1, Maryland chapter of Arthritis Foundation, grant HS10389 from AHRQ, K24 AR052361-01 from National Institute of Arthritis and Musculoskeletal and Skin Diseases, and T32 AR47512-03 from NIH Research objective Investigate a possible association between TNF-antagonist use and incident heart failure Study design Observational Overall N 2121 with RA Duration of study Medical and phDacy administrative claims from January 1998 to December 2002 (5 years), with medical record review for	Inclusion Criteria • At least two ICD9-CM diagnosis codes for RA (714.X) or CD (555.X) during study period, received an infusion or filled a prescription for a TNF-antagonist or filled at least three prescriptions for one of several selected immunosuppressive drugs. Exclusion Criteria • HIV, organ transplantation, or malignancy in 6 mos prior to index date	Interventions, Dose D1: IFX: dose NR D2: ETN: dose NR D3: Unexposed arm had to fill at least three prescriptions for MTX. Number in group D1: 330 D2: 808 D3: 983 Mean age (years) D1: 40 D2: 38 D3: 39 Sex, % female D1: 70 D2: 75 D3: 75 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean (SD) NR SJC, mean (SD) NR Corticosteroid use, % D1: 53 D2: 45 D3: 42 DMARD use, % D1: non anti-TNF alpha DMARD use 83% D2: non anti-TNF alpha DMARD use 85% D3: non anti-TNF alpha DMARD use 100% MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) D1:	ACR mean difference/ absolute difference (CI/SD/P Value) ACR 20: NR ACR 50: NR ACR 70: NR HAQ, mean difference/ absolute difference NR DAS, mean difference/absolute difference NR SF-36, mean difference/absolute difference NR Radiographic measures, mean difference/absolute difference NR Quality of life scales, mean difference/absolute difference NR Others, (please name); mean difference/absolute difference NR	Serious adverse events Cardiovascular events (specify), n: D1: Definite and possible heart failure; N = 1 (in IFX group) D2: Definite and possible heart failure; N = 4 (in ETN group) D3: Definite and possible heart failure; N = 1 (in unexposed group) Any other AEs: • Exposed group: patients receiving TNF-alpha antagonists • Unexposed Group: patients not receiving TNF-alpha antagonists, these patients did receive MTX, 6-mercaptopurine, azathioprine, or PRED. • Cumulative incidence of HF among exposed patients: 4.4 cases per 1000 persons • Cumulative incidence of HF among unexposed patients: 1.0 case per 1000 persons in unexposed group. • RA exposed compared with RA unexposed, RR = 4.3 (ns) • RA exposed (ETN) compared to RA unexposed, RR = 4.9 (ns) • RA exposed (IFX) compared to RA unexposed, RR = 3.0 (ns)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
identified cases Quality rating Fair			• Exposed D(IFX) • N = 330 • Age 40 ± 8 years • Women N = 230 (70%) • Duration of health plan enrollment 15 ± 10 mos • Number of physician visits 23 ± 23 • Proportion of patients hospitalized N = 36 (11%) • Comorbidities in 6 mos prior to index date: extra-articlar disease, N = 27(8%) • Joint deformity, N = 16 (5%) • Joint surgery, N = 20 (6%) • Coronary artery disease, N = 3 (1%) • Medication use in 6 mos prior to index date(mean ± SD of infusions or filled prescriptions): MTX, 9 ± 11 • Glucocorticoid use, N = 176 (53%) • NSAID use, N = 266 (81%) • Non anti-TNF-alpha DMARD use, N = 274 (83%) • As above, or glucocorticoids, N = 309 (94%) D2: • Exposed Drug (ETN) • N = 808 • Age 38 ± 10 years • Women N = 608 (75%) • Duration of health plan enrollment 21 ± 16 mos • Number of physician visits		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			24 ± 32 • Proportion of patients hospitalized N = 95 (12%) • Comorbidities in 6 mos prior to index date: extra-articlar disease, N = 36(4%) • Joint deformity, N = 39 (5%) • Joint surgery, N = 68 (7%) • Coronary artery disease, N = 12 (1%) • Medication use in 6 mos prior to index date (mean ± SD of infusions or filled prescriptions): MTX, 5 ± 10 • Glucocorticoid use, N = 365 (45%) • NSAID use, N = 711 (88%) • Non anti-TNF-alpha DMARD use, N = 684 (85%) • As above, or glucocorticoids, N = 730 (90%) D3: • Unexposed Group • N = 983 • Age 39 ± 10 years • Women N = 742 (75%) • Duration of health plan enrollment 17 ± 14 mos *(P* < 0.001) • Number of physician visits 19 ± 26 *(P* < 0.0001) • Proportion of patients hospitalized N = 59 (6%) *(P* < 0.0001) • Comorbidities in 6 mos prior to index date: extra-		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			articlar disease, N = 27(3%)(*P* < 0.01) • Joint deformity, N = 27 (3%) (*P* = < 0.05) • Joint surgery, N = 31 (3%) (*P* = < 0.0001) • Coronary artery disease, N = 6 (1%) (NS) • Medication use in 6 mos prior to index date (mean + or - SD of infusions or filled prescriptions): MTX, 13 ± 13 (*P* < 0.01) • Glucocorticoid use, N = 412 (42%) (*P* < 0.01) • NSAID use, N = 874 (89%) (*P* < 0.05) • Non anti-TNF-alpha DMARD use, N = 983 (100%)(*P* < 0.001) • As above, or glucocorticoids, N = 983 (100%) (*P* < 0.001) - Note: P-values compare pooled IFX and ETN RA patients with unexposed RA patients.		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: De Bandt et al., 2005[35] **Country, Setting:** France, clinical reports **Funding:** NR **Research Objective:** To report cases and incidence of anti-TNF-induced SLE from a French national survey **Study Design:** Case series **Overall N:** 10,700 (22 cases) **Study Duration:** varied	**Inclusion Criteria:** • Pts in France given INF or ETA; cases of SLE-like illness during anti-TNF txt were sought; retrospective survey of French rheumatologists and internists between June and October 2003 • All French hospital centres prescribing anti-TNF txts (ETA and INF at that time) were surveyed **Exclusion Criteria:** • Improper diagnosis of lupus	**Interventions, dose:** D1: Limited skin lupus **D2: Complete lupus** ETA: varied **INF: varied** **N:** D1: 10 **D2: 12** **Mean age, yrs:** D1: of RA onset 39 **D2: 36** **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **INF/ETA:** D1: 6 / 4 D2: 9 / 3	Incidence 15/7700: 0.19% with INF and 7/3800: 0.18% with ETA 32 initially reported, 10 were ruled out leaving 22 cases 10 pts only had anti-DNA antibodies and skin manifestations 1 could classify as 'limited skin lupus' or 'toxidermia' in a context of autoimmunity, and 12 pts had more complete drug-induced lupus with systemic manifestations	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable den Broeder et al., 2007[36] **Country and setting** The Netherlands, hospital **Source of funding** NR **Research objective** Identify risk factors for SSI in RA pts with special attention for anti-TNF tx **Study design** Observational **Overall N** 1219 **Duration of study** January 1997 (at Sint Maartenskliniek, January 2001; Radboud University Nijmegen Medical Centre, January 1997) through September 2004 **Quality rating** Fair: cohort baseline differences and number of patients between groups 1 and 2 decrease quality in strength of study	**Inclusion Criteria** • All RA patients that underwent elective orthopedic surgery between introduction of TNF inhibitors. **Exclusion Criteria** • Patients with no known follow up exceeding 1 year • Patients with another principal diagnosis • Patients with multiple operations who developed more than one SSI • Procedures where an infection was present at start of surgery.	**Interventions, Dose** D1: anti-TNF-naive patients (1) D2: stopped anti-TNF treatment (2A) D3: patients that continued anti-TNF treatment (2B) **Number in group** D1: 1023 D2: 104 D3: 92 Overall: 1219 **Mean age (years)** D1: 61 D2: 54 D3: 57 Overall: 60 **Sex, % female** D1: 77 D2: 75 D3: 82 Overall: 77 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 17 yrs (11) D2: 16 (9) D3: 17 (8) Overall: 17 (11) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean (SD)** NR **SJC, mean (SD)** NR **Corticosteroid use, %** D1: 30 D2: 40 D3: 42 Overall: 32 **DMARD use, %** D1: NR D2: NR D3: NR Overall: 16 **MTX naïve, %** D1: 0 D2: 0 D3: 0 Overall: 0 **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB**	**ACR mean difference/ absolute difference (CI/SD/P Value)** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value)** NR **DAS, mean difference/absolute difference (CI/SD/P Value)** NR **SF-36, mean difference/absolute difference (CI/SD/P Value)** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value)** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value)** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** • Seventeen cases in cohort 2 were excluded because documentation of anti-TNF treatment was incomplete (9 IFX, 5 ETN, 3 ADA), percentage of missing values was 3%. • Due to a logistical error, data on prior SSI/skin infections were missing for cohort 1 patients from Maartenskliniek. • For cohort 2, data were complete. Overall adverse events reported, n: D1: Total noninfectious complications: 115 D2: Total noninfectious complications:6 D3: Total noninfectious complications:13 Overall: Total noninfectious complications:134 **Serious adverse events** Death, n: D1: 4 D2: 0 D3: 0 Overall: 4 Cardiovascular events (specify), n: NR Hepatotoxicity/elevated liver enzymes, n: NR **Malignancies**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR **Other population characteristics, %, (CI/SD/P value)** D1: • Concomitant MTX (%): 34 • > 1 DMARD (%): 11 D2: • Concomitant MTX (%): 37 • > 1 DMARD (%): 54 D3: • Concomitant MTX (%): 38 • > 1 DMARD (%): 46		NR **Respiratory events** NR **Other infections** D1: Surgical site infections: 41 D2: Surgical site infections: 6 D3: Surgical site infections: 8 Overall: Surgical site infections: 55 (22 were backed by positive cultures) **GI** NR **Other** • Perioperative continuation of anti-TNF was not associated with a significant increase of SSI risk, according to entry model (OR, 1.56, 95% CI, 0.52-4.66) and when corrected for potential confounders (OR, 1.50, 95% CI, 0.43-5.2). • Wound dehiscence occurred more frequently in patients that continued anti-TNF compared to patients that temporarily discontinued anti-TNF treatment (OR, 11.2, 95% CI, 1.4-90). • Risk of wound dehiscence was, however, very low in patients that stopped anti-TNF treatment. • Compared with anti-TNF-naive patients OR for

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					wound dehiscence was lower but still significant (RR 2.4, 95% CI, 1.1-5.0).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dixon et al., 2006[37] **Country, Setting:** Britain Multicenter **Funding:** Schering Plouogh, Wyeth, Abbott, and Amgen all fund The British Society for Rheumatology Biologics Register (BSRBR) **Research Objective:** The rate of serious infection anti-TNF-pts compared with RA pts treated with traditional DMARDs **Study Design:** Prospective cohort study **Overall N:** 8,973 **Study Duration:** 11,220 PY	**Inclusion Criteria:** • ANTI-TNF cohort: diagnosed by physician w/ RA • Treated with ETA, INF, or ADA as first anti-TNF drug, at least 6 mos of followup by September 2005 • Comparison cohort: physician diagnosis of RA, active disease (guideline DAS28 >4.2), current txt with a DMARD, and no previous use of biologic drugs. • Comparison pts also completed at least 6 mos of followup by September 2005. **Exclusion Criteria:** • Anti-TNF cohort: pts who had been registered >6 mos after start of biologic therapy	**Interventions, dose:** D1: DMARD D2: All anti-TNF D3: ETA D4: INF **D5: ADA** **N:** D1: 1354 D2: 7664 D3: 3596 D4: 2878 D5: 1190 **Mean age, yrs:** D1: 60 D2: 56 D3: 56 D4: 56 D5: 57 **Sex, % female:** D1: 71 D2: 76 D3: 77 D4: 76 D5: 74 **Race, % white:** NR	Median disease duration, yrs: D1: 6 D2: 12 D3: 12 D4: 12 D5: 11 **TJC (median):** D1: 6 D2: 16 D3: 16 D4: 16 D5: 15 **SJC (median):** D1: 5 D2: 11 D3: 11 D4: 12 D5: 12 **DMARD use, %:** NR **Corticosteroid use, %:** D1: 22 D2: 47 D3: 47 D4: 48 D5: 44 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS mean:**	:In pts with active RA, anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD txt, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues	**Serious Infections**: • D1: N:56 (41 events/1000 PY) • D2: N:525 (53 events/1000 PY) **UTI:** • D1: N:3 (2.2 events/1000 PY) • D2: N:45 (4.6 events/1000 PY)	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: **Quality Rating:** Fair

D1: 5.1
D2: 6.6
D3: 6.6
D4: 6.6
D5: 6.6

Diabetes %:
D1: 5.5
D2: 5.4
D3: 6.0
D4: 4.6
D5: 5.5

COPD/asthma %:
D1: 20
D2: 13
D3: 14
D4: 12
D5: 13

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Dixon et al., 2006,[38] British Society for Rheumatoid Biologics Register **Country and setting** UK, hospitals/general practice **Source of funding** Financial support to BSRBR comes indirectly from following: UK companies marketing biologic agents in UK: Schering Plough, Wyeth Laboratories, Abbott Laboratories, and Amgen. The resources used to fund BSRBR are received under contract **Research objective** To compare rates of serious infection in RA patients treated with anti-TNF to those treated with traditional DMARDs **Study design** Observational **Overall N** 9018	**Inclusion Criteria** • Anti-TNF cohort: patients registered with BSRBR who had been diagnosed by a physician as having RA and who had been treated with ETN, IFX, or ADA as their first anti-TNF drug. • Patients had to have completed at least 6 mos of followup by September 2005 • Comparison cohort: biologic naive, a physician diagnosis of RA, current treatment with a DMARD. • Comparison patients also had to have completed at least 6 mos of followup by September 2005. **Exclusion Criteria** • In order to limit	**Interventions, Dose** D1: Other: NR (traditional DMARDs) D2: ETN: dosage and frequency NR IFX: dosage and frequency NR ADA: dosage and frequency NR **Number in group** D1: 1354 D2: 7664 Overall: 9018 **Mean age (years)** D1: 60 D2: 56 **Sex, % female** D1: 71 D2: 76 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 6 yrs (IQR = 1 - 15) D2: 12 yrs (IQR = 6 - 19) Overall: 100 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean (SD)** D1: median = 6 (IQR = 3 - 13) D2: median = 16 (IQR = 10 - 22) **SJC, mean (SD)** D1: median = 5, (IQR = 2 - 9) D2: median = 11 (IQR = 7 - 16) **Corticosteroid use, %** D1: 22 D2: 47 **DMARD use, %** D1: 100 D2: 100 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: 5.1 D2: 6.6 **Required treatment for latent TB** NR **Other population**	**ACR mean difference/ absolute difference (CI/SD/P Value)** ACR 20: ACR 50: ACR 70: **HAQ, mean difference/ absolute difference (CI/SD/P Value)** **DAS, mean difference/absolute difference (CI/SD/P Value)** **SF-36, mean difference/absolute difference (CI/SD/P Value)** **Radiographic measures, mean difference/absolute difference (CI/SD/P Value)** **Quality of life scales, mean difference/absolute difference (CI/SD/P Value)** **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Adverse events reported, n:** Urinary tract infection, n: D1: 3; Incidence rate/1,000 person-years: 2.2 (0.5 - 6.5) D2: 45; Incidence rate/1,000 person-yeears: 4.6 (3.3 - 6.1) Other infections (specify), n: D1: • All serious infections: n = 56 • Rate of infections/1,000 person-years (95% CI) = 41.4 (31.4 - 53.5) D2: • All serious infections: n = 525 • Rate of infections/1,000 person-years (95% CI) = 53.2 (48.9 - 57.8) Overall: • All serious infections, IRR, DMARD = ref, adjusted for age and sex: 1.47 (1.07 - 2.01) • Adjusted for aged, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking: 1.03 (0.68 - 1.57) D1: • Lower respiratory tract: 36 • Incidence rate/1,000 person-years: 26.6 (18.7 - 36.7) D2:

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Duration of study December 2001 to September 2005 **Quality rating** Fair	problems associated with recall and left censorship • Patients who had been registered > 6 mos after start of biologic therapy were excluded.		**characteristics, %, (CI/SD/P value)** D1: • HAQ score, mean: 1.5 • Extraarticular disease: 21% • Current smoker: 26% • Former smoker: 39% • Never a smoker: 35% • Diabetes: 5.5% • COPD/asthma: 20% D2: • HAQ score, mean: 2.1 • Extraarticular disease: 30% • Current smoker: 22% • Former smoker: 38% • Never a smoker: 40% • Diabetes: 5.4% • COPD/asthma: 13% •		• Lower respiratory tract: 203 • Incidence rate/1,000 person-years: 20.6 (17.9 - 23.6) D1: Skin and soft tissue: 4; Incidence rate/1,000 person-years: 3.0 (0.8 - 7.6) D2: Skin and soft tissue: 118; Incidence rate/1,000 person-years: 12.0 (9.9 - 14.3) D1: Bone and joint: 4; Incidence rate/1,000 person-years: 3.0 (0.8 - 7.6) D2: Bone and joint: 68; Incidence rate/1,000 person-years: 6.9 (5.4 - 8.7) D1: Bacterial intrcellular infections: 0 D2: Bacterial intrcellular infections: 19 (10 Mycobacterium TB, 2 Legionella pneumophila, 3 Listeria monocytogenes, 1 Mycobacterium fortuitum, and 3 Salmonella) • Subanalysis: No. of infections: DMARD = 56, ETN = 209, IFX = 255, ADA = 61; • Rate of infections/1,000 person-years (95% CI):

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					DMARD = 41.4 (31.4-53.5), ETN = 51.3 (44.7-58.5), IFX = 55.2 (48.8-62.2), ADA = 51.9 (39.9-66.2); • Adjusted IRR (DMARD = ref): ETN = 0.97 (0.63-1.50), IFX = 1.04 (0.68-1.61), ADA = 1.07 (0.67-1.72); • TB, crude IR: ETN = 0.5, IFX = 1.5, • ADA = 0.9; adjusted IRRs for TB (ETN = ref): IFX = 4.9 (95% CI, 0.5-49.8) and ADA = 3.5 (0.3-47.3)

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Author, year, study name, if applicable Dixon et al., 2007[38]; British Society for Rheumatology Biologics Register (BSRBR). **Country and setting** United Kingdom (UK) **Source of funding** British Society for Rheumatology is indirectly funded by Schering-Plough, Whety Laboratories, Abbot Laboratories, and Amgen **Research objective** Determine whether incidence of myocardial infarction (MI) was lower in pts treated with anti-TNFα than traditional DMARDs; to explore impact of response to tx on rates of MI in anti-TNFalpha cohort **Study design** Prospective Cohort Study **Overall N** N: 10,755; 74 individuals switched groups during course of study and were counted in both DMARDs and anti-	**Inclusion Criteria** • Registered with BSRBR • Diagnosed with RA • Followed up for more than 6 months by July 31, 2006 • Anti-TNFalpha cohort: treated with an anti-TNFalpha drug • Registered with BSRBR within 6 months of starting biologic therapy. • UK national guidelines require that patients to whom anti-TNFa drugs are prescribed have a Disease Activity Score in 28 joints > 5.1 despite previous therapy with at least 2 DMARDs, one of which must have been MTX. • DMARDs cohort: never taken biologic agents, diagnosed as	**Interventions, Dose** D1: Unspecified DMARDs: dose and frequency NR D2: • ETN • IFX • ADA • In anti-TNFalpha group, 3,844 pts received ETN, 2,944 pts received infliximib, and 1,871 pts received ADA. Dosages and frequencies were not reported. **Number in group** D1: 2,170 D2: 8,659 **Mean age (years)** D1: 60 D2: 56 **Sex, % female** D1: 72 D2: 76 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 7 years (IQR, 1 - 15) D2: 12 years (IQR, 6 - 19) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: 19.3 D2: 43.7 **DMARD use, %** D1: 100% D2: NR **MTX naïve, %** D1: NR D2: 0 (inferred) **Baseline DAS score, mean (SD)** D1: 5.0 (SD 1.4) D2: 6.6 (SD 1.0) **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1:	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** Overall attrition/withdrawal, n: • In general for BSRBR only 2.2% of all patients enrolled > 12 months before July 31, 2006 had no returned rheumatologist questionnaires and 17.2% had no returned patient diaries. • Only 0.6% had no follow up information from either source. • Patients with no returned information from rheumatologist were not included in this analysis. Overall adverse events reported, n: D1: 17 D2: 63; In subanalysis, nonresponders had 17 AEs and responders had 35 AEs. **Serious adverse events** Cardiovascular events (specify), n: D1: MI, 17 D2: MI, 63; In subanalysis, nonresponders had 17 MIs (n: 1,638), and responders had 35 MIs (n: 5,877). **Malignancies** NR **Respiratory events** NR **Other infections**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
TNFalpha groups. **Duration of study** Anti-TNFalpha Drepresented 13,233 person-years of follow up. DMARDs Drepresented 2,893 person-years of follow up. Median follow up for anti-TNFalpha cohort was 1.66 years; median follow up for DMARDs cohort was 1.34 years. **Quality rating** Fair: Drug specific data not reported	having active RA (guideline DAS more than 4.2). **Exclusion Criteria** NR		• BMI, mean ±SD kg/m2: 26.9 (5.7) • Smoking History, no. (%), current smoker 537 (25), Former Smoker 849 (39), Never Smoked 767 (35) • Prior MI, no (%), 116 (5.3) • Angina, no (%), 183 (8.4) • Hypertension, no (%), 672 (31.0) • Diabetes, no. (%), 132 (6.1) • Corticosteriods, no. (%), 418 (19.3) • Lipid-lowering Drugs, no. (%), 338 (15.6) • Antiplatelet Drugs. no (%), 291 (13.4) • NSAIDs, no. (%), 1344 (61.9) D2: • BMI, mean ±SD kg/m2: 26.7 ± 5.8) • Smoking History, no. (%), current smoker 1886 (22), Former Smoker 3298 (38), Never Smoked 3431 (40) • Prior MI, no (%), 250 (2.9) • Angina, no (%), 381 (4.4) • Hypertension, no (%), 2581 (29.8) • Diabetes, no. (%), 470 (5.4) • Corticosteriods, no. (%), 3793 (43.7) • Lipid-lowering Drugs, no. (%), 768 (8.9) • Antiplatelet Drugs. no (%), 648 (7.5) • NSAIDs, no. (%), 5705		NR **GI** NR **Other** • In DMARD group, Person-years, 2893 • Number of Reported MIs: 17 • Rate of MIs per 1000 person-years (95% CI): 5.9 (3.4-9.4) • Incident rate ratio, referent • Incidence rate ratio adjusted for age and sex, referent • Incidence rate ratio multivariate analysis, referent • In anti-TNFalpha DPerson-years, 13323 • Number of Reported MIs, 63 • Rate of MIs per 1000 person-years (95% CI), 4.8 (3.7 - 6.1) • Incident rate ratio, 0.81 (0.47 - 1.38) • Incidence rate ratio adjusted for age and sex, 1.13 (0.65 - 1.96) • Incidence rate ratio multivariate analysis, 1.44 (0.56 - 3.67) • In subanalysis, results among nonresponders, Person-years 1,815, Number of reported MIs: 17, rate of MIs per 1,000 person years was

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			(65.9) • A sub-analysis was done of non-responders and responders • Anti-TNFalpha Nonresponders, N: 1,638 • Mean Age (Y), 57 • Sex, female (%), 79 • Race, white (%), NR • Race, black (%), NR • Ethnicity, Latino (%) NR • Disease Duration (mean & SD), 11 (IQR, 6-19) • DMARD use (%), NR • Corticosteroid use (%) 45.3 • MTX naïve (%), 0 (inferred) • Treatment resistant (%) NR • Patients with early RA, three years or less, (%), NR • Baseline DAS score, mean (SD), 6.4 (SD 1.1) • Tender joint count, NR • Swollen joint count, NR • Required treatment for latent TB, NR Other • BMI, mean ±SD kg/m2: 26.9 (6.2) • Smoking History, no. (%) • Current smoker 382 (23) • Former Smoker 625 (38) • Never Smoked 621 (38) • Prior MI, no (%), 48 (2.9) • Angina, no (%), 85 (5.2) • Hypertension, no (%), 506 (30.9)		9.4 (95% CI, 5.5 - 15.0), Incident rate ratio, referent • Incidence rate ratio adjusted for age and sex, referent • Incidence rate ratio multivariate analysis, referent • Amon responders, Person-years 9,886, Number of reported MIs: 35, rate of MIs per 1,000 person-years (95% CI): 3.5 (2.5 - 4.9), Incident rate ratio, 0.38 (2.5 - 4.0) • Incidence rate ratio adjusted for age and sex, 0.38 (0.21 - 0.68) • Incidence rate ratio multivariate analysis, 0.36 (0.19 - 0.69), incidence rate ratio by sex, multivariate analysis (male) 0.31 (0.12 - 0.81), (female) 0.46 (0.20 - 1.06).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			• Diabetes, no. (%), 110 (6.7) • Corticosteriods%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Dixon WG et al., 2010[39] British Society for Rheumatology Biologics Register (BSRBR) **Country and setting** UK **Source of funding** the University of Manchester **Research objective** To compare directly the risk between drugs, to explore time to event, site of infection and the role of ethnicity. **Study design** Observational **Overall N** 13739 **Duration of study** Total follow-up time (person-yrs): DMARD: 7345	**Inclusion Criteria** • Patient with doctor's dx of RA • At least 1 returned consultant follow-up questionnaire before 3/31/08 • Anti-TNF cohort the anti-TNF drug must have been their first biolgical drug • DMARD cohort they must have been biologic naive **Exclusion Criteria** • NA	**Comparisons (dosage and frequency)** D1: Non-biologic DMARDs: Dosage and frequency NR D2: All anti-TNF: Dosage and frequency NR D3: ETN: Dosage and frequency NR D4: INF: Dosage and frequency NR D5: ADA: Dosage and frequency NR **Number in group** D1: 3232 D2: 10712 D3: 3913 D4: 3295 D5: 3504 **Mean age (years)** D1: 60 D2: 56 D3: 56 D4: 56 D5: 57 Overall: DMARD vs. All anti-TNF, *P*<0.001; Between the three anti-TNF drugs, *P*=0.012 **Sex, % female** D1: 72 D2: 76	**Mean disease duration, years** D1: 6 (1-15) D2: 11 (6-19) D3: 12 (6-19) D4: 12 (6-19) D5: 10 (5-18) Overall: DMARD vs. All anti-TNF, *P*<0.001; Between the three anti-TNF drugs, *P*<0.001 **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %:** D1: 100 **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):**	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** NR **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** Tuberculosis (n): D1: 0 D2: 40 (118/100,000 pys; 95% CI, 84-160) D3: 8 (53/100,000 pys; 95% CI, 23-105) D4: 12 (123/100,000 pys; 95% CI, 64-215) D5: 20 (217/100,000 pys; 95% CI, 132-335) Rates of TB D1: NR D2: NR D3: 39 events/100,000 person-yrs D4: 136 events/100,000 person-yrs D5: 144 events/100,000 person-yrs IRR for active TB Non-white vs. white patients=6.5 (2.8-15.3). UK population rate of TB: 12.3-14.7 events/100,000 person-yrs from 2001-2005).	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Anti-TNF: 34025 Median duration of follow-up/patient (yrs): DMARD: 2.30 Anti-TNF: 3.21		D3: 77 D4: 76 D5: 75 Overall: DMARD vs. All anti-TNF, *P*<0.001; Between the three anti-TNF drugs, *P*=0.108 **Race, % white** D1: 78 D2: 83 D3: 82 D4: 82 D5: 84 Overall: DMARD vs. All anti-TNF, *P*<0.001 Between the three anti-TNF drugs, *P*=0.363 **Race, % black** D1: Non-white: 2 D2: Non-white: 3 D3: Non-white:3 D4: Non-white: 4 D5: Non-white: 3 **Ethnicity, Latino** NR	205 patients switched from the DMARD cohort to the anti-TNF cohort		**Other infections:** NR **GI:** NR **Other:** NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year: Doran et al., 2002[40] **Country, Setting:** US, Minnessota cohort **Funding:** Immunnex; NIH **Research Objective:** Identify predictors of serious infections amnong pts with RA **Study Design:** Retrospective Cohort **Overall N:** 609 **Study Duration:** 39 yrs	**Inclusion Criteria:** • Diagnosed with RA according to ACR criteria **Exclusion Criteria:** • NR	**Interventions, dose:** **DMARDS** **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Age, /10-yr increment OR 1.49 95% CI,1.33-1.67 *P* < 0.001 • Alcoholism OR 2.00 95%CI,1.27-3.16 *P* = 0.003 • Leukopenia OR 2.17 95%CI,1.58-2.98 *P* < 0.001 • Organic brain disease OR 2.94 95%CI,2.08-4.16 *P* < 0.001 • DM OR 2.45 95%CI,1.84-3.27 *P* < 0.001 • Chronic lung disease OR 2.83 95%CI,2.15-3.72 *P* < 0.001 • Extraarticular RA OR 3.22 95%CI,2.17-4.77 *P* < 0.001 • RF OR 1.65 95%CI,1.24-2.20 *P* < 0.001 • RA nodules OR 1.76 95%CI,1.32-2.33 *P* < 0.001 • Functional capacity OR 1.87 95%CI,1.49-2.35 *P* < 0.001 • ESR OR 1.63 95%CI,1.25-2.13 *P* < 0.001 • Chemo OR 5.02 95%CI,2.44-10.3 *P* < 0.001 • Cyclophosphamide OR 6.14 95%CI,3.12-11.8 *P* < 0.001 • Cyclosporine OR 1.99 95%CI,1.25-3.16 *P* = 0.004 • Corticosteroids OR 1.90 95%CI,1.47-2.47 *P* < 0.001	NA	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

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Author, yr: Dougados et al., 1999[41] and Maillefert et al., 2003[42] **Country, Setting:** Finland, France, Germany (France only for 5 yr), multicenter **Funding:** Pharmacia Upjohn **Research Objective:** Clinical benefit of MTX + SSZ compared to either drug alone early, active RA pts fulfilling some criteria of poor potential long term outcome **Study Design:** RCT **Overall N:** 209 (146) **Study Duration:** 52 wks (5 yrs)	**Inclusion Criteria:** • Diagnosed according to ACR criteria • Duration < 1 yr • Presence of active disease as defined by DAS ≥ 3 (calculation based on Ritchie articular index, 44 SJC, and ESR) and presence of RF and/or HLA DR 1/4 • Concommitant drugs allowed were analgesics and NSAIDS **Exclusion Criteria:** • Prior txt with steroids, DMARDS, or any drugs to treat RA other than analgesic or NSAIDS • Pts with contraindications to use of SSZ or MTX	**Interventions, dose:** D1: SSZ + placebo D2: MTX + placebo D3: SSZ + MTX MTX: 7.5 mg wkly (2.5 mg 3 times per wk). After wk 16, could be increased to 15 mg wkly if efficacy inadequate SSZ: increased to 2 grams daily by d #9. Could be increased to 3 grams daily after wk 16 of study if efficacy was inadequate Other?: combo MTX + SSZ **N:** D1: 68 D2: 69 D3: 68 **Mean age, yrs:** D1: 52 D2: 50 D3: 52 **Sex, % female:** D1: 71 D2: 74 D3: 77 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 2.9 mos since diagnosis, 10.8 since onset D2: 2.3 mos from diagnosis, 18.4 from onset D3: 3.4 mos from diagnosis, 10.6 from onset **TJC, mean:** NR **SJC, mean:** D1: 10.5 D2: 9.4 D3: 9.4 **DMARD use, %:** All groups: 0 **Corticosteroid use, %** All groups: 0 MTX naive, %: All groups: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** All groups: 100	**DAS change:** D1: -1.15 D2: -0.87 D3: -1.26 (*P* = 0.019 from inter-group comparisons using analysis of variance) **RAI changes:** D1: -7.1 D2: -4.2 D3: -9.4 (*P* = 0.001) **ACR response, %:** D1: 59 D2: 59 D3: 65 (*P* = NR) **At 5 years** Txt of pts with early RA with combination therapy of MTX and SSZ during first yr did not result in any long term differences in disease activity, quality of life, or structural damage compared to monotherapy with either drug used alone **Mean DAS (SD):** D1 or D2: 2.2 (1) D3: 2.2 (1) Overall: (*P* = 0.9) **HAQ:** D1 or D2: 0.6 (0.7) D3: 0.6 (0.6) Overall: (*P* = 0.9)	**Overall:** D1: 75 D2: 75 D3: 91 **Abdominal Pain:** D1: 9 D2: 6 D3: 13 **Dizziness:** D1: 6 D2: 1 D3: 3 **Headache:** D1: 9 D2: 4 D3: 12 **Nausea:** D1: 32 D2: 23 D3: 49	**Overall Attrition Rate, %:** 27% (28.8) **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Duclos, 2006[43] **Country and setting** Monocenter French tertiary-referral rheumatology unit **Source of funding** Not reported **Research objective** Evaluate TNF blocker retention rates and their predisposing factors in daily practice. **Study design** Retrospective Cohort **Overall N** 770 (142 patients received more than one TNF blocker for 975 treatment courses) **Duration of study** 1997 to December 15, 2004 **Quality rating** Fair: single referral center population, different baseline population characteristics	**Inclusion Criteria** • Received a TNF blocker **Exclusion Criteria** • NR	**Interventions, Dose** D1: • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ADA: dosage and frequency NR D2: • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ADA: dosage and frequency NR **Number in group** D1: 440 D2: 290 Overall: 770 **Mean age (years)** D1: 55.1 D2: 41.6 Overall: 49.3 **Sex, % female** D1: 80.5 D2: 29.7 Overall: 60.4 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 13.5 yrs (9.5) D2: 13.6 (10.0) Overall: 13.4 (9.7) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR Overall: 16.1 (21.5) **DMARD use, %** NR Overall: 3.0 (2.1) **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** NR **HAQ,** **DAS** **SF-36** **Radiographic measures** **Quality of life scales** **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** • Percentage of patients who did not interrupt treatment due to inefficacy or intolerance was 82.5% ± 1.3 at 6 months, 64.0% ± 1.8 at 12 months, 50.3% ± 2.1 at 24 months, and 39.4% ± 2.4 at 36 months. • Retention rates were similar for 3 TNF blockers. • At 1 year, rates were 63.2% ± 2.9, 63.9% ± 2.6, and 68.2% ± 4.6, and at 2 years, rates were 47.5% ± 3.2, 50.8% ± 3.0, and 60.2% ± 5.6 for IFX, ETN, and ADA, respectively (*P* = 0.48). • Analyses according to reason for interruption did not find any difference in efficacy between 3 agents (*P* = 0.33), but showed a trend for a better tolerance with ETN and ADA versus with IFX (*P* = 0.06) **Overall adverse events reported, n:** **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR

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					GI NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Edwards et al., 2007[44] **Country and setting** United Kingdom, primary care database (GPRD) **Source of funding** Proctor & Gamble PhDaceuticals Government or non-profit organization-please list name.Medical Research Council and Southhampton Rheumatology Trust **Research objective** Evaluate effect of DMARDs on the likelihood of pts with RA developing septic arthritis (SA) **Study design** Cohort **Overall N** 136,997 (34,250 patients with RA, 102,747 controls) **Duration of study** June 1987-April 2002 **Quality rating** Fair	**Inclusion Criteria** • Diagnosis of RA (ICD-9 code 714.0) • At least 3 control subjects without RA, matched by age (within 5 years), sex, and practice, were defined for each RA case. **Exclusion Criteria** • Patients with RA who were first diagnosed subsequent to a diagnosis of SA	**Interventions, Dose** D1: • PNL: Dosage NR • MTX: Dosage NR • LEF: Dosage NR • SSZ: Dosage NR • Hydroxychlorquine: Dosage NR • Other: Any combination D2: • PNL: Dosage NR • MTX: Dosage NR • LEF: Dosage NR • SSZ: Dosage NR • Hydroxychlorquine: Dosage NR • Other: Any combination **Number in group** D1: 102,747 D2: 34,250 **Mean age (years)** D1: 55.3 D2: 55.6 *P* =.001 **Sex, % female** D1: 71.4 D2: 71.4 *P* =1.0 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: NR D2: 40 Overall: NR **DMARD use, %** D1: NR D2: 50 Overall: NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Smoking (ever vs. never), %: D1: 37.5	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • SA incidence (1992-1997): 0.29 (95% confidence interval [95% CI] 0.27–0.31) per 1,000 person-years for entire population studied (including RA cases and controls) and 0.11 (95% CI 0.09–0.12) per 1,000 person-years for control population. • In RA population, SA incidence was increased at 1.31 (95% CI 1.22–1.41) per 1,000 person-years. incidence rate of SA was 12.9 times greater among patients with RA than among RA controls (95% CI 10.1–16.5, *P* = 0.001). • A diagnosis of RA,

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			D2: 41.6 *P* = 0.001 Diabetes %: D1: 5.55 D2: 5.50 *P* = 0.7 Hypertension %: D1: 23.5 D2: 22.8 *P* = 0.01 Heart Failure: D1: 6.39 D2: 9.38 *P* = 0.001 Renal Failure %: D1: 0.86 D2: 1.83 *P* = 0.001 BMI IQR in kg meters squared: D1: 25.2 (22.7-28.2) D2: 24.9 (22.3-28.0) *P* = 0.001		hypertension, heart failure, or renal failure significantly increased risk of future SA, and incidence of SA was significantly higher while experiencing one or more of these risk factors than while not. • SA incidence rate while receiving a DMARD or PNL was 2.17 (95% CI 1.68–2.80, *P* = 0.001) times greater than while receiving no drugs,even after adjustment for RA. • Incident rate of SA in patients with RA receiving DMARDs was 2.14 (95% CI 1.64–2.78, *P* = .001) times greater than in patients with RA not receiving DMARDs, and corresponding rate ratio for RA controls was 2.80 (95% CI 1.03–,*P* = 0.045). • Incident rate ratios (IRRs) for developing SA while receiving DMARDs compared with receiving no DMARDs were different for different medications: SSZ (adjusted IRR 1.74, 95% CI 1.04–2.91, *P* 0.03), and PNL (adjusted IRR 2.94, 95% CI 1.93–4.46, *P* = 0.001) were associated with an increased incidence of SA when compared with not receiving any DMARD. use of other DMARDs including

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					MTX showed no such effect; adjusted IRR HCQ 0.59 (0.08-4.25); LEF no events; MTX 1.01 (0.44-2.34).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000[45] **Country, Setting:** Multinational, 117 centers **Funding:** NR **Research Objective:** To compare both short and long-term (up to 2 yr) clinical efficacy and safety of LEF and MTX for txt of RA **Study Design:** RCT **Overall N:** 999 **Study Duration:** 1 yr, optional second yr	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria: Active Disease • Previous use of DMARDs: only if discontinued 28 ds before trial • Duration of condition: for at least 4 mos, but no longer than 10 yrs • NSAIDs and steroids were allowed provided a stable dose of NSAIDs or steroid (≤ 10 mg/d) PNL for at least 28 ds prior to study entry • Women of childbearing age were required to use adequate contraception **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: Intra-articular corticosteriod injections w/in 6 wks of efficacy assessment	**Interventions, dose:** D1: LEF Yr 1 D2: MTX Yr 1 D3: LEF Yr 2 D4: MTX Yr 2 MTX: 7.5 to 15 mg/wk LEF: loading dose of 100 mg/d for 3 ds, followed by maintenance dose 20/ mg/d **N:** D1: 501 D2: 498 D3: 292 D4: 320 **Mean age, yrs:** D1: 58.3 D2: 57.8 D3: 57.7 D4: 57.0 **Sex, % female:** D1: 70.7 D2: 71.3 D3: 71.2 D4: 71.3 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 3.7 D2: 3.8 D3: 3.5 D4: 3.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: 66.3 D2: 66.9 D3: 64.7 D4: 66.9 **Corticosteroid use, %** D1: 36.3 D2: 33.5 D3: 14.0 D4: 11.3 **MTX naive, %:** NR **DMARD Txt resistant, %:** D1: 1.1 D2: 1.1 D3: 1.0 D4: 1.1 **Pts with Early RA (≤ 3 yrs):** NR	**At year 1** **ACR20:** D1: 50.5% D2: 64.8% ($P < 0.001$) **HAQ improvement:** Minimal quantitative difference between groups, but statistically significant (shown in figure only; $P < 0.05$) **Radiograph change, Larsen Scores:** D1 and D2: 0.03 increase (P = NS, NR) **Primary clinical efficacy endpoints**: **TJC:** D1: -8.3 D2: - 9.7 **SJC:** D1: -6.8 D2: -9.0 **Physician global assessment:** D1: -0.9 D2: -1.2 **Pt global assessment:** D1: -0.9 D2: -1.2 **At year 2** **ACR20, %:** D1: 64.3 D2: 71.7 (P = NS, NR)	**SAEs:** D1: 7% D2: 8% **Headache:** D1: 6.2 D2: 4.8 **Hepatotoxicity:** D1: 5.4 D2: 16.3 D3: 2.7 D4: 5.9 **Nausea:** D1: 11.2 D2: 15.7 **URTI:** D1: 5.2 D2: 5.0 D3: 4.5 D4: 5.6 **Deaths** MTX: 2	**Overall Attrition Rate, %:** • 26.3% (263/999) during yr 1 • Combined 2 yrs, attrition 50.3% (502/999) of those initially starting study at baseline • During yr 2, attrition 18.8% (115/612) of those agreeing to continue study for 2nd yr **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2006, DANCER trial[46] **Country and setting** Multinational, multicenter **Source of funding** Roche primarily, also support from Genentech and Biogen Idec **Research objective** Examine efficacy and safety of different RIT doses + MTX with or without glucocorticoids in pts resistant to DMARDs, including biologics **Study design** Controlled Trials **Overall N** 465 (Note: 465 pts were randomized adverse event and baseline data analyses usewhole population, efficacy analyses use an "ITT efficacy population" of N: 367.ITT population is limited toRF+ pts who were not exlcuded (13 RF+ pts were exclu	**Inclusion Criteria** • Treatment resistant, outpatients between ages of 18 - 80 years who had presented at least 6 mos prior to randomization with severe RA despite ongoing treatment with MTX for at least 12 weeks • Must have failed prior treatment with at least 1 but not more than 5 DMARDs (other than MTX) and/or biologic response modifiers • Pts taking glucocorticoids were included ifdosage had been stable for at least 4 weeks before trial entry • Pts who received intraarticular or parenteral glucocorticoids were included if most recent	**Interventions, dose** D1: • MethylPNL Placebo methylPNL IV: 30 - 60 minutes before infusion on days 1 and 15 - or - premed methylPNL 100 mg IV on days 1 and 15 - or - premed methylPNL 100 mg IV on days 1 and 15 plus 60 mg of oral PRED on days 2 - 7 and 30 mg on days 8 – 14 • PRED see "methylPNL" • MTX: weekly regimen 10 - 25 mg orally • Placebo placebo RIT: on days 1 and 15 • Folate: dosage and frequency NR D2: • MethylPNL Placebo methylPNL IV: 30 - 60 minutes before infusion on days 1 and 15 - or - premed methylPNL 100 mg IV on days 1 and 15 - or - premed methylPNL 100mg IV on days 1 and 15 plus 60 mg of oral PRED on days 2 - 7 and 30 mg on days 8 – 14 • PRED see "methylPNL" • MTX: weekly	**Mean disease duration, years** 10.8 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 D3: 100 **Tender Joint Count, mean** D1: 35 D2: 33 D3: 32 **Swollen Joint Count, mean** D1: 21 D2: 22 D3: 22 **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score** D1: 6.8 D2: 6.8 D3: 6.7 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1:	**ACR mean difference/ absolute difference** ACR 20: D1: 28 D2: 55 ($P \leq 0.001$) D3: 54 ($P \leq 0.001$) ACR 50: D1: 13 D2: 33 ($P \leq 0.001$) D3: 34 ($P \leq 0.001$) ACR 70: D1: 5 D2: 13 ($P = 0.029$) D3: 20 ($P = 0.0001$ **HAQ-DI, mean change from baseline** D1: -0.16 D2: -0.43 D3: -0.49 **DAS (*P* Value)** Adjusted mean change: D1: -0.67 D2: -1.79 ($P = 0.0001$) D3: -2.05 ($P = 0.0001$) **SF-36, mean difference/absolute difference** NR **Radiographic measures, mean difference/absolute difference** NR **Quality of life scales** NR **EULAR (%)** No response:	**Attrition/withdrawal** Overall, n: D1: 52 D2: 11 D3: 27 Withdrawals due to adverse events, n: D1: 0 D2: 3 D3: 6 Withdrawals due to lack of efficacy, n: D1: 46 D2: 8 D3: 16 Adherent/compliant, n: NR 13 RF+ pts (out of 380) were exlcuded from analyses because of unblinding, drug dispensing errors, and unverifiable data. **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR Other infections NR **GI** NR **Other** Data are from Safety Population N: 465 Adverse events affecting 5%

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Duration of study 24 weeks **Quality rating** Fair	administration was more than 4 weeks before screening. **Exclusion Criteria** • Significant systematic involvement secondary to RA • Evidence of significant other illness or laboratory adnormalities • History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies • Previous treatment with RIT or any lymphocyte-depleting therapies • History of recurrent significant infection.	regimen: 10 - 25 mg orally • RITIn RF+ positive patients: 500 mg on days 1 and 15 • Other: folate: dosage and frequency NR D3: • MethylPNL Placebo methylPNL IV: 30 - 60 minutes before infusion on days 1 and 15 - or - premed methylPNL 100 mg IV on days 1 and 15 -or - premed methylPNL 100mg IV on days 1 and 15 plus 60 mg of oral PRED on days 2 - 7 and 30 mg on days 8 – 14 • PRED see "methylPNL" • MTX: weekly regimen: 10 - 25mg orally • RITIn RF+ pts: 1,000 mg on days 1 and 15; In RF- pts: 1,000 mg on days 1 and 15 • Other: folate: dosage and frequency NR **Number in group** D1: 122 D2: 123 D3: 122 **Mean age, years (%)** 51.1 **Sex, % female**	• Data presented in table above are baseline disease characteristics for ITT efficacy D (N: 367). • Other population characteristics as follows are for "safety population" N: 465: (D1) Age, mean years: 51.1 %Female: 80, Duration of RA, mean years: 9.3, Previous DMARDs, mean number: 2.2 prior anti-tnf alpha treatment: 26%, MTX dose, mean mg/week: 15.6 D2: • Data presented in table above are baseline disease characteristics for ITT efficacy D (N: 367). • Other population characteristics as follows are for "safety population" N: 465: (D2) Age, mean years: 51.4 %Female: 83, Duration of RA, mean years: 11.1, Previous DMARDs, mean number: 2.5 prior anti-tnf alpha treatment: 33, MTX dose, mean mg/week: 16 D3: • Data presented in table above are baseline disease characteristics for ITT efficacy D (N: 367). Other population characteristics as follows are for "safety population"	D1: 63 D2: 28 D3: 34 Moderate/good response: D1: 37 D2: 73 D3: 67 Good response: D1. 4% D2: 14% D3: 28% *P* = 0.0001 for D2 and D4 vs. D1.	or more of patients in any one Dare reported, values are %. D1: All Events: 105, Exacerbations of RA: 44, Headache: 19, Nausea: 13, URI: 9, Nasopharyngitis: 8, Arthralgia: 5, Diarrhea: 8, Fatigue: 8, Hypertension: 4, Rigors: 3, Dizziness: 6, Serious noninfection adverse events: 2, Serious infections: 2; Arm 2: All Events: 100, Exacerbations of RA: 21, Headache: 14, Nausea: 8, URI: 10, Nasopharyngitis: 7, Arthralgia: 5, Diarrhea: 7, Fatigue: 5, Hypertension: 5, Rigors: 5, Dizziness: 4, Serious noninfection adverse events: 9, Serious infections: 0; Arm 3 All Events: 164, Exacerbations of RA: 27, Headache: 21, Nausea: 19, URI: 12, Nasopharyngitis: 10, Arthralgia: 11, Diarrhea: 6, Fatigue: 8, Hypertension: 12, Rigors: 13, Dizziness: 10, Serious noninfection adverse events: 9, Serious infections: 4

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		80 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	N: 465: • Prior anti-tnf alpha treatment: 28%, • MTX dose, mean mg/week: 14.9		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2006[47] **Country and setting** UK, US, Canada **Source of funding** Bristol-Myers Squibb **Research objective** Examine effect of ABA on HRQOL **Study design** Controlled Trials **Overall N** 339 **Duration of study** 1 year **Quality rating** Fair	**Inclusion Criteria** • American Rheumatism Association criteria for RA while meeting functional class I, II, or III according to revised criteria of ACR • Have > 10 swollen, > 12 tender joints, and CRP level > 1 mg/dl signifying active disease • Have been treated with MTX for at least 6 mos and on a stable dose for 28 days prior to enrollment • Be washed-out of all DMARD other than **Exclusion Criteria** • NR	**Interventions, Dose** D1: • MTX: 15.8 (SD 4.1) • Abatacept: 2 mg/kg administered at baseline, every two weeks for first month, then monthly thereafter D2: • MTX: 15.8 (SD 4.8) • Abatacept: 10 mg/kg administered at baseline, every two weeks for first month, then monthly thereafter D3: • MTX: 15.0 (SD 4.4) • Placebo **Number in group** D1: 105 D2: 115 D3: 119 Overall: 339 **Mean age (years)** D1: 54.4 D2: 55.8 D3: 54.7 **Sex, % female** D1: 62.9 D2: 74.8 D3: 66.4 **Race, % white** D1: 86.7 D2: 86.9 D3: 87.4	**Mean disease duration, years (SD)** D1: 9.7 (8.1) D2: 9.7 (9.8) D3: 8.9 (8.3) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean (SD)** D1: 28.2 D2: 30.8 D3: 29.2 **SJC, mean (SD)** D1: 20.2 D2: 21.3 D3: 21.8 **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** D1: 0 D2: 0 D3: 0 Overall: 0 **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P**	**ACR** NR **HAQ** NR **DAS** NR **SF-36, mean Changes in 8 categories of SF-36 scale PF (SE)** Physical functioning D1: 4.7 (0.9) D2: 7.2 (0.8) D3: 2.1 (0.8) Role limitations due to physical health (RP): D1: 5.3 (1.1) D2: 8.2 (1.0) D3: 4.1 (1.0) Bodily pain (BP): D1: 6.5 (0.9) D2: 9.3 (0.8) D3: 3.5 (0.8) General health perceptions (GH): D1: 4.1 (0.7) D2: 5.8 (0.7 D3: 2.3 (0.7) Vitality (VT): D1: 3.5 (0.8) D2: 7.9 (0.8) D3: 2.1 (0.8) Social functioning (SF): D1: 4.6 (1.0) D2: 7.6 (0.9) D3: 3.6 (0.9)	**Overall** Overall attrition/withdrawal, n: D1: 31 D2: 25 D3: 48 Overall: 104 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Race, % black NR **Ethnicity, Latino** NR	**value)** D1: All reported characteristics were similar at baseline including mean MTX dose and HRQOL score D2: All reported characteristics were similar at baseline including mean MTX dose and HRQOL score D3: All reported characteristics were similar at baseline including mean MTX dose and HRQOL score	Role limitations due to emotional health (RE): D1: 5.0 (1.4) D2: 6.8 (0.9) D3: 3.8 (1.0) Mental health (MH): D1: 3.5 (0.9) D2: 5.3 (0.8) D3: 2.6 (0.8) **Mean Changes in SF-36 summary measures, physical summary measure (SE)** Physical summary measure (PCS): D1: 5.2 (0.8) D2: 8.0 (0.8) D3: 2.6 (0.7) Mental summary measure (MCS): D1: 3.5 (1.0) D2: 5.7 (0.9) D3: 2.8 (0.9) **Radiographic measures** NR **Quality of life scales** D1: See SF-36 results D2: See SF-36 results D3: See SF-36 results Overall: See SF-36 results **Others, (please name)** Differences in Mean Change Scores in 8 categories of SF-36 scale: • Placebo vs. Abatacept 2mg/kg - Physical Functioning (PF) = 2.6	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				(*P* = 0.05) • Role limitations due to physical health (RP) = 1.2 • Bodily pain (BP) = 3.0 (*P* = 0.05) • General health perceptions (GH) = 1.8 • Vitality (VT) = 1.4 • Social functioning (SF) = 1.0 • Role limitations due to emotional health (RE) = 1.8 • Mental health (MH) = 0.9 Differences in Mean Change Scores in SF-36 summary measures: • Physical summary measure (PCS) = 2.6 (*P* = 0.05) • Mental summary measure (MCS) = 0.7 • Difference in Mean Change Score in SF-36 Utility Index: SF-6D = 0.00 - - Abatacept 2mg/kg vs. Abatacept 10 mg/kg - Physical Functioning (PF) = 2.5 (*P* = 0.05) • Role limitations due to physical health (RP) = 2.9 (*P* = 0.05) • Bodily pain (BP) = 2.8 (*P* = 0.05) • General health perceptions (GH) = 1.7 • Vitality (VT) = 4.4 (*P* = 0.001) • Social functioning (SF) = 3.0 (*P* = 0.05)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				• Role limitations due to emotional health (RE) = 1.8 • Mental health (MH) = 1.8 Differences in Mean Change Scores in SF-36 summary measures: • Physical summary measure (PCS) = 2.8 (*P* = 0.05) • Mental summary measure (MCS) = 1.9 • Difference in Mean Change Score in SF-36 Utility Index: SF-6D = 0.05 (*P* = 0.05) - - Placebo vs. Abatacept 10 mg/kg - Physical Functioning (PF) = 5.1 (*P* = 0.0001) • Role limitations due to physical health (RP) = 4.1 (*P* <0.01) • Bodily pain (BP) = 5.8 (*P* <0.0001) • General health perceptions (GH) = 2.5 (*P* = 0.001) • Vitality (VT) = 5.8 (*P* = 0.0001) • Social functioning (SF) = 4.0 (*P* = 0.01) • Role limitations due to emotional health (RE) = 3.0 (*P* = 0.001) • Mental health (MH) = 2.7 (*P* = 0.05) Differences in Mean Change Scores in SF-36 summary measures: • Physical summary	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				measure (PCS) = 5.4 (*P* = 0.0001) • Mental summary measure (MCS) = 2.9 (*P* = 0.05) • Difference in Mean Change Score in SF-36 Utility Index: SF-6D = 0.05 (*P* = 0.001)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2008, COMET[48] **Country and setting** Multinational, multicenter **Source of funding** Wyeth Research **Research objective** Compare remission and radiographic non-progression in pts treated with MTX monotherapy or MTX + ETN **Study design** Controlled Trials **Overall N** 542 **Duration of study** 52 weeks **Quality rating** Fair	**Inclusion Criteria** • MTX Naïve • Early RA defined as at least 3 mos but less than 2 yrs • Age 18 years or older with diagnosis of adult-onset RA • Disease duration of at least 3 mos but not more than 2 years • DAS28 of 3·2 or more • Either Westergren ESR of 28 mm/h or more or CRP of 20 mg/L or more. **Exclusion Criteria** • Previous treatment with MTX, ETN, or another TNF antagonist at any time • Had received treatment with other DMARDs or corticosteroid injections in4 weeks before baseline visits. • Important concurrent	**Interventions, dose** D1: • MTX: 7.5 mg orally once a week • Placebo ETN-matching placebo injections subcutaneously: once a week for 52 weeks • Other: In patients with tender or swollen joints, dose was titrated up over 8 weeks to a maximum of 20 mg a week D2: • MTX: 7.5 mg orally once a week • ETN: 50 mg by subcutaneous injection once a week for 52 weeks • Other: In patients with tender or swollen joints, dose was titrated up over 8 weeks to a maximum of 20 mg a week **Number in group** D1: 263 D2: 265 Overall: 528 **Mean age, years (SD)** D1: 52.3 D2: 50.5 Overall: 51.4 **Sex, % female** D1: 73 D2: 74	**Mean disease duration, months** D1: 9.3 (0.4) D2: 8.8 (0.4) Overall: 9.0 (0.3) **Patients with early RA, three years or less, %** D1: 100 D2: 100 Overall: 100 **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 24.8 (14.5) D2: 25.1 (14.6) Overall: 25.0 (14.5) **Swollen Joint Count, mean** D1: 17.6 (10.0) D2: 17.1 (10.5) Overall: 17.3 (10.2) **Corticosteroid use, %** D1: 50 D2: 49 Overall: 49 **DMARD use, %** D1: 24 D2: 18 Overall: 21 **MTX naïve, %** D1: 100 D2: 100 Overall: 100 **Baseline DAS28 mean (SD)** D1: 6.5 (1.0) D2: 6.5 (1.0) Overall: 6.5 (1.0)	**ACR mean difference/ absolute difference (%)** Week 52: ACR 20: D1: 67 (61-73) D2: 86 (82-90) Overall: Week 52: *P* = .0001 ACR 50: D1: 49 (43-55) D2: 71 (66-76) *P* =.0001 ACR 70: D1: 28 (22-34) D2: 48 (41-55) *P* =.0001 **HAQ,** Week 52 difference: D1: 0.7 D2: 1.0 *P* = 0.0001 **Remission DAS28: 2.6 (CI)** At week 52: D1: - 73 [28%] of 263 (23-33%) D2: -132 [50%] of 265 (44-56%) Overall: Week 4: DAS 44- effect difference 9.07% (95% CI 4.84-13.31%, *P* = 0·0001) Week 52: DAS 28 22.05%, 95% CI 13.96-30.15%, P <0.0001)/ Week 52: DAS 44: effect difference-23.56% (95% CI: 15.47-31.66%) **SF-36**	**Attrition/withdrawal** Overall, n: D1: 79 D2: 53 Withdrawals due to adverse events, n: D1: 34 D2: 28 Withdrawals due to lack of efficacy, n: D1: 24 D2: 9 Adherent/compliant, n: D1: 221 D2: 189 Overall adverse events reported, n: D1: 246 D2: 247 Overall: 493 **Serious adverse events** Death, n: NR Overall: 1 Cardiovascular events (specify), n: D1: 2 D2: 2 Overall: 4 Hepatotoxicity/elevated liver enzymes, n: D1: 0 D2: 3 Overall: 3 **Malignancies** Lymphoma or leukemia, n: D1: CLL: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	medical diseases and/or other relevant comorbidities.	Overall: 73 **Race, % white** D1: 88 D2: 87 Overall: 88 **Race, % black** NR **Ethnicity, Latino** NR	**Required treatment for latent TB** NR **HAQ mean (SD)** D1: 1.6 (0.7) D2: 1.7 (0.7) Overall: 1.7 (0.7)	NR **Radiographic measures (CI)** Week 52: mTSS change from baseline D1: - 2.44 (1.45 -3.43) D2: - 0.27 (-0.13- 0.68) Overall: mTSS-effect difference 20.98%, (12.97-29.09%, *P* = 0.0001) **Quality of life scales** NR **Mean DAS 28 swollen joint count- Week (CI/SD/P Value)** D1: 8 D2: 10.6 *P* = 0.0108 Radiographic nonprogression: mTSS:: 0.5 (%) D1: 59 (53-65) D2: 80 (75-85), *P* = 0.0001	D2: CLL: 1 Overall: CLL: 1 Skin cancer (basal cell or squamous cell), n: D1: 0 D2: 4 Overall: 4 Breast cancer, n: D1: 3 D2: 0 Overall: 3 Prostate cancer: D1: 0 D2: 1 Overall: 1 **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 1 D2: 1 Overall: 2 Upper respiratory infection, n: D1: 44 D2: 45 Overall: 99 **Other infections** Not specified, n: D1: 8 D2: 5 Overall: 14 Opportunistic Herpes Zoster: D1:1 D2: NR **GI** Nausea or vomiting, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 50 D2: 53 Overall: 103 Not specified, n: D1: 4 D2: 1 Overall: 5 **Other** Infusion/injection site reactions, n: D1: 1 D2: 2 Overall: 3 Demyelenation or multiple sclerosis, n: D1: 0 D2: 0 Overall: 0 Worsening of RA, n: D1: 5 D2: 2 Overall: 7 Cholelithiasis, n: D1: 0 D2: 2 Overall: 2 Intervertebral disc protrusion, n: D1: 0 D2: 2 Overall: 2 Osteoarthritis, n: D1: 2 D2: 0 Overall: 2 **Any other AEs:** Interstitial lung disease (2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					incombined-treatment group) and hip arthroplasty (2 in MTX group).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery el al., 2008, RADIATE Study[49] **Country and setting** Multinational multicenter **Source of funding** Hoffmann-La Roche Ltd, Chugai Pharma KK **Research objective** Examine safety and efficacy of Tocilizumab in pts refractory to TNF antagonist therapy **Study design** Controlled Trials **Overall N** 499 **Duration of study** 24 weeks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant inadequate response to 1 or more TNF antagonist withinpast year • 18 years old or older with moderate to severe RA for 6 mos or more • Swollen joint count of 6 or more • CRP of more than 1.0 mg/dl or ESR of more than 28 mm/h • Treatment with MTX for 12 weeks or more **Exclusion Criteria** • Treatment with cell depleting agents • Uncontrolled medical conditions • History of other inflammatory diseases or functional class 4 RA • History of malignancies or recurrent infections • Primary or secondary immunodeficiency	**Interventions, dose** D1: • MTX: 10-25 mg/week • Tocilizumab: 8 mg/kg every 4 weeks D2: • MTX: 10-25 mg/week • Tocilizumab: 4 mg/kg every 4 weeks D3: • MTX10-25 mg/week • Placebo every 4 weeks **Number in group** D1: 170 D2: 161 D3: 158 Overall: 498 **Mean age, years (SD)** D1: 53.9 D2: 50.9 D3: 53.9 **Sex, % female** D1: 84 D2: 81 D3: 79 Overall: 79.5 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 12.6 (9.3) D2: 11.0 (8.5) D3: 11.4 (9.2) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 D3: 100 Overall: 10 **Tender Joint Count, mean** D1: 31.7 (15.4) D2: 31.3 (15.1) D3: 30.4 (16.8) **Swollen Joint Count, mean** D1: 18.9 (10.9) D2: 19.5 (10.4) D3: 18.9 (11.1) **Corticosteroid use, %** Receiving oral steroids: D1: 52 D2: 58 D3: 58 Overall: 54.6 **DMARD use, %** D1: 100 D2: 100 D3: 100 Overall: 100 **MTX naïve, %** D1: 0 D2: 0 D3: 0 Overall: 0	**ACR mean difference/ absolute difference (*P* Value)** ACR 20: D1: 50 D2: 30.4 D3: 10.1 (*P* = 0.001) ACR 50: D1: 28.8 (*P* = 0.001) D2: 16.8 (*P* = 0.001) D3: 3.8 ACR 70: D1: 12.4 (*P* = 0.001) D2: 5.0 (*P* = 0.1) D3: 1.3 **HAQ** D1: -0.39 (*P* = 0.001) D2: -0.31 (*P* = 0.003) D3: -0.05 **DAS (%)** Low disease activity (DAS: 3.2): D1: 51.2 D2: 15.2 D3: 4.9% Remission (DAS: 2.6): D1: 30.1% (*P* = 0.001) D2: 7.6% (*P* = 0.053) D3: 1.6% **SF-36, mean difference/absolute difference** NR **Radiographic measures** Swollen joint count: D1: -7.8 (*P* = 0.001) D2: -6.8 (*P* = 0.001) D3: -0.5	**Attrition/withdrawal** Overall, n: D1: 23 D2: 25 D3: 33 Overall: 82 Withdrawals due to adverse events, n: D1: 11 D2: 10 D3: 10 Overall: 31 Withdrawals due to lack of efficacy, n: D1: 4 D2: 6 D3: 19 Overall: 29 1 control withdrew after randomization but before receiving study treatment due to latex allergy Patients received rescue therapy (8 mg/kg of tocilizumab plus MTX at week 16 in case of treatment failure defined as less than 20% improvement in both SJC and TJC): D1:20 D2:30 D3: 63 Overall adverse events reported, n: D1: 147 D2: 142 D3: 129 Overall: 418

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	• Hemoglobin less than 8.5 g/dl • Leucopenia • Neutropenia • Thrombocytopenia • Abnormal liver function • Ttriglycerides greater than 10 mmol/l • Recognized active TB, hepatitis B, or hepatitis C		**Baseline DAS score** D1: 6.79 (0.93) D2: 6.78 (0.97) D3: 6.80 (1.06) **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: HAQ-D1: 1.7 (0.6) D2: 1.7 (0.6) D3: 1.7 (0.6)	Tender joint count: D1: -14.8 (*P* = 0.001) D2: -10.5 (*P* = 0.001) D3: -0.3 **Quality of life scales, mean difference/absolute difference** NR **Good or moderate EULAR responses** D1: 67.7% (*P* = 0.001) D2: 46.5% (*P* = 0.001) D3: 16.5%	**Serious adverse events** Death, n: D1: 0 D2: 0 D3: 0 Overall: 0 Myocardial infarction, n: D1: 0 D2: 0 D3:1 Overall: 1 Hepatotoxicity/elevated liver enzymes, n: D1: 4 D2: 0 4 D3: 0 1 Overall: 0 9 **Malignancies** NR **Respiratory events** Tuberculosis: NR **Other infections** Infections: D1: 86 D2: 76 D3: 66 Overall: 228 Serious infections: D1: 8 D2: 3 D3: 5 Overall: 16 **GI** Other GI event (not specified), n: D1: 64 D2: 53 D3: 31

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Overall: 90 **Other** Infusion/injection site reactions, n: D1: 15 D2: 15 D3: 10 Overall: 40 HDL > 60 mg/dl, n: D1: 29 D2: 22 D3: 6 Overall: 57 LDL > 160 mg/dl, n: D1: 21 D2: 25 D3: 6 Overall: 52 Severe AE (resulting in inability to work or perform daily activities), n: D1: 24 D2: 22 D3: 31 Overall: 77 Serious AE (primarily related to complications of RA), n: D1: 11 D2: 12 D3: 18 Overall: 41 AE leading to discontinuation, n: D1: 10 D2: 10 D3: 8 AE leading to dose modification, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 12 D2: 24 D3: 1 Note that AE occurring in those receiving rescue therapy excluded from AE analysis

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2009[50] **Country and setting** Multinational; multicenter **Source of funding** Centocor Research and Development; Schering-Plough Research Institute **Research objective** To assess the safety and efficacy of GOL in MTX-naive patients with active RA. **Study design** RCT **Overall N** 637 **Duration of study** 24 wks **Quality rating** Fair	**Inclusion Criteria** • MTX naïve • Adults with ACR diagnosis of RA for at least 3 mos • Not received more than 3 wkly doses of MTX as RA tx • ≥ 4 swollen and tender joints • met ≥ 2 of the following criteria: (1) CRP of 1.5 mg/dl or more or ESR of 28 mm/hr or greater; (2) morning stiffness lasting 30 minutes or longer (3) bone erosion by radiography and/or MRI prior to tx initiation with study agent; (4) anti-cyclic citrullinated peptide antibody positivity or rheumatoid factor positivity; met prespecified TB screening criteria	**Interventions, Dose** D1: • MTX: 10 mg/wk escalated to 20 mg/wk • Placebo D2: • GOL: 100 mg every 4 wks • Placebo D3: • MTX: 10 mg/wk escalated to 20 mg/wk • GOL: 50 mg every 4 wks D4: • MTX: 10 mg/wk escalated to 20 mg/wk • GOL: 100 mg every 4 wks **Number in group** D1: 160 D2: 159 D3: 159 D4: 159 **Mean age (years)** D1: 48.6 D2: 48.2 D3: 50.9 D4: 50.2 Overall: NR **Sex, % female** D1: 83.8 D2: 84.3 D3: 84.9 D4: 78.6	**Mean disease duration, years** D1: 2.9 (4.8) D2: 4.1 (5.6) D3: 3.5 (5.65) D4: 3.6 (6.09) Overall: NR **Patients with early RA, three years or less, %:** D1: 72.5 D2: 63.5 D3: 73.0 D4: 69.8 Overall: NR **Treatment resistant, %:** NR **Tender Joint Count, mean** D1: 27.3 (16.16) D2: 27.3 (15.4) D3: 29.2 (26.0) D4: 27.4 (14.7) Overall: NR **Swollen Joint Count, mean** D1: 14.9 (10.01) D2: 15.2 (10.08) D3: 16.0 (9.98) D4: 15.8 (10.34) Overall: NR **Corticosteroid use, %** D1: 68.1 D2: 63.5 D3: 69.8 D4: 65.4 Overall: NR **DMARD use, %:** D1: 51.9 D2: 58.5	**ACR:** ACR 20: ITT pop D1: 49.4 D2: 51.6 D3: 61.6 (*P* = 0.028) D4: 61.6 (*P* = 0.028) ACR 50: ITT pop D1: 29.4 D2: 32.7 D3: 40.3 (*P* = 0.042) D4: 36.5 (*P* = 0.177) mITT pop D1: 29.4 D2: 33.1 D3: 40.5 (*P* = 0.038) D4: 36.5 (*P* = 0.177) ACR 70: ITT pop D1: 15.6 D2: 13.8 D3: 23.9 (*P* = 0.064) D4: 18.2 (*P* = 0.535) **HAQ:** **DAS:** **SF-36:** **Radiographic measures:** **Quality of life scales:** **Others:**	**Overall** Overall attrition/withdrawal (n): D1: 10 D2: 11 D3: 9 D4: 8 Withdrawals due to adverse events (n): Unclear Withdrawals due to lack of efficacy (n): Unclear Adherent/compliant (n): Unclear Other attrition related comments? Figure 1 describes the number of patients that discontinued a study agent and stratifies by SC and oral agents. The lists are not mutually exclusive, so it is unclear how many of the total withdrawals were due to adverse events or for reasons of efficacy. Overall adverse events reported (n): D1: 116 D2: 107 D3: 129 D4: 121 **Serious adverse events:** Death (n): D1: 0 D2: 0 D3: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Exclusion Criteria • Previous use of INF, ETN, ADA, RTX, natalizumab, or cytotoxic agents	Overall: NR **Race, % white** D1: 71.3 D2: 69.8 D3: 74.8 D4: 73.6 Overall: NR **Race, % black** D1: 3.8 D2: 2.5 D3: 0.6 D4: 0.6 Overall: NR **Ethnicity, Latino** D1: NR D2: NR D3: NR D4: NR Overall: NR	D3: 50.3 D4: 57.2 Overall: NR **MTX naïve, %:** 100 **Baseline DAS score** Using CRP D1: 5.0 (1.01) D2: 5.2 (0.98) D3: 5.1 (0.99) D4: 5.1 (1.0) Overall: NR Using ESR D1: 6.2 (1.17) D2: 6.3 (1.10) D3: 6.3 (1.11) D4: 6.3 (1.11) Overall: NR **Required treatment for latent TB** NR **Other population characteristics:**		D4: 1 Cardiovascular events (specify) (n): HTN D1: 3 D2: 4 D3: 8 D4: 6 Hepatotoxicity/elevated liver enzymes (n): ALT D1: 10 D2: 7 D3: 20 D4: 12 AST D1: 6 D2: 6 D3: 13 D4: 10 **Malignancies:** Lymphoma or leukemia (n): D1: 0 D2: 0 D3: 0 D4: 1 Skin cancer (basal cell or squamous cell) (n): D1: 1 D2: 0 D3: 0 D4: 0 Other cancer (specify) (n): Malignancy D1: 2 D2: 0 D3: 1 D4: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Breast cancer D1: 1 D2: 0 D3: 1 D4: 0 **Respiratory events:** Tuberculosis (n): D1: 0 D2: 0 D3: 1 D4: 0 Pneumonia (n): D1: NR D2: NR D3: NR D4: 2 Upper respiratory infection (n): D1: 14 D2: 9 D3: 13 D4: 19 **Other infections:** Infections D1: 52 D2: 55 D3: 54 D4: 50 Serious infections D1: 3 D2: 2 D3: 2 D4: 7 **GI:** Nausea D1: 16 D2: 11 D3: 22

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D4: 24 Vomiting D1: 3 D2: 2 D3: 4 D4: 7 Abdominal pain (n): D1: 1 D2: 6 D3: 9 D4: 5 Dyspepsia D1: 7 D2: 5 D3: 10 D4: 8 **Other:** Infusion/injection site reactions (n): D1: 3 D2: 17 D3: 7 D4: 14 Skin rash (n): D1: 7 D2: 6 D3: 8 D4: 5 Headache (n): D1: 10 D2: 7 D3: 6 D4: 11 Dizziness (n): D1: 1 D2: 3 D3: 7

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D4: 3 Serious AEs D1: 11 D2: 5 D3: 10 D4: 10

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Emery, 2010[51] COMET trial (do not combine with other COMET REF IDs) **Country and setting** multinational; multicenter **Source of funding** Wyeth Pharmaceuticals; Pfizer **Research objective** To evaluate how continuation of and alterations to initial year 1 combination ETN + MTX therapy and MTX monotherapy regimens affect long-term remission and radiograhic progression in early active RA **Study design** RCT **Overall N** 411	**Inclusion Criteria** • Early RA • Disease duration of 3-24 mos • Included in year 2 of study • Completed COMET trial by end of year 1 **Exclusion Criteria** • Previous treatment with MTX, ETN, or another TNF antagonist at any time • Had received treatment with other DMARDs or corticosteroid injections in4 weeks before baseline visits • Important concurrent medical diseases and/or other relevant comorbidities.	**Comparisons (dosage and frequency)** D1: • MTX: avg. of 16.2 mg once weekly • ETN: 50 mg once weekly • (ETN+MTX in year 1) D2: • ETN: 50 mg once weekly • (ETN+MTX in year 1) D3: • MTX: avg. 17.8 mg once a week • ETN: 50 mg once weekly • (MTX in year 1) D4: • MTX: avg.18.0 mg once weekly (MTX in year 1) **Number in group** D1: 108 D2: 108 D3: 88 D4: 94 Overall: 398 **Mean age (years)** D1: 52.4 D2: 52.2 D3: 55.6 D4: 53.2 Overall: 53.2 **Sex, % female**	**Mean disease duration, years** D1: 8.4 mos (5.7) D2: 9.1 mos (5.6) D3: 9.1 mos (6.0) D4: 8.7 mos (5.4) Overall: 8.8 mos (5.7) **TJC, mean** D1: 3.9 (7.3) D2: 3.7 (7.9) D3: 6.5 (10.2) D4: 6.1 (7.9) Overall: 4.9 (8.4) **SJC, mean** D1: 2.7 (6.1) D2: 1.5 (3.1) D3: 3.9 (6.4) D4: 3.1 (4.4) Overall: 2.7 (5.2) **Corticosteroid use, %** NR **DMARD use, %:** D1: 100 D2: 100 D3: 100 D4: 100 Overall: 100 **MTX naïve, %:** 0 **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** 100 **Baseline DAS score**	**ACR mean difference/ absolute difference (CI/SD/P Value):** ACR 20: D1: 86 (*P*<0.001 compared to MTX/MTX) D2: 80 (*P*=0.004, compared to MTX/MTX) D3: 81 D4: 61 ACR 50: D1: 70 (*P*<0.001 compared to MTX/MTX) D2: 64 (*P*=0.007 compared to MTX/MTX) D3: 66 D4: 46 ACR 70: D1: 57 (*P*<0.001 copmared to MTX/MTX) D2: 44 (*P*=0.034 compared to MTX/MTX) D3: 48 D4: 32 **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute**	**Overall** Overall attrition/withdrawal (n): D1: 7 D2: 18 D3: 16 D4: 23 Overall: 64 Withdrawals due to adverse events (n): D1: 3 D2: 5 D3: 7 D4: 9 Overall: 24 Withdrawals due to lack of efficacy (n): D1: 0 D2: 7 D3: 1 D4: 7 Overall: 15 Overall adverse events reported (n): D1: 91 D2: 89 D3: 71 D4: 79 Overall: 330 **Serious adverse events:** Death (n): D1: 0 D2: 0 D3: 0 D4: 1 Overall: 1 **Malignancies:** Malignancy	**Quality rating for efficacy/effectiveness?** Fair **Quality rating for observational studies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Duration of study total of 2 yrs (results from this study from wk 52 to wk 104)		D1: 72.2 D2: 75.9 D3: 59.1 D4: 81.9 Overall: 72.6 **Race, % white** D1: 87.0 D2: 88.0 D3: 88.6 D4: 88.3 D5Overall: 87.9 **Race, % black** NR **Ethnicity, Latino** NR	D1: 2.7 (1.2) D2: 2.6 (1.2) D3: 3.3 (1.4) D4: 3.4 (1.4) Overall: 3.0 (1.4) **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	**difference (CI/SD/P Value):** Diff from wk 104 and wk 52 D1: 0.00 D2: -0.5 (*P*<0.001 versus MTX/MTX) D3: 0.5 (*P*<0.05 versus ETN + MTX/ETN + MTX) D4: 0.1 **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** SHS change from wk 52 to wk 104, mean (95% CI) D1: -0.02 (-0.32 to 0.29; *P*=0.006 vs ETN + MTX/ETN) D2: 0.11 (-0.54 to 0.77) D3: 0.78 (-0.06 to 1.61) D4: 2.07 (0.42 to 3.72) **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute**	D1: 0 D2: 1 D3: 5 D4: 3 Overall: 9 **Respiratory events:** NR **Other infections:** Serious Infections D1: 1 D2: 2 D3: 1 D4: 2 Overall: 6 **GI:** NR **Other:** NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				difference (CI/SD/P Value): NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Emery et al., 2010[52] SERENE **Country and setting** multinational; multicenter **Source of funding** Hoffmann-La Roche, Genentech, Biogen Idec **Research objective** To study the efficacy and safety of RTX 2 x 500 mg and 2 x 1000 mg with MTX in active RA patients who had inadequate response to MTX and no prior biologic treatment **Study design** Controlled Trials **Overall N** 511 **Duration of study** 48 wks	**Inclusion Criteria** • Treatment resistant resistant to 10-25 mg MTX/wk for 12 wks or more • 18-80 yrs old • RA according to ACR (SJC and TJC of both at least 8 • CRP at least 0.6 mg/dl or ESR at least 28 mm/h) for 6 mos or more • Absolute neutrophil count of 1500 mcg/mcl or more • Hemoglobin of 8 g/dl or more • IgM of 40 mg/dl or more • IgG of 500 mg/dl or more **Exclusion Criteria** • Previous treatment with biologic	**Comparisons (dosage and frequency)** D1: • MTX: 10-25 mg/wk • Placebo D2: • MTX: 10-25 mg/wk • RTX: 500 mg IV infusion on day 1 and 15 D3: • MTX: 10-25 mg/week • RTX: 1000 mg IV infusion on day 1 and 15 **Number in group** D1: 172 D2: 167 D3: 170 **Mean age (years)** D1: 52.16 D2: 51.91 D3: 51.30 **Sex, % female** D1: 85.5 D2: 79.6 D3: 81.2 **Race, % white** D1: 82.6 D2: 80.2 D3: 80.6 **Race, % black** NR	**Mean disease duration, years** D1: 7.48 (7.642) D2: 7.10 (6.969) D3: 6.61 (7.294) **TJC, mean** D1: 30.2 (15.94) D2: 27.1 (14.10) D3: 28.7 (14.98) **SJC, mean** D1: 20.9 (11.26) D2: 18.6 (9.62) D3: 19.5 (10.32) **Corticosteroid use, %** D1: 47.7 D2: 47.9 D3: 39.4 **DMARD use, %:** NR **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** DAS28-ESR D1: 6.54 (1.015) D2: 6.40 (0.951) D3: 6.49 (1.061) DAS28-CRP D1: 5.95 (0.972) D2: 5.81 (0.912)	**ACR mean difference/ absolute difference (CI/SD/P Value):** ACR 20: Wk 24 D1: 23.3 D2: 54.5 (*P*<0.0001) D3: 50.6 (*P*<0.0001) Wk 48: D1: NR D2: 55.7 D3: 57.6 (*P*=NR) ACR 50: Wk 24 D1: 9.3 D2: 26.3 (*P*<0.0001) D3: 25.9 (*P*<0.0001) Wk 48 D1: NR D2: 32.9 D3: 34.1 (*P*=NR) ACR 70: Wk 24 D1: 5.2 D2: 9.0 (*P*=NR) D3: 10.0 (*P*=NR) D1: NR D2: 12.6 D3: 13.5 (*P*=NR) **HAQ, mean difference/ absolute difference (CI/SD/P Value):**	**Overall** Overall attrition/withdrawal (n): D1: 13 D2: 6 D3: 6 Withdrawals due to adverse events (n): D1: 2 D2: 2 D3: 3 Other attrition related comments? • Reported for 24 wks • Withdrawals due to AE exclude RA flare • Study reports that over 90% of patients completed 48 wks of study. Overall adverse events reported (n): D1: 128 D2: 128 D3: 138 **Serious adverse events:** Death (n): D1: 0 D2: 0 D3: 0 Any Cardiac Disorder Events D1: 4 D2: 5 D3: 7 Serious Cardiac Disorder Events	**Quality rating for efficacy/effectiveness?** Fair **Quality rating for observational studies** NR

Ethnicity, Latino NR	D3: 5.86 (0.967) **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	NR **DAS, mean difference/absolute difference (CI/SD/P Value):** DAS28-ESR Wk 24 D1: -0.75 D2: -1.76 (*P*<0.0001) D3: -1.69 (*P*<0.0001) Wk 48 D1: NR D2: -1.96 (*P*=NR) D3: -2.02 (*P*=NR) **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** Remission (DAS28-ESR<2.6) Wk 24 D1: 4 D2: 16 (*P*<0.01) D3: 16 (*P*<0.01)	D1: 2 D2: 2 D3: 1 **Malignancies:** Malignancy D1: 1 D2: 1 D3: 2 **Respiratory events:** NR **Other infections:** Any Infection D1: 74 D2: 69 D3: 61 Serious Infection D1: 4 D2: 1 D3: 2 **GI:** Any lower GI events D1: 20 D2: 16 D3: 16 Any serious GI Events D1: 3 D2: 1 D3: 1 **Other:** Infusion/injection site reactions (n): Day 1 D1: 24 D2: 31 D3: 42 Day 15 D1: 14 D2: 12 D3: 10

		Wk 48 D1: NR D2:15 (*P*=NR) D3: 19 (*P*=NR)	Any other AEs: Reported AEs only up to 24 wks

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, yr: Feltelius et al., 2005[53] **Country, Setting:** Sweden, Swedish Society of Rheumatology database **Funding:** Wyeth Research **Research Objective:** To describe a nationwide system for postmarketing follow up of new antirheumatic drugs; to analyze safety and effectiveness in an ETA-treated cohort **Study Design:** Case series **Overall N:** 1,073 **Study Duration:** >2 yrs	**Inclusion Criteria:** • Previous use of DMARDs: previous treatment with > 1 DMARD in addition to MTX • Active RA as evaluated by the attending physician **Exclusion Criteria:** • NR **Interventions:** **D1: ETA** **Etanercept:** 25mg twice weekly **N:** D1: 1073 **Mean age (yrs):** D1: 52 **Sex, % female:** **D1: 76.6** **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: 56.3 **Corticosteroid use, %:** D1: 95.2 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.9 D1: MTX use: 40.1	In 294 pts (27%) , at least 1 adverse drug reaction (ADR) was reported (421 reports; mean 1.5 report per patient; median 1; rand 1 to 6) 80 ADR reports (19%) were serious and 331 (79%)were non-serious 76 pts (7%) experienced at least one serious event and 114 (11%) had events exclusively classified as nonserious Incidence of adverse events remained constant over time	**Overall:** D1: 27 (% of pts) **Serious AEs:** D1: 7 (% of pts) **Infections:** D1: 22 (% of all AE diagnoses) **Serious Infections:** D1: 5.4 (% of all AE diagnoses) **Infusion or injection reaction:** NR **Abdominal Pain:** NR **Cardiovascular Events:** D1: 4.8 (% of all AE diagnoses) **Dizziness:** NR **Headache:** NR **Hepatotoxicity:** D1: liver/biliary 0.6% (of all AE diagnoses) **Malignancies:** NR **Nausea:** NR **URTI:** NR **UTI:** NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** Not applicable (Why not?) **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Fernandez-Nebro et al., 2007[54] **Country and setting** Spain, tertiary care center **Source of funding** NR **Research objective** Evaluate effectiveness and safety of anti-TNF therapies and to identify factors involved in this response **Study design** Dynamic Prospective Cohort Study **Overall N** 161 **Duration of study** 6 years (secondary outcomes [DAS28, HAQ, EULAR response] measured at 6 mos) **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant • No response to at least 2 DMARDs, including MTX • Required biological therapy inopinion of a physician. • No formal level of disease activity was required. • No restriction ofuse of DMARD, steroids and NSAIDs **Exclusion Criteria** • NR	**Interventions, dose** D1: IFX: Varied D2: ETN: Varied D3: ADA: Varied **Number in group** D1: 60 D2: 79 D3: 22 Overall: 161 **Mean age, years (SD)** D1: 54.0 (11.6) D2: 54.0 (12.4) D3: 54.0 (11.2) Overall: 54.0 (12) **Sex, % female** D1: 88 D2: 76 D3: 82 Overall: 81 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 9.6 (7.9) D2: 9.9 (7.9) D3: 9.5 (8.3) Overall: NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 D3: 100 Overall: 100 **Tender Joint Count, mean (SD)** D1: 16.6 (8.3) D2: 13.6 (7.9) D3: 13.3 (6.2) Overall: NR **Swollen Joint Count, mean (SD)** D1: 11.1 (7.3) D2: 9.7 (6.7) D3: 9.5 (7.8) Overall: NR **Corticosteroid use, %** D1: 65 D2: 67 D3: 48 Overall: NR **DMARD use, %** D1: 92 D2: 54 D3: 73 Overall: 70 **MTX naïve, %**	**ACR mean difference/ absolute difference** NR **HAQ (SD)** D1: -0.32 (0.37) (n: 60) D2: -0.46 (0.63) (n: 78) D3: NR Overall: -0.35 (0.54), (*P* = 0.0001) **DAS** D1: -1.3 (1.2) D2: -1.7 (1.5) D3: NR Overall: -1.5 (1.4) (*P* = 0.0001) **SF-36** NR **Radiographic measures** NR **Quality of life scales, mean difference/absolute difference** NR **EULAR at 6 mo (%)** IFX: • Good 11% • Moderate 49% • No response 40% ETN • Good 25% • Moderate 43% • No response 32% • Overall: (*P* = 0.218) MCID HAQ at 6 mo: • IFX: 58% • ETN: 57%	**Attrition/withdrawal** Withdrawals due to adverse events, n: Overall: 8.1% (n: 13) Primary efficacy endpoint of this study was time to treatment failure defined as definitive withdrawal of anti-TNF for any reason, or substitution or addition of concomitant DMARD to maintainefficacy ofanti-TNF. Overall adverse events reported, n: D1: 112 D2: 84 D3: 19 Overall: 215 **Serious adverse events** Death, n: D1: 1 D2: 1 D3: 0 Overall: 2 Cardiovascular events (specify), n: D1: 1 D2: 4 D3: 0 Overall: • Total cardiovascular problems: 9% (n: 15) • Arterial hypertension/ decompensation: 10 • Cardiac rhythm disorder: 2 • Acute myocardial infarction: 1 • Deep vein thrombosis: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR **Baseline DAS score** D1: 6.2 (1.3) D2: 5.9 (1.4) D3: 6.2 (0.9) Overall: NR **Required treatment for latent TB** NR **Other population characteristics, %** MTX use: D1: 83 D2: 52 D3: 50 LEF use: D1: 8 D2: 3 D3: 9 SSZ: D1: 0 D2: 0 D3: 5 Hydroxcholoquine (HCQ): D1: 0 D2: 0 D3: 5 MTX + HCQ D1: 0 D2: 0 D3: 5 Overall: NR	• *P* = 0.951 6 yr results: Time to failure (patient-years) • IFX: 105.7 • ETN: 145.5 • ADA: 23.1 Failure-Rate per 100 Patient-years (95% CI): • IFX: 40.7 (28.5-52.8) • ETN: 25.4 (17.2-33.6) • ADA: 39.0 (13.5-64.4) Time to treatment failure: • Multivariate Hazard Ratio ETN (Ref: IFX): 0.34 (95% CI 0.18-0.61) • Patients receiving ETN V IFX over first 24 mo remained for longer without treatment failure (*P* = 0.032) and had a lower failure rate through follow-up (rate ratio: 0.6 95% CI 0.4-0.9)	• Cardiac insufficiency: 1 Increased transaminases, n: D1: 9 D2: 2 D3: 0 Overall: 11 **Malignancies** Lymphoma or leukemia, n: D1: 0 D2: 0 D3: 0 Overall: 0 Skin cancer (basal cell or squamous cell), n: D1: 0 D2: basocellular carcinoma ofnasal dorsum: 1 D3: cutaneous basocellular carcinoma: 1 Overall: 2 Other cancer (specify), n: D1: pulmonary carcinoid tumor: 1 D2: pancreatic carcinoma: 1 monoclonal lymphoproliferation of B cells: 2; IgG-kappa monoclonal gammopathy: 1 D3: 0 Overall: 5 **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 0 D2: 0 D3: 1 Overall: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Other infections Urological sepsis, n: D1: 1 D2: 1 D3: 0 Overall: 1 Other infections, n: Brucellosis: 1 Septic arthritis: 1 Soft tissue: D1: 3 D2: 3 D3: 1 Herpes zoster: D1: 0 D2: 2 D3: 1 Overall: 12 **GI** NR **Other** Infusion/injection site reactions, n: D1: 7 D2: 2 D3: 1 Overall: 10 Skin rash, n: D1: 7 D2: 5 D3: 1 Overall: 13 Demyelenation or multiple sclerosis, n: D1: 0 D2: 0 D3: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Overall: 0 Worsening of ocular and oral dryness, n: D1: 0 D2: 7 D3: 0 Overall: 7 Total infections, n: D1: 30 D2: 24 D3: 8 Overall: 62 Herpes zoster, n: D1: 0 D2: 2 D3: 1 Overall: 3 Dryness worsening, n: D1: 0 D2: 7 D3: 0 Overall: 7 Onset of worsening high blood pressure: D1: 6 D2: 3 D3: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Finckh et al., 2007[55] (SCQM cohort) **Country and setting** Switzerland, university hospitals **Source of funding** Geneva University **Research objective** Compare effectiveness of RTX with alternative anti-TNF agents in managing pts who had inadequate response to anti-TNF therapy **Study design** Prospective Cohort **Overall N** 116 **Duration of study** January 1998 to end of September 2006 **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant at least one anti-TNF agent • Initiation of second or third alternative anti-TNF agent or RTX • Baseline assessment of DAS28 at time of treatment switch • At least 1 f/u assessment within first 12 mos • Diagnosis of RA by rheumatologist • Inadequate response to at least 1 anti-TNF agent **Exclusion Criteria** • A treatment switch because of personal preferences (i.e., in absence of an inadequate response to previous anti-TNF agent) and RTX therapy for lymphoma.	**Interventions, dose** D1: RIT: 2 infusions of 1,000 mg D2: • ETN: 50 mg subcutaneously weekly • IFX: 3mg/kg intravenously • ADA: 40 mg every two weeks **Number in group** D1: 50 D2: 66 Overall: NR **Mean age, median** D1: 55 D2: 54 *P* = 0.78 **Sex, % female** D1: 77 D2: 76 *P* = 0.87 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Disease duration mean, median** D1: 10 D2: 9 **Disease duration mean, IQR** D1: 6-18 D2: 5-16 *P* =39 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** At least 1 anti-TNF agent: D1: 100 D2: 100 Overall: NR **TJC, mean** D1: 11 D2: 10 *P* = 0.44 **SJC, mean** D1: 10 D2: 8 *P* = 0.17 **Corticosteroid use, %** D1: 58 D2: 55 *P* = 0.71 **DMARD use, %** MTX: D1: 52 D2: 39 *P* = 0.18 LEF: D1: 16	**ACR** NR **HAQ** NR **DAS** At 6 mos: D1: -1.6 mean decrease (95% CI) -1.97, -1.25 D2: -0.98 mean, (95% CI) -1.33, -0.62 *P* = 0.01 **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR	**Attrition/withdrawal** There were 209 patients in SCQM databank who received RTX or a 2nd or 3rd anti-TNF agent. Of these, 60 (29%) were excluded from this study b/c of missing follow up assessments, 22 (11%) were excluded b/c they switched to an alternative biologic therapy b/c of personal preferences and not as a result of inadequate response to anti-TNF therapy, 8 (4%) were excluded b/c of missing baseline assessment, and 3 (1%) b/c RTX was administered to treat concomitant lymphoma rather than RA **Respiratory events** Tuberculosis: NR Upper respiratory infection, n: NR **Other infections** NR **GI** NR **Other** Infusion/injection site reactions, n: D1: 1 D2: 9 *P* = 0.03 Allergic complications, n: D1: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	• Any observations after interruption of anti-TNF treatment or re-treatment with RTX were censored.		D2: 14 *P* =.72 Other DMARD: D1: 10 D2: 9 *P* = 0.87 None D1: 28 D2: 39 *P* = 0.20 **MTX naïve** NR **Baseline DAS score mean (CI)** D1: 5.43 (4.99-5.87) D2: 5.01 (4.70-5.32) *P* = 0.11 **No. of previous anti-TNF agents (SD)** D1: 1.96 - 0.7 () D2: 1.53 - 0.6 *P* = 0.001		D2: 0 *P* = 0.04

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Finckh et al., 2009[56] (SCQM cohort) **Country and setting** Switzerland, multicenter **Source of funding** Sanofi-Aventis, Geneva University, SCQM Foundation, Swiss National Science Foundation **Research objective** Compare retention rates, effectiveness and safety ofrapeutic regimen associating anti- TNF agents and LEF, MTX or other conventional DMARDs in a large population based RA cohort. **Study design** Population-based Cohort **Overall N** 1218 **Duration of study** March 1996-December 2006, mean patient follow up 17 mos **Quality rating** Fair	**Inclusion Criteria** • Diagnosis of RA by rheumatologist and treatment with INF, ETN, or ADA **Exclusion Criteria** • Absence of concomitant DMARDrapy, and simultaneous prescription of LEF and MTX in combination with anti-TNF agents.	**Interventions, Dose** D1: • MTX: 15mg/week (median dose at baseline) • Other: this D was anti-TNF agents (all combined) + MTX D2: • LEF: 20mg/day (median dose at baseline) • Other: anti-TNF agents (combined) + LEF D3: • Sulfasalazine, • Hydroxychlorquine, Anti-TNF agents (combined) + any oral DMARD that was not MTX or LEF (minocycline, azathioprine, cyclosporine A, D-penicillamine, oral or intramuscular gold salts) **Number in group** D1: 842 D2: 260 D3: 116 Overall: 1218 **Mean age (years)** D1: 53 D2: 53 D3: 55 *P* = 0.23 **Sex, % female**	**Mean disease duration, median** D1: 8.4 D2: 8.9 D3: 9.9 Overall: **Mean disease duration, IQR** D1: 3.7-14.9 D2: 3.3-14.2 D3: 4.4-15.8 *P* = 0.14 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** Anti-TNF failure: D1: 33 D2: 41 D3: 28 *P* = 0.06 **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** Concomitant steroid use ever: D1: 48 D2: 51 D3: 67 *P* =.001 **Previous DMARD use, median, n** D1: 1 D2: 2 D3: 2	**ACR** NR **HAQ, mean improvement after 1 year (CI)** D1: 0.12 (0.08-0.15) D2: 0.14 (0.07-0.20) D3: 0.13 (0.03-0.23) *P* = 0.09 **DAS, mean improvement after 1 year (CI)** D1: 0.74 (0.63-0.84) D2: 0.63 (0.45-0.82) D3: 0.86 (0.60-1.12 *P* = 0.33 **SF-36, mean difference/absolute difference** NR **Radiographic damage progression measures (CI)** D1: 0.91% (0.54-1.27) D2: 0.74% (0.21-1.27) D3: 0.71% (-0.02-1.44) *P* = 0.77 **Quality of life scales** NR	**Overall adverse events reported, n:** 178; *P* = 0.13 **Serious adverse events** NR **Malignancies** NR **Other infections** NR **GI** Allergic complications, n (CI): D1: 0.45 0.20-0.98) D2: NR D3: NR *P* = 0.04 **Any other AEs:** • A total of 178 combinationrapies were interrupted because of adverse events (28%). most common adverse events leading to treatment interruption were: allergic reactions (28%), infections (19%), skin reactions (19%), and gastrointestinal side effects (12%). • Hepatotoxicity (2%) and malignancies (6%) were rare causes of treatment interruption in this cohort.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D1: 76 D2: 79 D3: 78 *P* = 0.57 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Previous DMARD use, IQR** D1: 0-2 D2: 1-3 D3: 1-3 *P* = 0.001 **MTX naïve, %** NR **Baseline DAS28 score, mean (SD)** D1: 4.1 (1.5) D2: 4.5 (1.4) D3: 4.6 (1.4) *P* = 0.31 **Required treatment for latent TB** NR **HAQ, mean (SD)** D1: 1.24 (0.71) D2: 1.34 (0.67) D3: 1.33 (0.72)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Fleischmann et al., 2003;[57]; Tesser et al., 2004[58]; Schiff et al., 2006[59]; Fleischmann et al., 2006[60] **Country, Setting:** Multinational, multicenter **Funding:** Amgen **Research Objective:** Long term safety of AKA in a large population of pts with RA **Study Design:** RCT **Overall N:** 1414 (1399) enrolled (open label 1103) **Study Duration:** 6 mos (up to 30 mos open label for a total of 3 yrs)	**Inclusion Criteria:** • Age: 18+ • Diagnosed according to ACR criteria; duration 3+ mos • Stable doses of NSAIDs and Cs for one mo; and stable doses of DMARDs for 2 mos • NSAIDS, Cs, and DMARDs (except TNF inhibitors) **Exclusion Criteria:** • Pregnant or lactating • Uncontrolled medical condition • Malignancy other than basal cell carcinoma of skin or in situ carcinoma of cervix • Felty's syndrome • HIV • Leukopenia • Neutropenia • Tthrombocy-topenia Abnormal liver function test result Hepatitis B or C	**Interventions, dose:** D1: AKA (100mg/d) D2: placebo **N:** D1: 1116 D2: 283 **Mean age, yrs:** D1: 54.6 D2: 55.7 **Sex, % female:** D1: 74.7 D2: 74.6 **Race, % white:** D1: 87.8 D2: 90.1	**Mean disease duration, yrs:** D1: 10.2 (9.6) D2: 10.7 (9.5) **TJC, mean:** D1: 22.6 (14.7) D2: 22.6 (14.5) **SJC, mean:** D1: 18.8 (11.9) D2: 18.3 (11.7) **DMARD use excluding MTX, and TNF inhibitors %:** D1: 47.7 D2: 47.7 **Corticosteroid use, %:** D1: 57 D2: 60.8 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** D1: 51.9 D2: 59.4	6 mos-injection site reactions, AKA vs. placebo. (72.6% v. 32.9%) *P*-value NR • 13.4% AKA withdrew due to AE vs, 9.2% placebo (*P* = 0.057); overall discontinuation rates (21.6% vs. 18.7%) • Serious infections AKA vs. placebo (2.1% v. 0.4%), may be clinically significant. (*P* = 0.068) • Comorbid conditions, serious infectious events (2.5% vs. 0.0%; *P* = NR). • Trend towards increased risk of serious infectious events with AKA in pts with pulmonary comorbidities vs. placebo (3.4% v. 1.6%), *P* = NS • From 0-3 yrs rates per 100 yrs of patient exposure • ISRs (122.26 events), • Rheumatoid arthritis progression (67.80 events) • URTIs(26.09 events) Concomitant use of corticosteroids vs. not serious infection (7.13 events/100 PY v 2.87 events/100 PY). pneumonia (1.5 events/100 PY v 0.96 events/100 PY) Cellulitis (1.2 events/100 PY	**Overall:** D1: 92 D2: 92.2 D3: 96 **SAEs:** D1: 7.7 D2: 7.8 D3: 27 **Infections:** D1: 41.2 D2: 43.5 **Serious Infections:** D1: 2.1 D2: 0.4 D3: 8 **Infusion or injection reaction:** D1: 72.6 D2: 32.9 **URTI:** D1: 13.3 D2: 18.4 **UTI:** D1: 4.6 **D2: 5.3** **Adherence:** AKA vs. placebo: 100% adherent with use of study drug: 43.8% vs. 47.8; <70% adherent: 0.8% vs. 1.7%>40% missed no injections and >90% received at least 90% of intended doses	**Overall Attrition Rate, %:** 21 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				v 0.21 events/100 PY)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Fleischmann et al., 2009[61] ,FAST4WARD **Country and setting** 36 sites in Austria,Czech Republic andUSA between June 2003 and July 2004. Setting NR **Source of funding** UCB **Research objective** Examine efficacy and safety of CZP 400 mg monotherapy in pts who had failed at least one prior DMARD **Study design** Controlled Trials **Overall N** 220 **Duration of study** 24 weeks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant Failed ≥ 1DMARD • Aged 18-75 yrs • Adult onset RA (defined byACR criteria) for ≥ 6 mos • Failed ≥ 1 previous DMARD due to lack of efficacy or intolerance • Active disease at screening and baseline (defined by ≥ 9 tender joints, ≥ 9 swollen joints, ≥ 1 offollowing: ≥ 45 min morning stiffness, ESR ≥ 28 mm/h, or CRP > 10mg/l) • DMARDs discontinued ≥ 28-d or 5 half lives of drug prior to administration of first study dose (exception being LEF, which was eliminated using cholestyramine administration followed by a further 28-d	**Interventions, dose** D1: Certolizumab: 400mg every 4 weeks D2: Placebo: Every 4 weeks **Number in group** D1: 111 D2: 109 **Mean age, years (SD)** D1: 52.7 ± 12.7 D2: 54.9 ± 11.6 **Sex, % female** D1: 78.4% D2: 89.0% **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 8.7 yrs ± 8.2 D2: 10.4 ± 9.6 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** Failed ≥ 1 previous DMARD D1: 100 D2: 100 **Tender Joint Count, mean** D1: 29.6 ±13.7 D2: 28.3 ± 12.5 **Swollen Joint Count, mean** D1: 21.2 ± 10.1 D2: 19.9 ± 9.3 **Corticosteroid use, %** D1: 55.9 D2: 58.7 **DMARD use, %** # of prior DMARDS: D1: 2 ± 1.19 D2: 2 ± 1.25 **MTX naïve, %** D1: 18.0 D2: 18.3 **DAS28 (ESR) 3** D1: 6.3 ± 1.1 D2: 6.3 ± 0.9 **Required treatment for latent TB** NR **HAQ-DI (mean/SD)** D1: 1.4 ± 0.63	**ACR mean difference/ absolute difference (%)** ACR 20: D1: 45.5 D2: 9.3 *P* = 0.001 ACR 50: D1: 22.7 D2: 3.7 *P* = 0.001 ACR 70: D1: 5.5 D2: 0 *P =:* 0.05 **HAQ-DI, clinically meaningful improvement in physical function at week 24 (%)** D1: 49 D2: 12 *P* = 0.001 **DAS28(ESR)3 (least square mean change at wk 24 from baseline)** D1: -1.5 D2: -0.6 *P* = 0.001 **SF-36** D1: Data not shown D2: Data not shown *P* = 0.001 **Radiographic measures** NR **Quality of life scales** D1: HRQoL **Others, (please name)**	**Attrition/withdrawal (%)** Overall, n: D1: 35 (31.5) D2: 81 (74.3) Overall: 116 (52.7) Withdrawals due to adverse events, n: D1: 5 (4.5) D2: 2 (1.8) Overall: 7 (3.2) Withdrawals due to lack of efficacy, n: D1: 24 (21.6) D2: 75 (68.8) Overall: 99 (45.0) **Overall adverse events reported, n (%):** D1: 84/111 (75.7) D2: 63/109 (57.8) **Serious adverse events** Death, n: D1: 0 D2: 0 **Malignancies** Lymphoma or leukemia, n: D1: 0 D2: 0 Skin cancer (basal cell or squamous cell), n: D1: 0 D2: 0 Other cancer (specify), n: D1: 0 D2: 0 **Respiratory events** Tuberculosis: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	washout) **Exclusion Criteria** • Inflammatory arthritis other than RA • A history of chronic, serious or life-threatening infection • Any current infection • History of or chest x ray suggesting TB or a positive (defined by local practice) purified protein derivative (PPD) skin test (Patients positive for PPD who had received Bacille Calmette-Gue & acute • Rin (BCG) vaccination and had a negative chest x ray and no clinical symptoms of TB could be enrolled) • Received biological therapies for RA within 6 mos		D2: 1.6 ± 0.65	• Swollen joint count (least square mean change at wk 24 from baseline) CZ*P:* -11.6, Placebo: -6.3 (*P* = 0.001) (reduced by approximately 38% for CZP compared with 16% for placebo) • Tender joint count (least square mean change at wk 24 from baseline): CZ*P:* -16.0, placebo: -7.3 (*P* = 0.001) (reduced by approximately 40% for CZP compared with 14% for placebo) • Patient's global assessment of arthritis (least square mean change at wk 24 from baseline): CZ*P:* -0.7, Placebo: 0.0 (*P* = 0.001) • Patient's assessment of arthritis pain (clinically meaningful reductions in arthritis pain at wk 24): CZ*P:* 47%, Placebo: 17% (*P* <0.001) • Experienced minimally clinically important differences in Physical Component Summary: CZ*P:* 46%, Placebo: 16% (*P* = 0.001) • Experienced minimally clinically important differences in Mental Component Summary: CZ*P:* 34%, Placebo: 7% (*P* = 0.001) • Experienced minimally	Pneumonitis, n: D1: 0 D2: 1 **Other infections** Serious infections, n: D1: 2 (1.8%) D2: 0 **GI** NR **Other** Infusion/injection site reactions, n: D1: 4.5% D2: 13.8% Overall Serious AEs 1, n (%): D1: 8 (7.2) D2: 3 (2.8) Severe severity, n (%): D1: 8 (7.2) D2: 11 (10.1) Moderate severity, n (%): D1: 52 (46.8) D2: 40 (36.7) Mild severity, n (%): D1: 62 (55.9) D2: 43 (39.4) **Any other AEs:** SAE CZP: • Aggravated RA n: 2 • Bacterial arthritis n: 1 • Mastits n: 1 • Benign parathyroid tumour n: 1 • Uterine fibroids n: 1 • Postural dizziness n: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	• Prior treatment with TNFα inhibitors • Intra-articular, periarticular, intramuscular and intravenous corticosteroids (PRED equivalent 10 mg/day, stable for >4 weeks prior to enrollment and during study, non-steroidal anti-inflammatory drugs and analgesics were allowed)			clinically important improvemtns in fatigue: CZ*P:* 46%, Placebo: 17% (*P* = 0.001)	• Ischaemic stroke n: 1 SAE Placebo: • Vomiting: 1 • Pneumonitis: 1 • Chronic renal failure: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	**Baseline Disease and Treatment Characteristics**	Health Outcomes	Adverse Events, %
Author, yr: Flendrie et al., 2003[62] **Country, Setting:** Netherlands. University medical centre (Nijmegen) **Funding:** Not reported **Research Objective:** To determine the drug survival during treatment of RA pts with TNF blocking agents **Study Design:** Retrospective cohort study **Overall N:** 230 **Study Duration:** About 6 yrs. (maximum follow up times for 3 groups were 69, 35, and 30 mos)	**Inclusion Criteria:** • Age: adult • Diagnosed with RA according to ACR criteria1) started treatment with ADA, INF, or ETA prior to January 1 2003 at department of rheumatology of University Medical Centre Nijmegen. 2) pts receiving ADA had been treated in phase 1, 2, and 3 clinical trials. ADA was given in different dosages subcutaneously or intravenously. The pts then entered an open label extension study. 3) INF and ETA pts were treated in daily clinical practice and fulfilled the Dutch criteria for TNF blocking therapy; had moderate to high disease activity, and high dosage MTX and at least one other DMARD had failed **Exclusion Criteria:** NR	**Interventions:** D1: ADA D2: INF D3: ETA **N:** D1: 94 D2: 120 D3: 16 **Mean age (yrs):** D1: 55.2 D2: 56.4 D3: 50.6 : 55.5 **Sex, % female:** D1: 63 D2: 72 D3: 63 **Race, % white:** NR **Mean disease duration, yrs:** D1: 11.4 D2: 11.9 D3: 10.1 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: previous DMARD use, mean 4.5 D2: 4.1 D3: 3.3 **Corticosteroid use, %:**	About 70% of pts were still receiving TNF blocking agents after the first yr. One yr. drug survival percentages (percentage of pts still taking the drug) were 73% for ADA, 66% for INF, and 74% for ETA group. No significant differences between groups	**Overall:** D1: 12 D2: 30 **D3: 7** **Serious AEs:** NR Infections: D1: 2 D2: 6 **D3: 0** **Serious Infections:** D1: 6.4 D2: 7.2 **D3: 0** **Infusion or injection reaction:** D1: 3 D2: 14 **D3: 0** **Malignancies:** D1: 2 D2: 0 **D3: 0**	**Overall Attrition Rate, %:** 17 **ITT Analysis:** NA **Quality Rating:** Fair

	D1: 51 D2: 24 D3: 19 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 6.4 D2: 5.9 D3: 5.8 **RF positive:** D1: 93% D2: 82% D3: 88%	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Flendrie et al., 2005 [63] **Country, Setting:** Netherlands, Hospital rheumatology clinic **Funding:** NR **Research Objective:** Whether dermatological conditions after TNF-alpha-blocking therapy are a significant and clinically important problem in RA pts receiving TNF-alpha -blocking therapy. **Study Design:** Prospective cohort study with historic control **Overall N:** 578 **Study Duration:** 911PY	**Inclusion Criteria:** • Previous use of DMARDs: failure or intolerability of at least 2 DMARDS, including MTX, in adequate dosage regimens • Control pts selected from Nijmegen inception cohort • Pts required to meet Dutch guidelines for biological therapies: a moderate to high DAS score (DAS28 > 3.2) • Besides therapy with registrated TNF-alpha-blocking agents -INF, ETA, and ADA -some pts were treated in clinical trials with lenercept **Exclusion Criteria:** NR	**Interventions, dose:** D1: TNF-apha blockers D2: Control **N:** NR **Mean age at diagnosis, yrs:** D1: 44.5 D2: 54.6 **Sex, % female:** D1: 69 D2: 62 **Race, % white:** NR	**Median disease duration, yrs:** D1: 9.2 D2: 6.2 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **PNL at baseline (%)** D1: 39 D2: 7 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.9 D2: 3.6	Dermatological events recorded in 72/289 (25%) of RA pts receiving TNF-alpha-blocking therapy and in 37 (13%) of control group • OR of TNF-alpha-blocking therapy for dermatological referral was 2.26 (95% CI,1.46 to 3.50, *P* < 0.0005) • 128 dermatological events were recorded during follow-up in RA pts on TNF-alpha-blocking therapy (0.14 event per PY)	**Overall:** D1: 25 D2: 13 **Infections (skin):** D1: 9.3	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Fuerst et al., 2006[64] **Country and setting** Germany, hospital **Source of funding** Not reported **Research objective** Assess whether tx with MTX or LEF increases risk of wound healing after elective orthopedic surgery **Study design** Prospective Cohort Study **Overall N** 201 **Duration of study** 6 weeks+ **Quality rating** Fair	**Inclusion Criteria** • RA or PsA, 3+ months of continuous therapy with one of study drugs (MTX, LEF, ETA, INF, ADA, or ANA) • Undergoing elective orthopedic surgery **Exclusion Criteria** NR	**Interventions, Dose** D1: • MTX: 5-25 mg • Other: Corticosteroids: dose: 2-10 mg D2: • LEF: 10-30 mg • Other: Corticosteroids: 2.5-8 mg **Number in group** D1: 59 D2: 32 Overall: 201 **Mean age (years)** D1: 62.9 D2: 62.3 Overall: 62 **Sex, % female** D1: 72.9 D2: 78.1 Overall: 84.6 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 15.2 yrs D2: 14.3 yrs **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: 100% D2: 12.5% **DMARD use, %** D1: 0 D2: 0 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** ACR 20: No measures of efficacy or QOL were reported for this article ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NA **Overall adverse events reported, n:** SEE ADDITIONAL COMMENTS **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • LEF(+Cs) significantly increased risk for wound healing complications compared to MTX+Cs (40.6% vs. 13.6%, *P* = 0.01). • ETA and INF did not appear to increase risk of complications but N's were small (ETA: N = 16, 18.8% with complications • INF: N = 4, 1pt report complications-they were taking INF+LEF+Cs). • Logistic regression (wound complications, OR compared to those not receiving drug) MTX 0.99 (0.36-2.70), Corticosteroid

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					1.15 (0.51-2.59), LEF 3.48 (1.31-9.24), ETA 1.45 (0.35-5.93), INF 1.42 (0.35-5.92)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Furst, 2003[65] STAR Trial **Country, Setting:** US and Canada, multicenter (69 sites) **Funding:** Abbott Laboratories, Abbott Park II **Research Objective:** To evaluate the safety and efficacy of ADA when given with standard anti-rheumatic therapy in pts with active RA not adequately responding to standard therapies **Study Design:** RCT **Overall N:** 636 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA (ACR criteria) • Continued txt with standard anti-rheumatic therapy which included traditional DMARD, Cs, NSAID, or analgesics **Exclusion Criteria:** • Prior txt with Anti-CD4 therapy or biologic DMARD • Participated in other trials biolgic DMARD in RA • History of active: inflammatory arthritide other than RA or active listeriosis or mycobacterial infection • Major infection requiring hospitalization • Txt with IV antibiotics within 30 ds • Oral antibiotics within 14 ds • Any uncontrolled medical condition	**Interventions, dose:** D1: ADA (40mg s.c. eavery other week) D2: placebo **N:** D1: 318 D2: 318 **Mean age, yrs:** D1: 55 D2: 55.8 **Sex, % female:** D1: 79.6 D2: 79.2 **Race, % white:** D1: 89 D2: 85.8	**Mean disease duration, yrs:** D1: 9.3 D2: 11.5 **TJC, mean:** D1: 27.3 D2: 27.6 **SJC, mean:** D1: 20.9 D2: 21.3 **DMARD use, %:** NR **Corticosteroid use, %:** D1: 50.9 D2: 54.4 **MTX naive, %:** D1: 20.9 (11) D2: 21.3 (11.2) **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** D1: 50.9 D2: 54.4 **Baseline patient DAS (mean):** D1: 53.9 D2: 52.9 **Baseline physician DAS (mean):** D1: 59.9 D2: 59.6	**Health Outcome Measures:** • At endpoint, significantly more ADA (28.9%) pts achieved an ACR50 response than placebo pts (11.3%) ($P < 0.001$) • At endpoint, significantly more ADA (14.8%) pts achieved an ACR70 response than placebo pts (3.5%) ($P < 0.001$) **Intermediate Outcome Measures:** • At endpoint, significantly more ADA (52.8%) pts achieved an ACR20 response than placebo pts (34.9%) ($P < 0.001$)	**Overall:** D1: 86.5 D2: 82.7 **SAEs:** D1: 5.3 D2: 6.9 **Infections:** D1: 52.2 D2: 49.4 **Serious Infections:** D1: 1.3 D2: 1.9 **Rash:** D1: 10.7 D2: 6.0 **Infusion or injection reaction:** D1: 19.5 D2: 11.6 **URTI:** D1: 19.8 D2: 15.1 **UTI:** D1: 9.1 D2: 5.7 **Back pain:** D1: 5.3 D2: 1.6	**Overall Attrition Rate, %:** 9.1 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Galloway JB et al., 2011[66] British Society for Rheumatogy Biologics Register (BSRBR) **Country and setting** UK, multicenter **Source of funding** University of Manchester **Research objective** To evaluate the risk of serious infections (SIs) in patients with RA treated with anti-TNF therapy with emphasis on the risk across different ages. **Study design** Observational **Overall N** 15,396 (11,798 in anti-TNF cohort and 3,596 in non-biologic DMARD cohort) **Duration of**	**Inclusion Criteria** • Active RA • Enrolled in BSRBR • Had to have at least 1 returned consultant follow up questionnaire before 31 December 2008 **Exclusion Criteria** • NA	**Comparisons (dosage and frequency)** D1: Non-biologic DMARDs: Dosage and frequency NR D2: All anti-TNF: Dosage and frequency NR D3: ETN: Dosage and frequency NR D4: INF:Dosage and frequency NR D5: ADA: Dosage and frequency NR **Number in group** D1: 3598 D2: 11798 D3: 4129 D4: 3467 D5: 4202 **Mean age (years)** D1: 60 D2: 56 D3: 56 D4: 56 D5: 57 **Sex, % female** D1: 2982 D2: 8777 D3: 3182 D4: 2620 D5: 3149 **Race, % white** NR	**Mean disease duration, years** Median (IQR) D1: 6 (1-15) D2: 11 (6-19) D3: 12 (6-19) D4: 12 (6-19) D5: 10 (5-18) **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** D1: 23 D2: 44 D3: 48 D4: 46 D5: 39 **DMARD use, %:** D1: 100 **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** D1: 5.1 D2: 6.6 D3: 6.6 D4: 6.6 D5: 6.5 **Required treatment for**	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** NR **Serious adverse events:** Death (n): D1: 47 D2: 110 **Malignancies:** NR **Respiratory events:** NR **Other infections:** Other infections (specify) (n): D1: 296 D2: 1512 D3: 609 D4: 441 D5: 462 **GI:** NR **Other:** Patients experienced at least one serious infection (SI), Rate/1000 pyrs (95% CI) D1: 32 (28-36) D2: 42 (40-44) D3: 38 (35-42) D4: 46 (42-50) D5: 43 (39-47) Unadjusted HR D1: Ref D2: 15 (1.3-1.7) D3: 1.4 (1.2-1.6) D4: 1.6 (1.4-1.9) D5: 1.4 (1.2-1.7)	**Quality rating for efficacy/effectiveness?** **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
study Median duration of folow-up anti-THF cohort: 3.9 yrs (IQR, 2.4-4.9) Non-biologic DMARD cohort: 2.6 yrs (IQR, 1.4-3.8)		**Race, % black** NR **Ethnicity, Latino** NR	**latent TB** NR **Other population characteristics, %, (CI/SD/P value):** Diabetes, n D1: 234 D2: 675 D3: 254 D4: 165 D5: 252 COPD, n D1: 300 D2: 565 D3: 222 D4: 165 D5: 178		AdjHR (95% CI) (adjusted for age, gender, COPD, DM, smoking, disease duration, DAS, HAQ, entry yr, steroid use and MTX use) D1: Ref D2: 1.2 (1.1-1.5) D3: 1.2 (1.0-1.4) D4: 1.3 (1.1-1.6) D5: 1.3 (1.1-1.5) 30-day mortality rate D1: 16% (n=47) D2: 7% (n=110) *P*<0.001; adjusted OR, 05 (95% CI, 0.3-0.8)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek, 2002[67] **Country, Setting:** Sweden, primary care clinics, unversity clinic **Funding:** NR **Research Objective:** To assess efficacy and safety of ETA, INF, and LEF in a population-based setting **Study Design:** Nonrandomized open-label trial **Overall N:** 369 (33 pts tried 2 different txts and 1 tried all 3; 404 txts) **Study Duration:** 12 mos	**Inclusion Criteria:** • Age: 18+ • Previous use of DMARDs: required to have failed to respond to or not tolerated at least 2 DMARDs, including MTX • Diagnosis of RA according to clinical judgment of treating doctor • All pts included were required to have failed to respond to or not tolerated at least 2 DMARDs, including MTX • Pts were selected on basis of current disease activity and/or unacceptable steroid requirement as judged by treating doctor, but had different backgrounds concerning previous txt, concomitant diseases, and functional impairment and disability Other meds allowed	**Interventions, dose:** D1: ETA (25 mg/twice wkly) D2: INF (3 mg/kg or higher) D3: LEF (20 mg/d) **N:** D1: 166 D2: 135 D3: 103 **Mean age, yrs:** D1: 54 D2: 55.4 D3: 61.3 **Sex, % female:** D1: 78 D2: 79 D3: 82 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 14.9 D2: 14.1 D3: 14.9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: 100 D2: 100 D3: 100 **Corticosteroid use, %** D1: 83 D2: 81 D3: 73 **MTX naive, %:** D1: 0 D2: 0 D3: 0 **Txt resistant, %:** D1: 100 D2: 100 D3: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.8 D2: 5.6 D3: 5.4 **HAQ:**	**At 3 months** **ACR20/50:** INF significantly higher than LEF (data NR; $P < 0.01$) ETA higher ACR 20 response rate than INF (data NR; $P < 0.02$) ETA had a significantly higher ACR50 response rate than INF (data NR; $P < 0.05$) **At 6 months** **ACR 20/50:** ETA better than LEF (data NR; $P < 0.01$) ETA higher ACR 20 response rate than INF (data NR; $P < 0.02$) **At 12 months** No significant difference between ETA and INF ETA and INF led to significant reduction in prednisolone use starting at 2 wks No reduction in prednisolone use for LEF	**Infusion reaction:** 3.7% of INF pts experienced an infusion reaction	**Overall Attrition Rate, %:** N/A **ITT Analysis:** No **Quality Rating:** Fair

	Exclusion Criteria: NR •	D1: 1.55 D2: 1.47 D3: 1.46

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek et al., 2005[68] **Country, Setting:** Sweden, rheumatology centers **Funding:** Österlund and Kock Foundations, King Gustav V, and Reumatiker-förbundet **Research Objective:** To determine whether TNF blockers increase tumour risk in pts with RA **Study Design:** Retrospective cohort study **Overall N:** 1557 **Study Duration:** Median duration of anti-TNF txt was 1.7 yrs (5,571 PY)	**Inclusion Criteria:** • ACR criteria were fulfilled by 98% of cohort • Pts with RA treated with ETA or INF from South Swedish Arthritis Txt Group (SSATG), which includes pts from 8 rheumatologic centers • For comparison group, pts with RA not treated with anti-TNF drugs from a community based cohort in Malmo, a city from the SSATG catchment area. • Controls recruited from Malmo University outpatient rheumatology clinic and from 4 rheumatologists in private practice **Exclusion Criteria:** • Tumor diagnosis prior to study	**Interventions, dose:** D1: Anti-TNF txt **D2: Comparison** ETA: varied **INF: varied** **N:** D1: 757 D2: 800 Median age, yrs: D1: 56 D2: 64 **Sex, % female:** D1: 76 D2: 73 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 12 D2: 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **% with HAQ quartile >: 3:** D1: 61 D2: 41 **Median number of previous DMARDS:** D1: 3 D2: 1	**Anti-TNF vs. Control:** • All tumors: SIR 1.1 (95% CI, 0.6-1.8) vs. 1.4 (95% CI, 1.1-1.8) • Lymphomas: SIR 11.5 (95% CI,3.7 to 26.9) vs. 1.3 (95% CI,0.2 to 4.5) • All tumors excluding lymphomas: SIR 0.79 (95% CI, 0.4-1.42) vs. 1.39 (95% CI, 1.08-1.76) • Hazard ratio indicates a higher risk of lymphoma for anti-TNF drugs than for controls (RR: 4.9; 95% CI, 0.9-26.1)	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese, 2004[69] **Country, Setting:** US, multicenter, specialty clinic **Funding:** Amgen, Inc., Thousand Oaks, CA **Research Objective:** To determine potential for additive or synergistic effects of combination therapy with selective anti-TNF-alpha agent ETA and anti-IL1 agent AKA **Study Design:** RCT **Overall N:** 242 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • RA according to ACR criteria • Duration of condition: > 6 mos • 6+ swollen joints • 9+ tender/painful joints • At least 2 of: morning stiffness lasting 45 or more minutes, serum CRP of > 1.5 mg/dl, or ESR > 28 mm/hr; and, MTX > 16 wks, stable dose of 10-25 mg/wk > 8 wks; continued txt with stable doses of MTX and other stable medications, such as corticosteroids **Exclusion Criteria:** • Any DMARD other than MTX within past 4 wks • Txt with AKA or any protein-based TNF-alpha inhibitor Received any intraarticular or systemic corticosteroid injections within	**Interventions, dose:** D1: ETA (25 mg twice wkly) D2: ETA (12.5 mg once wkly) + AKA (100 mg/d) D3: ETA (25 mg twice wkly) + AKA (100 mg/d) **N:** D1: 80 D2: 81 D3: 81 **Mean age, yrs:** D1: 54.4 D2: 53.8 D3: 55.7 **Sex, % female:** D1: 82.5 D2: 71.6 D3: 77.8 **Race, % white:** D1: 86.3 D2: 77.8 D3: 75.3	**Mean disease duration, yrs:** D1: 9.7 D2: 9.5 D3: 10.6 **TJC, mean:** D1: 31 D2: 31 D3: 35.9 **SJC, mean:** D1: 21.4 D2: 19.8 D3: 23.4 **DMARD use, %:** NR **Corticosteroid use, %** D1: 48.8 D2: 54.3 D3: 44.4 **MTX naive, %:** Overall: 0 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** Overall: 100 **HAQ:** D1: 1.5	**At week 24** **ACR20, %:** D1: 68 D2: 51 D3: 62 D1 vs. D2 (*P* = 0.037) All others NS **ACR50, %:** D1: 41 D2: 39 D3: 31(*P* = 0.914) OR (ETA + AKA vs. ETA alone) 0.64 (90% CI, 0.37-1.09); sensitivity analysis yielded similar results **ACR70, %:** D1: 21 D2: 24 D3: 14 (*P* = NR) **Sustained ACR20 response:** Between 43% and 54% of subjects in each group (specifics NR) **EULAR response, %:** D1: 79 D2: 66 D3: 73 (*P* = NR) **Mean % reduction in DAS:** D1: 39 D2: 41 D3: 40 (*P* = NR)	**Overall:** D1: 90 D2: 95.1 D3: 93.8 **SAEs:** D1: 2.5 D2: 4.9 D3: 14.8 **Infections:** D1: 40 D2: 37 D3: 46.9 **Serious Infections:** D1: 0 D2: 3.7 D3: 7.4 **Infusion or injection reaction:** D1: 40 D2: 67.9 D3: 70.4 **URTI:** D1: 20 D2: 11.1 D3: 13.6	**Overall Attrition Rate, %:** 15.7 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	past 4 wks • Recent history of significant infection or other important concurrent illness •		D2: 1.5 D3: 1.6			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Genovese et al., 2008[70], TOWARD **Country and setting** International (18 countries, half ofstudy sites US-based), multi-center **Source of funding** F. Hoffmann-L Roche **Research objective** Examine efficacy and safety of tocilizumab combined with conventional DMARDs in pts with active RA **Study design** Controlled Trials **Overall N** 1220 **Duration of study** 24 wks **Quality rating** Fair	**Inclusion Criteria** • 18 years or older • Moderate-to-severe RA of at least 6 mos' duration • Diagnosed according toACR 1987 revised criteria for classification of RA • SJC of ≥ 6 • TJC of ≥ 8 • CRP level of ≥ 1 mg/dl or an ESR of ≥ 28 mm/hour received stable doses of permitted DMARDs (MTX, chloroquine, HCQ, parenteral gold, SSZ, azathioprine, and LEF) for at least 8 weeks prior to study entry. **Exclusion Criteria** • Unsuccessfully treated with an anti-TNF agent previously treated with any cell-depleting therapy were	**Interventions, dose** D1: • Tocilizumab: 8 mg/kg, 60-min infusion every 4 wks • Background of stable DMARD therapy D2: • Placebo: 60-min infusion every 4 wks • Background of stable DMARD therapy **Number in group** D1: 803 D2: 413 Overall: 1216 **Mean age, years (SD)** D1: 53 D2: 54 **Sex, % female** D1: 81 D2: 84 **Race, % white** D1: 72 D2: 72 **Race, % black** D1: 4 D2: 7 **Ethnicity** Asian D1: 9 D2: 10 American Indian D1: 10 D2: 8 Other	**Mean disease duration, years** D1: 9.8 (8.8) D2: 9.8 (9.1) **Patients with early RA, three years or less, %** Disease Duration = 2 yrs: D1: 19 D2: 20 **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 30.1 (16) D2: 29.1 (14.8) **Swollen Joint Count, mean** D1: 19.7 (11.6) D2: 18.7 (10.8) **Corticosteroid use, %** D1: 51.2 D2: 54.6 **DMARD use, %** D1: 100 D2: 100 Overall: 100 **MTX naïve, %** NR **Baseline DAS score** D1: 6.7 D2: 6.6 **Required treatment for latent TB** NR	**ACR** ACR 20: D1: 60.8 D2: 24.5 *P* = 0.0001 ACR 50: D1: 37.6 D2: 9.0 *P* = 0.0001 ACR 70: D1: 20.5 D2: 2.9 *P* = 0.0001 **HAQ,** HAQ-DI D1: -0.5 D2: -0.2 *P* = 0.0001 **DAS28** D1: -3.17 D2: -1.16 Overall: , *P* = 0.0001 **DAS28 = 2.6 (%)** D1: 30 D2: 3 *P* = 0.0001 **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name)** SJC, mean change from baseline:	**Overall** Overall attrition/withdrawal, n: D1: 53 D2: 43 Overall: 96 Withdrawals due to adverse events, n: D1: 32 D2: 8 Overall: 40 Adherent/compliant, n: D1: 751 D2: 370 Overall: 1121 **Overall adverse events reported, n:** D1: 584 D2: 253 Overall: 837 **Serious adverse events** Death, n: D1: 2 D2: 2 Overall: 4 **Malignancies** NR **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 3 D2: 2 Overall: 5 Upper respiratory infection, n: D1: 9% D2: 7% Overall: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	excluded	D1: 3 D2: 3		• Tocilizumab = -10.3 • Placebo = -4.9 • *P* = 0.0001 TJC, mean change from baseline: • Tocilizumab = -15.7 • Placebo = -8.5 • *P* = 0.0001 Good or Moderate Eular Response: • Tocilizumab = 80% • *P* = 0.0001 FACIT-F, mean change from baseline: • Tocilizumab = 8.0 • Placebo = 3.6 • *P* = 0.0001	**Other infections** NR **GI** Nausea or vomiting, n: D1: 4% D2: 3% Overall: NR Abdominal pain, n: D1: 3% D2: 1% Overall: NR Mouth ulceration, n (%): D1: 2 D2: 1 Overall: NR Stomatitis, %: D1: 1 D2: 0 Upper gastrointestinal tract events suggestive of gastric inflammation, gastritis, and ulcer, % D1: 3 D2: 1 **Other** Headache, n: D1: 6% D2: 4% Overall: NR Hypertension, %: D1: 5 D2: 3 Overall: NR Elevations in alanine amino-transferase level, from normal at baseline to > 3-

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					foldupper limit of normal, %: D1: 4 D2: 1 Elevated total cholesterol levels, %: D1: 23 D2: 6 Overall: NR Grade 3 neutropenia, %: D1: 3.7 D2: 0 Overall: NR Any other AEs: • Cellulitis: Tocilizumab : 5 • Placebo : 0, Overall : 5 • Herpes Zoster: Tocilizumab : 3 • Placebo : 0 • Overall : 3 Adverse events occurring in ≥ 5% of patients, Tocilizumab, Placebo, Overall: • Infections and infestations = 300, 131, 431 • Gastrointestinal disorders = 167, 61, 228; • Musculoskeletal and connective tissue disorders = 104, 74, 178 • Skin and subcutaneous tissue disorders = 133, 29, 162 • Nervous system disorders = 93, 36, 129 • Laboratory investigations = 94, 11,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					105 • General disorders and administration-site conditions = 66, 30, 96 • Injury, poisoning, and procedural complications = 63, 29, 92 • Respiratory, thoracic, and mediastinal disorders = 69, 21,90 • Vascular disorders = 54; 21; 75 Serious adverse events occurring in ≥ 3 patients, Tocilizumab, Placebo, Overall: • Infections and infestations = 22, 8, 30; • Musculoskeletal disorders = 2, 3, 5 • Gastrointestinal disorders = 9, 1, 10 • Nervous system disorders = 6, 2, 8 • Cardiac disorders = 3, 1, 4 • Injuries, poisoning = 7, 0, 7 • Renal and urinary disorders = 3, 0, 3;

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Goekoop-Ruiterman, 2005[71]; Allaart et al., 2006[72]; Goekoop-Ruiterman, 2007[73]; van der Kooij, 2009[74]; van der Kooij, 2009[75] BeST Study **Country and setting** The Netherlands 18 peripheral and 2 university hospitals **Source of funding** Schering-Plough and Centocor. Dutch College of Health Insurances **Research objective** Evaluate whether initial clinical and radiographic efficacy of combination therapies could be maintaned after 2[73] and 4 yrs[75] **Study design** RCT **Overall N** 508 **Duration of study** 2- and 4-year follow up data **Quality rating** Good	**Inclusion Criteria:** • Age > 18 yrs • RA according to ACR criteria • Duration of condition: 2 yrs • Active disease with at least 6 of 66 swollen joints • At least 6 of 68 tender joints • ESR > 28 mm/hr OR global health score greater than or equal to 20mm on 0 to 100 VAS • Concomittant NSAIDS and intraarticular steroids **Exclusion Criteria:** • Pregnant • Prior txt with: DMARDS other than antimalarials • Impaired renal or hepatic system	**Interventions, dose** D1: Sequential monotherapy D2: Step-up combination therapy D3: Initial combination therapy with PRED D4: Initial combination therapy with IFX **Number in group** D1: 126 D2: 121 D3: 133 D4: 128 Overall: 508 **Mean age, years (SD)** D2: 54 D3: 55 D4: 54 Overall: 54 **Sex, % female** D1: 86 D2: 86 D3: 86 D4: 85 Overall: 86 **Race, %** NR	**Mean disease duration, years** D1: 23 wks D2: 26 wks D3: 23 wks D4: 23 wks **Patients with early RA, three years or less** Overall: 100% **Treatment resistant, %** NR **Tender Joint Count, mean** NR **Swollen Joint Count, mean** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** Overall: 100 **Baseline DAS score, mean** D1: 4.5 +/- 0.9 D2: 4.5 +/- 0.8 D3: 4.4 +/- 0.9 D4: 4.3 +/- 0.9 **Required treatment for latent TB** NR	**ACR mean difference/ absolute difference** NR **HAQ (mean ±SD)** At 3 months: D1: 0.4 ± 0.6 D2: 0.3 ± 0.6 D3: 0.8 ± 0.7 D4: 0.7 ± 0.6 *P* = 0.050 for D1/D2 vs. D3/D4 At 6 months: D1: 0.5 ± 0.7 D2: 0.5 ± 0.7 D3: 0.9 ± 0.7 D4: 0.8 ± 0.6 *P* = 0.050 for D1/D2 vs. D3/D4 At 9 months: D1: 0.6 ± 0.7 D2: 0.6 ± 0.7 D3: 0.8 ± 0.7 D4: 0.8 ± 0.6 *P* = 0.050 for D1/D2 vs. D3/D4 At 12 months: D1: 0.7 ± 0.7 D2: 0.7 ± 0.7 D3: 0.9 ± 0.7 D4: 0.9 ± 0.7 *P* = 0.050 for D1 vs. D3/D4 At 15 months: D1: 0.7 ± 0.7 D2: 0.8 ± 0.7 D3: 0.7 ± 0.8 D4: 0.9 ± 0.7 *P* = NS	**Attrition/withdrawal** Withdrawals through 4 years of followup, n: D1: 11 D2: 20 D3: 14 D4: 9 Overall: 54 (11%) Over time, 27 (5%) patients who were equally distributed across treatment groups (*P* = 0.474) were lost to follow-up: 12 withdrew consent (7 declined follow-up, 4 discontinued all medications despite having no adverse events, and 1 moved from area), 7 had a revised diagnosis, 1 discontinued treatment because of an adverse event, 4 died, and 3 were lost to follow-up for other reasons (2 were admitted to a nursing home and 1 wanted to become pregnant) (Figure 1). Noncompliant but included in ITT, n (%): D1: 12 (10) D2: 11 (9) D3: 14 (11) D4: 6 (5) Deviated from study protocol, n: D1: 19 D2: 15 D3: 36 D4: 11

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				At 18 months: D1: 0.7 ± 0.7 D2: 0.8 ± 0.7 D3: 0.8 ± 0.8 D4: 0.9 ± 0.7 *P* = NS At 21 months: D1: 0.7 ± 0.7 D2: 0.8 ± 0.7 D3: 0.8 ± 0.7 D4: 0.9 ± 0.7 *P* = NS At 24 months: D1: 0.7 ± 0.7 D2: 0.8 ± 0.7 D3: 0.9 ± 0.7 D4: 0.9 ± 0.7 At 36 months: D1: 0.8 ± 0.7 D2: 0.7 ± 0.7 D3: 0.8 ± 0.8 D4: 0.9 ± 0.7 *P* = 0.66 At 48 months: D1: 0.8 ± 0.6 D2: 0.7 ± 0.8 D3: 0.8 ± 0.8 D4: 0.8 ± 0.8 *P* = 0.64 **DAS44 goal of 2.4 reached, %** D1: 75 D2: 81 D3: 78 D4: 82 *P* = NS Overall: 79 *P* = 0.554	(*P* = 0.343) **Overall adverse events reported, n** • 210 (41%) of patients had an adverse event in year 1 • 193 (38%) of patients had an adverse event in year 2 • Mean number of adverse events per patient was 1.9 (SD, 1.2) in first year and 1.8 (SD, 1.2) in the second year. • 56 serious adverse events were reported in the second year (16 events [13 patients] in group 1, 10 events [10 patients] in group 2, 17 events [11 patients] in group 3, and 13 events [8 patients] in group 4) **Serious adverse events** D1: NR D2: Cerebrovascular event: 1 D3: Malignant ovarian cancer: 1 D4: Mycardial infarction: 1, disseminated TB: 1 Cardiovascular events, n: D1: Atrial fibrillation: 1, myocardial infarction: 1, coronary artery bypass: 1 D2: NR D3: NR D4: Myocardial infarction: 1, unstable angina pectoris: 1 Hepatotoxicity/elevated liver enzymes, n: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Sustain DAS44 of less than or: 2.4. After 1 yr: D1: 53% D2: 64% D3: 71% D4: 74% *P* = 0.004 for 1 vs. 3 *P* = 0.001 for 1 vs. 4 *P* = NS and NR for others **SF-36** D1: SF-36 PCS (values are mean change from baseline, except baseline values): Baseline 32.9, 3 mos 5.8, 6 mos 8.0, 12 mos 8.9, 24 mos 11.9, SF-36 MCS at baseline, 3 months, 6 months, 12 months, and 24 mos (values are mean change from baseline, except baseline values): Baseline 47.5; 3 mos 2.1; 6 mos 3.1; 12 mos 4.3; 24 mos 4.3 D2: Baseline 32.9, 3 mos 3.9, 6 mos 8.5; 12 mos 11.2; 24 mos 12.3; SF-36 MCS at baseline, 3 mos, 6 mos, 12 mos, and 24 mos (values are mean change from baseline, except baseline values): Baseline 46.3; 3 mos 2.5; 6 mos 3.5; 12 mos 4.4; 24 mos 4.6 D3: Baseline 32.8, 3 mos 11.2, 6 mos 12.5; 12 mos 11.9; 24 mos 12.3; SF-36	**Malignancies** Basal cell carcinoma, n: D1: 1 D2: NR D3: NR D4: NR Other cancer (specify), n: D1: Renal cell carcinoma: 1 D2: Malignant prostate cancer: 1 D3: Malignant ovarian cancer: 1 D4: Basal cell carcinoma: 1 **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 1, D2: 1 D3: NR D4: NR Pleural effusion, n: D1: 1 D2: NR D3: NR D4: NR **Other infections** Urinary tract infection, n: D1: pyelonephritis, n: 1 D2: NR D3: NR D4: NR Other infections (specify), n: D1: viral infection, n: 1 D2: NR D3: NR D4: septic arthritis, n: 1 **GI**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				MCS at baseline, 3 mos, 6 mos, 12 mos, and 24 mos (values are mean change from baseline, except baseline values): Baseline 47.6; 3 mos 0.4; 6 mos 1.2; 12 mos 3.2; 24 mos 4.6 D4: Baseline 33.4, 3 mos 9.6, 6 mos 12.4; 12 mos 12.0; 24 mos 12.7; SF-36 MCS at baseline, 3 mos, 6 mos, 12 mos, and 24 mos (values are mean change from baseline, except baseline values): Baseline 47.6; 3 mos 3.1; 6 mos 4.1; 12 mos 4.3; 24 mos 4.0 Overall: At 3 and 6 mos, *P*=0.05 for SF-36 PCS comparing groups 1 and 2 to groups 3 and 4. Others were NS (For PCS: *P* = 0.93 at baseline, 0.10 at 12 months, 0.95 at 24 months; For MCS at each timepoint: 0.73, 0.22, 0.17, 0.83, 0.97) **Radiographic measures, mean difference (SD)** Progression of SHS at 12 mos: D1: 2.0 D2: 2.5 D3: 1.0 D4: 0.5 (*P* = 0.003 for group 1 vs. group 3; *P* = 0.001 for 1 vs.	GI bleed or ulcer, n: D1: NR D2: NR D3: NR D4: GI bleed, n: 1 **Other** Perforated gastric ulcer, n: D1: 1 D2: NR D3: NR D4: NR Complicated calcaneous fractures, n: D1: NR D2: 1 D3: NR D4: NR Any other AEs: D1: • Syncope: 1 • Ovarian cyst:: 1 • MTX intoxication: 1 • Malaise: 1 • Depressive symptoms: 1 D2: • Pacemaker implantation: 1 • Symptomatic gallstone disease: 1 • Surgery for carpal tunnel syndrome: 1 • Uterus extirpation: 1 • Placement of total hip prostheses: 2 D3: • Placement of total hip prostheses: 2 • implantation of intracardiac device: 1 • syncope due to aortic

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				4; *P* = 0.007 for 2 vs. 3; *P* = 0.001 for 2 vs. 4) Progression of SHS at 24 months, mean (SD): Total Sharp Score D1: 9.0 ± 17.9 D2: 5.2 ± 8.1 D3: 2.6 ± 4.5 D4: 2.5 ± 4.6 Sharp van der Heijde median Increase at 12 mos: D1: 2.0 D2: 2.5 D3: 1.0 D4: 0.5 *P* = 0.001 Total Sharp Score, median (IQR): D1: 2.0 (0.0 - 8.6) D2: 2.0 (0.3 - 7.0) D3: 1.0 (0.0 - 2.5) D4: 1.0 (0.0 - 3.0) Narrowing-score: D1: 4.3 ± 9.8 D2: 2.1 ± 3.8 D3: 1.5 ± 3.2 D4: 1.2 ± 2.9 *P* = 0.072 Relative risk for SHS-progression, at 24 months: D1: 1.0 D2: 0.91 (0.73, 1.12) D3: .74 (0.61, 0.89) D4: .73 (0.61, 0.88) Progression of SHS at 48 months, mean (SD): D1: 11.7 ± 17.3 D2: 9.7 (12.8)	valve dysfunction: 1 • limb amputation due to occlusion of the femoral artery: 1 • retinal hemorrhage: 1 • scleroderma: 1 • active RA: 1 D4: • Active RA: 1 • cholecystectomy: 1 • placement of total knee prostheses: 1 • placement of elbow protheses: 1 • one patient had 4 episodes of disseminated TB

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D3: 6.7 (9.6) D4: 5.4 (9.2) *P* = 0.002 D1 vs. D4 SHS median (IQR) D1: 50 (1.0 - 15.8) D2: 5.5 (1.0 - 13.8) D3: 3.0 (1.0 - 7.5) D4: 2.5 (0.5 - 6.5) Narrowing-score at 48 months, mean (SD): D1: 5.7 (10) D2: 4.0 (7.0) D3: 3.7 (6.7) D4: 2.4 (4.6) Narrowing-score median (IQR): D1: 1.8 (0.0 - 7.0) D2: 1.0 (0.0 - 4.5) D3: 1.0 (0.0 - 3.9) D4: 1.0 (0.0 - 2.5) *P* = 0.17 **Quality of life scales** NR **Others (CI/SD/P Value)** Baseline: D1: 47.5 D2: 47.1 D3: 47.3 D4: 47.0 At 3 months: D1: 10.6 D2: 9.5 D3: 16.7 D4: 17.3 At 6 months: D1: 12.6 D2: 15.4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D3: 16.4 D4: 19.1 12 months: D1: 15.2 D2: 16.3 D3: 16.9 D4: 19.3 *P* = *0*.001 for 3 for D1 and 2 compared to D3 and 4, *P* = 0.001 for D1 and 2 compared to D4 and D1 vs. D3	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Gomez-Reino, 2003[76] **Country, Setting:** Spain 71 Centers **Funding:** Agencia Española del Medicamento (Ministerio de Sanidad y Consumo) **Research Objective:** Long-term safety of INF and ETA, in rheumatic diseases based on a national active-surveillance **Study Design:** Retrospective cohort study **Overall N:** 1,540 (1578 txts) **Study Duration:** Mean 1.1 yrs	**Inclusion Criteria:** • Pts with rheumatic diseases being treated with biologic response modifiers registered in BIOBADASER **Exclusion Criteria:** NA	**Interventions, dose:** **D1: INF/ETA** ETA: varies **INF: varies** **N:** D1: 1540 (1578 txts) **Mean age, yrs:** D1: 51 **Sex, % female:** D1: 72 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **PsA:** D1: 5.8 **AS:** D1: 4.9	Background TB incidence in Spain in 2000 was 21/100,000 • 1,893 cases of TB per 100,000 pts in yr 2000 and 1,113 cases per 100,000 pts in yr 2001 in pts treated with TNF • RR of TNF pts compared general population 90.1 (95% CI,58.8-146.0) in yr 2000 and 53.0 (95% CI,34.5-89.0) in yr 2001 • Estimated annual incidence of TB among RA pts not exposed to TNF inhibitors was 95/100,000 • RR in RA pts who did not receive TNF of TB (adjusted for age and sex) was 4.13 (95% CI,2.59-6.83) relative to background rate • RR of TB in INF-treated RA pts vs. RA pts not exposed to this therapy was 19.9 (95% CI,16.2-24.8) in yr 2000 and 11.7 (95% CI,9.5-14.6) in yr 2001 • 15 pts with TB were diagnosed as having RA, and 2 additional pts with TB had PsA; all pts with active TB were being treated with INF; 59% were diagnosed with TB within 3 mos of txt initiation	**Infections:** D1: 7.7 **Infusion or injection reaction:** D1: 2 (INF) **URTI:** D1: 9 **UTI:** D1: 11	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Greenberg JD et al., 2010[77] Consortium of Rheumatology Researchers of North American (CORRONA) registry **Country and setting** US **Source of funding** National Institute of Arthritis and Musculoskeletal and Skin Disease; Arthritis Foundation **Research objective** To examine the association of MTX (MTX) and tumour necrosis factor (TNF) antagonists with the risk of infectious outcomes including opportunistic infections inpatients with rheumatoid arthritis (RA).	**Inclusion Criteria** • Patients with RA • Participants in CORRONA rheumatology practices enrolled from Oct 1, 2001-Sept 2006 • At least 1 follow-up visit **Exclusion Criteria** • NA	**Comparisons (dosage and frequency)** D1: MTX: dosage and frequency NR D2: Anti-TNF: dosage and frequency NR D3: MTX: dosage and frequency NR Anti-TNF: dosage and frequency NR D4: Other DMARDs: dosage and frequency NR **Number in group** D1: 4206 D2: 1804 D3: 2855 D4: 1274 **Mean age (years)** D1: 59.7 D2: 56.8 D3: 57.9 D4: 60.1 **Sex, % female** D1: 73.8 D2: 76.0 D3: 77.7 D4: 74.1 **Race, % white** D1: 86.8 D2: 86.7 D3: 86.2 D4: 88.2	**Mean disease duration, years** D1: 9.5 (9.8) D2: 11.4 (9.6) D3: 11.1 (9.6) D4: 10.1 (9.8) **TJC, mean** D1: 4.2 D2: 4.8 D3: 4.7 D4: 3.6 **SJC, mean** D1: 5.4 D2: 5.1 D3: 5.9 D4: 4.1 **Corticosteroid use, %** D1: 39.3 D2: 40.9 D3: 38.3 D4: 36.6 **DMARD use, %:** D1: 100 D2: 0 D3: 100 D4: 100 **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** NR	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** Overall adverse events reported (n): D1: 1714 D2: 890 D3: 1514 D4: 447 **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** Pneumonia (n): Non-pyogenic D1: 51 D2: 40 D3: 61 D4: 16 Pyogenic D1: 49 D2: 22 D3: 46 D4: 22 Upper respiratory infection (n): D1: 660 D2: 303 D3: 522 D4: 148 **Other infections:** Urinary tract infection (n): D1: 157 D2: 81 D3: 111 D4: 32	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Study design Observational **Overall N** 7971 **Duration of study** October 1, 2001 to September 30, 2006		**Race, % black** NR **Ethnicity, Latino** NR	**Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	NR	Cellulitis: D1: 59 D2: 49 D3: 71 D4: 18 **GI:** NR **Other:** Bursitis D1: 9 D2: 5 D3: 7 D4: 3 Sinusitis D1: 370 D2: 166 D3: 331 D4: 71 Infectious arthritis D1: 9 D2: 5 D3: 5 D4: 2 Septicaemia D1: 8 D2: 8 D3: 10 D4: 4 Other Site of Infection D1: 342 D2: 211 D3: 350 D4: 131 All Types of Infections, Unadjusted rate/100 pys- D1: 33.3	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					D2: 41.8 D3: 37.6 D4: 26.9 Rate of Infection, Adjusted rate/100 pys (95% CI) D1: 30.9 (29.2-32.7) D2: 40.1 (37.0-43.4) D3: (34.9-39.3) D4: 24.5 (21.8-27.5) IRR (95% CI) D1: 1.30 (1.12-1.50); *P*<0.001 D2: 1.52 (1.30-1.78); *P*<0.001 vs. D3 (ref group) PRED use>10 mg daily independently associated with risk of infection: IRR (95% CI), 1.30 (1.11-1.53); *P*<0.001	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Grijalva et al., 2007[78] **Country and setting** US - Tennessee Medicaid data **Source of funding** AHRQ **Research objective** Evaluate adherence and persistence during new episodes of traditional and biologic DMARD use **Study design** Retrospective Cohort Study **Overall N** 6018pts with 10,574 episodes of new DMARD use. **Duration of study** Cohort members were followed from date when selection criteria were met to end of study (December 31, 2004), date of death, date of diagnosis of a serious medical condition, or loss of enrollment from TennCare, whichever came earliest.	**Inclusion Criteria** • TennCare enrollees with RA • Filled 1 prescription during screening period **Exclusion Criteria** • <365 days of continuous enrollment prior to study entrance • Established serious medical conditions	**Interventions, Dose** D1: MTX: varied D2: Hydroxychlorquine: varied D3: SSZ: varied D4: LEF: varied D5: MethylPNL: varied Hydroxychlorquine: varied 7 other groups (all dose varied): INX, ETA, ADA, MTX+INX, MTX+ETA, MTX + ADA, AKA and AKA+MTX **Number in group** *N of new tx episodes*: D1: 3859 D2: 3174 D3: 944 D4: 558 D5: 904 D6: 75 D7: 374 D8: 120 D9: 98 D10: 262 D11: 107 D12: 72 **Mean age (years)** D1: 54 D2: 51 D3: 51 D4: 55 D5: 52 D6: 53 D7: 51 D8: 58 D9: 56	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)**	**ACR** ACR 20: No efficacy ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference** NR	**Overall** • Median Persistence in days, Cox Regression Model Adjusted* HR (95%CI): MTX 150, 1.0 (ref); HCQ 121, 1.03 (0.98-1.08); SSZ 53, 1.59 (1.47-1.72); LEF 136, 1.02 (0.93-1.11); MTX + HCQ 125, 1.05 (0.97-1.14); INX 85, 1.37 (1.09-1.73); ETA 175, 0.82 (0.73-0.92); ADA 134, 0.85 (0.67-1.08); MTX+IFX 155, 0.91 (0.73-1.15); MTX+ETA 147, 1.01 (0.87-1.17);MTX+ADA 219, 0.63 (0.48-0.84); ANK OR ANK+MTX 156, 0.94 (0.75-1.18). • Mean Medication Possession Ratio, linear regression Adjusted* coefficient (95%CI): 0.80, 1.0 (ref); HCQ 0.79, 0.00 (-0.01 to 0.001); SSZ 0.77, -0.02 (-0.04 to 0); LEF 0.85, 0.05 (0.04 to 0.07); MTX+HCQ 0.66, -0.11 (-0.13 to -0.09); IFX 0.90, 0.11 (0.06 to 0.16); ETN 0.83, 0.04 (0.02 to 0.06); ADA 0.85, 0.04 (0.001 to 0.08); MTX+IFX 0.66, -0.12 (-0.17 to-0.07); MTX+ETN 0.64, -0.11 (-0.14 to-0.08); MTX+ADA 0.72, -0.07 (-0.11 to -0.03); ANA or ANA+MTX 0.71, -0.08 (-0.13 to -0.02) *Adjusted for age, sex, race,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Quality rating Fair: Not controls for Disease Activity or Severity (would assume patients with higher severity/activity would be more likely to adhere), limited to a poor population in which access is likely to be an issue. Predetermined inclusion criteria of having fi		D10: 53 D11: 58 D12: 53 **Sex, % female** D1: 78.1 D2: 82.7 D3: 71.2 D4: 79.4 D5: 84.2 D6: 74.7 D7: 77.5 D8: 80.8 D9: 76.5 D10: 83.6 D11: 79.4 D12: 72.2 **Race, % white** D1: 72.4 D2: 71.2 D3: 76.5 D4: 72 D5: 69.9 D6: 66.7 D7: 70.9 D8: 64.2 D9: 72.4 D10: 64.9 D11: 61.7 D12: 63.9 **Race, % black** 1 **Ethnicity, Latino** NR			calendar year, residential location, disability, residence in nursing home, and risk score Overall adverse events reported, n: NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Grijalva et al., 2010[79] **Country and setting** USA; Tennessee Medicaid-enrolled patients **Source of funding** Vanderbilt Multidisciplinary Clinical Research Center (NIH/NIAMS Grant P60 AR056116) **Research objective** To compare serious infections following initiation of different RA regimens **Study design** Observational **Overall N** 21981 **Duration of study** 180 days of exposure during 2002-2005	**Inclusion Criteria** • RA patients with new episodes of DMARD use **Exclusion Criteria** NR	**Comparisons (dosage and frequency)** D1: TNF-α antagonists D2: LEF D3: SSZ D4: HCQ D5: MTX D6: low glucocorticoid regime D7: med glucocorticoid regime D8: high glucocorticoid regime **Number in group** D1: 2192 D2: 1097 D3: 1283 D4: 3398 D5: 4355 D6: 2058 D7: 11117 D8: 3406 **Mean age (years)** D1: Median 54 D2: 56 D3: 52 D4: 52 D5: 55 D6: 57 D7: 55 D8: 55 **Sex, % female** D1: 74.86 D2: 77.03	**Mean disease duration, years** NR **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** 100 **DMARD use, %:** 0 **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** NR **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** Pneumonia (n): Crude HR (95% CI) D1: 1.17 (0.67, 2.05) D2: 1.64 (0.79, 3.39) D3: 0.47 (0.14, 1.53) D4: 1.11 (0.67, 1.85) D5: 1.00 (reference) D6: 2.00 (1.1, 3.64) D7: 2.08 (1.31, 3.3) D8: 3.91 (2.31, 6.62) Age/gender adjusted HR (aHR) (95% CI) D1: 1.28 (0.73, 2.24) D2: 1.64 (0.79, 3.39) D3: 0.51 (0.16, 1.68) D4: 1.20 (0.72, 2) D5: 1.00 (reference) D6: 1.71 (0.94, 3.1) D7: 1.92 (1.22, 3.01) D8: 3.67 (2.19, 6.15) Propensity Score-adjusted HR (95% CI) D1: 1.61 (0.85, 3.03) D2: 1.65 (0.77, 3.54) D3: 0.60 (0.19, 1.97) D4: 1.24 (0.73, 2.08) D5: 1.00 (reference) D6: 2.30 (1.2, 4.41) D7: 2.36 (1.44, 3.87) D8: 4.33 (2.49, 7.54)	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		D3: 68.04 D4: 81.11 D5: 76.21 D6: 77.75 D7: 76.38 D8: 75.60 **Race, % white** D1: 83.90 D2: 84.32 D3: 84.88 D4: 79.64 D5: 80.60 D6: 80.47 D7: 84.72 D8: 84.44 **Race, % black** D1: 12.73 D2: 13.49 D3: 12.70 D4: 18.01 D5: 16.67 D6: 17.15 D7: 13.28 D8: 13.30 **Ethnicity, Latino** NR		NR	**Other infections:** Any infection Crude HR (95% CI) D1: 1.04 (0.66, 1.64) D2: 1.39 (0.78, 2.48) D3: 0.82 (0.4, 1.66) D4: 1.06 (0.71, 1.56) D5: 1.00 (reference) D6: 1.46 (0.88, 2.43) D7: 2.12 (1.47, 3.05) D8: 3.37 (2.19, 5.19) Age/gender adjusted HR D1: 1.12 (0.71, 1.77) D2: 1.39 (0.78, 2.48) D3: 0.89 (0.44, 1.8) D4: 1.13 (0.76, 1.67) D5: 1.00 (reference) D6: 1.28 (0.77, 2.13) D7: 1.98 (1.38, 2.83) D8: 3.21 (2.1, 4.9) Propensity Score-adjusted HR (95% CI) D1: 1.31 (0.78, 2.19) D2: 1.48 (0.81, 2.69) D3: 1.03 (0.51, 2.1) D4: 1.20 (0.81, 1.79) D5: 1.00 (reference) D6: 1.62 (0.94, 2.78) D7: 2.39 (1.63, 3.51) D8: 3.72 (2.37, 5.84) **GI:** NR **Other:** NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997[80] **Country, Setting:** Netherlands, 1 academic and 6 peripheral clinics **Funding:** Pharmachemie BV; Pharmacia AB **Research Objective:** Compare efficacy and safety of SSZ, MTX, and combination of both in pts with early RA **Study Design:** RCT **Overall N:** 105 **Study Duration:** 52 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed with RA according to ACR criteria: ACR criteria • RF positive and/or HLA-DR4 positive and/or HLA DR1 positive • Functional class of: DAS ≥ 3.0 • Duration of condition: < 12 mos • Analgesica and NSAIDS allowed **Exclusion Criteria:** • Prior txt with: DMARDS other than analgesics and NSAIDS • Other: contraindications to SSZ or MTX	**Interventions, dose:** D1: SSZ (1 g/day; max 3 g/day) D2: MTX (7.5 mg/wk; max 15 mg/wk) D3: MTX (7.5 mg/wk; max 15 mg/wk) + SSZ (1 g/day; max 3 g/day) **N:** D1: 34 D2: 35 D3: 36 **Mean age, yrs:** D1: 56.8 D2: 54.9 D3: 57.0 **Sex, % female:** D1: 61.8 D2: 65.7 D3: 66.7 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 3.1 mos D2: 3.0 mos D3: 2.6 mos **TJC, mean:** D1: 20.8 D2: 20.6 D3: 24.8 **SJC, mean:** D1: 17.0 D2: 19.9 D3: 20.8 **DMARD use, %:** Overall: 0 **Corticosteroid use, %** Overall: 0 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** D1: 4.6 D2: 4.7 D3: 5.0 **HAQ:**	No significant differences in efficacy between combination (MTX, SSZ) and single therapy (MTX or SSZ), only a trend favoring combination therapy, MTX and SSZ were comparable **At 52 weeks** **DAS mean change:** D1: -1.6 (95% CI, -2.0 to -1.2) D2: -1.7 (95% CI, -2.0 to -1.4) D3: -1.9 (95% CI, -2.2 to -2.3) **Ritchie mean change:** D1: -8.6 (95% CI, -10.7 to -6.5) D2: -8.2 (95% CI, -10.1 to -6.4) D3: -9.4 (95% CI, -11.1 to -7.7) **Swollen joints mean change**: D1: SSZ -7.9 (95% CI, -10.1 to -5.7) D2: -10.2 (95% CI, -12.5 to -8.0) D3: -11.3 (95% CI, -13.5 to -9.2) **HAQ change from**	**Overall:** D1: 88.2 D2: 77.1 D3: 88.9 **SAEs:** D1: 8.8 D2: 0 D3: 0 **Abdominal Pain:** D1: 26.5 D2: 20 D3: 36 **Cardiovascular Events (Dyspnea):** D1: 5.9 D2: 0 D3: 5.6 **Dizziness:** D1: 17.6 D2: 8.6 D3: 27.8 **Headache:** D1: 17.6 D2: 11.4 D3: 11.1 **Nausea:** D1: 29.4 D2: 25.7 D3: 63.9 **URTI** D1: 17.6	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			D1: 0.97 D2: 0.92 D3: 1.20	**baseline:** D1: -0.32 (95% CI, -0.53 to -0.10) D2: -0.46 (95% CI, -0.68 to -0.25) D3: -0.51 (95% CI, -0.76 to -0.26) **Number of pts with a response according to ACR criteria at end of study:** D1: 25 D2: 25 D3: 28 **Number of pts with good response according to EULAR definition:** D1: 14 D2: 15 D3: 14	D2: 20.0 D3: 27.8	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Harley, 2003[81] **Country, Setting:** US, Health Plan Data **Funding:** Centocor **Research Objective:** To examine txt compliance and dosage administration with MTX, ETC and INF therapy for RA **Study Design:** Observational-retrospective data analysis **Overall N:** 2662 **Study Duration:** 30 mos	**Inclusion Criteria:** • Commercial or Medicare enrollees **Exclusion Criteria:** • MTX, ETA or INF within 182 days of index date	**Interventions:** D1: INF D2: ETA D3: INF **N:** D1: 141 D2: 853 D3: 1668 **Mean age (yrs):** D1: 56.3 D2: 47.4 D3: 53.3 **Sex, % female:** D1: 27 D2: 26.3 D3: 26.9 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: 34 D2: 41 D3: 37.9 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Compliance with at least 80% of expected dosages: • ETA: 68.4; OR 0.462; 95 CI, 0.290-0736 • MTX: 63.7; OR 0.385; 95 CI, 0.245-0604 • INF: 80.9 • OR:Reference • $P < 0.05$ Dosage Increases: • MTX: 61.6% • INF: 37.4% • ETA: 7.4%	NR	**Overall Attrition Rate, %: NA** **ITT Analysis:** Not applicable **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Harrison, 2009 et al., British Society for Rheumatology Biologics Register (BSRBR)[82] **Country and setting** UK, hospitals/general practice **Source of funding** Financial support to BSRBR comes indirectly from following UK companies marketing biologic agents in UK: Schering Plough, Wyeth Laboratories, Abbott Laboratories, and Amgen. The resources used to fund BSRBR are received under contract **Research objective**	**Inclusion Criteria** • Treatment cohort (all anti-TNFa): first 4000 patients with RA starting each anti-TNFa therapy were required by National Institute for Health and Clinical Excellence to be registered with BSRBR and followed up for information on drug use, disease activity and adverse events. • All patients with a doctor diagnosis of RA who were receiving ETN, IFX or ADA as their first anti-TNFα therapy comprise anti-TNFα cohort	**Interventions, Dose** D1: Other: NR (traditional DMARDs) D2: • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ADA: dosage and frequency NR **Number in group** D1: 2880 D2: 9826 Overall: 12,706 **Mean age (years)** D1: 60 D2: 56.2 **Sex, % female** D1: 72 D2: 76 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 7 yrs (IQR: 1 - 15) D2: 11 yrs (IQR: 6 - 19) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** D1: 100 D2: 100 Overall: 100 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: 5.0 D2: 6.6 **Required treatment for latent TB** NR **Other population**	**ACR** NR **HAQ,** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** Withdrawals due to adverse events, n: D1: NA D2: 8 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** Psoriasis, n: D1: 0; Rate of psoriasis/1000 person years (95% CI): 0 (upper 97.5% CI O.71) D2: 25; Rate of psoriasis/1000 person years (95% CI): 1.04 (0.67 - 1.54) Overall: Psoriasis, n: 25 Subanalysis: Patients treated with ADA had a significantly increased risk

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
To compare incidence rates of psoriasis in RA patients treated with anti-TNFa therapy and traditional DMARDs **Study design** Prospective Cohort Study **Overall N** 12,706 **Duration of study** Approximately 1 to 2 years (current analysis based on early BSRBR data - follow up will continue for at least 5 years) **Quality rating** Fair	for this study. • Comparison cohort: biological naive, doctor-diagnosed RA, active disease (guideline DAS28 > 4.2), current treatment with a DMARD **Exclusion Criteria** • Comparison cohort: • No previous exposure to any anti-TNFa drug		**characteristics, %, (CI/SD/P value)** D1: Current Smoker: 24% Former Smoker: 40% Never smoked: 36% HAQ, median: 1.6 D2: Current Smoker: 22% Former Smoker: 38% Never smoked: 40% HAQ, median: 2.1		of psoriasis compared to thosetreated with ETN (IRR 4.6, 95% CI 1.7 to 12.1) and IFX (IRR 3.5, 95% CI 1.3 to 9.3) adjusted for age, sex, smoking status and calendar year of registration

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Hetland et al., 2010[83] **Country and setting** Denmark; natioal registry **Source of funding** Unrestricted grants to DANBIO from Abbott,Wyeth, and Schering-Plough (since 2004), Bristol-Myers Squibb, and Roche (since 2006), and UCB-Nordic (since 2007). The Danish Regions provided financial support for the activities related to quality improvement of biologic treatment.	**Inclusion Criteria** • RA, as diagnosed by the treating rheumatologist • Treated with 1 or more oral DMARD, but treatment failed to such an extent that therapy with either ADA, ETN, or INF **Exclusion Criteria** NR	**Comparisons (dosage and frequency)** D1: • MTX: 70%, mean of 20 mg/week • ADA: 40 mg every 2 wks D2: • MTX: 61%, mean of 15 mg/week • ETN: 45 mg every week D3: • MTX: 87%, mean of 15 mg/week • INF: 25 mg every 7 wks **Number in group** D1: 544 D2: 425 D3: 908 *Note that the #s here did not include the full 2326, it excludes those who withdrew (19%) **Mean age**	**Mean disease duration, years** D1: mean (range) 9 (0-51) D2: 8 (0-47) D3: 9 (0-68) **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** D1: PNL 40% D2: 43% D3: 50% **DMARD use, %:** D1: MTX 70% D2: 61% D3: 87% **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** D1: 5.3 D2: 5.4 D3: 5.4	**ACR mean difference/ absolute difference (CI/SD/P Value):** ACR 20: NR ACR 50: 6 mos D1: 8.7 D2: 10.4 D3: 3.6 12 mos D1: 12.4 D2: 12.4 D3: 5.8 ACR 70: 6 mos D1: 4.6 D2: 5.5 D3: 1.6 12 mos D1: 7.0 D2: 7.8 D3: 2.6 **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** DAS28 remission/	**Overall** Overall attrition/withdrawal (n): • ADA vs ETA 1.47 (1.20-1.80) • INF vs. ETA 1.98 (1.63-2.40) • INF vs ADA 1.35 (1.15-1.58) Withdrawals due to adverse events (n): • ADA vs ETA 1.50 (1.04-2.16) • INF vs. ETA 2.65 (1.88-3.73) • INF vs ADA 1.77 (1.34 - 2.34) Withdrawals due to lack of efficacy (n): • ADA vs ETA 1.47 (1.15-1.87) • INF vs. ETA 1.70 (1.35- 2.15 • INF vs ADA 1.16 (0.95-1.41) **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** NR **Other infections:**	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Research objective To compare TNF inhibitors directly regarding the rates of treatment response, remission, and the drug survival rate in patients with RA and to identify clinical prognostic factors for response. **Study design** Observational **Overall N** 2326 **Duration of study** 1 year		**(years)** D1: 56 D2: 58 D3: 57 **Sex, % female** D1: 75 D2: 72 D3: 73 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	Lundex corrected (n) 6 mos D1: 32/26 (536) D2: 26/21 (414) D3: 21/17 (889) DAS28 remission/ Lundex corrected (n) 12 mos D1: 39/27 (444) D2: 33/24 (377) D3: 27/16 (/690) **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** Adjusted ORs for	NR **GI:** NR **Other:** NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				ACR70 response • ADA vs INF: 2.05 (1.52 to 2.76) • ETN vs. INF: 1.78 (1.28 to 2.5) • ADA vs. ETN: 1.15 (0.82		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hjardem et al., 2007[84] **Country and setting** Danish, multicenter **Source of funding** Abbott, Wyeth, Schering-Plough **Research objective** Investigate efficacy of switching to a second biologic drug in RA **Study design** Population – based Dynamic Cohort Study **Overall N** 235 (switchers only) **Duration of study** Varied, NR **Quality rating** Fair: No controls for confounding, baseline difference in current mtx use	**Inclusion Criteria** • RA pt who had received 2+ biologics (IFX, ETN, or ADA only) **Exclusion Criteria** • Incomplete baseline data (DAS)	**Interventions, Dose** D1: IFX: varied, dose NR D2: ETN: varied, dose NR D3: ADA: varied, dose NR **Number in group** D1: 178 D2: 18 D3: 39 **Mean age (years)** D1: 55 D2: 54 D3: 52 **Sex, % female** D1: 77 D2: 61 D3: 74 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: mean (range): 9 yrs (4-17) D2: 11 (3-23) D3: 7 (3-17) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** D1: current MTX: 82 D2: 42 D3: 62 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: 5.8 (5.0-6.5) D2: 5.9 (5.4-6.5) D3: 5.6 (5.0-6.7) **Required treatment for latent TB**	**ACR** NR **HAQ** NR **DAS** D1: Efficacy outcomes stratified by 1st & 2nd drug and cannot be combined. **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference** NR	**Overall** All pts included in study withdrew from their tx, reasoning as follows (% withdrew for :Lack of Efficacy/Adverse Event/Other): IFX 45/34/21, ETN 44/22/34, ADA 54/21/26 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR **Other population characteristics, %, (CI/SD/P value)**		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hoff, M. et al., 2009[85] PREMIER **Country and setting** Norway, multicenter **Source of funding** Abbott Laboratories **Research objective** Examine effect of ADA on hand osteoporosis and relation to radiographic joint damage in 3 tx arms: ADA + MTX, ADA, and MTX to identify predictors of hand bone loss **Study design** Controlled Trials **Overall N** 768 **Duration of study** 2 yrs **Quality rating**	**Inclusion Criteria** • MTX Naïve • Early RA • Aggressive RA: ≥ 8 swollen joints, ESR ≥ 28 or CRP ≥ 1.5 mg/dl, erosions or rheumatoid factor positive. • No prior treatment with cyclophos-phamide, cyclosporine, azathioprine or more than 2 other DMARDs. **Exclusion Criteria** NR	**Interventions, dose** D1: • MTX: weekly by mouth (rapidly increased to 20 mg/week) • ADA: 40 mg subcutaneously every other week D2: • ADA: 40 mg subcutaneously every other week • Placebo D3: • MTX: weekly by mouth • Placebo **Number in group** D1: 261 D2: 261 D3: 246 Overall: 768 **Mean age, years (SD)** D1: 52.2 (13.8) D2: 51.9 (13.7) D3: 51.9 (13.3) **Sex, % female** D1: 71.6 D2: 78.5 D3: 73.6 **Race, % white** NR	**Mean disease duration, years (SD)** D1: 0.7 (0.8) D2: 0.7 (0.8) D3: 0.8 (0.9) **Patients with early RA, three years or less, %** D1: 100 D2: 100 D3: 100 **Treatment resistant, %** NR **TJC, mean (SD)** D1: 31.1 (14.1) D2: 31.7 (13.5) D3: 32.2 (14.3) **SJC, mean** D1: 21.2 (42.4) D2: 21.7 (10.2) D3: 21.6 (11.3) **Corticosteroid use, %** D1: 35.2 D2: 36 D3: 34.6 **DMARD use, %** D1: 32.2 D2: 33.3 D3: 31.7 **MTX naïve, %** D1: 100 D2: 100 D3: 100	**ACR** NR **HAQ (SD)** D1: 1.5 (0.6) D2: 1.6 (0.6) D3: 1.5 (0.7) **DAS** NR **SF-36** NR **Radiographic measures (SD)** Modified TSS change from baseline: Median at 26 weeks, n: D1: 0 (0.5) D2: 1.0 (3.4) D3: 0.5 (2.2) Median at 52 weeks: D1: 0 (0.9) D2: 2.0 (5.1) D3: 0.5 (3.3) Median at 104 weeks: D1: 0 (1.0) D2: 2.0 (6.4) D3: 1.0 (4.8) **Quality of life scales** NR	**Attrition/withdrawal** Overall, n: D1: 65 D2: 104 D3: 88 Overall: 257 Adherent/compliant, n: D1: 203 D2: 167 D3: 169 Overall: 539 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR **Other infections** NR **GI** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Fair		**Race, % black** NR **Ethnicity, Latino** NR	**Baseline DAS score (SD)** D1: 6.3 (0.9) D2: 6.4 (0.9) D3: 6.3 (0.9) **Required treatment for latent TB** NR **Median Modified TSS (SD)** D1: 12.8 (60.24) D2: 13.5(5.1-25.5) D3: 15.5 (7.5-28.5) Mean D1: 18.1 (20.3) D2: 18.4 (18.2) D3: 21.5 (21.8)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Hyrich et al., 2007[86] **Country, Setting:** Great Britain, multiclinic **Funding:** Schering Plough, Wyeth, Abbott, A mgen British Society for Rheumatology Biologics Register **Research Objective:** Compare outcome at 6 mos in unselected real-world RA pts treated with ETA or INF alone or with MTX or another DMARD **Study Design:** Prospective cohort study	**Inclusion Criteria:** • Age > 16 yrs • Diagnosed with RA according to 1987 ACR criteria; starting either ETA or INF as first biologic drug • Other meds were allowed **Exclusion Criteria:** NR	**Interventions, dose:** D1: ETA (25 mg 2x wk) D2: ETA + DMARD D3: ETA + MTX D4: INF (3 mg/kg wks 0,2,6 then every 8wks) D5: INF + DMARD D6: INF + MTX Some doses NR **N:** D1: 763 D2: 245 D3: 250 D4: 128 D5: 121 D6: 1204 **Mean age, yrs:** D1: 58 D2: 55 D3: 54 D4: 59 D5: 58 D6: 55 **Sex, % female:** D1: 80 D2: 79 D3: 76 D4: 79 D5: 74 D6: 77	**Mean disease duration, yrs:** D1: 16 D2: 15 D3: 13 D4: 16 D5: 14 D6: 14 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** D1: 54 D2: 51 D3: 44 D4: 69 D5: 59 D6: 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS,**	**At 6 months** **EULAR response:** D3 vs. D1: (OR 1.98, 95% CI, 1.45-2.71) D2 vs. D1 (OR 1.20, 95% CI, 0.89-1.61) D3 vs D2 (OR 1.66, 95% CI, 1.14-2.42) A better EULAR response in both MTX (OR 1.35 [95% CI, 0.92-2.00]) and DMARD (OR 1.26 [95% CI, 0.75-2.13]) subgroups as compared with INF monotherapy **DAS28**: D1: 4.8 +/-.4 D2: 4.6 +/- 1.5 D3: 4.3 +/- 1.5 D4: 5.0 +/- 1.6 D5: 4.9 +/- 1.6 D6: 4.6 +/- 1.6	**Adherence:** Drug survival at 6 mos: ETA 20% INF 21% ETA subgroups (22% mono, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy , vs. 22% DMARD co-therapy)	**Overall Attrition Rate, %:** 21 **ITT Analysis:** N/A **Quality; Rating:** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		Race, % white: NR	**mean:** D1: 6.8 D2: 6.6 D3: 6.6 D4: 6.8 D5: 6.8 D6: 6.7			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hyrich et al., 2006,[87] BSRBR **Country and setting** UK, hospitals/general practice **Source of funding** BSRBR receives financial support from following UK companies: Schering Plough, Wheth Laboratories, Abbott Laboratories and Amgen. Aforementioned resources are used by BSR to provide research grants to University of Manchester. **Research objective** Identify clinical factors present at start of anti-TNF-alpha therapy	**Inclusion Criteria** • Patients registered with BSRBR who had fulfilled1987 ACR criteria for RA • Started therapy with either ETN or IFX within 6 mos of registration • Only patients who had reached 6 mos of follow-up prior to 10/1/04 were considered for study. **Exclusion Criteria** NR	**Interventions, dose** D1: • ETN: 25 mg, twice/wk • Both study arms included participants who were concurrently using NSAIDs, corticosteroids, other DMARDs, or MTX (see patient characteristics for specifics) D2: • IFX: 3 mg/kg at weeks 0, 2, 6, and 8 weekly thereafter • Both study arms included participants who were concurrently using NSAIDs, corticosteroids, other DMARDs, or MTX (see patient characteristics for specifics) **Number in group** D1: 1267 D2: 1612 Overall: 2879 **Mean age, years (SD)** D1: 55	**Mean disease duration, years** D1: 14 D2: 14 Overall: 14 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean (SD)** D1: 16 (7) D2: 16 (7) Overall: 16 **SJC, mean (SD)** D1: 12 (6) D2: 12 (6) **Corticosteroid use, %** D1: 50 D2: 49 Overall: 49.3 **DMARD use, %** D1: 100 D2: 100 Overall: 100 **MTX naïve, %** D1: NR D2: NR Overall: 2% **Baseline DAS score** D1: 6.7 D2: 6.7	**ACR mean difference/ absolute difference (CI/SD/P Value)** ACR 20: NR ACR 50: NR ACR 70: NR **HAQ, mean difference/ absolute difference** NR **DAS, mean difference/absolute difference (CI/SD/P Value)** D1: NR D2: NR Overall: -2.1 **SF-36, mean difference/absolute difference** NR **Radiographic measures, mean difference/absolute difference** NR **Quality of life scales, mean difference/absolute difference** NR **Others, (please name), mean difference/absolute**	**Attrition/withdrawal** Overall, n: D1: 146 D2: 198 Withdrawals due to adverse events, n: D1: 129 D2: 166 Adherent/compliant, n: D1: 1149 D2: 1460 **Overall adverse events reported, n:** D1: 129 D2: 166

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
associated with response at 6 mos **Study design** Observational **Overall N** 2879 **Duration of study** 6 mos **Quality rating** Fair		D2: 55 Overall: 55 **Sex, % female** D1: 78 D2: 76 Overall: 77 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	Overall: 6.7 **Required treatment for latent TB** NR **Other population characteristics, %** Concurrent NSAIDs: D1: 65 D2: 67 Concurrent corticosteroids: D1: 50 D2: 49 Concurrent DMARDs: D1: 48 D2: 94 Concurrent MTX: D1: 28 D2: 86 Overall: NR	**difference (CI/SD/P Value)** Good EULAR response, n (%): • ETN: 245 (17.3) • IFX: 339 (18.70, Overall: 584 (18.1) • Concurrent MTX + ETN: 101 (41) • Concurrent steroids + ETN: 113 (46) • Concurrent NSAIDs + ETN: 117 (72) • Concurrent MTX + IFX: 300 (89) • Concurrent steroids + IFX: 155 (46) • Concurrent NSAIDs + IFX: 255 (75) Moderate EULAR response, n (%): • ETN: 727 (51.5) • IFX: 875 (48.3), Overall: 1602 (49.7) • Concurrent MTX + ETN: 200 (27) • Concurrent steroids + ETN: 352 (48) • Concurrent NSAIDs + ETN: 472 (65) • Concurrent MTX + IFX: 756 (86) • Concurrent steroids + IFX: 442 (51) • Concurrent NSAIDs +	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				IFX: 575 (66) No EULAR response, n (%): • ETN: 441 (31.2) • IFX: 596 (32.9), Overall: 1037 (32.2) • Concurrent MTX + ETN: 55 (18) • Concurrent steroids + ETN: 163 (55) • Concurrent NSAIDs + ETN: 176 (59) • Concurrent MTX + IFX: 326 (82) • Concurrent steroids + IFX: 195 (49) • Concurrent NSAIDs + IFX: 248 (62) Remission, n (%): • ETN: 120 (8.0) • IFX: 172 (9.0), Overall: 292 (8.6) Predictors of remission at 6 mos, OR (95% CI): • Concurrent MTX + ETN: 1.80 (1.14 - 2.85) • Concurrent steroid + ETN: 0.81 (0.52 - 1.25) • Concurrent NSAIDs + ETN: 1.79 (1.07 - 2.99) • Concurrent MTX + IFX: 1.24 (0.68 - 2.27) • Concurrent steroids + IFX: 1.10 (0.76 - 1.59)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				• Concurrent NSAIDs + IFX: 1.93 (1.23 - 3.03)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hyrich et al., 2007[88] **Country and setting** UK, hospitals/general practice **Source of funding** Schering Plough, Wyeth, Abbott, Amgen, British Society for Rheumatology Register **Research objective** Compare drug continuation rates between 1st and 2nd course of anti-TNF therapy **Study design** Prospective Cohort Study **Overall N** 6739 **Duration of study** Mean length of followup per	**Inclusion Criteria** • Patients registered with BSRBR with a diagnosis of RA (as determined by treating rheumatologist) who had reached a minimum of 6 months of followup by end of April 2005. **Exclusion Criteria** • NR	**Interventions, Dose** D1: ADA: 40 mg, every two wks D2: ETN: 25 mg, twice/wk D3: IFX: 3 mg/kg, administered at weeks 0, 2, 6, and 8 and every 8 weeks thereafter **Number in group** D1: 876 D2: 2826 D3: 3037 **Mean age (years)** 55 **Sex, % female** 77 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** Overall: 14 yrs (9) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** 49 **DMARD use, %** 100 **MTX naïve, %** 0 **Baseline DAS score, mean (SD)** 6.6 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Overall: HAQ: 2.1	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** Overall attrition/withdrawal, n: D1: 265 D2: 822 D3: 1273 Overall: 2360 Withdrawals due to adverse events, n: D1: 98 D2: 405 D3: 520 Overall: 1023 Withdrawals due to lack of efficacy, n: D1: 109 D2: 277 D3: 455 Overall: 841 Adherent/compliant, n: D1: 611 D2: 2004 D3: 1764 Overall: 4379 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
patient was 15 months (maximum 61 months). Due to difference in availability of 3 agents, mean followup of patients starting IFX (18 months) was longer than that of patients starting either ADA (11 months) or ET **Quality rating** Fair			• Receiving concomittant DMARDS, All: 69% • ETN group: 48, IFX group: 92 • ADA group: 58 Receiving concomitant MTX • All: 56% • ETN group: 30% • IFX group: 85% • ADA group: 40%		**Other infections** NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Jacobsson et al., 2005[89] **Country, Setting:** Sweden, population-based (2 Swedish registers) **Funding:** NR **Research Objective:** Risk of cardiovascular disease (CVD) in pts with RA treated with TNF inhibitors, compared to a standard RA population **Study Design:** Retrospective cohort study **Overall N:** 983 (combined cohort) **Study Duration:** NR	**Inclusion Criteria:** • Age-: 20 -79 yrs • Diagnosed according to 1987 ACR criteria • Case cohort • South Swedish Arthritis Txt Group (SSATG): pts with RA treated with anti-TNF agents and included in SSATG register between 2/1/99 and 12/31/01 **Exclusion Criteria:** • Previous hospital discharge due to CVD	**Interventions, dose:** D1: Anti-TNF exposed D2: Not Anti-TNF exposed **N:** D1: 531 D2: 452 Median age, yrs: D1: 55 D2: 61 **Sex, % female:** D1: 78 D2: 75 **Race, % white:** NR	Median disease duration, yrs: D1: 12 D2: 11 **TJC, mean:** NR **SJC, mean:** NR Median # of previous DMARDs used (IQR): D1: 4 (2-5) D2: 2 (1-4) PNL use, %: D1: 75 D2: 22 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR Median HAQ: D1: 1.50 D2: 1.13 VAS patient global	Decreased incidence and RR for the development of first-time CVD event when controlling for disease severity in pts with RA treated with TNF blocking therapy • Controlling for disability (HAQ), age-sex adjusted rate ratio was 0.46 (95% CI,0.25 - 0.85; *P* = 0.013) in anti-TNF treated vs. not treated • Anti-TNF group, 13 CVD events (in 656 PY at risk); age-adjusted incidence rate: 14 events/1000 PY • Unexposed comparison group, 85 CVD events (in 2056 PY at risk); age-adjusted incidence rate: 35.4 events/1000 PY • Relative risk: 0.62 (95% CI, 0.34 to 1.12; *P* = 0.111) • SMR revealed increased risk of new onset CVD in those not treated with TNF blockers in relation to	Cardiovascular Events: D1: n:13 (6 MI, 4 cerebrovascular disease, and 3 other) D2: n:85 (33 MIs, 15 cerebrovascular disease, 12 CHF, 2 ruptured aortic aneurysm, and 23 other)	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

		assessment median: D1: 69 D2: 48	background population of Malmo (SMR: 228, 95% CI,179 to 277) TNF blockers, risk of new onset CVD was lower, with CIs enclosing unity with background population (SMR: 157, 95% CI,72 -242)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Karanikolas et al., 2008[90] **Country and setting** Greece, multicenter **Source of funding** NR **Research objective** Understand if adding ANK totx regime will improve response of pts with suboptimal response to LEF, MTX, or CSA monotherapy **Study design** Open-label comparison **Overall N** 128 **Duration of study** 48wks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant defined as an inadequate response to non-biologic DMARD • 18 years or older • Active RA (defined as 9+ TJC, 6 SJC, and one offollowing: ESR ≤ 28mm/1st hr, ≥ 20mg/l and morning stiffness ≥ 45minutes), stable dose of non-biologic DMARD (LEF MTX or CSA), NSAIDS, & oral corticosteroids **Exclusion Criteria** • Treatment with TNF-antagonist or intra-articular or systemic	**Interventions, dose** D1: • MTX: Continued at 25mg/wk or maximum tolerated dose • ANK: 100mg/daily D2: • LEF: Continued at 20mg/wk or maximum tolerated dose • ANK: 100mg/daily D3: • ANK: 100mg/daily • CSA: 3.5mg or maximum tolerated dose **Number in group** D1: 48 D2: 42 D3: 38 **Mean age, years (SD)** D1: 48.1 D2: 47.2 D3: 47.6 **Sex, % female** D1: 68 D2: 69 D3: 70 **Race, % white** NR	**Mean disease duration, years** D1: 6.9 (5.1) D2: 6.8 (4.3) D3: 7.1 (4.7) **Patients with early RA,: 2 years or less, %** D1: 27 D2: 25 D3: 23 **Treatment resistant, %** D1: 100 D2: 100 D3: 100 Overall: 100 **Tender Joint Count, mean** NR **Swollen Joint Count, mean** NR **Corticosteroid use, %** D1: 60 D2: 62 D3: 63 **DMARD use, %** D1: 100 D2: 100 D3: 100 **MTX naïve, %** D1: 0 D2: NR D3: NR	**ACR** ACR 20: D1: 65 D2: 81 D3: 74 (Comparison: *P* = 0.218) ACR 50: D1: 38 D2: 64 D3: 47 (Comparison: *P* = 0.039) ACR 70: D1: 15 D2: 36 D3: 21 (Comparison: *P* = 0.057) **HAQ** NR for groups **DAS** NR, Reported in graph only **SF-36** NR **Radiographic measures** Comparisons: • SJC *P* = NS • TJC *P* = NS • HAQ *P* = NS **Quality of life scales** NR	**Attrition/withdrawal** Overall, n: D1: 9 D2: 3 D3: 5 Withdrawals due to adverse events, n: D1: 3* D2: 2* D3: 2 (*includes 1 death) Withdrawals due to lack of efficacy, n: D1: 2 D2: 1 D3: 3 Adherent/compliant, n: NR **Overall adverse events reported, n:** D1: 34 D2: 30 D3: 20 **Serious adverse events** Death, n: D1: 1 D2: 1 Arterial hypertension, n: D1: 0 D2: 4 D3: 2 Thrombocytopenia, n: D1: 1 D2: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	corticosteroids within 8 wks	**Race, % black** NR **Ethnicity, Latino** NR	**Baseline DAS score** D1: 6.55 D2: 6.93 D3: 6.97 **Required treatment for latent TB** NR		D3: 0 Hepatotoxicity/elevated liver enzymes, n: D1: 0 D2: 0 D3: 0 **Malignancies** Ovarian cancer, n: D1: 1 D2: 0 D3: 0 **Respiratory events** Tuberculosis: NR Upper respiratory infection, n: D1: 4 D2: 4 D3: 0 **Other infections** Urinary tract infection, n: D1: 1 D2: 2 D3: 0 Ocular infection, n: D1: 0 D2: 1 D3: 0 **GI** GI bleed or ulcer, n: D1: 0 D2: 0 D3: 1 **Other**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Infusion/injection site reactions, n: D1: 20 D2: 10 D3: 7 Skin rash, n: D1: 0 D2: 0 D3: 0 Headache, n: D1: 0 D2: 4 D3: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Kavanaugh et al., 2008,[91] TEMPO **Country and setting** Multinational, multicenter **Source of funding** Immunex Corporation & Wyeth Pharmaceuticals **Research objective** Evaluate clinical response between 12 and 24 wks in subjects with RA from TEMPO trial **Study design** Controlled Trials **Overall N** 682 **Duration of study** 52 weeks (TEMPO trial), 12 & 24 weeks outcomes reported here **Quality rating** Fair	**Inclusion Criteria:** • Age > 18 • Diagnosed according to ACR criteria • Functional class I-III • Less than satisfactory response to at least 1 DMARD other than MTX • Duration 6 mos to 20 yrs • RA defined as > 10 swollen and > 12 painful joints and at least one of: ESR > 28 mm/h, CRP > 20 mg/L, or morning stiffness for > 45 minutes • Folic acid 5 mg twice per wk • NSAIDs **Exclusion Criteria:**	**Interventions, dose** D1: • MTX: 7.5mg/wk escalated to 20mg/wk over 8wks • ETN: 25mg, 2/wk D2: ETN: 25mg, 2/wk D3: MTX 7.5mg/wk escalated to 20mg/wk over 8 wks **Number in group** D1: 231 D2: 223 D3: 228 Overall: 682 **Mean age, years (SD)** D1: see TEMPO[92] for baseline characteristics by arm Overall: 52.5 **Sex, % female** NR **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: NR D2: NR Overall: 6.8 yrs **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** NR	**ACR** At week 12 ACR 20: D1: 75.8 D2: 66.4 D3: 61.0 ACR 50: D1: 41.6 D2: 32.7 D3: 25.9 ACR 70: D1: 22.1 D2: 9.4 D3: 5.7 At week 24 ACR 20: D1: 84.8 D2: 77.1 D3: 77.2 ACR 50: D1: 57.6 D2: 44.4 D3: 41.7 ACR 70: D1: 32.0 D2: 14.8 D3: 14.0 **HAQ** NR **DAS** D1: NR (different stratification for	**Overall** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR **Other infections** NR **GI** NR **Other** NR

	• TNF antagonist, any immuno-suppressive drugs w/in 6 mos • Any investigational drug or biologic agent within 3 mos DMARD or corticosteroid injection within 4 mos Relevant comorbidity, Previous txt with MTX if pt experienced clinically toxic side effects or had no response		analysis) D2: NR D3: NR Overall: NR **SF-36** NR **Radiographic measures** D1: NR (different stratification for analysis) D2: NR D3: NR Overall: NR **Quality of life scales** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Kay et al., 2008[93] **Country and setting** Multlinational, multienter **Source of funding** Centocor **Research objective** Asssess efficacy, safety and pharmacology of subcutaneous GOL in pts with active RA despite tx with MTX **Study design** Controlled Trials **Overall N** 172 **Duration of study** 16 wks (efficacy), 20 wks (AEs) after week 20- drug and dosing schedules were adjusted and patients were followed for efficacy & AEs -AE	**Inclusion Criteria** • Active RA for 3+ mos (TJC and SJC ≥ 6 and 2 of following 3: CRP ≥ 1.5mg/dl, ESR ≥ 28mm, morning stiffness ≥ 30 minutes), Age ≥ 18 **Exclusion Criteria** • Abnormal lab results • Latent or active TB • Planning pregnancy or inadequate birth control • Other inflammatory disease • DMARD use w/in 4wks of study start • Failed 3+ DMARDS • Previous treatment with TNF-alpha	**Interventions, dose** D1: MTX: continued 10mg/wk Placebo ALL ARMS: continued (stable dose for > 4wks) corticosteroids (max 10mg PRED/day) and NSAIDs D2: MTX: continued 10mg/wk GOL: 50mg/4wks D3: MTX: continued 10mg/wk GOL: 50mg/2wks D4: MTX: continued 10mg/wk GOL: 100mg/4wks D5: MTX: continued 10mg/wk GOL: 100mg/2wks **Number in group** D1: 35 D2: 35 D3: 34 D4: 34 D5: 34 Overall: 172 **Mean age, median** D1: 52.0 D2: 57.0 D3: 48.0 D4: 57.5	**Mean disease duration, median (IQR)** D1: 5.6 (1.4, 10.9) D2: 8.2 (4.1, 14.3) D3: 8.2 (2.9, 12.8) D4: 6.3 (3.4, 14.1) D5: 9.0 (4.1, 14.1) Overall: 7.8 (3.0, 13.3) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, median** D1: 22 D2: 28 D3: 28 D4: 32 D5: 22 Overall: 26 **Swollen Joint Count, median** D1: 13 D2: 14 D3: 14 D4: 20 D5: 14 Overall: 15 **Corticosteroid use, %** NR **DMARD use, %** NR	**ACR** ACR 20: D1: 37.1 D2: 60.0 D3: 50.0 D4: 55.9 D5: 79.4* Overall: ALL - compared to Placebo 61.3 *P = 0.010 ACR 50: D1: 5.7 D2: 37.1* D3: 23.5* D4: 29.4* D5: 32.4* Overall: 30.7 *P = 0.003 ACR 70: D1: 0 D2: 8.6 D3: 14.7* D4: 17.6* D5: 8.8 Overall: 12.4 *P = 0.028 **HAQ** NR **DAS28-CRP mean (SD)** D1: -0.9 (1.0) D2: -1.9 (1.3) D3: -1.4 (1.3) D4: -1.9 (1.5) D5: -1.9(1.1) Overall: -1.8 (1.3) **DAS28-ESR mean (SD)**	**Attrition/withdrawal** Overall, n: D1: 6 D2: 4 D3: 6 D4: 5 D5: 2 Overall: 23 Withdrawals due to adverse events, n: D1: 3 D2: 2 D3: 3 D4: 2 D5: 1 Overall: 11 Withdrawals due to lack of efficacy, n: D1: 3 D2: 2 D3: 1 D4: 3 D5: 1 Overall: 10 **Overall adverse events reported, n:** Pts reporting 1+ AE: D1: 29 D2: 34 D3: 24 D4: 29 D5: 31 **Serious adverse events** Congestive cardiac failure,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
data reported (thru week 52) were not included inabstraction to prevent confusion. **Quality rating** Fair	antagonist (more reported online in journal suppl materials)	D5: 53.5 Overall: 53.5 **Sex, % female** D1: 74.3 D2: 85.7 D3: 67.6 D4: 76.5 D5: 79.4 Overall: 76.7 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**MTX naïve, %** D1: 0 D2: 0 D3: 0 D4: 0 D5: 0 Overall: 0 **Baseline DAS28/CRP score** D1: 5.3 D2: 5.3 D3: 4.8 D4: 5.4 D5: 5.1 Overall: 5.2 **DAS28/ESR - median** D1: 6.3 D2: 6.4 D3: 6.4 D4: 6.7 D5: 6.2 Overall: 6.4 **Required treatment for latent TB** D1: 0 (exluded) **HAQ disability index - median** D1: 1.3 D2: 1.7 D3: 1.6 D4: 1.8 D5: 1.3 Overall: 1.6	D1: -1.0 (1.1) D2: -2.1 (1.4) D3: -1.9 (1.5) D4: -2.1(1.7) D5: -2.3(1.2) Overall: -2.1 (1.4) **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name) mean difference/absolute difference (CI/SD/P Value)** ACR-N mean (SD): D1: -2.4 (50) D2: 22.7 (46.8) D3: 16.2 (57.4) D4: 24.8 (41.7) D4: 30.4 (42.3) D2 vs. D1:*P* = 0.006, D3 vs. D1 *P* = 0.095, D4 vs. D1: *P* = 0.01, D5 vs. D1: *P* < 0.01	n: D1: 0 D2: 1 D3: 0 D4: 0 D5: 0 Cardia tamponade, n: D1: 0 D2: 0 D3: 0 D4: 0 D5: 1 **Malignancies** Lung adenocarcinoma, n: D1: 0 D2: 0 D3: 1 D4: 0 D5: 0 **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 0 D2: 1 D3: 1 D4: 1 D5: 0 **Other infections** 1+ infection, n: D1: 13 D2: 12 D3: 6 D4: 9 D5: 9

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					GI Nausea, n: D1: 1 D2: 2 D3: 7 D4: 6 D5: 8 **Other** 1+ injection site disorder thru 20wk, n: D1: 4 D2: 5 D3: 2 D4: 5 D5: 13 Headache, n: D1: 7 D2: 6 D3: 5 D4: 7 D5: 3 **Any other AEs:** All AEs reported thru 20 weeks. Only those in ≥ 10% of all GOL groups combined or SAEs. Additional surveillance for AEs continued thru wk 52, however, treatment and dosing schedule was adjusted for 3/5 arms.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Keane, 2001[94] **Country, Setting:** Multinational, NA NA **Funding:** National Heart, Lung and Blood Institute; Massachusetts Thoracic Society; American Lung Association of Massachusetts **Research Objective:** To explore relationship between INF and tuberculosis based on data from MedWatch **Study Design:** Database analysis; AERS **Overall N:** 70 cases 47 Crohn's: 18 Other: 5	**Inclusion Criteria:** • If during or after txt with INF, patient received diagnosis of TB on basis of clinical, radiologic, and laboratory findings **Exclusion Criteria:** NR	**Interventions, dose:** **D1: TB pts** **INF: varies** **N:** D1: 57 Median age, yrs: D1: 57 **Sex, % female:** D1: 64 **Race, % white:** D1: NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** D1: 20 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Estimated incidence for pts with RA who have been treated with INF during previous is 24.4 cases per 100.000 per yr (95% CI,0.6 to 34.0); background incidence in US for pts with RA not exposed to TIM therapy: 6.2 cases per 100,000 per yr • Median interval from start of INF txt until development of TB: 12 wks; 68.6% developed TB after 3 or fewer INF infusions; reported frequency of TB in association with INF was much higher than reported frequency of other opportunistic infections associated with this drug	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Duration:
1-52 wks

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone, E. et al., 2008[95] RAPID 1 trial **Country and setting** Multinational, multicenter **Source of funding** UCB Inc. **Research objective** Evaluate efficacy and safety of 2 dosage regimens of CZP as adjunctive therapy to MTX in RA pts with an inadequate response to MTX **Study design** Controlled Trials **Overall N** 982 **Duration of study** 52 weeks **Quality rating** Fair	**Inclusion Criteria** • ≥ 18 years of age • Diagnosis of RA as defined byACR 1987 criteria for ≥ 6 mos prior to screening but for < 15 years • Active disease was defined as ≥ 9 tender and 9 swollen joints at screening and at baseline, with either an ESR ≥ 30 mm//hr or a CRP level > 15 mg/liter. • Pts were required to have received MTX for ≥ 6 onths prior to baseline. **Exclusion Criteria** • Diagnoses of any other inflammatory arthritis or	**Interventions, dose** D1: MTX Placebo D2: MTX Certolizumab: 400 mg at weeks 0, 2, and 4 followed by 200 mg every 2 weeks D3: MTX Certolizumab: 400 mg at weeks 0, 2, and 4 followed by 400 mg every 2 weeks **Number in group** D1: 199 D2: 393 D3: 390 Overall: 982 **Mean age, years (SD)** D1: 52.2 (11.2) D2: 51.4 (11.6) D3: 52.4 (11.7) **Sex, % female** D1: 83.9 D2: 82.4 D3: 83.6 **Race, % white** NR **Race, % black** NR	**Mean disease duration, years (SD)** D1: 6.2 (4.4) D2: 6.1 (4.2) D3: 6.2 (4.4) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean** D1: 29.8 (13.0) D2: 30.8 (12.4) D3: 31.1 (13.3) **SJC, mean** D1: 21.2 (9.7) D2: 21.7 (9.9) D3: 21.5 (9.8) **Corticosteroid use, %** NR **Previous DMARD use (except MTX), n (SD)** D1: 1.4 (1.4) D2: 1.3 (1.3) D3: 1.3 (1.3) **MTX naïve, %** NR **Baseline DAS score, median (range)** D1: 7.0 (4.9-8.7) D2: 6.9 (4.3-8.9) D3: 6.9 (4.8-9.1)	**ACR** ACR 20: Week 1: D1: 5.6 D2: 22.9 D3: 22.3 Overall:: D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0.001$ Week 24: D1: 13.6 D2: 58.8 D3: 60.8 Overall: D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0$. ACR 50: D1: In Figure, NR D2: In Figure, NR D3: In Figure, NR Overall: by week 2, ACR50 responses in certolizumab Dwere significanlty higher thanplacebo D($P \leq 0.01$ for each comparison); difference remained ($P \leq 0.001$ for weeks 4-52) ACR 70: D1: In Figure, NR D2: In Figure, NR D3: In Figure, NR Overall: by week 4,	**Attrition/withdrawal** Withdrawals due to adverse events, n: D1: 3 D2: 17 D3: 22 12 patients discontinued due to infection (6 from each CZP arm). Overall adverse events reported, n: D1: 125.9 D2: 96.6 D3: 94.5 **Serious adverse events** Death, n: D1: 1 (myocardial infarction) D2: 2 (hepatic neoplasm, cardiac arrest) D3: 4 (stroke, myocardial necrosis, cardiac arrest, atrial fibrillation) **Malignancies** Malignancy, incidence rate per 100 person years: D1: 1.1 D2: 2.3 D3: 1.3 **Respiratory events** Upper respiratory infection, incidence rate per 100 person years: D1: 5.5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	secondary noninflammatory arthritis that could have interfered with their evaluation ofeffects of certolizumab pegol on RA • History of TB or chest radiograph showing active or latent TB • High risk of infection • History of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, GI, endocrine, pulmonary, cardiac, neurologic, or cerebral disease • Those having received any biologic	**Ethnicity, Latino** NR	**Required treatment for latent TB** NA **Other population characteristics, %, (CI/SD/P value)** HAQ DI: D1: 1.7 (0.6 D2: 1.7 (0.6 D3: 1.7 (0.6	ACR70 responses in certolizumab 200 Dwas significanlty higher thanplacebo D($P \leq 0.05$); and by week 6, forcertolizumab 400 D($P \leq 0.05$); differences remained ($P \leq 0.001$ for weeks 10-52) **% Change** Baseline to week 1: D1: -2.4 D2: -13.5 D3: -10.9 Overall: D1 vs. D2 $P <$ 0.001, D1 vs. D3 $P <$ 0.001 Baseline to week 4: D1: -5.4 D2: -21.5 D3: -21.9 Overall: D1 vs. D2 $P <$ 0.001, D1 vs. D3 $P <$ 0.001 Baseline to week 12: D1: -8.2 D2: -30.4 D3: -27.6 Overall: D1 vs. D2 $P <$ 0.001, D1 vs. D3 $P <$ 0.001 **Mean change, baseline to week 52 (SD)**	D2: 7.9 D3: 6.7 **Other infections** Urinary tract infection, incidence rate per 100 person years: D1: 14.2 D2: 7.6 D3: 10.5 Other infections (specify), incidence rate per 100 person years: Nasopharyngitis: D1: 3.3 D2: 6.9 D3: 9.5 Lung/lower respiratory tract, incidence rate per 100 person years: D1: 0 D2: 1.0 D3: 1.3 Herpes viral, incidence rate per 100 person years: D1: 0 D2: 0.3 D3: 0.3 Bacterial peritonitis, incidence rate per 100 person years: D1: 0 D2: 0.3 D3: 0 Opportunistic infection,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	therapy within 6 mos (OR, had received ETN and/or ANK within 3 mos) of baseline and/or any privous biologic therapy resulted in a severe hypersensitivity or anaphylactic reaction • Those who had previously failed to respond to treatment with an anti-TNF agent.			D1: -2.4 (1.3) D2: -3.3 (1.3) D3: -3.4 (1.4) Overall: Baseline to week 52: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 **SF-36** NR **Radiographic measures** Sharp Baseline to week 52: D1: 2.8 D2: 0.4 D3: 0.2 Overall: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 **Quality of life scales** NR **% ChangeSJC** Baseline to week 1: D1: 4.5 D2: -18.2 D3: -18.8 Overall: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to week 4: D1: -10.3 D2: -37.3 D3: -40.4 Overall: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* <	incidence rate per 100 person years: D1: 0 D2: 0 D3: 0 **GI** Gastroenteritis, incidence rate per 100 person years: D1: 1.1 D2: 0.0 D3: 0.0 **Any other AEs:** Headache, incidence rate per 100 person years: D1: 12.0 D2: 7.3 D3: 5.7 Hypertension, incidence rate per 100 person years: D1: 2.2 D2: 8.2 D3: 10.2 Back pain, incidence rate per 100 person years: D1: 2.2 D2: 5.6 D3: 6.4 Injection site pain and injection site reaction 200mg (2% and 2.3%) or 400mg (1.3% and 0.8%), none in placebo group.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				0.001 Baseline to Week 12: D1: -10.7 D2: -56.7 D3: -61.5 Overall: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 TJC: Baseline to week1: D1: -6.7 D2: -18.9 D3: -19.1 Overall: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to week 4: D1: -11.4 D2: -36.2 D3: -37.0 D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to Week 12: D1: -10.8 D2: -52.6 D3: -56.8 D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Patient's global assessment: Baseline to week1: D1: -2.9 D2: -12.9 D3: -16.1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Overall: D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to week 4: D1: -6.5 D2: -10.4 D3: -27.9 D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to Week 12: D1: -4.9 D2: -38.3 D3: -39.2 D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Patient's assessment of arthritis pain: Baseline to week1: D1: -1.0, D2: -20.6, D3: -19.0 D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to week 4: D1: -5.0, D2: -26.6, D3: -28.8 D1 vs. D2 *P* < 0.001, D1 vs. D3 *P* < 0.001 Baseline to Week 12: D1: -4.8, D2: -38.2, D3: -39.6 D1 vs. D2 *P* < 0.001, D1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				vs. D3 $P < 0.001$ ESR (ratio): Baseline to week1: D1: 0.96, D2: 0.73, D3: 0.70 D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0.001$ Baseline to week 4: D1: 0.90, D2: 0.59, D3: 0.54 D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0.001$ Baseline to Week 12: D1: 0.84, D2: 0.53, D3: 0.52 D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0.001$	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone, E. et al.; 2009;[96] TEMPO and ERA **Country and setting** See original abstractions for TEMPO and ERA **Source of funding** Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth Research **Research objective** Examine clinical and radiographic responses to MTX, ETA, and ETA + MTX in pts with moderate vs. severe RA in early and late disease **Study design** Pooled data – post hoc analysis **Overall N**	**Inclusion Criteria** • MTX Naive • ERA sample only: early RA, pts who had had RA for no more than 3 years and had not been previously been treated with MTX. • TEMPO sample only: active RA not adequately responding to DMARD other than MTX; • Moderate RA was defined post hoc as DAS28 > 3.2 and ≤5.1; severe was > 5.1. • See original abstractions of TEMPO and ERA studies for further details **Exclusion Criteria**	**Interventions, Dose** D1: • MTX: TEMPO: twice weekly for 12 mos • ERA: 10 mg for 12 mos D2: • ETN: TEMPO & ERA: 25 mg twice weekly for 12 mos D3: • MTX: TEMPO: twice weekly for 12 mos • ETN: TEMPO: 25 mg twice weekly for 12 mos **Number in group** D1: • TEMPO: Moderate 16 Severe 211 • ERA: Moderate 33 Severe 178 D2: • TEMPO: Moderate 8 Severe 214 • ERA: Moderate 32 Severe 171	**Mean disease duration, years (years)** TEMPO Moderate: D1: 3.2 D2: 5.1 D3: 6.1 Severe: D1: 7.1 D2: 6.4 D3: 6.8 Overall: 6.6 ERA Moderate: D1: NR D2: NR D3:NR Severe: 1 **Patients with early RA, three years or less, %** TEMPO NR ERA D1: 100 D2: 100 D3: NR Overall: 100 **Treatment resistant, %** NR **TJC, mean (SD)** NR **SJC, mean (SD)**	**ACR mean difference/ absolute difference (%)** TEMPO ACR 20: Moderate D1: 75 D2: 75 D3: 82 Severe: D1: 75 D2: 76 D3: 85 ERA Moderate D1: 55 D2: 66 Severe: D1: 65 D2: 70 Overall: P NS ACR 50: TEMPO Moderate D1: 31 D2: 25 D3: 71 Severe: D1: 43 D2: 50 D3: 69 Overall: P NS ERA Moderate	**Overall** Adherent/compliant, n: D1: TEMPO: 227; ERA: 211 D2: TEMPO: 222; ERA: 203 D3: TEMPO: 228 Overall: TEMPO: 677; ERA: 414; COMBO: 1091 see original abstractions for TEMPO and ERA for attrition and withdrawal information **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
1091 **Duration of study** 12 mos **Quality rating** Fair	• See original abstractions for TEMPO and ERA	D3: • TEMPO: Moderate 17 Severe 211 Overall: • TEMPO: 677 • ERA: 414 • COMBO: 1091 **Mean age (years)** TEMPO: 53; ERA: 50 **Sex, % female** NR **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	NR **Corticosteroid use, %** NR **DMARD use, %** MTX: TEMPO: 43 ERA: 0 **MTX naïve, %** TEMPO NR ERA D1: 100 D2: 100 Overall: 100 **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: • HAQ: TEMPO: Moderate 0.92, SD 0.67 Severe 1.77, SD 0.66 D2: NR D3: NR	D1: 39 D2: 53 Severe: D1: 40 D2: 47 ACR 70: TEMPO Moderate D1: 13 D2: 13 D3: 65 Severe: D1: 19 D2: 25 D3: 40 Overall: TEMPO D3 *P* <0.05 ERA Moderate D1: 18 D2: 22 D3: Severe: D1: 21 D2: 24 **HAQ score,** HAQ score TEMPO (SD) Moderate: D1: 0.6 (0.1) D2: 0.6 (0.2) D3: 0.4 (0.2) Severe:	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D1: 1.1 (0.1) D2: 1.0 (0.1) D3: 0.8 (0.0) ERA Moderate: D1: 0.6 (0.1) D2: 0.4 (0.1) Severe: D1: 0.8 (0.0) D2: 0.8 (0.1) HAQ less than or equal to 0.5 (%): TEMPO Moderate: D1: 50 D2: 50 D3: 82 Severe: D1: 33 D2: 34 D3: 41 ERA Moderate: D1: 58 D2: 75 Severe: D1: 44 D2: 42 HAQ mean change from baseline to 12 mos (SD): TEMPO Moderate: D1: 0.29 (0.12)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D2: 0.42 0.21) D3: 0.74 (0.18) Severe: D1: 0.68 (0.05) D2: 0.74 (0.05) D3: 1.00 (0.05) ERA Moderate: D1: 0.44 (0.09) D2: 0.45 (0.09) Severe: D1: 0.77 (0.05) D2: 0.75 (0.05) Overall: HAQ score: • TEMPO D1 *P* <0.05 • ERA D2 *P* <0.05 • TEMPO D3 *P* <0.05 • HAQ less than or equal to 0.5: ERA D2 *P* <0.001 TEMPO D3 *P* <0.001 • HAQ change in mean scores: TEMPO D1 *P* <0.05 ERA D1 *P* <0.05 ERA D2 *P* <0.05 **DAS (%)** DAS28 remission (%): TEMPO Moderate: D1: 44 D2: 38 D3: 77	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Severe: D1: 15 D2: 17 D3: 35 ERA: Moderate: D1: 33 D2: 47 D3: Severe: D1: 15 D2: 14 D3: DS28 low disease activity (%): TEMPO Moderate: D1: 56 D2: 63 D3: 82 Severe: D1: 28 D2: 31 D3: 50 ERA Moderate: D1: 55 D2: 56 Severe: D1: 28 D2: 26 DAS28 mean change from baseline to 12 mos (SD):	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				TEMPO Moderate: D1: 1.6 (0.3) D2: 1.5 (0.4) D3: 2.5 (0.3) Severe: D1: 2.6 (0.1) D2: 2.7 (0.1) D3: 3.5 (0.1) ERA Moderate D1: 1.2 (0.2) D2: 1.7 (0.2) D3: Severe D1: 2.4 (0.1) D2: 2.4 (0.1) D3: Overall: • DAS28 remission: TEMPO D1 *P* <0.05 ERA D1 *P* <0.05 ERA D2 *P* <0.001 TEMPO D3 *P* <0.001 • DAS28 low disease activity: TEMPO D1 *P* <0.05 ERA D1 *P* <0.05 ERA D2 *P* <0.001 TEMPO D3 *P* <0.05 • DAS28 change in mean scores: TEMPO D1 *P* <0.05 ERA D1 *P* <0.001 TEMPO D2 *P* <0.05	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				ERA D2 *P* <0.05 TEMPO D3 *P* <0.05 **SF-36** NR **Radiographic measures (SD)** TSS Progression: Moderate: D1: 0.62 (1.94) D2: -0.51 (1.04) D3: Severe: D1: 2.95 (13.08) D2: 0.55 (4.70) D3: -0.53 (3.64) ERA: Moderate: D1: 2.15 (6.27) D2: -0.04 (1.36) Severe: D1: 1.71 (3.99) D2: 0.89 (2.70) No radiographic progression (%): TEMPO Moderate D1: 44 D2: 75 D3: NR Severe D1: 51 D2: 59 D3: NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				ERA: Moderate D1: 47 D2: 69 D382 Severe: D1: 49 D2: 65 D3: 71 Overall: NR **Quality of life scales** NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone et al., 2009[97] **Country and setting** Multinational **Source of funding** Centocor Research and development **Research objective** Evaluate efficacy and safety of GOL intx of patients with active RA despite MTX therapy **Study design** Controlled Trials **Overall N** 444 **Duration of study** 24 weeks **Quality rating** Good	**Inclusion Criteria** • 18 years of age or older • Diagnosis of RA for at least 3 mos before screening • On a stable MTX dose of 15 mg/week or greater but 25 mg/week or less during4-week period immediately preceding screening • Patients were to have tolerated 15 mg/ week or greater of MTX for at least 3 mos before screening and to have active RA. • Patients who were using NSAIDs or other analgesics for RA had to be taking stable	**Interventions, dose** D1: MTX: dosage NR but stable throughout 24 week study period. Patients with less than 20% improvement in SJC and TJC by week 16 began receiving 50mg GOL/4wks forremainder ofstudy Placebo D2: GOL: 100mg every 4 weeks Placebo: Patients with = 20% improvement in SJC and TJC and TJC at week 16 began receiving active MTX forremainder ofstudy D3: MTX: stable dose, NR (looks likely to be 15mg/wk not explicit in methods) GOL: 50mg every 4 weeks. Patients with <20% improvement in	**Mean disease duration, median (IQR)** D1: 6.5 (3.1-11.9) D2: 5.9 (2.4-12.2) D3: 4.5 (2.1-9.7) D4: 6.7 (2.4-14.3) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, median (IQR)** D1: 21.0 (14.0-34.0) D2: 22.0 (14.0-32.0) D3: 26.0 (16.0-39.0) D4: 23.0 (15.0-33.0) **Swollen Joint Count, median (OQR)** D1: 12.0 (8.0-19.0) D2: 11.0 (8.0-17.0) D3: 13.0 (8.0-22.0) D4: 12.0 (8.0-18.0) **Corticosteroid use, %** D1: 65.4 D2: 67.7 D3: 75.3 D4: 69.7 **DMARD use, other than MTX %** D1: 70.7 D2: 75.9 D3: 78.7	**ACR** ACR 20: At 14 weeks: D1: 33.1 D2: 44.4%, *P* = 0.059 D3: 55.1, *P* = 0.001 D4: 56.2, *P* = 0.001 At 24 weeks: D1: 27.8 D2: 35.3, *P* = 0.187 D3: 59.6, *P* = 0.001 D4: 59.6%, *P* = 0.001 ACR 50: At 14 weeks: D1: 9.8 D2: 20.3, *P* = 0.016 D3: 34.8, *P* = 0.001 D4: 29.2, *P* = 0.001 At 24 weeks: D1: 13.5 D2: 19.5, *P* = 0.187 D3:, 37.1, *P* = 0.001 D4: 32.6, *P* = 0.001 ACR 70: At 14 weeks: D1: 3.8 D2: 7.5, *P* = 0.184 D3: 13.5, *P* = 0.008 D4: 9.0, *P* = 0.104 At 24 weeks: D1: 5.3 D2: 11.3, *P* = 0.075 D3: 20.2, *P* = 0.001 D4: 14.6, *P* = 0.017	**Attrition/withdrawal** Overall, n: D1: 10 D2: 9 D3: 2 D4: 7 Overall: 28 Withdrawals due to adverse events, n: D1: 6 D2: 6 D3: 2 D4: 5 Overall: 19 Withdrawals due to lack of efficacy, n: D1: 2 D2: 1 D3: NR D4: NR Overall: 3 Adherent/compliant, n: D1: 123 D2: 125 D3: 87 D4: 82 Overall: 417 D1: 1 lost to follow-up, 1 "other" D2: 1 discontinued oral study agent D3: NR D4: 1 lost to follow-up, 1 discontinued oral study

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	dose for at least 2 wks before first dose of study agent. • Patients who were taking oral corticosteroids had to have been receiving a stable dose equivalent to 10 mg/day or less of PRED for at least 2 wks before first dose of study agent. **Exclusion Criteria** • Known hypersensitivity to human immunoglobulin proteins or other components of GOL • Any previous use of any anti-TNF agent, RIT, RIT or cytotoxic agents	SJC and TJC at week 16 began receiving 100mg of GOL/4 wks forremainder ofstudy D4: MTX: Stable dose and frequency NR GOL: 100mg/4wks **Number in group** D1: 133 D2: 133 D3: 89 D4: 89 **Mean age, years (SD)** D1: 52 (42-58) D2: 51 (42-59) D3: 52 (43-57) D4: 50 (45-56) **Sex, % female** D1: 82 D2: 105 D3: 72 D4: 72 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	D4: 75.3 **MTX naïve, %** NR **Baseline DAS score, n (CI)** D1: DAS28 using CRP: 4.860 (4.194-5.480); DAS28 using ESR: 6.111 (5.260-6.574) D2: DAS28 using CRP: 4.803 (4.151-5.558); DAS28 using ESR: 6.013 (5.198-6.800) D3: DAS28 using CRP: 5.100 (4.060-5.651); DAS28 using ESR: 6.105 (5.366-6.940) D4: DAS28 using CRP: 4.902 (4.320-5.521); DAS28 using ESR: 5.905 (5.292-6.805) **Required treatment for latent TB (%)** D1: 23.3 D2: 19.5 D3: 20.2 D4: 19.1	**Improvement from baseline in HAQ-DI at 24 weeks: (CI/SD/P Value)** D1: -0.13 (-0.38-0.13) D2: -0.13 (-0.63-0.25), *P* = 0.240 D3: -0.38 (-0.75--0.13), *P* = 0.001 D4: -0.50 (-0.75--0.13), *P* = 0.001 **DAS** D1: DAS28 (ESR) remission: 14 weeks: 1.5%, 24 weeks: 6.0%, DAS28 (ESR) sustained remission: 24 weeks: 0.8%, EULAR responders (DAS28 calculated using ESR): 14 weeks: 44.4%, 24 weeks: 42.1% D2: DAS28 (ESR) remission: 14 weeks: 8.3%, *P* = 0.010, 24 weeks: 12.0%, P= 0.087; DAS28 (ESR) sustained remission: 24 weeks: 6.3%, P= 0.018; EULAR responders (DAS28 calculated using ESR): 14 weeks: 59.4%, P= 0.014; 24 weeks: 51.9%, P= 0.110 D3: DAS28 (ESR)	agent Overall adverse events reported, n: D1: 89 D2: 98 D3: 87 D4: 78 Overall: 352 **Serious adverse events** Death, n: D1: NR D2: 1 D3: NR D4: NR Overall: 1 **Malignancies** Lymphoma or leukemia, n: NR Skin cancer (basal cell or squamous cell), n: D1: 1 D2: 2 D3: NR D4: NR Overall: 3 Other cancer (specify), n: D1: NR D2: NR D3: NR D4: Breast: 1 Overall: 1 **Respiratory events** Tuberculosis: NR Pneumonia, n: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	• Pts should not have received ANK • DMARDs other than MTX or intravenous, intramuscular, or intra-articular corticosteroids within 4 weeks beforefirst dose of study agent or alefacept or efalizumab within 3 mos beforefirst dose ofstudy agent.			remission: 14 weeks: 15.7%, P<0.001; 24 weeks: 20.2%, P= 0.001; DAS28 (ESR) sustained remission: 24 weeks: 10.2%, P= 0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 70.8%, P<0.001; 24 weeks: 71.9%, P<0.001 D4: DAS28 (ESR) remission: 14 weeks: 18.0%, P<0.001; 24 weeks: 22.5%, P<0.001; DAS28 (ESR) sustained remission: 24 weeks: 11.9%, P<0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 75.3%, P<0.001; 76.4%, P<0.001 **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, mean difference/absolute difference** ACR90 (14 weeks):	Upper respiratory infection, n: NR **Other infections** Urinary tract infection, n: D1: 1 D2: NR D3: NR D4: 2 Overall: 3 Other infections (specify), n: D1: NR D2: Sepsis: 2 D3: Cellulitis: 1 D4: Cellulitis: 1, Sepsis: 2, lower RTI: 1, Overall: 7 Other GI symptoms, n: D1: 0 D2: Colitis: 1, Diarrhoea: 1 D3: 0 D4: 0 Overall: 2 **Other** Infusion/injection site reactions, n: D1: 4 D2: 10 D3: 5 D4: 5 Overall: 24 Infective arthritis, n: D1: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D1: 0.8 D2: 0.8, *P* = 1.000 D3: 2.2, *P* = 0.344 D4: 0.0, *P* = 0.412 ACRIO (24 weeks): D1: 0.8 D2: 2.3, *P* = 0.314 D3: 5.6, *P* = 0.028 D4: 2.2, *P* = 0.344 ACR-N (14 weeks): D1: 0.00 (-28-25.50) D2: 10.50 (-11.80-42.60), *P* = 0.042 D3: 28.20 (0.00-60.00), *P* = 0.001 D4: 25.00 (0.00-54.50), *P* = 0.001 ACR-N (24 weeks): D1: 0.00 (-25.00-22.20) D2: 0.00 (-25.40-37.10), *P* = 0.151 D3: 36.60 (0.00-60.40), *P* = 0.001 D4: 28.60 (0.00-55.30), *P* = 0.001	D2: 1 D3: 0 D4: 0 Overall: 1 Bacterial arthritis, n: D1: 0 D2: 0 D3: 0 D4: 1 Overall: 1 Subcutaneous abscess, n: D1: 0 D2: 0 D3: 1 D4: 0 Overall: 1 Skin laceration, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone et al., 2009 and 2010, Go-Forward[97,98] **Country and setting** Multinational **Source of funding** Centocor Research and development **Research objective** Evaluate efficacy and safety of GOL intx of patients with active RA despite MTX therapy **Study design** Controlled Trials **Overall N** 444 **Duration of study** 24 weeks with open label extension up to 52 weeks **Quality rating** Good	**Inclusion Criteria** • 18 years of age or older • Diagnosis of RA for at least 3 mos before screening • Stable MTX dose of 15 mg/week or greater but 25 mg/week or less during 4-week period immediately preceding screening • Tolerated 15 mg/ week or greater of MTX for at least 3 mos before screening and have active RA. • Patients taking NSAIDs or other analgesics for RA had to be taking stable dose for at least 2 wks before first	**Interventions, dose** D1: MTX: dosage NR but stable throughout 24 week study period. Patients with less than 20% improvement in SJC and TJC by week 16 began receiving 50mg GOL/4wks for remainder ofstudy Placebo D2: GOL: 100mg every 4 weeks Placebo: Patients with = 20% improvement in SJC and TJC and TJC at week 16 began receiving active MTX forremainder ofstudy D3: MTX: stable dose, NR (looks likely to be 15mg/wk not explicit in methods) GOL: 50mg every 4 weeks. Patients with <20% improvement in SJC and TJC at	**Mean disease duration, median (IQR)** D1: 6.5 (3.1-11.9) D2: 5.9 (2.4-12.2) D3: 4.5 (2.1-9.7) D4: 6.7 (2.4-14.3) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, median (IQR)** D1: 21.0 (14.0-34.0) D2: 22.0 (14.0-32.0) D3: 26.0 (16.0-39.0) D4: 23.0 (15.0-33.0) **Swollen Joint Count, median (OQR)** D1: 12.0 (8.0-19.0) D2: 11.0 (8.0-17.0) D3: 13.0 (8.0-22.0) D4: 12.0 (8.0-18.0) **Corticosteroid use, %** D1: 65.4 D2: 67.7 D3: 75.3 D4: 69.7 **DMARD use, other than MTX %** D1: 70.7 D2: 75.9 D3: 78.7	**ACR** ACR 20: At 14 weeks: D1: 33.1 D2: 44.4%, *P* = 0.059 D3: 55.1, *P* = 0.001 D4: 56.2, *P* = 0.001 ACR 50: At 14 weeks: D1: 9.8 D2: 20.3, *P* = 0.016 D3: 34.8, *P* = 0.001 D4: 29.2, *P* = 0.001 ACR 70: At 14 weeks: D1: 3.8 D2: 7.5, *P* = 0.184 D3: 13.5, *P* = 0.008 D4: 9.0, *P* = 0.104 **DAS** D1: DAS28 (ESR) remission: 14 weeks: 1.5%, 24 weeks: 6.0%, EULAR responders (DAS28 calculated using ESR): 14 weeks: 44.4%, 24 weeks: 42.1% D2: DAS28 (ESR) remission: 14 weeks: 8.3%, *P* = 0.010, EULAR responders (DAS28 calculated using ESR): 14 weeks: 59.4%, P= 0.014; D3:	**Attrition/withdrawal** Overall, n: D1: 10 D2: 9 D3: 2 D4: 7 Overall: 28 Withdrawals due to adverse events, n: D1: 6 D2: 6 D3: 2 D4: 5 Overall: 19 Withdrawals due to lack of efficacy, n: D1: 2 D2: 1 D3: NR D4: NR Overall: 3 Adherent/compliant, n: D1: 123 D2: 125 D3: 87 D4: 82 Overall: 417 D1: 1 lost to follow-up, 1 "other" D2: 1 discontinued oral study agent D3: NR D4: 1 lost to follow-up, 1 discontinued oral study

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	dose of study agent. • Patientstaking oral corticosteroids had to have been receiving a stable dose equivalent to 10 mg/day or less of PRED for at least 2 wks before first dose of study agent. **Exclusion Criteria** • Known hypersensitivity to human immunoglobulin proteins or other components of GOL • Prior use of any anti-TNF agent, RIT or cytotoxic agents • Prior use of ANK • DMARDs other than MTX or intravenous,	week 16 began receiving 100mg of GOL/4 wks forremainder ofstudy D4: MTX: Stable dose and frequency NR GOL: 100mg/4wks **Number in group** D1: 133 D2: 133 D3: 89 D4: 89 **Mean age, years (SD)** D1: 52 (42-58) D2: 51 (42-59) D3: 52 (43-57) D4: 50 (45-56) **Sex, % female** D1: 82 D2: 105 D3: 72 D4: 72 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	D4: 75.3 **MTX naïve, %** NR **Baseline DAS score, n (CI)** D1: DAS28 using CRP: 4.860 (4.194-5.480); DAS28 using ESR: 6.111 (5.260-6.574) D2: DAS28 using CRP: 4.803 (4.151-5.558); DAS28 using ESR: 6.013 (5.198-6.800) D3: DAS28 using CRP: 5.100 (4.060-5.651); DAS28 using ESR: 6.105 (5.366-6.940) D4: DAS28 using CRP: 4.902 (4.320-5.521); DAS28 using ESR: 5.905 (5.292-6.805) **Required treatment for latent TB (%)** D1: 23.3 D2: 19.5 D3: 20.2 D4: 19.1	DAS28 (ESR) remission: 14 weeks: 15.7%, P<0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 70.8%, P<0.001; D4: DAS28 (ESR) remission: 14 weeks: 18.0%, P<0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 75.3%, P<0.001; **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, mean difference/absolute difference** ACR90 (14 weeks): D1: 0.8 D2: 0.8, *P* = 1.000 D3: 2.2, *P* = 0.344 D4: 0.0, *P* = 0.412 ACR-N (14 weeks): D1: 0.00 (-28-25.50) D2: 10.50 (-11.80-42.60), *P* = 0.042 D3: 28.20 (0.00-60.00), *P* = 0.001	agent Overall adverse events reported, n: D1: 89 D2: 98 D3: 87 D4: 78 Overall: 352 **Serious adverse events** Death, n: D1: NR D2: 1 D3: NR D4: NR Overall: 1 **Malignancies** Lymphoma or leukemia, n: NR Skin cancer (basal cell or squamous cell), n: D1: 1 D2: 2 D3: NR D4: NR Overall: 3 Other cancer (specify), n: D1: NR D2: NR D3: NR D4: Breast: 1 Overall: 1 **Respiratory events** Tuberculosis: NR Pneumonia, n: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	intramuscular, or intra-articular corticosteroids within 4 weeks before first dose of study agent or alefacept or efalizumab within 3 mos beforefirst dose of study agent.			D4: 25.00 (0.00-54.50), *P* = 0.001	Upper respiratory infection, n: NR **Other infections** Urinary tract infection, n: D1: 1 D2: NR D3: NR D4: 2 Overall: 3 Other infections (specify), n: D1: NR D2: Sepsis: 2 D3: Cellulitis: 1 D4: Cellulitis: 1, Sepsis: 2, lower RTI: 1, Overall: 7 Other GI symptoms, n: D1: 0 D2: Colitis: 1, Diarrhoea: 1 D3: 0 D4: 0 Overall: 2 **Other** Infusion/injection site reactions, n: D1: 4 D2: 10 D3: 5 D4: 5 Overall: 24 Infective arthritis, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Bacterial arthritis, n: D1: 0 D2: 0 D3: 0 D4: 1 Overall: 1 Subcutaneous abscess, n: D1: 0 D2: 0 D3: 1 D4: 0 Overall: 1 Skin laceration, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1 **Adverse events at 52 weeks-** N (%) and Events per 100 patient yrs Any adverse event D1:98 (73.7) 546 (486 to 612) D2: 108 (81.2) 514 (471 to 560) D3: 167 (78.8) 459 (425 to 495) D4:122 (85.9) 595 (552 to 641) Serious adverse events D1: 6 (4.5) 15 (6 to 29) D2: 16 (12.0) 28 (19 to 40) D3: 17 (8.0) 14 (9 to 22) D4: 26 (18.3) 34 (24 to 46) Any infection D1:42 (31.6) 132 (104 to 167) D2: 69 (51.9) 133 (112 to

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					158) D3:98 (46.2) 114 (98 to 133) D4:75 (52.8) 156 (135 to 181) Serious infections D1:1 (0.8) 2 (0 to 10) D2:5 (3.8) 8 (3 to 15) D3:4 (1.9) 3 (1 to 8) D410 (7.0) 10 (5 to 18)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Kievit et al., 2008,[99] DREAM **Country and setting** The Netherlands **Source of funding** Dutch affiliations of Wyeth Pharmaceuticals, Abbott Pharmaceuticals and Roche Pharmaceuticals enabled data collection for DREAM cohort. Sponsors had no influence on content of this manuscript. Funding from Dutch National Health Insurance Board **Research objective** Evaluate effects of ADA, ETN and IFX on disease activity, functional ability, QOL and	**Inclusion Criteria** • All RA patients seen in 11 rheumatology centers who started for first time on 1 of anti-TNFa agents. • In Netherlands, patients can start with an anti-TNFa treatment when they have at least moderate disease activity (Disease Activity Score (DAS28) > 3.2 and failed on at least 2 DMARDs including MTX (MTX) at an optimal dose of 25 mg/week. **Exclusion Criteria** NR	**Interventions, dose** D1: • ADA Patients starting with ADA and ETN did so at registered dose in 97% and 98% of cases, respectively. • Within 12 mos, 7.1% and 4.8% of ADA and ETN patients had a dose increase. • Median of12-month averaged dose was 40 mg per 2 weeks for ADA. D2: • ETN Patients starting with ADA and ETN did so at registered dose in 97% and 98% of cases, respectively. • Within 12 mos, 7.1% and 4.8% of ADA and ETN patients had a dose increase. • Median of12-month averaged dose was 50 mg per week for ETN. D3: • IFX patients started in 80% of cases	**Mean disease duration, years** D1: 7.7 D2: 6 D3: 7.7 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score** D1: 5.3 D2: 5.5 D3: 5.2 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Number of previous	**ACR** NR **HAQ, mean (SD)** Absolute difference in HAQ from baseline at 3, 6, 9, and 12 mos: At 3 mos, decrease: D1: -0.35 (0.5) D2: -0.33 (0.5) D3: -0.19 (0.5) At 6 mos, decrease: D1: -0.42 (0.5) D2: -0.35 (0.5) D3: -0.23 (0.5) At 9 mos, decrease: D1: -0.4 (0.5) D2: -0.36 (0.6) D3: -0.26 (0.5) At 12 mos, decrease: D1: -0.42 (0.6) D2: -0.35 (0.6) D3: -0.26 (0.5) D1: Missing HAQ values, all groups combined(%): baseline 9.9 • 3 mos 9.2 • 6 mos 12.2 • 9 mos 15.6 • 12 mos 16.3. *P* value for ADA compared to IFX: *P* = 0.05 for all time points	**Overall** Overall attrition/withdrawal, n (%): D1: 22 D2: 21 D3: 31 Overall: • IFX compared to ADA, *P* = 0.049 • IFX compared to ETN, *P* = 0.024 • Overall: occurrence of adverse events was reason for discontinuation in 48% of patients • Overall: 33%reason was a lack of efficacy Adherent/compliant, n: • After discontinuation ofinitial anti-TNFa treatment, 42% of ADA and ETN users switched to another anti-TNFa treatment, and 67% of IFX switched.same anti-TNFa treatment was rechallenged in 8%, 15% and in 2%, respectively. • Another option was to start with one ofconventional DMARD therapies, which occurred in 27% ofADA

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
medication costs **Study design** Prospective cohort comparison **Overall N** N: 707 Between February 2003 and August 2007, 916 patients were included. In total, 707 patients had at least 1-year follow-up and fully accessible data at time of analysis (August 2007). **Duration of study** One year **Quality rating** Fair		with an average dose of 3 mg/kg per 8 weeks, in 18% of cases with an average dose of 4 mg/kg per 8 weeks and 2% started with higher dosages. • All patients who started with average dose of 4 mg/kg dose did **Number in group** D1: 267 D2: 289 D3: 151 **Mean age, years (SD)** D1: 55.1 D2: 54.6 D3: 57.8 **Sex, % female** D1: 70.0 D2: 68.9 D3: 70.2 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	DMARDs D1: 3 D2: 3 D3: 3 HAQ D1: 1.3 D2: 1.4 D3: 1.4 With one or more erosions (%) D1: 71.7 D2: 65.3 D3: 72.7	• *P* value for ETN compared to IFX: *P* = 0.05 only at 3 mos **DAS** D1: Absolute difference in DAS28 from baseline at 3, 6, 9, and 12 mos (values are means with SD): 3 mos, decrease -1.6 (1.3) • EULAR response 76%*, 6 mos, decrease -1.8 (1.4) • EULAR response 78%*, 9 mos, decrease -1.8 (1.4) • EULAR response 79%*, 12 mos, **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others** • Mean score and 95% CI, at each follow up for DAS28, SF-36, and HAQ were presented in graphs, so numbers are NR. • Repeated measures analyses (linear mixed model) showed	patients, 25% of ETN patients and 20% of IFX patients. • Remaining patients did not start with another consecutive treatment after stopping with initial anti-TNFa treatment, but they remained on their co-medication. • Complete data of first 12 mos after treatment initiation with a TNF blocking agent were analysed on an ITT basis. • This means that all patients were analysed ingroup of medication on which they initially started, regardless of whether they received or adhered that treatment for full 12 mos. **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				significant differences in DAS28 course over 12 mos between IFX and both ADA and ETN patients (*P* = 0.001) and between ADA and ETN patients (*P* = 0.031). • Figures for HAQ and EQ-5D show same trend: functionality and QoL was best for ADA patients. However,repeated measures analyses did not show any significant differences.	NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Kim et al., 2007[100] **Country and setting** Korea; multicenter **Source of funding** Abbott Laboratories **Research objective** To investigate the efficacy and safety of 40 mg ADA with MTX versus placebo with MTX in Korean RA patients with an insufficient responses to MTX **Study design** Controlled Trials **Overall N** 128 **Duration of**	**Inclusion Criteria** • Treatment resistant • ≥18 yrs old • Met ACR criteria for diagnosis of active RA • ≥ 6 swollen joints and ≥ 9 tender joints at both screening and baseline visits • Received at least 1 prior DMARD other than MTX but could have had efficacy failures to no more than 4 standard DMARDs other than MTX • Been treated with MTX for at least 6 mos • Been receiving stable	**Comparisons (dosage and frequency)** D1: • MTX: dose NR • ADA: 40 mg, every other week D2: • MTX: NR • Placebo **Number in group** D1: 65 D2: 63 Overall: 128 **Mean age (years)** D1: 48.5 D2: 49.8 Overall: NR **Sex, % female** D1: 95.4 D2: 85.7 Overall: 90.6 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 6.8 (4.2) D2: 6.9 (4.5) Overall: NR **TJC, mean** D1: mean (SD): 19.2 (9.2) D2: mean (SD): 20.3 (8.6) Overall: NR **SJC, mean** D1: mean (SD): 12.2 (5.6) D2: mean (SD): 12.8 (5.8) Overall: NR **Corticosteroid use, %** NR **DMARD use, %:** D1: 100 D2: 100 Overall: 100 **MTX naïve, %:** D1: 0 D2: 0 Overall: 0 **Treatment resistant, %:** D1: 100 D2: 100 Overall: 100	**ACR mean difference/ absolute difference (CI/SD/P Value):** ACR 20: D1: 61.5 D2: 36.5 Overall: *P*<0.01 ACR 50: D1: 43.1 D2: 14.3 Overall: *P*<0.001 ACR 70: D1: 21.5 D2: 7.9 Overall: *P*< 0.05 **HAQ, mean difference/ absolute difference (CI/SD/P Value):** Disability Index of the KHAQ, mean (SD) D1: -0.5 (0.55) D2: -0.2 (0.50) Overall: *P*=0.002 **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):**	**Overall** Overall attrition/withdrawal (n): D1: 6 D2: 4 Overall: 10 Withdrawals due to adverse events (n): D1: 4 D2: 4 Overall: 8 Adherent/compliant (n): D1: 59 D2: 59 Overall: 118 Overall adverse events reported (n): D1: 84.6% D2: 82.5% Overall: NR **Serious adverse events:** Death (n): D1: 1 D2: NR **Malignancies:** Lymphoma or leukemia (n): D1: 0 D2: 0 Overall: 0 Skin cancer (basal	**Quality rating for efficacy/effectiveness?** Fair **Quality rating for observational studies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
study 24 wks	dosage for at least 4 wks prior to screening **Exclusion Criteria** • Patients with acute inflammatory joint diseases other than RA • Active Listeria or tuberculosis infection • Positive serology for human immuno-deficiency virus antibody, hepatitis B surface antigen, or hepatitis C antibody • Calcified granuloma and/or pleural		**Patients with early RA, three years or less, %:** NR **Baseline DAS score** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** Duration of morning stiffness, mean (SD) D1: -116.7 (165.3) D2: -16.7 (166.5) Overall: NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** TJC, mean (SD): D1: -9.5 (9.61) D2: -3.4 (11.50) Overall: *P*=0.002 SJC mean (SD): D1: -7.9 (6.78) D2: -2.0 (7.17) Overall: *P*<0.001 CRP, mg/L, mean (SD): D1: -1.4 (3.23) D2: -0.4 (1.94) Overall: *P*=0.001	cell or squamous cell) (n): D1: 0 D2: 0 Overall: 0 Other cancer (specify) (n): D1: 0 D2: 0 Overall: 0 **Respiratory events:** Pneumonia (n): D1: 2 D2: NR Overall: NR Upper respiratory infection (n): D1: 18 D2: 18 Overall: 36 **Other infections:** NR **GI:** NR **Other:** Infusion/injection site reactions (n): Injection site pain: D1: 2 D2: 5 Overall: 7 Headache (n): D1: 4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Physician's Global Assessment of Disease Activity, mm VAS, mean (SD): D1: -29.2 (27.48) D2: -9.6 (26.47) Overall: P < 0.001 Patient's Global Assessment of Disease Activity, mm VAS, mean (SD): D1: -23.7 (26.54) D2: -10.7 (24.85) Overall: P = 0.004 Patient's Global Assessment of Pain, mm VAS, mean (SD): D1: -23.7 (22.86) D2: -7.3 (27.50) Overall: P < 0.001	D2: 3 Overall: 7 Vasovagal attack: D1: 1 D2: NR Overall: NR Acute respiratory distress syndrome: D1: 1 D2: NR Overall: NR Cough: D1: 7 D2: 2 Overall: 9 Rhinorrhea: D1: 6 D2: 1 Overall: 7 Fatigue (n): D1: 5 D2: 3 Pruritus (n): D1: 4 D2: 1 Alanine aminotransferase increased (n): D1: 4 D2: 0 Aspartate aminotransferase increased (n):	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					D1: 4 D2: 1 Hypercholesterolemia (n): D1: 4 D2: 0 RA flare-up (n): D1: 0 D2: 4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kirwan et al., 2004[101] **Country, Setting:** Belgium, Sweden, and United Kingdom, multicenter (16) **Funding:** Astra-Zeneca **Research Objective:** To compare BUD, a locally acting glucocorticoid with minimal systemic exposure, with conventional glucocorticoid txt and placebo in RA **Study Design:** RCT **Overall N:** 143 **Study**	**Inclusion Criteria:** • Age 18 to 80 yrs • Diagnosed according to ACR criteria • Functional class I-III • Stable doses of NSAIDs (30 ds) and/or DMARDs (90 ds) **Exclusion Criteria:** • Pregnant or lactating • Glucocorticoids by any route for at least 30 ds • Systemic lupus erythematosus • Polymyalgia rheumatica • Psoriatic arthropathy • Spondylo-arthropathy • Smyloidosis • Active peptic ulcer disease • Uncontrolled DM • Other significant disease	**Interventions, dose:** D1: BUD (3 mg/d) D2: BUD (9 mg/d) D3: PNL (7.5 mg/d) D4: Placebo **N:** D1: 37 D2: 36 D3: 39 D4: 31 **Mean age, yrs:** D1: 54.2 D2: 57.8 D3: 53.4 D4: 54.7 **Sex, % female:** D1: 70 D2: 77 D3: 62 D4: 77 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 13.1 D2: 8.5 D3: 7.0 D4: 7.2 **TJC, mean:** D1: 14.2 D2: 11.8 D3: 12.3 D4: 12.6 **SJC, mean:** D1: 12.9 D2: 9.8 D3: 11.6 D4: 11.8 **DMARD use, %:** D1: 76 D2: 69 D3: 67 D4: 65 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR	Functional capacity and health related quality of life are secondary outcomes for this study **ACR20, %:** D1: 22 D2: 42 D3: 56 D4: 25 D2 vs D3, *P* = 0.11 **TJC:** D1: 2.23 (-0.63 to 5.1) D2: 3.65 (0.75 to 6.54) (*P* < 0.05) D3: 4.83 (2.01 to 7.65) *(P* < 0.001) **SJC:** D1: 1.53 (0.92 to 3.98) D2: 3.81 (1.3 to 6.52) *(P* < 0.01) D3: 3.67 (1.25 to 6.09) *(P* < 0.01) **Pain:** D1: 6.6 (-5.8 to 18.9) D2: 11.4 (-1.3 to 24) D3: 22.3 (10 to 34.6) *(P* < 0.001) **DAS, patient:** D1: 7.9 (-4.7 to 20.5) D2: 16.4 (3.6 to 29.3) (*P* < 0.05) D3: 24.5 (12.1 to 37) *(P* <	**Overall:** D1: 89 D2: 94 D3: 85 D4: 90 **SAEs:** D1: 5 D2: 0 D3: 5 D4: 6 **Abdominal Pain:** D1: 11 D2: 8 D3: 10 D4: 6 **Headache:** D1: 11 D2: 14 D3: 15 D4: 3 **URTI:** D1: 19 D2: 11 D3: 15 D4: 3	**Overall Attrition Rate, %:** 16 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Duration: 12 wks	• Local or systemic infection Allergy to BUD or other glucocorticoids; txt w/ live viruses (i.e., polio) or live bacteria (i.e., tubercle bacilli) during previous 90 days • Undergone resection of stomach or more than 100 cm of small bowel		**Baseline DAS, mean:** NR **HAQ:** D1: 1.61 D2: 1.57 D3: 1.51 D4: 1.52	0.001) **DAS, physician:** D1: 0.25 (-0.12 to 0.62) D2: 0.45* (0.07 to 0.82) (*P* < 0.05) D3: 0.66 (0.3 to 1.03) *(P* < 0.001) **HAQ:** D1: 0.009 (-0.19 to 0.21) D2: 0.107 (-0.31 to 0.09) D3: 0.383 (0.188 to 0.578) (*P* < 0.001) Difference: D3 vs. D1: 0.393; *P* < 0.001 D3 vs. D2: 0.276; *P* < 0.01 **SF-36:** D1: 2 (-2 to 6) D2: 3.7 (-0.4 to 7.8) D3: 7.4 (3.5 to 11.4) *(P* < 0.001) **SF-36 Mental Subscale** D1: 4.8 (-0.8 to 10.4) D2: 6.0 (0.4 to 11.7) (D3 vs D1; *P* < 0.05) D3: 7.2 (1.7 to 12.8) (D3 vs D2; *P* < 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004[92]; van der Heijde, 2005[102], van der Heijde, 2006[103], van der Heijde, 2006[104] TEMPO study **Country, Setting:** Multinational (Europe), multicenter **Funding:** Wyeth Research **Research Objective:** To compare safety and efficacy of combination of ETA and MTX with monotherapies in pts with RA who had failed previous DMARD txt **Study Design:** RCT	**Inclusion Criteria:** • Age ≥ 18 • Diagnosed according to ACR criteria • Functional class I-III • Less than satisfactory response to at least 1 DMARD other than MTX • Duration 6 mos to 20 yrs • RA defined as > 10 swollen and > 12 painful joints and at least one of: ESR > 28 mm/h, CRP > 20 mg/L, or morning stiffness for > 45 minutes • Folic acid 5 mg twice per wk • NSAIDs **Exclusion Criteria:** • TNF antagonist, any immuno-suppressive drugs w/in 6 mos • Any	**Interventions, dose:** D1: MTX (20 mg/wk) D2: ETA (25 mg 2x wkly) D3: ETA (25 mg 2x wkly) + MTX (7.5 titrated to 20 mg/wk) **N:** D1: 228 (152) D2: 223 (163) D3: 231 (188) Overall (at 2yrs): 503 **Mean age, yrs:** D1: 53 D2: 53.2 D3: 52.5 Overall (at 2yrs): 52.1 **Sex, % female:** D1: 79 D2: 77 D3: 74 Overall (at 2yrs): 76 **Race, % white:** D1: 98 D2: 99 D3: 98 Overall (at 2yrs): 99	**Mean disease duration, yrs:** D1: 6.8 D2: 6.3 D3: 6.8 **TJC, mean:** D1: 33.1 D2: 35 D3: 34.2 **SJC, mean:** D1: 22.6 D2: 23 D3: 22.1 **DMARD use, %:** NR **Corticosteroid use, %** D1: 64 D2: 57 D3: 62 **MTX naive, %:** D1: 58 D2: 58 D3: 56 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:**	**At 24 weeks** **AUC of ACR-N, %-yrs:** D1: 12.2 D2: 14.7 D3: 18.3 ($P < 0.0001$) **ACR20, %:** D1: 75 D2: 76 D3: 85 ($P = 0.0151$) **ACR50, %:** D1: 43 D2: 48 D3: 69 ($P < 0.0001$) **ACR70, %:** D1: 19 D2: 24 D3: 43 ($P < 0.0001$) **At 52 weeks** **DAS < 1.6 remission, %:** D1: 13 D2: 16 D3: 35 (D3 vs. D2: $P < 0.0001$; D2 vs. D1: $P = 0.5031$) **HAQ, decline:** D1: 0.65 D2: 0.7 D3: 1.0 ($P < 0.05$) D3 therapy significantly more likely to attain HAQ DI similar to population	**Overall:** D1: 81 (87) D2: 86 (92) D3: 81 (86) **Infections:** D1: 64 (75) D2: 59 (71) D3: 67 (76) **Serious Infections:** D1: 4 (7) D2: 4 (6) D3: 4 (6) **Infusion or injection reaction:** D1: 2 (2) D2: 21 (21) D3: 10 (11) **Abdominal Pain:** D1: 18 D2: 12 D3: 18 **Hypertension:** D1: 5 D2: 13 D3: 9 **Headache:** D1: 14 D2: 15 D3: 15 **Nausea:** D1: 32 (39) D2: 10 (13)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Overall N: 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos • Previous txt with MTX if pt experienced clinically toxic side effects or had no response		D1: 5.5 D2: 5.7 D3: 5.5 **Sharp:** D1: 26.8 D2: 21.8 D3: 21.8 **JSN:** D1: 13.3 D2: 11.5 D3: 10.3	norms (< 0.5) than monotherapy **Radiograhic outcomes** **Total Sharp Score change:** D1: 0.28 D2: 0.52 D3: -0.54; D3 vs D2; *P* = 0.0006 D2 vs D1; *P* = 0.047 **Erosion score change:** D1: 1.68 D2: 0.21 D3: -0.30; D3 vs D2; *P* = 0.0001 D2 vs D1; *P* = 0.008 **JSN score change:** D2: 0.32 D3: -0.23; *P* = 0.0007 **At 2 years** **Total Sharp score change:** D1: 1.12 D2: 1.10 D3: -0.56; *P* = 0.05 D3 vs D2; *P* = 0.05 D2 vs D1; *P* = NR **Erosion score change** D2: 0.36 D3: -0.76 P < 0.05 **JSN score change**	D3: 24 (29)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				D2: 0.74 D3: 0.20; *P* = NS, NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kremer, 2002[105] **Country, Setting:** US and Canada, multicenter (20 outpatient practice centers) **Funding:** Aventis Pharmaceuticals **Research Objective:** To evaluate efficacy and safety of LEF vs. Placebo when added to ongoing stable dose MTX therapy in pts with persistently active RA **Study Design:** RCT **Overall N:** 263 **Study Duration:**	**Inclusion Criteria:** • Age: 18 or 75 • Diagnosed with RA according to ACR criteria: Active:>9 tender joints, >6 sollen joints, >45 mornign stiffness • Previous use of DMARDs: Failed in 11 pts • Other (Please include concomitant drugs that are allowed)? MTX (15-20mg/wk or 10-15mg/wk if max tolerated dose) for at least 6 mos, AND stable dosing for at least 8 wks **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: prohibited DMARDs in past 30 ds • Impaired renal or hepatic system: Hep B or C, 3 or more elevations of AST or ALT,	**Interventions, dose:** D1: MTX + LEF D2: MTX + Placebo Methotrexate: 15 -20 mg/wk or 10 -15 mg/wk if toleration problems Leflunomide: 100 mg 2 ds then 10mg/d or 10mg/every other d if adverse effects Placebo: Folate 1 mg/d for ALL **N:** D1: 130 D2: 133 **Mean age, yrs:** D1: 55.6 D2: 56.6 **Sex, % female:** D1: 76.2 D2: 80.5 **Race, % white:** D1: 90.8 D2: 87.2	**Mean disease duration, yrs:** D1: 10.5 D2: 12.7 **TJC, mean:** D1: 26.9 D2: 26.4 **SJC, mean:** D1: 17.3 D2: 18.7 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **HAQDI:** D1: 1.6 D2: 1.5	**ACR20:** • LEF 46.2%; Placebo 19.5% *P* <0.001 **HAQ:** • LEF -0.42 • Placebo -0.09 *P* < 0.001 • SF-36: LEf + 6.8 Placebo + 0.3 *P* < 0.001	**Overall:** D1: 89.2 D2: 89.5 Infections: D1: 40.8 D2: 51.9 Dizziness: D1: 7.7 D2: 5.3 **Headache:** D1: 10 D2: 8.3 **Nausea:** D1: 16.2 D2: 11.3 **URTI:** D1: 22.3 **D2: 24.1** **Adherence:** Overall, 98% adherent Mean adherence **Adherence:** • Rates 80 120% • Lef 87.7% • Placebo 90.2%	**Overall Attrition Rate, %:** Discontinuation Rates: LEF 23.1 Placebo 24.8% **ITT Analysis:** Yes **Quality Rating:** Fair

24 wks	elevated SrCR • Psoriatic Arthritis or other acute inflammatory joint disease not RA	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Kremer et al., 2010[106] LITHE Study; Venkiteshwaran et al., 2009 CDER Statistical Review Application Number 125276 **Country and setting** Multinational and multicenter **Source of funding** Roche **Research objective** Efficacy and safety of TCZ plus MTX vs. MTX alone in preventing structural joint damage and improving physical function and disease activity in patients with	**Inclusion Criteria** • Treatment resistant • Inadequate response to MTX • RA diagnosis according to ACR criteria • Moderate to severe in the investigator's opinion and lasted for ≥ 6 mos • ≥1 radiographic-ally confirmed joint erosion despite having received MTX for at least 12 wks before baseline (stable at 10-25 mg/wk for ≥ 8 wks) **Exclusion Criteria** • Serious concomitant	**Comparisons (dosage and frequency)** D1: TCZ: 8 mg/kg every 4 wks D2: TCZ: 4 mg/kg every 4 wks D3: Placebo: NA (Rescue at 16 wks) D4: D5: **Number in group** D1: 398 D2: 399 D3: 393 **Mean age (years)** D1: 53.4 D2: 51.4 D3: 51.3 **Sex, % female** D1: 82 D2: 84 D3: 83 **Race, % white** D1: NR D2: NR D3: NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 9.3 (0.6-48.8) D2: 9.4 (0.5-43.2) D3: 9.0 (0.5- 44.3) **TJC, mean** D1: 29.3 D2: 27.9 D3: 27.9 **SJC, mean** D1: 17.3 D2: 17.0 D3: 16.6 **Corticosteroid use, %** D1: 62 D2: 69 D3: 70 **DMARD use, %:** D1: Past use 75.4 D2: 78..4 D3: 71.2 **MTX naïve, %:** D1: 0 D2: 0 D3: 0 **Treatment resistant, %:** D1: 100 D2: 100 D3: 100 **Patients with early RA, three years or**	**ACR mean difference/ absolute difference (CI/SD/P Value):** ACR 20: Week 24 D1: 56% D2: 51% D3: 27% Week 52 NR ACR 50: Week 24 D1: 32% D2: 25% D3: 10% Week 52 NR ACR 70: Week 24 D1: 13% D2: 11% D3: 2% Week 52 NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** AUC HAQ-DI change from baseline to week 52 (LOCF) D1: -144.1 units, *P*<0.0001 vs.	**Overall** Overall attrition/withdrawal (n): NR Overall: 167 Withdrawals due to adverse events (n): D1: 33 (8%) D2: 28 (7%) D3: 11 (3%) Withdrawals due to lack of efficacy (n): D1: 2 D2: 4 D3: 12 Overall adverse events reported (n): Per 100 PY D1: 325.4 D2: 324.0 D3: 279.6 **Serious adverse events:** Death (n): D1: 4 D2: 0 D3: 2 **Malignancies:** Skin cancer (basal cell or squamous cell) (n): NR Overall: 5	**Quality rating for efficacy/effectiveness?** Fair **Quality rating for observational studies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
moderate to severe RA and inadequate responses to MTX. **Study design** RCT **Overall N** 1196 **Duration of study** One year RCT (with 16 week escape) then open label	diseases • Significant systemic involvement of RA • Functional class IV RA • Other inflammatory joint diseases • Current/ recurrent infections • Abnormal ALT or AST (>1.5X ULN), total bilirubin (>ULN), hemoglobin (<8.5 g/dL), or triglycerid		**less, %:** NR **Baseline DAS score** D1: 6.6 D2: 6.5 D3: 6.5 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	placebo D2: -128.4 units, *P*<0.0001 vs. placebo D3: -58.1 HAD-DI change to week 24 D1:-0.4 (0.6) D2: -0.4 (0.5) D3: -0.1 (0.5) **DAS, mean difference/absolute difference (CI/SD/P Value):** Mean improvements at 52 wks D1: -3.8, vs. placebo *P*<0.0001 D2: -3.0, vs. placebo *P*<0.0001 D3: -2.0 DAS28 clinical remission (<2.6) D1: 47.2% (127/269), vs. placebo *P*<0.0001 D2: 30.2% (70/232), vs. placebo *P*<0.0001 D3: -2.0; 7.9% (12/151) **SF-36, mean difference/absolute difference (CI/SD/P Value):**	nonmelanoma skin cancers and 1 unclassified skin cancer Other cancer (specify) (n): D1: 1 (uterine) D2: 5 (lung, cervical, breast, 2 prostate) D3: 1 (breast) **Respiratory events:** Pneumonia (n): Pnuemonia/bronchitis, n (%) D1: 2 (0.5) D2: 3 (0.8) D3: 2 (0.5) **Other infections:** Serious infections per 100 PY D1: 4.0 D2: 3.7 D3: 2.3 **GI:** NR **Other:** Infusion/injection site reactions (n): D1/D2: 6 (4 were serious anaphylactic reaction/shock events) D3: NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** Reduction in structural damage at 52 wks (extrapolated) D1: 74%, *P*<0.0001 compared with placebo D2: 70%, *P*<0.0001 compared with placebo **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** Change in total Genant modified Sharp score ≤0 from baseline to week 52 D1: 84% D2: 81% D3: 67% *P*≤0.0001, linear extrapolation,		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				exploratory analysis		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006[107] **Country, Setting:** Sweden, multicenter **Funding:** Osterlund and Kock Foundations, 80-yr Fund of King Gustav V, and Reumatikerfor-bundet **Research Objective:** LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA pts treated in clinical practice **Study Design:** Prospective cohort study **Overall N:** 949	**Inclusion Criteria:** • Unsuccessful txt with 2 DMARDS including MTX • Pts diagnosed with RA according to clinical judgment of treating physician • Treated at 8 centers in Southern Sweden during March 1999 through January 2004 • Meds allowed, NR **Exclusion Criteria:** • Prior txt with biologic therapy	**Interventions, dose:** D1: ETA (25 mg s.c. twice wkly) D2: INF (≥3 mg/kg at 0, 2, 6, and 12 wks and then every 8 wks) **N:** D1: 309 D2: 640 **Mean age, yrs:** D1: 55.1 D2: 56.2 **Sex, % female:** D1: 82 D2: 75 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 14.7 D2: 12.7 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.9 D2: 5.6 **MTX use, %:** D1: 31 D2: 73 **HAQ:** D1: 1.6 D2: 1.4	**At 3 months** D1: 63 D2: 45 ($P < 0.001$) **At 6 months** D1: 61 D2: 47 (P = NS) **At 12 months** **LUNDEX values** (index of drug efficacy in clinical practice)**:** D1: ~ 55% (~ 4 0% at 3 yrs) D2: ~ 45% (~ 30% at 3 yrs) **ACR20, %:** D1: 69 D2: 53 (P = 0.001) **At 24 months** **ACR20, %:** D1: 65 D2: 56 (P = NS) **At 36 months** **ACR20, %:** D1: 63 D2: 61 (P = NS) **ACR50, %:** D1: 39 D2: 39 (P = NS) **ACR 70, %:**	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** N/A **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Study Duration: Varied (results reported for 3 yrs)				D1: 16 D2: 18 (*P* = NS) **EULAR (moderate), %:** D1: 46 D2: 29 (*P* = NS) **EULAR (good), %:** D1: 36 D2: 45 (*P* = NS) **Intermediate Outcome Measures:** INF had significantly lower adherence compared to ETA (*P* < 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Kristensen et al., 2006[108] **Country and setting** Southern Sweden, 8 hospital centers **Source of funding** Osterlund and Kock Foundations, King Gustav V 80-year fund, Reumatikerforbundet **Research objective** Compare therapy aderence of ETN and IFX during first TNF-blocking treatment course and to identify potential predictors for tx termination andimpact of concomitant MTX on other DMARDs **Study design** Observational **Overall N** 1,161	**Inclusion Criteria** • Diagnonsis of RA according to clinical judgment of treating physician (98% fullfilled ACR classification) • Biologic naïve, no formal level of disease activity • Pts should have received at least 2 DMARDs, including MTX prior to inclusion without satisfactory response **Exclusion Criteria** • Having received biologic therapy prior to inclusion in study.	**Interventions, dose** D1: LEF ETN: 25 mg subcutaneously 2 times/week Azathioprine D2: IFX3 mg/kg at 0, 2, and 6 weeks and then every 8th week depending on primary or secondary failure IFX could be increased in increments of 100 mg to max of 500 mg administered at 4 to 8 week intervals Azathioprine D3: MTX: 16.1 mg/wk ETN: 25 mg subcutaneously 2x per week D4: MTX: 14.3 mg/wk IFX: 3 mg/kg at 0, 2, and 6 weeks and then every 8th week depending on primary or secondary failure IFX could be increased in increments of 100	**Mean disease duration, mos** D1: 185.3 (121.4) D2: 192.9 (132.4) D3: 132.8 (107.3) D4: 133.5 (113.8) D5: 180.1 (115.1) D6: 165.4 (118.5) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** Inadequate response to previous DMARD including MTX (%) D1: 100 D2: 100 D3: 100 D4: 100 D5: 100 D6: 100 **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %** D1: 0 D2: 0 D3: 100 D4: 100 D5: 100	**ACR mean difference/ absolute difference (CI/SD/P Value)** ACR 20: NR ACR 50: NR ACR 70: NR **HAQ, mean difference/ absolute difference** NR **DAS, mean difference/absolute difference** NR **SF-36, mean difference/absolute difference** NR **Radiographic measures, mean difference/absolute difference** NR **Quality of life scales, mean difference/absolute difference** NR **Others, (please name) mean difference/absolute difference (CI/SD/P Value)** There were no differences	**Attrition/withdrawal** Adherent/compliant, %: At 1 year: D1: 74 D2: 47 D3: 89 D4: 69 D5: 85 D6: Unadjusted At 4 years: D1: 53 D2: 18 D3: 75 D4: 38 D5: 71 D6:NR At 5 years D1: NR D2: NR D3: 65 D4: 36 D5: NR D6: NR For treatment failure withdrawal, IFX had sig more withdrawals than ETN only for subarm of patients receiving MTX ($P = 0.026$) and Monotherapy ($P = 0.002$) Patients receiving concomitant MTX compared to monotherapy

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Duration of study March 1999 to December 2004 clinical data collected at 0, 3, 6, and 12 mos and subsequently every 3 to 6 mos. **Quality rating** Fair		mg to max of 500 mg administered at 4 to 8 week intervals D5: LEF: NR SSZ: NR Hydroxychlorquine: NR Azathioprine ETN: 25 mg subcutaneously 2x per week D6: LEF: NR SSZ: NR Hydroxychlorquine: NR Azathioprine: NR IFX: 3 mg/kg at 0, 2, and 6 weeks and then every 8th week depending on primary or secondary failure **Number in group** D1: 193 D2: 104 D3: 179 D4: 501 D5: 68 D6: 116 **Mean age, years (SD)** D1: 57.7 D2: 61.0 D3: 53.4	D6: 100 **MTX naïve, %** D1: 0 D2: 0 D3: 0 D4: 0 D5: 0 D6: 0 **Baseline DAS score (SD)** D1: 5.9 (1.1) D2: 5.7 (1.2) D3: 5.5 (1.0) D4: 5.5 (1.2) D5: 5.8 (1.2) D6: 5.8 (1.1) **Required treatment for latent TB** NR **Other population characteristics, %, (SD)** HAQ: D1: 1.60 (0.65) D2: 1.69 (0.58) D3: 1.30 (0.61) D4: 1.34 (0.62) D5: 1.61 (0.58) D6: 1.57 (0.58) VAS global (mm): D1:): 66 (21) D2: 67 (22) D3: 60 (22) D4: 60 (22) D5: 71 (17) D6: 70 (18)	in DAS28 at treatment termination between patients terminating because of failure in IFX D(DAS28= 5.1 95% CI, 4.9-5.4) compared with ETN D (DAS28= 5.1 95% CI, 4.8-5.4)	had fewer dropouts due to AE ($P < 0.001$) Adjusted HR for terminating treatment: IFX V ETN: 2.92 (95% CI, 2.32-3.69) Monotherapy V MTX: 1.82 (95% CI, 1.45-2.29) Other DMARDs V MTX: 1.45 (9% CI 1.12-1.87) Monotherapy V other DMARDS: 1.22 (95% CI, 1.22 (95% CI, 0.94-1.61) Adjusted HR for terminating treatment (all reasons, time-dependent cox regression analysis): IFX V ETN: 2.83 (95% CI, 2.27-3.54) Monotherapy V MTX: 1.48 (95% CI, 1.19-1.85) Other DMARDs V MTX: 1.33 (95% CI, 1.08-1.55) Monotherapy V other DMARD: 1.10 (95%CI 0.86-1.40) Adjusted HR for terminating treatment (AE): Monotherapy V MTX: 2.14 (95% CI, 1.61-2.84) Other DMARD V MTX: 1.75 (95% CI, 1.28-2.04) Monotherapy V other DMARD: 1.23 (95% CI,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D4: 55.0 D5: 54.0 D6: 57.4 **Sex, % female** D1: 84 D2: 78 D3: 78 D4: 74 D5: 84 D6: 75 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	VAS pain (mm): D1: 65 (22) D2: 64 (24) D3: 60 (22) D4: 60 (23) D5: 66 (19) D6: 70 (17) EVAL global (mm): D1: 60 (24) D2: 58 (23) D3: 56 (24) D4: 57 (23) D5: 56 (21) D6: 57 (22)		0.88-1.71) Adjusted HR for terminating treatment (Treatment Failure): Monotherapy V MTX: 1.31 (95% CI, 0.86-1.99) Other DMARD V MTX: 1.07 (95% CI, 0.66-1.73) Monotherapy V other DMARD: 1.22 (95% CI, 0.72-2.06)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Kristensen et al., 2007[109] **Country and setting:** NR **Funding:** The Oak Foundation, Osterlund and Kock Foundations, Reumatikerforbundet, and the King Gustav V 80-year fund. **Aims of Review:** To compare NNTs based on the 3 different types of NNT calculations for ADA, ETN, and INF combined with MTX, from the published double-blind, 12-month RCTs in established RA. **Quality Rating:** Fair	**Study design:** Systematic Review **Number of Patients:** 1,126 **Studies Included:** N = 3	**Characteristics of Included Studies:** Double-blind RCTs with a minimum of 2 arms comparing ADA, ETN, or INF and concomitant use of MTX compared to MTX alone; explicit data on the ACR50 response after at least 12 months of follow-up was collected in all included studies. **Characteristics of Included Populations** RA patients with an average disease duration of at least 5 years **Characteristics of Interventions:** 1 INF trial (doses: 3 mg/8 wks, 3 mg/4 wks, or placebo) 1 ETN trial (doses: 2 x 25 mg/wk or placebo) 1 ADA trial (doses: 40 mg/2 wks or placebo)	**Study Results:** NNT (control event-adjusted; among randomized) INF 3mg/8 wks: 8 (4-66) INF 3mg/4 wks: 4 (3-11) ETN 2 x 25 mg/wk: 4 (3-6) ADA 40 mg/2 wks: 4 (3-6) NNT (unadjusted; among randomized) INF 3mg/8 wks: 8 (5-38) INF 3mg/4 wks: 4 (3-7) ETN 2 x 25 mg/wk: 4 (3-6) ADA 40 mg/2 wks: 4 (3-5) NNT (unadjusted; 1-year completers) INF 3mg/8 wks: 8 (4-35) INF 3mg/4 wks: 4 (3-9) ETN 2 x 25 mg/wk: 5 (4-9) ADA 40 mg/2 wks: 3 (2-4)	**Adverse Events:** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006[107] **Country, Setting:** Sweden, multicenter **Funding:** Osterlund and Kock Foundations, 80-yr Fund of King Gustav V, and Reumatikerfor-bundet **Research Objective:** LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA pts treated in clinical practice **Study Design:** Prospective cohort study **Overall N:** 949 **Study Duration:** Varied (results reported for 3 yrs)	**Inclusion Criteria:** • Unsuccessful txt with 2 DMARDS including MTX • Pts diagnosed with RA according to clinical judgment of treating physician • Treated at 8 centers in Southern Sweden during March 1999 through January 2004 • Meds allowed, NR **Exclusion Criteria:** • Prior txt with biologic therapy	**Interventions, dose:** D1: ETA (25 mg s.c. twice wkly) D2: INF (≥3 mg/kg at 0, 2, 6, and 12 wks and then every 8 wks) **N:** D1: 309 D2: 640 **Mean age, yrs:** D1: 55.1 D2: 56.2 **Sex, % female:** D1: 82 D2: 75 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 14.7 D2: 12.7 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.9 D2: 5.6 **MTX use, %:** D1: 31 D2: 73 **HAQ:** D1: 1.6 D2: 1.4	**At 3 months** D1: 63 D2: 45 ($P < 0.001$) **At 6 months** D1: 61 D2: 47 (P = NS) **At 12 months** **LUNDEX values** (index of drug efficacy in clinical practice)**:** D1: ~ 55% (~ 4 0% at 3 yrs) D2: ~ 45% (~ 30% at 3 yrs) **ACR20, %:** D1: 69 D2: 53 (P = 0.001) **At 24 months** **ACR20, %:** D1: 65 D2: 56 (P = NS) **At 36 months** **ACR20, %:** D1: 63 D2: 61 (P = NS) **ACR50, %:** D1: 39 D2: 39 (P = NS) **ACR 70, %:** D1: 16 D2: 18 (P = NS) **EULAR (moderate), %:** D1: 46 D2: 29 (P = NS)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** N/A **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				EULAR (good), %: D1: 36 D2: 45 (*P* = NS) **Intermediate Outcome Measures:** INF had significantly lower adherence compared to ETA (*P* < 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Lacaille, 2008[110] **Country and setting** Province of BC, Canada, administrative data **Source of funding** Bristol-Myers Squibb, Canadian Arthritis Network, Arthritis Society of Canda **Research objective** Determine effect of nonbiologic DMARDs on infection risk in RA **Study design** Retrospective longitudinal cohort study **Overall N** 27,710 **Duration of study** 7 years (162,720 person years of follow-up) **Quality rating** Fair: analysis did not adjust for all confounders, such as baseline disease activity or severity (however it did adjust for RA duration); Use of administrative	**Inclusion Criteria** • RA diagnosis • At least 2 physician visits more than 2 months apart with an RA ICD-9 RA diagnostic code **Exclusion Criteria** • At least 2 visits subsequent to second RA visit with diagnoses of other inflammatory arthritides (systemic lupus erythematosus, other connective tissue diseases, PsA, ankylosing spondylitis, and other spondylarthri-tides) • Those with a diagnosis of RA not confirmed by a rheumatologist	**Interventions, Dose** D1: MTX: dosage NR D2: LEF: dosage NR D3: DMARD and corticosteroid (CS): dosage NR D4: DMARD alone D5: Corticosteroid alone: 10.4 mg PRED other CS NR **Number in group** D1: NR D2: NR D3: NR D4: NR D5: NR Overall: 27,710 **Mean age (years)** D1: NR D2: NR D3: NR D4: NR D5: NR Overall: 57 ±17 **Sex, % female** D1: NR D2: NR D3: NR D4: NR D5: NR Overall: 67 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: NR D2: NR D3: NR D4: NR D5: NR Overall: 5 years or less: 36%; more than 5 years: 17% **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: NR D2: NR D3: NR D4: NR D5: NR Overall: 44 **DMARD use, %** D1: NR D2: NR D3: NR D4: NR D5: NR Overall: 45 **MTX naïve, %** NR	**ACR** NA **HAQ,** NA **DAS** NA **SF-36** NA **Radiographic measures** NA **Quality of life scales** NA **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** Overall attrition/withdrawal, n: NA **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** Unadjusted rate of infection per person yr of follow-up, n: D1: 1.28 (95% CI 1.25-1.32) D2: 1.67 (95% CI 1.41-1.97) D3: 1.12 (95% CI 1.08-1.16) *P* = 0.0001; Serious infections: 1.63 (95% CI 1.5-1.77) *P* = 0.0001 D4: 0.9 (95% CI 0.88-0.93) *P* = 0.0001; Serious infections: 0.92 (95% CI 0.85-1.0) *P* = 0.0502 D5: 1.15 (95% CI 1.11-1.19) *P* = 0.0001; Serious infections: 1.9 (95% CI 1.75-2.05) *P* = 0.0001 Overall: NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
billing data.			**Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Langer, 2003[111] **Country, Setting:** Germany, multiple sites, daily clinical practice **Funding:** Amgen **Research Objective:** To assess the response rate, time to response, efficacy and safety of anakinra during 52 wks of therapy after launch in daily clinical practice in Germany and to gain knowledge of the routine application of anakinra in RA pts under special conditions (RA pts who failed TNF-blocking drugs) **Study Design:** Case series; postmarketing surveillance **Overall N:** 454 **Study Duration:** 52 wks	**Inclusion Criteria:** • Age: adult • Patients who fell within approved indication for anakinra • Pts with RA who had been ineffectively treated with at least 2 DMARDs including MTX **Exclusion Criteria:** NR	**Interventions:** D1: AKA, all pts D2: AKA, TNF-blocker naive D3: AKA, TNF-blocker pretreated Anakinra **N:** D1: 166 D2: 105 **D3: 61** **Mean age (yrs):** D1: 53.7 D2: 54.7 **D3: 51.9** **Sex, % female:** D1: 78.9 D2: 78.1 **D3: 80.3** **Race, % white:** NR **Mean disease duration, yrs:** D1: 12.3 D2: 12.0 **D3: 12.8** **TJC, mean:** D1: 12.8 D2: 12.4 D3: 13.4 **SJC, mean:** D1: 10.5 D2: 10.4	Pts responded well to AKA therapy; 67.5% had good (21.0%) or moderate (46.5%) EULAR response after 6 mos. of therapy • DAS decreased by 44% for all pts • Tender joint count decreased by 53%, swollen joint count by 49%, pain by 31%, and global health by 28% • Response to AKA was rapid, within 1 mo; shown in figures • Data suggest AKA is effective in pts who have failed anti-TNF therapy with comparable results to anti-TNF naive pts • 69.4% of TNF-blocker pretreated pts had a good or moderate EULAR response at 6 mos. compared to 66.3% of TNF-blocker naive pts • Disease activity decreased by 39% and 47% respectively • Pain decreased by 35% and 29% respectively • Tender joint count by 49% vs. 55% Swollen joint count 44% vs. 52%	See adverse events	**Overall:** D1: 41.2 **Serious AEs:** D1: 4.2 **Infections:** D1: 6.6 **Serious Infections:** D1: 1.5 **Infusion or injection reaction:** D1: 20.7 **Abdominal Pain:** NR **Cardiovascular Events:** NR **Dizziness:** NR **Headache:** **D1: 2** **Hepatotoxicity:** NR **Malignancies:** NR **Nausea:** NR **URTI:** NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** **Fair**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		D3: 10.8 **DMARD use, %:** D1: on MTX: 66.3 D2: 72.4 D3: 55.7 **Corticosteroid use, %:** D1: 84.9 D2: 81.9 D3: 90.1 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 5.8 D2: 5.6 D3: 6.1 D1: morning stiffness (minutes) 112.5 D2: 104.1 D3: 126.6 D1: # of previous DMARDs: 3.6 D2: 3.0 D3: 4.4	Global health by 33% vs. 26%			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Lebwohl, 2005[112] **Country, Setting:** US, clinical trial participants receiving ETA from private and institutional practices **Funding:** Amgen Inc. **Research Objective:** Incidence of cutaneous SCC in pts with rheumatoid arthritis receiving ETA for up to 5 yrs **Study Design:** Postmarketing database review **Overall N:** 1,442 (4257 PY) **Study Duration:** Mean 3.7 yrs	**Inclusion Criteria:** • Participant in 1 of various studies* of ETA in pts with rheumatoid arthritis • Pts had active RA; and, received 10 to 50 mg ETA subcutaneously twice weekly for majority of time they received study drug. Specific inclusion criteria varied by included study **Exclusion Criteria:** NR	**Interventions, dose:** **D1: ETA** **N:** D1: 1442 **Mean age, yrs:** D1: 49.9 **Sex, % female:** D1: 76.5 **Race, % white:** D1: 87.4	**Mean disease duration, yrs:** D1: 7.1 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**Health Outcome Measures:** • Total # of cases of SCC reported from post-marketing database population: 4 cases **Age and sex-matched expected incident cases based on:** • From Arizona general population-based incidence study: 13.1 cases • From Minnesota general population-based incidence study: 5.9 cases • Number of cases of SCC per PY of exposure to ETA **In clinical trial population: 0.9/1000 PY** • From post-marketing surveillance data: .01/1000 PY **Summary Statement:** The incidence of SCC among pts taking ETA is likely no different from that of the general population.	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Lee, 2002[113] **Country, Setting:** US, clinics **Funding:** NR **Research Objective:** To identify post-licensure cases of opportunistic histoplasmosis in pts treated with INF and ETA **Study Design:** Database analysis; AERS **Overall N:** 10 cases (from FDA passive surveillance database for monitoring postlicensure AEs) **Study Duration:** varied	**Inclusion Criteria:** • Any report of histoplasmosis in a patient receiving ETA or INF had been received by AERS by July 2001 **Exclusion Criteria:** NR	**Interventions, dose:** D1: ETA D2: INF D3: Overall ETA: varied INF: varied **N:** D1: 9 D2: 1 D3: 10 **Mean age, yrs:** D1: 11-78 (range) D3: median: 43.5 **Sex, % female:** D1: 4/9 (44.4%) D2: 0/1 (0%) D3: 40 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant immunosuppressive:** D1: 100 D2: 100	**Cases of histoplasmosis reported to the AERS by July 2001** • 9 cases among pts receiving INF • 1 case among pts receiving ETA **Through August 2001, number of pts treated** • With INF: ~150,000 • With ETA: ~96,500 **Histoplasmosis case rates per 100,000 pts receiving drug** • INF: ~6/100,000 • ETA: ~1/100,000 **Deaths due to histoplasmosis** • INF: 1/10 • ETA 0/1 **Summary:** More cases of histoplasmosis were reported to AERS by July 2001 among pts receiving INF than those receiving ETA. When accounting for actual number of pts taking each of drug, histoplasmosis case rate was ~6 times higher among pts receiving INF than among those receiving ETA	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Lee et al., 2007[114] **Country and setting:** NR **Funding:** NR **Aims of Review:** To examine whether combination therapy with the TNF blockers and MTX is effective compared to MTX mono-therapy and if ADA, ETN, and INF have the same effect in patients suffering from active RA **Quality Rating:** fair	**Study design:** Systematic Review and Meta-analysis **Number of Patients:** 1, 040 **Studies Included:** N = 3	**Characteristics of Included Studies:** A study was included in the analysis if: (1) it was published before February 2006; (2) it was original data; (3) it was a double blind, RCT that completed 50-55 weeks of trials and (4) it compared TNF inhibitors plus MTX with MTX alone in patients with a **Characteristics of Included Populations** Patients with active RA despite treatment with DMARDs **Characteristics of Interventions:** 1 ETN trial: 25 mg twice weekly 1 INF trial: 3 mg/kg intravenously every 8 wks 1 ADA trial: 40 mg subcutaneously every 2 wks	**Study Results:** Meta-analysis results: TNF blockers + MTX vs. MTX monotherapy ACR20: RR, 1.89 (95% CI, 0.89- 4.00) ACR50: RR, 2.61 (95% CI, 1.20- 5.66) ACR70: RR, 3.43 (95% CI, 1.74- 6.75) Adjusted indirect comparisons of the anti-TNF inhibitors: ETN vs. INF ACR20: RR, 0.45 (95% CI, 0.27-0.73); *P* = 0.001 ACR50: RR, 0.59 (95% CI, 0.27-1.29); *P* = 0.19 ACR70: RR, 0.44 (95% 0.10-2.03); *P* = 0.29 ETN vs. ADA ACR20: RR, 0.46 (95% 0.34-0.61); *P* < 0.0001 ACR50: RR, 0.37 (95% 0.22-0.60); *P* < 0.0001 ACR70: RR, 0.44 (95% 0.21-0.93); *P* = 0.03 INF vs. ADA ACR20: RR, 1.03 (95% 0.59-1.78); *P* = 0.92 ACR50: RR, 0.62 (95% 0.25-1.49); *P* = 0.28 ACR70: RR, 0.99 (95% 0.19-5.13); *P* = 0.99	**Adverse Events:** Meta-analysis results: TNF blockers + MTX vs. MTX monotherapy Withdrawals due to lack of efficacy: RR, 0.38 (95% CO 0.22-0.64) Withdrawals due to adverse events: RR, 1.05 (95% CI, 0.52-2.09) Adjusted indirect comparisons of the anti-TNF inhibitors: ETN vs. INF Withdrawals due to lack of efficacy: RR, 0.52 (95% 0.19-1.42); *P* = 0.20 Withdrawals due to adverse events: RR, (95% 1.01 0.30-3.42); *P* = 0.98 ETN vs. ADA Withdrawals due to lack of efficacy: RR, 1.12 (95% 0.32-3.94); *P* = 0.86 Withdrawals due to adverse events: RR, 0.38 (95% 0.17-0.86); *P* = 0.02 INF vs. ADA Withdrawals due to lack of efficacy: RR, 2.16 (95% 0.77-6.07); *P* = 0.14 Withdrawals due to adverse events: RR, 0.37 (95% 0.11-1.36); *P* = 0.14

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Li et al., 2008, AIM Trial[115,116] **Country and setting** multinational, multicenter **Source of funding** NR **Research objective** Examine relationship between external help home use and clinical/ patient-reported outcomes and whether ABA + MTX tx reduces need for external home help **Study design** Controlled Trials **Overall N** 0 **Duration of study** 12 mos **Quality rating** Fair	**Inclusion Criteria** • NR, see #3475 **Exclusion Criteria** • NR, see #3475	**Interventions, Dose** D1: • MTX: dosage and frequency NR, see #3475 • Placebo D2: • MTX: dosage and frequency NR, see #3475 • Abatacept patients 60 kg or less: 500 mg • Patients 60-100 kg: 750 mg • Patients greater than 100 kg: 1000 mg • Dosing schedule: 30 minute IV infusion given at baseline, days 15 and 30, and monthly thereafter **Number in group** D1: 219 D2: 433 Overall: 590 **Mean age (years)** D1: NR, see #3475 D2: NR Overall: 51.0 **Sex, % female** Overall: 80 **Race, % white** Overall: 87 **Race, % black** Overall: 2.4 **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR Overall: 8.7 yrs (7.3) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **TJC, mean (SD)** Overall: 31.8 (13.3) **SJC, mean (SD)** Overall: 21.8 (8.8) **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR Overall: 6.8 (0.9) **Required treatment for latent TB** NR **Other population characteristics, n (%)** EHH use: D1: 75 (38) D2: 157 (40) Mean number of days of EHH: D1: 16 D2: 15 Overall: 15.6 (11.3)	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name)** • FOR PLACEBO GROUP: EHH use at 12 mos (among those who reported no EHH use at baseline): 21 (17%) • No EHH use at 12 mos: 42.5% • Needing full help at 12 mos: 12.3%. • FOR ABA group: 22 (9%), 53.2% 9.0% • Mean improvements from baseline in EHH at 12 mos were greater in ABA Gthan placebo G (AUC 361.8 (*P* = 0.001). • After 12 mos, proportions of patients who were shifted to lesser help categories were similar between 2 groups, with fewer patients requiring full help of > 2 weeks of help.	**Overall** Overall attrition/withdrawal, n: D1: 43 D2: 19 Withdrawals due to adverse events, n: D1: 4 D2: 18 Withdrawals due to lack of efficacy, n: D1: 40 D2: 13 Adherent/compliant, n: D1: 3 D2: 1 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Li et al., 2010[117] **Country and setting** United States; Medicaid patients **Source of funding** Abbott Labs **Research objective** To examine adherence, discontinuation, and switching of RA biologics over a 1-year period after initiation of the biologic treatment in Medicaid patients with RA **Study design** Observational **Overall N** 2638 **Duration of study** 12 mos	**Inclusion Criteria** • Treatment resistant • Continuous eligibility under fee-for-service Medicaid in the 12-month pre-index and 12-month post-index dates • At least 1 inpatient or 2 outpatient diagnoses of RA across Medicaid or Medicare claims in the 12-month pre-index date **Exclusion Criteria** • Previous use of any RA biologic in the 12-month pre-index date	**Comparisons (dosage and frequency)** D1: ETN: 25 mg twice a week D2: ANK: 100 mg daily D3: INF: NR **Number in group** D1: 1359 D2: 267 D3: 1012 **Mean age (years)** D1: 54.9 D2: 55.9 D3: 63.3 **Sex, % female** D1: 88.4 D2: 91.8 D3: 87.6 **Race, % white** D1: 45.8 D2: 47.9 D3: 49.6 **Race, % black** D1: 12.6 D2: 14.6 D3: 13.0 **Ethnicity, Latino** D1: 18.3 D2: 20.2 D3: 13.9	**Mean disease duration, years** NR **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** D1: 76.5 D2: 77.9 D3: 71.2 **DMARD use, %:** D1: 83.4 D2: 82.0 D3: 85.5 **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** Adherent/compliant (n): D1: 435 (32%) D2: 28 (10.5%) D3: 435 (43%) *P*<0.05 for ANK compared to the other arms Adherence defined as PDC of 0.80 or greater. **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** NR **Other infections:** NR **GI:** NR **Other:** NR	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Mean PDC over 12 mos D1: (ref group): 0.57 D2: 0.36 (P<0.05) D3: 0.64 (P<0.05) Discontinuation with continuous gap of 120 days or more D1: 34.5% D2: 70.0% (P<0.05) D3: 33.6% Continuous gap of 90 days or more D1: 40.7% D2: 76.0% (p<0.05) D3: 40.		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2005[118] **Country, Setting:** Germany, population-based **Funding:** Joint grant from Essex, Wyeth, Amgen, and Abbott **Research Objective:** Incidence rates of serious and non-serious infections in pts with RA who start txt with a biologic agent, and to compare these rates with those in pts with RA who receive conventional txt **Study Design:** Prospective cohort study **Overall N:** 1529 **Study Duration:** Up to 12 mos	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to ACR criteria new txt with ETA, INF, or AKA • Controls: pts started on DMARD therapy after failure of > 1 other DMARD, or with additional DMARD added to existing DMARD **Exclusion Criteria:** • NR	**Interventions, dose:** D1: ETA D2: INF D3: AKA D4: DMARDS (control) **N:** D1: 512 D2: 346 D3: 70 D4: 601 **Mean age, yrs:** D1: 53.7 D2: 53.6 D3: 54.3 D4: 56.5 **Sex, % female:** D1: 78.1 D2: 70.8 D3: 77.1 D4: 82.7 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 9 D2: 8 D3: 13 D4: 6 **TJC, mean:** D1: 13.3 D2: 12.7 D3: 12.6 D4: 10 **SJC, mean:** D1: 10.5 D2: 10.8 D3: 10.2 D4: 7.7 **DMARD use, %:** D1: 51.6 D2: 89.6 D3: 71.4 D4: 0 **Glucocorticoids use, %:** D1: 87.4 D2: 85.2 D3: 87 D4: 77.2 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 6.1	See AEs	**Overall:** D1: 22.6 per 100 PY D2: 28.3 per 100 PY D3: 17.5 per 100 PY (95% CI,8.8-31.2) D4: 6.8 per 100 PY **SAEs:** D1: 6.4 per 100 PY D2: 6.2 per 100 PY D3: 3.2 per 100 PY (95% CI,0.4-11.5) D4: 2.3 per 100 PY **Infections:** D1: 15 D2: 21 D4: 6 **Serious Infections:** D1: 6.4 per 100 PY D2: 6.2 per 100 PY Drug 3D4: 2.3 per 100 PY **URTI:** D1: 7.0 D2: 11.4 D3: 1.8	**Overall Attrition Rate, %:** 11.1 **ITT Analysis:** Yes **Quality Rating:** Fair

	D2: 6.0 D3: 6.1 D4: 5.4 **MTX use:** D1: 33 D2: 64.5 D3: 61.4 D4: 20.1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2006[119] **Country, Setting:** Germany Registry Data **Funding:** Pharmas: Essex, Wyeth, A mgen, Abbott **Research Objective:** To investigate frequency of remission and improved functional status in pts with 2 or more DMARD failures who have received new txt with biologics **Study Design:** Prospective cohort study **Overall N:** 1,083 **Study Duration:** 1 yr	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed with RA according to ACR criteria • Failed at least 2 prior treatments with DMARDs **Exclusion Criteria:** • Only 1 DMARD failure • No failure of MTX • Rec'd new txt ≥ 1 days before study entry • DAS < 3.2 at baseline	**Interventions, dose:** D1: Biologics (ADA, ANA, ETN, INF) (dose NR) D2: DMARDs as a class (dose NR) **N:** D1: 818 D2: 265 **Mean age, yrs:** D1: 53.7 D2: 57.4 **Sex, % female:** D1: 76.6 D2: 83.8 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 10 D2: 9 **TJC, mean:** D1: 12.9 D2: 10.5 **SJC, mean:** D1: 10.5 D2: 8.2 **DMARD use, %:** 100 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 6.1 D2: 5.5 **# previous DMARDs:** D1: 4.0 D2: 2.8	Biologics had double chance of remission compared to conventional DMARD therapies, via multivariate regression (OR: 1.95; 95% CI, 1.20-3.19) Severely disabled pts (≤ 50% of full function) in D1 (biologics) significantly more likely to achieve physical independence (≥ 67% of full function) than D2 (DMARDs/controls) (OR 3.88, 95% CI, 1.7-8.8) Functional remission (≥ 83% of full function) more often achieved in D1 (biologics)than in D2 (DMARDs/controls) (OR 2.18 95% CI, 1.04-4.6) **At 12 months** **DAS28 remission, %:** D1: 24.9 D2: 12.4 ($P < 0.004$) **ARA remission, %:** D1: 16.1 D2: 8.3 ($P < 0.036$) **Pts in remission by DAS Criteria, %:** D1: 16.3 D2: 15.3 **Pts in ARA Remission, %:** D1: 13.2 D2: 10.2 Approximately half of pts in remission at 6 mos relapsed	NR	**Overall Attrition Rate, %:** 14% **ITT Analysis:** No **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				until 12 mos, %: D1: 55 D2: 58 Patients with moderate disease acitvity (DAS28, 3.2-5.1) at start of treatment, had high remission rates in biologics group: • DAS 30.6 • ARA 16.9% Sustained remission at 6 and 12 months achieved in <10 % of patients		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Listing et al., 2008[120] **Country and setting** Germany **Source of funding** Unconditional, joint grants from Essex and Wyeth since 2001, from Essex, Wyeth, and Amgen since January 2003, and from Essex, Wyeth, Amgen, and Abbott since September 2003 **Research objective** Determine hazard risk of developing or worsening heart failure in RA pts treated with tumor necrosis factor inhibitors. **Study design** Cross Sectional Cohort Study **Overall N** 4,248 **Duration of study** 5 years **Quality rating** Good	**Inclusion Criteria** • Treated with ADA, ETN, IFX, or conventional DMARD **Exclusion Criteria** • Treated with ANK	**Interventions, Dose** D1: ETN: dose NR IFX: dose NR ADA: dose NR D2: Conventional DMARDs: dose NR **Number in group** D1: 2,757 D2: 1,491 **Mean age (years)** D1: 53.7 D2: 56.1 *P* = 0.00001 **Sex, % female** D1: 78.1 D2: 78.9 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: median duration 9 years D2: median duration 6 years *P* = 0.00001 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** D1: mean 9.3 D2: mean 6.8 *P* = 0.00001 **Corticosteroid use, %** D1: 83.9 D2: 76.1 D 3*P* = 0.00001 **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: mean 5.8 D2: mean 5.1 D 3*P* = 0.00001 **Required treatment for latent TB** NR **Other population**	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** • At followup, 101 pts (2.4%) had died, 14 due to heart failure. Four hundred twelve patients (9.7%) dropped out, and 168 (4.0%) had not attended last 2 or 3 followup visits. annual loss-to-followup rate (with loss-to-followup defined as dropping out or failure to attend last 2 or 3 visits) was 5.1%. annual dropout rate was 3.9% on average, and total dropout rate at 48 months was 15.5% (Kaplan-Meier estimate). Patients who dropped out did not differ significantly from those who completed study with regard to age, sex, treatment with TNFα inhibitors, or cardiovascular disease status, but they did have slightly more active disease at start of treatment (mean ± SD DAS28 score 5.7 ± 1.3 versus 5.5 ± 1.3). **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			characteristics, %, (CI/SD/P value) D1: Comorbidiities: Heart failure 75 (2.7%); Coronary heart disease 149 (5.4%); cardiovascular disease total 1,026 (37.3%); Diabetes 226 (8.2%); Chronic lung disease 201 (7.3%); Rhuematoid factor positive 2,219 (80.5%). D2: Comorbidiities: Heart failure 23 (1.5%), *P* = 0.014; Coronary heart disease 105 (7.0%), *P* = 0.033; cardiovascular disease total 569 (38.2%), *P* = 0.566; Diabetes 128 (8.6%), *P* = 0.673; Chronic lung disease 95 (6.4%), *P* = 0.256; Rhuematoid factor positive 1,069 (71.7%), *P* = 0.00001.		**Respiratory events** NR **Other infections** NR **GI** NR **Other** • Adjusted hazard ratios (HR) for developing heart failure de novo: Anti-TNF vs. conventional DMARDs (multivariate analysis final model): adjusted HR: 1.66, 95% CI: 0.67, 4.10; *P* = 0.28 • Adjusted HR for heart failure: Anti-TNF vs. conventional DMARDs (multivariate analysis final model): adjusted HR: 1.49, 95% CI 0.70, 3.18; *P* = 0.31 • Adjusted HR for heart failure in 98 patients with prevalent heart failure Anti-TNF vs. conventionals 1.18 95% CI 0.30-4.733.90 *P* = 0.81. • Patients with heart failure prior to study entry compared to patients without CVD at study entry had an adjusted HR of 23.88 (95% CI 8.04, 70.90) *P* = 0.0001. • In a multivariate analysis adjusted HR was 15.99 (95% Ci 5.40, 47.36), *P* = 0.0001.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• And in a simplified model to offset efficacy of anti-TNF treatment, adjusted HR was 18.06 (95% Ci 6.10, 53.49) *P* = 0.0001. • When incident heart failure cases were compared to matched controls, controls had a significantly lower mean DAS28 score at follow up compared to cases (4.4 vs. 5.1, *P* = 0.03). • Adverse events were not systematically reported; there were 101 deaths, 14 of which were result of heart failure. • Twenty five patients experienced heart failure for first time during study period. • A worsening of severity of prevalent heart failure was observed in 12 of 98 patients.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Maini et al. 2004[18] **Country, Setting:** Multinational Multicenter **Funding:** Centocor **Research Objective:** Efficacy and safety of repeated administration of infliximab plus MTX over a 2-yr period in pts with RA **Study Design:** RCT plus extension **Overall N:** 428 (259 in extension) **Study Duration:** 54 wks plus additional yr of follow-up	**Inclusion Criteria:** • Age 18-75 • Active RA despite MTX **Exclusion Criteria:** • NR	**Interventions, dose:** D1: INF D2: Placebo **Mean age, yrs:** Overall: **54** **Sex, % female:** Overall: 78 **Race, % white:** NR	**Mean disease duration, yrs:** D1: **TJC, mean:** Overall: **31** **SJC, mean:** Overall: **20** **DMARD use, %: NR** **Corticosteroid use, %: NR** **MTX naïve, %:** NR **DMARD Txt resistant, %:** NR **Patients with Early RA (≤ 3 yrs):** NR	The incidence of serious adverse events remained constant over time	Serious adverse events were reported by similar proportions of pts who received MTX only (33%) and infliximab plus MTX (29%) • Number of observed cancer cases vs. number expected Placebo 0 vs. 1.02 INF 5 vs. 5.15	**Overall Attrition Rate, %:** • At 52 wks 27% • At 2 yrs 17% of those that continued into extension **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Maini et al., 2006,[121] CHARISMA **Country and setting** Rheumatology Centers, Europe **Source of funding** Chugai Pharmaceuticals (a member ofRoche Group) **Research objective** Establish safety and efficacy of repeat infusions of tocilizumab alone and in combination with MTX **Study design** Controlled Trials **Overall N** 359 **Duration of study** 16 wks (20 wks for Safety) **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant • Patients must have shown an inadequate response to MTX or a disease flare while receiving MTX (at a dosage of 10-25 mg weekly) during a minimum of 6 mos of therapy. • Inadequate response was defined as presence of active disease, as described above, despite MTX therapy • Dagnosis of RA according to ACR revised criteria • Disease duration of at least 6 mos • Active disease (defined as ≥ 6 tender joints and 6 swollen joints, based on a 28-joint count) • ESR of ≥ 28 mm/hour, and/or a CRP level ≥	**Interventions, dose** D1: • Tocilizumab: 2 mg/kg every 4 weeks • Placebo MTX placebo: once/week D2: • Tocilizumab: 4 mg/kg every 4 weeks • Placebo MTX placebo: once/week D3: • Tocilizumab: 8 mg/kg every 4 wks • Placebo MTX placebo: once/week D4: • MTX: once/week • Tocilizumab: 2 mg/kg every 4 weeks D5: • MTX: once/week • Tocilizumab: 4 mg/kg every 4 wks D6: Tocilizumab: 8 mg/kg every 4 wks + MTX once/week D7: MTX: once/wk + placebo infusions every 4 wks **Number in group** D1: 53 D2: 54 D3: 52 D4: 52 D5: 49 D6: 50 D7: 49 Overall: 359	**Mean disease duration, mos** D1: 9.19 D2: 9.79 D3: 9.21 D4: 9.33 D5: 7.82 D6: 10.62 D7: 11.24 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 D3: 100 D4: 100 D5: 100 D6: 100 D7: 100 Overall: 100 **TJC, mean** D1: 15 D2: 15 D3: 15 D4: 15 D5: 13 D6: 15 D7: 16 Overall: 15 **SJC, mean** D1: 11 D2: 11 D3: 12 D4: 11 D5: 11 D6: 11 D7: 12	**ACR** ACR 20: D1: 31 D2: 61 D3: 63 D4: 64 D5: 63 D6: 74 D7: 41 • 4 mg/kg and 8 mg/kg of tocilizumab vs. placebo plus MTX ($P < 0.05$) • 2 mg/kg of tocilizumab vs. placebo plus MTX (NS) • Tocilizumab (2 mg/kg, 4 mg/kg, and 8 mg/kg) plus MTX vs. ACR 50: D1: 6 D2: 28 D3: 41 D4: 32 D5: 37 D6: 53 D7: 29 8 mg/kg of tocilizumab plus MTX vs. placebo plus MTX ($P < 0.05$). All others NS. ACR 70: D1: 2 D2: 6 D3: 16 D4: 14 D5: 12 D6: 37 D7: 16 8 mg/kg of tocilizumab plus	**Attrition/withdrawal** Overall, n: D1: 12 D2: 11 D3: 8 D4: 6 D5: 7 D6: 7 D7: 9 **Withdrawals due to adverse events, n:** AE and Possible Drug-Related Toxicity: D1: 4 D2: 6 D3: 5 D4: 3 D5: 6 D6: 6 D7: 4 Withdrawals due to lack of efficacy, n: D1: 6 D2: 5 D3: 2 D4: 1 D5: 1 D6: 1 D7: 6 Adherent/compliant, n: D1: 41 D2: 43 D3: 44 D4: 46 D5: 42 D6: 43 D7: 40 **Overall adverse events**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	1.0 mg/dl. • If patients required concomitant treatment with nonsteroidal antiinflammatory drugs and/or oral steroids, dose must have been stable for at least 4 weeks prior to study entry and during course ofstudy (for steroids, ≥ 10 mg PNL or equivalent). **Exclusion Criteria** • Leukopenia and/or thrombocytopenia, any hepatic dysfunction as shown by aspartate transaminase and alanine transaminase levels > 1.5-fold upper limit of normal or significant renal impairment (serum creatinine level > 1.5-fold upper limit of normal) • Patients who received	**Mean age, years** D1: 52.2 D2: 49.3 D3: 50.1 D4: 49.2 D5: 50.2 D6: 50.1 D7: 50.9 Overall: 50.3 **Sex, % female** D1: 83 D2: 76 D3: 73 D4: 87 D5: 76 D6: 78 D7: 78 Overall: 79 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	Overall: 11 **Corticosteroid use, %** NR **DMARD use, %** D1: 100 D2: 100 D3: 100 D4: 100 D5: 100 D6: 100 D7: 100 Overall: 100 **MTX naïve, %** D1: 0 D2: 0 D3: 0 D4: 0 D5: 0 D6: 0 D7: 0 Overall: 0 **Baseline DAS score** D1: 6.48 D2: 6.55 D3: 6.43 D4: 6.58 D5: 6.34 D6: 6.47 D7: 6.75 **Required treatment for latent TB** NR	MTX vs. placebo plus MTX ($P < 0.05$). All others NS. **HAQ** NR **DAS** D1: NR (in figure only) D2: NR (in figure only) D3: NR (in figure only) D4: NR (in figure only) D5: NR (in figure only) D6: -3.57 D7: NR (in figure only) monotherapy with 2 mg/kg of tocilizumab vs. placebo + MTX (P = NS) **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR • Mean difference/absolute difference (CI/SD/P Value): • Rate of Remission According toDAS: 8 mg/kg of tocilizumab + MTX: 34%, Monotherapy with 8 mg/kg tocilizumab: 17%, Placebo + MTX: 8%, other arms and overall: NR • Mean Reduction in SJCs Monotherapy with 8 mg/kg of tocilizumab vs. placebo + MTX ($P < 0.01$), 8 mg/kg of tocilizumab + MTX vs. placebo + MTX ($P < 0.001$), other drugs:	**reported, n:** Patients with 1 or more treatment-emergent AE: D1: 30 D2: 27 D3: 31 Treatment-related AE: D1: 13 D2: 14 D3: 15 **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR **Other infections** Limb abscess D1: 1 All else NR Osteomyelitis: D1: 1 All else NR Respiratory infection: D1: 2 All else NR Infective arthritis: D3: 1 All else NR Sepsis D3: 1 All else NR Anaphylactic shock/reaction and hypersensitivity: D1: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	DMARDs (excluding MTX) within 4 weeks prior tostart ofstudy • Patients who received anti-TNF agents within 12 weeks or LEF within 6 mos of infusion of study medication.			NR • Mean Reduction inTJC: 8 mg/kg of tocilizumab plus MTX vs. placebo + MTX (*P* < 0.009), other drugs: NR • CRP/ESR: NR for all drugs (in figure only)	D2: 1 D3: 0 D4: 0 D5: 0 D6: 0 D7: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Malysheva et al., 2008[122] **Country and setting** Germany **Source of funding** Not reported **Research objective** Assess incidence and severity of DMARD-induced AEs in pts taking/not taking glucocorticoids and whether glucocorticoids can prolong survival time of DMARD in pts receiving combination therapy **Study design** Retrospective Cohort Study **Overall N** 154 **Duration of study** 2-62 months **Quality rating** Fair	**Inclusion Criteria** • ACR criteria for RA **Exclusion Criteria** • Previous history of active gastrointestinal problems • Serious complicating diseases such as arterial hypertension, psychiatric, or mental problems • Diabetes mellitus • Patients with steroid pulse therapy	**Interventions, Dose** D1: MTX: 7.5-20 mg/week D2: MTX: 7.5-20 mg/week Other: 7.5 mg/day or less glucocorticoids D3: Hydroxychlorquine: 200-400 mg/day D4: Hydroxychlorquine: 200-400 mg/day Other: 7.5 mg/day or less glucocorticoids D5: SSZ: 1-2 g/day Other: with and without 7.5mg/day glucocorticoid **Number in group** D1: 74 D2: 51 D3: 69 D4: 22 D5: 28 // 19 Overall: 154 **Mean age (years)** NR Overall: 47.2 **Sex, % female** NR Overall: 84 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** Overall: 17.8 yrs (3.9) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** • Time in months until withdrawal of DMARD due to AD (mean + SD)- MTX: 21.8 (2.9) • MTX + GC: 43.3 (2.7) • SSZ: 10.4 (2.3) • SSZ + GC: 22.5 (1.9) • Time in months until occurence of AE: MTX: 3.0 (0.6) • MTX + GC: 18.8 (1.3) • HCQ: 34.5 (4.6) • HCQ + GC: 54.4 (5.1) • Time to cessation due to loss of efficacy: SSZ: 16.8 (1.2); SSZ + GC: 31.3 (2.9)	**Overall** Use of GC significantly increased time until withdrawal of DMARD therapy due to AE (18.6 ± 2.3 vs. 12.5 ± 1.4 mo; *P* = 0.05). However, timing of withdrawal of DMARD due to loss of efficacy was not different between RA patients taking GC and GC-naïve patients, probably due to higher level of disease activity in RA patients with GC comedication. Stratifying for DMARD revealed that comedication with GC significantly increased duration of therapy with SSZ from 10.4 ± 2.3 to 22.5 ± 1.9 months (SSZ + GC; *P* = 0.05) and for MTX from 21.8 ± 2.9 to 43.3 ± 2.7 months (MTX + GC; *P* = 0.01). GC comedication significantly increased time until occurrence of AE for MTX (3.0 ± 0.6 vs. 18.8 ± 1.3 mo; *P* = 0.05), HCQ (34.5 ± 4.6 vs. 54.4 ± 5.1 mo; *P* = 0.05). Patients taking SSZ, time to cessation due to loss of efficacy increased significantly under GC comedication, from 16.8 ± 1.2 to 31.3 ± 2.9 months *(P* = 0.05). **Overall adverse events reported, n:** D1: 9

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D2: 17 D3: 19 D4: 12 D5: 4//5 Overall: 64 **Serious adverse events** NR **Malignancies** Other cancer (specify), n: NR Overall: unspecified: 5 **Respiratory events** NR **Other infections** NR **GI** NR **Other** Grade 1 AE (mild, not requiring treatment), n: D1: 3 D2: 7 D3: 1 D4: 1 D5: 2//1 Grade 2 AE (moderate, resolved with treatment), n: D1: 4 D2: 5 D3: 17 D4: 9 D5: 1//2 Grade 3 AE (severe, result in inability to carry on normal activities and requiring professional medical attention), n: D1: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D2: 4 D3: 4 D4: 1 D5: 4//1 • Overall: nephrectomy: 1 • Osteoporosis (DMARD monotherapy versus DMARD + GC): 16 vs. 22 • Diabetes mellitus: 4 vs. 10 • Malignancy: 6 vs. 3 • Thyroid dysfunction: 5 vs. 5 • Infections: 2 vs. 3 • Gastrointestinal Complications: 11 vs. 6 • Mucocutaneous complications: 5 vs. 7 • Intolerance: 6 vs. 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Marchesoni et al., 2009[123] LOHREN registry **Country and setting** Italy, Lombary **Source of funding** NR **Research objective** To evaluate survival of INF, ETN, and ADA in a RA patient cohort **Study design** Observational **Overall N** 1064 **Duration of study** 36 mos	**Inclusion Criteria** • Patients with RA according to ACR with at least one dose of anti-TNF treatment **Exclusion Criteria** • Active infection • History of malignancy • Pre-malignant condition • Class 3/4 congestive heart failure • Demyelinating disorders	**Comparisons (dosage and frequency)** D1: INF: dose NR D2: ADA: dose NR D3: ETN: dose NR **Number in group** D1: 519 D2: 303 D3: 242 Overall: 1064 **Mean age (years)** D1: 55.72 D2: 56.07 D3: 55.81 Overall: 55.84 **Sex, % female** D1: 81.5 D2: 85.1 D3: 84.3 Overall: 83.2 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 9.28 (7) D2: 9.56 (7.9) D3: 9.63 (7.11) Overall: 9.44 (7.29) **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** D1: 80.7 D2: 76.9 D3: 84.3 Overall: 84.2 **DMARD use, %:** NR **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** D1: 6.01 (0.94) D2: 5.68 (0.96) D3: 5.93 (1.02) Overall: 5.90 (0.97) **Required treatment for latent TB** NR **Other population characteristics,**	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** Overall attrition/withdrawal (n): D1: 226 D2: 111 D3: 68 Overall: 405 Withdrawals due to adverse events (n): D1: 106 D2: 60 D3: 28 Overall: 194 Withdrawals due to lack of efficacy (n): D1: 104 D2: 45 D3: 31 Overall: 180 Long-term survival rate at 36 mos (INF vs. ADA vs. ETN): 49.1% vs. 53.6% vs. 62.5% RR of discontinuation due to all causes compared to ETN • ADA: 1.45 (1.05 to 2.00, *P*=0.024) • INF: 1.50 (1.10 to 2.05; *P*=0.011) RR of discontinuation due to loss of effica **Serious adverse events:** Death (n): D1: 3 D2: 5	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			%, (CI/SD/P value):	NR	D3: 5 Overall: 13 **Malignancies:** Malignancies: D1: 6 D2: 8 D3: 4 Overall: 18 **Respiratory events:** NR **Other infections:** Serious infections (specify) (n): D1: 42 D2: 20 D3: 11 Overall: 73 **GI:** NR **Other:** Infusion/injection site reactions (n): D1: 48 D2: 8 D3: 2 Overall: 58	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable McDonald, J.R. et al., 2009[124] **Country and setting** United States; Veterans hospital **Source of funding** US Department of Veterans Affairs, Veterans Health Administration, and National Institutes of Health **Research objective** Examine HZ risk, risk factors, treatments and outcomes with a focus on contribution of different classes of immunosuppressive medications to risk of HZ **Study design** Retrospective Cohort Study **Overall N** 20,357 **Duration of study** October 1998 to June 2005 **Quality rating** Fair	**Inclusion Criteria** • Ad Veterans who had an ICD-9-CM code diagnosis of RA during study period and who, after a ≥ 4 month history of receiving medications from VA during study period, subsequently received a first prescription for a DMARD. **Exclusion Criteria** • Diagnosis of HZ at any time prior to receiving a DMARD or who did not have ≥ 2 separate outpatient or inpatient clinical encounters during study period.	**Interventions, Dose** D1: • SSZ: dose NR • HCQ: dose NR • Auronofin, injectable gold, penicillamine: NR D2: • MTX: dose NR • LEF: dose NR • ANK: dose NR • Azathioprine, cyclophosphamid, cyclosporine: dose NR D3: • ETN: dose NR • IFX: dose NR • ADA: dose NR **Number in group** D1: 9673 D2: 12888 D3: 3661 Overall: 20357 **Mean age (years)** D1: 61.9, SD 12.8 D2: 63.7, SD 12.0 D3: 59.3, SD 11.6 **Sex, % female** D1: 10.9 D2: 8.7 D3: 9.0 **Race, % white** D1: 65.2 D2: 67.5 D3: 70.1 **Race, % black**	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: PRED: 34.5 D2: PRED: 62.7 D3: PRED: 55.0 **DMARD use, %** D1: HCQ: 72.8; SSZ: 39.7; MTX: 0; LEF: 0; CSA: 0; CYC: 0; ANK: 0; ETN: 0; IFX: 0; ADA: 0 D2: HCQ: 28.7; SSZ: 17.3; MTX: 83.7; LEF: 19.8; CSA: 2.7; CYC: 2.7; ANK: 0.5; ETN: 0; IFX: 0; ADA: 0 D3: HCQ: 22.0; SSZ: 17.0; MTX: 51.5; LEF: 19.8; CSA: 1.3; CYC: 0.6; ANK: 1.5; ETN: 68.9; IFX: 22.0; ADA: 32.4 **MTX naïve, %** D1: 100 D2: NR D3: NR	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** Antiviral Treatment: • Oral: D1 65.4, D2 65.5, D3 69.8, D2 vs. D1: *P* > 0.5, D3 vs. D1: *P* > 0.1; • Intravenous: D1 1.0, D2 6.8, D3 3.1, D2 vs. D1: *P* = 0.001, D3 vs. D1: *P* > 0.1; • HZ complication: HZ Meningitis: D1 0.5, D2 0.5, D3 0, D2 vs. D1: *P* > 0.1, D3 vs. D1: *P* > 0.5; • Other HZ nervous system complication: D1 20.7, D2 18.6, D3 17.7, D2 vs. D1: *P* > 0.5, D3 vs. D1: *P* > 0.5; • Ophthalmic HZ: D1 7.2, D2 6.8, D3 5.2, D2 vs. D1: *P* > 0.5, D3 vs. D1: *P* > 0.1; • Other HZ complication: D1 6.3, D2 6.8, D3 4.2, D2 vs. D1: *P* > 0.5, D3 vs. D1: *P* >	**Overall** NA **Overall adverse events reported, n: NA** **Serious adverse events** NA **Malignancies** NA **Respiratory events** NA **Other infections** NA **GI** NA **Other** NA

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D1: 13.6 D2: 10.1 D3: 8.9 **Ethnicity, Latino** NR	**Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: Episodes of HZ (%): 2.2; Episodes of HZ per 1000 patient-years: 8.00 D2: Episodes of HZ (%): 3.2; Episodes of HZ per 1000 patient-years: 11.18 D3: Episodes of HZ (%): 2.6; Episodes of HZ per 1000 patient-years: 10.60 Overall: Episodes of HZ per 1000 patient-years: D2 vs. D1 *P* = 0.001; D3 vs. D1 *P* = 0.001	0.1; • Hospitalization for HZ: D1 2.9, D2 6.1, D3 4.2, D2 vs. D1: *P* > 0.5, D3 vs. D1: *P* > 0.1;	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Mease et al., 2008, DANCER trial[46,125] **Country and setting** United States multicenter **Source of funding** Genentech, Inc. **Research objective** Evaluate effect of RIT treatment on HRQOL **Study design** Controlled Trials **Overall N** 367 **Duration of study** 24 weeks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant failed to respond to treatment with at least 1 but not more than 5 DMARD or biologic agents • SJC of 8 or more • TJC of 8 or more • CRP serum levels of 1.5 mg/dl or more or erythrocyte sedimentation rate of 28 mm/h or more despite ongoing MTX treatment of more than 12 weeks • See[46] for more details **Exclusion Criteria** • See[46]	**Interventions, Dose** D1: • MTX: 10-25 mg/week • PlaceboIV infusion on days 1 and 15 D2: • MTX: 10-25 mg/week • RIT: 500 mg IV infusion on days 1 and 15 D3: • MTX: 10-25 mg/week • RIT: 1000 mg IV infusion on days 1 and 15 **Number in group** D1: 122 D2: 123 D3: 122 Overall: 367 **Mean age (years)** D1: 50.8 D2: 51.4 D3: 52.1 Overall: 51.0 **Sex, % female** D1: 79.5 D2: 83.7 D3: 76.2 Overall: 80.0 **Race, % white** D1: 77.9 D2: 76.4 D3: 82.8 Overall: 79.0 **Race, % black** NR	**Mean disease duration, years (SD)** D1: 9.6 yrs (7.7) D2: 11.2 (8.5) D3: 11.3 (8.5) Overall: 11.0 (NR) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 D3: 100 Overall: 100 **TJC, mean (SD)** D1: 35 D2: 33 D3: 32 **SJC, mean (SD)** D1: 21 D2: 22 D3: 22 **Corticosteroid use, %** NR **DMARD use, %** D1: 27 D2: 39 D3: 31.1 Overall: 32.4 **MTX naïve, %** D1: 0 D2: 0 D3: 0 Overall: 0 **Baseline DAS score, mean (SD)**	**ACR** NR **HAQ,** D1: NR, in figure only D2: NR, in figure only D3: NR, in figure Overall: • Significant differences were seen for 1000mg Gps. placebo after 8 weeks *(P* = 0.05) and were maintained over 24 weeks. • For 500mg group, significant differences vs. placebo were seen by 12 weeks *(P* NR). • At week 24, 34.4% vs. 62.6% vs. 67.2% achieved prespecified MCID of 0.22 points *(P* = 0.05 for both groups vs. placebo) **DAS** NR **SF-36 (SD)** Mean changes from baseline to 24 weeks: physical component summary (PCS): D1: 2.36 (0.78) D2: 7.08 (0.77) D3: 7.40 (0.78) Mental component summary: D1: 1.88 (1.00) D2: 4.49 (1.22) D3: 3.03 (1.11) Physical function: D1: 2.18 (0.83) D2: 6.44 (0.90) D3: 5.79 (0.88)	**Overall** Overall attrition/withdrawal, n: D1: see below D2: see below D3: see below Overall: 33-53 Withdrawals due to adverse events, n: NR Withdrawals due to lack of efficacy, n: NR Adherent/compliant, n: NR Missing outcome data (% without baseline and endpoint scores): • For SF-36, 26% vs. 9% vs. 4% • For HAQ, 27% (placebo) vs. 2% (combined RIT groups) • For FACIT-Fatigue, 27% vs. 1%. **Overall adverse events reported, n:** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Ethnicity, Latino NR	D1: 6.85 (0.74) D2: 6.84 (0.79) D3: 6.67 (0.82) Overall: 6.79 (NR) **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** NA	Role-physical: D1: 0.64 (1.25) D2: 7.19 (0.98) D3: 5.51 (1.22) Bodily pain: D1: 4.16 (0.89) D2: 8.96 (0.97) D3: 8.51 (0.85) General health: D1: 2.15 (0.89) D2: 3.94 (0.80) D3: 4.52 (0.87) Vitality: D1: 2.69 (0.95) D2: 6.71 (0.96) D3: 6.02 (0.98) Social function: D1: 2.68 (1.11) D2: 6.97 (1.22) D3: 5.93 (0.98) Role-emotional: D1: 0.95 (1.39) D2: 5.54 (1.57) D3: 3.27 (1.57) Mental health: D1: 2.34 (1.03) D2: 3.96 (1.04) D3: 2.83 (1.01) Overall: • For 500 mg vs. placebo and 1000 mg vs. placebo, respectively: PCS, *P* = 0.001 for both comparisons • MCS, *P* = 0.087, *P* = 0.167 • Proportion of patients achieving an MCID	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				(minimal clinically important difference) of 5 points on PCS: 23.8% vs. 55.3% vs. 52.5%, significantly higher (*P* = 0.05) for both groups vs. placebo • MCS scores were not significantly different (data NR) **Radiographic measures** NR **Quality of life scales** D1: FACIT-Fatigue, change from baseline: 3.91 D2: 7.63 D3: 8.20 *P* = 0.009 placebo vs. 500 mg group *P* = 0.001 for 1000 mg vs. placebo	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Michaud, K. et al.; 2006[126] **Country and setting** United States; doctors offices **Source of funding** National Database for Rheumatic Diseases **Research objective** Determine sinus disease rates are increased in pts with RA and whether tx alters risk of sinus disease. **Study design** Cohort Study **Overall N** 7,243 patients with RA **Duration of study** longitudinal (length not specified); questionnaire completion December 2003 **Quality rating** Fair	**Inclusion Criteria** • NDB participants who completed a questionnaire in December 2003 that included questions related to sinus problems. **Exclusion Criteria** • NR	**Interventions, Dose** D1: • PRED: NR • MTX: NR • LEF: NR • SSZ: NR • Hydroxychlorquine: NR • ETN: NR • IFX: NR • ADA: NR **Number in group** D1: 7243 **Mean age (years)** D1: 62.2, SD 12.4 **Sex, % female** D1: 78.5 **Race, % white** D1: 92.7 **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: PRED: 34.1 **DMARD use, %** D1: HCQ: 19.0; MTX: 57.5; IFX: 31.9; LEF: 14.6; ETN: 14.5; ADA: 3.0; SSZ: 5.8 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** NR **HAQ,** D1: 1.03, CI 1.07 - 1.25, SD 0.72, *P* = 0.05 **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** • Association of sinus problems: OR (95% CI); • Fatigue (0-10 scale, unnamed): 4.2, CI 1.05 - 1.09, SD 2.87, *P* = 0.05; • Pain (0-10 scale, unnamed): 3.5, CI 1.03 - 1.07, SD 2.68, *P* = 0.05	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** OR (95% CI) for visits to physician for sinus problems: • MTX: 1.06 (0.93, 1.20) 0.371 • PRED: 0.98 (0.86, 1.11) 0.776 • IFX: 1.00 (0.88, 1.15) 0.973 • HCQ: 1.08 (0.93, 1.25) 0.313 • LEF: 0.84 (0.70, 0.99) 0.041 • ETN: 1.21 (1.02, 1.42) 0.025 • ADA: 1.09 (0.79, 1.51) 0.600 • SSZ: 0.68 (0.51, 0.90) 0.007

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Migliore et al. 2009[127] **Country and setting** Italy, Multicenter **Source of funding** NR **Research objective** To determine the safety profiles for ETN, INF and ADA in patients of 65+ yrs, undergoing anti-TNF treatment for an active inflammatory disease such as rheumatoid arthritis **Study design** Observational **Overall N** 138 **Duration of study** Duration of treatment with anti-TNF: 39 mos (SD 14)	**Inclusion Criteria** • Age 65 or more with RA **Exclusion Criteria** • Treated for other conditions, or with other anti-TNFs or different doses	**Comparisons (dosage and frequency)** D1: ETN:50 mg/week D2: ADA: 40 mg every 2 wks D3: INF: 3-5 mg/kg every 6 to 8 wks **Number in group** D1: 54 D2: 39 D3: 45 Overall: 138 **Mean age (years)** Ages 65-70 D1: 41 (76%) D2: 17(44%) D3: 13(29%) Overall: 71 (51%) Ages 71-75 D1: 4 (7%) D2: 5 (38%) D3: 23 (51%) Overall: 42 (30%) Age 76 or older D1: 9 (17%) D2: 7 (18%) D3: 9 (20%) Overall: 25 (18%) Overall, across all groups: 71.2 **Sex, % female** D1: NR D2: NR D3: NR	**Mean disease duration, years** NR Overall: 11.6 (7.8) **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %:** 100 **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** NR **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** Tuberculosis (n): NR Pneumonia (n): NR Upper respiratory infection (n): NR **Other infections:** Urinary tract infection (n): NR Other infections (specify) (n): Infections (total, not stratified by age) Total D1: 10 D2: 10 D3: 10 Mild D1: 2 D2: 8 D3: 5 Moderate D1: 2 D2: 0 D3: 1 Severe D1: 0 D2: 0 D3: 1 Infections, age 65-70	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		Overall: 79% **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR		NR	Total D1: 4 D2: 4 D3: 3 Mild D1: 4 D2: 4 D3: 3 Moderate D1: 0 D2: 0 D3: 0 Severe D1: 0 D2: 0 D3: 0 Infections, age 71-75 Total D1: 1 D2: 1 Mild D1: 0 D2: 0 Moderate D1: 0 D2: 0 Severe D1: 0 D2: 0 Infections, age 76+ Total D1: 5 D2: 3 D3: 3 Mild D1: 4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					D2: 3 D3: 3 Moderate D1: 1 D2: 3 D3: 1 Severe D1: 0, D2: 0 D3: 1 **GI:** NR **Other:** Allergic reactions (total, not stratified by age) Total D1: 4 D2: 2 D3: 5 Mild D1: 2 D2: 1 D3: 2 Moderate D1: 2 D2: 1 D3: 2 Severe D1: 0 D2: 0 D3: 1 Allergic reactions, age 65-70 Total D1: 2 D2: 4 D3: 1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					Mild D1: 1 D2: 2 D3: 1 Moderate D1: 1 D2: 2 D3: 0 Severe D1: 0 D2: 0, D3: 0 Allergic reactions, age 71-75 Total D1: 1 D2: 1 D3: NR Mild D1: 1 D2: 0 D3: NR Moderate D1: 0 D2: 1 D3: 0 Severe D1: 0 D2: 0 D3: 1 Allergic reactions, age 76+ Total D1: 1 D2: 0 D3: 0	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					Mild D1: 0 D2: 0 D3: 0 Moderate D1: 1 D2: 0 D3: 0 Severe D1: 0 D2: 0 D3: 0	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Miyasaka, 2008,CHANGE study[128] **Country and setting** Japan, Multicenter **Source of funding** Abbott Japan Co., Ltd. and Eisai Co. **Research objective** Compare effects of 3 doses of ADA vs. placebo in Japanese RA pts **Study design** Controlled Trials **Overall N** 352 **Duration of study** 24 weeks **Quality rating** Fair	**Inclusion Criteria** • 20 years or older • Met ACR criteria for active RA • Failed 1 DMARD • 10 or more swollen joints and 12 or more tender joints (excluding distal interphalangeal joints) and a CRP concentration 2 mg/dL or more **Exclusion Criteria** • Acute inflammatory joint diseases other than RA • Active Listeria or TB, lymphoma, or leukemia, or any malignancy except for successfully treated nonmetastatic basal-cell carcinoma ofskin, HIV, hepatitis B virus surface antigen, or anti-hepatitis C virus antibody • Ongoing or	**Interventions, dose** D1: ADA: 20 mg every other week D2: ADA: 40 mg every other week D3: ADA: 80 mg every other week D4: Placebo **Number in group** D1: 87 D2: 91 D3: 87 D4: 87 Overall: 352 **Mean age, years (SD)** D1: 54.8 D2: 56.9 D3: 54.3 D4: 53.4 Overall: 54.9 **Sex, % female** D1: 79.3 D2: 79.1 D3: 82.8 D4: 77 Overall: 79.5 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, mean years (SD)** D1: 10 (7.7) D2: 9.9 (7.9) D3: 9.5 (8.3) D4: 8.4 (8.2) Overall: 9.5 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 24.6 D2: 24.4 D3: 24.9 D4: 23.7 Overall: 24.4 **Swollen Joint Count, mean** D1: 19.2 D2: 19.1 D3: 20.8 D4: 19.3 Overall: 19.6 **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score** NR **Required treatment for latent TB** NR	**ACR mean difference/ absolute difference (%)** ACR 20: Week 12, n: D1: 39 (44.8) D2: 39 (49.2) D3: 47 (54) D4: 11 (12.6) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: $P < 0.05$, $P < 0.05$, $P < 0.05$ Week 24, n: D1: 25 (28.7) D2: 40 (44) D3: 44 (50.6) D4: 12 (13.8) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: $P < 0.05$, $P < 0.0001$, $P < 0.0001$ ACR 50: Week 12, n D1: 16 (18.4) D2: 19 (20.9) D3: 23 (26.4) D4: 3 (3.3) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: $P = 0.05$, $P = 0.05$, $P = 0.05$ Week 24, n: D1: 14 (16.1) D2: 22 (24.2) D3: 28(32.2) D4: 5 (5.7) Overall :Placebo vs. ADA 20, ADA 40, ADA 80: $P =$ NS, $P = 0.05$, $P = 0.05$ ACR 70:	**Attrition/withdrawal** Overall, n: D1: 7 D2: 16 D3: 4 D4: 7 Overall: 34 Withdrawals due to adverse events, n: D1: 5 D2: 12 D3: 3 D4: 4 Overall: 24 Other reasons for discontinuation included withdrawal of consent, protocol violations, and administrative reasons. 107 patients received rescue medication after 8+ weeks of double-blind study treatment (45, 26, 17, and 19 in placebo and ADA 20, 40, and 80 mg groups, respectively) 3 discontinuations that occurred during rescue period occurred in one patient each from placebo, ADA 40 mg, and ADA 80 mg groups. Overall adverse events reported, n: D1: 80 D2: 90 D3: 81 D4: 71 Overall: 322

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	active infection • Advanced or poorly controlled diabetes • CNS demyelinating disorders • Pregnancy		Mean Subject's global assessment of disease activity VAS (mm): D1: 73.1 D2: 71.2 D3: 75.7 D4: 64.6 Overall: NR Mean Subject's assessment of pain VAS (mm): D1: 69 D2: 68.1 D3: 70.4 D4: 62.7 Overall: NR Mean HAQ DI score: D1: 1.57 D2: 1.64 D3: 1.77 D4: 1.39 Overall: NR Mean Duration of morning stiffness (min): D1: 216.7 D2: 193.3 D3: 202.3 D4: 195.5 Overall: NR Any morning stiffness (%): D1: 81.4 D2: 76.9 D3: 88.4 D4: 86.2 Overall: NR	Week 12, n: D1: 6 (6.9) D2: 15 (16.5) D3: 10 (11.5) D4: 1 (1.1) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: *P* = NS, *P* = 0.05, *P* = 0.05 Week 24, n (%) D1: 9 (10.3) D2: 11 (12.1) D3: 13 (14.9) D4: 1 (1.1 Overall: Placebo vs. ADA 20, ADA 40, ADA 80: *P* = 0.05, *P* = 0.05, *P* = 0.05 **HAQ,** 12 week, mean difference (SD): D1: 0.2 (0.5) D2: -0.3 (0.6) D3: -0.4 (0.5) D4: -0.1 (0.6) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: *P* = 0.05, *P* = NS, *P* = 0.05 24 week, mean difference (SD): D1: -0.2 (0.5) D2: -0.2 (0.6) D3: -0.4 (0.6) D4: -0.1 (0.6) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: *P* = NS, *P* = NS, *P* = NS **DAS** NR **SF-36**	**Serious adverse events** Death, n: D1: 0 D2: 1 D3: 1 D4: 0 **Malignancies** NR **Respiratory events** Tuberculosis, n: 2,747 Upper respiratory infection, n: Overall: ADA 4.5% vs. Placebo 2.3% **Other infections** NR **GI** NR **Other** Fractures, n: Infusion/injection site reactions, n: D1: 27 D2: 28 D3: 29 D4: 2 Serious AE, n: D1: 10 D2: 17 D3: 8 D4: 8 Overall: 43 Severe AE, n: D1: 3 D2: 4 D3: 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				NR **Radiographic measures** NR **Quality of life scales** NR **Others** TJC week 12: D1: -8.3 D2: -11.2 D3: -10.1 D4: -0.6 Overall: Placebo vs. 20, 40, 80: *P* = 0.05, *P* = 0.05, *P* = 0.05 TJC week 24: D1: -6.6 D2: -10.7 D3: -10.0 D4: -0.5 Overall: Placebo vs. 20, 40, 80: *P* = NS, *P* = 0.05, *P* = 0.05 SJC week 12: D1: -6.8 D2: -8.1 D3: -8.7 D4: -1.6 Overall: Placebo vs. 20, 40, 80: *P* = 0.05, *P* = 0.05, *P* = 0.05 SJC week 24: D1: -5.9 D2: -8.2 D3: -8.7 D4: -1.8 Overall: Placebo vs. 20, 40, 80: *P* = 0.05, *P* = 0.05, *P* = 0.05	D4: 5 Overall: 17 Infectious AE, n: D1: 30 D2: 41 D3: 37 D4: 32 Overall: 140 Serious Infectious AE, n: D1: 4 D2: 6 D3: 3 D4: 1 Overall: 14 Immunologic reaction: • ADA 20: 4 • ADA 40: 2 • ADA 80: 0 • Placebo: 0 • Overall: 6 Malignancies: • ADA 20: 0 • ADA 40: 0 • ADA 80: 0 • Placebo: 2 • Overall: 2 Opportunistic infection including TB: ADA 20: 0 ADA 40: 0 ADA 80: 0 Placebo: 0 Overall: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Patient's global assessment of disease activity week 12: D1: -19.9 D2: -19.1 D3: -25.9 D4: -2.1 Overall: Patient's global assessment of disease activity week 12 vs. 20, 40, 80: *P* = 0.05, *P* = 0.05, *P* = 0.05 Patient's global assessment of disease activity week 24: D1: -16.6 D2: -19.9 D3: -25.8 D4: -2.6 Overall: Placebo vs. 20, 40, 80: *P* = NS, *P* = 0.05, *P* = 0.05 Patient's assessment of pain 12 week: D1: -17.3 D2: -17.2 D3: -20.5 D4: -2.3 Overall: Placebo vs. 20, 40, 80: *P* = NS, *P* = 0.05, *P* = 0.05 Patient's assessment of pain 24 week: D1: -12.8 D2: -17.4 D3: -20.3 D4: -3.5 Overall: Placebo vs. 20, 40, 80: *P* = NS, *P* = 0.05, *P* = NS	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mohan et al, 2001[129] **Country, Setting:** US, NA Medwatch, AERS **Funding:** NR **Research Objective:** To review occurrence of neurologic events suggestive of demylenation during anti TNF alpha therapy for inflammatory arthritides **Study Design:** Database analysis; AERS **Overall N:** 20 cases **Study Duration:** 4 mos	**Inclusion Criteria:** • Pts with refractory RA who developed confusion and difficulty walking • Other meds allowed: MTX, prednisone, amlodipine, estradiol, zolpidem, dexamethasone, a;prasolam, hydrocodone, naproxen sodium, acyclovir, metronidazole, ceftriaxone, ranitidine, atenolol, fluoxetine, piroxicam **Exclusion Criteria:** NA	**Interventions, dose:** **NR** **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR NR	In addition to 1 case reported of suspected demyelination, 17 cases of demyelination after ETA and 2 cases after INF txt were detected in MedWatch	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mohan et al., 2004[130] **Country, Setting:** Multinational, population-based **Funding:** NR **Research Objective:** To summarize all cases of TB following use of ETA reported to AERS from November 1998 through March 2002 **Study Design:** Database analysis; AERS **Overall N:** 25 cases **Study Duration:** NA	**Inclusion Criteria:** • All pts receiving ETA and reported to have active TB **Exclusion Criteria:** NR	**Interventions, dose:** **D1: ETA** **N:** D1: 25 cases **Mean age at diagnosis, yrs:** D1: 59 **Sex, % female:** D1: 72 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	As of April 2002, a total of 25 reports of TB associated with ETA therapy reported to FDA from 11/1998 through 3/2002 • 17 cases (68%) were reported from US, 7 (28%) from Europe, and 1 (4%) from India • 46% of 24 pts with a reported clinical manifestation had pulmonary TB • 2 deaths occurred among 25 pts • 17 US cases of TB have been reported to the FDA • According to ETA manufacturer, 113,238 pts treated with ETA in US between 11/1998 and 5/2002, with estimated 172,212 PY of exposure; thus reporting rate of TB among pts in US receiving ETA is ~10 cases / 100,000 PY of exposure	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999[131]; Korpela, 2004[132]; Puolakka, 2004[133] FIN-RACo Study **Country, Setting:** Finland, NR **Funding:** Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital **Research Objective:** Efficacy and tolerability of combo of DMARDs vs. a single DMARD **Study Design:** RCT **Overall N:** 199 randomized, 187 completed 2 yrs, 160 at 5 yrs **Study Duration:** 24 mos (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 65 • Diagnosed with RA according to ACR criteria: active disease, 1987 criteria • Duration of condition: < 2 yrs **Exclusion Criteria:** • Previous use of DMARDs • Underwent glucocorticoid glucocorticoid therapy within the previous • 2 weeks • serious comorbidity • suspected inabilty to • comply with the protocol • hypersensitivity to any study medication • history of cancer • pregnant women • women of childbearing age who were not using reliable methods of contraception	**Interventions, dose:** D1: Combo: MTX + HCQ + SSZ + PNL D2: Single DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 months **N:** D1: 97 D2: 98 **Mean age, yrs:** D1: 45 D2: 46 **Sex, % female:** D1: 58 D2: 66 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 7.3 mos D2: 8.6 mos **TJC, mean:** D1: 18 D2: 20 **SJC, mean:** D1: 14 D2: 14 **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Larsen Score:** D1: 0 D2: 2	**At 2 years** **Eroded joints, number:** D1: 2 D2: 3 (*P* = 0.006) btw groups Progression of radiological joint damage lower in combination versus monotherapy **Larsen Erosion Score improvement:** D1: 2 D2: 10 (*P* = 0.002) **Median increase in Larsen Score:** D1: 1.5 D2: 2.0 (*P* < 0.001) **Clinical remission, %:** D1: 37.9 D2: 18.4 (*P* = 0.011) **ACR50, %:** D1: 71 D2: 58 (*P* = 0.058) Median work disability per pt-observation yr, days: D1: 12.4 D2: 32.2 (*P* = 0.008) **At 5 years** Eroded joints, number: D1: 3 D2: 6 **Larsen Erosion Score:** D1: 11 D2: 24 (*P* = 0.001) **Median increase in Larsen**	**Overall:** D1: 70 D2: 71 **SAEs:** D1: 3 D2: 5 **Cardiovascular Events:** D1: 1 MI D2: 2 MIs **Malignancies:** 1 prostate cancer; 1 multiple myeloma **URTI:** 1 pneumonia	**Overall Attrition Rate, %:** 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Score: D1: 1.5 D2: 2.0 (*P* < 0.001) **5 year Remiission** D1: 28 D2: 22 (*P* = NS) **Increase in Larsen score** D1: lower than (*P* = 0.004)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999[131]; Mottonen, 2002[134]; Korpela, 2004[132]; Puolakka, 2004[133] FIN-RACo Study **Country, Setting:** Finland, NR **Funding:** Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital **Research Objective:** Efficacy and tolerability of combo of DMARDs vs. a single DMARD **Study Design:** RCT **Overall N:** 199 randomized, 187 completed 2 yrs, 160 at 5 yrs **Study Duration:**	**Inclusion Criteria:** • Age: 18 to 65 • Diagnosed with RA according to ACR criteria: active disease, 1987 criteria • Duration of condition: < 2 yrs **Exclusion Criteria:** • Previous use of DMARDs • Underwent glucocorticoid therapy within the previous • 2 weeks • serious comorbidity • suspected inability to • comply with the protocol • hypersensitivity to any study medication • history of cancer • pregnant women • women of childbearing age who were not using reliable methods of contraception	**Interventions, dose:** D1: Combo: MTX + HCQ + SSZ + PNL D2: Single DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 mos **N:** D1: 97 D2: 98 **Mean age, yrs:** D1: 45 D2: 46 **Sex, % female:** D1: 58 D2: 66 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 7.3 mos D2: 8.6 mos **TJC, mean:** D1: 18 D2: 20 **SJC, mean:** D1: 14 D2: 14 **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Larsen Score:** D1: 0 D2: 2	**At 2 years** **Eroded joints, number:** D1: 2 D2: 3 (P = 0.006) btw groups Progression of radiological joint damage lower in combination versus monotherapy **Larsen Erosion Score improvement:** D1: 2 D2: 10 (P = 0.002) **Median increase in Larsen Score:** D1: 1.5 D2: 2.0 (P < 0.001) **Clinical remission, %:** D1: 37.9 D2: 18.4 (P = 0.011) **ACR50, %:** D1: 71 D2: 58 (P = 0.058) Median work disability per pt-observation yr, days: D1: 12.4 D2: 32.2 (P = 0.008) **At 5 years** Eroded joints, number: D1: 3 D2: 6	**Overall:** D1: 70 D2: 71 **SAEs:** D1: 3 D2: 5 **Cardiovascular Events:** D1: 1 MI D2: 2 MIs **Malignancies:** 1 prostate cancer; 1 multiple myeloma **URTI:** 1 pneumonia	**Overall Attrition Rate, %:** 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) **ITT Analysis:** Yes **Quality Rating:** Fair

24 mos (5 yr followup)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Nadareishvili et al., 2008[135] **Country and setting** US, multicenter **Source of funding** Centocor, Sanofi-Aventis, Bristol Myers Squibb, Abbott, Amgen, Wyeth-Australia, Merck, Pfizer **Research objective** To determine risk of stroke in patients with RA and risk factors associated with stroke **Study design** Nested Case / Control, Prospective Cohort Study **Overall N** 269 **Duration of study** varied (prospective cohort) **Quality rating** Fair: Possibility that databank has a higher proportion of moderate-serverly ill RA pts decreases generalizability. Use of covariates in statistical analyses	**Inclusion Criteria** • RA, Ischemic stroke **Exclusion Criteria** • intracerebral, subarachnoid, subdural, and epidural hemorrhages, as well as transient ischemic attacks	**Interventions, Dose** D1: Other: Patients grouped by Case vs. Control; included txts relevant to this review: PRED, LEF, SSZ, HCQ, MTX, and anti-TNF (combined ETA, INF, and ADA) dosing not reported **Number in group** D1: 41 D2: 791 Overall: 269 **Mean age (years)** D1: at stoke: 69.8 D2: 69.9 Overall: mean time of databank follow-up: 4.0 years **Sex, % female** D1: 73.2 D2: 74.6 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** ACR 20: No measures of efficacy or QOL were reported for this article, go to AEs ACR 50: NR ACR 70: NR **HAQ,** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Results of multivariate analysis of association of RA therapy (within a 6mo window prior to event) and ischemic stroke in RA: PRED OR: 1.75, *P* = 0.114 [95%CI 0.87-3.53]; MTX OR: 0.63 *P* = 0.191 [CI: 0.32-1.26]; Anti-TNF OR: 0.79, *P* = 0.584 [CI: 0.34-1.82]. • A significant increased risk was found for Rofecoxib (not included in this review). • An analysis assessing length of treatment exposure was associated with stroke; a univariate but not multivariate effect

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
decreases potential for bias. Recall bias avoided by a review of medical records of pts reporting strokes.					was seen for PRED OR: 1.19, *P* = 0.039 [CI: 1.00-1.40]; no other drug effects seen. • Further analysis suggested a possible dose effect for PRED. NOTE: A second set of analyses were conducted using only drug pts were on at baseline. I did not think this was as comprehensive as this analysis so I did not include it - SWL

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Naranjo et al., 2008[136] **Country and setting** Multinational, multicenter **Source of funding** Abbott Laboratories **Research objective** Assess prevalence of CV morbidity in RA patients and its association with traditional risk factors, clinical features, and DMARD use **Study design** Cross – Sectional Cohort Study **Overall N** 4363 **Duration of study** varied (prospective cohort) **Quality rating** Fair	**Inclusion Criteria** • RA diagnosis **Exclusion Criteria** • NR	**Interventions, Dose** D1: MTX D2: Glucocorticoids D3: Antimalarials D4: SSZ D5: Gold D6: LEF D7: TNF-alpha blockers Dosing not reported **Number in group** Overall: 4364 **Mean age (years)** Overall: 57 **Sex, % female** Overall: 78 **Race, % white** Overall: 90 **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** Overall: 11 yrs (9) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference** NR	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • All results adjusted for age, gender, disease activity/severity, rheumatoid arthritic characteristics (e.g. RF+), and traditional cardiovascular risk factors (e.g. hypertension). • CV All/MI/Stroke: MTX 0.85(0.81-0.89)/0.82 (0.74-0.91)/0.89 (0.82-0.98), Glucocorticoids: 0.95 (0.92-0.98)/ 0.96(0.91-1.0)/0.98(0.93-1.03), SSZ 0.92 (0.87-0.98)/ 0.82 (0.69-0.98)/ 0.90 (0.79-1.03) • LEF 0.59 (0.43-0.79)/0.52(0.26-1.06)/0.91 (0.65-1.28)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• TNF-alpha 0.64 (0.49-0.83)/0.42 (0.21-0.81)/ 0.64 (0.39-105)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Nishimoto et al, 2009, SATORI[137] **Country and setting** 25 sites in Japan, setting NR **Source of funding** Chugai Pharmaceutical **Research objective** Investigate efficacy and safety of tocilizumab monotherapy in pts with inadequate response to MTX **Study design** Controlled Trials **Overall N** 127 **Duration of study** 24 wks **Quality rating** Fair	**Inclusion Criteria** • Ages 20 to 75 years old • Active RA as define byACR • RA > 6 mos • MTX 8 mg/week for at least 8 weeks prior to enrollment • At least 6 tender joints (of 49 evaluated) • At least 6 swollen joints (of 46 evaluated) • ESR of at least 30 mm/h or CRP of at least 10 mg/l at enrollment • Inadequate response to MTX defined aspresence of active disease • White blood cell counts at least 3.5 x 109/l • Lymphocyte counts at least 0.5 x 109/l • Platelet count of at least lower limit of normal as defined by respective local laboratory used • Sexually active	**Interventions, dose** D1: MTX: 8 mg/wk (control) Placebo toculizumab placebo D2: Tocilizumab: 8 mg/kg every 4 wks Placebo MTX placebo **Number in group** D1: 66 D2: 61 Overall: 127 **Mean age, years (SD)** D1: 50.8 ± 12.2 D2: 52.6 ± 10.6 **Sex, % female** D1: 75.0 D2: 90.2 Overall: 81.1 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 8.7 yrs ± 7.1 D2: 8.5 ± 8.4 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 14.2 ± 8.6 D2: 13.8 ±7.5 **Swollen Joint Count, mean** D1: 12.7 ± 7.5 D2: 12.4 ± 5.9 **Corticosteroid use, %** NR **# failed DMARD use, (mean/range)** D1: 3.6 (1-8) D2: 3.3 (1-8) **MTX naïve, %** D1: 0 D2: 0 Overall: 0 **Baseline DAS28 score** D1: 6.2 ± 0.9 D2: 6.1 ± 0.9 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1:	**ACR** ACR 20 (% at week 24): D1: 25 D2: 80.3 *P* = 0.001 ACR 50 (% at last observation): D1: 10.9 D2: 49.2 ACR 70 (% at last observation): D1: 6.3 D2: 29.5 **HAQ (%)** Decrease of at least 0.22 units in HAQ at last OBS D1: 34 D2: 67 *P* = 0.001 **DAS28 at last OBS (%)** Good D1: 3.2 D2: 65.5 Good or Moderate D1: 39.7 D2: 96.6 *P* = 0.001 **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others** Remission at last OBS	**Attrition/withdrawal** Overall, n (%): D1: 33 (50) D2: 7 (11) Overall: 40 (31.5) Withdrawals due to adverse events, n (%): D1: 3 (4.6) D2: 2 (3.28) Overall: 5 (3.94) Withdrawals due to lack of efficacy, n (%): D1: 20 (30.3) D2: 1 (1.64) Overall: 21 (16.6) Note: In control (MTX) group, 2 patients withdrew before treatment but after randomization, these are included in attrition count **Overall adverse events reported, n (%):** D1: 104 AE in 46/64 patients (71.9) D2: 211 AE in 56/61 patients (91.8) Overall: 315 AE in 102/125 patients (81.6) **Serious adverse events** NR Hepatotoxicity/elevated liver enzymes, n: D1: 0 D2: 0 Overall: 0 **Malignancies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	premenopausal women were required to have a negative urine pregnancy test at entry to study and to use effective contraception during study period. **Exclusion Criteria** • Treatment with anti-TNF agents or LEF (within 12 weeks prior tofirst dose) • Plasma exchange therapy or surgical treatments (within 4 weeks prior to first dose) • DMARDs other than MTX or immuno-suppressants (within 2 weeks prior to first dose) • Functional class IV using Steinbrocker's criteria • Aspartate transaminase (AST), Alanine		• Functional class I/II/III/IV: 7:50:7:0 • RA stage I/II/III/IV: 3:18:17:26 D2: • Functional class I/II/III/IV: 2:49:10:0 • RA stage I/II/III/IV: 1:20:22:18	(defined as DAS28: 2.6): • MTX arm: 1.6 • TOC arm: 43.1% • *P* = 0.001	**Respiratory events** Tuberculosis: NR Pneumonia, n (%): D1: 1 (1.56) D2: 1 (1.64) Overall: 2 (1.6) Upper respiratory infection, n (%): D1: "upper respiratory tract Inflammation" 4 (6.3) D2: Inflammation 3 (4.9) Overall: 7 (5.6%) **Other infections** Stomatitis, n (%): D1: 0 D2: 7 (11.5) Overall: 7 (5.6) **GI** NR Diarrhea (%) D1: 1 (1.6) D2: 4 (6.6) Overall: 5 (4) **Other** Fractures, n: D1: 2 (3.13%) (spinal compression fracture and femoral neck fracture) D2: NR Overall: 2 (1.6%) Infusion/injection site reactions, n (%): D1: NR D2: 7 (8 events 7 patients) (11.5) Overall: 7 (5.6) Skin rash, n (%):

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	transaminase (ALT) and serum creatinine at least 1.5-fold upper limit of normal, were HBs antigen and/ or HCV antibody positive, had pulmonary fibrosis or active pulmonary disease • History of serious adverse drug reaction to MTX, concomitant pleural effusion, ascites, varicella infection • Excessive users of alcohol on a regular basis. • Patients were also excluded if they had significant cardiac, blood, respiratory system, neurologic, endocrine, renal, hepatic, or gastrointestinal disease, or had an active infection				D1: 2 (3.1) D2: 4 (6.6) Overall: 6 (4.8) Headache, n (%): D1: 2 (3.1) D2: 4 (6.6) Overall: 6 (4.8) Nasopharyngitis, n (%): D1: 7 (10.9) D2: 11 (18.0) Overall: 18 (14.4) Serious AE (pneumonia, spinal compression fracture, femoral neck fracture), n (%): D1: 3/64 (4.7) D2: 4/61 (6.6) Hyperlipidemia, n (%): D1: 1 (1.6) D2: 4 (6.6) Overall: 5 (4) Lab test abnormalities, n (%): D1: 15 (23) D2: 34 (56) Overall: 49 (39.2)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	requiring medication within 4 weeks before first dose or medical history of a serious allergic reaction. • Sexually active premenopausal women were required to have negative urine pregnancy test at entry to study and to use effective contraception during study period. • Oral corticosteroids (PNL, less than or equal to 10 mg/day) were allowed ifdosage had not been changed within 2 weeks.				

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Nuki et al. 2002[138] **Country, Setting:** Multinational multicenter **Funding:** Amgen **Research Objective:** Long-term efficacy of anakinra, in pts with RA **Study Design:** RCT plus extension **Overall N:** 472 (309 enrolled in 54 wk extension) **Study Duration:** 76 wks	**Inclusion Criteria:** • ACR criteria • Disease duration of ≥ 12 mos < 8.5 yrs **Exclusion Criteria:** NR is this article	**Interventions, dose:** D1: Anakinra D2: Placebo **N:** D1: 351 D2: 121 **Mean age, yrs:** D1: 53.4 D2: 52.2 **Sex, % female:** D1: 76.6 **D2: 70.2** **Race, % white:** NR	**Mean disease duration, yrs:** D1: 4.1 D2: 3.7 **TJC, mean:** D1: 34.8 D2: 32.8 **SJC, mean:** D1: 26.3 D2: 25.6 **DMARD use, %:** D1: 73.5 D2: 80.0 **Corticosteroid use, %** D1: 43.6 D2: 39.7 **MTX naïve, %:** NR **DMARD Txt resistant, %:** NR **Patients with Early RA (≤ 3 yrs):** NR	See AEs	Number of occurrences per subject-yr of exposure n for safety: D1: 427 D2: 121 **ISRs:** D1: 2.00 **D2: 0.82** Frequency of injection site reactions (ISRs) was 0.82 per patient-yr of exposure in placebo group (first 24 wks) and 1.01, 2.43, and 3.73 for 30-mg, 75-mg, and 150-mg doses over 72 wks	**Overall Attrition Rate, %:** **At 24 wks 27%** At 76 wks 32% of those that continued into extension **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: O'Dell et al., 1996[139] **Country, Setting:** US, multicenter (Rheumatology clinics) **Funding:** Lederle, Sanofi, Winthrop, and Pharmacia provided study drugs **Research Objective:** To determine whether DMARDs were effective as combination therapy for RA and whether combinations studied had better efficacy than MTX alone **Study Design:** RCT **Overall N** 102 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age 19-70 • Diagnosed w/ ACR criteria > 6 mos • Poor response to at least 1 DMARD • At least 3 of: ESR ≥ 28 mm/hr, morning stiffness ≥ 45 mins, ≥ 8 tender joints, ≥ 3 swollen joints; stable therapy w/ Css ≤ 10 mg/day; • NSAIDs allowed **Exclusion Criteria:** • Pregnant or lactating • Prior combo treatment with any 2: gold, HCQ, penicil-lamine, SSZ, MTX • Impaired renal or hepatic system • Stage IV disease • Allergy to study drugs • Pulmonary or CVD • Visual difficulties	**Interventions:** D1: MTX (7.5 to 17.5 mg/week) D2: SSZ (1 g/day) + HCQ (400 mg/day) D3: MTX + SSZ+HCQ **N** D1: 36 D2: 35 D3: 31 **Mean age, yrs:** D1: 50 D2: 49 D3: 50 **Sex, % female:** D1: 69 D2: 74 D3: 65 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 10 D2: 6 D3: 10 **TJC, mean:** D1: 31 D2: 32 D3: 29 **SJC, mean:** D1: 31 D2: 31 D3: 27 **DMARD use, %:** All groups: 100 **Current Corticosteroid use, %)** D1: 53% D2: 46% D3: 52% **MTX naive, %:** D1: 92 D2: 89 D3: 87 **Treatment resistant, %:** All 100 **Pts with Early RA (≤3 yrs):** All groups: 0 **Baseline DAS, mean:** NR **Duration of morning**	Outcome improved by at least 50%, as determined by whether 3 following requirements had been fulfilled (modified Paulus composite criteria): morning stiffness of less than 30 minutes' duration, decreased by 50%; joint tenderness decreased by 50%; joint swelling decreased by 50%; ESR < 30 mm per hour in women and < 20 mm per hour in men Comparison between MTX + SSZ+HCQ and each of other groups with respect to good responses was statistically significant (P = 0.003 by log-rank test) **At 2 years** Maintenance of at least 50% improvement at 9 mos to end of 2-year treatment period (total n=50): D1: 33%, 12/36 pts D2: 40%, 14/35 pts D3: 77%, 24/31 pts (D3 vs D2, P = 0.003 and D3 vs. D1, P < 0.001 for respective comparisons between D3 (3-drug group) and D2; D3 vs D1)	Similar withdrawal rates due to Adverse Events across groups Treatment with all 3 drugs did not produce more toxic effects than did MTX alone D1: discontinued treatment because of toxic effects: • 2 w/ pneumonia; • 1 each had stomatitis, diarrhea, nausea, and vertigo; • 1 pt had sepsis and died. D2: 3 discontinued due to pneumonia, diarrhea, and Crohn's disease; D3: 3 in 3-drug group discontinued due to nausea, cervical cancer, and weight gain. No pt had serum aspartate aminotransferase values more than twice upper limit of normal D3: higher serum creatinine values than D2 or D1 at nine mos (P = 0.03)	**Overall Attrition Rate, %:** 51% **ITT Analysis:** Yes **Quality Rating:** Fair for KQ1 Good for KQ3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
	Retinal disease • Macular degeneration • Active peptic ulcer disease		**stiffness (minutes):** D1: 190 D2: 156 D3: 135 **RF:** D1: 89% D2: 85% D3: 84%			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al., 2002[140] **Country, Setting:** US, multicenter (7) **Funding:** Pharmacia & Upjohn, Mylan,Sanofi-Winthrop- meds. Albert G. and Bernice F. Hansen Foundation **Research Objective:** Efficacy of combination therapy with MTX, HCQ, and SSZ to MTX + HCQ and to MTX + SSZ in txt of RA **Study Design:** RCT **Overall N:** 171 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 19-80 yrs • Diagnosed with RA according to ACR criteria • Duration of condition: > 6 mos • Active disease with at least 3 of 4 following features: ESR > 28 mm/hour, duration of morning stiffness ≥ 45 minutes, ≥ 8 tender joints, and ≥ 3 swollen joints **Exclusion Criteria:** • Previous combination therapy with any medications studied • Significant liver or renal disease Stage IV disease Allergy to any study drugs women of childbearing age not using adequate contraception • Significant hematologic, pulmonary, or CVD	**Interventions, dose:** D1: MTX and HCQ D2: MTX and SSZ D3: MTX, HCQ, and SSZ: All pts MTX: accelerated from 7.5 mg/wk to 17.5 mg/wk in all pts not in remission SSZ: escalated from 500 mg twice daily to 1gram twice daily in pts not in remission HCQ: 200 mg twice daily **N:** D1: 58 D2: 55 D3: 58 Overall: 171 **Mean age, yrs:** D1: 50.9 D2: 52.5 D3: 48.9 Overall: 50.9 **Sex, % female:** D1: 78 D2: 84 D3: 76 Overall: 79 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 7.9 +/- 10 D2: 5.8 +/- 5.9 D3: 6.9 +/- 8.4 **TJC (mean +/- SD):** D1: 15.7 +/- 8.2 D2: 15.6 +/- 7.4 D3: 19.7 +/- 9.2 **SJC, mean:** D1: 21.1 +/- 8.3 D2: 19.1 +/- 7.9 D3: 24.0 +/- 8.8 **DMARD use, %:** NR **Corticosteroid use, %** D1: 71 D2: 56 D3: 50 **MTX naive, %:** D1: 43.1 D2: 54.5 D3: 41.4 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **% RF positive:** D1: 88 D2: 88 D3: 89	**At 2 years** **ACR 20, %:** D1: 60, 35/58 pts D2: 49 27/55 pts D3: 78, 45/58 pts (D3 vs D2; *P* = 0.002) (D3 vs. D1; (*P* = 0.05) **ACR 50, %:** D1: 40 D2: 29 D3: 55 (D3 vs D2; *P* = 0.005) (D3 vs. D1, *P* = 0.10) **ACR 70, %:** D1: 26 D2: 18 D3: 16 (*P* = NS) Changes in values for ACR core set, improvement in triple therapy group was greater than either of other 2 txt groups. TJC differences were statistically significant, D3 vs D1 (*P* ≤ 0.005) **Reduced morning stiffness, minutes:** D1: -59.2 +/- 103.3 D2: -53.2 +/- 89.5 D3: -109.3 +/- 86.4 minutes (D3 vs. D1; *P* = 0.01) (D3 vs. D2; *P* = 0.006)	**Overall:** D1: 8.6 D2: 9.1 D3: 6.9 **Infections:** D2: 1.8 **Serious Infections:** D1: 1.7 **Cardiovascular Events:** D1: 1.7 (1 MI) **Headache:** D2: 1.8 **Hepatotoxicity:** D3: 1.7 **Malignancies:** D3: 1.7 (1 non-Hodgkins lymphoma)	**Overall Attrition Rate, %:** 14.6% (25/171 subjects) **ITT Analysis:** Yes **Quality Rating:** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			ESR: D1: 28.5 +/- 20.3 D2: 34.1 +/- 26.5 D3: 30.1 +/- 21.0			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al., 2006[141] **Country, Setting:** US, multicenter **Funding:** NR **Research Objective:** Determine safety and efficacy of ETA in combination with SSZ, hydroxychloro-quine, IM Gold over 48 wks **Study Design:** Observational **Overall N:** 119 **Study Duration:** 48 wks	**Inclusion Criteria:** • Age: 19-75 • Diagnosed according to ACR criteria; stable SSZ or HCQ doses; 10mg or less/d steroids > 4wks • Active disease with 6 or more swollen and tender joints **Exclusion Criteria:** • Pregnant or lactating • ETA • Biologics in past 4 wks • Impaired renal or hepatic system • Antibody to TNFalpha • Anti CD4 antibody • Diphterial interleukin 2 fusion protein • Active or chronic infections	**Interventions, dose:** D1: ETA (25mg sc twice weekly) + SSZ D2: ETA (25mg sc twice weekly) + HCQ D3: (Gold + ETA) **N:** D1: 50 D2: 50 D3: 19 **Mean age, yrs:** D1: 47 D2: 49.7 **Sex, % female:** D1: 78 D2: 76 **Race, % white:** D1: 88 D2: 92	**Mean disease duration, yrs:** D1: 8.1 D2: 8.7 **TJC, mean:** D1: 16.5 D2: 16.4 **SJC, mean:** D1: 17.7 D2: 17.1 **DMARD use, %:** NR **Corticosteroid use, %:** D1: 58 D2: 68 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR HAQ: D1: 1.32 D2: 1.33	Pts in each ETA combination showed significant improvement at 24 and 48 wks • No significant differences for ACR20/50 BETWEEN combination groups at 24 or 48 wks (NR). At 24 and 48 wks, ETA/SSZ combo showed highest ACR70 response (NR) • At 24 wks change in HAQ SSZ -0.56+/-0.77 HCQ -0.71+/-0.65 *P* = NR	NR	**Overall Attrition Rate, %:** 30% **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Pallavicini et al., 2010[143] **Country and setting** Italy, 4 tertiary centers and 2 general population cancer registries **Source of funding** NR **Research objective** To compare cancer risk in a RA cohort population treated with TNF antagonists, and identify the characteristics of the patients at higher risk **Study design** Observational **Overall N** 1064 **Duration of study** average follow up 23.22 mos	**Inclusion Criteria** • RA patients treated with anti-TNF agents **Exclusion Criteria** • NA	**Comparisons (dosage and frequency)** D1: • ETN: dosage and frequency NR • INF: dosage and frequency NR • ADA: dosage and frequency NR D2: General population **Number in group** D1: 1064 **Mean age (years)** D1: 55.84 **Sex, % female** D1: 83 **Race, % white** D1: NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1:<5 yrs=324; 5-10 yrs=338; >10 yrs=402 **TJC, mean** D1: 11.35 **SJC, mean** D1: 10.06 **Corticosteroid use, %** D1: NR **DMARD use, %:** D1: 100 **MTX naïve, %:** D1: NR **Treatment resistant, %:** D1: 100 **Patients with early RA, three years or less, %:** D1: NR **Baseline DAS score** D1: 5.90 **Required treatment for latent TB** D1: NR **Other population characteristics, %, (CI/SD/P value):** NR	**ACR mean difference/ absolute difference (CI/SD/P Value):** **NRHAQ, mean difference/ absolute difference (CI/SD/P Value):** **NR** **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** NR	**Overall** NR **Serious adverse events:** NR **Malignancies:** Risk of cancer: ETN: reference group ADA: HR 1.66 (95% CI 0.50-5.52); *P*=0.407 INF: HR 0.59 (95% CI 0.17-2.09); *P*=0.412 **Respiratory events:** NR **Other infections:** NR **GI:** NR **Other:** NR	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Pan, S.M. et al.; 2009[144] **Country and setting** Switzerland; doctors offices, non-academic hospitals, academic centers **Source of funding** Swiss Clinical Quality Management was sponsored by Abbott, Essex, Roche, Bristol-Myers Squibb, Mepha, Novartis, and Sanofi-Aventis **Research objective** Compare tx retention rates between ETN, IFX, and ADA and compare causes of discontinuation **Study design** Population Based Cohort Study **Overall N** 2364 **Duration of study** January 1997 to December 2006 **Quality rating** Fair	**Inclusion Criteria** • Existence in Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry treated with an anti-TNF agent between January 1997 and December 2006. **Exclusion Criteria** • NR	**Interventions, Dose** D1: IFX: dosage and frequency NR D2: ETN: dosage and frequency NR D3: ADA: dosage and frequency NR **Number in group** D1: 595 D2: 887 D3: 882 Overall: 2364 **Mean age (years)** D1: 53, SD 13 D2: 54, SD 14 D3: 55, SD 13 *P* = 0.16 **Sex, % female** D1: 76 D2: 78 D3: 79 *P* = 0.42 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 10 yrs, SD 9 D2: 10 yrs, SD 9 D3: 10 yrs, SD 9 *P* = 0.2 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: 52 D2: 52 D3: 49 **DMARD use, %** D1: MTX: 74; LEF: 17; Other: 17; No DMARD: 11 D2: MTX: 55; LEF: 17; Other: 19; No DMARD: 29 D3: MTX: 61; LEF: 18; Other: 20; No DMARD: 22 Overall: MTX: *P* = 0.001; LEF: *P* = 0.765; Other: *P* = 0.246; No DMARD: *P* = 0.001 **MTX naïve, %** NR **Baseline DAS score, mean**	**ACR** NR **HAQ,** D1: Baseline: 1.32, SD 0.72 D2: Baseline: 1.25, SD 0.76 D3: Baseline: 1.17, SD 0.71 Baseline: *P* = 0.117 **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** Causes of treatment discontinuation (Hazard models with D1 as reference): All adverse events: D2 0.79 (0.55-1.13), D3 0.67 (0.45-0.97), *P* = 0.02; Acute systemic reaction: : D2 0.40 (0.21-0.78), D3 0.56 (0.29-1.09), *P* = 0.018; Dermatologic disease: D2 0.85 (0.43-1.70), D3 1.04 (0.54-2.02), *P* = 0.81; Infection: D2 1.14 (0.68-1.92), D3 0.56 (0.30-1.04), *P* = 0.18; Malignancy: D2 0.54 (0.16-1.85), D3 0.20 (0.37-1.06), *P* = 0.12; Miscellaneous: D2 0.81	**Overall** Overall attrition/withdrawal, n: D1: 209 D2: 237 D3: 213 Overall: 659 Withdrawals due to adverse events, n: D1: 154 D2: 172 D3: 149 Overall: 318; *P* = 0.093 Withdrawals due to lack of efficacy, n: D1: 90 D2: 125 D3: 112 Overall: 327; *P* = 0.17 Adherent/compliant, n: D1: 386 D2: 650 D3: 669 Overall: 1705 Overall adverse events reported, n: D1: 108 D2: 118 D3: 92 Overall: 318 **Serious adverse events** Death, n: D1: 2 D2: 0 D3: 2 Overall: 4; *P* = 0.33 **Malignancies**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			(SD) D1: 4.27, SD 1.52 D2: 4.23, SD 1.53 D3: 4.14, SD 1.42 *P* = 0.066 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: Glucocorticoids: 52%; Failure of previous anti-TNF agent: 23%; RADAI: 4.29, SD 2.14 D2: Glucocorticoids: 52%;; Failure of previous anti-TNF agent: 19%; RADAI: 4.31, SD 2.24 D3: Glucocorticoids: 49%; Failure of previous anti-TNF agent: 27%; RADAI: 4.16, SD 2.15 Overall: Glucocorticoids: *P* = 0.409; Failure of previous anti-TNF agent: *P* = 0.001; RADAI: *P* = 0.37	(0.55-1.19), D3 0.85 (0.58-1.25), *P* = 0.55; All nontoxic causes: D2 0.90 (0.64-1.26), D3 0.82 (0.58-1.18), *P* = 0.38; Ineffectiveness: D2 0.95 (0.71-1.26), D3 0.82 (0.61-1.11), *P* = 0.42; Remission: D2 0.85 (0.22-3.3), D3 1.10 (0.36-3.44), *P* = 0.91; Desire for Pregnancy: D2 0.75 (0.10-5.55), D3 1.89 (0.24-14.9), *P* = 0.95; Preference: D2 0.68 (0.37-1.45), D3 0.85 (0.41-1.77), *P* = 0.68	Malignancy), n: D1: 8 D2: 5 D3: 2 Overall: 15; *P* = 0.12 **Respiratory events** NR **Other infections** NR **GI** NR **Other** Infusion/injection site reactions, n: D1: 50 D2: 24 D3: 31 Overall: 105; *P* = 0.001 Infection, n: D1: 26 D2: 41 D3: 22 Overall: 89; *P* = 0.088 Dermatologic disease, n: D1: 16 D2: 20 D3: 29 Overall: 65; *P* = 0.09 General (inc fatigue, headache, weight changes), n: D1: 14 D2: 13 D3: 9 Overall: 36; *P* = 0.46 Neuropsychiatric:, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 15 D2: 13 D3: 21 Overall: 49; *P* = 0.22 Any other AEs: Opthamologic: D1: 3 D2: 7 D3: 2 Overall: 12, *P* = 0.29 Ear nose throat: D1: 2 D2: 3 D3: 0 Overall: 5, *P* = 0.29 Cardiovacular: D1: 7 D2: 14 D3: 6 Overall: 27, *P* = 0.23 Pulmonary: D1: 3 D2: 10 D3: 5 Overall: 18, *P* = 0.22 Gastroenterological: D1: 11 D2: 17 D3: 16 Overall: 44, *P* = 0.67 Renal disease: D1: 4 D2: 7 D3: 0 Overall: 11, *P* = 0.03 Hematologic: D1: 2 D2: 4 D3: 2 Overall: 8, *P* = 0.75 Osteoarticular:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 6 D2: 4 D3: 4 Overall: 14, *P* = 0.63

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Russell et al., 2006 and 2007, AIM[145]; Kremer et al., 2006[116], AIM **Country and setting** NR **Source of funding** Bristol-Myers Squibb **Research objective** Examine impact of ABA tx on HRQOL in patients with RA **Study design** Controlled Trials **Overall N** 0 **Duration of study** 12 mos **Quality rating** Fair	**Inclusion Criteria** • Diagnosis of RA according to ARA and classification within functional status I, II, or III according to revised criteria of ACR • RA disease duration of > 1 year from initial diagnosis • Treatment with MTX for at least 3 months, and at a stable dose for 28 days before treatment • Washout of all DMARDs other than MTX at least 28 days before treatment • Active disease • Characterized by > 10 swollen joints, > 12 tender joints, and CRP > 10 mg/l. **Exclusion Criteria** NR	**Interventions, Dose** D1: • MTX: 15 mg or more per week • Abatacept: fixed dose of 10 mg/kg at days 1, 15, 29, and every 28 days thereafter for up to 1 year D2: • MTX: 15 mg or more per week • Placebo: dose NR **Number in group** D1: 433 D2: 219 Overall: 652 **Mean age (years)** D1: 51.5 D2: 50.4 Overall: 51.5 **Sex, % female** D1: 77.8 D2: 81.7 Overall: 79.2 **Race, % white** D1: 87.5 D2: 88.1 Overall: 87.7 **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 8.5 (7.3) D2: 8.9 (7.1) Overall: 8.6 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** D1: 100 D2: 100 Overall: 100 **MTX naïve, %** D1: 0 D2: 0 Overall: 0 **Baseline DAS score, mean (SD)** D1: 6.4 D2: 6.4 Overall: NR **Required treatment for latent TB** NR **Other population**	**ACR mean difference/ absolute difference (%)** ACR 20: At 6 months: D1: 67.9 (N: 424) D2: 39.7 (N: 214) *P* = 0.001, difference 28 percentage points, 95% CI: 19.8 - 36.7 percentage points At 1 year: D1: 73.1 (N: 424) D2: 39.7 (N: 214) Overall: difference: 33.4 percentage points, 95% CI: 25.1 - 41.7 ACR 50: At 6 months: D1: 39.9 (N: 424) D2: 16.8 (N: 214) Overall: Difference at 6 mos: 23 percentage points, 95% CI: 15 - 31.1 percentage points *(P* = 0.001) At 1 year: D1: 48.3 (N: 424) D2: 18.2 (N: 214) Overall:Difference at 1 year: 30.1 percentage points, 95% CI: 21.8, 38.5 percentage points *(P* = 0.001) ACR 70: At 6 months: D1: 19.8 (N: 424) D2: 6.5 (N: 214) Overall: Difference at 6	**Attrition/withdrawal** Overall, n: D1: 48 D2: 57 Overall: 105 Withdrawals due to adverse events, n: D1: 18 D2: 4 Overall: 22 Withdrawals due to lack of efficacy, n: D1: 13 D2: 40 Overall: 53 Adherent/compliant, n: D1: 385 D2: 162 Overall: 547 **Overall adverse events reported, n:** D1: 378 D2: 184 Overall: NR **Serious adverse events** Death, n: D1: 1 D2: 1 Overall: NR Cardiac disorders, n: D1: 4 D2: 2 Hypertension: D1: 24 D2: 3 Overall: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			characteristics, %, (CI/SD/P value) MTX dose (mg/week): D1: 16.1 D2: 15.7 Pain (VAS 100 mm) : D1: 63.3 D2: 65.9 Patient global assessment of disease activity (VAS 100 mm): D1: 62.7 D2: 62.8 DAS28 (CRP): D1: 6.4 D2: 6.4 SF-36 Physical functioning (PF): D1: 28.7 D2: 28.3 SF-36 Mental health (MH): D1: 39.4 D2: 39.7 SF-36 Physical component summary (PCS): D1: 30.6 D2: 30.7 SF-36 Mental component summary (MCS): D1: 41.8 D2: 40.8 HAQ Disability Index (0-3): D1: 1.7 D2: 1.7 Fatigue (VAS 100 mm): D1: 63.2	mos: 13.3 percentage points, 95% CI: 7.0 - 19.5 percentage points *(P* = 0.001) At 1 year: D1: 28.8 (N: 424) D2: 6.1 (N: 214) Overall: Difference at 1 year: 22.7 percentage points, 95% CI: 15.6 - 29.8 percentage points *(P* = 0.001) **HAQ-DI (%)** Significantly Improved D1: 63.70 D2: 39.30 Modified worst-case sensitivity analysis D1: 64 D2: 42 Worst-case analysis D1: 64 D2: 64 Overall: [from #3475] *P* = 0.001, difference 24.4 (CI 15.9-32.9) **DAS** NR **SF-36** D1: NR - reported in figure only D2: NR - reported in figure only Overall: • PCS, abatacept vs. placebo, day 29: *(P* = 0.01) • MCS, abatacept vs.	**Malignancies** NR Neoplasms, n: D1: 4 D2: 2 Overall: NR **Respiratory events** NR **Other infections, n** Nasopharyngitis: D1: 66 D2: 25 Pharyngitis: D1: 26 D2: 10 Sinusitis: D1: 18 D2: 15 Bronchitis: D1: 18 D2: 12 Serious Infections (not prespecified): D1: 17 D2: 5 Bronchopneumonia: D1: 2 D2: 5 Cellulitis: D1: 1 D2: 0 Sepsis: D1: 1 D2: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D2: 66.2	placebo, 6 months: (*P* = 0.01) • Fatigue, abatacept vs. placebo, day 29: (*P* = 0.01) • Physical function, abatacept vs. placebo, day 57: (*P* = 0.05) **Radiographic measures** D1: (Note: for radiographic data, N: 391 for abatacept group) mean change from baseline for total score: 1.21 D2: (Note: for radiographic data, N: 195 for placebo group) mean change from baseline • for total score: 2.32 Overall: NR **Quality of life scales** NR **Others, (please name)** • Achieved normative PCS benchmark, 6 months: abatacept: 47.1%, Placebo: 30.7, overall, Number Needed to Treat: 6 • Achieved normative MCS benchmark, 6 months: abatacept: 60.4%, Placebo: 50.5%, overall, Number Needed to Treat: 10 • Percentage of patients who exhibited improved HRQOL scores by at least 0.5 SD over 12 month	Abscess: D1: 1 D2: 0 Bacterial arthritis: D1: 1 D2: 0 Bronchopulmonary aspergillosis: D1: 1 D2: 0 Acute pyelonephritis: D1: 1 D2: 0 Limb abscess: D1: 0 D2: 1 Overall: NR **GI** Nausea or vomiting, n: D1: 52 D2: 24 Overall: NR Abdominal pain, n: D1: 19 D2: 13 Overall: NR Diarrhea, n: D1: 47 D2: 21 Dyspepsia, n: D1: 27 D2: 10 **Other** Acute infusional adverse events, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				period of study: PCS (abatacept: 67.2%, Placebo: 51.1%, *P* = 0.001), HAQ (abatacept: 72.4%, Placebo: 55.2%, *P* = 0.001), Fatigue (abatacept: 64.9%, Placebo: 47.4%, *P* = 0.001)	D1:38 D2: 9 Per-Infusional adverse event, n: D1: 106 D2: 37 Overall: NR Skin rash, n: NR Demyelenation or multiple sclerosis, n: NR Progressive multifocal leukoencephalopathy, n: D1: NR D2: NR Overall: NR Headache, n: D1: 76 D2: 26 Overall: NR Dizziness, n: D1: 40 D2: 16 Overall: NR Musculoskeletal and connective tissue disorders, n: D1: 20 D2: 10 Cough, n: D1: 29 D2: 13 Influenza, n: D1: 31 D2: 12

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Back pain, n: D1: 40 D2: 12

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Saag et al., 1994[146] **Country, Setting:** US, multicenter **Funding:** General Clinical Research Program, NIH and Halifax Clinical Research Center **Research Objective:** To determine whether low dose steroids in txt of RA independently cause an increased incidence of steroid-associated SAEs **Study Design:** Observational **Overall N:** 224 **Study Duration:** At least one yr (4.9 +/-3.9 yrs of txt).	**Inclusion Criteria:** • Age > 16 • Diagnosed according to ACR criteria • On low-dose steroids ≥ 1 yr; matched for age, sex, race, and duration of disease prior to study inception; allowed occasional intraarticular or parenteral steroids or oral steroid pulses to certain defined limits. • SAARDs were allowed **Exclusion Criteria:** • CXT, chlorambucil, nitrogen mustard, or experimental antirheumatic drugs • Impaired renal or hepatic system Concurrent or alternative rheumatic disorder	**Interventions, dose:** D1: Treated (with low dose long-term corticosteroids) D2: Untreated (with low dose long-term corticosteroids) Prednisone: corticosteroids, less than or equal to 15mg/d of PRE (or equivalent dose of an alternative steroid) **N:** D1: 112 D2: 112 **Mean age, yrs:** D1: 51.8 D2: 51.7 **Sex, % female:** D1: 75 D2: 75 **Race, % white:** D1: 98.2 D2: 98.2	**Mean disease duration, yrs:** D1: 4.9 +/-6.3 D2: 4.9 +/-6.7 **TJC, mean:** NR **SJC, mean:** NR **Average no of SAARDs:** D1: 0.47 +/-0.82 D2: 0.13 +/-0.37 **Corticosteroid use, %:** D1: 100 D2: NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF:** D1: 77.7 D2: 58.0 **ESR:** D1: 50 +/-29.7 D2: 36.4 +/-30.5 **Extra-articular disease**	n for Treated and Untreated groups respectively: Fracture 21 and 8; GI bleed or ulcer 11 and 4; cataracts 17 and 5; diabetic complications 8 and 3; herpes zoster 8 and 1; glaucoma 1 and 1; death 2 and 0. • OR of 32.3 (95% CI,4.6, 220) (*P* = 0.0004) for pts treated with > 10 up to 15mg/d PRE equivalent; OR of 4.5 (95% CI,2.1, 9.6) (*P* = 0.0001) for pts treated with 5-10mg/d; Prednisone dose <5mg/d did not show a significant increase in risk of having an AE compared to the untreated group; • *Although PRE average dose and cumulative dose had small but significant emsitmated relative risks (OR 1.21, 95%CI,1.0-1.5 for both), PRE use (yes/no) was most highly linked to infection (OR 8.0, 95% CI,1.0-64.0, *P* < 0.05) • Fracture (OR 3.9, 95% CI,0.8-18.1, *P* < 0.09) • First GI event: OR 3.3 (95% CI,0.9-12.1, *P* < 0.07)	**Overall:** D1: n:92 AEs D2: n:31 **Serious Infections:** D1: n:14 D2: n:4 **Cardiovascular Events:** D1: n:10 (4 myocardial infarctions, 6 strokes) D2: n:5 (4 myocardial infarction, 1 stroke)	**Overall Attrition Rate, %:** NA **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	• Bedridden status • Referral 2nd to a steroid complication		D1: 16.1% D2: 6.3%			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Salliot et al., 2006[147] **Country, Setting:** France, tertiary care **Funding:** NR **Research Objective:** To evaluate rate of infections in rheumatic pts treated with TNF-alpha blockers in daily practice and to determine potential risk factors of infections **Study Design:** Case series **Overall N:** 709 w/ follow-up at least once and 623 w/ with a control period **Study Duration:** NR	**Inclusion Criteria:** • Pts receiving a TNF-alpha blocker and with a follow-up • Those with control period before txt initiation **Exclusion Criteria:** NA	**Interventions, dose:** D1: Follow up D2: Follow up and control **N:** D1: 709 D2: 623 **Mean age, yrs:** D1: 45.9 D2: 46.5 **Sex, % female:** D1: 60.4 D2: 60.4 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 11.8 D2: 12.1 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** D1: 58.5 D2: 58.3 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** D1: 43.7 D2: 43.6	34.5% experienced infection during course of txt; Incidence rate: 48.2 per 100 PY • 6.2 percent experienced a serious infection; incidence rate: 10.4 per 100 PY • Infections by txt: • Any: INF 69.8 ETA 44.1 Adalimumab 37.3 per 100 PY • Serious: INF 10.2 ETA 12.3 Adalimumab 5.3 per 100 PY	**Infections:** D1: 50.5 D2: 34.2 D3: 15.3 **URTI:** D1: 13.4 D2: 9.4 D3: 9.9 **UTI:** D1: 5.1 D2: 1.1 D3: 1.6	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schaible et al., 2000[148] **Country, Setting:** US; safety database of efficacy trials **Funding:** Centocor **Research Objective:** Long term safety of infliximab **Study Design:** Observational **Overall N:** 963 **Study Duration:** Up to 3 yrs	**Inclusion Criteria:** 12 clinical trials **Exclusion Criteria:** NR	**Interventions:** Infliximab N:963 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Acute infusion reactions (headache, fever, chills, urticaria, chest pain: infliximab 17% versus placebo 7%; *P* = NR • 0.5% of infliximab pts had severe infusion reactions • Less than 2% discontinued treatment because of infusion reactions **Infections:** • Infliximab 26% over 27 wks of follow-up versus placebo 16% over 20 wks of follow-up) • Incidence of serious infections per patient-yr infliximab 0.064 versus placebo 0.114	See outcomes	**Overall Attrition Rate, %:** **ITT Analysis:** Not applicable **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schiff et al., 2006[149] **Country, Setting:** Mulitnational, multicenter **Funding:** Abbott Labs **Research Objective:** To assess safety of adalimumab in global clinical trials and postmarketing surveillance among pts with rheumatoid arthritis **Study Design:** Retrospective cohort study; postmarketing surveillance **Overall N:** 10,050 (12506 PY) **Study Duration:** Varied	**Inclusion Criteria:** • Pts from RCTs, open label extensions, and two phase IIIb open label trials were and post-marketing spontaneous reports of adverse events in US **Exclusion Criteria:** NA	**Interventions, dose:** NR **N:** 10,050 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**Rates per 100 PY:** • TB: 0.27 • Histoplasmosis: 0.03 • Demyelinating diseases: 0.08 • Lymphoma: 0.12 • SLE/lupus-like syndrome: 0.10 • Congestive heart failure: 0.28	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Schiff et al., 2008, ATTEST[150] **Country and setting** International, Multi-center **Source of funding** Bristol-Myers Squibb, Princeton, New Jersey, USA **Research objective** Evaluate change from baseline in DAS for ABA vs. placebo and reduction in DAS28 for IFX vs. placebo and ABA vs. IFX **Study design** Controlled Trials **Overall N** 431 **Duration of study** ABA vs. placebo and IFX vs. placebo: 197 days ABA vs. IFX: 365 days **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant • ACR criteria for RA • ≥ 18 years old • RA ≥ 1 year, inadequate response to MTX, as demonstrated by ongoing active disease (at randomization SJC >10, TJC >12, and CRP >1 mg/dl • All patients had received MTX >15 mg/week for >3 mos prior to randomization (stable for at least 28 days) and washed out all DMARDs (>28 days prior) except for MTX • Anti-TNF-therapy naive **Exclusion Criteria** • Positive screen for TB by purified protein derivative testing and chest x ray.	**Interventions, dose** D1: • MTX: dosage and frequency NR • Abatacept: 500-1000 mg, days 1, 15, 29, and every 28 days thereafter D2: • MTX: dosage and frequency NR • Placebo D3: • MTX: dosage and frequency NR • IFX: 3 mg/kg, days 1, 15, 43, 85, and every 56 days thereafter **Number in group** D1: 156 D2: 110 D3: 165 Overall: 431 **Mean age, years (SD)** D1: 49.0 (12.5) D2: 49.4 (11.5) D3: 49.1 (12.0) **Sex, % female** D1: 83.3 D2: 87.3 D3: 82.4 **Race, % white** D1: 80.8 D2: 76.4 D3: 80.6 **Race, % black** NR	**Mean disease duration, years (SD)** D1: 7.9 (8.5) D2: 8.4 (8.6) D3: 7.3 (6.2) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 31.3 (13.9) D2: 30.3 (11.7) D3: 31.7 (14.5) **Swollen Joint Count, mean** D1: 21.3 (8.6) D2: 20.1 (7.0) D3: 20.3 (8.0) **Corticosteroid use, %** D1: 75.6 D2: 70 D3: 71.5 Overall: 72.6 **DMARD use, %** D1: 100 D2: 100 Overall: 100 **MTX naïve, %** D1: 0 D2: 0 D3: 0 Overall: 0 **Baseline DAS score** D1: 6.9 D2: 6.8 D3: 6.8	**ACR** ACR 20: Day 197 D1: 66.7 D2: 41.8 D3: 59.4 Overall: ABA vs. Placebo: (*P* = 0.001), IFX vs. Placebo: (*P* = 0.006) Day 365: D1: 72.4 D2: 41.8 D3: 55.8 Overall: ABA vs. IFX: estimate of difference of 16.7 (5.5, 27.8) ACR 50: Day 197: D1: 40.4 D2: 20 D3: 37 • Overall: ABA vs. Placebo: (*P* = 0.001), IFX vs. Placebo: (*P* = 0.004) Day 365: D1: 45.5 D2: 20 D3: 36.4 Overall: Overall: ABA vs. IFX: estimate of difference (95% CI): 9.1 (-2.2, 20.5) ACR 70: Day 197 D1: 20.5 D2: 9.1 D3: 24.2 Overall: ABA vs. Placebo: (*P*	**Attrition/withdrawal** Overall, n: D1: 17 D2: 6 D3: 24 Overall: 47 Withdrawals due to adverse events, n: D1: 4 D2: 1 D3: 12 Overall: 17 Withdrawals due to lack of efficacy, n: D1: 4 D2: 2 D3: 6 Overall: 12 Adherent/compliant, n: D1: 139 D2: 104 D3: 141 Overall: 384 **Overall adverse events reported, n:** Day 197 D1: 129 D2: 92 D3: 140 Overall: 361 Day 365 D1: 139 D2: 92 D3: 154 Overall: 293 **Serious adverse events** Death, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Ethnicity, Latino NR	**Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Erythrocyte sedimentation rate, mm/h (SD): D1: 49.4 (31.2) D2: 47.0 (32.6) D3: 47.8 (30.4) Overall: NR HAQ-DI, 0-3 (SD): D1: 1.8 (0.6) D2: 1.8 (0.7) D3: 1.7 (0.7) Overall: NR Total patients on concomitant medications, n (%): D1: 156 (100) D2: 110 (100) D3: 165 (100) Overall: 431 (100) MTX Dose, mg/week (SD): D1: 16.5 (3.7) D2: 16.6 (3.7) D3: 16.3 (3.6) Overall: NR MTX Duration, months (SD): D1: 18.3 (20.0) D2: 23.7 (25.6) D3: 23.6 (26.8) Overall: NR Corticosteroids, n (%): D1: 118 (75.6) D2: 77 (70.0) D3: 118 (71.5)	= 0.019), IFX vs. Placebo: (*P* = 0.002) Day 365: D1: 26.3 D2: 9.1 D3: 20.6 Overall: ABA vs. IFX): estimate of difference (95% CI): 5.7 (-4.2, 15.6) **HAQ, mean difference/ absolute difference (CI/SD/P Value)** Proportion demonstrating improvement in physical function Day 197 D1: 61.5 D2: 40.9 D3: 58.8 Overall: Proportion demonstrating improvement in physical function, ABA vs. Placebo: (*P* = 0.001), IFX vs. Placebo: (*P* = 0.005) Day 365 D1: 57.7 D2: 40.9 D3: 52.7 Overall: ABA vs. IFX: estimate of difference (95% CI): 5.0 (-6.5, 16.5) **DAS** Day 197 D1: 2.53 D2: -1.48 D3: 2.25 Overall: ABA vs. Placebo: (*P*	Day 197 D1: 1 D2: 0 D3: 1 Overall: 2 Day 365 D1: 1 D2: 0 D3: 2 Overall: 3 **Malignancies** Malignant neoplasms, n: Day 197: D1: 1 D2: 1 D3: 2 Overall: 4 Day 365: D1: 1 D2: 1 D3: 2 Overall: 3 **Respiratory events** Tuberculosis, n: 2863 Pneumonia, n: Day 197: D1:2 D2:0 D3:2 Overall: 4 Day 365: D1: 2 D2: 0 D3: 3 Overall: 5 **Other infections** Infections and Infestations, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			Overall: 313 (72.6) NSAIDs, n (%): D1: 133 (85.3) D2: 93 (84.5) D3: 142 (86.1) Overall: 368 (85.4)	= 0.001), IFX vs. Placebo: (*P* = 0.001) Day 365 D1: -2.88 D2: -1.48 D3: -2.25 Overall: ABA vs. IFX: estimate of difference (95% CI): -0.62 (-0.96, -0.29) **SF-36** NR Overall: Day 197, ABA vs. Placebo: PCS (*P* = 0.001) and MCS (*P* = 0.004) ofSF-36 IFX vs. Placebo: PCS (*P* = 0.002) and MCS (*P* = 0.027) of SF-36 ABA vs. IFX, PCS (difference of 1.93, 95% CI: 0.02, 3.84) MCS (difference of 1.92, 95% CI: -0.30, 4.15) **Radiographic measures** NR **Quality of life scales** NR **Others, (please name)** Day 197: • Proportion of patients achieving a good EULAR response, ABA: 20&, Placebo: 10.8%, IFX: 22.9% • LDAS, ABA: 20.7%, Placebo: 10.8%, IFX: 25.6%	Day 197: D1: 2 D2:3 D3: 7 Overall: 12 Day 365: D1: 3 D2: 0 D3: 14 Overall: 17 **GI** Nausea or vomiting, n: Day 197: D1: 2 D2: 1 D3: 6 Overall: 9 Day 365: D1: 3 D2: D3: 7 Overall: 10 **Other** NR Headache, n: Day 197: D1: 2 D2: 2 D3: 7 Overall: 11 Day 365: D1: 2 D2: D3: 7 Overall: 9 Dizziness, n: Day 197:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				• DAS28 (ESR)-defined remission, ABA: 11.3%, Placebo: 2.9%, IFX: 12.8% Day 365: • Proportion of patients achieving a good EULAR response (ABA 32.0 vs. INF 18.5%, estimate of difference (95% CI): 13.5% (3.6, 23.3)) • LDAS (ABA 35.3 vs. INF 22.4%, estimate of difference (95% CI): 12.9 (2.1, 23.7)) • DAS28 (ESR)-defined remission (ABA 18.7 vs. INF 12.2%, estimate of difference (95% CI): 18.7 (-2.2, 15.2))	D1: 0 D2: D3: 2 Overall: 2 Day 365: D1: 1 D2: 0 D3: 4 Overall: 5 Autoimmune symptoms and disorders: Day 197: • ABA: 1 • Placebo: 1 • IFX: 1 Day 365: • ABA: 2 • IFX: 1 Hypotension Day 197: • ABA: 0 • Placebo: 0 • IFX: 7 Day 365: • ABA: 0 • IFX: 8 Flushing Day 197: • ABA: 1 • Placebo: 0 • IFX: 4 Day 365 • ABA: 1 • IFX 5 Dyspnea Day 197:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• ABA: 0 • Placebo: 0 • IFX: 4, Day 365: • ABA: 0 • IFX: 5; Urticaria Day 197: • ABA: 0 • Placebeo: 1 • IFX: 4 Day 365: • ABA: 0 • IFX: 8; Pruritus Day 197: • ABA: 0 • Placebo: 0 • IFX: 2 Day 365: • ABA: 0 • IFX: 5 Sinusitis Day 197: • ABA: 1 • Placebo: 0 • IFX: 0 Day 365: • ABA: 1 • IFX: 0 Postoperative wound infection Day 197: • ABA: 0 • Placebo: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• IFX: 0 Day 365: • ABA: 0 • IFX: 1 Soft tissue abscess Day 197: • ABA: 0 • Placebo: 1 • IFX: 0 Day 365: • ABA: 0 • IFX: 0 Infective bursitis Day 197: • ABA: 0 • Placebo: 1 • IFX: 0 Day 365: • ABA: 0 • IFX: 0 Bronchitis Day 197: • ABA: 0 • Placebo: 0 • IFX: 1 Day 365: • ABA: 0 • IFX: 1 Cellulitis Day 197: • ABA: 0 • Placebo: 0 • IFX: 1 Day 365: • ABA: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• IFX: 1 Gastroenteritis Day 197: • ABA: 0 • Placebo: 0 • IFX: 1 Day 365: • ABA: 0 • IFX: 1 Herpes zoster Day 197: • ABA: 0 • Placebo: 0 • IFX: 1 Day 365: • ABA: 0 • IFX: 1 Lung infection pseudomonal Day 197: • ABA: 0 • Placebo: 0 • IFX: 1 Day 365: • ABA: 0 • IFX: 1 Pneumocystis jiroveci pneumonia Day 197: • ABA: 0 • Placebo: 0 • IFX: 1 Day 365: • ABA: 0 • IFX: 1 Infection skin ulcer

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Day 197: • ABA: 0 • Placebo: 0 • IFX: 0 Day 365: • ABA: 1 • IFX: 0 Encephalitis herpetic Day 197: • ABA: 0 • Placebo: 0 • IFX: 0 Day 365: • ABA: 0 • IFX: 1 Erysipelas, Day 197: • ABA: 0 • Placebo: 0 • IFX: 0 Day 365: • ABA: 0 • IFX: 1 Lobar pneumonia Day 197: • ABA: 0 • Placebo: 0 • IFX: 0 Day 365: • ABA: 0 • IFX: 1 Septic shock Day 197: • ABA: 0 • Placebo: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• IFX: 0 Day 365: • ABA: 0 • IFX: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Schipper et al., 2009[151] Nijmegen RA Inception Cohort **Country and setting** Netherlands **Source of funding** Wyeth **Research objective** To compare the efficacy of a swtich to MTX monotherapy with that of the addition of MTX to SSZ in RA patients who had failed SSZ monotherapy **Study design** Observational **Overall N** 230 **Duration of study** 52 wks	**Inclusion Criteria** • Early RA symptoms less than 1 year • Treatment resistant SSZ monotherapy • RA according to to 1987 ACR • ≥18 yrs old • No prior use of DMARDs **Exclusion Criteria** • Use of concomitant DMARD therapy other than MTX or SSZ at baseline	**Comparisons (dosage and frequency)** D1: MTX: 7.5 - 30 mg/week D2: • MTX: 7.5 - 30 mg/week • SSZ: 750- 3000 mg daily **Number in group** D1: 124 D2: 106 **Mean age (years)** D1: 63.8 D2: 61.8 **Sex, % female** D1: 70 D2: 74 **Race, % white** D1: NR D2: NR **Race, % black** D1: NR D2: NR **Ethnicity, Latino** D1: NR D2: NR	**Mean disease duration, years** median (IQR): D1:14 wks (5.3, 67.3) D2: 47 wks (20.2, 109.0) **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** D1: 8 D2: 9 **DMARD use, %:** Previous DMARDS other than SSZ: D1: 15 D2: 13 **MTX naïve, %:** NR **Treatment resistant, %:** D1: 100 D2: 100 **Patients with early RA, three years or less, %:** D1: 100 D2: 100 **Baseline DAS score** D1: 5.1 (1.3) D2: 4.9 (1.3) **Required treatment for latent TB** D1: NR D2: NR **Other population**	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** At 6 mo: D1: -0.9 (1.3) D2: -0.8 (1.3) Overall: difference b/t groups: -0.05 (0.16); *P*=0.737 At 12 mo: D1: -1.1 (1.3) D2: -0.9 (1.2) Overall: difference b/t groups 0.05 (0.15); *P*=0.756 **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR	**Overall** Overall attrition/withdrawal (n): D1: 42 D2: 53 Overall: 95 Withdrawals due to adverse events (n): D1: 23 D2: 12 Overall: 35 Withdrawals due to lack of efficacy (n): D1: 5 D2: 18 Overall: 23 **Serious adverse events:** NR **Malignancies:** NR **Respiratory events:** NR **Other infections:** NR **GI:** NR **Other:** NR	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			characteristics, %, (CI/SD/P value): NR	**Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Schneeweiss et al., 2007[152] **Country and setting** USA, Pennsylvania Medicare beneficiaries **Source of funding** Engalitcheff Arthritis Outcomes Initiatives, Baltimore, Maryland **Research objective** Assess association between initiation of anti-TNF therapy and risk of serious bacterial infections in routine care **Study design** Cohort Study **Overall N** 15,597 courses of therapy and 5,676 patient years of exposure **Duration of study** 1/1/1995 - 12/31/2003 **Quality rating** Fair	**Inclusion Criteria** • Medicare beneficiaries ages 65 and older with RA who initiated use of a DMARD, including anti-TNF and glucocorticoids, between 1995 and 2003; patients had to demonstrate use of health care system by filling at least 1 prescription for any drug and having at least 1 physician service in each of 2 consecutive 6-month periods in addition to being enrolled in PhDaceutical Assistance Contract for Elderly (PACE) program **Exclusion Criteria** • < 3 recoreded RA diagnoses: Any cancer (except nonmelanoma skin cancer) or	**Interventions, Dose** D1: MTX: dosage and frequency NR D2: ETN: dosage and frequency NR IFX: dosage and frequency NR ADA: dosage and frequency NR D3: Other: Glucocorticoids: dosage and frequency NR D4: LEF: dosage and frequency NR Other: cyclosporine, azathioprine: dosage and frequency NR D5: SSZ: dosage and frequency NR Hydroxychlorquine: dosage and frequency NR Other: gold, penicillamine, minocycline: dosage and frequency NR **Number in group** D1: 1900 D2: 469 D3: 10617 D4: 654 D5: 1957 Overall: 15,597 **Mean age (years)** D1: 76 D2: 75 D3: 79 D4: 76 D5: 76	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** D1: 100 D2: 100 D3: NR D4: 100 D5: 100 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR Overall: 2 hospitalizations for pulmonary TB **Other population characteristics, %, (CI/SD/P value)**	**ACR** NR **HAQ,** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** 4.4% of patients dropped out due to disenrollment from PACE plan. Authors also state that most patients dropped out of study because of treatment discontinuation or because they developed study outcome, however, they do not report raw data for that. **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** Pneumonia, n: D1: No. of events: 16, Event rate per 100 patient years (95% CI): 1.47 (0.75 - 2.18) D2: No. of events: 14, Event rate per 100 patient years (95% CI): 2.33(1.12-3.54) D3: No. of events: 67, Event rate per 100 patient years (95% CI): 3.16 (2.41-3.91) D4: No. of events: 6, Event rate per 100 patient years (95% CI): 1.43 (0.29-2.57) D 5: No. of events: 13, Event rate per 100 patient years (95% CI): 0.91 (0.42-

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	human immuno-deficiency virus/acquired immuno-deficiency syndrome	**Sex, % female** D1: 88 D2: 91 D3: 88 D4: 91 D5: 89 Overall: 89 **Race, % white** D1: 92 D2: 92 D3: 93 D4: 92 D5: 92 Overall: 92.5 **Race, % black** D1: 7 D2: 7 D3: 6 D4: 7 D5: 7 Overall: 7 **Ethnicity, Latino** NR	Followup, mean years: D1: 0.58 D2: 1.29 D3: 0.20 D4: 0.64 D5: 0.73 Overall: NR Nursing home resident, %: D1: 7 D2: 4 D3: 7 D4: 7 D5: 5 Overall: 6.5 Any hospitalization prior to index date, %: D1: 25 D2: 21 D3: 30 D4: 22 D5: 24 Overall: 28 Charlson comorbidity score, mean ± SD D1: 1.0 ± 1.5 D2: 0.5 ± 1.2 D3: 1.3 ± 1.9 D4: 0.6 ± 1.4 D5: 1.1 ± 1.5 Overall: NR No. of physician visits, mean ± SD D1: 6.7 ± 5.3 D2: 7.7 ± 5.5 D3: 6.0 ± 4.9 D4: 7.3 ± 6.0 D5: 6.7 ± 5.3 Overall: NR		1.40) Overall: No. of events: 116 **Other infections** Septicemia or bacteremia, n: D1: No. of events: 24, Event rate per 100 patient years (95% CI): 2.20(1.33-3.07); Osteomyelitis, No. of events: 7, Event rate per 100 patient years (95% CI): 0.27 (0.07-0.48); Any bacterial infection, No. of events: 41, Event rate per 100 patient years (95% CI): 3.77 (2.64-4.9) D2: No. of events: 13, Event rate per 100 patient years (95% CI): 2.16 (1.00-3.32); Osteomyelitis, No. of events: 3, Event rate per 100 patient years (95% CI): 0.49 (000-1.05); Any bacterial infection, No. of events: 29, Event rate per 100 patient years (95% CI): 4.89 (3.15-6.62) D3: No. of events: 133, Event rate per 100 patient years (95% CI): 6.34 (5.3-7.38); Osteomyelitis, No. of events: 17, Event rate per 100 patient years (95% CI): 0.80 (0.42-1.18); Any bacterial infection, No. of events: 196, Event rate per 100 patient years (95% CI): 9.39 (8.14-10.6) D4: No. of events: 15, Event

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			No. of different non-DMARDs used before index date, mean ± SD D1: 6.6 ± 4.4 D2: 8.2 ± 5.1 D3: 8.4 ± 4.8 D4: 8.2 ± 4.9 D5: 6.8 ± 4.5 Overall: NR No. of different DMARD classes used before index date, mean ± SD D1: 0.6 ± 0.7 D2: 1.4 ± 1.0 D3: 0.3 ± 0.5 D4: 1.1 ± 0.9 D5: 0.5 ± 0.6 Overall: NR Any intraarticular procedures, %: D1: 36 D2: 46 D3: 24 D4: 34 D5: 34 Overall: 27.5 Any extraarticular manifestations, %: D1: 3 D2: 4 D3: 2 D4: 4 D5: 3 Overall: 2.5 At least 1 marker of inflammation tested during previous 180 days, %: D1: 37		rate per 100 patient years (95% CI): 3.66 (1.84-5.48); Osteomyelitis, No. of events: 2, Event rate per 100 patient years (95% CI): 0.48 (000-1.14); Any bacterial infection, No. of events: 22, Event rate per 100 patient years (95% CI): 5.36 (3.18-7.54) D5: No. of events: 33, Event rate per 100 patient years (95% CI): 2.31 (1.53-3.09); Osteomyelitis, No. of events: 9, Event rate per 100 patient years (95% CI): 0.63 (0.22-1.04); Any bacterial infection, No. of events: 53, Event rate per 100 patient years (95% CI): 3.75 (2.70-4.74) Overall: No. of events: 218; Osteomyelitis, No. of events: 38; Any bacterial infection, No. of events: 341 **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D2: 39 D3: 20 D4: 36 D5: 33 Overall: 25.2 Any orthopedic surgeries, %: D1: 41 D2: 50 D3: 28 D4: 38 D5: 37 Overall: 32 Diabetes mellitus, %: D1: 8 D2: 9 D3: 9 D4: 10 D5: 8 Overall: 4 At least 1 antibiotic dispensed during previous 180 days, %: D1: 30.5 D2: 40 D3: 40 D4: 43 D5: 30 Overall: 28 Previous hospitalization for serious bacterial infections, %: D1: 3 D2: 2 D3: 3 D4: 3 D5: 3 Overall: 3.2 Vaccination for Influenza, %:		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D1: 8 D2: 20 D3: 12 D4: 12 D5: 7 Overall: 11 Vaccination for Pneumococcal, %: D1: 3 D2:4 D3: 3% D4: 2 D5: 3 Overall: 3.1		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Setoguchi et al., 2006[153] **Country, Setting:** US and Canada, 3 databases **Funding:** Novartis and NIH **Research Objective:** To estimate association between treatment with biologic DMARDs and development of cancer in pts with RA **Study Design:** Cohort Study **Overall N:** 7,830 **Study Duration:** 1994 to 2004 in US 1996 to 2003 in Canada	**Inclusion Criteria:** • Age ≥ 65 • 1 claim with a diagnosis of RA and who were dispensed at least 1 prescription of any DMARD or corticosteroid after first RA diagnosis **Exclusion Criteria:** • Diagnosis of any cancer (except nonmelanoma skin cancer) or human immuno-deficiency virus infection	**Interventions:** D1: Biologic DMARD **D2: MTX** **N:** D1: 1152 D2: 7306 **Mean age (yrs):** D1: 71.4 D2: 73.4 **Sex, % female:** D1: 75.3 D2: 73.1 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** D1: 51.3 **D2: 41.5** **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	RA pts vs. overall population • Non-Hodgkin's lymphoma-PY 33,335.0 Observed 58 Expected 26.0 SIR 2.2 95% CI,1.71-2.87 • Multiple myeloma-PY yrs 33,410.0 Observed 19 Expected 9.3 SIR 2.0 95% CI,1.26-3.12 • Melanoma-PY 33,377.7 Observed 29 Expected 12.8 SIR 2.3 95% CI,1.55-3.22 • Colorectal cancer-PY 32,844.9 Observed 118 Expected 97.3 SIR 1.2 95% CI,1.01-1.45 • Lung cancer-PY 31,532.8 Observed 169 Expected 95.6 SIR 1.8 95% CI,1.52-2.05 • Urinary tract/bladder cancer-PY 33,367.0 Observed 54 Expected 26.4 SIR 2.0 95% CI,1.55-2.65 • Biologics vs. MTX • Unadjusted Lymphoproliferative HR 1.20 (95% CI,0.57-2.51) Hematologic HR 1.45 (95% CI,0.76-2.74) Solid HR 0.91 (95% CI,0.66-1.25) Overall HR 1.00 (95% CI,0.75-1.33)	See health outcomes	**Overall Attrition Rate, %:** NA **ITT Analysis:** Not applicable Observational study **Quality Rating:** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Setoguchi et al., 2008[154] **Country and setting** USA, Medicare and drug benefit programs in Pennsylvania and New Jersey **Source of funding** Not reported **Research objective** Estimate risk of heart failure hospitalization in elderly TNFα users with and without previous heart failure **Study design** Retrospective Cohort Study **Overall N** 5593 **Duration of study** January 1, 1994 - December 31, 2004 **Quality rating** Good: For an observational study, this is quite good with appropriate adjustment and analysis	**Inclusion Criteria** • ≥ 65 years old • At least one recorded diagnosis of RA • Filled at least 1 prescription of any TNFA (ETN, IFX, ADA) or MTX after first RA diagnosis • At least one clinical service during each of 4 consecutive 6-month periods before use of DMARDs **Exclusion Criteria** • Pts who had a diagnosis of heart failure in an outpatient file but none noted in a hospital discharge summary	**Interventions, Dose** D1: • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ADA: dosage and frequency NR D2: MTX: dosage and frequency NR D3: • ETN: dosage and frequency NR • IFX: dosage and frequency NR • ADA: dosage and frequency NR D4: MTX: dosage and frequency NR **Number in group** D1: 225 D2: 808 D3: 777 D4: 3783 Overall: 5593 **Mean age (years)** D1: 73 D2: 77 D3: 72 D4: 74 **Sex, % female** D1: 89 D2: 84 D3: 90 D4: 89 **Race, % white** D1: 88 D2: 92	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: 67 D2: 56 D3: 59 D4: 48 **DMARD use, %** D1: 100 D2: 100 D3: 100 D4: 100 Overall: 100 **MTX naïve, %** D1: NR D2: 0 D3: NR D4: 0 **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB**	**ACR** NR **HAQ,** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NA **Overall adverse events reported, n:** NR **Serious adverse events** Death, n: NR Overall: All TNFA users: 22; All MTX users: 85; Overall: 107 Cardiovascular events (specify), n: D1: Heart failure admissions: 33 per 304 person-years, incidence rate: 108 D2: Heart failure admissions: 101 per 1333 person-years, incidence rate: 76 D3: Heart failure admissions: 26 per 1375 person-years, incidence rate: 19 D4: Heart failure admissions: 126 per 9290 person-years, incidence rate: 14 Overall: All TNFA users, Heart failure admissions: 59 per 1680 person-years, incidence rate: 35 All MTX users, Heart failure admissions: 227 per 10623 person-years, incidence rate: 21 **Malignancies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D3: 89 D4: 91 **Race, % black** NR **Ethnicity, Latino** NR	NR **Other population characteristics, %, (CI/SD/P value)** D1: • Average follow-up, mean (SD): 1.6 (1.5) • RA severity-related covariates RA-related surgery: 7% • Extra-articular manifestations: 39% • Arthocentesis: 64% • Injection (joint, tendon, etc): 23% • Corticosteorids: 67% • Other cytotoxic DMARDs: 24% • Noncytotoxic DMARDs: 35% • COX2 inhibitors: 48% • MI hospitalization: 17% • Ischemic heart disease: 66% • Valvular heart disease: 45% • Cardiomyopathy: 18% • Cardiac surgery: 10% • 1 Prior HF hospitalization: 13% • 2 Prior HF hospitalization: 5% • 3 Prior HR hospitalizations: 1% • Vascular surgery: 29% • Ventricular arrhythmia/ cardiac arrest: 2% • Atrial fibrilation: 39% • Other dysrhythmias: 24%		**Respiratory events** NR **Other infections** NR **GI** NR **Other** • Effects of TNFAs compared to MTX on HF and/or death, With previous heart failure, fully adjusted: HR: 1.75, 95% CI (0.86 - 3.56) • Without previous heart failure, fully adjusted: HR: 2.07, 95% CI (1.00 - 4.25) • 2 groups combined: HR: 1.70, 95% CI (1.07 - 2.69) • Risk of death among patients with previous HF (TNFA users compared with MTX users): adjusted HR: 4.19, 95% (CI 1.48 - 11.89)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			• Intervention for arrhythmia: 4% • Cerebrovascular diseases: 29% • Hypertension: 92% • Hyperlipidemia: 64% • Diabetes: 48% • Chronic kidney diseases: 33% • Dialysis: 1% • Anemia: 64% • Hypothyroidism: 17% • Chronic airway diseases: 60% • Cancer: 22% • Anxiety or depression 55% D2: • Average follow-up, mean (SD): 1.7 (1.9) • RA-related surgery: 4% • Extra-articular manifestations: 34% • Arthocentesis: 53% • Injection (joint, tendon, etc): 12% • Corticosteorids: 56% • Other cytotoxic DMARDs: 4% • Noncytotoxic DMARDs: 22% • COX2 inhibitors: 26% • MI hospitalization: 15% • Ischemic heart disease: 63% • Valvular heart disease: 39% • Cardiomyopathy: 19% • Cardiac surgery: 9% • 1 Prior HF hospitalization: 17%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			• 2 Prior HF hospitalization: 2% • 3 Prior HR hospitalizations: 1% • Vascular surgery: 27% • Ventricular arrhythmia/ cardiac arrest: 2% • Atrial fibrilation: 37% • Other dysrhythmias: 21% • Intervention for arrhythmia: 6% • Cerebrovascular diseases: 34% • Hypertension: 87% • Hyperlipidemia: 53% • Diabetes: 47% • Chronic kidney diseases: 25% • Dialysis: 0% • Anemia: 52% • Hypothyroidism: 17% • Chronic airway diseases: 53% • Cancer: 19% • Anxiety or depression 48% D3: • Average follow-up, mean (SD): 1.8 (1.6) • RA-related surgery: 10% • Extra-articular manifestations: 28% • Arthocentesis: 58% • Injection (joint, tendon, etc): 16% • Corticosteorids: 59% • Other cytotoxic DMARDs: 24% • Noncytotoxic DMARDs: 32% • COX2 inhibitors: 48%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			• MI hospitalization: 3% • Ischemic heart disease: 21% • Valvular heart disease: 20% • Cardiomyopathy: 5% • Cardiac surgery: 1% • Vascular surgery: 12% • Ventricular arrhythmia/ cardiac arrest: 1% • Atrial fibrilation: 8% • Other dysrhythmias: 8% • Intervention for arrhythmia: 1% • Cerebrovascular diseases: 13% • Hypertension: 72% • Hyperlipidemia: 58% • Diabetes: 31% • Chronic kidney diseases: 15% • Dialysis: 0% • Anemia: 55% • Hypothyroidism: 12% • Chronic airway diseases: 34% • Cancer: 13% • Anxiety or depression: 43% D4: • Average follow-up, mean (SD): 2.5 (2.4) • RA-related surgery: 6% • Extra-articular manifestations: 23% • Arthocentesis: 48% • Injection (joint, tendon, etc): 11% • Corticosteorids: 48% • Other cytotoxic		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			DMARDs: 5% • Noncytotoxic DMARDs: 26% • COX2 inhibitors: 24% • MI hospitalization: 3% • Ischemic heart disease: 19% • Valvular heart disease: 16% • Cardiomyopathy: 5% • Cardiac surgery: 1% • Vascular surgery: 14% • Ventricular arrhythmia/ cardiac arrest: 0% • Atrial fibrilation: 8% • Other dysrhythmias: 6% • Intervention for arrhythmia: 1% • Cerebrovascular diseases: 16% • Hypertension: 70% • Hyperlipidemia: 46% • Diabetes: 27% • Chronic kidney diseases: 10% • Dialysis: 0% • Anemia: 47% • Hypothyroidism: 11% • Chronic airway diseases: 29% • Cancer: 14% • Anxiety or depression: 35%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Shin et al., 2006[155] **Country, Setting:** US **Funding:** NR **Research Objective:** Review occurence and clinical features of Guillan Barre syndrome and Miller Fisher Syndrome during TNF alpha antagonist therapy **Study Design:** Database analysis; AERS **Overall N:** 16 cases **Study Duration:** NR	**Inclusion Criteria:** • TNF alpha antagonist therapy in AERS database **Exclusion Criteria:** NA	**Interventions, dose:** NR ETA INF **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Guillain-Barre was temporally associated with INF in 10 pts, ETA in 5 pts. This compares to an annual incidence of Guillain Barre Syndrome of 1-3/100,000 population	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Slifman, 2003[156] **Country, Setting:** Multinational, multicenter **Funding:** NR **Research Objective:** To evaluate postlicensure cases of opportunistic infection, including Listeria monocytogenes, in pts treated with TNFs **Study Design:** Database analysis; AERS **Overall N:** 15 cases **Study Duration:** Varied	**Inclusion Criteria:** • Age: 17 to 80 • Pts with Listeria monocytogenes treated with ETA or INF for RA or Crohn's disease • Concurrent use of immuno-suppressant drugs allowed **Exclusion Criteria:** • NA	**Interventions, dose:** D1: INF or ETA ETA: varied INF: varied **N:** D1: 15 **Median age, yrs:** D1: 69.5 **Sex, % female:** D1: 53.3 **Race, % white:** D1: NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RA:** D1: 64%	For all ages and indications, the estimated rate of cases (reporting rates) of listeriosis reported to FDA within first yr of starting txt with inf was 43 cases per 1,000,000 persons (8/186,500) • RA pts treated with inf (US cases only), estimated rate of cases of listeriosis reported to FDA was 61 cases per 1,000,000 persons (5/82,000) • In 2000, annual incidence of listeriosis in US for all ages was estimated to be 3 cases per 1,000,000 • 6 deaths reported (5 INF, 1 ETA) • Among reports from US only, this series included 8 cases of Listeria infection, all of which were associated with INF txt	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smitten et al., 2007[157] **Country and setting** US & UK. mulitcenter **Source of funding** Data provided by Bristol-Myers Squibb Company and Harvard PhDaco-epidemiology Program **Research objective** Determine if RA pts have an elevated risk for herpes zoster & if their risk is associated with DMARD tx **Study design** Retrospective Cohort Study **Overall N** PhDetrics (PM) Database: 12272 with RA; UK General Practice Research Database (GPRD) 38621 with RA **Duration of study** PhDetrics: mean = 12.3 mos GPRD: mean = 38.8 mos	**Inclusion Criteria** • PhDetrics: enrolled on 1/61 health care plans in US, RA Cohort had to be 18+ and have at least 1 ICD-9 code for RA. • GPRD: at least 18 years of age at cohort entry who had at least 90 days of up-to-standard data **Exclusion Criteria** • PhDetrics: RA Cohort - ICD9 714.3 (Juvenile Chronic Polyarthritis), 714.9 (unspecified inflammatory polyarthropathies). • Patients who were enrolled in Medicare gap plans, were missing a value for age or sex, had = 90 days of continuous enrollment, or had a diagnosis of herpes zoster in 90 days prior	**Interventions, Dose** D1: Oral DMARDS D2: Biologics D3: Corticosteroids D4: Combination therapy **Number in group** D1: 1611 D2: 11277 D3: 1719 D4: 12033 Overall: NR **Mean age (years)** D1: 55.4 D2: 51.1 D3: 63.9 D4: 60.6 Overall: NR **Sex, % female** D1: 75.4 D2: 73.1 D3: 74.1 D4: 72.5 Overall: NR **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Compared to pts who had not received DMARDS or Corticosteroids, pts in both databases showed an increased risk for herpes zoster if treated with traditional DMARDS alone (PhDetrics: 1.37, 95%CI:1.18-1.59; GPRD 1.27, 95%CI:1.10-1.48), Oral Corticosteroids alone (PhDetrics: 2.51 95%CI: 2.05-3.06; GPRD 1.46 95%CI: 1.24-1.70) and Traditional DMARDS + Corticosteroids (PhDetrics: 2.39 CI:1.99-2.88); GPRD: 1.82 CI:1.46-2.26) PhDetrics pts on biologics DMARDS alone (1.54, 1.04-2.29), Biologic

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Quality rating Fair: Matching did not account for Disease Activity or Severity which could confound results. Higher DAS = increased disregulation of immune sys? or different dose of drugs could lead to levels of impact on immune system response?	to cohort entry were excluded				DMARDS + Corticosteroids (2.44, 1.26-4.73), and or Biologics + Traditional DMARDS + Corticosteroids (1.96, 0.99-3.86) showed an increased risk for herpes zoster while pts treated with a combination of Biologics + Traditional DMARDS (1.38,0.83-2.27) did not show a significantly increase risk. (referant for all comparisons - no DMARD or Corticosteroid)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smitten et al., 2008[158] **Country and setting** United States **Source of funding** Data provided by Bristol-Myers Squibb Company and Harvard PhDaco-epidemiology Program **Research objective** Assess whether risk of hospitalized infection in RA pts is higher during use of newer biological DMARDs **Study design** Retrospective Cohort Study **Overall N** 24,530 (RA cohort only) **Duration of study** 26.6 months (mean follow-up time of RA cohort) **Quality rating** Good: large sample size but unevenly distributed between treatment Ds; disease severity not	**Inclusion Criteria** • At least 18 years old, with at least 2 physician visits 2 months apart for RA with an ICD-9-CM code of 714 **Exclusion Criteria** • ICD-9-CM codes: 714.3 (juvenile chronic polyarthritis), 714.4 (chronic postrheumatic arthropathy), 714.9 (unspecified inflammatory polyarthropathy) ; subjects missing values for age or sex; experienced an outcome of interest in 90 days period to cohort entry; enrolled in plans that provide supplementary insurance to Medicare	**Interventions, Dose** D1: Biological DMARDs (IFX, ETN, ADA, ANK) D2: MTX: dose NR D3: Hydroxychlorquine: dose NR D4: LEF: dose NR D5: SSZ: dose NR D6: Oral Corticosteroids (separate D) **Number in group** D1: 2,248 D2: 5,077 D3: 2,992 D4: 907 D5: 858 D6: 4,390 Overall: 24,530 **Mean age (years)** D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: Age 18-44: 26.5%; Age 45-64: 66.3%; Age 65+: 7.2% **Sex, % female** D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 75.7	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 17.9 **DMARD use, %** D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: Traditional: 41.17 Biologic: 9.17 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)**	**Overall** NA Overall adverse events reported, n: D1: 254 D2: 352 D3: 172 D4: 90 D5: 44 D6: 442 Overall: 1,993 **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 434 Upper respiratory infection, n: NR **Other infections** Urinary tract infection, n: D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 250 Other infections (specify), n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
accounted for		**Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Overall: 0 comorbid conditions: 77.0% 1-2 comorbid conditions: 21.8%; 3+ comorbid conditions: 59.4%		D1: Hospitalized infections: 254 D2: 352 D3: 172 D4: 90 D5: 44 D6: 442 Overall: • Overall hospital infections: 1,993 • Skin: 257 • Sepsis: 198 • Opportunistic: 11 • Serious (requiring outpatient parenteral antibiotics): 3,010 **GI** NR **Other** • Number of Hospitalized Infections-Oral Corticosteroids 5 mg/day or less: 144; 6-10 mg/day: 119; greater than 10 mg/day: 179 Unadjusted and Adjusted Rate Ratio (95% CI), respectively, for hospitalized infection in patients with RA: • D1: 1.05 (0.91-1.22); 1.21 (1.02-1.43) • D2: 0.76 (0.67-0.86); 0.81 (0.70-0.93) • D3: 0.68 (0.58-0.81); 0.74 (0.62-0.89) • D4: 1.05 (0.84-1.33); 1.02 (0.79-1.32) • D5: 0.66 (0.48-0.91); 0.82 (0.58-1.38)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• D6: 1.83 (1.62-2.07); 1.92 (1.67-2.21) • 5 mg/day or less oral corticosteroids: 1.28 (1.06-1.55); 1.32 (1.06-1.63); 6-10 mg/day oral corticosteroids: 1.79 (1.44-2.21); 1.94 (1.53-2.46); greater than 10 mg/day oral corticosteroids: 2.89 (2.39-3.49); 2.98 (2.41-3.69)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Smolen et al., 1999;[159]; Smolen et al., 1999[160]; Sharp et al., 2000[161]; Larsen et al., 2001[162]; Scott et al., 2001[163] **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of LEF was compared to placebo and SSZ **Study Design:** RCT **Overall N:** 266 (358 including placebo arm) **Study Duration:** 24 wks (12 and 24 month followup)	**Inclusion Criteria:** • Age: ≥ 18 • Active RA defined by: ≥ 6 tender and swollen joints, based on a 28-joint count, physician and pt global assessments of RA activity of "fair, poor, or very poor", CRP > 2.0 mg/dL or ESR > 28 mm/h • Functional class I – III • Other DMARDs discontinued ≥ 4 wks • Stable doses of NSAIDS permitted -acetylsalicylic acid, oral steroids (prednisolone ≤ 10 mg/day), and up to 3 intra-articular steroid injections, not exceeding 60 mg triamcinolone • Intra-articular steroid injections not permitted during first 6 mos **Exclusion Criteria:** • Pregnant or lactating	**Interventions:** D1: LEF D2: SSZ **N:** D1: 133 D2: 133 **Mean age, yrs:** D1: 58.3 D2: 58.9 **Sex, % female:** D1: 75.9 D2: 69.2 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 7.6 D2: 7.4 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: 60.2 D2: 48.9 **Corticosteroid use, %:** D1: 28.6 D2: 27.8 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF positive:** D1: 79% D2: 80%	**At 24 weeks** **ACR 20, %:** D1: 55 D2: 56 **ACR 50, %:** D1: 33 D2: 30 **Improving HAQ scores, change (%):** D1: -0.50 (45) D2: -0.29 (29) (*P* = 0.0086) **Change in Sharp; number, change (SD):** D1: 87 1.23 (2.85) D2: 84 2.32 (10.11) **Larsen score change:** D1: 0.01 D2: 0.01 (*P* = NS) **At 1 year** **Change in Sharp; number, change (SD):** D1: 60 0.97 (6.11) D2: 53 1.38 (2.88) **Larsen score change:** D1: 0.02 D2: 0.02 (*P* = NS) **At 2 years** **Larsen score change:** D1: -0.07 D2: -0.02 (*P* = NS) Similar ACR20 response rates D1: 48; D2: 44; *P*=NR	**SAEs:** D1: 5 D2: 7 **Headache:** D1: 7 D2: 11 **Nausea:** D1: 10 D2: 17 **URTI:** D1: 14 D2: 15 **Diarrhea:** D1: 17 **D2: 9** **Alopecia:** D1: 8 **D2: 5** **Rash:** D1: 10 **D2: 9** **Withdrawal due to AEs:** D1: 14 **D2: 19** 2 cases of reversible agranulocytosis in SSZ	**Overall Attrition Rate, %:** 33% at 24 wks **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smolen et al., 2008, OPTION[164] **Country and setting** International, multicenter **Source of funding** F Hoffman-La Roche and Chugai Pharmaceutical **Research objective** Assess efficacy of tocilizumab in RA pts who were receiving background MTX therapy **Study design** Controlled Trials **Overall N** 622 (623 were randomized, however 1 subject never received study drug and was withdrawn. Data tables have total n of 622) **Duration of study** 24 wks (Safety: 32 wks) **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant, adult patients • Inadequate response to MTX • Moderate to severe active RA (diagnosed according to ACR criteria) criteria of more than 6 mos' duration • Inadequate response to MTX • Active disease was defined by an SJC of 6 or more plus a TJC of 8 or more and CRP over 10 mg/L or ESR of 28 mm/h or more • Patients had to have received MTX for 12 weeks or longer beforestart ofstudy (stable dose of 10-25 mg/week for 8 weeks or longer) **Exclusion Criteria** • Autoimmune	**Interventions, dose** D1: • MTX: 10 - 25 mg once/week • Tocilizumab: 4 mg/kg every 4 wks D2: • MTX: 10 - 25 mg once/week • Tocilizumab: 8 mg/kg every 4 wks D3: • MTX: 10 - 25 mg once/week • Placebo **Number in group** D1: 213 D2: 205 D3: 204 Overall: 622 **Mean age, years (SD)** D1: 51.4 D2: 50.8 D3: 50.6 Overall: NR **Sex, % female** D1: 82 D2: 85 D3: 78 Overall: 82 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 7.4 D2: 7.5 D3: 7.8 Overall: NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 33.2 (15.6) D2: 31.9 (15.5) D3: 32.8 (16.1) **Swollen Joint Count, mean** D1: 20.0 (10.9) D2: 19.5 (11.3) D3: 20.7 (11.7) **Corticosteroid use, %** D1: 55 D2: 55 D3: 54 Overall: 55 **DMARD use, %** D1: 100 D2: 100 D3: 100 Overall: 100 **MTX naïve, %** D1: 0 D2: 0 D3: 0 Overall: 0 **Baseline DAS score** D1: 6.8	**ACR** ACR 20: D1: 48 D2: 59 D3: 26 Overall: 4 mg/kg vs. Placebo (P = 0.0001), 8 mg/kg vs. Placebo (P = 0.0001) ACR 50: D1: 31 D2: 44 D3: 11 Overall: 4 mg/kg vs. Placebo (P = 0.0001), 8 mg/kg vs. Placebo (P = 0.0001) ACR 70: D1: 12 D2: 22 D3: 2 Overall: 4 mg/kg vs. Placebo (P = 0.0001), 8 mg/kg vs. Placebo (P = 0.0001) **HAQ,** D1: -0.52 D2: -0.55 D3: -0.34 Overall: 4 mg/kg vs. Placebo (P = 0.0296), 8 mg/kg vs. Placebo (P = 0.0082) **DAS28 = 2.6 (%)** D1: 13 D2: 27 D3: 0.8 Overall: 4 mg/kg vs. Placebo (P = 0.0002), 8 mg/kg vs. Placebo (P = 0.0001) **SF-36** Physical	**Attrition/withdrawal** Overall, n: D1: 25 D2: 13 D3: 12 Overall: 50 Withdrawals due to adverse events, n: D1: 14 D2: 12 D3: 6 Overall: 32 Withdrawals due to lack of efficacy, n: D1: 2 D2: 0 D3: 3 Overall: 5 Adherent/compliant, n: D1: 186 D2: 191 D3: 189 Overall: 566 **Overall adverse events reported, n:** D1: 151 D2: 143 D3: 129 Overall: 423 **Serious adverse events** Cardiovascular events (specify), n: D1: 0 D2: 1 D3: 1 **Malignancies** Skin cancer (basal cell or

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	diseases or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fi brosis, or Felty's syndrome) • Functional class IV RA • Previous or current inflammatory joint disease other than RA • Currently active or previous recurrent bacterial, viral, fungal, or other infections including, but not limited to, TB and atypical mycobacterial disease, clinically significant abnormalities on chest radiograph, hepatitis B and C, and recurrent herpes zoster (Also, investigators were encouraged to exclude		D2: 6.8 D3: 6.8 **Required treatment for latent TB** NR	D1: 9.7 D2: 9.5 D3: 5.0 Overall: 4 mg/kg vs. Placebo (P = 0.0001), 8 mg/kg vs. Placebo (P = 0.0001) Mental D1: 5.7 D2: 7.3 D3: 2.7 Overall: 4 **Radiographic measures** NR **Quality of life scales** Patient pain VAS (mm): D1: -25.0 D2: -29.8 D3: -14.0 Patient global VAS (mm): D1: -28.8 D2: -32.7 D3: -17.8 FACIT-fatigue score: D1: 7.3 D2: 8.6 D3: 4.0 **Others, (please name)** EULAR Good Response (%) • 4 mg/kg: 21 • 8 mg/kg: 38 • Placebo: 3 Moderate Response (%) • 4 mg/kg: 41 • 8 mg/kg: 41 • Placebo: 32	squamous cell), n: D1: 0 D2: 0 D3: 1 Other cancer (specify), n: D1: 0 D2: 0 D3: 1 (unspecified) **Respiratory events** Tuberculosis, n: 3,570 Pneumonia, n: D1: 0 D2: 1 D3: 1 Overall: Pneumocystis jirovecii pneumonia, n: D1: 0 D2: 0 D3: 1 Overall: D1: 2 D2: 1 Upper respiratory infection, n: D1: 12 D2: 17 D3: 13 Overall: 42 **Other infections** Urinary tract infection, n: D1: 0 D2: 0 D3: 1 Overall: 1 Nasopharyngitis, n: D1: 11

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	potential pts if, in their judgment, they had a history of unacceptably frequent recurrent infections.) • Active liver disease, indicated by screening and baseline concentrations of alanine or aspartate aminotransferase of 1 - 5 time supper limit of normal or more • Previous unsuccessful treatment with an anti-TNF agent (i.e., lack of efficacy or significant safety issues, terminations due to cost or injection discomfort were not excluded)			No response (%) • 4 mg/kg: 38 • 8 mg/kg: 20, • Placebo 65 Overall: • 4 mg/kg vs. Placebo (*P* = 0.0001) • 8 mg/kg vs. Placebo (*P* = 0.0001) SJC Mean change from baseline • 4 mg/kg: -8.5 • 8 mg/kg: -10.5 • Placebo: -4.3 • Overall: 4 mg/kg vs. Placebo (*P* = 0.0001), 8 mg/kg vs. Placebo (*P* = 0.0001) TJC Mean change from baseline • 4 mg/kg: -14.5 • 8 mg/kg: -17.1 • Placebo: -7.4 • Overall: 4 mg/kg vs. Placebo (*P* = 0.0001), 8 mg/kg vs. Placebo (*P* = 0.0001)	D2: 12 D3: 10 **GI** Dyspepsia and abdominal pain, n: D1: 17 D2: 20 D3: 11 Overall: 48 Any GI disorder, n: D1: 46 D2: 48 D3: 44 Overall: 138 **Other** Skin rash, n: D1: 13 D2: 11 D3: 3 Overall: 27 Headache, n: D1: 15 D2: 14 D3: 9 Overall: 28 Mouth ulcers, n: D1: 4 D2: 5 D3: 1 Overall: 10 Peptic ulcers, n: D1: 1 D2: 0 D3: 2 Overall: 3 Raised anlanine aminotransferase, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 12 D2: 11 D3: 3 Overall: 26 Raised aspartate aminotransferase, n: D1: 1 D2: 2 D3: 1 Overall: 4 Cough: • 4 mg/kg: 7 • 8 mg/kg: 3 • Placebo: 3 • Overall: 13 Pharyngeal pain, • 4 mg/kg: 2 • 8 mg/kg: 4 • Placebo: 3 • Overall: 9 Dyspnoea • 4 mg/kg: 3 • 8 mg/kg: 3 • Placebo: 0 • Overall: 6 Aggravation of RA • 4 mg/kg: 7 • 8 mg/kg: 7 • Placebo: 13 • Overall: 27

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smolen et al., 2009, RAPID 2[165] **Country and setting** Multinational **Source of funding** UCB **Research objective** Evaluate efficacy and safety of CZP vs. placebo, + MTX, in pts with active RA **Study design** Controlled Trials **Overall N** 619 **Duration of study** 24 weeks **Quality rating** Good	**Inclusion Criteria** • ≥ 18 years old • Diagnosis of RA by ACR criteria, prior MTX ≥ 6 mos (stable dose ≥ 10 mg/wk for ≥ 2 mos) **Exclusion Criteria** • Other biological agent for RA within 6 mos before enrollment (3 mos for ETN and ANK), previous treatement with biological with severe hypersensitivity or anaphylactic reaction • No initial response to previous anti-TNF therapy, chest x-ray findings for TB, positive PPD (unless thought to be due to BCG vaccination).	**Interventions, dose** D1: MTX: ≥ 10 mg/wk Placebo: saline SC q 2 weeks D2: MTX: ≥ 10 mg/wk Certolizumab 400 mg SC at weeks 0, 2, and 4 then 200 mg q 2 weeks D3: MTX: ≥ 10 mg/wk Certolizumab: 400 mg SC at weeks 0, 2, and 4 then 400 mg q 2 weeks **Number in group** D1: 127 D2: 246 D3: 246 **Mean age, years (SD)** D1: 51.5 yr (11.8) D2: 52.2 (11.1) D3: 51.9 (11.8) **Sex, % female** D1: 84.3 D2: 83.7 D3: 78.0 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 5.6 yr (3.9) D2: 6.1 (4.1) D3: 6.5 (4.3) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** D1: 30.4 (3.4) D2: 30.1 (14.5) D3: 30.0 (13.9) **Swollen Joint Count, mean** D1: 21.9 (9.7) D2: 20.5 (9.6) D3: 21.0 (10.2) **Corticosteroid use, %** D1: 59.8 D2: 55.3 D3: 61.8 **DMARD use, %** **MTX naïve, %** D1: 0 D2: 0 D3: 0 **Baseline DAS score** D1: 6.83 (0.87) D2: 6.85 (0.84) D3: 6.80 (0.79) **Required treatment for latent TB** **Other population characteristics, %, (SD)**	**ACR mean difference/ absolute difference (CI)** ACR 20: D1: 8.7 D2: 57.3, OR 14.4 (6.7-31.0), *P* = 0.001 D3: 57.6, 14.3 (6.7-30.8), *P* = 0.001 ACR 50: D1: 3.1 D2: 32.5, OR 14.8 (5.3-41.6), *P* = 0.001 D3: 33.1, 15.3 (5.5-42.9), *P* = 0.001 ACR 70: D1: 0.8 D2: 15.9, OR 23.8 (3.2-175.9), *P* = 0.01 D3: 10.6, 15.5 (2.1-115.4), *P* = 0.01 **HAQ-DI, adj mean change (SE)** D1: -0.14 (0.04) D2: -0.50 (0.03), *P* = 0.001 D3: -0.50 (0.03), *P* = 0.001 **HAQ-DI, % mean % improvement (SD)** D1: 3.7 (59.4) D2: 31.8 (38.5), *P* = 0.001 D3: 32.0 (35.1) *P* = 0.001 **DAS28 (SD)** D1: -0.50 (1.05) D2: -2.27 (1.38), *P* = 0.001 D3: -2.46, *P* = 0.001 **SF-36 PCS, adj mean change, n** D1: 0.9	**Overall** Overall attrition/withdrawal, n: D1: 110 D2: 72 D3: 65 Withdrawals due to adverse events, n: D1: 2 D2: 11 D3: 6 Withdrawals due to lack of efficacy, n: D1: 107 D2: 54 D3: 53 Adherent/compliant, n: D1: 1 D2: 1 D3: 2 Withdrawal due to patient indecision or other: D1: NR D2: 6 D3: 4 Overall adverse events reported, n: D1: 66 D2: 139 D3: 125 **Serious adverse events** Death, n: D1: 0 D2: 1 D3: 1 Hepatotoxicity/elevated liver enzymes, n: D1: 4

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			MTX (mg/wk) mean: D1: 12.2 (3.3), D2: 12.5 (3.6) D3: 12.6 (3.7) HAQ-DI mean: D1: 1.6 (0.6) D2: 1.6 (0.6) D3: 1.6 (0.6) mTSS mean: D1: 46.5 (58.6) D2: 39.6 (50.1) D3: 46.7 (56.0)	D2: 5.2 (*P* = 0.001) D3: 5.5 (*P* = 0.001) **SF-36 PCS, adj mean change, PF** D1: 0.6 D2: 12.1 (*P* = 0.001) D3: 12.4 (*P* = 0.001) **Radiographic measures (CI)** mTSS: D1: 1.2 (0.5-2.0) D2: 0.2 (-0.1-0.6), *P* = 0.01 D3: -0.4 (-0.7- to 0.1), *P* = 0.001 **Quality of life scales** NR	D2: 3 D3: 3 Overall: 4 **Malignancies** NR Other cancer (specify), n: D1: 1 (bladder) D2: 1 (testicular) D3: 1 (colon) **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: 0 D2: 0 D3: 1 Upper respiratory infection, n: D1: 2 D2: 11 D3: 4 **Other infections** Urinary tract infection, n: D1: 9 D2: 11 D3: 5 Other infections (specify), n: D1: 0 D2: 1 case each of erysipelas, gastroenteritis, postop wound infection, tooth abscess D3: 1 case of erysipelas, 2 cases of sinusitis **GI** NR **Other**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Headache, n: D1: 1 D2: 9 D3: 8 Any other AEs: For safety analysis two patients inplacebo group that received CZP 200 mg were included inCZP 200 mg group.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smolen et al., 2009[166] ASPIRE **Country and setting** Multinational Unversity hospitals **Source of funding** Centocor **Research objective** Examine radiographic progression and disease activity states in pts treated with MTX or INF + MTX **Study design** Controlled Trials **Overall N** 1049 **Duration of study** 54 wks **Quality rating** Fair	**Inclusion Criteria:** • Age: 18-75 • Diagnosed according to 1987 ACR criteria • Persistent synovitis for > 3 mos and < 3 yrs • > 10 swollen joints, and > 12 tender joints • 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C-reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS • 20 mg MTX (required) **Exclusion Criteria:** • Prior txt with: MTX, received other DMARDs within 4 wks of entry • Used ETN, INF, ADA or other anti-TNF-á agent	**Interventions, dose** D1: MTX: wk 54 mean: 15.1mg/wk Placebo D2: MTX wk54 mean: 15.5mg/wk IFX: 3mg/kg D3: MTX: mean wk 54: 14.9mg/wk IFX: 6mg/kg **Number in group** D1: 298 D2: 373 D3: 378 **Mean age, years (SD)** D1: 50 D2: 51 D3: 49 **Sex, % female** D1: 74.8 D2: 71.6 D3: 67.7 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** NR **Patients with early RA, three years or less, %** D1: 100 D2: 100 D3: 100 **Treatment resistant, %** NR **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %** D1: 100 D2: 100 D3: 100 Overall: 100 **MTX naïve, %** NR **Baseline DAS-ESR score (SD)** D1: 6.69 (1.04) D2: 6.62 (1.07) D3: 6.72 (1.01) **Required treatment for latent TB** NR	**ACR** NR **HAQ** NR **DAS** D1: % remission at 54 wks by DAS28-ESR: MTX: 16.3% D2: MTX+INF: 24.7% **SF-36** NR **Radiographic measures** D1: • Changes in TSS wk 14/54 by disease activity (remission, low, moderate, high) wk 14/wk54. MTX 0.1, 2.8*, 2.1**, 6.5**/1.1, 2.2**, 3.9**, 5.8** • MTX+IFX -0.3, 0.0, 0.3, 1.3/-0.2, -0.4, 0.6, 2.1. [COMPARED TO IFX+MTX *P = 0.05, **P = 0.01] D2: • MTX+IFX -0.3, 0.0, 0.3, 1.3/-0.2, -0.4, 0.6, 2.1. **Quality of life scales** NR **Others, (please name)** • % remission, low, mod, or high disease by SDAI at wk 14/54 MTX: 2.8, 14.6, 45.5, 37.2/ 12.3, 29.5, 29.5, 28.6 (14 & 54 wks between groups, Ps: 0.001)	**Attrition/withdrawal** NR **Overall adverse events reported, n:** **NR** **Serious adverse events** NR **Malignancies** NR **Respiratory events** Tuberculosis: NR **Other infections** NR **GI** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	• hepatitis B or C virus, CHF, or lymphoma or other malignancy within past 5 yrs (excluding excised skin cancers)			• MTX+INF: 10.7, 26.0, 37.4, 25.9/21.3, 35.5, 28.5, 14.7.	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smolen et al., 2009 [167] GO-AFTER Study **Country and setting** multinational; clinics; hospitals **Source of funding** Centocor Research and Development; Schering-Plough Research Institute **Research objective** To assess the efficacy and safety of GOL for patients with active RA who had previously received one or more TNF-alpha inhibitors **Study design** RCT **Overall N** 461 **Duration of study** 24 wks **Quality rating** Fair	**Inclusion Criteria** • ≥ 18 years old • Active RA • ≥ 4 tender and swollen joints • Treated with at least 1 alpha-TNF inhibitor **Exclusion Criteria** • Inflammatory diseases • Serious AEs with previous TNF-alpha inhibitor • Ever received natalizumab or RTX • Received ANK < 4 wks or alefacept or efalizumab < 3 mos before the first dose of study drug • Had ever received cytotoxic drugs • History of latent or active granulomatous infection except latent TB • BCG vaccination < 12 mos before screening • Opportunistic	**Interventions, Dose** D1: GOL: 50 mg every 4 wks D2: GO: 100 mg every 4 wks D3: Placebo **Number in group** D1: 153 D2: 153 D3: 155 **Mean age (years)** D1: 55 D2: 55 D3: 54 **Sex, % female** D1: 74 D2: 80 D3: 85 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 9.6 (5.6 - 17.2) D2: 8.7 (5.3 - 13.2) D3: 9.8 (4.9 - 17.6) **Patients with early RA, three years or less, %:** NR **Treatment resistant, %:** NR **Tender Joint Count, mean** D1: ≥ 4 D2: ≥ 4 D3: ≥ 4 **Swollen Joint Count, mean** D1: ≥ 4 D2: ≥ 4 D3: ≥ 4 **Corticosteroid use, %** NR **DMARD use, %:** NR **MTX naïve, %:** NR **Baseline DAS score** NR **Required treatment for latent TB** D1: 10 (7%) D2: 7 (5%) D3: 10 (6%) **Other population characteristics:**	**ACR:** ACR 20: Week 14 D1: 35 D2: 38 D3: 18 Week 24 D1: 34 D2: 44 D3: 17 ACR 50: Week 14 D1: 16 D2: 20 D3: 6 Week 24 D1: 18 D2: 20 D3: 5 ACR 70: Week 14 D1: 10 D2: 9 D3: 2 Week 24 D1: 12 D2: 10 D3: 3 **HAQ:** HAQ-DI Week 14 D1: -13.4 (-27.3 to 0.0 (*P* = 0.0005) D2: -17.6 (-43.8 to D3: 0 (-17.6 to 13.3) 0.0 (*P* < 0.0001) Week 24	**Overall** Overall attrition/withdrawal (n): D1: 13 D2: 15 D3: 31 Overall: 59 Withdrawals due to adverse events (n): D1: 4 D2: 2 D3: 10 Overall: 16 Withdrawals due to lack of efficacy (n): D1: 6 D2: 5 D3: 11 Overall: 22 Adherent/compliant (n): NR Other attrition related comments? Attrition numbers include those that received rescue tx Overall adverse events reported (n): D1: 101 D2: 119 D3: 112 **Serious adverse events:** Cardiovascular events (specify) (n): HTN D1: 5 D2: 10 D3: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	infection < 6 mos before screening • Serious infection < 2 mos before screening • History of chronic infection • Demyelinating disease • Congestive heart failure • Severe, progressive, uncontrolled renal, hepatic, haematological, GI, endocrine, pulmonary, cardiac, neurological, psychiatric, or cerebral disease • Had transplanted organ or malignancy in past 5 yrs			D1: -13.3 (-33.3 to 0.0 (*P* = 0.0003) D2: -14.3 (-44.1 to 0.0 (*P* < 0.0001) D3: 0 (-25 to 17.6) **DAS:** Week 14 D1: -15.7 (-31.6 to -6.8 (*P* < 0.0001) D2: -21.5 (-38.3 to -7.5 (*P* < 0.0001) D3: -4.2 (-19.8 to 8.7) Week 24 D1: -18.6 (-36 to -2.6 (*P* < 0.0001) D2: -25.8 (-40.5 to -12.2 (*P* < 0.0001) D3: -1.6 (-17.8 to 14.8) **SF-36:** NR **Radiographic measures:** NR **Quality of life scales:** NR **Others:**	**Malignancies:** D1: 1 D2: 1 D3: 1 **Respiratory events:** Pneumonia (n): D1: 2 D2: 0 D3: 1 Upper respiratory infection (n): D1: 11 D2: 21 D3: 10 **Other infections:** Urinary tract infection (n): D1: 1 D2: 0 D3: 0 Other infections (specify) (n): Infections D1: 53 D2: 55 D3: 51 **GI:** Bowel obstruction (n): Diaherra D1: 5 D2: 12 D3: 7 Gastroenteritis D1: 0 D2: 0 D3: 1 **Other:** Infusion/injection site reactions (n):

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 9 D2: 16 D3: 6 Any other AEs: AE numbers do not include those who received Rescue therapy

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Sokolove et al., 2010[168] **Country and setting** USA; Multicenter registry **Source of funding** Consortium of Rheumatology Researchers of North America **Research objective** To compare LFT elevations in patients with rheumatoid arthritis receiving ADA, ETN or INF enrolled in the Consortium of Rheumatology Researchers of North America from October 2001 to March 2007. **Study design** Observational **Overall N** 6861 **Duration of study**	**Inclusion Criteria** • Patients receiving anti-TNF and/or all non- biological DMARDs with normal baseline ALT and/or AST values, including MTX and/or LEF, with available follow-up determinations **Exclusion Criteria** • PsA	**Comparisons (dosage and frequency)** D1: Oral DMARDs: MTX, LEF and all other non-biological DMARDs as a group (SSZ,HCQ, azathioprine, gold, penicillamine). D2: ADA: NR D3: ETN: NR D4: INF: NR **Number in group** D1: 4147 D2: 849 D3: 1383 D4: 1449 **Mean age (years)** D1: 61.2 D2: 56.14 D3: 55.6 D4: 60.4 **Sex, % female** D1: 72.8 D2: 79.5 D3: 79.9 D4: 73.7 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 9.8 (9.8) D2: 11.3 (9.6) D3: 12.0 (9.9) D4: 11.3 (9.3) **TJC, mean** D1: 3.25 D2: 4.77 D3: 3.81 D4: 3.63 **SJC, mean** D1: 4.25 D2: 5.67 D3: 4.02 D4: 5.02 **Corticosteroid use, %** NR **DMARD use, %:** NR **MTX naïve, %:** NR **Treatment resistant, %:** NR **Patients with early RA, three years or less, %:** NR **Baseline DAS score** D1: 3.47 (1.5) D2: 3.89 (1.7) D3: 3.56 (1.5) D4: 3.56 (1.4) **Required treatment for latent TB**	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** NR **Serious adverse events:** Hepatotoxicity/elevated liver enzymes (n): LFT >1× ULN, AOR D2: 1.35(95% CI 1.09 to 1.66) D3: 1.00 (95% CI 0.83 to 1.21) D4: 1.58 (95% CI 1.35 to 1.86) ALT and/or AST >2× ULN, AOR D2: 1.72 (95% CI 0.99 to 3.01) D3: 1.10 (95% CI 0.64 to 1.88) D4: 2.40 (95% CI 1.53 to 3.76) AST/ALT >2× ULN: 0.7 **Malignancies:** NR **Respiratory events:** NR **Other infections:** NR **GI:** NR **Other:** Any other AEs: LFT results (AST/ALT) based on primary model #1 of prevalent TNF-I users in patients on MTX, LEF and other	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Mean follow-up per person was 17 mos			NR **Other population characteristics, %, (CI/SD/P value):** NR	NR	non-biological DMARD	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Solomon et al., 2006[169] **Country and setting** US, multicenter **Source of funding** Merck, Pfizer, & Savient, NIH, Engalitcheff Arthritis Outcomes Initiative **Research objective** Investigate effects of various immunosuppressive medications on risk CVD in elderly pts with RA **Study design** Nested Case – Control Cohort **Overall N** 3501 (pts could be sampled more than once as controls) **Duration of study** NA - median duration 24 mos for cases & 22 mos for controls **Quality rating** Fair	**Inclusion Criteria** • PA Medicare enrollees also beneficiaries in state drug assistance program • Pts received 2+ diagnoses of RA (diagnoses seperated by min 1 wk) • Filled a prescription for immuno-suppressive meds **Exclusion Criteria** • <12 mos of registry data prior to study entry	**Interventions, Dose** D1: Case (MI or Stroke) D2: Control **Number in group** D1: 946 D2: 9460 **Mean age (years)** D1: 81 D2: 80 **Sex, % female** D1: 89 D2: 92 **Race, % white** D1: 93 D2: 94 **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** Inflamation markers (lab test ordered) D1: 34% D2: 36% Joint aspirations or injections	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NR **Overall adverse events reported, n:** NR - see comments for AE data **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Adjusted* risk for CV events (Composite/MI/Stoke) OR, 95% CI. MTX monotherapy 1.0, ref/1.0, ref/ 1.0, ref • Biologics monotherapy (ADA, ETN, IFX, or AKA) 1.0, 0.5-1.9/ 1.7, 0.5-5.7/ 1.5, 0.6-4.1 • Biologic + MTX 0.8, 0.3-2.0/ 1.8, 0.5-6.8/ 1.3, 0.4-4.0 • Glucocorticoid monotherapy 1.5, 1.1-2.1/ 1.5, 0.9-2.5/ 1.7, 1.1-2.6 [*adjusted for prior MI, prior CV accident, diabetes, race, n physician visits, n of different medications, use of

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			(had 1+ of these procedures) D1: 41% D2: 40%		beta-blockers, use of clopidogrel, and no current use of immunosuppressive agents]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004;[170] Smolen, 2006[171] ASPIRE Trial **Country, Setting:** Multinational, unversity hospitals **Funding:** Centocor **Research Objective:** To compare benefits of initiating txt with MTX and anti-TNFá with those of MTX txt alone in pts with RA of < 3 yrs duration **Study Design:** RCT **Overall N:** 1049 **Study Duration:** 54 wks	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to 1987 ACR criteria • Persistent synovitis for > 3 mos and < 3 yrs • > 10 swollen joints, and > 12 tender joints • 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C-reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS • 20 mg MTX (required) **Exclusion Criteria:** • Prior txt with: MTX, received other DMARDs within 4 wks of entry • Used ETA, INF, ADA or other anti-TNF-á agent • History of TB; HIV, hepatitis B or C virus, CHF, or lymphoma or other malignancy	**Interventions, dose:** D1: MTX (20 mg/wk) + placebo D2: MTX + INF (3 mg/kg/wk) D3: MTX + INF (6 mg/kg/wk) **N:** D1: 282 D2: 359 D3: 363 **Mean age, yrs:** D1: 50 D2: 51 D3: 50 **Sex, % female:** D1: 75 D2: 71 D3: 68 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 0.9 D2: 0.8 D3: 0.9 **TJC, mean:** D1: 34 D2: 32 D3: 33 **SJC, mean:** D1: 22 D2: 21 D3: 22 **DMARD use, %:** D1: 35 D2: 29 D3: 32 **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** NR **JSN:** D1: 3.0 D2: 2.9 D3: 2.9	**At weeks 30 to 54** **HAQ:** D1: 0.68 D2: 0.80 D3: 0.88; (D2 vs. D1; *P* = 0.03) (D3 vs. D1; *P* < 0.001) **At 54 weeks** **HAQ > 0.22, %:** D1: 65.2 D2: 76.0 D3: 75.5 (D2 vs. D1; *P* = 0.003) (D3 vs. D1; *P* < 0.004) **ACR20, %:** D1: 53.6 D2: 62.4 D3: 66.2 (D2 vs. D1; *P* = 0.028) (D3 vs. D1; *P* < 0.001) **ACR50, %:** D1: 32.1 D2: 45.6 D3: 50.4 (D2 vs. D1; *P* = 0.001) (D3 vs. D1; *P* < 0.001) **ACR70, %:** D1: 21.2 D2: 32.5 D3: 37.2 (D2 vs. D1; *P* = 0.002) (D3 vs. D1; *P* < 0.001) **ACR-N, %:** D1: 26.4 D2: 38.9	**SAEs:** D1: 11 D2: 14 D3: 14 **Serious Infections:** D1: 2.1 D2: 5.6 D3: 5.0 **Infusion or injection reaction:** D1: 7 D2: 21 D3: 15 **TB:** D1: 0 D2: 0.8 D3: 0.3 **Nausea:** D1: 18 D2: 20 D3: 17 **URTI:** D1: 21 D2: 25 D3: 28	**Overall Attrition Rate, %:** 14.9 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	within past 5 yrs (excluding excised skin cancers)		**HAQ:** D1: 1.5 D2: 1.5 D3: 1.5	D3: 46.7 (P < 0.001) **Modified Sharp:** D1: 3.7 D2: 0.4 D3: 0.5 (P < 0.001) **Increase in radiographic score, %:** INF: 39 vs. MTX 61 (P < 0.001) **Employability:** INF+MTX (OR 2.4, P < 0.001) MTX (P = 0.56) Combo has higher probability of improvement than MTX alone **Net increase in employability:** MTX+INF: 8% MTX-only: 2% **Employability status changed from employable to unemployable, %:** INF: 8 MTX-only: 14 (P = 0.05) **SF-36 Physical component summary scores** D1: 11.7 D2: 13.2 D3: 10.1 D3 vs. D1, P = 0.10 D3 vs. D2; P = 0.003 **Modified Sharp/van der Heijde Score change:**		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				D1: 3.7 D2: 0.4 D3: 0.5 *P* < 0.001 **Erosion Score change:** D1: 3.0 D2: 0.3 D3: 0.1 *P* < 0.001 **JSN Score change:** D1: 0.6 D2: 0.1 D3: 0.2 *P* < 0.001		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999[172]; Strand et al., 1999[173]; Cohen et al., 2001[174] **Country, Setting:** US and Canada, multicenter (47 university & private rheumatology practices) **Funding:** Hoescht Marion Roussel **Research Objective:** Efficacy and safety of LEF with placebo and MTX in active RA **Study Design:** RCT **Overall N:** 482 (active arms-364) **Study Duration:** 12 mos (w/ 1 year followup)	**Inclusion Criteria:** • Age: 18 or older • Diagnosed according to ACR criteria; DMARDs discontinued at least 30 days prior • Duration of condition at least 6 mos • 10 mg stable prednisone (or equivalent) • NSAIDs if dosages stable at least 30 days prior to enrollment **Exclusion Criteria:** • Pregnant or lactating • Prior treatment with: MTX • Inflammatory joint disease not caused by RA, • History of clinically significant drug or alcohol abuse, or admitted to consumption of more than 1 alcoholic drink per day	**Interventions:** D1: LEF (20 mg/week) D2: MTX (7.5 to 15 mg/week) **N:** D1: 182 D2: 182 **Mean age, yrs:** D1: 54.1 D2: 53.3 **Sex, % female:** D1: 72.5 D2: 75.3 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 7.0 D2: 6.5 **TJC, mean:** D1: 15.5 D2: 15.8 **SJC, mean:** D1: 13.7 D2: 13.0 **DMARD use, %:** D1: 55.5 D2: 56.0 **Corticosteroid use, %:** D1: 53.8 D2: 52.7 **MTX naive, %:** Both groups 100 **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF positive:** D1: 64.8 D2: 59.4 **MHAQ:** D1: 0.8 D2: 0.8	**At 12 mos** **ACR 20, %** D1: 52 D2: 46 **ACR 50, %** D1: 34 D2: 23 **ACR 70, %** D1: 20 D2: 9 **MHAQ mean change** D1: -0.3 D2: -0.2 **Sharp score change** D1: 0.53 (n:131) D2: 0.88 (n= 138) (P = 0.05) **Mean change HAQ-DI** D1: -0.45 (n= 164) D2: -0,26 (n= 168) (P ≤ 0.01) **Mean change SF-36 physical component** D1: 7.6 (n= 157) D2: 4.6 (n=162) **Work productivity mean change** D1: 9.8 (n= 138) D2: 7.5 (n= 148)	**SAEs:** D1: 1.1 D2: 2.7 **Infections:** D1: 56.6 D2: 59.9 **Abdominal Pain:** D1: 13.7 D2: 15.4 **Nausea:** D1: 20.9 D2: 19.2 **Back pain:** D1: 8 D2: 2 **Diarrhea:** D1: 36.8 D2: 21.6 **Oral Ulcers:** D1: 6.8 D2: 10.5 **GI Events:** D1: 5.5 D2: 1.7 **Elevated Transaminases:** D1: 7.1 **D2: 4.4**	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Strand et al., 2006[175] **Country and setting** Multinational **Source of funding** Roche, Genentech **Research objective** Evaluate long-term impact on physical function of a single course of rituximab in rheumatoid factor, seropositive patients with active rheumatoid arthritis (RA) despite ongoing methotrexate treatment. **Study design** Controlled Trials **Overall N** 161 **Duration of study** 2 yrs. **Quality rating** Poor: very high attrition rate	**Inclusion Criteria** • Age ≥ 21 years • Fulfillment of revised 1987 American Rheumatism Association criteria • Active disease (defined as ≥ 8 swollen and ≥ 8 tender joints and at least 2 of following: a serum CRP level ≥1.5mg/dl, ESR ≥ 30mm/h, or morning stiffness ≥45 minutes) despite treatment with > 10mg of MTX per week; RF ≥ 20 IU per ml.; failed at least 1 DMARD. **Exclusion Criteria** • Autoimmune disorder other than RA (except concurrent Sjogren's) • American Rheumatism Association functional class IV disease • Active	**Interventions, Dose** D1: • Methotrexate ≥ 10 mg/wk • Median dose of MTX at study entry was 12.5-15 mg/week • Placebo D2: • Methotrexate: Median dose of MTX at study entry was 12.5-15 mg/week • Rituximab1000 mg days 1 and 15 D3: • Methotrexate: Median dose of MTX at study entry was 12.5-15 mg/week • Rituximab1000 mg days 1 and 15 • Other: Cyclophosphamide 750 mg days 3 and 17; Median dose of MTX at study entry was 12.5-15 mg/week D4: • Methotrexate > or equal to 10 mg/wk; Median dose of MTX at study entry was 12.5-15 mg/week • Rituximab1000 mg days 1 and 15 **Number in group** D1: 40 D2: 40 D3: 41	**Mean disease duration, years (SD) yrs** D1: 11.0 (7.1) D2: 9.3 (5.5) D3: 9.8 (6.1) D4: 11.5 (7.3) **Patients with early RA, three years or less, %** D1: 0 D2: 0 D3: 0 D4: 0 **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** D1: 32 (12.8) D2: 33.8 (14.8) D3: 32.7 (13.8) D4: 32.2 (15.9) **Swollen Joint Count, mean (SD)** D1: 18.6 (9.6) D2: 20.5 (11.2) D3: 19.4 (10.2) D4: 22.7 (12.7) **Corticosteroid use, %** NR **DMARD DMARDs failed (other than MTX), n (SD)** D1: 2.6 (1.3) D2: 2.5 (1.6) D3: 2.6(1.4) D4: 2.5(1.4) **MTX naïve, %** NR	**ACR mean difference/ absolute difference (%)** Week 24 ACR 20: D1: 15 (38) D2: 26 (65), *P* = 0.05 D3: 31 (76), *P* = 0.01 based on Fisher's exact test for comparisons with placebo + MTX group; Wk 48: 19 (46%), *P* < D4: NR ACR50: D1: 5 (13) D2: 13 (33) D3: 17 (41), *P* = 0.01 based on Fisher's exact test for comparisons with placebo + MTX group D4: NR ACR 70: D1: 2 (5) D2: 6 (15) D3: 6 (15) D4: 9 (23), *P* = 0.05 Week 48: ACR 20 (%): D1: 8 (20) D2: 12 (30) D3: ACR 50 (%): D1: 2 (5) D2: 5 (13) D3: 10 (24), *P* = 0.05 ACR 70: D1: 0% D2: 3(8%)	**Attrition/withdrawal** Overall, n: D1: 34 D2: 36 D3: 32 D4: 22 Overall: 124 Withdrawals due to adverse events, n: D1: 4 D2: **5 D3: 4 D4: 1 Overall: 14 Withdrawals due to lack of efficacy, n: D1: 17 D2: 5 D3: 4 D4: 4 Overall: 30 Adherent/compliant, n: NR *OTHER • D1: 13 • D2: 26 • D3: 25 • D4: 17 Overall OTHER: 81 *The majority of protocol discontinuations classified as 'other' were owing to requirement for retreatment with rituximab under a separate protocol; **includes 1 death due to pneumonia. Overall adverse events reported, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	rheumatoid vasculitis • History of systemic diseases associated with arthritis • Chronic fatigue syndrome • Serious & uncontrolled coexisting diseases • Active infection • History of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms • Primary or secondary immuno-deficiency • History of cancer (except basal cell carcinoma of skin that had been excised).	D4: 40 **Mean age (years)** D1: 53.7 (11.2) D2: 53.5 (10.2) D3: 52.9 (9.9) D4: 53.5 (11.9) **Sex, % female** D1: 80 D2: 72.5 D3: 82.9 D4: 75.0 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Baseline DAS28 score, mean (SD)** D1: 6.9 (0.7) D2: 6.8 (1.0) D3: 6.9 (0.8) D4: 6.8 (0.9) **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** HAQ-DI baseline mean (± SD): D1: 2.0 (0.5) D2: 2.0 (0.6) D3: 1.8 (0.7) D4: 1.8 (0.6) MD global,(± SD): D1: 66.7 (15.7) D2: 66.7 (16.2) D3: 67.4 (14.5) D4: 65.6 (14.0) Pt global,(± SD): D1: 65.4 (20.3) D2: 67.8 (22.8) D3: 63.4 (20.5) D4: 61.4 (20.4) Pt pain assessment (VAS, mm): D1: 62.6 (16.1) D2: 62.2 (20.2) D3: 57.5 (20.0) D4: 54.6 (17.8) ESR (mm/h): D1: 51.5 (31.8) D2: 46.9 (22.9)	D3: 4 (10) D4: 6 (15%), *P* = 0.05 Week 104: ACR 20: D1: 5 (13%) D2: 3 (8%) D3:NR ACR 50: D1: 4 (10%) D2: 3 (8%) D3: 4 (ACR 70: D1: 3 (8%) D2: NR D3: 3 (8) D4: 4 (10%) **HAQ, mean difference/ absolute difference (CI/SD/P Value)** D1: Mean change from baseline at Wk 12 (n = 39): -0.3 *(P* > or equal to 0.0001); Wk 24 (n = 37): -0.4 *(P* = 0.0002); Wk 48 (n = 25): -0.3 *(P* > or equal to 0.005); Wk 72 (n = 15): -0.3 *(P* > or equal to 0.05) D2: Mean change from baseline at Wk 12 (n = **DAS** **SF-36** **Radiographic measures** NR **Quality of life scales** NR	D1: 4 D2: 5 D3: 4 D4: 1 Overall: 14 **Serious adverse events** Death, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1 **Malignancies** NR **Respiratory events** Pneumonia, n: D2: 1 (reported above as well as it led to death) Upper respiratory infection, n: D1: 6 (through wk24 for all Ds in this category) D2: 4 D3: 2 D4: 4 **Other infections** NR **GI** Nausea or vomiting, n: D1: 1 D2: 2 D3: 4 D4: 0 **Other** Infusion/injection site reactions, n: (through wk24 for all Ds in this category)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D3: 54.9 (28.6) D4: 53.3 (23.4) Week104: 1 (3) Overall: Overall HAQ-DI baseline mean (± SD): (1.8-2.0)	**Others** % of patients continuing protocol participation Week 24: D1: 92.5 D2: 95.0 D3: 90.2 D4: 97.5 Week 48: D1: 62.5 D2: 77.5 D3: 82.9 D4: 95.0 Week 72: D1: 37.5 D2: 42.5 D3: 53.7 D4: 70.0 Week 104: D1: 15.0 D2: 10.0 D3: 21.9 D4: 45.0 % of patients reporting improvements in HAQ-DI that met or exceeded MCID (a reduction of > or equal to 0.25) Week 12: D1: (n = 39): 38 D2: (n = 39): 63 D3: (n = 40): 61 D4: (n = 40): 55 Week 24: D1: (n = 37): 45 D2: (n = 38): 68 D3: (n = 37): 59 D4: (n = 39): 63	D1: 12 D2: 18 D3: 13 D4: 13 Skin rash, n: (through wk 24 for all Ds in this category) D1: 1 D2: 4 D3: 4 D4: 1 Other AEs 1, n: D1: Hypotension (through wk24 for all Ds inse categories): 7; hypertension, 6 *a change of more than 30 mm Hg in systolic or diastolic blood pressure from pressure at screening was classified as hypotension or hypertension D2: Hypotension Through wk 24 for all groups in these categories. Arthralgia, n: D1: 3 D2: 3 D3: 1 D4: 4 Back pain: D1: 2 D2: 4 D3: 3 D4: 0 Through wk 24 for all groups in these categories. Cough, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Week 48: D1: (n = 25): 28 D2: (n = 31): 43 D3: (n = 34): 39 D4: (n = 38): 68 Week 72: D1: (n = 15): 18 D2: (n = 17): 18 D3: (n = 22): 22 D4: (n = 28): 48	D1: 0 D2: 5 D3: 1 D4: 2 Pruritus, n D1: 0 D2: 4 D3: 4 D4: 0 Through wk 24 for all groups in this category. Dyspnea, n: D1: 0 D2: 4 D3: 0 D4: 0 Any event up to Wk 24: D1: 32 D2: 32 D3: 30 D4: 34 Any event up to Wk 48: D1: 34 D2: 36 D3: 35 D4: 35 Serious adverse event up to week 24: D1: 3 D2: 2 D3: 6 D4: 3 Serious adverse event up to week 48: D1: 4 D2: 4 D3: 7 D4: 4

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Any event associated with first infusion D1: 12 D2: 18 D3: 13 D4: 13 Exacerbation of RA through wk 24: D1: 16 D2: 6 D3: 6 D4: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Strangfeld et al., 2009[176] **Country and setting** German, multicenter **Source of funding** Essex, Wyeth, Abbott, Amgen, Hoffman-La Roche, Bristol-Meyers Squibb **Research objective** Investigate if TNF-alpha inhibitors as a class, or by mode of impact, are related to higher rates of herpes zoster in RA pts **Study design** Prospective Cohort Study **Overall N** 5040 **Duration of study** varied, up to 36 mos from May 2001 to December 2006 **Quality rating** Good	**Inclusion Criteria** • RA pts initiating biologic therapy or switching to another DMARD (Oral or Biologic) **Exclusion Criteria** • Missing follow up data • (152 patients or 2.9% of eligible)	**Interventions, Dose** D1: Oral DMARDS D2: Biologics D3: Corticosteroids D4: Combination therapy **Number in group** D1: 1252 D2: 591 D3: 1423 D4: 1774 **Mean age (years)** D1: 53.8 D2: 52.9 D3: 54.2 D4: 56.2 **Sex, % female** D1: 77.8 D2: 73.3 D3: 80.2 D4: 78.6 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: median (IQR): 9 (4-16) D2: 8.5 (4-14) D3: 10 (5-17) D4: 6 (3-12) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** Glucocorticoid/ Prenisolone: D1: 86.1/35.1 D2: 84.4/36.7 D3: 81.6/29.2 D4: 76.5/19.3 **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: 5.8 (1.3) D2: 5.9 (1.2) D3: 5.7 (1.3) D4: 5.0 (1.3) **Required treatment for latent TB**	**ACR** ACR 20: No efficacy outcomes reported ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NR **Overall adverse events reported, n:** D1: NR - see additional comments for germane analyses **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Adjusted (Age & Propensity score) HR for Herpes Zoster. • Glucocorticoids 1-9 mgs 1.86 (95%CI 0.92-3.78) • Glucocorticoids 10+mg 2.52 (1.12-5.65) [ref - 0mgs of glucocorticoids]. • Anti-TNF combined D1.63 (0.97-2.74), ETN 1.36 (0.73-2.55), IFX or ADA 1.82 (1.05-3.15) [ref - traditional DMARDs]. • Results from subsample (N = 1344) of patients who could act as own control - HR for Herpes Zoster. ETN 1.09 (0.39-3.06); IFX 2.43

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR **Other population characteristics, %, (CI/SD/P value)** NR		(0.94-6.26); ADA 3.01 (1.36-6.64) [ref - traditional DMARDs]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Strangfeld et al., 2010[177] **Country and setting** Germany **Source of funding** Essex Pharma, Wyeth pharma, Amgen, Biovitrum, Abbott, Bristol-Myers Squibb, Roche, UCB **Research objective** To investigate the risk of new or recurrent malignancy in patients with RA receiving biologics compared to conventional DMARDs **Study design** Observational **Overall N** 5120 **Duration of study** 60 mos	**Inclusion Criteria** • Treatment resistant failure of at least one other DMARD **Exclusion Criteria** • NR	**Comparisons (dosage and frequency)** D1: Prior malignancies-conventional DMARD D2: Prior malignancies-biologic (ETN, ADA, INF, ANK) D3: Without prior malignancies-conventional DMARD D4: Without prior malignancies-biologics (ETN, ADA, INF, ANK) **Number in group** D1: 55 D2: 67 D3: 1719 D4: 3279 Overall: 5120 **Mean age (years)** D1: 63.2 D2: 64.0 D3: 55.9 D4: 53.6 Overall: comparison b/t strata: *P*<0.001 **Sex, % female** D1: 74.5 D2: 67.2 D3: 78.7 D4: 78.2	**Mean disease duration, years** D1: median (IQR): 7 (3, 13) D2: median (IQR): 10 (6, 16.5) D3: median (IQR): 6 (2.5, 12) D4: median (IQR): 9 (5, 17) Comparison b/t strata: *P*=0.286 **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** NR **DMARD use, %:** No of previous DMARDs: D1: 1.9 (1.0) D2: 3.7 (1.5) D3: 1.9 (1.1) D4: 3.6 (1.4) Comparison b/t strata: *P*= 0.656 **MTX naïve, %:** D1: NR D2: NR D3: NR D4: NR Overall: 2.7 **Treatment resistant, %:** NR **Patients with early RA,**	**ACR mean difference/ absolute difference (CI/SD/P Value):** NR **HAQ, mean difference/ absolute difference (CI/SD/P Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):**	**Overall** Overall adverse events reported (n): D1: 5 D2: 9 D3: 4 D4: 1 Overall: 19 **Serious adverse events:** Death (n): D1: 0 D2: 0 D3: 4 D4: 1 Overall: 5 **Malignancies:** Recurrent cancer D1: 5; crude incidence rates: 31.4 (95% CI,10.2 to 73.4) D2: 9; crude incidence rates: 45.5 (95% CI, 20.8 to 86.3) D3: NR Overall: (incidence rate ratio anti-TNFá agents vs. DMARDs: 1.4 (95% CI, 0.5 to 5.5) *P*=0.63) 74 patients among the 4,998 patients who did not have a prior malignancy developed an incident tumor. **Respiratory events:** NR **Other infections:** NR	**Quality rating for efficacy/effectiveness?** NR **Quality rating for observational studies** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		Race, % white NR **Race, % black** NR **Ethnicity, Latino** NR	**three years or less, %:** NR **Baseline DAS score** D1: Mean (SD): 5.4 (1.1) D2: Mean (SD): 5.7 (1.3) D3: Mean (SD): 5.0 (1.3) D4: Mean (SD):5.8 (1.3) Comparison b/t strata: *P*=0.282 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR		**GI:** NR **Other:** Number of co-morbidities, mean (SD): • Pts who developed malignancies during the study: 2.5 (2.1) • Pts who did not develop malignancies during the study: 1.7(1.9) COPD • Pts who developed malignancies during the study: 11/74 (14.9%) • Pts who did not develop malignancies during the study: 223/4924 (4.5%) *P*<0.0001 Chronic gastrointestinal diseases • Pts who developed malignancies during the study: 13/74 (17.6%) • Pts who did not develop malignancies during the study: 406/4924 (8.2%) *P*=0.008 Chronic renal diseases • Pts who developed malignancies during the study: (4/74 (5.4%)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					• Pts who did not develop malignancies during the study: 159/4924 (3.2%) *P*=0.22 The univariate analysis showed that patients with a very active disease (DAS28 >5.1, mean: 5.93) during follow-up had a 2 times higher cancer risk than those with low disease activity (DAS28 <3.2, mean: 2.75) Overall number of observed cancers in patients exposed to anti-TNFá agents: non-significantly lower than the expected number from the general population (standardized incidence rate ratio: 0.75, 95% CI 0.54 to 1.01). No difference was found for patients not exposed to biologics.	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Suissa et al., 2004[178] **Country, Setting:** US, 2 large databases **Funding:** Aventis **Research Objective:** Assess risk of hepatic events associated with the use of LEF and other DMARDS compared to MTX **Study Design:** Observational **Overall N:** 41,885 **Study Duration:** 3 yrs	**Inclusion Criteria:** • Age: 18 and older • Previous use of DMARDs: after 9/1/98 • ICD 9 code for RA **Exclusion Criteria:** •< 3 mos eligibility in health insurance plan •Pts with outcome 3 mos before cohort study	**Interventions, dose:** NR **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	When compared to MTX, No increased risk with LEF(rate ratio 0.9, 95% CI, 0.2-4.9), or with traditional DMARDS (RR 2.3; 95% CI, 0.8-6.5) • There is an increased risk with biologic DMARDS (RR:5.5; 95% CI, 1.2-24.6) • Rate of nonserious hepatic events was also increased with biologic DMARDS (RR 1.5; 95% CI, 1.0-2.3), but not LEF (RR:0.9; 95% CI, 0.7-1.3) and traditional DMARDS (RR 1.1; 95% CI, 0.8-1.4)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA: cohort **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Suissa et al., 2006[179] **Country, Setting:** Canada, PharMetrics claims database **Funding:** Sanofi-Aventis; Canadian Institutes of Health Research **Research Objective:** To assess risk of ILD in pts with RA treated with LEF. **Study Design:** Retrospective Cohort Study **Overall N:** 62,734 **Study Duration:** Sept 1, 1998 through Dec 31, 2003	**Inclusion Criteria:** • Age: 18 or older • DMARD-treated cohort defined as all subjects who received at least 1 prescription for a DMARD on or after September 1, 1998, mo LEF was approved in US **Exclusion Criteria:** • No DMARD prescription • Subjects with outcome of interest during 1-yr period prior to cohort entry	**Interventions, dose:** D1: Cases of ILD **D2: Controls** **N:** D1: 74 D2: 7400 **Mean age, yrs:** D1: 62 D2: 61 **Sex, % female:** D1: 70 D2: 74 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Risk of ILD in pts treated with LEF compared with those not treated with LEF; adjusted OR 1.9, 95% CI,1.1-3.6 (all ORs reported here were adjusted for the concurrent use of the other DMARDs, the other anti-RA drugs, as well as sex and comorbid conditions) • Increase was less and was not significant with use of MTX (OR 1.4; 95% CI,0.8-2.3) • No increase in risk of ILD with LEF among pts who had no previous MTX use and no interstitial lung disease prior to cohort entry (37 cases and 4,259 controls); OR 1.2; 95% CI,0.4-3.1. This group did have an increased risk of ILD with MTX treatment (OR 3.1; 95% CI,1.5-6.4). Among those who had previously taken MTX or who had a previous diagnosis of ILD (37 cases and 3,141 controls), the risk of ILD was elevated with LEF treatment (OR 2.6; 95% CI,1.2-5.6) but was decreased with MTX treatment (OR 0.4; 95% CI,0.2-0.9)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: nested case control design **Quality Rating:** Fair

Nes

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Suissa et al., 2006[180] **Country and setting** North America - claims data **Source of funding** Sanofi-Aventis Canadian Institutes of Health Research, Fonds de la recherche en sante du Quebec **Research objective** Assess risk of AMI associated with use of DMARDS and other RA txt **Study design** **Nested Case control Cohort** **Overall N** 6138 for case-control with 1:10 ratio selected from eligible RA cohort of 107,908 subjects **Duration of study** vaired, mean = 14 mos (11). All subjects were followed from date of cohort entry until one of following occurred: termination of health	**Inclusion Criteria** • RA pts with 1 year of eligibility in database **Exclusion Criteria** • AMI during 1 year prior to cohort entry	**Interventions, Dose** D1: Other: Case (Acute Myocardial Infarction - AMI) D2: Other: Control **Number in group** D1: 558 D2: 5580 **Mean age (years)** D1: 65 D2: 65 **Sex, % female** D1: 55 D2: 55 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** NR **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** Glucocorticoid therapy: D1: 15.1 D2: 12.0 **DMARD use, %** D1: 25.4 D2: 30.4 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: Mean follow up: 14 mos	**ACR** ACR 20: D1: Efficacy outcomes NR ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference** NR	**Overall** Overall attrition/withdrawal, n: D1: NA, LTF NR for database **Overall adverse events reported, n:** NR - see additional comments for germane analyses **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Adjusted* RR of AMI for current users of RA medications: MTX monotherapy 0.81 (95%CI 0.60-1.08) • LEF 0.28 (0.12-0.64) • Biologic Agents (IFX, ETN, & ANA combined) 1.30 (0.92-1.83) • All other DMARDS (includes HCQ, SSZ, & 10 other txt) 0.67 (0.46-0.97) • Glucocorticoids 1.32 (1.02-1.72) [*Adjusted for age & comorbidities]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
plan enrollment, death, end of study period (December 31, 2003), or outcome of interest, namely AM			(11) D2: 14 mos (11)		
Quality rating Fair					

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Svennsson et al., 2003[181] **Country, Setting:** Sweden, multicenter (5 rheumatologic units covering both urban and rural districts) **Funding:** Swedish Rheumatism Association and Vardal Foundation **Research Objective:** To study and compare outcomes of 2 different DMARD/corticosteroid options in txt of early RA in clinical practice **Study Design:** RCT **Overall N:** 245 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Diagnosed according 1987 revised ACR • Duration of condition: less than 2 yrs • Considered to be in need of Css or DMARDS by treating physician's judgment • NSAIDS and analgesics allowed **Exclusion Criteria:** • Prior txt with: DMARDS or Cxs • Per authors--regarded as not suitable for various medical or non-medical reasons	**Interventions:** D1: PNL + MTX D2: SSZ + PNL at lowest possible dose **Overall:** PNL: 7.5 to 15 mg daily for 1 to 3 mos. with subsequent reduction to lowest possible dose MTX: 5 to 15 mg per wk SSZ: 2 to 3 grams daily **N:** D1: 113 D2: 108 **Mean age (yrs):** D1: median 54 D2: median 52 **Sex, % female:** D1: 59 D2: 67 **Race, % white:** **NR Mean disease duration, yrs:** D1: 6 mos. D2: 7 mos	**TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** D1: 0 D2: 0 **Corticosteroid use, %:** D1: 0 D2: 0 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **DAS28 median:** D1: 5 D2: 4.9 **Larsen:** D1: 5 D2: 3 **HAQ:** D1: 0.9 D2: 0.9 **RF +:** D1: 71 D2: 39	No significant differences between txt groups for individual response, remission, function, or radiologic progression **Response (EULAR individual response criteria for good/moderate/no response, %)** D1: 30/40/30. D2: 33/30/37% (*P* = 0.319) **Remission, %** D1: 29 D2: 19 (*P* = 0.095) **Mean change in HAQ** D1: 0.35 D2: -0.38 (*P* = 0.752) **Mean change in Larsen score** 6.2 vs. 4.1 (*P* = 0.298) **Completers, %** D1: 81% D2: 53% Survival analysis between 2 groups (using withdrawals due to AEs or inefficacy as terminal event) showed a highly significant difference in survival times between 2 groups (*P* = 0.0005)	**Overall:** D1: 9.9 **D2: 31.6**	**Overall Attrition Rate, %:** 39.6 **ITT Analysis:** No another type of analysis was used (define): Although they state it was an ITT analysis, statistical analysis based on 221 of the 245 pts with available data for clinical outcomes and for about 72% of the cases for Larsen score (based on available **Quality Rating:** Poor for efficacy, fair for adverse events

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Svensson et al., 2005[182] **Country, Setting** Sweden, multicenter **Funding:** Swedish Rheumatism Association and others **Research Objective** Efficacy of low-dose PNL on joint damage and disease activity in pts with early RA being treated concomitantly with DMARDs **Study Design:** RCT **Overall N:** 250 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age 18 to 80 yrs • Diagnosed according ARA 1987 revised criteria • Duration ≤ 1 yr: pt in BARFOT study • DAS28 score >3.0 • Started by treating rheumatologist on first DMARD • Concomitant NSAIDS txt permitted • Intraarticular steroid injections allowed except 2 wks prior to any clinical evaluation **Exclusion Criteria:** • Pregnant or lactating • Glucocorti-coids, DMARDs • Contraindi-	**Interventions, dose:** D1: DMARD (SSZ 2 g/day or MTX mean dose 10 mg/week, dosages NR) + PNL (7.5 mg/d) D2: DMARD only **N:** D1: 119 D2: 131 **Mean age, yrs:** D1: 51 D2: 59 **Sex, % female:** D1: 65 D2: 63 **Race, % white:** D1: NR D2: NR	**Mean disease duration, yrs:** D1: 6.5 mos D2: 5.8 mos **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** Overall: 100 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** D1: 5.28 D2: 5.42 **HAQ:** D1: 1.01 D2: 0.98 **SOFI:** D1: 8 D2: 9	**At 2 yrs:** DAS < 2.6 disease remission, % achieved D1: 55.5 D2: 32.8 (*P* = 0.0005) DAS28, scores over time ± SD D1: 5.3 ± 1.1 at baseline to 2.7 ± 1.5 after 1 yr and 2.7 ± 1.3 after 2 yrs D2: 5.4 ± 1.0, 3.3 ± 1.5, and 3.2 ± 1.4 HAQ scores mean decrease over time : D1: 1.0 at baseline to 0.4 at 1 year and 0.5 D2: 1.0, 0.6, and 0.7 (*P* value NR) Improvement in mean SOFI index D1: mean decreased from 8 at baseline to 4 at 1 year and 4 after 2 years D2: 9, 6, and 7 respectively (*P* value NR) Total sharp score, median IQR change i D1: 1.8 (IQR 0.5-6.0) D2: 3.5 (IQR 0.5-10.0) (*P* = 0.019) Newly eroded joints per pt, median D1: 0.5 (IQR 0-2) D2: 1.25 (IQR 0-3.25) (*P* = 0.007)	NR	**Overall Attrition Rate, %:** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

	cation for glucocorticoid therapy • Previous fragility fractures, pts < 65 years with T score <-2.5 on bone mineral densitometry	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable van Halm, V.P. et al.; 2006[183] **Country and setting** Amsterdam, Netherlands; outpatient clinic **Source of funding** Not reported **Research objective** Investigate possible associations between CVD and use of conventional DMARDs in RA **Study design** Case Control Cohort **Overall N** 613 **Duration of study** Recruitment: 1953 - 2002; Follow-up: 2002 - 2004. **Quality rating** Fair	**Inclusion Criteria** • Fulfillment of American College of Rheumatology criteria of RA. **Exclusion Criteria** • NR	**Interventions, Dose** D1: • PRED: dosage and frequency NR • MTX; dosage and frequency NR • SSZ; dosage and frequency NR • Hydroxychlorquine: dosage and frequency NR D2: • PNL: dosage and frequency NR • MTX: dosage and frequency NR • SSZ: dosage and frequency NR • Hydroxychlorquine: dosage and frequency NR **Number in group** D1: 541 D2: 72 **Mean age (years)** D1: 62, SD 11 D2: 67, SD 10 *P* = 0.001 **Sex, % female** D1: 72 D2: 58 *P* = 0.02 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino**	**Mean disease duration, years (SD)** D1: 7.7 yrs, IQR: 5-11 D2: 10.6, IQR: 8-13 *P* = 0.001 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: PRED ever: 31 D2: PRED ever: 25 Overall: PRED ever: *P* = 0.32 **DMARD use, %** D1: • Median use: 2 • IQR: 2-3 • SSZ HCQ or MTX never: 5 • SSZ ever: 78 • HCQ ever: 40 • MTX ever: 72 D2: • Median use: 3, IQR: 1-3 • SSZ HCQ or MTX never: 17 • SSZ ever: 65 • HCQ ever: 38 • MTX ever: 44 Overall: • Median use: *P* = 0.01	**ACR** NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NA **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** Model 2 OR (95% CI) corrected for age, gender, smoking, RA duration, htn, diabetes, and hypercholesteremia with all comparisons to never MTX, SSZ, or HCQ; MTX 0.47 (0.07-3.23) • SSZ 0.31 (0.07-1.33) • HCQ 0.45 (0.10-2.04) • MTX and SSZ 0.24 (0.07-0.85) • MTX and HCQ 0.54 (0.08-3.66) • SSZ and HCQ 0.34 (0.05-2.16) • MTX, SSZ, and HCQ 0.27 (0.07-0.99)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		NR	• SSZ HCQ or MTX never: *P* = 0.001 • SSZ ever: *P* = 0.02 • HCQ ever: *P* = 0.67 • MTX ever: *P* = 0.001 **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: • Erosive pts (%): 80 • DMARD naive (%): 3 • Hypertension: 19% • Hypercholesterolemia: 2% D2: • Erosive pts (%): 92 • DMARD naive (%): 10 • Hypertension: 49% • Hypercholesterolemia: 21% Overall: • Erosive pts: *P* = 0.02 • DMARD naive: *P* = 0.002 • Hypertension: *P* = 0.001 • Hypercholesterolemia: *P* = 0.001		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: van Riel et al., 2006[184] **Country, Setting:** Multinational, multicenter **Funding:** Wyeth **Research Objective:** Evaluate efficacy and safety of ETA monotherapy vs. ETA + MTX in RA pts with inadequate response to MTX **Study Design:** RCT, open-label **Overall N:** 315 **Study Duration:** 16 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed according to ACR criteria • Functional class of: I-III • Previous use of DMARDs • Inadequal control of RA symptoms on MTX ≥ 12.5 mg/wk for ≥3 mos **Exclusion Criteria:** • DMARDS other than MTX within 12 wks of screening; prednison ≥10 mg/d • Corticosteroid injections within 6 wks • 'Significant' concurrent medical illness	**Interventions, dose:** D1: ETA (25 mg s.c. twice wkly) D2: ETA (25 mg s.c. twice wkly) + MTX (≥12.5 mg/wk) **N:** D1: 159 D2: 155 **Mean age, yrs:** D1: 53 D2: 54 **Sex, % female:** D1: 79.2 D2: 76.8 **Race, % white:** D1: 99.4 D2: 98.7	**Mean disease duration, yrs:** D1: 10.0 D2: 9.8 **TJC, mean:** D1: 14.6 D2: 14.7 **SJC, mean:** D1: 11.2 D2: 11.9 **DMARD use, %:** NR **Corticosteroid use, %** D1: 49.1 D2: 55.5 **MTX naive, %:** Overall: 0 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 6.2 D2: 6.3 **HAQ:** D1: 1.6 D2: 1	**DAS28 improvement of > 1.2 units, %:** D1: 72.8 D2: 75.2 Difference -2.3 (95% CI, -13.1-8.2; *P* = 0.658) **EULAR response maintained, %:** D1: 80.0 D2: 82.4 (*P* = NR) **ACR 20, %:** D1: 71.0 D2: 67.1 Difference 3.9 (95% CI, -6.4-14,2; *P* = 0.46) **ACR 50, %:** D1: 41.9 D2: 40.1 Difference 1.8,(95% CI, -9.2-12.8 ; *P* = 0.75) **ACR 70, %:** D1: 17.4 D2 : 18.4 Difference -1.0 (95% CI, -9.6-7.6; *P* = 0.82)	**Overall:** D1: 62.9 D2: 70.3 **SAEs:** D1: 5.0 D2: 4.5 **Infections:** D1: 24.5 D2: 32.3 **Serious Infections:** D1: 0.6 D2: 0.3 **Infusion or injection reaction:** D1: 6.3 D2: 6.5 **Dizziness:** D1: 0.6% D2: 0 **Headache:** D1: 8.8 D2: 6.5 **URTI:** D1: 8.2 D2: 12.9	**Overall Attrition Rate, %:** 17.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable van Riel et al., 2008,[185] ADORE trial **Country and setting** Multinational multicenter **Source of funding** Wyeth Research **Research objective** Assess efficacy of ETN vs. ETN + MTX in RA patients using pt reported outcomes **Study design** Controlled Trials **Overall N** 315 **Duration of study** 16 weeks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant, unsatisfactory response to MTX 12.5 mg a week for at least 3 mos • 18 years old or older • ACR functional class I-III • DAS28 of 3.2 or greater or combination of ≥ 5 swollen joints • ≥ 5 painful joints • ESR of 10 mm/h or more • 16 years old or older during onset of RA • No DMARD use other than MTX within 12 weeks of screening **Exclusion Criteria** • Patients requiring concurrent use of PRED greater than 10 mg/day or equivalent	**Interventions, Dose** D1: ETN: 25 mg twice a week D2: MTX: 12.5 mg per week ETN: 25 mg twice a week **Number in group** D1: 160 D2: 155 Overall: 315 **Mean age (years)** D1: 53 D2: 54 **Sex, % female** D1: 79.2 D2: 76.8 **Race, % white** D1: 99.4 D2: 98.7 **Race, % black** D1: 0.0 D2: 1.3 **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 10.0 yrs (NR) D2: 9.8 (NR) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** D1: 100 D2: 100 Overall: 100 **TJC, mean (SD)** D1: 14.6 D2: 14.7 **SJC, mean (SD)** D1: 11.2 D2: 11.9 **Corticosteroid use, %** D1: 49.1 D2: 55.5 **DMARD use, %** NR **MTX naïve, %** D1: 0 D2: 0 Overall: 0 **Baseline DAS score, mean (SD)** D1: 6.2 D2: 6.3	**ACR** NA **HAQ, mean change from baseline (SD)** D1: -0.59 (0.69) D2: -0.59 (0.58) Overall: NS, Difference between groups (95% CI): 0.029 (-0.115, 0.172) **DAS** NA **SF-36** NR **Radiographic measures** NA **Quality of life scales** EQ-5D VAS (0-100): • D1: 19.76 (27.24) • D2: 21.00 (26.61) • Difference between groups (95% CI): -2.593 (-7.667, 2.482);- EQ-5D (0-1): • D1: 0.1883 (0.33) • D2: 0.2399 (0.32) • Difference between groups (95% CI): -0.024 (-0.82, 0.034) EQ-5D Usual Activities: • D1: 0.3077 (0.61) • D2: 0.2867 (0.55) • Difference between groups (95% CI): 0.017 (-0.102, 0.137)	**Overall** Overall attrition/withdrawal, n: D1: 18 D2: 13 Overall: 30 Withdrawals due to adverse events, n: D1: 6 D2: 9 Overall: 15 Withdrawals due to lack of efficacy, n: D1: 9 D2: 0 Overall: 9 **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR
			Required treatment for latent TB		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable van Riel et al., 2008, ADORE trial[185] (original ADORE publication was van Riel 2006) (continued)	• Presence of known relevant concurrent diseases • Use of bolus corticosteroids within 6 weeks or intra-articular corticosteroid injection within 9 weeks of screening • Previous treatment with ETN or other biological treatments		NR **Other population characteristics, %, (CI/SD/P value)** Mean HAQ: D1: 1.6 D2: 1.7	EQ-5D Self Care: • D1: 0.1731 (0.55) • D2: 0.3533 (0.55) Difference between groups (95% CI): -0.129 (-0.233, -0.025; (*P* = 0.0154) EQ-5D Pain/Discomfort: • D1: 0.3718 (0.62) • D2: 0.4400 (0.65) Difference between groups (95% CI): -0.04 (-0.159, 0.078) EQ-5D Mobility: • D1: 0.3077 (0.50) • D2: 0.2318 (0.52) • Difference between groups (95% CI): 0.058 (-0.047, 0.164) EQ-5D Anxiety/Depression: • D1: 0.2323 (0.59) • D2: 0.24 (0.65) • Difference between groups (95% CI): 0.029 (-0.089, 0.147) Patient global assessment of disease (PGAD) (0-10): • D1: -2.78 (2.60) • D2: -2.95 (2.59) • Difference between groups (95% CI): -0.174 (-0.692, 0.345) Pain VAS (0-10): • D1: -29.40 (25.09) • D2: -29.93 (27.25) Difference between groups	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				(95% CI): -1.327 (-7.039, 4.386)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable van Vollenhoven et al., 2009[186] Swefot Trial **Country and setting** Sweden; multicenter **Source of funding** Schering-Plough; Swedish Rheumatism Association **Research objective** To compare the addition of SSZ and HCQ versus the addition of INF to MTX in patients with early RA **Study design** Controlled Trials **Overall N** 258 **Duration of study** 12 mos	**Inclusion Criteria** • Early RA; symptom duration <1 yr • Treatment resistant resistant to 3-4 mos of MTX treatment indicated by DAS28>3.2 • ≥18 yrs old • ACR dx of RA • no previous treatment with DMARDs • No oral glucocorticoid or stable glucocorticoid therapy for at least 4 wks of at most 10 mg daily PNL or equivalent • DAS28 >3.2 **Exclusion Criteria** • Contraindications of any trial drugs	**Comparisons (dosage and frequency)** D1: • MTX: up to 20 mg per wk • SSZ: 1000 mg twice a day • HCQ: 400 mg a day D2: • MTX: up to 20 mg a week • INF: 3 mg/kg at wk 0, 2, 6 and every 8 wks thereafter **Number in group** D1: 130 D2: 128 Overall: 258 **Mean age (years)** D1: 52.9 D2: 51.1 Overall: NR **Sex, % female** D1: 78 D2: 76 Overall: NR **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 6.3 mos (3.6) D2: 6.2 mos (3.5) Overall: NR **TJC, mean** NR **SJC, mean** NR **Corticosteroid use, %** D1: 8 D2: 6 Overall: NR **DMARD use, %:** D1: 100 D2: 100 Overall: 0 **MTX naïve, %:** D1: 0 D2: 0 Overall: 0 **Treatment resistant, %:** D1: 100 D2: 100 Overall: 100 **Patients with early RA, three years or less, %:** D1: 100 D2: 100 Overall: 100 **Baseline DAS score** At baseline: D1: 5.98 (0.96) D2: 5.91 (0.93)	**ACR mean difference/ absolute difference (CI/SD/P Value):** ACR 20: ITT population: D1: I28 D2: 42 Overall: RR 1.48 (1.06 to 2.08; *P*=0.0266) mITT population: D1: 45 D2: 59 Overall: RR 1.31 (1.03 to 1.66; *P*=0.0257) ACR 50: ITT population: D1: 15 D2: 25 Overall: RR 1.71 (1.02 to 2.86; *P*=0.0424) mITT population: D1: 34 D2: 48 Overall: RR 1.43 (1.06 to 1.93; *P*=0.0226) ACR 70: ITT population: D1: 7 D2: 12 Overall: RR 1.69 (0.77 to 3.73; *P*=0.2044) mITT population: D1: 15 D2: 28 Overall: RR 1.83 (1.12 to 2.98; *P*=0.0156) **HAQ, mean difference/ absolute difference (CI/SD/P**	**Overall** Overall attrition/withdrawal (n): D1: 41 D2: 23 Overall: 64 Withdrawals due to adverse events (n): D1: 14 D2: 10 Overall: 24 Withdrawals due to lack of efficacy (n): D1: 18 D2: 3 Overall: 21 Adherent/compliant (n): D1: NR D2: NR Overall: NR Other attrition related comments? D1: 5 pts received treatment and 5 switched treatment D2: 8 never received treatment and 5 switched treatment Overall adverse events reported (n): D1: 48 D2: 32 **Serious adverse events:** Death (n): D1: 0 D2: 0	**Quality rating for efficacy/effectiveness?** Fair **Quality rating for observational studies** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			At randomization D1: 4.79 (1.05) D2: 4.91 (0.98) Overall: NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value):** NR	**Value):** NR **DAS, mean difference/absolute difference (CI/SD/P Value):** NR **SF-36, mean difference/absolute difference (CI/SD/P Value):** NR **Radiographic measures, mean difference/absolute difference (CI/SD/P Value):** NR **Quality of life scales, mean difference/absolute difference (CI/SD/P Value):** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value):** NR	Cardiovascular events (specify) (n): HTN D1: 2 D2: 0 Hepatotoxicity/elevated liver enzymes (n): Liver D1: 1 D2: 5 **Malignancies:** NR **Respiratory events:** Upper respiratory infection (n): D1: 2 D2: 2 **Other infections:** Other infections (specify) (n): D1: 0 D2: 5 **GI:** Other GI symptoms (specify) (n): D1: 15 D2: 1 **Other:** Fractures (n): Musculoskeletal D1: 0 D2: 1 Skin rash (n): Skin and allergic reactions D1:3 D2: 11	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					Demyelenation or multiple sclerosis (n): Central and peripheral nervous system D1: 6 D2: 1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wallis et al., 2004[187] **Country, Setting:** Multinational, multicenter **Funding:** NR **Research Objective:** The relationship between the use of tumor necrosis factor antagonists and onset of granulomatous infection was examined **Study Design:** Database analysis;AERS **Overall N:** 649 cases **Study Duration:** various	**Inclusion Criteria:** • All pts treated with INF or ETA • Other meds allowed • Concurrent use of immuno-suppressant drugs **Exclusion Criteria:** • NA	**Interventions, dose:** D1: INF (various) **D2: ETA (various)** **N:** D1: 566 cases (>233,000 treated) D2: 83 cases (>113,000 treated) **Mean age, yrs:** D1: 60 D2: 58 **Sex, % female:** D1: 66 D2: 59 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** D1: 41 D2: 66 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** D1: 43 D2: 41	NR	**Granulomatous infections, rate per 100,000** D1: 239 D2: 74 ($P < .001$) D1 risk of granulomatous infection was 3.25-fold greater among pts than D2. **Tuberculosis infections, rate per 100,000** D1: 144 D2: 35 ($P < .001$)	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wasserman et al., 2004[188] **Country, Setting:** Canada, Quaternary care center **Funding:** Schering-Plough **Research Objective:** Description of infusion-related reactions to INF (during or within 1 hour of infusion) in pts with active rheumatoid arthritis **Study Design:** Case series **Overall N:** 113 pts, 1,183 infusions **Study Duration:** Mean 60.6 wks	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to ACR; failed at least 3 DMARDs • Active disease; stable doses of corticosteroids (10 mg/d) and/or NSAIDs **Exclusion Criteria:** • Biologically-based therapies • Current signs and symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, GI, endocrine, pulmonary, cardiac, neurological, or cerebral disease • History of lymphopro-liferative disease • Any known malignant disease • Screened for TB	**Interventions, dose:** D1: INF INF: 3 mg/kg wks 0,2,6 then every 8, dose could be increased to 5 mg/kg at wk 14 based on clinical grounds **N:** D1: 113 pts; 1,183 infusions **Mean age, yrs:** D1: 45.7 **Sex, % female:** D1: 87 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 13.6 **TJC, mean:** D1: 21.3 **SJC, mean:** D1: 10.8 **DMARD use, %:** NR **PRE use, %:** D1: 59 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** D1: 100	104 infusion-related reactions out of 1183 infusions performed (8.8%) and 60 of 113 pts (53%) experienced at least one reaction during course of txt • Infusion related reactions; Allergic-45 (3.8%); Cardiopulmonary-35 (3.0%); Misc.-24 (2.0%) • Reactions following pretxt or not with diphenhydramine at infusions 3 and 4 • Pretreated 14.7% vs. Not pretreated 14.3%	**Overall:** D1: 8.8 **Headache:** D1: 9	**Overall Attrition Rate, %:** **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006[189] **Country, Setting:** US, Rheumatology practices (509) **Funding:** Immunex Corporation **Research Objective:** To evaluate effectiveness of select biologics, MTX (MTX), and other DMARDs in management of adult RA in routine clinical practice **Study Design:** Prospective cohort study **Overall N:** 5,397 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age: 18 or older • Diagnosed with RA according to ACR criteria: 1987 ACR • Pts requiring a change in RA txt **Exclusion Criteria:** • Pregnant or lactating • Active infection, • Concurrent enrollment in a clinical trial	**Interventions, dose:** D1: MTX (10 to 15 mg/wk) D2: ETN (50 mg/wk) D3: ETN (50 mg/wk) +MTX D4: INF (3.8 mg/8wks) D5: INF (3.8 mg/8wks) + MTX (15 mg/wk) D6: LEF (20 mg/d) D7: LEF (20 mg/d) +MTX (15 mg/wk) D8: MTX (15 mg/wk) +HCQ (400 mg/d) D9: MTX (15 mg/wk) +HCQ (400 mg/d) +SSZ (2000 mg/d) **N:** D1: 941 D2: 1251 D3: 1783 D4: 120 D5: 540 D6: 204 D7: 191 D8: 325 D9: 42 **Mean age, yrs:** D1: 56.8 D2: 53.2 D3: 52.6 D4: 60.2 D5: 58.5 D6: 57.7 D7: 55.5 D8: 53.8 D9: 47.8 **Sex (% female**	**Mean disease duration, yrs:** D1: 3.5 D2: 9.2 D3: 7.7 D4: 10.6 D5: 9.5 D6: 10.1 D7: 7.4 D8: 4.6 D9: 7.2 **TJC, mean:** D1: 13 D2: 13.4 D3: 13.3 D4: 14.8 D5: 3.9 D6: 12.8 D7: 12.2 D8: 11.8 D9: 10.1 **SJC, mean:** D1: 11.3 D2: 11.1 D3: 11.5 D4: 13.9 D5: 12.0 D6: 11.8 D7: 11.4 D8: 9.2 D9: 10.2 **DMARD use, %:** D1: 25 D2: 75 D3: 96 D4: 85 D5: 96 D6: 75	**mACR20, %:** D1: 37 D2: 41 D3: 43 **D4**: 26 D5: 35 **Adjusting for baseline covariates** D3: vs. **D1**(OR, 1.29, 95% CI, 1.09-1.52; *P* < 0.01) **D2** vs. **D1** (OR, 1.23, 95% CI, 1.02-1.47; *P* < 0.05) **D1** vs. **D5** (OR, 0.96 CI 0.76-1.21 *P* = 0.72) **D1** vs. **D4** (OR, 0.66, 95% CI, 0.43-1.02; *P* = 0.06) **Mean change HAQ improvement, %** D1: 7 D2: 17 (*P* < 0.001) D3: 17 (*P* < 0.001) **mACR20 response** **D5** vs. **D1**: (OR, 0.68, 95% CI, 0.48-0.96; *P* < 0.05) **D6** vs. **D1** (OR, 0.76, 95% CI, 0.54-1.06; *P* = 0.11) **D8** vs, **D1**: (OR, 0.94, 95% CI, 0.72-1.23; *P* = 0.64) **D9** vs. **D1**: (OR, 0.57, 95% CI, 0.27-1.18; *P* = 0.13) **SJC % improvement** **D1** vs. **D1**: 34 (N/A) **D2** vs. **D1**: 53 (*P* < 0.0001) **D4** vs. **D1**: 29 (*P* = NS) **D3** vs. **D1**: 55 (*P* < 0.0001) **D5** vs. **D1**:48 (*P* < 0.01)	NR	**Overall Attrition Rate, %:** 33.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
		D1: 75 D2: 75 D3: 79 D4: 71 D5: 77 D6: 76 D7: 78 D8: 80 D9: 79 **Race, % white:** D1: 77 D2: 81 D3: 81 D4: 78 D5: 81 D6: 78 D7: 82 D8: 83 D9: 79	D7: 95 D8: 78 D9: 88 **Corticosteroid use, %** D1: 53 D2: 48 D3: 51 D4: 63 D5: 57 D6: 48 D7: 56 D8: 50 D9: 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF factor positive:** D1: 72 D2: 65 D3: 69 D4: 68 D5: 69 D6: 75 D7: 73 D8: 71 D9: 71	**TJC % improvement** D1: 34(N/A) D2 vs. D1: 53% (*P* < 0.001) D4 vs. D1: 29% (*P* = NS) D3 vs. D1: 55% (*P* < 0.0001) D5 vs. D1: 48% (*P* = NS) **HAQ % improvement amongst pts < 65 yrs** D2: 22 D4: 4 (*P* = NR)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Weinblatt et al., 2006[190] **Country, Setting:** Multinational Multicenter ASSURE Trial **Funding:** Bristol-Myers Squibb **Research Objective:** To assess safety of ABA in pts with active RA who had been receiving 1 traditional nonbiologic and/or biologic DMARDs **Study Design:** RCT **Overall N:** 1456 **Study Duration:** One yr	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed according to ACR criteria • I class I-IV • DMARDs • Stable, low-dose oral Css and/or stable doses of NSAIDs • Stable CHF, asthma, COPD, and DM **Exclusion Criteria:** • Pregnant or lactating • History of TB • Impaired renal or hepatic system • Mycophenolate mofetil, CYP, other calcineurin inhibitors, D-penicillamine, cyclophos-phamide, apheresis unstable or uncontrolled diseases, or any autoimmune disorder as the main diagnosis • Bacterial infections • Active herpes zoster < 2 mos, hepatitis B or C	**Interventions, dose:** D1: Non-bio and ABA D2: Non-bio and placebo D3: Bio and ABA D4: Bio and placebo ABA: 500 mg a body weight <60 kg, 750 mg for 60-100 kg, and 1 gram for >100 kg **N:** D1: 856 D2: 418 D3: 103 D4: 64 **Mean age, yrs:** D1: 52.2 D2: 52.0 D3: 54.6 D4: 52.8 **Sex, % female:** D1: 83.1 D2: 83.7 D3: 75.7 D4: 75.0 **Race, % white:** D1: 83.9 D2: 83.3 D3: 97.1 D4: 92.2	**Mean disease duration, yrs:** D1: 9.5 D2: 9.5 D3: 11.3 D4: 11.3 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **HAQ:** D1: 1.5 D2: 1.5 D3: 1.5 D4: 1.6	ABA and placebo groups exhibited similar frequencies of adverse events (90% and 87%, respectively), serious adverse events (13% and 12%, respectively), and discontinuations due to adverse events (5% and 4%, respectively) • Serious infections were more frequent in the ABA group than in the placebo group (2.9% vs. 1.9%) • Serious adverse events occurred more frequently in the subgroup receiving ABA plus a biologic agent (22.3%) than in other subgroups (11.7-12.5%) • Sub analysis of Pts w/ COPD and DM (placebo vs. ABA)(%) COPD • Overall AEs 88.2 vs.97.3 • Respiratory oriented 23.5 vs. 23.5 • SAEs 5.9 vs. 27 DM • Overall AEs 90.3 vs. 93.8 • Infections 58.1 vs. 50.8 • SAEs 12.9 vs. 21.5 Change in HAQ from baseline • Placebo -0.25 vs. ABA-0.46 ($P < 0.001$)	**Overall:** D1: 89.7 D2: 86.1 D3: 95.1 D4: 89.1 **SAEs:** D1: 11.7 D2: 12.2 D3: 22.3 D4: 12.5 **Infections:** D1: 54.9 D2: 53.6 D3: 65.0 D4: 57.8 **Serious Infections:** D1: 2.6 D2: 1.7 D3: 5.8 D4: 1.6 **Malignancies:** D1: 3.2 D2: 3.8 D3: 6.8 D4: 1.6	**Overall Attrition Rate, %:** 15 **ITT Analysis:** Yes **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Weinblatt, M. et al 2007[191] **Country and setting** United States multicenter **Source of funding** Bristol-Myers Squibb **Research objective** Investigate efficacy and safety of ABA in combination with ETN in patients with active RA **Study design** Controlled Trials **Overall N** 121 **Duration of study** DB Phase: 1 year LTE: 2 years **Quality rating** Fair	**Inclusion Criteria** • ≥ 18 years of age • Met criteria ofACR for RA • In functional class, I, II, or III • Must have received ETN 25 mg twice weekly for ≥ 3 mos and have ≥ 8 swollen joints (66-joint count) and ≥ 10 tender joints (68-joint count). • CRP elevation was not required for entry. **Exclusion Criteria** • Active or latent infection • Recent opportunist infection • TB requiring treatment within previous 3 years • History of cancer within previous 5 years • History of drug or alcohol misuse • Pregnant and nursing women.	**Interventions, dose** D1: • ETN: 25 mg twice weekly • Abatacept: 2 mg/kg on days 1, 15 and 30, and every 4 weeks thereafter after 1 year switched to 10 mg/kg D2: • ETN: 25 mg twice weekly • Placebo: after 1 year switch to 10 mg/kg abatacept **Number in group** D1: 85 D2: 36 Overall: 121 **Mean age, years (SD)** D1: 49.8 (23-73) D2: 54.3 (28-71) **Sex, % female** D1: 78 D2: 72 **Race, % white** D1: 94 D2: 100 **Race, % black** D1: NR D2: 0 **Ethnicity, Latino** D1: NR D2: 0	**Mean disease duration, years (SD)** D1: 13 (10.1) D2: 12.8 (8.6) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** D1: 28.7 (14) D2: 29.2 (13.2) **Swollen Joint Count, mean (SD)** D1: 19.6 (9.4) D2: 20.1 (10.5) **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score (SD)** D1: 61.8 (17.2) D2: 62.1 (13.5) **Required treatment for latent TB** NR **Other population characteristics, n (SD)** Patient assessment of pain: D1: 66.5 (16.6) D2: 53.2 (23.2)	**ACR** Modified ACR 20: At 6 months: D1: 48.2 D2: 30.6 *P* = 0.072 At 1 year: D1: 48.2 D2: 30.6 Overall: NR Modified ACR 50: At 6 months: D1: 25.9 D2: 19.4 *P* = 0.448 At 1 year: D1: 28.2 D2: 16.7 Overall: NR Modified ACR 70: At 6 months: D1: 10.6 D2: 0.0 *P* = 0.042 At 1 year: D1: 9.4 D2: 5.6 *P* = 0.481 **HAQ (SD/P Value)** Change from baseline to 1-year D1: -0.3 (0.5, *P* = 0.001) D2: -0.2 (0.4, *P* = 0.040 Change from 1-year to 2-years: D1: -0.1 (0.3, *P* = NS) D2: 0 (0.2, *P* = NS)	**Attrition/withdrawal** Overall after 1 year, n: D1: 27 D2: 14 Withdrawals due to adverse events, n: D1: DB Phase: 10 LTE: 8 D2: 1 Withdrawals due to lack of efficacy, n: D1: 9 D2: 12 Adherent/compliant after 1 year, n: D1: 58 D2: 22 Attrition rate difficult to determine b/c they do not clearly indicate how many patients remained in either drug after LTE completion they list only total LTE completion (N = 61). Overall adverse events reported, n: D1: DB Phase: 79 LTE: 78 D2: 32 Overall: 189 **Serious adverse events** Death, n: D1: DB Phase: 0 LTE: 1 D2: 0 Overall: 1 **Malignancies**

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			mHAQ: D1: 1.0 (0.5) D2: 0.9 (0.5)	**DAS** Change from baseline to 1-year: D1: -25.7 (27.0, *P* = 0.001) D2: -18.2 (20.4, *P* = 0.001) Change from 1-year to 2-years: D1: -7.6 (20.6, *P* = 0.0135) D2: -0.6 (23.1, *P* = NS) **SF-36** Change after 1-year of LTE MCS: D1: 7.08 D2: 2.14 PCS: D1: 9.11 D2: 3.19 Change after 2 years of LTE MCS: D1: 4.68 D2: 7.54 PCS: D1: 6.65 D2: 3.44 **Radiographic measures** NR **Quality of life scales** NR	NR **Respiratory events** Tuberculosis: NR Upper respiratory infection, n: D1: DB Phase: 20, LTE: 10 D2: 5 Overall: 35 **Other infections** NR **GI** Nausea or vomiting, n: D1: DB Phase: 13, LTE: 12 D2: 1 Overall: 26 Other GI symptoms, n: D1: Diarroea: DB Phase: 12, LTE: 13 D2: Diarrhea: 2 Overall: 27 **Other** Skin rash, n: D1: DB Phase: 11 LTE: 10 D2: 3 Overall: 24 Headache, n: D1: DB Phase: 20, LTE: 10 D2: 5 Overall: 35 Dizziness, n: D1: DB Phase: 13, LTE: 8 D2: 2 Overall: 23 Fatigue, n: D1: DB Phase: 14, LTE: 14

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D2: 6 Overall: 34 Sinusitis, n: D1: DB Phase: 14, LTE: 18 D2: Sinusitis: 3 Overall: 35 Arthralgia, n: D1: DB Phase: 13, LTE: 5 D2: 3 Overall: 21 Cough, n: D1: DB Phase: 11, LTE: 11 D2: 3 Overall: 25 Vascular disorders: D1: DB Phase: 0, LTE: 6 D2: 1 Malignancies D1: DB Phase: 0, LTE: 3 D2: 0 Gastrointestinal disorders: D1: DB Phase: 0, LTE: 3 D2: 0 Infections and infestations: D1: DB Phase: 3, LTE: 1 D2: 0 Nervous system disorders: D1: DB Phase: 2, LTE: 1 D2: 0 Respiratory, thoracic and mediastinal disorders: D1: DB Phase: 30, LTE: 32 D2: 7

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Wells et al., 2008;[192] Westhovens et al., 2006;[193] Hassett et al., 2008[194] ATTAIN **Country and setting** See 458 (from orignal report) **Source of funding** Bristol-Meyers Squibb **Research objective** • To examine impact of ABA on HRQOL • To evaluate patient-recorded outcomes including SF-36, activity limitation, fatigue **Study design** Controlled Trials **Overall N** 391 **Duration of study** 24 weeks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant defined as inadequate response to anti-TNF • ≥10 swollen and ≥12 tender joints • CRP levels of at least 1 mg/dl (upper limit of normal range: 0.5 mg/dl). **Exclusion Criteria** • Patients not treated with oral DMARDs or ANK for ≥ 3 mos prior to the study or not receiving a stable dose for at least 28 days • Use of myco-phenolate mofetil, cyclosporine, other calcineurin inhibitors and D-penicillamine • Women who were pregnant or nursing	**Interventions, Dose** D1: Abatacept: 10 mg/kg DMARDS D2: Placebo DMARDS **Number in group** D1: 258 D2: 133 **Mean age (years)** D1: 53.4 D2: 52.7 **Sex, % female** D1: 77.1 D2: 79.7 **Race, % white** D1: 96.1 D2: 93.2 **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 12.2 (8.5) D2: 11.4 (8.9) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** 100% **TJC, mean (SD)** D1: 22.3 (10.2) D2: 22.0 (10.0) **SJC, mean (SD)** D1: 31.2 (13.0) D2: 32.8 (13.4) **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: 6.5 D2: 6.5 Overall: 6.5 **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)**	**ACR** NR **HAQ,** D1: HAQ-DI -0.5 (SD 0.6) D2: -0.1 (0.4) *P* = 0.0001 Treatment difference = -0.33, 95% CI, (-0.44 to -0.22) **DAS** NR **SF-36** Physical component score, % (SD): D1: 6.5 (SD 9.6) D2: 1.0 (SD 7.7) Patients doing better (%): D1: 44.6 D2: 23.1 Patients doing same (%): D1: 45.8 D2: 63.1 Patients doing worse (%): D1: 9.6 D2: 13.9 Overall: Mental component score (MCS), % (SD) D1: 5.4 (SD 11.7) D2: 1.7 (SD 10.2) Patients doing better (%): D1: 43.0 D2: 31.5 Patients doing same (%): D1: 45.840.3	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D2: 45.4 Patients doing worse (%): D1: 16.7 D2: 23.1 Overall: • Physical Component Score, *P* = 0.0001, Percentage of Patients Doing Better/Same/Worse, *P* = 0.0002, Treatment Difference = 5.5, 95% CI, (3.6 to 7.4) • Mental Component Score, *P* = 0.0025, Percentage of Patients Doing Better/Same/Worse, *P* = 0.0723, Treatment Difference = 3.7, 95% CI, (1.3 to 6.1) **Radiographic measures** NR **Quality of life scales** NR **Others, (please name)** • Fatigue VAS: ABA = -22.1 (SD = 28.6), Placebo = -5.3 (SD = 27.4), *P* = 0.0001 • [From #2964] Fatigue Treatment difference = -16.8, 95% CI, (-22.8 to -10.8) • [From #2714] Required Help or Care at Baseline: ABA = 89%, Placebo = 87% • Required Help or Care at Final Visit: ABA = 70%,	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Placebo = 76% • Percent Difference in Required Help or Care between Baseline and Final Visit: ABA = 19%, Placebo = 11% • Psychosocial Independence: Changes in Mean Scores from Baseline to Final Visit in Psychosocial Independence between ABA and Placebo: ABA greater by 0.46 units, 95% CI, (0.17-0.75), *P* = 0.002 • Changes in Mean Scores from Baseline to Final Visit in Physical Independence between ABA and Placebo: ABA greater by 0.59 units, 95% CI, (0.35-0.82), *P* = 0.001	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Westhovens et al., 2006[195] START Trial **Country, Setting:** Multinational, multicenter **Funding:** Centocor **Research Objective:** The risk of serious infections in INF therapy, and safety in combination with background txts during 1 yr in pts with RA with various comorbidities **Study Design:** RCT **Overall N:** 1084 **Study Duration:** 54 wks of which 22 wks wast RCT then open label extension	**Inclusion Criteria:** • Adults w/ RA according to ACR criteria • MTX ≥ 3 mos • Chloroquine, AZA, penicillamine, oral or intramuscular gold • HCQ, SSZ, LEF, CYP, oral Css, or NSAIDS **Exclusion Criteria:** • TB • Opportunistic or serious infections, HIV, lympho-proliferative disease or malignancy • CHF investigational drug (3 mos or 5 half-lives, whichever was greater), with cyclophos-phamide, nitrogen mustard, chlorambucil, or other alkylating agents more than 5 mg/kg cyclosporine, or biologic	**Interventions, dose:** D1: Placebo + MTX (up to 25 mg/wk) D2: INF 3 mg/kg (at wks 0, 2, 6, and 14) + MTX (up to 25 mg/wk) D3: INF 10 mg/kg (at wks 0, 2, 6, and 14) + MTX (up to 25 mg/wk) **D4: D2 + D3** **N:** D1: 363 D2: 360 **D3: 361** **Mean age, yrs:** D1: median 52 D2: 53 **D3: 52** **Sex, % female:** D1: 83.2 D2: 80.0 **D3: 77.8** **Race, % white:** NR	**Median disease duration, yrs:** D1: 8.4 D2: 7.8 D3: 6.3 **TJC, mean:** D1: 22 D2: 22 D3: 22 **SJC, mean:** D1: 15 D2: 15 D3: 15 **DMARD use, %:** D1: 70 D2: 70.8 D3: 69.8 **Corticosteroid use, %:** D1: 59.2 D2: 59.2 D3: 59 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Median HAQ score:** D1: 1.5 D2: 1.5	**At week 22** **ACR20 response, %** D1: 26 D2: 58 D3: 61 (*P* < 0.0001) **ACR50 response, %** D1: 9.7 D2: 32.1 D3: 35.4 (*P* < 0.0001) **ACR70 response, %** D1: 4.7 D2: 14.0 D3: 16.1 (*P* < 0.0001) **DAS28 , (+/-)** D1: 4.4 (1.4) D2 **and** D3: 3.4 (1.3) (*P* < 0.001) **Remission, %** D1: 14 D2: 31 D3: 32 (*P* < 0.0001)	**Overall:** D1: 66.2 D2: 69.7 D3: 72.3 D4: 71.0 **SAEs:** D1: 7.5 D2: 7.8 D3: 7.5 D4: 7.8 **Serious Infections:** D1: 1.7 D2: 1.7 D3: 5.0 D4: 3.3 **Cardiovascular Events:** D1: 3.3 D2: 4.5 D3: 5.9 D4: 5.2 **Headache:** D1: 6.1 D2: 9.7 D3: 10.2 D4: 10.0 **Hepatotoxicity (ALT increase):** D1: 2.8 D2: 3.6 D3: 5.3 D4: 4.4 **Malignancies:** D1: 1.7 D2: 4.2 **Nausea:**	**Overall Attrition Rate, %:** 17.1 **ITT Analysis:** Yes **Quality Rating:** Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			D3: 1.5 **% RF positive:** D1: 80.7 D2: 82.8 D3: 76.8		D1: 8.0 D2: 6.4 D3: 6.4 D4: 6.4 **URTI:** D1: 10.5 D2: 9.7 D3: 11.9 D4: 10.8 **UTI:** D1: 0 D2: 0 D3: 0.6 D4: 0.3	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Westhovens et al., 2009[196] **Country and setting** Multinational **Source of funding** Bristol-Myers Squibb **Research objective** To assess the efficacy and safety of ABA in MTX-naive patients with early RA and poor prognostic factors. **Study design** RCT **Overall N** 509 **Duration of study** 2 yrs **Quality rating** Good	**Inclusion Criteria** • MTX naive or previous exposure of 10mg/wk or less for three wks or less, with none administered for 3 mos before providing informed consent • Early RA of 2 yrs or less • ≥ 12 tender and 10 swollen joints • C-reactive protein (CRP) 0.45 mg/ dl or greater • RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/ wrists/feet **Exclusion Criteria** • Women who were pregnant or breastfeeding • Patients with active Mycobacterium tuberculosis requiring	**Interventions, Dose** D1: • MTX: 7.5 mg/wk; 15 mg/wk at wk 4 and 20 mg/wk at wk 8 • ABA: 10 mg/kg D2: • MTX: 7.5mg/wk; 15 mg/wk at wk 4 and 20mg/wk at wk 8 • Placebo **Number in group** D1: 256 D2: 253 Overall: 509 **Mean age (years)** D1: 50.1 D2: 49.7 Overall: NR **Sex, % female** D1: 76.6 D2: 78.7 Overall: NR **Race, % white** D1: 78.9 D2: 86.6 Overall: NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years** D1: 6.2 (7.5) D2: 6.7 (7.1) Overall: NR **Patients with early RA, three years or less, %:** 100 **Treatment resistant, %:** NR **Tender Joint Count, mean** D1: 31.3 (14.8) D2: 30.8 (14.0) Overall: 31.0 **Swollen Joint Count, mean** D1: 22.9 (11.3 D2: 21.9 (10.1) Overall: 22.4 **Corticosteroid use, %** D1: 51.2 D2: 49.0 Overall: NR **DMARD use, %:** Other non- biological DMARD (HCQ) D1: 1.6 D2: 2.0 Overall: NR SSZ D1: 0 D2: 0.4 Overall: NR **MTX naïve, %:** 100 **Baseline DAS score**	**ACR:** ACR 20: NR ACR 50: Yr 1 D1: 57.4 D2: 42.3 D1 vs. 2: *P*< 0.001 ACR 70: Yr 1 D1: 42.6 D2: 27.3 D1 vs. 2: *P*< 0.001 **HAQ:** HAQ-DI D1: -0.96 (SE 0.04) D2: -0.76 (SE 0.04) **DAS:** CRP D1: -3.22 (SE 0.09) D2: -2.49 (SE 0.09) *P* < 0.001 **SF-36:** Mental component D1: 8.15 (SE 0.64) D2: 6.34 (SE 0.64) D1 vs. 2: *P* = 0.046 Physical component D1: 11.68 (SE 0.62) D2: 9.18 (SE 0.63) D1 vs. 2: *P* = 0.005 **Radiographic measures:** Yr 1 TS D1: 0.63 D2: 1.06 D1 vs. 2: *P* = 0.040 ES	**Overall** Overall attrition/withdrawal (n): D1: 24 D2: 26 Withdrawals due to adverse events (n): D1: 9 D2: 11 Withdrawals due to lack of efficacy (n): D1: 0 D2: 8 Overall adverse events reported (n): D1: 217 D2: 211 Overall: 428 **Serious adverse events:** Death (n): D1: 2 D2: 4 Overall: 6 **Malignancies:** Other cancer (specify) (n): Pancreatic D1: 1 D2: 0 Overall: NR **Respiratory events:** Tuberculosis (n): D1: 0 D2: 0 Overall: 0 Pneumonia (n): D1: 1 D2: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	treatment within 3 yrs.		D1: 6.3 (1.0) D2: 6.2 (1.0) Overall: 6.3 **Required treatment for latent TB** NR **Other population characteristics:** HAQ-DI mean (SD) D1: 1.7 (0.7) D2: 1.7 (0.7) Overall: NR	D1: ES:0.50 D2: 0.89 D1 vs. 2: *P* = 0.033 JSN D1: 0.13 D2: 0.17 D1 vs. 2: *P* = 0.353 No radiographic progression D1: (T< or = 0): 61.2% (95% CI, 55.0-67.3) D2: (T< or = 0): 52.9% (95% CI, 46.6-59.2) D1 and D2: 8.3% (95% -1.0 to 17.5) **Quality of life scales:** NR **Others:** Yr 1 ACR90 D1, 16.4% D2: 6.7% D1 vs D2: *P* < 0.001	Overall: 4 Upper respiratory infection (n): D1: 26 D2: 26 Overall: 52 **Other infections:** Other infections (specify) (n): Infections (not specified) D1: 132 D2: 139 Serious infections (not including pneumonia) Gastroenteritis D1: 1 D2: 1 Cellulitis D1: 1 D2: NR Pseduomonal lung infection D1: 1 D2: NR Post operative lung infection D1: 1 D2: NR Breast cellulitis/staphycoccal infection D1: NR D2: 1 **GI:** NR **Other:** Infusion/injection site reactions (n): D1: 16 D2: 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Overall: 21 Dizziness (n): D1: 5 D2: 2 Overall: 7 Any other AEs: Most frequently reported adverse events in D1: • Nausea:10% pts • Upper respiratory tract infection: 10% pts • Headache: 10% pts D2: NR Pregnancy (protocol violations) D1: 2 D2: NR Spontaneous abortion between days 1 and 30 after 1 infusion of ABA D1: 1 D2: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004[197] **Country, Setting:** US, 908 practices **Funding:** National Data Bank for Rheumatic Diseases (US) funded by pharma **Research Objective:** The rate of and standardized incidence ratio for lymphoma in pts with RA and in RA patient subsets by txt group **Study Design:** Prospective cohort study **Overall N:** 18,572 **Study Duration:** Up to 3 yrs	**Inclusion Criteria:** • Participants in National Data Bank for Rheumatic Diseases (NDB) long-term study of outcomes of RA • Cases were identified from this group as those who developed lymphoma during the 2 ½ yr observational period **Exclusion Criteria:** • Cases were rejected if not enough information could be obtained to verify patient's lymphoma	**Interventions, dose:** D1: INF (varied) D2: ETA (varied) D3: MTX (varied) D4: No MTX/ No Biologics **N:** D1: 6433 D2: 2729 D3: 5593 D4: 4474 **Mean age, yrs:** D1: 60.7 D2: 56.4 D3: 61.2 D4: 60.4 **Sex, % female:** D1: 77.3 D2: 79.3 D3: 75.7 D4: 75.7 **Race, % white:** NR	**Mean disease duration, yrs:** D1: 13.7 D2: 14.1 D3: 13.5 D4: 13.5 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 1.2 D2: 1.2 D3: 1.1 D4: 1.0 **VAS QoL:** D1: 65.8 D2: 64.3 D3: 66.7 D4: 65.9 **Pain:**	SIR for whole population regardless of txt was 1.9 (95%CI, 1.3-2.7); indicating a greater risk for lymphoma in pts with RA • SIR for pts taking biologics (INF or ETA) was 2.9 (95%CI, 1.7-4.9). • No significant differences were observed between txt groups • Only 233 pts received AKA and no lymphomas occurred in this group • Overall, lymphoma incidence rate per 100,000 PY was 99 (95%CI,69-142); for various durations of RA, rates were: 0-5 yrs: 171 (95%CI,82-360), 5-10 yrs: 70 (95%CI,29-168), 10-15 yrs: 20 (95%CI,3-145), >15 yrs: 121 (95% CI, 74-198)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			D1: 4.2 D2: 4.3 D3: 3.7 D4: 3.9			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004[198] **Country, Setting:** US, multicenter (National Data Bank for Rheumatic Diseases) **Funding:** Centocor, Inc **Research Objective:** To determine frequency of heart failure in pts with RA, and to determine its predictors, particularly use of anti-TNF therapy **Study Design:** Retrospective cohort study **Overall N:** 15,739 (RA plus OA subjects) **Study Duration:**	**Inclusion Criteria:** • Participation in National Data Bank for Rheumatic Diseases study of outcomes of arthritis; patient at participating rheumatology clinic **Exclusion Criteria:** • NR	**Interventions, dose:** D1: Any Anti-TNF D2: INF D3: ETA D4: No anti-TNF D5: Total Population Overall **N:** NR **Mean age, yrs:** D1: 60 D2: 61.5 D3: 56.7 D4: 61.5 D5: 51 **Sex, % female:** D1: 78 D2: 77 D3: 80 D4: 76 D5: 77 **Race, % white:** D1: 95 D2: 96 D3: 92 D4: 92 D5: 94	**Mean disease duration, yrs:** D1: 14.2 D2: 13.8 D3: 15.2 D4: 15.5 D5: 14.9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** Overall: 86 **PRE use (%)** D1: 47 D2: 49 D3: 39 D4: 33 D5: 39 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** D1: 3.7 D2: 3.7 D3: 3.6 D4: 3.5 D5: 3.6 **MTX use:** D1: 67	**Heart Failure** • 461 cases in 13,171 pts with RA (overall risk of 3.5%); after adjusting for demographic characteristics; Risk: 3.9% (95% CI,= 3.4% to 4.3%) • Among all cases of heart failure, pts receiving anti-TNF therapy were less likely to have heart failure than those not receiving anti-TNF therapy (-1.2%; 95% CI,-1.9 --0.5%) • Overall, adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in remaining pts (*P* = 0.03) • Frequency of heart failure was 5.2% in men and 3.0% in women • In examining incident cases of heart failure in pts under age 50, no increase was found (0/1569 pts using anti-TNF vs. 3/1401 not using anti-TNF therapy)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			D2: 76 D3: 44 D4: 47 D5: 56			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe et al., 2006[199] **Country, Setting:** US, Rheumatology Clinics **Funding:** Bristol-Meyers-Squibb **Research Objective:** To evaluate txt of RA and risk of hospitalization for pneumonia **Study Design:** Prospective cohort study **Overall N:** 16,788 **Study Duration:** 3.5 yrs	**Inclusion Criteria:** • Participants in NDB longitudinal study of RA outcomes including 5,317 enrolled as part of an INF safety registry and 1,852 as part of a LEF safety registry • Other meds allowed **Exclusion Criteria:** • NA	**Interventions, dose:** D1: Cohort Prednisone MTX LEF SSZ Hydroxychlorquine ETA INF Adalimumab Other various RA txts **N:** NR **Mean age, yrs:** D1: 62 **Sex, % female:** D1: 77.2 **Race, % white:** D1: 89.7% white, 4.8% black, 3.0% Hispanic, 1.0 Asian/Pacific Islander, 1.1% American Indian or Alaskan native, 0.5% Other	**Mean disease duration, yrs:** D1: 16.3 **TJC, mean:** NR **SJC, mean:** NR **DMARD use mean (lifetime #):** D1: 3.3 **Corticosteroid use, %:** D1: 38.1 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Effect of txt variables on risk of pneumonia (adjusted for demographic variables-age, sex, smoking, education, and enrollment) • Prednisone HR 1.7 [95% CI, 1.5-2.1]) • LEF HR 1.3 [95% CI, 1.0-1.5], *P* = 0.036) • •SSZ HR 0.7 [95% CI, 0.4-1.0], *P* = 0.053) • ETA HR 0.8 [95% CI, 0.6-1.0], *P* = 0.051) • INF HR 1.1 [95% CI, 0.9-1.4], *P* = 0.322) • Adalimumab HR 1.1 [95% CI, 0.6-1.9], *P* = 0.747) • MTX HR 1.0 [95% CI, 0.8-1.2], *P* = 0.927) • Hydroxychloroquine HR 0.9 [95% CI, 0.7-1.2], *P* = 0.481)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Wolfe et al., 2007[200] **Country and setting** US, multicenter **Source of funding** Centocor, Amgen, Abbott, Bristol-Meyers-Squibb, Aventis, NIH **Research objective** Investigate association of serious ILD and RA treatments **Study design** Retrospective Cohort Study **Overall N** 17598 **Duration of study** Varied, cohort followed up to 3.5 yrs beginning in 2001 **Quality rating** Fair: Some confounding factors were controlled for but authors assert there are others (e.g. dr.s who prescribed a TNF-therapy to treat ILD, Dr.s prescribe LEF instead of MTX in pts with a history of lung disease) that present	**Inclusion Criteria** • National Databank for Rheumatic Diseases (NDB) includes patients receiving treatment for RA • Patients hospitalized with interstitial lung diease (HILD) were considered cases **Exclusion Criteria** • NR	**Interventions, Dose** D1: Hospitilization for Interstitial Lung Disease (HILD) Case/Control (both Ds include treatment with: PRED, MTX, LEF, IFX, HCQ, ETN, SSZ, ADA, & ANK as well as others drugs not included in this review D2: **Number in group** D1: 100 D2: 17498 **Mean age (years)** D1: 64.4 D2: 61.9 **Sex, % female** D1: 80.0 D2: 77.0 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 15.3 (11.2) D2: 15.9 (11.2) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** NR **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: HAQ/prior lung problems: 1.4 (0.8)/66.7% D2: 1.1 (0.7)/16.7% (for BOTH HAQ & Prior lung problems *P* = 0.001)	**ACR** ACR 20: D1: No efficacy outcomes reported ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** Withdrawals due to adverse events, n: D1: 8% of pts drop from National Data Bank for Rheumatic Diseases every year **Overall adverse events reported, n:** D1: NR - see additional comments for germane analyses **Serious adverse events** NR **Malignancies** NR **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Hazard Ratio for HILD from current treatements (adjusted for age, sex, and prior lung disease): PRED 2.5 (95%CI 1.5-4.1, *P* = 0.000), INX 0.7 (0.4-1.3), ETN 0.9 (0.4-1.7), LEF (1.3 (0.7-2.3), HCQ 1.0 (0.5-1.9), SSZ 1.4 (0.5-3.7), MTX 1.2 (0.7-1.9). • Hazard Ratio for HILD from past treatments (adjusted for age, sex, and prior lung disease): PRED

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
problems for assessing c					3.0 (CI: 1.0-8.9, *P* = 0.044), IFX 2.1 (CI:1.1-3.8, *P* = 0.019), ETN 1.7 (CI: 1.0-3.0, *P* = 0.056), LEF 1.4 (0.8-2.4), HCQ 0.7 (0.4-1.2), SSZ 0.7 (0.4-1.2), MTX 0.7 (0.4-1.4), ADA 1.1 (0.4-2.7), AKA 1.0 (0.3-3.3). • Odds Ratio for death from ILD by treatment at time of hospitalization (adjusted for age, sex, and baseline HAQ): ETN 4.9* (CI: 1.0-23.1, *P* = 0.044), LEF 3.5 (CI: 0.9-13.5, *P* = 0.073), MTX 0.4 (0.1-1.4), INX 0.6 (0.1-2.5), PRED 0.9 (0.2-4.1). [*ETN OR for death reported differently in text - 4.0, CI is same in both places]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Wolfe & Michaud, 2007[201] **UPDATES PREVIOUS REPORT** Wolfe & Michaud, 2004[197] **Country and setting** US, multicenter **Source of funding** Centocor, Sanofi-Aventis, Bristol-Meyers Squibb, Abbott, Amgen, Wyeth-Australia, Merck, & Pfizer **Research objective** Assess relationship between anti-TNF therapy, MTX, and lymphoma in pts with RA **Study design** Retrospective Cohort Study **Overall N** 19591 (for RA SIR calculation), 19562 for treatment analysis **Duration of study** mean 3.7 years **Quality rating** Fair: additional information about differences in Case/Control	**Inclusion Criteria** • RA diagnosed by rheumatologist **Exclusion Criteria** • incomplete treatment data in registry, completed = 2 semiannual questionairres, diagnosis of lymphoma prior to database entry	**Interventions, Dose** D1: Case (Lymphoma)/Control (includes pts on MTX, INF, ETA, & ADA) **Number in group** D1: 19591 **Mean age (years)** D1: 59.0 **Sex, % female** D1: 77.2 **Race, % white** NR **Race, % black** NR **Ethnicity, Latino** NR	**Mean disease duration, years (SD)** D1: 14.1 yrs **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** NR **DMARD use, %** D1: % provided is for **MTX naïve, %** NR **Baseline DAS score, mean (SD)** NR **Required treatment for latent TB** NR **Other population characteristics, %, (CI/SD/P value)** D1: HAQ: 1.1 (0.7)	**ACR** ACR 20: D1: No efficacy outcomes reported ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** NR **Overall adverse events reported, n:** NR **Serious adverse events** NR **Malignancies** Lymphoma or leukemia, n: D1: NR, SEE ADDITIONAL COMMENTS **Respiratory events** NR **Other infections** NR **GI** NR **Other** • After adjusting for inflammatory activity, pts treated with any Anti-TNF (IFX, ETN, or ADA) did not have an increases risk for lymphoma compared to RA pts who had not received Anti-TNFs (OR 1.0, 95%CI: 0.6-1.8, *P* = 0.875). • IFX vs. all others (OR 1.2 CI:0.6-2.2, *P* = 0.646); ETN vs. all others (OR 0.7, CI:0.3-1.6, *P* = 0.422); ADA* 4.5 (0.9-23.1, *P* = 0.064) *Authors questioned reliability of this result based

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
population sociodemographic characteristics & medical history/severity would allow for a better assessment of potential confounding variables					on small sample (N = 56) who had only used ADA

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Wolfe & Muchaud, 2007[202] **Country and setting** US, multicenter **Source of funding** Abbott, Amgen, Bristol-Meyers Squibb, Centocor, Merck, Pfizer, and Wyeth Australia **Research objective** Assess risk of malignancy among biologic treated pts **Study design** Retrospective Cohort Study **Overall N** 13,869 RA patients (13,001 in conditional logistic regression) **Duration of study** Mean: 4.1 years (minimum 1 year follow up) **Quality rating** Fair	**Inclusion Criteria** • RA **Exclusion Criteria** • < 1 cancer free phase in NDB prior to initiating study or = 2 observational periods recorded in NDB • Previous diagnoses for individual cancers (e.g. lung) excluded pt from analysis for that specific outcome	**Interventions, Dose** D1: All RA pts in NDB database (pts on biologics including INF, ETN, ADA, & ANK) **Number in group** D1: 13,001 **Mean age (years)** D1: 58.5 **Sex, % female** D1: 78 **Race, % white** D1: 92.5 **Race, % black** D1: 3.9 **Ethnicity, Latino** D1: 1.9	**Mean disease duration, years (SD)** D1: 16.7 yrs (12.7) **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean (SD)** NR **Swollen Joint Count, mean (SD)** NR **Corticosteroid use, %** D1: PRED: 45.6 **DMARD use, %** D1: combined use of **MTX naïve, %** NR **Baseline DAS score, mean (SD)** D1: First Patient Activity Scale score: 3.7 (2.2) **Required treatment for latent TB** NR **Other population characteristics, %,** NR	**ACR** ACR 20: D1: No efficacy outcomes reported ACR 50: NR ACR 70: NR **HAQ** NR **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR **Others, (please name); mean difference/absolute difference (CI/SD/P Value)** NR	**Overall** Overall attrition/withdrawal, n: D1: NA, LTF NR for database **Overall adverse events reported, n:** D1: NR, SEE ADDITIONAL COMMENTS **Serious adverse events** NR **Malignancies** Other cancer (specify), n: D1: NR, SEE ADDITIONAL COMMENTS **Respiratory events** NR **Other infections** NR **GI** NR **Other** • Biologics were associated with an increased risk of nonmelanotic skin cancer (OR 1.5, 95% CI 1.2-1.8) and melanoma (OR 2.3, 95% CI 0.9-5.4). • No other malignancy was associated with biologic use; OR (overall risk) of any cancer was 1.0 (95% CI 0.8-1.2). *P* = NS for all other cancers and all cancers combined (cancer assessed [with 10+ cases]: bladder, breast, colon, esophogas, leukemia, lung, lymphoma, Non-

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Hodgkins, pancrease, prostate, & solid* [*excludes lymphoma, leukemia, myeloma, and nonmelanoma skil malignancies]. • Stratified by tx: Melanoma - IFX 2.6 (1.0-6.7), ETN* 2.4 (1.0-5.8), ADA* 0.8 (0.1-6.6), ANK* 4.2 (0.9-20.0) • Skin (excludes melanoma)- IFX 1.7 (1.3-2.2), ETN 1.2 (1.0-1.5), ADA 0.9 (0.5-1.8), ANK 1.4 (0.7-2.8) • Other cancers by drug *P* = NS [*indicates less than 10 cases by treatment]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Zhang, et al., 2006[203] **Country and setting** China, multicenter **Source of funding** NR **Research objective** Report efficacy and safety of IFX intreatment of active RA in Chinese pts. **Study design** Controlled Trials **Overall N** 173 **Duration of study** 18 weeks **Quality rating** Fair	**Inclusion Criteria** • Treatment resistant MTX • Diagnosis of RA by ACR criteria, and active disease at screening despite treatment with MTX for 3 mos or over and at a stable dose (7.5-20 mg/wk) for at least 4 weeks • Active disease based on: 1) 3 or more swollen joints, 2) 8 or more tender joints, 3) 2 offollowing items: morning stiffness greater than or equal to 45 min at screening • ESR that exceeded 28 mm/h • CRP that was greater than 1.5 times that of upper limit of normal • Screening laboratory tests had to meet following	**Interventions, dose** D1: MTX: stable dose IFX: 3 mg/kg body weight at weeks 0, 2, 6, and 14 D2: MTX: stable dose Placebo: 3 mg/kg body weight at weeks 0, 2, 6, and 14 **Number in group** D1: 87 D2: 86 Overall: 173 **Mean age, years (SD)** D1: 47.9, SD: 10.1 D2: 48.9, SD: 8.0 *P* = 0.461 **Sex, % female** D1: 85.1 D2: 84.9 **Race, % white** NA **Race, % black** NA **Ethnicity, Latino** NA	**Mean disease duration, years** D1: 85.6 months, SD: 74.0 D2: 96.0 months, SD: 74.6 *P* = 0.360 **Patients with early RA, three years or less, %** NR **Treatment resistant, %** NR **Tender Joint Count, mean** NR **Swollen Joint Count, mean** NR **Corticosteroid use, %** D1: Never: 44.8 D2: Never: 36.1 **DMARD use, %** NR **MTX naïve, %** NA **Baseline DAS score** NR **Required treatment for latent TB** NR	**ACR** At week 18: ACR 20: D1: 75.86 D2: 48.84 *P* = 0.0003 ACR 50: D1: 43.68 D2: 25.58 *P* = 0.011 ACR 70: D1: 22.99 D2: 13.95 *P* = 0.137 **HAQ,** At week 18 vs. baseline: D1: -0.76 D2: -0.45 *P* = 0.0016 **DAS** NR **SF-36** NR **Radiographic measures** NR **Quality of life scales** NR	**Attrition/withdrawal** Overall, n: D1: 9 D2: 15 Overall: 24 Withdrawals due to adverse events, n: D1: 6 D2: 4 Overall: 10 **Overall adverse events reported, n:** D1: 57 D2: 48 Overall: 105 **Serious adverse events** Heart failure, n: D1: 0 D2: 0 **Malignancies** Tumour, n: D1: 0 D2: 0 **Respiratory events** Tuberculosis: NR Pneumonia, n: D1: NA D2: 1 **Other infections** Urinary tract infection, n: D1: NR D2: 1 **GI** Abdominal pain, n: D1: 1 D2: NA

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	criteria: haemoglobin = 85 g/L, white blood cell count = 4 times 10^9/L, serum neutrophils = 1. 5 times 10^9/L, platelets = 100 times 10^9/L, serum aminotrans-ferase concentration = 1.5 time suppoer limit of normal, serum creatinine of = 120 umol/L • Stable dose of glucocorticoster oid for 4 weeks before screening and does not exceed 10 mg/day of PRED or equivalent. **Exclusion Criteria** • Patients with positive TB skin tests (induration = 15 mm), hepatitis, AIDS, tumor, infections, congestive heart failure, demyelinating disease,				**Other** Skin rash, n: D1: 2 D2: NA Demyelenation or multiple sclerosis, n: D1: 0 D2: 0 Progressive multifocal leukoencephalopathy, n: D1: 1 D2: NA Other AEs 1, n: D1: adult onset of Still's disease: 1 D2: edema of lower limb: 1 Other AEs 2, n: D1: Pharyngitis: 1 D2: Exacerbation of swollen joints: 3 Other AEs 3, n: D1: NR D2: Abnormality in serum alanine transaminase: 1 **Any other AEs** Respiratory: D1: 12 D2: 12 Liver: D1: 10 D2: 7 Skin: D1: 9 D2: 4 Urinary:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	commenced on treatment with other DMARDs within 4 weeks prior to screening, treatment with thalidomide or other TNF antagonists within 3 mos of entry to study.				D1: 7 D2: 6 Hematological: D1: 7 D2: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Zink, 2005[204] **Country, Setting:** Germany, clincal **Funding:** Essex Pharma, Wyeth Pharma, Amgen, and Abbott **Research Objective:** To compare drug continuation rates in pts. with RA who start on a biological agent or on a DMARD after previous DMARD failure **Study Design:** Retrospective cohort study **Overall N:** 1,523 **Study Duration:** 1 yr	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed with RA according to ACR criteria • Previous use of DMARDs: at least 2 **Exclusion Criteria:** NR	**Interventions (dose):** D1: ETA D2: INF D3: AKA D4: Total Control Group D5: LEF D6: LEF + MTX Dosages NR **N:** D1: 511 D2: 343 D3: 70 D4: 599 D5: 120 D6: 141 **Mean age, yrs:** D1: 53.7 D2: 53.6 D3: 54.3 D4: 56.5 D5: 58 D6: 57.4 **Sex, % female:** D1: 77.9 D2: 71.1 D3: 77.1 D4: 82.8 D5: 85.8 D6: 78.0 **Race, % white:** NR	**Mean disease duration (yrs):** D1: 9 D2: 8.5 D3: 13 D4: 6 D5: 9 D6: 7 **TJC, mean:** D1: 13.3 D2: 12.6 D3: 12.6 D4: 10 D5: 10.6 D6: 10.9 **SJC, mean:** D1: 10.4 D2: 10.7 D3: 10.2 D4: 7.7 D5: 7.4 D6: 8.5 **DMARD use (#):** D1: 3.9 D2: 3.7 D3: 4.2 D4: 2.1 D5: 2.4 D6: 2.2 **Corticosteroid use, %:** NR **MTX naive, %:** NR	**Continuation rates** D1 and D2 similar D3 significantly lower **Txt continuation at 1 yr, %** D1: 68.6 ETA+ MTX : 71.6 D2: 65.4 D6: 66.2 D3: 59 AKA vs. ETA; *P* = 0.004; ANA vs. INF; *P* = 0.03 **Txt discontinuation because of adverse events, %:** D2: 18.7 INF+MTX: 18.2 D1: 12.6% ETA+MTX 13.3 D3: 16.3 **Txt discontinuation because of lack of efficacy, %:** D1: 19.9 ETA + MTX :16.9; D2: 45 INF+MTX: 17.9 D3: 29.6	NR	**Overall Attrition Rate, %:** N/A **ITT Analysis:** N/A: registry **Quality Rating:** Good

Evidence Table 2. Systematic reviews and meta-analyses

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Alonso-Ruiz et al., 2008[205] **Country and setting:** Multinational **Funding:** NR **Aims of Review:** To perform a systematic review of RCTs of anti-TNFα drugs in RA followed by a metaanalysis of the efficacy and safety of different doses of INF, ETN and ADA **Quality Rating:** Good	**Study design:** Systematic Review and meta-analyses **Number of Patients:** 7087 **Studies Included:** N = 13	**Characteristics of Included Studies:** RCTs of INF, ETN, or ADA of at least 6 months duration with efficacy measured by ACR response **Characteristics of Included Populations** Patients had to satisfy the ACR criteria for dianosis of RA and have active disease **Characteristics of Interventions:** All were trials of INF, ETN, or ADA. 4 INF + MTX vs. MTX trials (INF doses ranged from 3 mg/kg to 10 mg/kg, administered every 8 wks; 1 trial included a 3 and 10 mg/kg arm administered every 4 wks too.) 4 ETN trials: 1 ETN + MTX vs. MTX; 1 ETN vs. placebo; 1 ETN vs. MTX; 1 ETN + MTX vs. MTX vs. ETN (ETN doses were either 10 mg or 25 mg administered twice weekly) 5 ADA trials: 2 ADA + MTX vs. MTX; 1 ADA vs. placebo; 1 ADA + DMARD vs. DMARD; 1 ADA + MTX vs. MTX vs. ADA (ADA doses were 20 mg or 40 mg adminstered once per wk or 2 wks; 1 trial included an 80 mg/2 wk arm)	**Study Results:** Any anti-TNFα drug (all doses) vs. control treatment (13 studies): ACR20: RR, 1.81 (95% CI, 1.43-2.29); NNT, 6 (5-7) ACR50: RR, 2.46 (95% CI, 1.75-3.45); NNT, 5 (5-6) ACR70: RR, 2.77 (95% CI, 1.85-4.15); NNT, 7 (7-9) Any anti-TNFα drug (recommended doses) vs. control treatment : ACR20: RR, 1.8 (95% CI, 1.4-2.3); NNT, 5 (5-6) ACR50: RR, 2.4 (95% CI, 1.7-3.4); NNT, 5 (5-6) ACR70: RR, 2.7 (95% CI, 1.8-4.1); NNT, 7 (7-9) ADA (all doses) vs. control treatment ACR20: RR, 1.9 (95% CI, 1.3-2.8); NNT, 6 (5-7) ACR50: RR, 2.7 (95% CI, 1.6-4.4); NNT, 6 (5-7) ACR70: RR, 3.3 (95% CI, 1.8-6.3); NNT, 9 (7-11) ADA (recommended doses) vs. control treatment ACR20: RR, 2.0 (95% CI, 1.3-2.9); NNT, 5 (4-6) ACR50: RR, 2.8 (95% CI, 1.6-4.7); NNT, 5 (5-6) ACR70: RR, 3.5 (95% CI, 1.9-6.7); NNT, 7 (6-8) ETN (all doses) vs. control treatment ACR20: RR, 1.7 (95% CI, 1.1-2.6); NNT, 7 (5-10)	**Adverse Events:** Any anti-TNFα drug vs. control treatment Withdrawal due to adverse event: RR, 1.25 (95% CI, 0.65-2.39); NNH, NS Total adverse event: RR, 1.0 (1.0-1.5); NNH 27 (17-59) Serious adverse event: RR, 1.1 (0.8-1.6); NNH, NS Infections: RR, 1.9 (0.9-1.2); NNH, NS Serious infections: RR, 1.4 (0.8-2.2) NNH, NS Infusion Reactions: RR, 3.0 (1.0-8.6); NNH, 8 (7-10) Malignancies: RR, 1.5 (0.8-3.0); NNH, NS Mortality: RR, 0.8 (0.3-2.1); NNH, NS ADA vs. control treatment Withdrawal due to adverse event: RR, 1.4 (1.0-2.0); NNH, 47 (26-251) Total adverse event: RR, 1.1 (0.9-1.1); NNH, NS Serious adverse event: RR, 1.0 (0.7-1.4); NNH, NS Infections: RR, 1.1 (0.9-1.2); NNH, NS Serious infections: RR, 1.2 (0.6-2.8); NNH, NS

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			ACR50: RR, 2.1 (95% CI, 1.1-3.9); NNT, 6 (5-9) ACR70: RR, 2.0 (95% CI, 0.9-4.4); NNT, NS ETN (recommended doses) vs. control treatment ACR20: RR, 1.7 (95% CI, 1.1-2.7); NNT, 6 (5-8) ACR50: RR, 2.2 (95% CI, 1.1-4.3); NNT, 6 (4-7) ACR70: RR, 2.1 (95% CI, 0.9-4.5); NNT, NS INF (all doses) vs. control treatment ACR20: RR, 1.8 (95% CI, 1.2-2.8); NNT, 5 (4-6) ACR50: RR, 2.6 (95% CI, 1.5-4.7); NNT, 5 (5-6) ACR70: RR, 2.9 (95% CI, 1.4-5.8); NNT, 8 (6-10) INF (recommended doses) vs. control treatment ACR20: RR, 1.7 (95% CI, 1.1-2.6); NNT, 5 (4-6) ACR50: RR, 2.2 (95% CI, 1.2-4.1); NNT, 6 (5-7) ACR70: RR, 2.4 (95% CI, 1.2-5.0); NNT, 9 (7-13) Efficacy of anti-TNFα drugs (recommended doses) in combination with MTX compared with MTX alone in patients with insufficient responses to MTX ACR20: RR, 2 .6 (95% CI, 2.0 5-3.31) ACR50: RR, 4 .13 (95% CI, 2.59-6 .59) ACR70: RR, 4.14 (95% CI,	Infusion Reactions: RR, 2.7 (1.7-4.2); NNH, 9 (7-14) Malignancies: RR, 1.1 (0.4-2.7); NNH, NS Mortality: RR, 1.3 (0.4-4.7); NNH, NS ETN vs. control treatment Withdrawal due to adverse event: RR, 0.7(0.5-0.9); NNH, -26 (-143 to -14) Total adverse event: RR, 1.0 (0.9-1.1); NNH, NS Serious adverse event: RR, 0.9 (0.5-1.6); NNH, NS Infections: RR, 1.0 (0.9-1.0); NNH, NS Serious infections: RR, 0.9 (0.4-2.3); NNH, NS Infusion Reactions: RR, 5.1 (2.9-8.8); NNH, 5(4-6) Malignancies: RR, 1.9 (0.6-5.7); NNH, NS Mortality: RR, 1.5 (0.2-9.5); NNH, NS INF vs. control treatment Withdrawal due to adverse event: RR, 2.0 (1.3-3.1); NNH, 24 (17-41) Total adverse event: RR, 1.0 (0.9-1.0); NNH, NS Serious adverse event: RR, 1.4 (1.0-2.0); NNH, 31 (17-

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			2.43-7.05)	167)
			Efficacy of anti-TNFα drugs (recommended doses) plus MTX compared to MTX alone in patients with no previous resistance to MTX ACR20: RR, 1.15 (95% CI, 1.07-1.22) ACR50: RR, 1.56 (95% CI, 1.41-1.72) ACR70: RR, 1.77 (95% CI, 1.52-2.05)	Infections: RR, 1.2 (1.1-1.3); NNH, 10 (7-24) Serious infections: RR, 1.8 (0.9-3.4); NNH, NS Infusion Reactions: RR, 2.7 (1.7-4.2); NNH, 9 (7-14) Malignancies: RR, 2.6 (0.6-11.6); NNH, NS Mortality: RR, 0.5 (0.2-1.4); NNH, NS

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Bergman et al., 2010[206] **Country and setting:** Multinational **Funding:** Hoffmann La-Roche **Aims of Review:** ACR response between TCZ and other biologic agents in patients with rheumatoid arthritis who have inadequate response to disease-modifying antirheumatic drugs **Quality Rating:** Fair	**Study design:** Systematic review and meta-analysis **Number of Patients:** 10,419 **Studies Included:** N = 18	**Characteristics of Included Studies:** Double-blind, randomized, placebo controlled trials, 24 to 30 weeks **Characteristics of Included Populations** Adults with RA **Characteristics of Interventions:** RCTs - study duration of at least 6 months;	**Study Results:** Fixed-Effects Model Relative Risk (95% CrI) / Random-Effects Model Relative Risk (95% CrI) Biologic agent vs.placebo, Fixed-Effects Model Relative Risk (95% CrI) ACR20 TCZ: 2.0 (1.9-2.2) TNF- inhibitors :1.9 (1.7-2.1) ABA: 1.9 (1.7-2.1) RTX: 1.8 (1.5-2.2) ACR50 TCZ: 3.5 (3.0, 4.0) TNF- inhibitors: 2.8 (2.4, 3.2) ABA: 2.7 (2.2, 3.3) RTX: 2.8 (1.8, 4.0) ACR70 TCZ: 6.8 (4.9, 9.4) TNF- inhibitors: 3.8 (3.1, 4.8) ABA: 3.4 (2.5, 4.8) RTX: 4.3 (2.2, 8.9) Biologic agent vs.placebo, Random-Effects Model Relative Risk (95% CrI) ACR20 TCZ: 2.1 (1.6-2.5) TNF:- inhibitors: 2.0 (1.7-2.3) ABA: 1.9 (1.4-2.3) RTX: 1.9 (1.3-2.5) ACR50 TCZ: 3.6 (2.5, 5.0) TNF- inhibitors: 3.2 (2.5, 4.3) ABA: 2.7 (1.7, 4.0) RTX: 2.9 (1.5, 4.9) ACR70 TCZ: 6.9 (4.5, 10.8)	**Adverse Events:** NA

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			TNF- inhibitors: 4.0 (3.0, 6.0) ABA: 3.6 (2.2, 6.2) RTX: 4.4 (1.9, 10.5) Pairwise comparison of biologic agents ACR20 TCZ vs.TNF- inhibitors 1.1 (1.0, 1.2) / 1.1 (0.8, 1.3) TCZ vs.ABA 1.1 (1.0, 1.2) / 1.1 (0.8, 1.6) TCZ vs.RTX 1.1 (0.9, 1.4) / 1.1 (0.8, 1.7) ABA vs.TNF- inhibitors 1.0 (0.9, 1.1) / 0.9 (0.7, 1.2) RTX vs.TNF- inhibitors 1.0 (0.8, 1.2) / 1.0 (0.6, 1.3) RTX vs.ABA 1.0 (0.8, 1.2) / 1.0 (0.7, 1.5) ACR50 TCZ vs.TNF- inhibitors 1.3 (1.1, 1.5) / 1.1 (0.7, 1.6) TCZ vs.ABA 1.3 (1.0, 1.6) / 1.3 (0.8, 2.3) TCZ vs.RTX 1.3 (0.9, 1.9) / 1.2 (0.7, 2.5) ABA vs.TNF- inhibitors 1.0 (0.8, 1.2) / 0.9 (0.5, 1.3) RTX vs.TNF- inhibitors 1.0 (0.7, 1.5) / 0.9 (0.5, 1.6) RTX vs.ABA 1.0 (0.7, 1.5) / 1.1 (0.5, 2.1) ACR70 TCZ vs.TNF- inhibitors 1.8 (1.2, 2.6) / 1.7 (1.0, 2.8) TCZ vs.ABA 2.0 (1.3, 3.1) / 1.9 (1.0, 3.6) TCZ vs.RTX 1.6 (0.7, 3.3) / 1.6 (0.6, 4.0) ABA vs.TNF- inhibitors 0.9 (0.6, 1.2) / 0.9 (0.5, 1.5)	

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			RTX vs.TNF- inhibitors 1.1 (0.5, 2.4) / 1.1 (0.4, 2.6) RTX vs.ABA 1.3 (0.6, 2.8) / 1.2 (0.5, 3.2)	

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Bernatsky et al., 2010[207] **Country and setting:** Study conducted in Canada - components are multinationals **Funding:** NR **Aims of Review:** a systematic review and synthesis of observational studies of TNF antagonists and infection risk. **Quality Rating:** Fair	**Study design:** Systematic review and meta-analysis **Number of Patients:** NR **Studies Included:** N = 7	**Characteristics of Included Studies:** 5 cohort and 2 nested case-control studies **Characteristics of Included Populations** Patients with RA and serious infections **Characteristics of Interventions:** Anti-TNFs	**Study Results:** Anti-TNF therapy appeared to significantly increase risk of serious infection (pooled adjusted RR 1.37, 95% CI, 1.18-1.60).	**Adverse Events:** The summary RR, suggested about a 40% increased risk of serious infections in patients with RA exposed to TNF antagonists (RR, 1.37; 95% CI, 1.18-1.60).

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Bongartz, 2006, multinational, Mayo foundation, Abbott & Centocor[208] **Study Design:** Systematic literature search with meta-analysis **Aims of the Review:** • To assess extent to which anti-TNF antibody therapy may increase risk of serious infection and malignancies in pts with RA by performing a meta-analysis • To derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy **Number of Pts:** 5014 (9 trials)	**Studies included:** • Keystone (2004) • St Clair (2004) • Furst (2003) • Lipsky (2000) • van de Putte (2003) • Weinblatt (2003) • Maini (1998) • van de Putte (2004) • Westhovens (2004) **Characteristics of included studies:** • RCTs of INF and ADA in which pts had ACR-diagnosed RA and were randomized to anti-TNF vs. placebo (or anti-TNF antibody + traditional DMARD vs. placebo + traditional DMARD) • Both pt and observer were masked • Trial had to be at least 12 wks in duration **Characteristics of included populations:** • Pts with an ACR diagnosis of RA who were randomized to receive Anti-TNF or placebo **Characteristics of interventions:** Anti-TNF (dosing varied) or Control	• In pts with RA, anti-TNF treatment leads to increased risk of serious infections and a dose-dependent increased risk of malignancies. Serious infections reported in 126 anti-TNF- treated pts vs. 26 control group pts (OR, 2.0; 95% CI, 1.3-3.1) • Malignancies reported in 24 / 3493 (0.8%) pts who received > 1 dose of anti-TNF vs. 2 / 1512 (0.2%) pts on control • Pooled OR for malignancies in anti-TNF group vs. placebo group: 3.3 (95% CI, 1.2-9.1) • Number needed to harm was 154 (95% CI 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (39-125) within a treatment period of 3 to 12 months	Overall AEs reported: • Malignancy: Anti-TNF (23/3192) Control (3/1428) OR: 3.3 (95% CI 1.2 – 9.1) • Serious Infections: Anti-TNF (126/3493) Control (26/1512) OR: 2.0 (1.3-3.1)	**Publication Bias Assessed:** Not reported **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes - briefly describe in box: EMBASE, MEDLINE, Cochrane Library, and electronic abstracts of the annual scientific meetings both the European League Against Rheumatism and the American College of Rheumatology – through December 2005 **Quality Rating:** Fair

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Bongartz et al., 2009[209] **Country and setting:** Multinational **Funding:** Wyeth **Aims of Review:** To assess the risk of malignancy with ETN **Quality Rating:** Good	**Study design:** Systematic review and meta-analysis **Number of Patients:** 3316 patients, 2244 who received ETN (contributing 2484 person-years of follow-up) and 1072 who received control therapy (1051 person-years). **Studies Included:** N = 9 (8 published, 1 unpublished)	**Characteristics of Included Studies:** RCTS at least 12 weeks long **Characteristics of Included Populations** Patients with RA **Characteristics of Interventions:** ETA vs. Control	**Study Results:**	**Adverse Events:** Malignancies in 26 patients in the ETN group (incidence rate (IR) 10.47/1000 person-years) and 7 in the control group (IR 6.66/1000 person-years). A Cox's proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI, 0.79-4.28) for the ETN group compared with the control group.

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Clark, 2004[210], International: Europe, U.S., Canada, Australia, Health Technology Assessment Programme (U.K.) **Study Design:** Systematic review and meta-analysis analysis **Aims of Review:** To review evidence on clinical benefits, hazards, and cost-effectiveness of AKA in adult RA pts **Number of Pts:** 2,905	**Studies included:** Efficacy Trials: • Bresnihan (1998) • Cohen (2001) • Cohen (2002) • Unpublished report by Amgen (2001; STN 103950 Clinical Review; low-dose for 3 mos) Safety Trial: • Fleischmann (2001) **Characteristics of included studies:** • RCTs (except 1) of AKA or AKA + MTX in pts with highly active RA • Fleischmann control arm consisted of placebo + DMARD txt **Characteristics of included populations:** • Mean ages 50s • Duration 6 mos to 10 yrs • Majority had failed at least 1 DMARD and some were taking MTX up to trial start • Majority taking low-dose steroids and NSAIDs **Characteristics of interventions:** • AKA alone: • AKA from 2.5 mg/day to	Adjusted indirect comparisons with anti TNF agents (ETN, INF) suggested that AKA may be significantly less effective at relieving clinical symptoms than anti-TNF agents (-0.21; 95% CI, -0.32 to -0.10) Adjusted indirect comparisons: • RD (95% CI) • TNF+MTX vs. MTX 0.37 (0.28 to 0.45) • AKA+MTX vs. MTX 0.16 (0.09 to 0.23) • AKA+MTX vs. TNF+MTX -0.21 (-0.32 to -0.10)	Withdrawals due to adverse events: • Control: 4.1% to 9% • AKA: 5% to 13% Specific adverse events: • SAEs: Control: 3.2% to 11.6% AKA: 4.4% to 12.8% • Malignancy: Control: 0% to 1.8% AKA: 0% to 1.1% • Injection Site Reactions: Control: 3% (low-dose study) to 33% AKA: 19.8% (low-dose study) to 73% • Any infection: Control: 13.3% (low-dose study) to 50% AKA: 13.5% (low-dose study) to 48.4% • Serious infections: Control: 0.4% to 1.4% AKA: 0.8% to 2.1% • Neutropenia: Control: 0% to 4% AKA: 0% to 9% • Antibodies to IL-1Ra: Control: 0% to 1.8% AKA: 0.9% to 5%	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
	150 mg/day • AKA + MTX: AKA 0.04 mg/kg per day to 2.0 mg/kg per day or fixed dose 100 mg/day			

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Devine et al., 2011[211] **Country and setting:** Multinational **Funding:** NR **Aims of Review:** efficacy of biologic disease-modifying antirheumatic drugs (DMARDs) vs.placebo with or without MTX, in treating rheumatoid arthritis. **Quality Rating:** Fair	**Study design:** Systematic review and meta-analysis **Number of Patients:** 6 months: 11,589 12 months: 6051 **Studies Included:** 6 months: 23 RCTs 12 months: 10 RCTs	**Characteristics of Included Studies:** RCTs at least 22 weeks outcomes **Characteristics of Included Populations** Patients with RA and and patient populations defined as DMARD-IR or MTX (MTX)-inadequate responders **Characteristics of Interventions:** Biologic DMARDs with or without MTX or other nonbiologic DMARDs, compared with placebo with or without MTX or other nonbiologic DMARDs	**Study Results:** Log Odds Ratio Estimates for the 6-Month and 12-Month Models by Drug 6-month model Certolizumab μ1 2.60 0.44 1.83-3.59 1 TCZ μ2 1.67 0.19 1.31-2.07 2 RTX μ3 1.61 0.59 0.55-2.85 3 INF μ4 1.57 0.27 1.03-2.10 4 ETN μ5 1.43 0.25 1.00-2.00 5 ADA μ6 1.37 0.22 0.94-1.83 6 GOL μ7 1.36 0.38 0.64-2.14 7 ABA μ8 1.16 0.27 0.61-1.68 8 ANK μ9 0.98 0.28 0.47-1.58 9 MTX 0.78 0.19 0.39-1.17 Baseline disease duration 1 0.08 0.04 < 0.01-0.18 Baseline HAQ score 2 -0.45 0.53 -1.49-0.63 Variance 2 0.05 0.02 < 0.01-0.28 12-month model Certolizumab μ1 2.02 0.44 1.16-2.83 1 RTX μ2 1.95 0.90 0.47-4.00 2 ADA μ3 1.37 0.28 0.83-1.89 3 INF μ4 1.36 0.31 0.80-1.99 4 ETN μ5 0.86 0.32 0.28-1.43 5 ABA μ6 0.63 0.30 0.08-1.24 6 MTX 0.84 0.21 0.42-1.26 Baseline disease duration 1 0.10 0.04 < 0.01-0.17 Baseline HAQ score 2 0.46 0.78 -1.11-1.89 Variance 2 0.02 0.06 < 0.01-0.88	**Adverse Events:** NR

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Gartlehner et al., 2006[212] US **Study Design:** META-ANALYSISanalysis (random effects model); systematic review **Aims of the Review:** To assess comparative efficacy and safety of biologic agents for RA **Number of Patients:** ADA: 2,354 ETN: 1,151 INF: 704 AKA:1,039 (#'s refer to 17 sudies used for adjusted indirect comparisons of efficacy)	**Studies included:** • 26 controlled trials • 18 additional studies assessed safety **Characteristics of included studies:** • Often limited to 1 year of follow-up • Reported on DAS-28 • Radiographic progression, functional capacity, and QOL **Characteristics of included populations:** • Narrowly defined populations • Mean age 53.4 • 76% female • 89% caucasion **Characteristics of interventions:** • All efficacy studies except 1 were funded by the pharmaceutical industry • All 12 weeks plus of duration (for observational studies it was 3 months or greater and 100 or more patients)	Adjusted indirect comparison indicate no significant differences in efficacy between antiTNF drugs • Anti-TNF drugs appear to be more efficacious than AKA but do not differ among each other. Inddirect comparisons of INF and of anti-TNF drugs as a class compared to AKA yielded a statistically significant greater efficacy on ACR 20 [RR 0.58 (95%CI 0.38-0.90) and RR 0.61 (95% CI 0.39-0.96), respectively], but not ACR 50 • Few studies assessed longterm radiographic outcomes. In general, rate of radiographic progression was significantly lower in patients treated with biologics than in placebo-treated patients, regardless of concomitant DMARD therapy. Similarly, QoL improved significantly for patients treated with biologics	Because of lack of sound long-term safety data, evidence is insufficient to draw firm conclusions about comparative safety of biologics • Higher rates of injection site reactions for AKA than ADA and ETN (56% vs. 19% vs. 25%)	**Publication Bias Assessed:** Yes **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes - briefly describe in box: Searched Medline, Embase, Cochrane and International Pharmaceutical Abstracts from 1980-2006. Also explored CDER database. **Quality Rating:** Good

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Gaujoux-Viala et al., 2010[213] **Country and setting:** NR **Funding:** NR **Aims of Review:** To analyze the literature on the efficacy on signs and symptoms, disability and structure, of oral DMARDS and to assess safety, with a special focus on cancers and infections **Quality Rating:** Fair	**Study design:** Systematic Review and Meta-analysis **Number of Patients:** Efficacy studies: 14, 159 Adverse event studies: NA **Studies Included:** Efficacy studies: 97 Safety studies: 39	**Characteristics of Included Studies:** RCTs reporting the efficacy on signs and symptoms, disability and/or structure of oral DMARDs vs.placebo (except for MTX) or other nonbiologic DMARDs, in patients with RA *from online supplemental material **Characteristics of Included Populations** Patients with RA **Characteristics of Interventions:** MTX: • 17 studies • 4,147 patients • age: 49.7±3.4 • % female: 72.4 • disease duration, yrs: 6.7±4.5 LEF: • 9 studies • 3,617 patients • age: 54.3±4.2 • % female: 74.5 • disease duration, yrs: 6.3±2.5 SSZ: • 22 trials • 2,813 patients • age: 52.1±4.0 • % female: 68.8 • disease duration, yrs: 5.6 ± 3.6 Hydroxychloroquine: • 20 studies • 2,182 patients • age: 45.5±6.0 • % female: 73.5 • disease duration, yrs: 3.8±3.0	**Study Results:** MTX vs. LEF SJC (4 studies, 1889 patients): Standardized Response Mean (SRM), 0.09 (95% CI, −0.12-0.30) Pain (4 studies, 1475 patients): SRM, −0.04 (95% CI, −0.33-0.26) Disability (4 studies, 1,465 patients): SRM, −0.09 (95% CI, −0.30-0.11) ACR20 response (4 studies, 1889 patients): OR, 1.04 (95% CI, 0.60-1.79) Structure (2 studies, 895 patients): SRM, 0.03 (95% CI, −0.10-0.16) MTX vs. SSZ SJC (2 studies, 206 patients): SRM, 0.59 (95% CI, −1.96-3.15) Disability (2 studies, 208 patients): SRM, 0.62 (95% CI, −0.86-2.10) ACR50 response (2 studies, 193 patients): OR, 1.57 (95% CI, 0.82-3.00) MTX monotherapy vs. MTX combo, DMARD naive No significant advantage of combo with MTX vs. MTX monotherapy for pain, Health Assessment Questionnaire, or ACR20, 50, or 70	**Adverse Events:** MTX monotherapy vs. MTX combo, DMARD naïve Withdrawals due to lack of efficacy or toxicity were similar in both groups: RR, 1.16 (95% CI, 0.70-1.93) MTX monotherapy vs. MTX combos, DMARD inadequate responders 8 trials show insignificant differences in withdrawals between MTX combo and monotherapy. One exception: O'Dell's study of 102 DMARD inadequate responders. The combo of MTX + SSZ and hydroxychloroquine showed fewer withdrawals than MTX alone: RR, 0.30 (95% CI, 0.14 to 0.65).

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			ACR20: OR, 0.53 (95% CI, 0.21-1.33) • MTX monotherapy vs. MTX combos, DMARD inadequate responders • SJC (3 studies): SRM, −0.78 (95% CI, −1.30 to −0.25) • Pain (3 studies): SRM, −0.64 (95% CI, −1.01 to −0.28) • HAQ (3 studies) SRM, −1.21 (95% CI, −2.07 to −0.36) ACR20 (2 studies): RR, = 0.26 (95% CI, 0.16 to 0.40) SSZ monotherapy vs. SSZ combo In 6 trials (657 patients), no significant difference for SJC, function, or ACR20, 50 or 70. Significant finding: Structural damage (1 trial) favoring the combination MTX+SSZ+hydroxychloro-quine: SRM, −1.70 (95% CI, −2.03 to −1.37)25 Pain (1 trial) favoring SSZ monotherapy: SRM, 4.10 (95% CI, 2.91-5.29)	

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Hochberg et al., 2003[214] Multinational NR **Study Design:** Systematic review and indirect comparisons **Aims of the Review:** Differences in efficacy of TNF alpha blocking agents, as measured by rate ratios for American College of Rheumatology (ACR) 20/50/70 responses, in patients with RA with an incomplete response to methotrexate. **Number of Patients:** 1053 380 placebo 673 active	**Studies included:** • Maini et al. 1999 • Lipsky et al. 2000 • Weinblatt et al 1999 • Weinblatt et al. 2003 **Characteristics of included studies:** Placebo controlled, double blind, randomised clinical trials of at least 24 weeks' **Characteristics of included populations:** NR- assuming that it is adults with active RA with lack of response to MTX **Characteristics of interventions:** the addition of TNF blocking agents (INF, ETN and ADA) to methotrexate in a "step-up" strategy	Indirect comparisons, Relative Risk (95% CI) • ETNnercept vs. adalimumab ACR 20 1.10 (0.57 to 2.12) 2.60 (0.35 to 19.0) • Infliximab vs. adalimumab 1.07 (0.66 to 1.73) 1.35 (0.47 to 3.85) • ETNnercept vs. infliximab 1.03 (0.49 to 2.18) 1.92 (0.22 to 17.0)	NR	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** Yes - briefly describe in box **Quality Rating:** Fair

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
Author: Kirwan, 2009[215] **Country and setting:** Multi-national **Funding:** Chochrane Collaboration	**Study design:** Systematic Review and meta-analyses **Overall study N:** 1414 **Study aims:** To perform a systematic qualitative review of studies evaluating glucocorticoid efficacy in inhibiting the progression of radiological damage in rheumatoid arthritis.	**Main results:** • Comparison 1. Glucocorticoids vs. comparator • Erosion outcomes refer to erosion scores expressed as percentage of max possible score for method used by individual studies. • Outcome 1. SMD in progression of erosion scores = 0.40 in favor of glucocorticoids (95% CI 0.27, 0.54) (from abstract) • Outcome 2. Change in erosions at 1 year as proportion of maximum score (N = 15, # of Participants = 1421) SMD = 0.39 (95% CI, 0.27, 0.52) in favor of glucocorticoids • Outcome 3. Erosions at 1 year, data from 1 & 2 year studies (N = 10, # of partcipants = 940) SMD = -0.43 (95% CI, -0.62, -0.23) in favor of glucocorticoids • Outcome 4> Erosions at 2 years, data from 1 & 2 year studies (N = 10, # of participants = 967) SMD = -0.40 (95% CI, -0.56, -0.24) in favor of glucocorticoids • Outcome 5. Joint Space Narrowing at 1 year as a proportion of maximum score (n = 6, # of participants = 711) SMD = -0.27 (95% CI, -0.50, -0.04) in favor of glucocorticoids	**Review based on focused question of interest:** Yes **Did search strategy employ comprehensive, systematic literature search?** Yes A search ofMEDLINE (from1966 to 22 February 2005) and Cochrane Central Register of Controlled Trials was undertaken, using terms 'corticosteroids' and 'rheumatoid arthritis' expanded according to Cochrane Collaboration recommendations. Identified abstracts were reviewed and appropriate reports obtained in full. Additional reports were identified from reference lists and from expert knowledge. **Eligibility criteria clearly described?** Yes Randomized controlled or cross-over trials in adults with a diagnosis of rheumatoid arthritis in which prednisone or a similar glucocorticoid preparation was compared to either placebo controls or active controls (i.e. comparative studies) and where there was evaluation of radiographs of hands, or hands and feet, or feet by any standardised technique. Eligible studies had at least one treatment arm with glucocorticoids and one without glucocorticoids. **Review studies independently reviewed by at least 2 persons?** Yes **Standard method of critical appraisal before including?** Yes	**Comments:** • Sensitivity analyses looked at several different ways of combining studies, and in all cases a similar benefit for glucocorticoid therapy was demonstrated (concomitant medication, length of study, when only low dose steroid studies were included, when step-down glucocorticoids were used, etc.) • Total of 14 comparisons, each with multiple outcomes, reported in review. Comparison 1 was abstracted; others have not been abstracted. The comparisons are: Comp 1. Glucocorticoids vs comparator Comp 2. Glucocorticoids + DMARD + NSAID vs DMARD + NSAID Comp 3. Glucocorticoids vs NSAID Comp 4. Oral low dose Glucocorticoids + DMARD + NSAID vs DMARD = NSAID Comp 5. Step down Glucocorticoids + DMARD + NSAID vs DMARD = NSAID Comp 6. Studies with less than 26 week of Glucocorticoid treatment Comp 7. Studies with more than 26 weeks of Glucocorticoid treatment Comp 8. Glucocorticoids vs comparator using modelled SDs

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
		• Outcome 6. Joint Space Narrowing at 2 years as a proportion of maximum score (N = 4, # of participants - 512) SMD = -0.31 -(95% CI, -0.51, -0.11) in favor of glucocorticoids • Outcome 7. Joint Space Narrowing at 1 year data from 1 & 2 year studies (N = 4, # of participants = 473). SMD -0.22 (-0.51, 0.07) • Outcome 8. Joint Space Narrowing at 2 years data from 1 & 2 year studies (N = 3, # of participants = 345) SMD = -0.28 (95% CI, -0.57, 0.01) • Outcome 9. Proportion of patients progressing at year 1 (N = 4, # of participants = 261). Risk Ratio = 0.60 (95% CI, 0.48, 0.74), in favor of glucocorticoids **Adverse events:** • NR		Comp 9. Glucocorticoids vs comparators using only studies with modelled SDs Comp 10. Glucocorticoids vs. comparator using original SDs in studies with modelled SDs Comp 11. Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed treatment Comp 12. Glucocorticoids vs. comparator sensitivity analyses by quality standards - Blinding of Patients Comp. 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat Comp 14. Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinded Assessors

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Kuriya et al., 2010[216] **Country and setting:** NR **Funding:** NR **Aims of Review:** To examine the efficacy of MTX monotherapy compared with combination therapy with a biologic when used as initial tx in early RA (ERA) pts. **Quality Rating:** Good	**Study design:** Systematic Review and Meta-analysis **Number of Patients:** 2,763 **Studies Included:** N = 7	**Characteristics of Included Studies:** Included studies were double-blind, randomised, active-comparator, controlled clinical trials that studied the efficacy of initial combination therapy (MTX + biologic) compared with MTX monotherapy in adult pts with clinically active ERA **Characteristics of Included Populations** Pts were adults with clinically active ERA, defined as disease duration < 3 years, and with no or minimal previous exposure to MTX (≤ 4 weeks). Previous treatment with corticosteroids, SSZ or hydroxychloroquine/chloroquine was permitted. **Characteristics of Interventions:** 3 INF trials: 3 mg/kg, q 8 weekly 2 ADA trials: 40 mg, q 2 weekly 1 ETN trial: 50 mg, q weekly 1 ABA trial: 10 mg/kg, q 4 weekly	**Study Results:** Clinical Remission (Combo vs. Monotherapy, RR, (95% CI): 1.74 (1.54-1.98) Radiographic Non-progression (Combo vs. Monotherapy, RR, (95% CI): 1.30 (1.01-1.68)	**Adverse Events:** NA

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Leombruno et al., 2009[217] **Country and setting:** multi-national **Funding:** NR **Aims of Review:** To evaluate the safety of biological treatments for RA using results from RCTs **Quality Rating:** Fair	**Study design:** Meta-analysis **Number of Patients:** 8,808 **Studies Included:** N = 18	**Characteristics of Included Studies:** The study must be an RCT with more than 30 patients randomly assigned to either an anti-TNF or a control group (non-DMARD or placebo) over a minimum of 10 wks. A Jadad score of ≥ 2 was required and tx arms of combination biological therapies were excluded. **Characteristics of Included Populations** Patients with RA **Characteristics of Interventions:** ADA: • 6 trials • doses: 20-80 mg every wk or 20-80 mg every other wk • all but 1 on background of MTX or other DMARD. ETN: • 7 trials • doses: 10-25 mg twice per wk • 2 on background MTX • 1 on background SSZ INF: • 5 trials • doses: 1-10 mg/kq every 4 wks or 3-10 mg/kg every 8 wks • all on background of MTX	**Study Results:**	**Adverse Events:** Death, OR (CI) ADA: 2.04 (0.64 - 6.51) ETN: 2.34 (0.67 - 8.12) INF: 0.62 (0.21 - 1.79) Anti-TNF: 1.39 (0.74 - 2.62) Serious adverse events, OR (CI) ADA: 1.12 (0.86 - 1.45) ETN: 1.04 (0.73 - 1.47) INF: 1.17 (0.86 - 1.59) Anti-TNF: 1.11 (0.94 - 1.32) Serious infections, OR (CI) ADA: 1.53 (0.83 - 2.81) ETN: 0.89 (0.56 - 1.42) INF: 1.46 (0.86 - 2.47) Anti-TNF: 1.21 (0.89 - 1.63) Lymphomas, OR (CI) ADA: 1.07 (0.28 - 4.09) ETN: 1.42 (0.27 - 7.61) INF: 1.42 (.27 - 7.62) Anti-TNF: 1.26 (0.52 - 3.06) Non-cutaneous cancers and melanomas, OR (CI) ADA: 1.37 (0.49 - 3.89) ETN: 1.11 (0.42 - 2.96) INF: 1.70 (0.39 - 7.32) Anti-TNF: 1.31 (0.69 - 2.48) Non-melanoma skin cancers, OR (CI) ADA: 1.37 (0.49 - 3.89) ETN: 1.03 (0.38 - 2.77) INF: 1.70 (0.39 -7.32) Anti-TNF: 1.27 (0.67 - 2.42)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Maetzel, et al. 2000[218] Multinational Arthritis and Autoimmunity Research Centre, Aventis Canada, Inc. **Study Design:** Meta-analysis **Aims of Review:** To summarize evidence on treatment withdrawal rates reported in observational studies and RCTs of MTX, SSZ, HCQ (and parenteral gold) among RA patients. **Number of Pts:** Cannot determine	**Studies included:** 159 studies (71 RCTs, 88 observational studies) (159 satisfied screening criteria; 110 studies included in meta-analysis) **Characteristics of included studies:** Studies reporting information on number of patients withdrawing **Characteristics of included populations:** RA Patients being treated with MTX, parenteral gold (GST), SSZ, and HCQ **Characteristics of interventions:** MTX, GST, SSZ, and HCQ	RA patients stay significantly longer on MTX than on other DMARDs. (Higher % stay on MTX vs. SSZ because of toxicity [RR 1.68, $P < 0.0001$]). Majority of withdrawals from SSZ and HCQ result from lack of efficacy. Withdrawal rates similar in observational studies vs RCTs.	See main results	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** NR **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Fair

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Martinez Lopez et al., 2009[219] **Country and setting:** Multinational **Funding:** Abbott Immunology **Aims of Review:** To analyze the safety of MTX in RA regarding the reproductive system. **Quality Rating:** Fair	**Study design:** Systematic Review **Number of Patients:** 366 **Studies Included:** N = 6	**Characteristics of Included Studies:** RCTs, cohort studies, longitudinal observation studies and surveys **Characteristics of Included Populations** RA patients who were 18 years or older; using MTX at doses usually taken in rheumatology (7.5-25 mg/w) **Characteristics of Interventions:** No true cohorts, only descriptions of cases obtained from retrospective clinical record searches or from surveys. The studies reported outcomes on male or female fertility; pregnancy complications; malformations, miscarriages, induced abortions, still births and breast feeding complications	**Study Results:** There were 101 MTX exposed pregnancies in the studies. The pooled outcomes (elective abortions not included) demonstrated: 19 miscarriages (23% of preganancies); 55 live births (66% of preganancies) and 5 of these had neonatal malformations (5% of pregnancies). The rate of induced abortions is 18%. No study filled the selection criteria for MTX and lactation or male fertility. However, there were case reports that generated possible indirect evidence of MTX in human breast milk and and reversible infertility.	**Adverse Events:** N/A

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
Author: Mertens, 2009[220] **Country and setting:** Multi-national (Europe, USA, Canada, Australia) **Funding:** Internal sources: • Minneapolis VA Medical Center • NIH CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research) • National Institute of Health External sources: • No sources of support supplied	**Study design:** Systematic review and meta-analysis **Overall study N:** • N = 2872 (788 placebo, 2084 ANK) in systematic review • Data not presented for 26 randomized pts (7 placebo, 19 ANK); therefore, N = 2846 (781 placebo, 2065 ANK) for analysis **Study aims:** 1. What is the clinical effectiveness of Anakinra for the treatment of RA in terms of: a. relieving symptoms? b. delaying disease progression? 2. What are the risks (frequency and severity of adverse events) associated with Anakinra treatment in these patients?	**Main results:** Result 1. • ANK (< 50 mg/day) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI) • ACR 20: 1.38 (1.01, 1.89) • ACR 50: 3.37 (0.82, 13.77) • ACR 70: 4.45 (0.26, 76.62) • Withdrawals: 0.85 (0.62, 1.18) • Mean Difference (IV, Fixed, 95% CI) • Change in pain VAS score: 0.85 (0.62, 1.18) • Change in HAQ score: -0.2 (-0.33, -0.07) • Change is ESR: -10.0 (-15.67, -4.33)(1 study) • Change in CRP: -0.9 (-1.64, -0.16) (1 study) • Change in Larsen score: -2.80 (-5.47, -0.13) Result 2. • ANK (50 - 150 mg/day) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI) • ACR 20: 1.61 (1.32, 1.98) • ACR 50: 2.51 (1.56, 4.03) • ACR 70: 3.71 (1.44, 9.57) • Withdrawals: 1.04 (0.86, 1.27) • Mean Difference (IV, Fixed, 95% CI) • Change in pain VAS score: -0.10 (-0.15, -0.04) • Change in HAQ score: -0.19 (-0.30, -0.09) • Change is ESR: -10.04 (12.75, -7.33) • Change in CRP: -0.6 (-1.26, 0.06) (results from 1 study only) • Change in Larsen score: -2.45 (-4.53, -0.36) **Adverse events:** • ANK (50 - 150 mg/day) vs. • Placebo, Risk Ratio (M-H, Fixed, 95% CI)	**Review based on focused question of interest:** Yes **Did search strategy employ comprehensive, systematic literature search?** Yes Searched Cochrane Central Register of Controlled Trials, MEDLINE (1950 to JanuaryWeek 4 2008), EMBASE (1980 to 2008), and CINAHL (1982 to November 2007); also reviewed reference lists of identified publications, including previous meta-analyses, to identify any additional studies/citations; further information was sought from authors/industry if needed. **Eligibility criteria clearly described?** Yes **Review studies independently reviewed by at least 2 persons?** Yes **Standard method of critical appraisal before including?** Yes	**Comments:** • Due to large variability in doses, 2 groups were created for analysis: data from doses < 50 mg/day of ANK and data from doses 50 to 150 mg/day. This was clinical decision based on fact that recommended daily dose is 100 mg daily. • One of 5 included studies separted during analysis because of design differences (included another biologic). • Pain VAS and radiographic scales and CRP were reported in just 1 of 5 studies.

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
		• Infections: 1.08 (0.80, 1.45) • Serious Infections: 3.15 (0.81, 12.20) • Adverse Events: 1.05 (0.94, 1.17) • Serious Adverse Events: 1.04 (0.70, 1.56) • Injection site reactions: 2.45 (2.17, 2.77) • Deaths: 1.01 (0.11, 9.04)		

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Nam et al., 2010[221] **Country and setting:** Multinational **Funding:** NR **Aims of Review:** To review the evidence for the effi cacy and safety of biological agents in patients with rheumatoid arthritis (RA) to provide data to develop treatment recommendations by the European League Against Rheumatism (EULAR) Task Force **Quality Rating:** Fair	**Study design:** Systematic review and meta-analysis **Number of Patients:** NR **Studies Included:** 87 articles and 40 abstracts	**Characteristics of Included Studies:** For efficacy 1)double-blind randomised controlled trials (RCTs); (2) trials of ≥6 months' duration; (3) studies with ≥ 50 patients; (6) publications in English. And for safety (1) registries and observational studies; (2) inclusion of a control group; (3) report of incidence of events in the context of population-based expected incidences **Characteristics of Included Populations** Patients with RA **Characteristics of Interventions:** Studies evaluating 1 of the 9 biological DMARDs	**Study Results:** Efficacy - # of patients withdrawn for lack of efficacy • TNF inhibitors 5 studies n = 882 RR, 0.25 (95% CI, 0.13-0.48) *P* = 0.0001 • Sulfasalazine 5 studies n = 434 RR, 0.45 (95% CI, 0.23-0.89) *P* = 0.02 • Gold salts 2 studies n = 320 RR, 0.25 (95% CI, 0.11-0.53) *P* = 0.0003 • Leflunomide 1 study n = 190 RR, 0.44 (95% CI, 0.23-0.83) *P* = 0.01 • All DMARDs 12 studies n = 1081 RR, 0.39 (95% CI, 0.27-0.57) *P* = 0.00001 • All treatment 18 studies n = 2148 RR, 0.35 (95% CI, 0.25-0.49) *P* = 0.00001	**Adverse Events:** Toxicity - Withdrawals for adverse events • TNF inhibitors 5 studies n = 882 RR, 2.20 (95% CI, 0.82-5.91) *P* = 0.12 NNT/NNH, 0.25 • Sulfasalazine 5 studies n = 434 RR, 1.76 (95% CI, 0.98-3.14) *P* = 0.06 NNT/NNH, 0.93 • Gold salts 2 studies n = 320 RR, 2.34 (95% CI, 1.10-4.97) *P* = 0.03 NNT/NNH, 0.79 • Leflunomide 1 study n = 190 RR, 3.86 (95% CI, 1.20-12.39) *P* = 0.02 NNT/NNH, 0.45 • All DMARDs 12 studies n = 1081 RR, 2.32 (95% CI, 1.55-3.47) *P* = 0.0001 NNT/NNH, 0.86 • All treatment 18 studies n = 2148 RR, 2.33 (95% CI, 1.61-3.37) *P* = 0.00001 NNT/NNH, 0.62

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes
Author, year, country, funding: Osiri et al., 2002[142] Multinational Cochrane Collaboration **Study Design:** Systematic review of RCTs and CCTs **Aims of the Review:** • To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA • META-ANALYSIS-analysis stratified comparison between LEF and Placebo or other DMARDs by outcomes at different length of txts **Number of Pts:** 1,144 LEF 312 to Placebo 680 to MTX 132 to SSZ Only 920 used in meta-analysis-analysis 2 yr extension: LEF:158 SSZ: 60 MTX 101	**Studies included:** • 6 trials **Characteristics of included studies:** • Randomized, double-blind, placebo and/or active controlled **Characteristics of included populations:** • All with active RA **Characteristics of interventions:** • 5,10 or 25 mg/d vs. placebo or MTX or SSZ	LEF significantly better than placebo at 6,12 and 24 mos. • LEF vs. MTX • ACR 20: Significantly more responders for MTX than LEF at 12 mos; OR: 1.43 (1.15-1.77) • No significant differences at 2 yrs but more responders with MTX than with LEF; OR, 1.28 (0.98-1.67) • ACR 50, ACR 70: differences in ACR 50/70 repsonses between LEF and MTX were NS	Total withdrawals lower in LEF group (10% greater than Placebo (70/416 vs. 18/311)); LEF not diff in efficacy and tolerability than MTX and SSZ, except that LEF was more efficaious than SSZ at 24 mos; AEs+ GI sympotms, elevated liver funcitn tests, alopecia, and infections	**Publication Bias Assessed**: NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Osiri et al., 2009[222] **Country and setting:** Multinational **Funding:** Cochrane Collaboration **Aims of Review:** To determine the efficacy and toxicity of LEF (monotherapy or combined with another DMARD) compared to placebo or other DMARDs in the treatment of RA. **Quality Rating:** Good	**Study design:** Systematic Review and meta-analyses **Number of Patients:** NR **Studies Included:** N = 33	**Characteristics of Included Studies:** All randomized controlled trials (RCTs) or controlled clinical trials (CCTs) comparing LEF as monotherapy or in combination with another DMARD to placebo or other DMARDs. **Characteristics of Included Populations** Patients were at least 18 yrs old, had a clinical diagnosis of RA according to the ACR 1987 revised criteria, and had active disease as shown by these outcomes: 1) number of 10der joints; 2) number of swollen joints; 3) duration of morning stiffness; 4) acute phase reactants. **Characteristics of Interventions:** Studies comparing LEF treatment (as monotherapy or in combination with other DMARDs) at a dose of 20 to 25 mg/day (with or without a loading daily dose of 100 mg given in the first 1 to 3 days) with placebo or other DMARDs were included. The duration of treatment in the trials must have been at least 3 mos (or 12 wks).	**Study Results:** ACR20, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 3 mos: 0.96 (0.84-1.10) • LEF vs. MTX, at 4 mos: 0.95 (0.50-1.81) • LEF vs. MTX, at 6 mos (24 wks): 0.96 (0.87-1.06) • LEF vs. MTX, at 12 mos: 1.08 (0.75-1.55) • LEF vs. MTX, at 2 yrs: 1.05 (0.81-1.37) • LEF vs. SSZ, at 6 mos: 1.03 (0.83-1.28) • LEF vs. SSZ, at 12 mos: 1.03 (0.83-1.29) • LEF vs. SSZ, at 24 mos: 0.73 (0.57-0.93) • LEF+MTX vs.MTX, at 24 wks: 0.42 (0.29-0.63) • LEF+SSZ vs. placebo+SSZ, at 24 wks: 0.96 (0.49-1.88) • LEF vs. anti-TNF+MTX, at 24 wks: 1.14 (0.97-1.34) • Lef+ADA vs. ADA, at 12 wks: 0.83 (0.69-0.99) ACR50, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: 0.86 (0.52-1.44) • LEF vs. MTX, at 2 yrs: 0.82 (0.60-1.10) • LEF vs. SSZ, at 6 mos: 0.92 (0.64-1.31) • LEF vs. SSZ, at 12 mos: 0.93 (0.63-1.36) • LEF vs. SSZ, at 24 mos: 0.48 (0.28-0.80)	**Adverse Events:** Total withdrawals, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs.SSZ, at 6 mos: 0.75 (0.53-1.07) • LEF vs.SSZ, at 12 mos: 1.07 (0.43-2.63) • LEF vs. SSZ, at 24 mos: 0.79 (0.39-1.59) • LEF vs. MTX, at 12 mos: 1.26 (1.08-1.48) • LEF vs. MTX, at 2 yrs: 1.15 (0.83-1.61) • LEF + MTX vs. MTX, at • 24 wks: 0.93 (0.60-1.43) • LEF + SSZ vs. placebo + SSZ, at 24 wks: 1.34 (0.77-2.34) • LEF/LEF+ MTX vs. placebo/Lef + MTX, at 48 wks: 1.4 (0.65-3.00) • LEF + MTX vs. MTX, at 3 • mos: 0.75 (0.39-1.43) • LEF+ MTX vs. MTX, at 24 mos: 1.25 (0.52,-3.01) Withdrawals due to adverse events, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ, at 6 mos: 0.77 (0.45-1.33) • LEF vs. SSZ, at 12 mos: 0.38 (0.08-1.90) • LEF vs. SSZ, at 24 mos: 0.67 (0.25-1.76) • LEF vs. MTX, at 6 mos: 0.24 (0.10-0.57) • LEF vs. MTX, at 12 mos: 1.43 (1.13-1.83) • LEF vs. MTX, at 2 yrs:

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			• LEF+MTX vs.MTX, at 24 wks: 0.23 (0.11-0.48) • LEF+SSZ vs. placebo+SSZ, at 24 wks: 0.10 (0.01-1.79) • LEF vs. MTX, at 24 wks: 0.83 (0.53-1.32) • LEF vs. anti-TNF+MTX, at 24 wks: 1.39 (0.97-1.99) • Lef+ADA vs. ADA, at 12 wks: 0.84 (0.58-1.20) ACR70, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: 0.44 (0.26-0.77) • LEF vs. MTX, at 2 yrs: 0.72 (0.44-1.18) • LEF vs. SSZ, at 6 mos: 0.66 (0.28-1.55) • LEF vs. SSZ, at 12 mos: 1.14 (0.57-2.25) • LEF vs. SSZ, at 24 mos: 0.70 (0.34-1.43) • LEF+MTX vs.MTX, at 24 wks: 0.23 (0.07-0.77) • LEF vs. MTX, at 24 wks: 0.5 (0.10-2.53) • LEF vs. anti-TNF+MTX, at 24 wks: 3.75 (1.35-10.43) HAQ, Mean Difference (IV, Fixed, 95% CI) • LEF vs. MTX, at 3 mos: 0.01 (-0.12, 0.14) • LEF vs. MTX, at 6 mos: -0.01 (-0.11-0.09) • LEF vs. MTX, at 12 mos: -0.02 (-0.09-0.05) • LEF vs. MTX, at 2 yrs: 0.05 (-0.04-0.14) • LEF vs. SSZ, at 6 mos: -0.25	1.38 (0.77-2.47) • LEF + MTX vs. MTX, at 24 wks: 1.82 (0.83-3.97) • LEF/Lef + MTX vs. placebo/LEF + MTX, at 48 wks: 1.0 (0.21-4.83) • LEF vs. LEF + MTX, at 3 • mos: 0.46 (0.03-8.03) • LEF + MTX vs. MTX, at 3 • mos: 0.86 (0.41-1.81) • LEF + MTX vs. MTX, at 24 mos: 1.4 (0.46-4.23) Reported adverse events, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 6 mos: 0.55 (0.42-0.73) • LEF + MTX vs. MTX, at 24 mos: 3.5 (1.29-9.49) Alopecia, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ: 1.57 (0.63-3.93) • LEF vs. MTX: 1.72 (1.32-2.24) • LEF/Lef + MTX vs. placebo/LEF + MTX, at 48 wks: 8.0 (1.02-62.74) GI symptoms, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ: 0.88 (0.63-1.22) • LEF vs. MTX: 0.50 (0.28-0.92) Allergy or rash, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ: 1.0 (0.52-1.92)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			(-0.42- -0.08) • LEF vs. SSZ, at 12 mos: -0.14 (-0.33-0.05) • LEF vs. SSZ, at 24 mos, -0.29 (-0.57- -0.01) • LEF+MTX vs. MTX, at 24 wks: -0.30 (-0.42- -0.18) • LEF+SSZ vs. placebo+SSZ, at 24 mos: -0.07 (-0.20-0.06) • LEF vs. anti-TNF, at 24 wks: 0.49 (0.34-0.64) HAQ-DI, Mean Difference (IV, Fixed, 95% CI) • LEF+SSZ vs. placebo+SSZ, at 24 mos: -0.08 (-0.23-0.07) • Lef/ILEF+ MTX vs. placebo/LEF + MTX, at 48 wks: 0.21 (0.05-0.37) MHAQ, Mean Difference (IV, Fixed, 95% CI) • LEF vs. MTX, at 6 mos: -0.12 (-0.22- -0.02) • LEF vs. MTX, at 12 mos: -0.14 (-0.25- -0.03) • LEF vs. MTX, at 24 mos: -0.15 (-0.29- -0.01) • LEF vs. MTX, at 4 mos: -2.34 (-7.64-2.96) Chinese disability, Mean Difference (IV, Fixed, 95% CI) • LEF vs. MTX, at 3 mos: -0.09 (-0.18- -0.00) • LEF vs. MTX, at 6 mos: -0.05 (-0.20-0.10) SF-36, Mean Difference, Physical Component Scores (IV, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: -3.0 (-5.41- -0.59)	• LEF vs. MTX: 1.51 (1.19-1.92) • LEF + SSZ vs. placebo + SSZ, at 24 wks (rash): 1.12 (0.32-3.93) • LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks (rash): 0.86 (0.30-2.46) Nausea, Risk Ratio (M-H, Fixed, 95% CI) • LEF + SSZ vs. placebo + SSZ, at 24 wks: 3.57 (0.41-30.90) • LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 1.33 (0.31-5.80) Diarrhea, Risk Ratio (M-H, Fixed, 95% CI) • LEF + SSZ vs. placebo + SSZ, at 24 wks: 2.68 (0.29-24.93) • LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 5.33 (1.61-17.71) Hyper10sion, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ: 1.0 (0.21-4.87) • LEF vs. MTX: 2.29 (1.42-3.69) W8 loss, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ: 3.0 (0.62-14.60) • LEF vs. MTX: 0.81 (0.39-1.66) Infections, Risk Ratio (M-H,

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			• Lef/LEF + MTX vs.placebo/LEF + MTX, at 48 wks: -1.90 (5.14-1.34) SF-36, Mean Difference, Mental Component Scores (IV, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: -0.6 (-3.01-1.81) • Lef/LEF + MTX vs.placebo/LEF + MTX, at 48 wks: -2.7 (5.63-0.23) Work Productivity Scores, Mean Difference (IV, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: -2.30 (-6.37-1.77) • DAS28 response rate, Risk Ratio (M-H, Fixed, 95% CI) • LEF + SSZ vs. SSZ, at 24 wks: 0.76 (0.47-1.24) DAS28 score change, Mean Difference (IV, Fixed, 95% CI) • LEF + SSZ vs. SSZ, at 24 wks: 0.10 (-0.41-0.61) • LEF vs. MTX, at 16 wks: 0.57 (0.24-0.90) • LEF vs. MTX, at 24 wks: -0.10 (-0.41-0.21) • LEF vs. anti-TNF+MTX, at 24 wks: 0.80 (0.43-1.17) • DAS28 responders, Risk Ratio (M-H, Fixed, 95% CI) • LEF + SSZ vs. SSZ, for 24-wk completers: 0.61 (0.36-1.04) EULAR remission (DAS28 <3.2), Risk Ratio (M-H, Fixed, 95% CI) • LEF vs.MTX, at 16 wks: 1.24	Fixed, 95% CI) • LEF vs. SSZ: 0.25 (0.03-2.21) • LEF vs. MTX: 0.97 (0.81-1.15) • LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 2.5 (0.81-7.70) Elevated liver function tests, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ: 0.6 (0.15-2.46) • LEF vs. MTX: 0.66 (0.31-1.39) • LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 1.07 (0.53-2.15) Elevated liver function tests, reported as adverse event, Risk Ratio (M-H, Random, 95% CI) • LEF vs. SSZ, at 6 mos: 0.6 (0.15-2.46) • LEF vs. MTX, at 6 mos: 0.52 (0.24-1.15) • LEF vs. MTX, at 1 year: 0.65 (0.17-2.45) • LEF vs. MTX, at 2 yrs: 0.80 (0.30-2.14) Elevated liver function tests, withdrawals Risk Ratio (M-H, Random, 95% CI) • LEF vs. SSZ, at 6 mos: 1.0 (0.14-6.99) • LEF vs. MTX, at 6 mos: 0.18 (0.02-1.63) • LEF vs. MTX, at 1 year: 0.90 (0.28-2.86)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			(0.64-2.42) • DAS28 remission, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 1.0 (0.22-4.56) • LEF vs. anti-TNF+MTX, at 24 wks: 1.67 (0.38-7.39) • LEF vs. Lef+MTX, at 3 mos: 1.35 (0.18-10.09) DAS28 low disease activity, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 1.0 (0.28-3.63) • LEF vs. anti-TNF+MTX, at 24 wks: 3.33 (1.17-9.51) DAS28 moderate disease activity, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 1.05 (0.76-1.44) • LEF vs. anti- TNF+MTX, at 24 wks: 0.56 (0.30-1.04) DAS28 high disease activity, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 0.5 (0.05-5.22) • LEF vs. anti-TNF+MTX, at 24 wks: 0.33 (0.02-6.44) EULAR good response, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. LEF + MTX, at 3 mos: 0.37 (0.10-1.34) • LEF + ADA vs. ADA, at 12 wks: 0.71 (0.47-1.05) EULAR moderate response, Risk Ratio (M-H, Fixed, 95%	• LEF vs. MTX, at 2 yr: 0.33 (0.08-1.42) Serious adverse events, (M-H, Fixed, 95% CI) • LEF + SSZ vs. placebo + SSZ, at 24 wks: 1.79 (0.47-6.77) • LEF/Lef + MTX vs. placebo/Lef + MTX, at 48 wks: 0.87 (0.44,-1.72)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			CI) • LEF vs. Lef+MTX, at 3 mos: 0.80 (0.47-1.35) • LEF + ADA vs. ADA, at 12 wks: 0.83 (0.73-0.93) • EULAR response-no improvement, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. LEF + MTX, at 3 mos: 4.27 (0.64-28.56) EULAR response rate, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 16 wks: 1.05 (0.89-1.23)	

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes
Author, yr, country, funding: Rheumatoid Arthritis Clinical Trial Archive Group, 1995,[223] Multinational, NIH grants **Study Design:** Systematic review **Aims of the Review:** To evaluate whether age and renal impairment affect rate of side effects or efficacy of MTX in RA pts **Number of Pts:** 496	**Studies included:** 11 MTX clinical trials: • Weinblatt, et al., 1985 • Furst, et al., 1989 • Schmid, et al., unpublished study • Williams, et al., 1985 • Wilke, et al., unpublished study • Weinblatt, et al., 1990 • Williams, et al., 1992 • Suarez et al 1988 • Morassut, et al., 1989 • Hamdy, et al., 1987 • Bell, et al., 1988. **Characteristics of included studies:** • RCTs • Placebo control or comparative trial • MTX as 1 treatment arm • Adult RA pts • Trial completed (although not necessarily published) by end of 1991, and trial 12 weeks or longer (to end or to crossover) **Characteristics of included populations:** • Adult RA pts treated with MTX **Characteristics of interventions:** • All pts treated with MTX (doses NR)	Study compares subgroups of pts treated with MTX • Neither age nor renal impairment had any effect on efficacy of MTX • Odds of major clinical improvement by age were 1.0 for < 60 yr old group (referent), 1.4 (0.7, 2.6) for 60-64, 1.0 (0.5, 2.2) for 65-69, and 0.7 (0.3, 1.7) for ≥ 70 (efficacy regression analyses controlled for age group, sex, renal function, study of origin, initial tender joint count, grip strength, steroid dose, NSAID used at baseline, and maximum MTX dose) • Odds of major clinical improvement by creatinine clearance were 1.0 for ≥99.8 ml/min (referent), 0.6 (0.3, 1.0) for 78.6-99.9 ml/min, 1.1 (0.6, 2.0) for 62.6-78.6 ml/min, and 1.0 (0.5, 2.1) for < 62.6 ml/min • Age did not affect rate of toxicity. Those in the oldest group were not at a higher risk of side effects from MTX	No significant difference for liver toxicity between different creatinine clearance groups 1.0 (referent) 1.8 (1.0, 3.4) 1.2 (0.6, 2.3) 1.8 (0.8, 3.7) • Toxicity regressions adjusted for age, sex, creatinine clearance, baseline NSAID use (yes/no), maximum MTX dose, and study of origin	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** Yes **Quality Rating:** Fair

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
Author: Salliot, 2009[224] **Country and setting:** NR **Funding:** NR	**Study design:** Systematic Review and meta-analyses **Overall study N:** N = 4,767 (745 rituximab, 1960 abatacept, 2062 anakinra), 2112 placebo **Study aims:** To assess if biological agents, ie rituximab, abatacept, and anakinra increase risk of serious infections.	**Main results:** Pooled ORs Regardless of Dose: • Rituximab Pooled OR = 1.45 (0.56 - 3.73) • Abatacept Pooled OR = 1.35 (0.78 - 2.32) • Anakinra Pooled OR = 2.75 (0.90 - 8.35) Pooled ORs Stratified by High and Low Dose: Rituximab • High Dose v Placebo 1.68 (0.64 - 4.35) • Low Dose V Placebo 0.24 (0.01 - 4.33) • High Dose v Low Dose 7.20 (0.43 - 120.66) Abatacept • High Dose v Placebo 1.35 (0.78 - 2.33) • Excluding patients receiving concominant treatment with other biologic DMARDs, pooled OR = 1.24 (0.70 - 2.29) • Low Dose v Placebo 0.84 (0.13 - 5.30) • High Dose v Low Dose 2.16 (0.52 - 8.98) • Excluding patients receiving concominant treatment with other biologic DMARDs, pooled OR = 2.0 (0.48 - 8.33) Anakinra • High Dose v Placebo 3.40 (1.11 - 10.46) • Excluding patients with comorbidity factors, pooled OR = 1.67 (0.51 - 5.41) • Low Dose v Placebo 0.51 (0.03 - 8.27) • High Dose v Low Dose 9.63 (1.31 - 70.91) • Excluding patients with comorbidity factors, pooled OR = 6.41 (0.81 - 50.30) **Adverse events:** Rituximab: • Among 17 patients who had 1 serious infection: 5 had bronchopneumonia (1 presented with 2 episodes of	**Review based on focused question of interest:** Yes **Did search strategy employ comprehensive, systematic literature search?** Yes. A systematic literature search of literature published up to December 2007 was performed in PUBMED, EMBASE and Cochrane library databases; without limitation of years of publication or journal, using followings key-words: “rheumatoid arthritis,” “abatacept,’ “rituximab,” “anakinra,” “clinical controlled trials,” “clinical trials,” “randomised controlled trials,” “clinical trials phase II, III, IV”. We also included congress abstracts of American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) meetings from 2004 to 2006, because we assumed that any abstract published prior to 2004 had been published in a formal fulllength work. Moreover, to complete our search with unpublished data, Food and Drug Administration (FDA), European Agency for Evaluation of Medicinal Products (EMEA) and manufacturers (Roche, Amgen and Bristol- Myers Squibb) were contacted. **Eligibility criteria clearly described?** Yes.	**Comments:** NR

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
		Pseudomonas aeruginosa pneumonia), 2 septic arthritis (of whom one Staphylococcus aureus septicaemia), 3 pyelonephritis and 2 gastroenteritis and 1 each epiglottitis, cellulitis of a toe, and acute hepatitis B. One fatal bronchopneumonia occurred in a patient receiving rituximab. Abatacept: • 49 serious infections occurring with abatacept were mainly bronchopulmonary, streptococcal and pyogenic septicaemia, staphylococcal arthritis, abscesses, gastrointestinal (6 of whom 3 diverticulitis), dermatological infections (6 of whom 1 was a cellulitis) and pyelonephritis. One case of unconfirmed tuberculosis and 1 case of pulmonary aspergillosis were reported. Last patient (who had history of tuberculosis and pulmonary fibrosis) died of aspergillosis and of Pseudomonas aeruginosa septicaemia. Anakinra: • Among 30 serious infections occurring in anakinra-treated groups, 11 were pneumonia. Others were osteomyelitis, cellulitis, bursitis, herpes zoster, infected bunion and gangrene (1 of each). No related death or opportunistic infections were described.	Inclusion criteria were randomised placebo controlled trials in adult patients with RA according to ACR criteria. Publications had to be written in English, French or Spanish. Patients had to be randomised to receive placebo or 1 of 3 biological agents (rituximab, anakinra and abatacept), as monotherapy or with concomitant biological or non-biological DMARDs. Reviews and articles reporting trials that were not placebo-controlled were excluded. **Review studies independently reviewed by at least 2 persons?** No. One reviewer selected studies and abstracted data. **Standard method of critical appraisal before including?** NR	

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Schipper et al., 2009[225] **Country and setting:** Multinational **Funding:** NR **Aims of Review:** To review the effects of the combination of MTX and SSZ in naïve patients and patients with an insufficient response, using the results of published parallel and add-on clinical trials in RA. **Quality Rating:** Fair	**Study design:** Systematic Review **Number of Patients:** NR **Studies Included:** N = 4	**Characteristics of Included Studies:** RCT of at least 12 weeks duration with a parallel or an add-on design, **Characteristics of Included Populations** RA patients fulfilling the ACR 1987 revised criteria; either naıve to MTX and SSZ (parallel trials) or had failed to 1 of them (add-on trials). **Characteristics of Interventions:** Placebo-controlled, double blind RCTs and compared the efficacy of combined MTX and SSZ to each individual agent and randomized open study comparing the combination of MTX and SSZ with MTX alone.	**Study Results:** Trials with naive patients: Mean DAS changes: sub-additive efficacy (1.3 and 1.9 respectively) ACR 20: 80% ACR50: 33% ACR70: 3% Trials with patients who failed SSZ: Mean DAS changes: additive efficacy. ACR 20: 29% ACR50: 11% ACR70: 4%	**Adverse Events:** From the 2 parallel trials, the first RCT showed more toxicity (nausea) of the MTX-SSZ combination compared with the single-drug arms. The second study showed more adverse events (nausea) in the combination group. The 2 add-on trials showed that the addition of MTX to SSZ in patients who had failed to the latter drug was clinically significantly superior to a switch to MTX alone, without increased toxicity.

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2009[226] **Country and setting:** Multinational **Funding:** Government **Aims of Review:** To provide estimates of the benefits and safety of biologics in patients with RA **Quality Rating:** Good	**Study design:** Overview of SERs using ne2rk meta-analyses of Cochrane SERs **Number of Patients:** NR **Studies Included:** 6 SERs; 31 studies	**Characteristics of Included Studies:** In most of the included trials, each biologic was compared with a placebo, usually in combination with traditional DMARDs (usually MTX) or other biologics **Characteristics of Included Populations** Eligibility criteria and patient populations were similar across reviews: adults with RA who met the ACR criteria for RA **Characteristics of Interventions:** ADA: All RCTs or CCTs comparing ADA (alone or combo with DMARDs) with placebo or other DMARDs ABA: All RCTs comparing ABA (alone or combo with DMARDs) with placebo or other DMARDs; no restrictions on dosage or duration of the intervention ANK: All RCTs comparing ANK (alone or combo with DMARDs or other biologics) with placebo or other DMARDs or biologics ETN: All RCTs or CCTs of at least 6 months' duration comparing ETN with placebo, ETN with MTX, or ETN + MTX with MTX alone INF: All RCTs comparing INF (1, 3, 5 or 10 mg/kg) + MTX with MTX alone, or INF with placebo, with a minimum duration of 6 months and at least 2 infusions RIT: All RCTs comparing RIT (300, 350, 500 or 600 mg/m2) (alone or combo with DMARD) with placebo or other DMARDs or biologic	**Study Results:** Benefit (ACR 50), Biologic vs. Placebo, OR (95% CI), NNT • ABA: 2.98 (1.79-4.97), NNT, 4 (3-9) • ADA: 3.70 (2.4-5.7), NNT, 4 (3-6) • ANK: 1.68 (0.83-3.41), NNT, NS • ETN: 4.97 (2.70-9.13), NNT, 3 (2-5) • INF: 2.92 (1.37-6.24), NNT, 4 (2-18) • RIT: 4.10 (2.02-8.33), NNT, 3 (1-7) • Overall (all biologics vs. placebo): 3.35 (2.62-4.2) Indirect comparison of ACR 50 between biologics, Ratio of odds ratios (95% CI) • ABA vs. ADA: 0.81 (0.43-1.49) • ABA vs. ANK: 1.77 (0.78-4.00) • ABA vs. ETN: 0.60 (0.29-1.25) • ABA vs. INF: 1.02 (0.43-2.40) • ABA vs. RIT: 0.73 (0.32-1.65) • ADA vs. ANK: 2.20 (1.01-4.75) • ADA vs. ETN: 0.74 (0.37-1.48) • ADA vs. INF: 1.26 (0.56-2.86) • ADA vs. RIT: 0.90 (0.41-1.96) • ANK vs. ETN: 0.34 (0.14-0.81)	**Adverse Events:** Safety (withdrawal due to an adverse event), OR (95% CI), NNT • ABA: 1.24 (0.88-1.76), NNT, NS • ADA: 1.54 (1.12-2.12), NNT, 39 (19-162) • ANK: 1.67 (1.22-2.29), NNT, 31 (17-92) • ETN: 0.82 (0.56-1.19), NNT, NS • INF: 2.21 (1.28-3.82), NNT, 18 (8-72) • RIT: 1.34 (0.65-2.76), NNT, NS • Overall: 1.39 (1.13-1.71) Indirect comparison of withdrawal due to adverse events between biologics, Ratio of odds ratios (95% CI) • ABA vs. ADA: 0.80 (0.51-1.26) • ABA vs. ANK: 0.74 (0.47-1.17) • ABA vs. ETN: 1.52 (0.93-2.49) • ABA vs. INF: 0.56 (0.30-1.05) • ABA vs. RIT: 0.93 (0.43-2.02) • ADA vs. ANK: 0.92 (0.60-1.42) • ADA vs. ETN: 1.89 (1.18-3.04) • ADA vs. INF: 0.70 (0.38-1.28) • ADA vs. RIT: 1.15 (0.54-2.48) • ANK vs. ETN: 2.05 (1.27-

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			• ANK vs. INF: 0.58 (0.22-1.52) • ANK vs. RIT: 0.41 (0.16-1.05) • ETN vs. INF: 1.70 (0.68-4.22) • ETN vs. RIT: 1.21 (0.51-2.90) • INF vs. RIT: 0.71 (0.27-1.89) ACR50 Subgroup data, OR (95% CI): Concomitant use of MTX Yes: 3.16 (2.40-4.16) No: 4.18 (2.48-7.06) Rheumatoid arthritis duration Early: 2.05 (1.24-3.38) Established: 3.47 (2.26-5.33) Late: 4.02 (2.89-5.59) Biologic is TNF-inhibitor Yes: 3.57 (2.57-4.97) No: 3.10 (2.12-4.53) Prior drugs failed Biologic: 4.09 (2.17-7.69) DMARD: 3.27 (2.46-4.35) None: 3.00 (1.11-8.13) Combination biologic therapy Yes: 1.00 (0.45-2.23) No: 3.60 (2.89-4.49) Duration of randomized trial Short: 4.03 (2.93-5.54) Intermediate: 2.92 (1.91-4.46) Long: 1.73 (0.78-3.82) Prior failure of TNF biologic Yes: 4.11 (2.21-7.63) No: 3.24 (2.48-4.22)	3.29) • ANK vs. INF: 0.76 (0.41-1.39) • ANK vs. RIT: 1.25 (0.58-2.69) • ETN vs. INF: 0.37 (0.19-0.70) • ETN vs. RIT: 0.61 (0.28-1.35) • INF vs. RIT: 1.66 (0.69-3.98) Withdrawal due to adverse event Subgroup data, OR (95% CI): Concomitant use of MTX Yes: 1.30 (1.02-1.65) No: 1.70 (1.12-2.57) Rheumatoid arthritis duration Early: 1.45 (0.92-2.28) Established: 1.25 (0.87-1.78) Late: 1.52 (1.09-2.11) Biologic is TNF-inhibitor Yes: 1.27 (0.94-1.69) No: 1.55 (1.14-2.11) Prior drugs failed Biologic: 1.74 (1.02-2.96) DMARD: 1.41 (1.11-1.79) None: 0.85 (0.41-1.76) Duration of randomized trial Short: 1.46 (1.07-1.99) Intermediate: 1.31 (0.94-1.82) Long; 1.47 (0.71-3.03) Prior failure of TNF biologic Yes: 1.76 (1.01-3.06) No: 1.34 (1.06-1.69)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2009[227] **Country and setting:** NR **Funding:** Cochrane Collaboration; The Oak Foundation, Switzerland; NIH CTSA Award **Aims of Review:** To compare the efficacy and safety of ABA, ADA, ANK, ETN, INF, and RIT in RA pts **Quality Rating:** Fair	**Study design:** Systematic Review **Number of Patients:** NR **Studies Included:** N=6 (Note - 6 Cochrane reviews; data from 7 studies on ABA, 8 on ADA, 5 on ANK, 4 on ETN, 4 on INF, 4 on RIT)	**Characteristics of Included Studies:** Systematic reviews containing at least 1 RCT, with clinically relevant outcomes, and clear inclusion/exclusion criteria; completed, updated, and available Cochrane Systematic reviews of biologic DMARDs as of May 30, 2009 **Characteristics of Included Populations** 18 yo or older; RA according to 1987 ACR criteria (populations characteristics similar among reviews) **Characteristics of Interventions:** Biologic DMARDs along or in combo with other biologics/traditional DMARDs compared to placebo along or placebo + biologics/traditional DMARDs. Biologics were of the following dosing regimens: • ADA: 500 mg IV q 4 weeks for 2 weeks if <60 kg (750 mg if 60-100kg; 1000 mg if >100 kg) • ADA: 40 mg SQ q 2 wks • ANK: 100 mg SQ QD • ETN: 25 mg SQ twice a wk • INF: 3 mg/kg IV q 8 wks • RIT: 2-1000 mg IV doses 2 wks apart	**Study Results:** ACR50 (OR, 95% CI, reference group is placebo) • ABA: 2.98 (1.79 to 4.97) • ADA: 3.70 (2.40 to 5.70) • ANK: 1.68 (0.83 to 3.41) • ETN: 4.97 (2.70 to 9.13) • INF: 2.92 (1.37 to 6.14) • RIT: 4.10 (2.02 to 8.33) Indirect comparions (only significant OR reported): • ANK less efficacy than ETN: 0.34 (0.14 to 0.81, *P* = 0.05) • ADA greater efficacy than ANK: 2.20 (1.01 to 4.75, *P* = 0.046)	**Adverse Events:** Withdrawals due to ADEs (OR, 95% CI, reference group is placebo): • ABA: 1.24 (0.88-1.76) • ADA: 1.54 (1.12-2.12) • ANK: 1.67 (1.22-2.24) • ETN: 0.82 (0.56-1.19) • INF: 2.21 (1.28-3.82) • RIT: 1.34 (0.65-2.76) Indirect comparisons (only signficant OR reported): ADA more withdrawals due to ADEs than ETN: 1.89 (1.18 to 3.04; *P* = 0.009) ANK more withdrawals due to ADE than ETN: 2.05 (1.27 to 3.29; *P* = 0.003) ETN less withdrawals due to ADEs than INF: 0.39 (0.19 to 0.70; *P* = 0.002)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2010[228] **Country and setting:** Multinational **Funding:** NIH **Aims of Review:** To compare the efficacy and safety of GOL in adults with rheumatoid arthritis. **Quality Rating:** Good	**Study design:** Systematic Review **Number of Patients:** 1714 **Studies Included:** N = 4	**Characteristics of Included Studies:** (RCTs) or Controlled Clinical Trials (CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation) **Characteristics of Included Populations** Adults 18 years or older, with RA meeting the 1987 American College of Rheumatology Classification criteria for RA. 1 study was prior mtx failure and biologic failure (smolen 99), 3 studies were naïve populations **Characteristics of Interventions:** Interventions compared are GOL alone or in combination with DMARDs or biologics vs.placebo plus MTX or GOL alone or in combination with DMARDs or biologics compared to other DMARDs or biologics. There were no restrictions with regard to dosage or duration of intervention.	**Study Results:** Compared to patients treated with placebo+MTX, patients treated with the FDA-approved dose of GOL+MTX (50 mg every 4 weeks) were 2.6 times more likely to reach ACR50 at 14-24 wks (95%confidence interval (CI) 1.3 to 4.9; *P* = 0.005 and NNT = 5, 95% CI, 2-20). GOL pts were 1.5 times more likely to reach ACR20 (CI) 1.3-4.9. GOL pts were 2.8 times more likely to reach ACR70 (CI) 1.3-5.98. GOL-treated patients were significantly more likely to achieve DAS remission (RR, 5.1 (CI) 1.7-15.7): Absolute risk difference = 10% (95% CI, 6%-14%). NNTB = 6 (95% CI, 2-35). GOL treated patients had a significantly greater change in DAS28 scores compared to placebo (*P* = 0.0003). GOL +MTX pts had greater improvement in functional ability (HAQ) and HAQ score decrease RR, 1.79 (CI) 1.38-2.31,*P* < 0.0001: Absolute risk difference, -20% (95% CI, -25%- -15%). Relative percent change, 11% (95% CI, -14% to-8.3%) NNT, 3 (95% CI, 3-4) compared to MTX + placebo (all statistically significant).	**Adverse Events:** Patients treated with the FDA-approved dose of GOL+MTX (50 mg every 4 weeks) no more likely to have any adverse event (relative risk 1.1, 95% CI, 0.9-1.2; *P* = 0.44), and 0.5 times as likely to have overall withdrawals (95% CI 0.3-0.8; *P* = 0.005). No significant differences were noted between GOL and placebo regarding serious adverse events, infections, serious infections *P* = 0.8, lung infections *P* = 0.9, tuberculosis *P* = 0.5, cancer *P* = 0.8, withdrawals due to adverse events *P* = 0.2 and inefficacy *P* = 0.1 and deaths *P* -0.99. No radiographic data were reported. GOL 100 mg every 4 weeks + MTX vs.placebo + ethotrexate: There was no significant difference between the number of adverse events and serious adverse events occurring for GOL treated patients compared to placebo treated patients with (*P* = 0.14) and (*P* = 0.9) respectively.There was no statistically significant difference between the number of infections between the GOL and placebo groups (*P* = 0.7).There was no statistically significant

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
				difference between the number of serious infections between the GOL and placebo groups (*P* = 0.3). There were no patients experiencing tuberculosis in either treatment or placebo groups. There was no statistically significant difference between the number of lung infections between the GOL and placebo groups (*P* = 0.1). There was no statistically significant difference between the GOL and placebo groups (*P* = 0.7) for cancer. Patients treated with GOL were 0.7 times less likely to withdraw compared to placebo.There was no statisticallysignificant difference between the number of patients withdrawing due to inefficacy in the placebo and treatment groups (*P* = 0.41), adverse eventss *P* = 0.24 or deaths *P* = 0.99. GOL 50 mg every 2 weeks + MTX vs.placebo + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events, infections, serious infections *P* = 0.97, cancer *P* = 0.5, withdrawals due to adverse events *P* = 0.97 and inefficacy *P* = 0.3. No deaths in either group.

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
				GOL 100 mg every 2 weeks + MTX vs.placebo + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events *P* = 0.7, infections, serious infections *P* = 0.5, withdrawals due to adverse events *P* = 0.3 and inefficacy *P* = 0.3. No deaths in either group. GOL 100 mg every 4 weeks + placebo (oral) vs.placebo (injections) + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events *P* = 0.7, infections *P* = 0.3, serious infections *P* = 0.7, withdrawals due to adverse events *P* = 0.4 and deaths *P* = 0.5. There were no inefficacy withdrawals.

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2010[229] **Country and setting:** NR **Funding:** Cochrane Collaboration; NIH CTSA K12 Award Aims of Review: To assess the efficacy and safety of TCZ in RA pts **Quality Rating:** Fair	**Study design:** Systematic Review **Number of Patients:** 3,334 **Studies Included:** N = 8	**Characteristics of Included Studies:** All multi-center trials; RCTs (or quasi-randomized trials) **Characteristics of Included Populations** 18 yo or older (some studies 20 yo or older); 1987 ACR criteria for RA for 6 months or more; mean age in early 50s **Characteristics of Interventions:** TCZ alone or in combination with DMARDs or biologics vs.placebo or other DMARDs or biologics; no restriction with dosage and duration of intervention; all patients on stable dose of MTX (10-25 mg a week)	**Study Results:** All results reported for 8 mg/kg TCZ +MTX vs. placebo +MTX. ACR50 (RR, 95% CI, TCZ vs. placebo): 3.17 (2.72 to 3.67); DAS remission (DAS<2.6): 8.74 (6.26 to 11.8); clinically significant HAQ decrease (HAQ improvement of >0.3 or MHAQ decease >0.22): 1.79 (1.62 to 1.94)	**Adverse Events:** TCZ 1.2 times more likely to have ADE vs.placebo (74% vs. 65%); serious ADEs: 1.17 (0.83 to 1.64); withdrawals due to ADEs: 1.43 (0.95 to 2.12)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes
Author, year, country, funding: Wailoo et al., 2006[230] AHRQ Study Design: Decision analytic model and meta-analysisanalysis Aims of the Review: Cost effectiveness of ETN, ADA,, ANA and INF alone and in sequence Number of Patients: 17,000 in disease registry (National Databank for Rheumatic Diseases) and 6694 in RCTs	Studies included: Disease registry (National Databank for Rheumatic Diseases) and 6694 in 13 RCTs Characteristics of included studies: Treatment duration of at least 6 months Characteristics of included populations: Adult patients with RA Characteristics of interventions: Placebo and MTX controlled	Odds ratio of ACR50 • INF/ETN 1.17 (0.68, 2.08) • ADA/ETN 1.02 (0.54, 1.97) • ADA/INF 0.87 (0.47, 1.57)	NR	Publication Bias Assessed: Yes Heterogeneity Assessed: NR Standard Method of Study Appraisals: NR Comprehensive Search Strategy: Yes Quality Rating: Fair

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Wiens et al., 2009[231] **Country and setting:** NR **Funding:** NR Aims of Review: To evaluate the efficacy and safety of ETN for treating RA **Quality Rating:** Fair	**Study design:** Systematic review and meta-analysis **Number of Patients:** 2385 **Studies Included:** N = 8	**Characteristics of Included Studies:** RCTs **Characteristics of Included Populations** • Mean age: 47.5 to 54 yo • Mean disease duration: 0.7 to 13 years • Mean no. of previous DMARDs: 0.5 to 3.3 • Mean no. of swollen joints: 13.2 to 25 • Mean no. of 10der joints: 14 to 35 • % on steroids: 39 to 81 • Mean baseline HAQ score: 1.1 to 1.9 note: n ot all baseline characteristics reported in all studies **Characteristics of Interventions:** SQ doses of ETN compared to placebo group, with or without MTX. ETN dose was 25 mg twice a week or 50 mg weekly.	**Study Results:** ETN vs. control at 6 months • ACR20: 55% vs. 19%; RR, 2.94 (95% CI, 2.27-3.81) • ACR50: 26% vs. 6%; RR, 5.28 (95% CI, 3.12-8.92) • ACR70: 7% vs. 1%; RR, 4.83 (95% CI, 1.74-13.47) ETN vs. control at 12 months • ACR20: 77% vs. 67%; RR, 1.14 (95% CI, 1.07-1.23) • ACR50: 59% vs. 43%; RR, 1.36 (95% CI, 1.21-1.53) • ACR70: 34% vs. 21%; RR, 1.56 (95% CI, 1.30-1.88)	**Adverse Events:** ETN vs. control • Serious AEs: RR, 0.88 (95% CI, 0.66-1.17; *P* = 0.38) • Serious infections: RR, 0.87 (95% CI, 0.60-1.26; *P* = 0.57) • Malignancy: RR, 1.48 (95% CI, 0.66-3.35); *P* = 0.32) • Deaths: RR, 1.51 (95% CI, 0.34-6.63; *P* = 0.58)

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Wiens et al., 2010[232] Country and setting: Multinational **Funding:** Brazilian National Council of Scientific and Technological Development. Aims of Review: To evaluate the efficacy and safety of using the anti-tumor necrosis factor- (anti-TNF-) drugs ADA, ETN, and INF for the treatment of rheumatoid arthritis. **Quality Rating:** Fair	**Study design:** Systematic Review **Number of Patients:** 6503 **Studies Included:** N = 21	**Characteristics of Included Studies:** RCTs **Characteristics of Included Populations** Mean age 48-57, Disease duration 0.6 to 12 yrs, prior DMARDs 0-3, Treatment duration 12-2yrs **Characteristics of Interventions:** Studies that compared the anti-TNF-drug with placebo, with or without concomitant MTX in both groups. From these RCTs, those that used the usual dosages for each of the anti-TNF- drugs—ADA 20 mg once/week or 40 mg every other week subcutaneously, ETN 25 mg twice/week or 50 mg once/week subcutaneously, and INF 3 mg/kg intravenously at weeks 0, 2, 6, and then every 8 weeks.	**Study Results:** With short-term treatment (12-30 wks), ETN demonstrated the highest risk ratios (RRs) for reaching ACR20 and ACR50. ADA demonstrated the highest RR, for achieving ACR70 ACR 20 • ETN: 2.94, 95% CI: 2.27-3.81 • ADA: 2.26, 95% CI: 1.82-2.81 • INF 1.87, 95% CI: 1.43, 2.45 ACR 50 • ETN: 5.28, 95% CI: 3.12-8.92 • ADA: 3.50, 95% CI: 2.75-4.44 • INF: 2.68, 95% CI: 1.79-3.99 ACR 70 • ETN: 4.83, 95% CI: 1.74-13.47 • ADA: 5.36, 95% CI: 3.76-7.64 • INF: 2.68, 95% CI: 1.78-4.03 Over a long-term treatment course (1-3 yrs), ADA demonstrated the highest RRs (95% CIs) for these parameters: 1.85 (1.07-3.19), 2.80 (1.16-6.77), and 3.23 (1.37-7.61) for ACR20, ACR50, and ACR70, respectively.	**Adverse Events:** No statistically significant differences were noted in the safety of any of the 3 drugs compared with placebo (*P* > 0.05 for all parameters). INF had the highest RRs for withdrawing from the study due to lack of efficacy (2.05, 95% CI, 1.33-3.16) and adverse events (0.41, 95% CI, 0.18-0.95).

References

1. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005 Jul;52(7):1986-92.
2. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005 Oct;64(10):1421-6.
3. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005 Oct;64(10):1414-20.
4. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum 2009;60(11):3180-9.
5. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006 Mar;54(3):692-701.
6. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000 Nov 30;343(22):1586-93.
7. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002 Jun;46(6):1443-50.
8. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care 2002 Mar;8(3):231-40.
9. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol 2005 Jul;32(7):1232-42.
10. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum 2004 Jun;50(6):1959-66.
11. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46(7):1157-60.
12. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997 Aug 2;350(9074):309-18.
13. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002 Feb;46(2):347-56.
14. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum 2009;61(3):300-4.
15. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006;43(6):717-22.
16. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006 Jan;54(1):26-37.
17. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63(2):149-55.
18. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004 Apr;50(4):1051-65.
19. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant

therapy study. Arthritis Rheum 2005;52(4):1020-30.
20. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002 Dec;46(12):3151-8.
21. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66(6):732-9.
22. Cannon GW, Holden WL, Juhaeri J, et al. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol 2004 Oct;31(10):1906-11.
23. Capell H, Madhok R, Porter D, et al. Combination therapy with sulphasalazine and methotrexate is more effective than either drug alone in rheumatoid arthritis (ra) patients with a suboptimal response to sulphasalazine: Results from the double blind placebo controlled mascot study. Ann Rheum Dis 2007 Feb;66(2):235-41.
24. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol 2005 Nov;32(11):2130-5.
25. Choy EH, Smith CM, Farewell V, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 2008;67(5):656-63.
26. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003 Jul 1;107(25):3133-40.
27. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54(9):2793-806.
28. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2008;59(6):785-93.
29. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis 2009;68(2):216-21.
30. Combe BG, Codreanu C, Fiocco U, et al. Double-blind comparison of Etanercept and Sulphasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving Sulphasalazine. Ann Rheum Dis 2006 Apr 10.
31. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis 2009;68(7):1146-52.
32. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(4):1125-33.
33. Curtis JR, Xi J, Patkar N, et al. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(12):4226-7.
34. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford) 2007;46(11):1688-93.
35. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 2005;7(3):R545-51.
36. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol 2007;34(4):689-95.
37. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in

rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006 Jul 25;54(8):2368-76.
38. Dixon WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis and Rheumatism 2007;56(9):2905-12.
39. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69(3):522-8.
40. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002 Sep;46(9):2294-300.
41. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 1999;58(4):220-5.
42. Maillefert JF, Combe B, Goupille P, et al. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. Ann Rheum Dis 2003;62(8):764-6.
43. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33(12):2433-8.
44. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. Arthritis Rheum 2007;57(7):1151-7.
45. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2000;39(6):655-65.
46. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment - results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006 May 1;54(May):1390-400.
47. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol 2006 04/01/;33(Apr):681-9.
48. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372(9636):375-82.
49. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67(11):1516-23.
50. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60(8):2272-83.
51. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum 2010;62(3):674-82.
52. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis 2010;69(9):1629-35.
53. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated

with etanercept. Ann Rheum Dis 2005 Feb;64(2):246-52.
54. Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol 2007;34(12):2334-42.
55. Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56(5):1417-23.
56. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis 2009;68(1):33-9.
57. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum 2003 Apr;48(4):927-34.
58. Tesser J, Fleischmann R, Dore R, et al. Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. J Rheumatol 2004;31(4):649-54.
59. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum 2004 Jun;50(6):1752-60.
60. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006 Aug;65(8):1006-12.
61. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis 2009 Jun;68(6):805-11.
62. Flendrie M, Creemers MC, Welsing PM, et al. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 2003 Nov;62 Suppl 2:ii30-3.
63. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005;7(3):R666-76.
64. Fuerst M, Mohl H, Baumgartel K, et al. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatol Int 2006;26(12):1138-42.
65. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003 Dec;30(12):2563-71.
66. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford, England) 2011;50(1):124-31.
67. Geborek P, Crnkic M, Petersson IF, et al. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis 2002 Sep;61(9):793-8.
68. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005 May;64(5):699-703.
69. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum 2004 May;50(5):1412-9.
70. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic

drug therapy study. Arthritis and Rheumatism 2008;58(10):2968-80.
71. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005 Nov;52(11):3381-90.
72. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 2006 Nov-Dec;24(6 Suppl 43):S-77-82.
73. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146(6):406-15.
74. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum 2009 Jan 15;61(1):4-12.
75. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009;68(6):914-21.
76. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003 Aug;48(8):2122-7.
77. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis 2010;69(2):380-6.
78. Grijalva CG, Chung CP, Arbogast PG, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45(10 Supl 2):S66-76.
79. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford) 2010;4982-90.
80. Haagsma CJ, van Riel PL, de Jong AJ, et al. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol 1997;36(10):1082-8.
81. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care 2003 Oct;9(6 Suppl):S136-43.
82. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009;68(2):209-15.
83. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab results from eight years of surveillance of clinical practice in the Nationwide Danish DANBIO Registry. Arthritis Rheum 2010;62(1):22-32.
84. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis 2007;66(9):1184-9.
85. Hoff M, Kvien TK, Kalvesten J, et al. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis 2009;68(7):1171-6.
86. Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006 May 30;54(6):1786-94.
87. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45(Dec):1558-65.

88. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007;56(1):13-20.
89. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005 Jul;32(7):1213-8.
90. Karanikolas G, Charalambopoulos D, Vaiopoulos G, et al. Adjunctive anakinra in patients with active rheumatoid arthritis despite methotrexate, or leflunomide, or cyclosporin-A monotherapy: a 48-week, comparative, prospective study. Rheumatology (Oxford) 2008;47(9):1384-8.
91. Kavanaugh A, Klareskog L, van der Heijde D, et al. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis 2008;67(10):1444-7.
92. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004 Feb 28;363(9410):675-81.
93. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58(4):964-75.
94. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001 Oct 11;345(15):1098-104.
95. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58(11):3319-29.
96. Keystone E, Freundlich B, Schiff M, et al. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol 2009;36(3):522-31.
97. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68(6):789-96.
98. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Annals of the rheumatic diseases 2010(6):1129-35.
99. Kievit W, Adang EM, Fransen J, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis 2008;67(9):1229-34.
100. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol 2007;10(1):9-16.
101. Kirwan JR, Hallgren R, Mielants H, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis 2004;63(6):688-95.
102. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis 2005 Nov;64(11):1582-7.
103. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis 2006 Mar;65(3):328-34.
104. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006 Apr;54(4):1063-74.
105. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis

despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137(9):726-33.
106. Kremer JL, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The LITHE study. Arthritis Rheum 2010.
107. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum 2006 Feb;54(2):600-6.
108. Kristensen LE, Saxne T, Nilsson JA, et al. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8(6):R174.
109. Kristensen LE, Christensen R, Bliddal H, et al. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: A systematic literature review. Scandinavian Journal of Rheumatology 2007;36(6):411-7.
110. Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 2008;59(8):1074-81.
111. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res 2003;23(4):119-28.
112. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol 2005 Jul;141(7):861-4.
113. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 2002 Oct;46(10):2565-70.
114. Lee YH, Woo JH, Rho YH, et al. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatology international 2008;28(6):553-9.
115. Li T, Gignac M, Wells G, et al. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther 2008;30(4):734-48.
116. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis - a randomized trial. Ann Intern Med 2006 Dec;144:865-76.
117. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. Value Health 2010;13(6):805-12.
118. Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005 Nov;52(11):3403-12.
119. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther 2006;8(3):R66.
120. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum 2008;58(3):667-77.
121. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006;54(9):2817-29.
122. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol 2008;35(6):979-85.
123. Marchesoni A, Zaccara E, Gorla R, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 2009;1173837-46.

124. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis 2009;48(10):1364-71.
125. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol 2008;35(1):20-30.
126. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol 2006;33(12):2412-5.
127. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol 2009;22(2):415-26.
128. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008;18(3):252-62.
129. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001 Dec;44(12):2862-9.
130. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis 2004 Aug 1;39(3):295-9.
131. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of Combination Therapy With Single-Drug Therapy in Early Rheumatoid Arthritis: a Randomised Trial. Lancet 1999;353(9164):1568-73.
132. Korpela M, Laasonen L, Hannonen P, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the Fin-Raco Study. Arthritis Rheum 2004;50(7):2072-81.
133. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum 2004;50(1):55-62.
134. Mottonen T, Hannonen P, Korpela M, et al. Delay to Institution of Therapy and Induction of Remission Using Single-Drug or Combination-Disease-Modifying Antirheumatic Drug Therapy in Early Rheumatoid Arthritis. Arthritis Rheum 2002;46(4):894-8.
135. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum 2008;59(8):1090-6.
136. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10(2):R30.
137. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19(1):12-9.
138. Nuki G, Bresnihan B, Bear MB, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002 Nov;46(11):2838-46.
139. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996 May 16;334(20):1287-91.
140. O'Dell JR, Leff R, Paulsen G, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46(5):1164-70.
141. O'Dell JR, Petersen K, Leff R, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol 2006 Feb;33(2):213-8.
142. Osiri M, Shea B, Robinson V, et al. Leflunomide for treating rheumatoid

arthritis. Cochrane Database Syst Rev 2002(3):CD002047.
143. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev 2010;9(3):175-80.
144. Pan SM, Dehler S, Ciurea A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009;61(5):560-8.
145. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis 2007 Feb;66(2):189-94.
146. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994 Feb;96(2):115-23.
147. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford) 2007 July 31, 2006;46(2):327-34.
148. Schaible TF. Long term safety of infliximab. Can J Gastroenterol 2000 Sep;14(Suppl C):29C-32C.
149. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006 Jul;65(7):889-94.
150. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67(8):1096-103.
151. Schipper LG, Fransen J, Barrera P, et al. Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add? Rheumatology (Oxford) 2009;48(10):1247-53.
152. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007;56(6):1754-64.
153. Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum 2006 Sep;54(9):2757-64.
154. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J 2008;156(2):336-41.
155. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum 2006 May;54(5):1429-34.
156. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum 2003 Feb;48(2):319-24.
157. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57(8):1431-8.
158. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35(3):387-93.
159. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. Lancet 1999;353(9149):259-66.
160. Smolen JS. Efficacy and safety of the new DMARD leflunomide: comparison to placebo and sulfasalazine in active rheumatoid arthritis. Scand J Rheumatol 1999;112(Supplement):15-21.
161. Sharp JT, Strand V, Leung H, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 2000;43(3):495-505.
162. Larsen A, Kvien TK, Schattenkirchner M, et al. Slowing of disease progression in rheumatoid arthritis patients during long-term treatment with leflunomide or sulfasalazine. Scand J Rheumatol 2001;30(3):135-42.

163. Scott DL, Smolen JS, Kalden JR, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001;60(10):913-23.
164. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371(9617):987-97.
165. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68(6):797-804.
166. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68(6):823-7.
167. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374(9685):210-21.
168. Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69(9):1612-7.
169. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum 2006 12/01/;54(Dec):3790-8.
170. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004 Nov;50(11):3432-43.
171. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006 Mar;54(3):716-22.
172. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159(21):2542-50.
173. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum 1999 Sep;42(9):1870-8.
174. Cohen S, Cannon G, Schiff M, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of leflunomide in the treatment of rheumatoid arthritis. Arthritis Rheum 2001;44(9):1984-92.
175. Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology (Oxford) 2006;45(12):1505-13.
176. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. Jama 2009;301(7):737-44.
177. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther 2010;12(1):R5.
178. Suissa S, Ernst P, Hudson M, et al. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med 2004 Jul 15;117(2):87-92.
179. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum 2006 May;54(5):1435-9.
180. Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55(4):531-6.
181. Svensson B, Ahlmen M, Forslind K. Treatment of early RA in clinical practice: a comparative study of two different DMARD/corticosteroid options. Clin Exp Rheumatol 2003 May-Jun;21(3):327-32.
182. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and

increases the remission rate: a two-year randomized trial. Arthritis Rheum 2005;52(11):3360-70.
183. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8(5):R151.
184. van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Ann Rheum Dis 2006 Feb 7.
185. Van Riel PLCM, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Ann Rheum Dis 2008;67(8):1104-10.
186. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374(9688):459-66.
187. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004 May 1;38(9):1261-5.
188. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 2004 Oct;31(10):1912-7.
189. Weaver AL, Lautzenheiser RL, Schiff MH, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin 2006 Jan;22(1):185-98.
190. Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum 2006 Aug 31;54(9):2807-16.
191. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis 2007 Feb;66(2):228-34.
192. Wells G, Li T, Maxwell L, et al. Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis 2008;67(2):260-5.
193. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology 2006;45(Oct):1238-46.
194. Hassett AL, Li T, Buyske S, et al. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin 2008;24(5):1443-53.
195. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006 Apr;54(4):1075-86.
196. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009 Dec;68(12):1870-7.
197. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004 Jun;50(6):1740-51.
198. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med 2004 Mar 1;116(5):305-11.
199. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis

factor therapy. Arthritis Rheum 2006 Feb;54(2):628-34.
200. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol 2007;36(3):172-8.
201. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56(5):1433-9.
202. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis Rheum 2007;56(9):2886-95.
203. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR J Rheumatol 2006;9(2):127-30.
204. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 2005 Sep;64(9):1274-9.
205. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: Systematic review and metaanalysis of efficacy and safety. BMC Musculoskeletal Disorders 2008;9.
206. Bergman GJ, Hochberg MC, Boers M, et al. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2010;39(6):425-41.
207. Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. J Rheumatol 2010;37:928-31.
208. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006 May 17;295(19):2275-85.
209. Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis 2009;68(7):1177-83.
210. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess 2004 May;8(18):iii-iv, ix-x, 1-105.
211. Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. Pharmacotherapy 2011;31(1):39-51.
212. Gartlehner G, Hansen RA, Jonas BL, et al. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol 2006 Dec;33(12):2398-408.
213. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010 Jun;69(6):1004-9.
214. Hochberg MC, Tracy JK, Hawkins-Holt M, et al. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2003 2003;62 Suppl 2:ii13-6.
215. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007(1):CD006356.
216. Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis 2010;69(7):1298-304.
217. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68(7):1136-45.
218. Maetzel A, Wong A, Strand V, et al. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2000 Sep;39(9):975-81.

219. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol 2009;27(4):678-84.
220. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev 2009(1):CD005121.
221. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69(6):976-86.
222. Osiri M, Shea B, Welch V, et al. Leflunomide for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev 2003;1:Art. No.: CD002047.
223. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol 1995;22(2):218-23.
224. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009;68(1):25-32.
225. Schipper LG, Fransen J, Barrera P, et al. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology (Oxford) 2009;48(7):828-33.
226. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Can Med Assoc J 2009;181:787.
227. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2009(4).
228. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev 2010(1):CD008341.
229. Singh Jasvinder A, Beg S, Lopez-Olivo Maria A. Tocilizumab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2010(7).
230. Wailoo A, Brennan A, Bansback N, et al. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program. AHRQ Technology Assessment Program. 2006.
231. Wiens A, Correr CJ, Pontarolo R, et al. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol 2009;70(4):337-44.
232. Wiens A, Venson R, Correr CJ, et al. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy 2010;30(4):339-53.

Appendix F. Criteria for Assessing the Quality of Individual Studies

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Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the U.S. Preventive Services Task Force and the NHS Centre for Reviews and Dissemination. To assess the quality of observational studies, we used criteria outlined by Deeks et al., 2003.[1]

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alteration, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer-based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alteration, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Observational Studies:

Assessment of Internal Validity

1. Were both groups selected from the same source population?

2. Did both groups have the same risk of having the outcome of interest at baseline?

3. Were subjects in both groups recruited over the same time period?

4. Was there any obvious selection bias?

5. Were ascertainment methods adequate and equally applied to both groups?

6. Was an attempt made to blind the outcome assessors?

7. Was the time of followup equal in both groups?

8. Was overall attrition high ($\geq$ 20%)?

9. Was differential attrition high ($\geq$ 15%)?

10. Did the statistical analysis consider potential confounders or adjust for different lengths of followup?

11. Was the length of followup adequate to assess the outcome of interest?

1. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173.

For Systematic Reviews and Meta-analyses:

1. Is the review based on a focused question of interest?
2. Did the search strategy employ a comprehensive, systematic, literature search?
3. Are eligibility criteria for studies clearly described?
4. Did at least 2 persons independently review studies?
5. Did authors use a standard method of critical appraisal before including studies?
6. Was publication bias assessed?
7. Was heterogeneity assessed and addressed?
8. Did statistical analysis maintain trials as the unit of analysis?

Appendix G. Clinical and Self-Reported Scales and Instruments Commonly Used in Studies of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis

Introduction

This appendix provides a brief overview of the various scales and self-reported measures that investigators used to assess outcomes in all the studies reviewed in this systematic review. The main outcome categories involve radiologic assessments of joint damage (erosion or narrowing) and various instruments that patients or subjects used to report on functional capacity or quality of life; the latter fall into two groups, one related to general health measures and one related to condition- or disease-specific instruments. General measures used in rheumatoid and psoriatic arthritis studies are described first; then the disease-specific measures used in rheumatoid and psoriatic arthritis studies are described separately. The new 2010 American College of Rheumatology ACR criteria are presented at the end of the document.

Radiographic Measures

Radiographic assessment of joint damage in hands (including wrists) or both hands and feet are critical to clinical trials in rheumatoid arthritis. The damage can be both joint space narrowing and erosions, and the underlying construct is sometimes referred to as radiographic progression (i.e., changes, whether positive or negative) as detected by radiography and interpretation. Several approaches exist, but the two commonly used are the Sharp Score (and variants) and the Larsen Score. These and other scoring methods have recently been reviewed by Boini and Guillemin;[1] additional citations or sources are given in the brief descriptions below.

Sharp Score and Sharp/van der Heijde Score

The Sharp Score is a means of evaluating joint damage in joints of the hands, including both erosion and joint space narrowing.[2] Although it has undergone modifications since its introduction, the version proposed in 1985 has become the standard approach. In this method, 17 joint areas in each hand are scored for erosions; 18 joint areas in each hand are scored for joint space narrowing. The score per single joint for erosions ranges from 0 to 5 and for joint space narrowing from 0 to 4. In both cases, a higher score is worse. Erosion scores range from 0 to 170 and joint space narrowing scores range from 0 to 144. Thus, the "total Sharp Score" is the sum of the erosion and joint space narrowing scores, or 0 to 314.

The Sharp/van der Heijde (SHS) method, introduced in 1989, overcame one drawback to the Sharp Score, namely its focus on only hands, given that feet can also be involved early in rheumatoid arthritis. Therefore, the SHS method was developed to take account of erosions and joint space narrowing in both hands and feet.[3-4] As with the Sharp Score, higher scores reflect worse damage. Erosion is assessed in 16 joints in each hand and 6 joints in each foot. Each joint is scored from 0 to 5 with a maximal erosion score of 160 in the hands and 120 in the feet. Joint space narrowing and subluxation are assessed in 15 joints in the hands and 6 joints in the feet. Each joint is scored from 0 to 4 with a maximal score of 120 in the hands and 48 in the feet. The

erosion and joint space narrowing scores are combined to give a total SHS score with a maximum of 448 (weighted toward hands because more joints are scored).

Numerous variants on the Sharp or SHS scores have been developed, differing subtly in terms of the numbers of joints measured and other details.[5] Generally, all the Sharp methods are very detailed assessments and the approach, although reliable and sensitive to change, is considered time-consuming and tedious. For a speedier approach, Larsen and colleagues developed a simpler approach.

Larsen Scale for Grading Radiographs

The Larsen Scale is an overall measure of joint damage, originally devised in the 1970s and updated most recently in the late 1990s.[6-10] It produces both a score for each joint (hands and feet) and an overall score that reflects measurement and extent of joint damage. Scores range from 0 ("normal conditions," i.e., intact bony outlines and normal joint space) to 5 ("mutilating abnormality," i.e., original bony outlines have been destroyed), so higher scores reflect greater damage. Scores can range from 0 to 250.

General Health Measures

Health Assessment Questionnaire

The Health Assessment Questionnaire (HAQ) is a widely used self-report measure of functional capacity; it is a dominant instrument in studies of patients with arthritis (particularly trials of drugs in patients with rheumatoid arthritis), but it is considered a generic (not disease-specific) instrument. Detailed information on its variations, scoring, etc., can be found at www.chcr.brown.edu/pcoc/EHAQDESCRSCORINGHAQ372.PDF (accessed for this purpose 1/18/2007) or www.hqlo.com/content/1/1/20 (accessed for this purpose 1/18/2007) and in the seminal reports by Fries et al.[11] and Ramey et al.[12]

The full, five-dimension HAQ consists of four domains: disability, discomfort and pain, toxicity, and dollar costs, plus death (obtained through other sources). More commonly, "the HAQ" as used in the literature refers to the shorter version encompassing the HAQ Disability Index (HAQ-DI), the HAQ pain measure, and a global patient outcome measure. The HAQ-DI is sometimes used alone.

The HAQ-DI, with the past week as the time frame, focuses on whether the respondent "is able to…" do the activity and covers eight categories in 20 items: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The four responses for the HAQ-DI questions are graded as follows: without any difficulty = 0; with some difficulty = 1; with much difficulty = 2; and unable to do = 3. The highest score for any component question in a category determines the category score. The HAQ-DI also asks about the use of aids and devices to help with various usual activities. Two composite scores can be calculated, one with and one without the aids/devices element; both range from 0 to 3.

The HAQ pain domain is measured on a doubly-anchored horizontal visual analog scale (VAS) of 15 cm in length; one end is labeled "no pain" (score of 0) and the other is labeled "very severe pain" (score of 100). Patients mark a spot on the VAS, and scores are calculated as the length from "no pain" in centimeters (cm) multiplied by 0.2 to yield a value that can range between 0 and 3.

With respect to interpretation, HAQ-DI scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.

The HAQ global health status scale measures quality of life (essentially, as how the patient is feeling) with a 15 cm doubly-anchored horizontal VAS scored from 0 (very well) to 100 (very poor).

Medical Outcomes Study Short Form 36 Health Survey

The Medical Outcomes Study Short Form 36 Health Survey (SF-36) is an internationally known generic health survey instrument. Information can be found at www.sf-36.org/tools/sf36.shtml (accessed for this purpose 2/18/2007) and in a large number of articles documenting its psychometric properties.[13-19] It comprises 36 items in eight independent domains tapping functioning and well-being: physical functioning, role-physical, bodily pain, and general health in one grouping (physical health) and vitality, role-emotional, social functioning, and mental health in another grouping (mental health). The SF-36 provides a separate scale score for each domain (yielding a profile of health) and two summary scores, one for physical health and one for mental health. Each scale is scored from 0 to 100 where higher scores indicate better health and well-being.

A "version 2" of the SF-36 was introduced in the late 1990s to correct some drawbacks in formatting, wording, and other issues and to update the norm-based scoring with 1998 data. It can be fielded in two versions varying by recall period: 4-week recall (the usual approach) and 1-week recall (acute). More recently, it has been tested and used for computer adaptive testing according to item response theory principles.

EuroQol EQ-5D Quality of Life Questionnaire

A third generic quality-of-life instrument is the EuroQol EQ-5D Quality of Life Questionnaire, typically known just as the EQ-5D. More information can be found at http://www.euroqol.org/ (accessed for this purpose 1/18/2007) and in key descriptive articles,[20] one of which is about patients with rheumatoid arthritis.[21]

The EQ-5D covers health status in five domains (three questions each): mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. It is intended for self-response but can be used in other administration modes. Each item can take one of three response levels – no problems, some moderate problems, extreme problems – identified as level 1, 2, or 3, respectively. This yields a profile of one level for each of the five domains; this is essentially a five-digit number, and no arithmetic properties attach to these values. Users can convert health states in the five-dimensional descriptive system into a weighted health state index by applying scores from EQ-5D "value sets" elicited from general population samples to the profile pattern (e.g., 1, 2, 3, 3, 1).

The EQ-5D also has a global health VAS scale (20 cm) scored from 0 to 100.

Rheumatoid Arthritis Measures

American College of Rheumatology 20/50/70

The American College of Rheumatology (ACR) criteria are concerned with *improvement* in counts of tender and swollen joints and several domains of health.[22] A principal aim of these criteria is use in studies (particularly trials) of drugs for rheumatoid arthritis. More information can be found at www.rheumatology.org/publications/response/205070.asp and www.hopkins-arthritis.som.jhmi.edu/edu/acr/acr.html#remis_rheum (both accessed for this purpose 1/18/2007). Originally these latter involved patient assessment, physician assessment, erythrocyte sedimentation rate, pain scale, and functional questionnaire.

Today, based on work done in the mid 1990s,[23] values for clinical trial patients are defined as improvement in both tender and swollen joint counts and in three of the following: patient's assessment of pain; patient's global assessment of disease activity, patient's assessment of physical function (sometimes referred to as physical disability), the physician's global assessment of disease activity, and acute phase reactant (C-reactive protein, or CRP). The 20, 50, or 70 designations (sometimes called the ACR Success Criteria) refer to improvements in percentage terms to 20 percent, 50 percent, or 70 percent in the relevant dimensions. A physician's global assessment of 70 percent improvement is considered remission.

Thus, patients are said to meet ACR 20 criteria when they have at least 20 percent reductions in tender and swollen joint counts and in at least three of the domains. ACR 50 and ACR 70 criteria are defined in a manner similar to that for ACR 20, but with improvement of at least 50 percent and 70 percent in the individual measures, respectively. The table illustrates, in a study context, how a patient might be said to have an ACR 50 response.

Outcomes Measured	Baseline	Endpoint
Tender joints count *	12	6
Swollen joints count *	8	3
Patient's pain score*	60	20
Patient's physical function (disability) score	80	60
Physician's global activity score*	50	20
C-reactive protein*	3.6	1.4

* At least 50 percent improvement between baseline and endpoint measurements.

Ritchie Articular Index

This is a long-standing approach to doing a graded assessment of the tenderness of 26 joint regions, based on summation of joint responses after applying firm digital pressure.[24] Four grades can be used: 0, patient reported no tenderness; +1, patient complained of pain; +2, patient complained of pain and winced; and +3, patient complained of pain, winced, and withdrew. Thus, the index ranges from 0 to 3 for individual measures and 0 to 78 overall, with higher scores being worse tenderness.

Certain joints are treated as a single unit, such as the metacarpal-phalangeal and proximal interphalangeal joints of each hand and the metatarsal-phalangeal joints of each foot. For example, the maximum score for the five metacarpal-phalangeal joints of the right hand would

be 3, not 15. No weights are used for different types of joints (e.g., by size), because the issue is one of measuring changes (improvements) in tenderness; this is especially relevant for rheumatoid arthritis.

Disease Activity Score

The Disease Activity Score (DAS) is an index of disease activity first developed in the mid 1980s. The history of its development and current definitions, scoring systems, and other details can be found at http://www.das-score.nl/www.das-score.nl/ (accessed for this purpose 1/19/2007) and in recent articles.[4,25] The DAS originally included the Ritchie Articular Index (see above), the 44 swollen joint count, the erythrocyte sedimentation rate, and a general health assessment on a VAS. A cut-off level of the DAS of 1.6 is considered to be equivalent with being in remission.

More recently, an index of RA disease activity using only 28 joints – the DAS 28 – has been developed, focusing on joint counts for both tenderness (TJC) and swelling (SJC). It also uses either the patient's or a physician's global assessment (PGA) of disease activity (on a 100 mm VAS) and the erythrocyte sedimentation rate (ESR) or C-reactive protein. The formula for calculating a DAS 28 score is as follows: = $(0.56 \times TJC^{1/2}) + (0.28 \times SJC^{1/2}) + (0.7 \times \ln [ESR]) + (0.014 \times PGA [in mm])$. Numerous formulas to calculate a variety of DAS and DAS 28 scores exist (see the website above), such as when a global patient assessment of health is unavailable.

The DAS 28 yields a score on a scale ranging from 0 to 10. A DAS 28 of 2.6 is considered to correspond to remission; a DAS 28 of 3.2 is a threshold for low disease activity; and a DAS 28 of more than 5.1 is considered high disease activity

EULAR Response Criteria

The European League Against Rheumatism (EULAR) response criteria classify patients as good, moderate, or nonresponders based on both change in disease activity and current disease activity, using either the DAS or the DAS28 (see description above).[26] For example, to be classified as a good responder a patient must have relevant change in DAS ($\geq$1.2) and low current disease activity ($\leq$2.4), while a nonresponder must have $\leq$0.6 change in DAS and high disease activity (>3.7).[27]

The EULAR criteria have been validated in multiple clinical trials, and confirmed in an analysis of nine clinical trials that concluded a high level of agreement and equal validity between ACR and EULAR improvement classifications.[28] Good and moderate responders showed significantly more improvement in functional capacity and significantly less progression of joint damage than patients classified as nonresponders.[28]

Psoriatic Arthritis Measures

Psoriatic Arthritis Response Criteria

The psoriatic arthritis response criteria (PsARC) was initially designed for use in a clinical trial that compared sulphasalazine to placebo in the setting of the Veterans Administration.[29] It has since been used as the primary or secondary outcome in all the studies that examined biologics versus placebo in the treatment of PsA. The PsARC includes improvement in at least two of the following, one of which had to be a joint count, and no worsening of any measure:

tender or swollen joint count improvement of at least 30%, patient global improvement by one point on a five-point Likert scale, or physician global improvement on the same scale.[29]

American College of Rheumatology 20

The ACR 20 (American College of Rheumatology 20 percent response) is the other outcome that is used as the primary outcome in clinical trials of biologics. The measurement is similar to that of the ACR 20 used for rheumatoid arthritis with modifications made that increased the number of joints tested from 68 tender and 66 swollen to 76 and 78, respectively, with the addition of distal interphalangeal joints of the feet and carpometacarpal joints of the hands.[29] The outcomes from the ACR 20 are generally poorer when compared to the PsARC due to the variation in items measured; this is due in part to the need to see an improvement in tender *and* swollen joints in the ACR 20 versus an improvement in tender *or* swollen joint counts.

2010 Rheumatoid Arthritis Criteria

Target population (Who should be tested?)

Patients who

- have at least 1 joint with definite clinical synovitis (swelling)
  - Criteria aimed at classification of newly presenting patients; patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA; patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA
- with the synovitis not better explained by another disease
  - Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted

Classification criteria for RA	**Score**

Score-based algorithm:
• Add score of categories: Joint involvement, serology, reactants, duration
  o Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted
• Score of ≥6/10 needed for classification of a patient as having definite RA
  o Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time	

Joint involvement Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis; d Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment;* categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement	
1 large joint • "Large joints" refers to shoulders, elbows, hips, knees, and ankles	**0**
2-10 large joints	**1**
1-3 small joints (with or without involvement of large joints) • "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.	**2**
4-10 small joints (with or without involvement of large joints)	**3**

>10 joints (at least 1 small joint) • In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.)	**5**
Serology *(at least 1 test result is needed for classification)*[††] • Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay; where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody	
Negative RF *and* negative ACPA	**0**
Low-positive RF *or* low-positive ACPA	**2**
High-positive RF *or* high-positive ACPA	**3**
Acute-phase reactants *(at least 1 test result is needed for classification)* • Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate	
Normal CRP *and* normal ESR	**0**
Abnormal CRP *or* abnormal ESR	**1**
Duration of symptoms • Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status	
<6 weeks	**0**
≥6 weeks	**1**

Adapted from: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010 Sep; 62(9): 2569–2581

The Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) was developed to measure the effect of treatments in clinical trials of psoriasis and is utilized to capture the psoriasis component found in psoriatic arthritis. The scale was originally published in 1978 in a trial of 27 patients suffering from severe chronic generalized psoriasis that were treated with Ro 10-9359, a retinoic acid derivative.[30] The PASI is a composite index of disease severity incorporating measures of scaling, erythema, and induration, and it is weighted by severity and affected body surface area. A PASI >12 defines severe, PASI 7-12 moderate, and PASI <7 mild psoriasis.

References

1. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis. 2001 Sep;60(9):817-27.

2. Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum. 1985 Dec;28(12):1326-35.

3. van der Heijde D, Dankert T, Nieman F, Rau R, Boers M. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford). 1999 Oct;38(10):941-7.

4. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999 Mar;26(3):743-5.

5. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis. 2003 Jul;62(7):597-604.

6. Larsen A. Radiological grading of rheumatoid arthritis. An interobserver study. Scand J Rheumatol. 1973;2(3):136-8.

7. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh). 1977 Jul;18(4):481-91.

8. Scott DL, Coulton BL, Bacon PA, Popert AJ. Methods of X-ray assessment in rheumatoid arthritis: a re-evaluation. Br J Rheumatol. 1985 Feb;24(1):31-9.

9. Larsen A. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J Rheumatol. 1995;22:1974-5.

10. Edmonds J, Saudan A, Lassere M, Scott DL. Introduction to reading radiographs by the Scott modification of the Larsen method. J Rheumatol. 1999;26:740-2.

11. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.

12. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 -- Status and Review. In: Spilker B, ed. *Quality of Life and Pharmacoleconomics in Clinical Trials*. 2nd ed. Philadelphia: Lippincott-Raven Publischers 1996:227-37.

13. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988 Jul;26(7):724-35.

14. Stewart AL, Ware JE. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press 1992.

15. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.

16. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992 May;30(5 Suppl):MS253-65.

17. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247-63.

18. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and

reliability across diverse patient groups. Med Care. 1994 Jan;32(1):40-66.

19. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care. 1995 Apr;33(4 Suppl):AS264-79.

20. Kind P. The EuroQol instrument: An index of health-related quality of life. Quality of life and PharmacoEconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers 1996.

21. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997 May;36(5):551-9.

22. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993 Jun;36(6):729-40.

23. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.

24. Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med. 1968 Jul;37(147):393-406.

25. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7(4):R796-806.

26. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum*. 1996/01/01 ed 1996:34-40.

27. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Rheum Dis Clin North Am*. 2009/12/08 ed 2009:745-57, vii-viii.

28. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. *J Rheumatol*. 1999/03/25 ed 1999:705-11.

29. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.

30. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

Appendix H. Excluded Studies

Characteristics of Studies with Poor Internal Validity

Study	Design	Sample Size	Intervention	Reason for Exclusion
Anis et al., 2009[1]	RCT subanalysis	205	Etanercept	High risk of bias due to loss of effect of randomization
Bathon et al., 2006[2]	Pooled data analysis	2,402	Etanercept	Selection bias
Bazzani et al., 2009[3]	Prospective cohort registry study	1010	Etanercept Adalimumab Infliximab corticosteroid	Selection bias
Bejarno et al., 2008[4]	RCT	148	Adalimumab Methotrexate	Very high LTF
‡Burmester et al., 2007[5]	Prospective cohort open-label study	6610	Adalimumab Combo therapy with 1+ DMARD	high risk of bias; confounding by indication
Chopra et al., 2008[6]	Prospective cohort study	230	Leflunomide Methotrexate	High LTF; completers analysis for outcome of interest; selection bias
Cohen et al, 2010[7]	Post hoc analysis of RCT data	468	Rituximab Methotrexate	High risk of bias due to loss of effect of randomization
Cole et al., 2007[8]	Retrospective cohort study	303	Etanercept Adalimumab Infliximab Methylprednisolone	Inadequate control for potential confounders; retrospective study with chart review; groups not similar at baseline; small sample size
De Stefano, 2010[9]	Non-randomized controlled trial	120	Anti-TNF therapy Methotrexate Leflunomide	High LTF; no randomization; non-ITT analysis
de Nijs et al., 2001[10]	Cross-sectional	410	Corticosteroids	Selection bias
Faarvang et al., 1993[11]	RCT	91	Hydroxychloroquine Sulfasalazine	No ITT analysis; high LTF
Fleischmann et al., 2003[12]	Pooled data analysis	1128	Etanercept	Selection bias
Flendrie et al., 2005[13]	Observational	162	Leflunomide infliximab	High LTF; selection bias
Ghosh et al., 2008[14]	RCT	110	Methotrexate Sulfasalazine Hydroxychlorquine	Randomization/ allocation not adequately reported; inadequate reporting of baseline measures
Guignard et al., 2008[15]	Retrospective cohort study	2707	Anti-TNF therapy Non anti-TNF therapy	No adjustment for confounders and effect modifiers; small sample size; single center
Hafstrem et al., 2009[16]	RCT	150	Prednisolone	High LTF
Hansen et al., 1999[17]	RCT	102	DMARDs Prednisolone	High attrition; no ITT analysis

Study	Design	Sample Size	Intervention	Reason for Exclusion
Heiberg et al., 2006[18]	Observational	183	Adalimumab Methotrexate	High potential for selection bias and confounding; baseline differences between groups
Iwatani et al., 2006[19]	Cross-sectional prospective cohort	313	Sulfasalazine Methotrexate Bucillamine	Selection bias; high potential for confounding
Jones, et al., 2010[20]	RCT	570	Tocilizumab Methotrexate	Attrition NR; quality of randomization and allocation concealment unclear
Karlsson et al., 2008[21]	Prospective cohort study	473	Second-line anti-TNF therapy Third-line anti-TNF therapy	High LTF; Poor inter-rater reliability
Kimel et al., 2008[22]	RCT	525	Adalimumab Methotrexate	Selection bias; High LTF; no ITT analysis; analyses do not directly compare the two treatment groups
Lee et al., 2008[23]	Adjusted indirect comparison	N/A	Anti-TNF therapy Methotrexate	High risk of bias due to small number of studies (3) included in indirect comparisons
Mariette et al., 2010[24]	Case-control study	111	Etanercept Infliximab Adalimumab	Small sample size; control for confounding unclear
Mattey et al., 2009[25]	Observational	154	Infliximab Etanercept	No baseline characteristics reported; no adjustments made for different lengths of treatment
Mertz and Blair, 2007[26]	Retrospective observational Study	287	Anti-TNF therapy Methotrexate Azathioprine Leflunomide Prednisone	Confounding by indication; selection bias; groups not similar at baseline
Nagashima et al., 2006[27]	Prospective cohort	1358	Sulfasalazine Methotrexate	No adjustments for confounding; unequal treatment duration; unclear if groups are similar at baseline
Osiri et al., 2006[28]	Prospective cohort	152	Methotrexate Sulfasalazine Leflunomide	High potential for bias due to confounding by indication
Schoels et al., 2007[29]	Prospective cohort study	1214	Methotrexate Sulfasalazine Leflunomide Other unspecified DMARS	Attrition data not reported; not clear if groups are similar at baseline

Study	Design	Sample Size	Intervention	Reason for Exclusion
Seong et al., 2007[30]	Retrospective cohort study	1478	Anti-TNF naïve Infliximab Etanercept	Selection bias; groups not comparable at baseline; high potential for confounding
Soderlin et al., 2007[31]	Prospective cohort	357	Biologics Methotrexate	High LTF; important potential confounders not accounted for
‡Strand et al., 2006 [32]	RCT	161	Rituximab Methotrexate	Very high LTF
Todoerti et al., 2010[33]	RCT	210	Prednisone	Poor reporting of outcomes; statistical methods or study design to reduce confounding unclear
van der Heijde et al., 2007[34]	RCT	414	Etanercept Methotrexate	High LTF
van Vollenhoven et al., 2010[35]	Observational	664	Adalimumab Methotrexate	High LTF; important baseline differences between groups; high risk of selection bias
Weisman et al., 2007[36]	RCT	564	Etanercept Placebo	High LTF; not powered to detect a difference in these rare outcomes; some baseline differences in cardiovascular risk factors

NR, not reported; ITT, intention to treat; LTF, loss to followup; RCT, randomized controlled trial.

‡Rated fair for adverse events or included in adverse events meta-analysis

References

1. Anis A, Zhang W, Emery P, et al. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford) 2009;48(10):1283-9.

2. Bathon JM, Fleischmann RM, Van der Heijde D, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):234-43.

3. Bazzani C, Filippini M, Caporali R, et al. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: Clinical outcomes. Autoimmunity Reviews 2009;8(3):260-5.

4. Bejarano V, Quinn M, Conaghan PG, et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 2008;59(10):1467-74.

5. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66(6):732-9.

6. Chopra A, Saluja M, Lagu-Joshi V, et al. Leflunomide (Arava) is a useful DMARD in Indian (Asian) patients: a clinic-based observational study of 1-year treatment. Clin Rheumatol 2008;27(8):1039-44.

7. Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis 2010;69(6):1158-61.

8. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007;27(4):369-73.

9. De Stefano R, Frati E, Nargi F, et al. Comparison of combination therapies in the treatment of rheumatoid arthritis: leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. Clin Rheumatol 2010;29(5):517-24.

10. de Nijs RN, Jacobs JW, Bijlsma JW, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology (Oxford). 2001 Dec;40(12):1375-83.

11. Faarvang K, Egsmose C, Kryger P, et al. Hydroxychloroquine and Sulphasalazine Alone and in Combination in Rheumatoid Arthritis: a Randomised Double Blind Trial. Annals of the rheumatic diseases. 1993;52(10):711-5.

12. Fleischmann RM, Baumgartner SW, Tindall EA, et al. Response to etanercept (Enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trial results. J Rheumatol. 2003 Apr;30(4):691-6.

13. Flendrie M, Creemers MC, Welsing PM, et al. The influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in patients with rheumatoid arthritis; a longitudinal observational study. Rheumatology (Oxford). 2005 Apr;44(4):472-8.

14. Ghosh B, Halder S, Ghosh A, et al. Early rheumatoid arthritis: Clinical and therapeutic evaluation in a tertiary care centre in India. Indian Journal of Rheumatology 2008;3(2):48-51.

15. Guignard S, Gossec L, Bandinelli F, et al. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. Clin Exp Rheumatol 2008;26(3 Suppl 49):S23-9.

16. Hafstrem I, Albertsson K, Boonen A, et al. Remission achieved after 2 years treatment with low-dose prednisolone in addition to diseasemodifying anti-rheumatic drugs in

early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: An open 2-year continuation study. 2009.

17. Hansen M, Podenphant J, Florescu A, et al. A Randomised Trial of Differentiated Prednisolone Treatment in Active Rheumatoid Arthritis. Clinical Benefits and Skeletal Side Effects. Annals of the rheumatic diseases. 1999;58(11):713-8.

18. Heiberg MS, RÃ¸devand E, Mikkelsen K, et al. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: Results from a 6-month longitudinal, observational, multicentre study. Annals of the rheumatic diseases 2006;65(10):1379-83.

19. Iwatani M, Inoue E, Nakamura T, et al. Efficacy profile of bucillamine in rheumatoid arthritis patients in a large observational cohort study, IORRA. Mod Rheumatol 2006;16(6):376-80.

20. Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. Expert Rev Clin Immunol 2010;6(2):189-95.

21. Karlsson JA, Kristensen LE, Kapetanovic MC, et al. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford) 2008;47(4):507-13.

22. Kimel M, Cifaldi M, Chen N, et al. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35(2):206-15.

23. Lee YH, Woo JH, Rho YH, et al. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatology international 2008;28(6):553-9.

24. Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-TNF: Results of the 3-year prospective French RATIO registry. Annals of the rheumatic diseases 2010;69(2):400-8.

25. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36(6):1180-7.

26. Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci 2007;1111343-57.

27. Nagashima M, Matsuoka T, Saitoh K, et al. Treatment continuation rate in relation to efficacy and toxicity in long-term therapy with low-dose methotrexate, sulfasalazine, and bucillamine in 1,358 Japanese patients with rheumatoid arthritis. Clin Exp Rheumatol 2006;24(3):260-7.

28. Osiri M, Deesomchok U, Tugwell P. Disease activity and functional changes of RA patients receiving different DMARDs in clinical practice. Clin Rheumatol. 2006;25(5):721-7.

29. Schoels M, Kapral T, Stamm T, et al. Step-up combination versus switching of non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a retrospective observational study. Ann Rheum Dis 2007;66(8):1059-65.

30. Seong SS, Choi CB, Woo JH, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol. 2007 Apr;34(4):706-11.

31. Soderlin MK, Lindroth Y, Jacobsson LT. Trends in medication and health-related quality of life in a population-based rheumatoid arthritis register in Malmo, Sweden. Rheumatology (Oxford) 2007;46(8):1355-8.

32. Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2

years. Rheumatology (Oxford) 2006;45(12):1505-13.

33. Todoerti M, Scire CA, Boffini N, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Ann N Y Acad Sci 2010;1193(1):139-45.

34. van der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56(12):3928-39.

35. van Vollenhoven RF, Cifaldi MA, Ray S, et al. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res (Hoboken) 2010;62(2):226-34.

36. Weisman MH, Paulus HE, Burch FX, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology (Oxford) 2007;46(7):1122-5.

Appendix I. Strength of Evidence Tables

Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

For each comparison, the following tables provide the strength of evidence for disease activity and radiographic outcomes within a single row, if both outcomes were available. Information related to disease activity is provided in the upper part of each row; information related to radiographic outcomes is provided in the lower part of each row, when available.

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD: Corticosteroid vs. Corticosteroid 1 RCT N =143	Medium RCT/ fair	Unknown, single study	Direct	Precise	No difference in ACR 20 and DAS for prednisolone and budesonide	Low
LEF vs. MTX 2 RCTs N = 1481	Low RCTs/ Fair Low RCTs/Fair	Consistent Consistent	Direct Indirect	Imprecise Precise	No difference in ACR 20 at 1 to 2 years No difference in radiographic changes at 2 years	Low Low
LEF vs. SSZ 1 RCT N =358	Medium RCT/Fair Medium RCT/Fair	Unknown, single study Unknown, single study	Direct Indirect	Imprecise Imprecise	Mixed results for ACR20 response at 2 yrs Similar Radiographic changes at 2 years	Insufficient Low
SSZ vs. MTX 3 RCTs N = 1001	Low RCTs/Fair Low RCTs/Fair	Consistent Consistent	Direct Indirect	Precise Imprecise	No difference in disease activity No difference in radiographic changes	Low Low
Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticosteroids: SSZ + MTX vs. SSZ or MTX 3 RCTs, 1 Prospective cohort; N = 709 2 RCTs N = 374	Low 1 RCT/Fair Low 2RCTs, 1 prospective cohort/Fair Low 2RCTs/Fair	Unknown, single study Consistent Consistent	Direct Direct Indirect	Imprecise Precise Precise	Sulfasalazine + MTX improves disease activity (DAS), but no difference in ACR No differences in disease activity in patients with early RA No difference in radiographic changes	Low Moderate Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
MTX + HCQ + SSZ vs. 1 or 2 oral DMARDs 2 RCTs N = 273	Low RCTs/Good	Consistent	Direct	Imprecise	Improvement in disease activity in 3 versus 2 oral DMARDs	Moderate
Oral DMARD + corticosteroid vs. Oral DMARD	Low RCTs/fair	Inconsistent	Direct	Imprecise	Mixed results for disease activity	Insufficient
2RCTs N = 717	Low RCT/ Fair	Consistent	Indirect	Imprecise	Less radiographic changes with oral DMARD plus prednisone	Low
Biologic DMARDs vs. Biologic DMARDs Mixed treatment comparison (MTC) 30 RCTs N = 6888*	High MTC	Unknown, Single study	Indirect	Imprecise	No significant differences in disease activity (ACR 50) in MTC analyses for abatacept, adalimumab, golimumab,infliximab rituximab and tocilizumab in patients resistant to MTX	Low
Biologic DMARDs vs. Biologic DMARDs: ABA vs. INF 1 RCT N = 431; (MTC) 30 RCTs N = 6888*	Medium RCT/Fair, MTC	Inconsistent	Direct and Indirect	Imprecise	Abatacept improves disease activity over 1 year more than infliximab No differences in ACR 50 in MTC analyses	Low
ADA vs ETN 1 prospective cohort N = 2326	High Cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in disease activity (ACR 70 respons) after 6 months	Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
ADA vs. INF 2 prospective cohorts N = 3033 Mixed treatment comparisons (MTC) 30 RCTs N = 6888*	High Prospective cohorts/Fair, MTC	Consistent	Direct and Indirect	Imprecise	Adalimumab improves disease activity over 1 year more than infliximab No differences in MTC analyses	Low
ANA vs. Biologics (MTC) 30 RCTs N = 6888*	High, MTC	Unknown, single study	Indirect	Imprecise	Less improvement in disease activity (ACR 50) for anakinra compared to etanercept and anakinra. Comparisons with abatacept, golimumab, infliximab, rituximab and tocilizumab did not reach statistical significance.	Low
ETN vs. Biologics (MTC) 30 RCTs N = 6888*	High, MTC	Unknown, single study	Indirect	Imprecise	In MTC analyses, greater improvement in disease activity (ACR 50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab, rituximab and tocilizumab. No significant differences when compared with golimumab.	Low
ETN vs. INF 1 open label trial, 5 prospective cohorts N = 5883 (MTC) 30 RCTs N = 6888*	High Open label trial, prospective cohorts/Fair, MTC	Consistent	Direct and indirect	Imprecise	Faster onset of efficacy for ETN but no differences at 1 year or later MTC analyses (ACR 50: OR 4.17, 95% CI, 2.00-11.17)	Low
RTX vs. anti TNF 1 prospective cohort N = 116	High Prospective cohort/Fair	Unknown, single study	Direct	Precise	RTX reduces DAS 28 at 6 months more than anti-TNF	Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Biologic DMARDs vs. Oral DMARDs 4RCTs/2Cohorts N = 3696	Low RCTs/ Cohorts/Fair	Consistent	Direct	Imprecise	Higher response rates for biologic DMARDs (ADA, ANA, ETN, INF,) vs. oral DMARDs (MTX, LEF) in patients with inadequate response to prior DMARDs	Moderate
Biologic DMARDs vs. Oral DMARDs:	Low RCT/Fair	Unknown, single study	Direct	Precise	Lower response rates for ADA vs. MTX in early RA	Low
ADA vs. MTX 1 RCT N = 799	Low RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic progression for ADA vs. oral DMARD in early RA	Low
ETN vs. Oral DMARDs 2RCTs, 1nonrandomized trial N =1687	Medium RCT, nonrandomized trial/Fair Low, RCTs/Fair	Consistent Consstent	Direct Indirect	Imprecise Imprecise	Greater improvement in disease activity in ETN vs. oral DMARD Less radiographic progression for ETN vs. oral DMARD	Low Low
TCZ vs. MTX 1 RCT N = 127	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Great improvement in disease activity for Tocilizumab than MTX (8mg/wek) at 24wks	Insufficient[a]
Biologic DMARDs + Biologic DMARDs vs. Biologic DMARDs: (1) ETN + AKA vs. ETN (2) ETN + ABA vs. ETN 2 RCTs N = 363	Low 2 RCTs/Fair	Consistent	Direct	Imprecise	No difference in disease activity	Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Any Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs	Low RCTs/Fair, Cohorts/2 good	Consistent	Direct	Imprecise	Improved disease activity with biologic plus MTX	Moderate
5 RCTs,4 cohorts; N = 9804	Low/Fair	Consistent	Indirect	Imprecise	Less radiographic change with biologic plus MTX	Low
2 RCTs N = 1485						
Biologic DMARDs + Oral DMARDs vs.	Low 1RCT/Fair	Unknown, single study	Direct	Precise	Higher ACR50 response for ADA + MTX	Low
Biologic DMARDs: ADA+ MTX vs. ADA 1 RCT N = 799	Low 1RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ADA + MTX	Low
ETN + DMARD vs. ETN 3 RCTs, 3 cohorts	Medium RCTs/Fair, cohorts /2Good,Fair	Consistent	Direct	Imprecise	Trend toward improved disease activity for ETN+ MTX vs. ETN	Low
N = 8529	Low 1RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ETN + MTX vs. ETN	Low
INF + MTX vs. MTX 1 Prospective cohort N = 2711	Medium Prospective cohort/Good	Unknown, single study	Direct	Precise	Improved disease activity for INF + MTX vs. INF	Low
RTX +MTX vs. RTX 1 RCT N = 161	Low RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for RTX + MTX vs. RTX	Low
Any Biologic DMARDs + Oral DMAR vs Oral DMARD	Low RCTs/ 1 Good	Consistent	Direct	Precise	Greater improvement in disease activity for biologic + oral DMARD	High
7 RCTs N = 4482	Low 3RCTs/1Good	Consistent	Indirect	Imprecise	Less radiographic change for biologic + oral DMARD	Moderate

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Biologic DMARDs + Oral DMARDs vs. Oral DMARDs:	Low RCT/Good	Unknown, single study	Direct	Precise	Greater improvement in disease activity (ACR50) for ABA + MTX vs MTX	Low
ABA + MTX vs. MTX 1 RCT N = 509	RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic change for ABA + MTX	Low
ADA + MTX vs. MTX 1 RCT N = 799	Medium 1 RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for ADA + MTX vs. MTX	Low
	Medium RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ADA + MTX	Low
ETN + oral DMARD vs. oral DMRD (MTX or SSZ) 3 RCTs N = 1488	Low 3RCTs/Fair	Consistent	Direct	Imprecise	Improved disease activity for ETN + oral DMARD vs. oral DMARD	Moderate
	Medium 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ETN + MTX vs. MTX	Low
GOL + MTX vs. MTX 1 RCT N = 637	Medium 1RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity (ACR50) for GOL + MTX vs. MTX	Low
INF + MTX vs. MTX 1 RCT N = 1049	Medium 1 RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for INF + MTX vs. MTX	Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs + Oral DMARDs: ANK + MTX vs. ANT + LEF; ETN + DMARD vs. INF + DMARD; Anti-TNF + MTX vs. anti-TNF vs. LEF 3 prospective cohorts N = 4225	Medium Prospective cohorts/Fair	Consistent	Direct	Imprecise	No significant difference between Biologic DMARD + Oral DMARD vs. Biologic DMARD + oral DMARD (ANK, INF, ETN, ADA with MTX or LEF)	Low
Strategies in Early RA: Two oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT N = 155	Low 1RCT/Good	Unknown, single study	Direct	Precise	Improved disease activity in combination group at 28 weeks, but no difference by 52 weeks	Low
	Low 1RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic progression in combination group up to 5 years	Low
Three oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT N = 199	Medium RCT/Fair	Unknown, single study	Direct	Precise	Higher remission in combination group at 2 years but not significant at 5 yrs	Low
	Medium RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic progression in combination group up to 5 years	Low
Three oral DMARDs vs. Biologic plus oral DMARD 1 RCT N = 258	Medium RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for Biologic DMARD plus oral DMARD compared to three oral DMARDs	Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
(1)Sequential monotherapy vs. (2)Step-up combination therapy vs. (3)initial combination therapy with prednisone vs.(4) initial combination therapy with infliximab 1 RCT N = 508	Low 1RCT/Good	Unknown, single study	Direct	Precise	No difference in remission by four years.	Low
	Low 1RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic progression in groups 3 and 4 by four years	Low

ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; MTC, mixed treatment comparison; N, number; RA, rheumatoid arthritis rituximab, RIT; RCT, randomized controlled trial; sulfasalzine, SSZ; TCZ, tocilizumab; TNF, tumor necrosis factor; vs., versus.

[a]The dose of MTX used in this study is below the dose usually considered therapeutic. Thus this study does not provide evidence to determine how tocilizumab compares with MTC as it is generally used in clinical practice.

Strength of evidence for functional capacity and quality of life outcomes (KQ2)

For each comparison, the following tables provide the strength of evidence for functional capacity and quality of life outcomes within a single row, if both outcomes were available. Information related to functional capacity is provided in the upper part of each row; information related to quality of life is provided in the lower part of each row, when available. If only one study provided all of the evidence for a comparison and had consistent results for functional capacity and quality of life outcomes (i.e. finding no difference or one treatment better than the other), we inserted a single set of entries in the row, rather than repeat the same information twice.

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD: Corticosteroid vs. Corticosteroid 1 RCT N =143	Medium RCT/ fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with prednisolone than with budesonide	Low
Leflunomide vs. MTX 2 RCTs N = 1481	Low RCTs/ 2 fair	Inconsistent	Direct	Imprecise*	No clinically significant difference for change in functional capacity.	Low
	Medium RCT/1 fair	Unknown, single study	Direct	Precise	Although some results reached statistically significant differences favoring leflunomide (mean improvement in HAQ-DI: -0.45 vs. -0.26, $P \leq 0.01$), neither study reported a difference reaching the MCID. Greater improvement in quality of life (SF-36 physical summary score, but not mental summary score) with LEF than MTX	Low
Leflunomide vs. Sulfasalazine 1 RCT N = 358	Medium RCT/fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with LEF than SSZ	Low
Sulfasalazine vs. MTX 3 RCTs N = 479	Low RCTs/Fair	Consistent	Direct	Precise	No difference in functional capacity	Moderate

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticoster-oids: SSZ + MTX vs. SSZ or MTX monotherapy 3 RCTs N = 479	Low RCTs/Fair	Consistent	Direct	Precise	No difference in functional capacity	Moderate
Oral DMARD + corticosteroid vs. Oral DMARD	Low RCTs/ Good, Fair	Consistent	Direct	Imprecise	Greater improvement in functional capacity for subjects treated with oral DMARD plus prednisolone	Moderate
2 RCTs N = 717	Low RCT/Good	Unknown, single study	Direct	Imprecise	No difference in quality of life	Low
1 RCT N = 467						
Biologic DMARD vs. Biologic DMARD: ABA vs. INF 1 RCT N = 431	Medium RCT/Fair	Unknown, single study	Direct	Imprecise Imprecise	No difference in functional capacity Statistically significant difference between groups for quality of life (SF-36 PCS but not MCS) that did not reach the MCID.	Low Low
ETN vs. INF 3 prospective cohort studies; N = 2239	Medium Prospective cohorts/3 Fair Medium to High Prospective cohort/1 Fair	Inconsistent Unknown, single study	Direct Direct	Imprecise Precise	Mixed results for functional capacity (2 of 3 studies reported no difference; 1 favored ETN) Reported statistically significantly greater improvement in quality of life with ETN (P = 0.001), but data NR (in Figure only) and CIs appear to overlap in the Figure	Insufficient Insufficient
ADA vs. ETN 1 prospective cohort N = 707	Medium to High Prospective cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in functional capacity No difference in quality of life	Low

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
ADA vs. INF 1 prospective cohort; N = 707	Medium to High Prospective cohort/Fair	Unknown, single study	Direct	Precise	Statistically significant difference between groups favoring ADA for improvement in functional capacity that did not reach the MCID (mean change in HAQ: -0.42 vs. -0.26, *P* < 0.05) Reported statistically significantly greater improvement in quality of life with ADA (*P* = 0.001), but data NR (in Figure only) and CIs appear to overlap in the Figure	Low Insufficient
Biologic DMARD vs. Oral DMARD: ADA vs. MTX 1 RCT N = 799	Medium RCT/Fair	Unknown, single study	Direct	Precise	No difference in functional capacity for MTX naïve subjects with early RA	Low
ETN vs. MTX 2 RCTs N =1318	Low RCTs/1 Good, 1 Fair	Inconsistent	Direct	Imprecise	Mixed results for functional capacity	Insufficient
1 RCT N = 632	Medium RCT/1 Fair	Unknown, single study	Direct	Imprecise	Faster improvement in quality of life with ETN (greater improvement at 12 weeks, but no difference from weeks 16 to 52)	Low
TCZ vs. MTX 1 RCT N = 127	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with TCZ than MTX (8mg/week) for patients with active RA and an inadequate response to MTX	Insufficient[a]
Biologic DMARD + Biologic DMARD vs. Biologic DMARD: ETN + ABA vs. ETN 1 RCTs N = 121	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	No difference functional capacity Greater improvement in physical, but not mental, health-related quality of life	Low

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Any Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs[b]	Low RCTs/1 Good, 1 Fair	Consistent	Direct	Imprecise	Greater improvement in functional capacity with biologic + MTX	Moderate
2 RCTs N = 1495	Low RCT/1 Good	Unknown, single study	Direct	Precise	Greater improvement in quality of life with biologic + MTX	Low
Biologic DMARD + MTX vs. Biologic DMARD in MTX naïve subjects or those not recently on MTX[b]**: ADA+ MTX vs. ADA** 1 RCT N = 799	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with ADA + MTX for MTX-naïve subjects with early RA.	Low
ETN + MTX vs. ETN 1 RCTs, 1 cohort study N = 696	Low RCT/ Good	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with ETN + MTX for subjects with active RA who failed at least 2 oral DMARDs, but were not on MTX for at least 6 months.	Low
Biologic DMARD + Oral DMARD vs. Biologic DMARD in subjects with active RA despite treatment with the same Oral DMARD[b] **: ETN + DMARD vs. ETN** 2 RCTs, 1 cohort study N = 3609	Low RCTs/2 Fair Cohort/Fair	Consistent	Direct	Precise	No difference in functional capacity No difference in quality of life	Moderate

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Any Biologic DMARDs + Oral DMARD vs. Oral DMARD 7 RCTs, 1 cohort study N = 7516	Low RCTs/ 5 Fair, 2 Good Cohort/Fair Low RCTs/3 Fair, 1 Good	Consistent Consistent	Direct Direct	Precise Precise	Greater improvement in functional capacity with biologic + oral DMARD Greater improvement in quality of life with biologic + oral DMARD	High Moderate
Biologic DMARD + Oral DMARD vs. Oral DMARD: ABA + MTX vs. MTX 1 RCT N = 509	Low RCT/Good	Unknown, single study	Direct	Imprecise	Statistically significant differences for improvement in functional capacity and quality of life (SF-36 PCS) with ABA + MTX, but differences did not reach MCIDs	Low
ADA + MTX vs. MTX 1 RCT N = 799	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with ADA + MTX	Low
ETN + oral DMARD vs. oral DMARD (MTX or SSZ) 3 RCTs, 1 cohort study N = 4522	Low RCTs/2 Fair, 1 Good Cohort/Fair Low RCTs/ 1 Fair, 1 Good	Consistent Consistent	Direct Direct	Precise Precise	Greater improvement in functional capacity with ETN + oral DMARD Greater improvement in quality of life with ETN + oral DMARD	Moderate Moderate
GOL + MTX vs. MTX 1 RCT N = 637	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	Greater numerical improvement in functional capacity with GOL 50 + MTX compared with MTX, but difference was not statistically significantly (Median % improvement in HAQ-DI: 43.65 vs. 36.95, *P* = 0.141)	Low
INF + MTX vs. MTX 1 RCT N = 1049	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with INF + MTX	Low

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Biologic DMARD + Oral DMARD vs. Biologic DMARD + Oral DMARD: Anti-TNF + MTX vs. anti-TNF + LEF 1 cohort N = 1218	Medium Cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in functional capacity	Low
Strategies in Early RA: Two oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT N = 155	Low RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity (comparing groups at 28 weeks), but no difference by 56 weeks	Low
Three oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT N = 199	Medium RCT/Fair	Unknown, single study	Direct	Precise	Less work disability in the combination strategy group	Low
Other combination strategies: Sequential monotherapy vs. Step-up combination therapy vs. initial combination therapy with prednisone vs. initial combination therapy with infliximab 1 RCT N = 508	Low RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity in groups 3 and 4 than in groups 1 and 2(statistically significantly better at 3, 6, 9, and 12 months). By two years, improvement was maintained in all groups, but there were no statistically significant differences between groups Similar pattern was found for improvement in physical health-related quality of life	Low

ABA, abatacept; ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; MCID, minimal clinically important difference; MTX, methotrexate; N, number; RCT, randomized controlled trial; TCZ, tocilizumab; vs., versus.

*This was considered imprecise based on the high degree of uncertainty around the effect size, partly due to one of the studies not reporting any quantitative information.

[a]The dose of MTX used in this study is below the dose usually considered therapeutic. Thus, this study does not provide evidence to determine how tocilizumab compares with MTX as it is generally used in clinical practice.

[b]For Biologic DMARD + Oral DMARD vs. Biologic DMARD, we stratified by population because results differed based on the population enrolled

Strength of evidence for Harms, Tolerability, Adverse Effects or Adherence for Corticosteroids (KQ3)

For each comparison, the following tables (Table 3 and 4) provide the strength of evidence for harms, tolerability, adverse effects, and adherence. The table is organized by drug comparisons among corticosteroids, oral DMARDs, and biologic DMARDs. Comparisons are further grouped by subheadings for overall tolerability specific adverse event categories, and adherence. Categories with no evidence are excluded from the table.

Table 3. Strength of evidence for corticosteroids (KQ3)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability : Corticosteroid vs. Corticosteroid 1 RCT N = 143	Medium RCT/ fair	Unknown, single study	Direct	Precise	Similar tolerability with budesonide and prednisolone	Low
Overall Tolerability: Corticosteroid vs. no corticosteroid 1 cohort study N = 224	Medium Retrospective cohort/1 fair	Unknown, single study	Indirect	Imprecise	Dose dependent increased risk of fracture, infection, and GI events	Insufficient
Cardiovascular and Cerebrovascular Events: Corticosteroid vs. no corticosteroid 1 RCT N = 467 4 observational N = 122,817	Medium RCT/fair observational/ 4 fair	Inconsistent	Direct	Imprecise	Mixed results; decreased cardiovascular risk in one study, but increased risk of cardiovascular events and stroke in others	Low
Infection: Corticosteroid vs. no corticosteroid 9 observational N = 268,383	Low observational/ 7 fair, 2 good	Consistent	Indirect	Precise	Corticosteroids increase risk of serious infection, TB, and herpes zoster	Moderate
Other Adverse Events: Corticosteroid vs. no corticosteroid 3 observational N = 161,838	Medium observational/ 3 fair	Unknown, single studies	Indirect	Imprecise	Risk of septic (infectious) arthritis and interstitial lung disease increased with corticosteroids	Low

RCT, randomized controlled trial; TB, tuberculosis; vs., versus.

Table 4. Strength of evidence for oral DMARDs (KQ3)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability: Oral DMARD vs. Oral DMARD 3 RCT N = 1839 1 observational N = 40,594; 3 meta-analysis N = 7,245	Low RCTs/3 fair Retrospective cohort/1 fair meta-analysis/2 good, 1 fair	Inconsistent	Direct	Precise	Similar tolerability and discontinuation rates for HCQ, LEF, MTX, and SSZ, with the exception of one study noting better tolerability for LEF and one study noting better tolerability with MTX	Low
Overall Tolerability: Oral DMARD vs. Oral or Biologic DMARD combination 6 RCTs N = 841 2 observational N = 349 2 meta-analysis N = 1,735	Low RCTs/2 good, 4 fair cohort/2 fair meta-analysis/1 good, 1 fair	Inconsistent	Direct	Precise	Similar withdrawal rates due to adverse events with exception of one study showing increased withdrawal for SSZ + MTX combination; DMARD combination may have more adverse events	Moderate
Overall Tolerability: Oral DMARD + Corticosteroid vs. Oral DMARD 4 RCT N = 1202 1 observational N = 154	Low RCTs/1 good, 3 fair retrospective cohort/1fair	Consistent	Direct	Precise	Similar tolerability and rates of serious adverse events; addition of corticosteroid to oral DMARD lowered withdrawal due to adverse events	Moderate

Table 4. Strength of evidence for oral DMARDs (KQ3)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Cardiovascular and Cerebrovascular Events: **Oral DMARD vs.** **Oral DMARD vs. Oral DMARD combination** 4 observational N = 119,929	Medium observational/ 4 fair	Consistent	Indirect	Imprecise	Oral DMARDs and combinations of oral DMARDS may reduce cardiovascular risk; risk reductions were larger in magnitude with LEF	Low
Hepatic Events: **Oral DMARD vs.** **Oral DMARD vs. Biologic DMARD** 2 observational N = 82,479	Medium observational/ 2 fair	Consistent	Indirect	Imprecise	Similar hepatic event rates for LEF, MTX, and other oral DMARDs	Low
Infection: **Oral DMARD vs.** **Oral DMARD** 6 observational N = 142,522	Medium observational/ 4 fair, 2 good	Inconsistent	Direct	Imprecise	Mixed results; inconsistent differences for infection rates for comparisons of HCQ, LEF, MTX, and SSZ	Low
Oral DMARD vs. no Oral DMARD 6 observational N = 236,151	Medium observational/ 6 fair	Inconsistent	Indirect	Imprecise	Mixed results; increased risk of infection in some studies, while other show decreased infection risk	Insufficient
Interstitial Lung Disease: **Oral DMARD vs.** **Oral DMARD** 2 observational N = 80,332	Medium observational / 2 fair	Inconsistent	Direct	Imprecise	Mixed results; increased risk with LEF in one study, while another study found no differences among HCQ, LEF, MTX, and SSZ	Insufficient
Malignancy: **Oral DMARD vs.** **Oral DMARD vs. corticosteroid** 2 observational N = 16,545	Medium observational / 1 good, 1 fair	Consistent	Direct	Imprecise	No differences in lymphoma for MTX and SSZ, and no difference in non-melanoma skin cancer for LEF and MTX	Low

Table 4. Strength of evidence for oral DMARDs (KQ3)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Other Adverse Events: **Oral DMARD vs. Oral DMARD** 1 RCT N = 795 3 observational N = 80,332 1 review N = 366	Medium RCT/1 good; observational / 3 fair; review 1 fair	Unknown, single studies	Indirect	Imprecise	Oral DMARDs increase risk of septic arthritis; LEF + corticosteroids increase risk of wound healing complications; no association of oral DMARDs with sinus problems; no increased risk of renal damage with combination; insufficient information on fertility, pregnancy, and lactation	Low

DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; RCT, randomized controlled trial; SSZ, sulfasalazine.

* Eligible RCTs included double-blind, randomized, placebo- or MTX-controlled trials lasting at least 12 weeks to determine comparative tolerability, safety, or efficacy. To be included, trials must have reported on at least one of the following: overall withdrawals, withrawals because of lack of efficacy, or withdrawals because of adverse events.

Table 5. Strength of evidence for biologic DMARDs (KQ3)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability: Withdrawals Total: Biologic DMARD vs. Placebo 41 RCT N = 18,029 Studies included in mixed treatment comparison meta-analysis	Medium RCTs*	Inconsistent	Indirect	Precise	Odds ratio of withdrawal overall: 0.51 (0.40-0.65) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol, etanercept, and rituximab had more favorable overall withdrawal profiles than most other biologic DMARDs	Low
Overall Tolerability: Withdrawals due to Lack of Efficacy: Biologic DMARD vs. Placebo 34 RCT N = 13,079 Studies included in mixed treatment comparison meta-analysis	Medium RCTs*	Consistent	Indirect	Precise	Odds ratio of withdrawal due to lack of efficacy: 0.21 (0.17-0.27) Indirect Comparisons: Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab and golimumab had fewer withdrawals than anakinra due to lack of efficacy.	Low
Overall Tolerability: Withdrawals due to Adverse Events: Biologic DMARD vs. Placebo 43 RCT N = 11,243 Studies included in mixed treatment comparison meta-analysis	Medium RCTs*	Consistent	Indirect	Precise	Odds ratio of withdrawal due to adverse events: 1.43 (1.18-1.74) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol and infliximab had more withdrawals due to adverse events than abatacept, etanercept, and rituximab. Etanercept had fewer withdrawals due to adverse events than adalimumab, anakinra, or tocilizumab	Low
Overall and Serious Adverse Events: Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 1 observational N = 2,364	Medium RCT/fair; retrospective cohort/fair	Consistent	Direct	Precise	Serious adverse events were more common with INF than with ABA, ADA, or ETN	Low

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall and Serious Adverse Events: Biologic DMARD vs. No Biologic DMARD 34 RCT N = 18,979 6 observational N = 18,476 6 meta-analysis N = 29,348	Low RCT/31 fair; 3 good; observational /6 fair; meta-analysis/2 good, 4 fair	Inconsistent	Indirect	Precise	Mixed results; similar adverse event profiles among biologic DMARDs, with some studies indicating higher adverse event rates for biologic DMARDs given alone or in combination with oral DMARDs compared with placebo or no treatment.	Low
Cardiovascular and Cerebrovascular Events : Biologic DMARD vs. No Biologic DMARD 1 RCT N = 150 11 observational N = 159,735	High RCT/1 fair; cohort, case-control, or other design/ 8 fair, 3 good	Inconsistent	Indirect	Imprecise	Mixed results; 1 cohort study found protective effect for heart failure, while 3 others found increased risk of heart failure with biologic DMARDs. 1 nested-case control study found no difference in risk for cardiovascular events, while 2 other studies found a protective effect with biologic DMARDs. 1 case-control study found no increased risk of stroke, and 2 cohort studies found no increased risk of MI.	Low
Infections: Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 2 observational N = 24,369	Medium RCT/1 fair; Prospective cohort/2 fair	Inconsistent	Direct	Imprecise	Mixed results; 1 RCT reported more infections with INF than ABA (*P* = NR). 2 prospective cohort studies reported no differences in risk of serious infections comparing among ADA, ETA, and INF.	Low

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Infections: Biologic DMARD vs. No Biologic DMARD 6 RCT N = 5,014; 26 observational N = 391,403 6 meta-analysis	Low RCT/5 fair, 1 good; observational / 20 fair, 6 good meta-analysis/5 fair, 1 good	Inconsistent	Indirect	Precise	Mixed results; most studies found either a trend towards increased infections or statistically significant increase in infections with biologic DMARDs. One meta-analysis reported a pooled odds ratio for serious infections of 2.0 (95% CI, 1.3-3.1) relative to placebo, another reported an increased risk of infection only with INF, and another found an increased risk of infection only with ANK	Moderate
Infusion and Injection Site Reactions: Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 1 observational N = 14,013 1 meta-analysis	Medium RCT/1 fair; prospective cohort/1 fair, meta-analysis/1 good	Consistent	Direct	Precise	Mixed results; 1 RCT reported more infusion reactions with INF than ABA (*P* = NR) and 1 retrospective cohort study reported more infusion reactions INF than with ADA and ETA. 1 meta-analysis found more reactions with ANK than ADA or ETA.	Low
Interstitial Lung Disease: Biologic DMARD vs. Biologic DMARD 1 observational N = 17,598	Medium prospective cohort/1 fair	Unknown	Direct	Imprecise	Current treatment with ETA and INF not associated with hospitalization for interstitial lung disease; Past treatment was for ETA (HR, 1.7; 95% CI, 1.0-3.0; *P* = 0.056) and INF (HR, 2.1; 95% CI, 1.1-3.8; *P* = 0.019)	Low
Malignancies: Biologic DMARD vs. Oral DMARD 6 observational N = 135,498	Medium Cohort/5 fair, 1 good	Inconsistent	Indirect	Imprecise	Mixed results; higher risk of lymphoma with biologic DMARDs in 1 study, but no difference in risk in another study. No increased risk of solid cancers or other malignancies for biologic DMARDs	Low

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Malignancies: Biologic DMARD vs. no Biologic DMARD 6 observational N = 70,377 4 meta-analysis 1 AERS data	Medium Observational/ 6 fair, meta-analysis/3 fair, 1 good	Unknown	Direct	Imprecise	Mixed results; some studies suggest small increased risk of malignancies including: lymphoma, nonmelanotic skin cancer, and melanoma	Low

ABA, abatacept; ADA, adalimumab; ANK, anakinra; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; N, number; RA, rheumatoid arthritis; RCT, randomized controlled trial; vs., versus.

[a]The dose of MTX used in this study is below the dose usually considered therapeutic. Thus this study does not provide evidence to determine how tocilizumab compares with MTC as it is generally used in clinical practice.

Table 6. Strength of evidence for adherence (KQ3)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD 5 RCT N = 1,924	High RCT/5 fair	Inconsistent	Direct	Imprecise	No apparent differences in adherence among oral DMARDs	Low
Biologic DMARD vs. Biologic DMARD 5 observational N = 14,250	High cohort/5 fair	Inconsistent	Direct	Imprecise	Better adherence for INF than ETN in 1 study, similar adherence for INF and ETN in a second study, worse adherence for INF than ETN in a third study	Insufficient
Biologic DMARD vs. Oral DMARD 1 observational N = 6,018	High Cohort/1 fair	Unknown	Direct	Imprecise	Better adherence for LEF, ADA, ETN, and INF monotherapy compared with MTX	Low
Biologic DMARD vs. placebo 2 RCT N = 2,066	Medium RCT/1 good, 1 fair	Consistent	Indirect	Imprecise	No apparent differences in adherence	Insufficient

ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; INF, infliximab; leflunomide, LEF; MTX, methotrexate; N, number; RCT, randomized controlled trial; vs., versus.

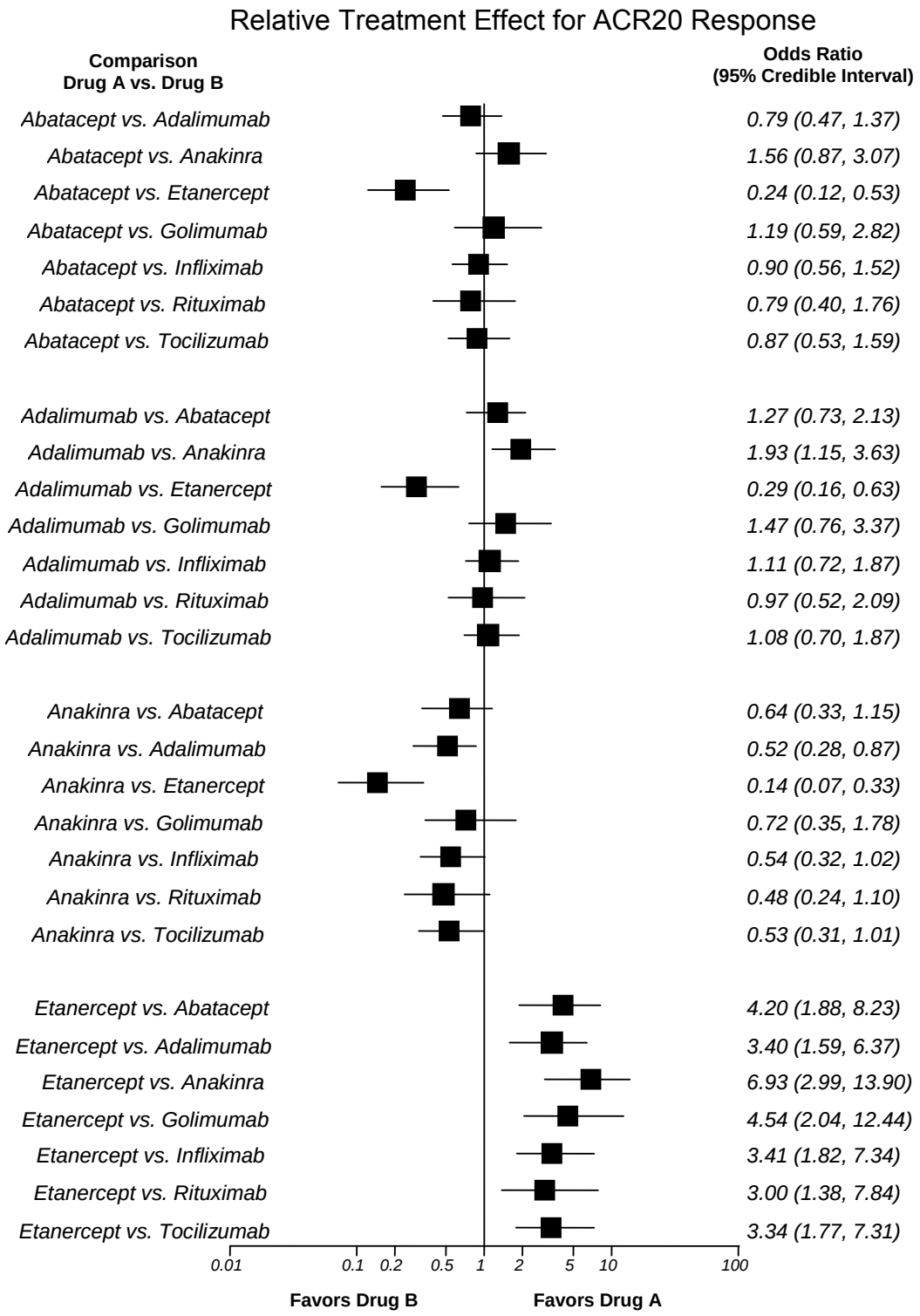
Table 7. Strength of evidence for Benefits and Harms for Selected Populations (KQ4)

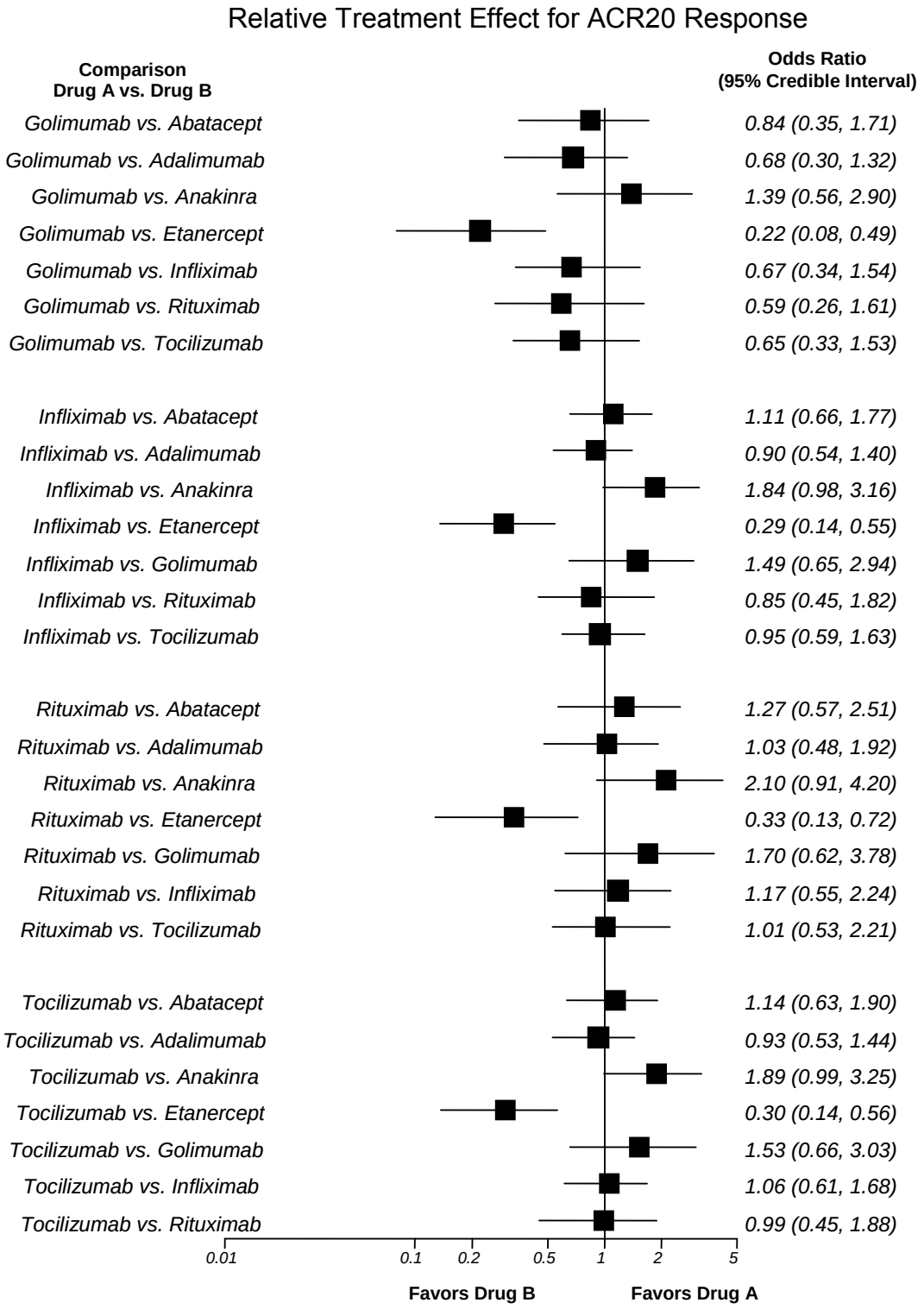
For each comparison, the following table provides the strength of evidence for benefits and harms. The table is organized by subgroup, then by drug comparisons.

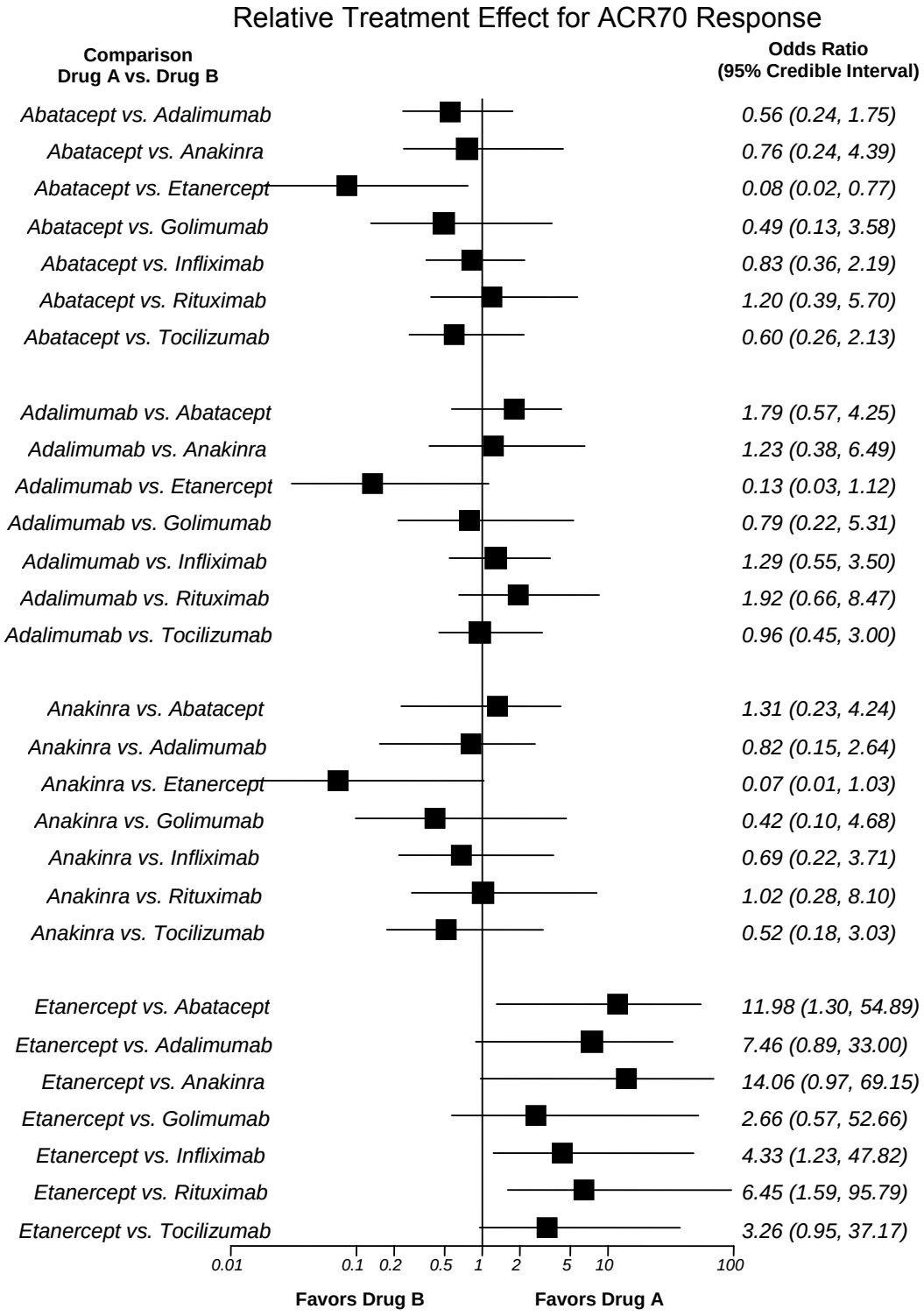
Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Stage of Disease: MTX vs. ETA vs. MTX+ETA 1 Post hoc analysis N = 1,091	Medium to High Posthoc analysis/Fair	Unknown, single study	Direct	Imprecise	Moderate RA groups on MTX monotherapy or combinations had better DAS28 scores than those with severe disease; HAQ scores better in moderate RA groups on monotherapy; severe RA monotherapy groups had greater mean change scores in DAS28 from baseline than moderate RA	Low
Age: MTX in age groups 1 Systematic Review N = 496	Medium Systematic Review/Fair	Unknown, single study	Direct	Imprecise	Inverse relationship between age and risk for major clinical improvement	Low
Age: Various agents in the elderly 1 Case control study N = 946	Medium to High Case control study/Fair	Unknown, single study	Direct	Imprecise	Oral glucocorticoids and cytotoxic immunosuppressive agents (such as LEF) increased risks for cardiovascular events. No differences in cardiovascular events for biologics (ADA, ETN, INF, ANK)	Low
Concomitant Therapies: ANK 1 RCT N = 1,399	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	No differences in adverse events when taking antihypertensive, antidiabetic, or statin pharmacotherapies	Low
Comorbidities: ANK use in those with high risk comorbid conditions 1 RCT N = 951	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	No differences between treatment groups in regard to serious adverse events or overall infectious events	Low
Comorbidities: MTX use in those with renal impairment 1 Systematic Review N = 496	Medium Systematic Review/Fair	Unknown, single study	Direct	Imprecise	Risk of severe toxicity and respiratory toxicity higher in those with greater renal impairment	Low

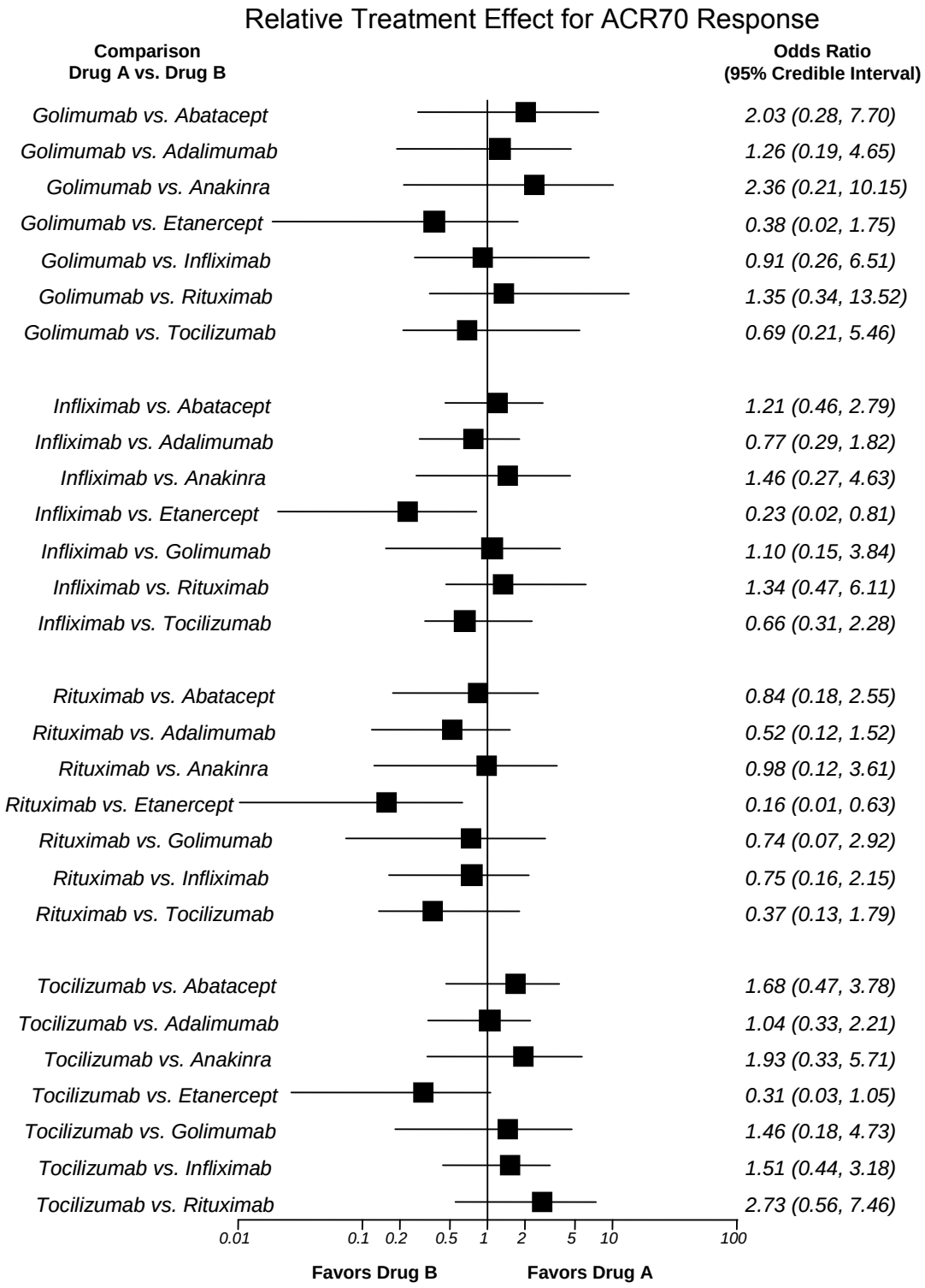
AKA, anakina; CHF, congestive heart failure; DAS, disease activity score; ETA, etanercept; HAQ, health assessment questionnaire, MTX methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Appendix J. Mixed Treatment Comparisons Results: ACR 20 and ACR 70


Relative Treatment Effect for ACR20 Response
Comparison
Drug A vs. Drug B
Odds Ratio
(95% Credible Interval)
Abatacept vs. Adalimumab
0.79 (0.47, 1.37)
Abatacept vs. Anakinra
1.56 (0.87, 3.07)
Abatacept vs. Etanercept
0.24 (0.12, 0.53)
Abatacept vs. Golimumab
1.19 (0.59, 2.82)
Abatacept vs. Infliximab
0.90 (0.56, 1.52)
Abatacept vs. Rituximab
0.79 (0.40, 1.76)
Abatacept vs. Tocilizumab
0.87 (0.53, 1.59)
Adalimumab vs. Abatacept
1.27 (0.73, 2.13)
Adalimumab vs. Anakinra
1.93 (1.15, 3.63)
Adalimumab vs. Etanercept
0.29 (0.16, 0.63)
Adalimumab vs. Golimumab
1.47 (0.76, 3.37)
Adalimumab vs. Infliximab
1.11 (0.72, 1.87)
Adalimumab vs. Rituximab
0.97 (0.52, 2.09)
Adalimumab vs. Tocilizumab
1.08 (0.70, 1.87)
Anakinra vs. Abatacept
0.64 (0.33, 1.15)
Anakinra vs. Adalimumab
0.52 (0.28, 0.87)
Anakinra vs. Etanercept
0.14 (0.07, 0.33)
Anakinra vs. Golimumab
0.72 (0.35, 1.78)
Anakinra vs. Infliximab
0.54 (0.32, 1.02)
Anakinra vs. Rituximab
0.48 (0.24, 1.10)
Anakinra vs. Tocilizumab
0.53 (0.31, 1.01)
Etanercept vs. Abatacept
4.20 (1.88, 8.23)
Etanercept vs. Adalimumab
3.40 (1.59, 6.37)
Etanercept vs. Anakinra
6.93 (2.99, 13.90)
Etanercept vs. Golimumab
4.54 (2.04, 12.44)
Etanercept vs. Infliximab
3.41 (1.82, 7.34)
Etanercept vs. Rituximab
3.00 (1.38, 7.84)
Etanercept vs. Tocilizumab
3.34 (1.77, 7.31)
0.01
0.1
0.2
0.5
1
2
5
10
100
Favors Drug B
Favors Drug A


Relative Treatment Effect for ACR20 Response
Comparison
Drug A vs. Drug B
Odds Ratio
(95% Credible Interval)
Golimumab vs. Abatacept
0.84 (0.35, 1.71)
Golimumab vs. Adalimumab
0.68 (0.30, 1.32)
Golimumab vs. Anakinra
1.39 (0.56, 2.90)
Golimumab vs. Etanercept
0.22 (0.08, 0.49)
Golimumab vs. Infliximab
0.67 (0.34, 1.54)
Golimumab vs. Rituximab
0.59 (0.26, 1.61)
Golimumab vs. Tocilizumab
0.65 (0.33, 1.53)
Infliximab vs. Abatacept
1.11 (0.66, 1.77)
Infliximab vs. Adalimumab
0.90 (0.54, 1.40)
Infliximab vs. Anakinra
1.84 (0.98, 3.16)
Infliximab vs. Etanercept
0.29 (0.14, 0.55)
Infliximab vs. Golimumab
1.49 (0.65, 2.94)
Infliximab vs. Rituximab
0.85 (0.45, 1.82)
Infliximab vs. Tocilizumab
0.95 (0.59, 1.63)
Rituximab vs. Abatacept
1.27 (0.57, 2.51)
Rituximab vs. Adalimumab
1.03 (0.48, 1.92)
Rituximab vs. Anakinra
2.10 (0.91, 4.20)
Rituximab vs. Etanercept
0.33 (0.13, 0.72)
Rituximab vs. Golimumab
1.70 (0.62, 3.78)
Rituximab vs. Infliximab
1.17 (0.55, 2.24)
Rituximab vs. Tocilizumab
1.01 (0.53, 2.21)
Tocilizumab vs. Abatacept
1.14 (0.63, 1.90)
Tocilizumab vs. Adalimumab
0.93 (0.53, 1.44)
Tocilizumab vs. Anakinra
1.89 (0.99, 3.25)
Tocilizumab vs. Etanercept
0.30 (0.14, 0.56)
Tocilizumab vs. Golimumab
1.53 (0.66, 3.03)
Tocilizumab vs. Infliximab
1.06 (0.61, 1.68)
Tocilizumab vs. Rituximab
0.99 (0.45, 1.88)
0.01
0.1
0.2
0.5
1
2
5
Favors Drug B
Favors Drug A


Relative Treatment Effect for ACR70 Response
Comparison
Drug A vs. Drug B
Odds Ratio
(95% Credible Interval)
Abatacept vs. Adalimumab
0.56 (0.24, 1.75)
Abatacept vs. Anakinra
0.76 (0.24, 4.39)
Abatacept vs. Etanercept
0.08 (0.02, 0.77)
Abatacept vs. Golimumab
0.49 (0.13, 3.58)
Abatacept vs. Infliximab
0.83 (0.36, 2.19)
Abatacept vs. Rituximab
1.20 (0.39, 5.70)
Abatacept vs. Tocilizumab
0.60 (0.26, 2.13)
Adalimumab vs. Abatacept
1.79 (0.57, 4.25)
Adalimumab vs. Anakinra
1.23 (0.38, 6.49)
Adalimumab vs. Etanercept
0.13 (0.03, 1.12)
Adalimumab vs. Golimumab
0.79 (0.22, 5.31)
Adalimumab vs. Infliximab
1.29 (0.55, 3.50)
Adalimumab vs. Rituximab
1.92 (0.66, 8.47)
Adalimumab vs. Tocilizumab
0.96 (0.45, 3.00)
Anakinra vs. Abatacept
1.31 (0.23, 4.24)
Anakinra vs. Adalimumab
0.82 (0.15, 2.64)
Anakinra vs. Etanercept
0.07 (0.01, 1.03)
Anakinra vs. Golimumab
0.42 (0.10, 4.68)
Anakinra vs. Infliximab
0.69 (0.22, 3.71)
Anakinra vs. Rituximab
1.02 (0.28, 8.10)
Anakinra vs. Tocilizumab
0.52 (0.18, 3.03)
Etanercept vs. Abatacept
11.98 (1.30, 54.89)
Etanercept vs. Adalimumab
7.46 (0.89, 33.00)
Etanercept vs. Anakinra
14.06 (0.97, 69.15)
Etanercept vs. Golimumab
2.66 (0.57, 52.66)
Etanercept vs. Infliximab
4.33 (1.23, 47.82)
Etanercept vs. Rituximab
6.45 (1.59, 95.79)
Etanercept vs. Tocilizumab
3.26 (0.95, 37.17)
0.01
0.1
0.2
0.5
1
2
5
10
100
Favors Drug B
Favors Drug A


Relative Treatment Effect for ACR70 Response
Comparison
Drug A vs. Drug B
Odds Ratio
(95% Credible Interval)
Golimumab vs. Abatacept
2.03 (0.28, 7.70)
Golimumab vs. Adalimumab
1.26 (0.19, 4.65)
Golimumab vs. Anakinra
2.36 (0.21, 10.15)
Golimumab vs. Etanercept
0.38 (0.02, 1.75)
Golimumab vs. Infliximab
0.91 (0.26, 6.51)
Golimumab vs. Rituximab
1.35 (0.34, 13.52)
Golimumab vs. Tocilizumab
0.69 (0.21, 5.46)
Infliximab vs. Abatacept
1.21 (0.46, 2.79)
Infliximab vs. Adalimumab
0.77 (0.29, 1.82)
Infliximab vs. Anakinra
1.46 (0.27, 4.63)
Infliximab vs. Etanercept
0.23 (0.02, 0.81)
Infliximab vs. Golimumab
1.10 (0.15, 3.84)
Infliximab vs. Rituximab
1.34 (0.47, 6.11)
Infliximab vs. Tocilizumab
0.66 (0.31, 2.28)
Rituximab vs. Abatacept
0.84 (0.18, 2.55)
Rituximab vs. Adalimumab
0.52 (0.12, 1.52)
Rituximab vs. Anakinra
0.98 (0.12, 3.61)
Rituximab vs. Etanercept
0.16 (0.01, 0.63)
Rituximab vs. Golimumab
0.74 (0.07, 2.92)
Rituximab vs. Infliximab
0.75 (0.16, 2.15)
Rituximab vs. Tocilizumab
0.37 (0.13, 1.79)
Tocilizumab vs. Abatacept
1.68 (0.47, 3.78)
Tocilizumab vs. Adalimumab
1.04 (0.33, 2.21)
Tocilizumab vs. Anakinra
1.93 (0.33, 5.71)
Tocilizumab vs. Etanercept
0.31 (0.03, 1.05)
Tocilizumab vs. Golimumab
1.46 (0.18, 4.73)
Tocilizumab vs. Infliximab
1.51 (0.44, 3.18)
Tocilizumab vs. Rituximab
2.73 (0.56, 7.46)
0.01
0.1
0.2
0.5
1
2
5
10
100
Favors Drug B
Favors Drug A

Appendix K. Mixed Treatment Comparisons Sensitivity Analysis Methods

Mixed Treatment Comparison Sensitivity Analysis Methods

A total of 34 studies were identified for potential inclusion in the MTC meta-analysis comparing the efficacy of biologic DMARDs. The potential studies were:

- Three studies evaluating abatacept: AIM 2006,[1]Kremer 2003,[2] and ATTEST 2008,[3]
- Eight studies evaluating adalimumab: ARMADA 2003,[4] STAR 2003,[5] Keystone 2004,[6] van de Putte 2003,[7] van de Putte 2004,[8] Kim 2007,[9] CHANGE 2008,[10] and Chen 2008,[11]
- Three studies evaluating anakinra: Cohen 2002,[12] Cohen 2004,[13] and Bresnihan 1998,[14]
- Three studies evaluating certolizumab pegol: RAPID-1 2008,[15] RAPID-2 2009,[16] and FAST4WARD 2009,[17]
- Four studies evaluating etanercept: Moreland 1999,[18] Weinblatt 1999,[19] Lan 2004,[20] Moreland 1997,[21]
- Two studies evaluating golimumab: GO-FORWARD 2009,[22] and Kay 2008,[23]
- Six studies evaluating infliximab: ATTRACT 1999,[24] Abe 2006,[25] Kavanaugh 2000,[26] START 2006,[27] Zhang 2006,[28] ATTEST 2008,[3] (listed twice as it included comparisons with both abatacept and infliximab)
- Two studies evaluating rituximab: Edwards 2004,[29] and SERENE 2010,[30]
- Four studies evaluating tocilizumab: LITHE 2010,[31] OPTION 2008,[32] TOWARD 2008,[33] and CHARISMA 2006,[34]

We reviewed all 34 studies for sources of heterogeneity and to consider whether to remove any studies that we did not feel were appropriate to include in the analyses. We considered factors such as handling of missing data, early escape design, unexpected high or low treatment response, study duration, and use of monotherapy treatment. Table 1 summarizes our approach for addressing the potential sources of heterogeneity. Based on our findings, we decided to exclude four studies, CHANGE 2008,[10] RAPID-1 2008,[15] RAPID-2 2009,[16] and FAST4WARD 2009,[17] because of heterogeneity due to early escape study design. Other sources of heterogeneity were explored through four sensitivity analyses. The results of these analyses are presented and discussed in Chapter 3.

Table 1. Approach for Addressing Potential Sources of Heterogeneity

Potential Source of Heterogeneity	Description	Approach
Missing Data	**Trials were evaluated for their handling of missing data for ACR50. The majority of trials either used a Last Observation Carried Forward (LOCF) approach for the components that comprise ACR50 or imputed missing ACR data at the endpoint as non-responders (NRI).**	**Use of different imputation approaches could lead to important differences in estimated treatment effects. Studies were reviewed to investigate whether one biologic exclusively used one approach compared to another biologic. Since ACR data for any one biologic included a mix of studies that used both LOCF and NRI, no trials were excluded based on choice of imputation approach alone.**
Early escape design	Trials were evaluated for offering rescue therapy or early escape for patients who failed to achieve a minimal ACR response at a pre-specified time point in the trial.	Several trials offered some sort of rescue therapy at a pre-defined timepoint in the study, but only four trials had a mandatory early escape design and did not report outcomes prior to the early escape. There were a large number of crossovers (from placebo to active treatment) in these studies that might lead to inaccurate calculations of treatment effects. As a result, four studies (CHANGE 2008,[10] RAPID-1 2008,[15] RAPID-2 2009,[16] and FAST4WARD 2009,[17]) were not included in our main MTC analysis. These four studies included all three potentially eligible studies of certolizumab pegol. We added the four studies back in a sensitivity analysis to gauge potential impact on overall results. As a result of this approach, certolizumab pegol is now only included in the sensitivity analysis results in Chapter 3. A fifth study, GO-FORWARD 2009,[22] evaluating goliumumab also had a mandatory early escape design, but ACR50 data were available at time of early escape, so this study was kept in the analysis and the outcomes prior to early escape were used.
Monotherapy	**Some trials included in the MTC did not have patients in the relevant arms on a background dose of Methotrexate.**	In order to separate out the effects that combination therapy may have on the relative treatment effects, monotherapy trials were removed in a sensitivity analysis.
Study Duration	**Studies included in the main MTC meta-analysis had durations of three months or more.**	**In order to evaluate whether study duration influenced our findings, and to compare with other analyses that have used a 6 month cutoff, the ACR50 analysis was rerun with studies of durations of 22 weeks or longer (approximately 6 months).**
High or low ACR response	**Trials were evaluated for unexpected high treatment response or low placebo response.**	Two trials with etanercept, Lan 2004,[20] and Moreland 1997,[21] had both a high ACR50 response and low placebo response. Due to the relatively large differences between treatment and placebo response, we removed these two trials in a sensitivity analysis.

References

1. Kremer JM, Genant HK, Moreland LW, Russell AS, Westhovens R, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis - A randomized trial. Annals of Internal Medicine (USA) 2006:865-76.

2. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003:1907-15.

3 .Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008:1096-103.

4. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45.

5. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003 Dec;30(12):2563-71.

6. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11.

7. van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003 Dec;62(12):1168-77.

8. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004 May;63(5):508-16.

9. Kim HY, Lee SK, Song YW, Yoo DH, Koh EM, Yoo B, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology 2007:9-16.

10. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008:252-62.

11. Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. 2009.

12. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.

13. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8.

14. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998:2196-204.

15. Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008:3319-29.

16. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009:797-804.

17. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11.

18. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.

19. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9.

20. Lan JL, Chou SJ, Chen DY, Chen YH, Hsieh TY, Young M, Jr. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004 Aug;103(8):618-23.

21. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997 Jul 17;337(3):141-7.

22. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009:789-96.

23. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008:964-75.

24. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.

25. Abe T, Takeuchi T, Miyasaka N, Hashimoto H, Kondo H, Ichikawa Y, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006 Jan;33(1):37-44.

26. Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol. 2000 Apr;27(4):841-50.

27. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86.

28. Zhang FC, Hou Y, Huang F, Wu DH, Bao CD, Ni LQ, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China. *APLAR Journal of Rheumatology* 2006:127-30.

29. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81.

30. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis*. 2010/05/22 ed 2010:1629-35.

31. Kremer JL, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The LITHE study. *Arthritis Rheum* 2010.

32. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008:987-97.

33. Genovese MC, McKay JD, Nasonov EL, Mysler EF, Da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis and Rheumatism* 2008:2968-80.

34. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006:2817-29.