Comparative Effectiveness Review

Number 11

Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults

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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 State Children's Health Insurance Program (SCHIP).

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 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 strengths 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 Comparative Effectiveness Reviews 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 e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Contents

Tables

Figures

Appendixes

Executive Summary

Background

Rheumatoid and psoriatic arthritis are among the most disabling forms of arthritis. Rheumatoid arthritis (RA), which affects 1 percent of the U.S. adult population (or upwards of 2 million individuals), 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. Psoriatic arthritis (PsA) affects fewer people than RA (approximately 1 million people in the United States). PsA is associated with the skin disease psoriasis. It has a highly variable presentation, which generally involves pain and inflammation in joints and progressive joint involvement and damage. Like RA, PsA can be disabling.

Treatment of patients with RA and PsA aims to control pain and inflammation and, ultimately, to slow the progression of joint destruction and disability. Available therapies for RA include corticosteroids; synthetic disease-modifying antirheumatic drugs, or DMARDs (hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine); and biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab). Three biologics (adalimumab, etanercept, and infliximab) are also classified as anti-tumor necrosis factor (anti-TNF) drugs.

Experts have not arrived at a consensus about the comparative efficacy of different types of combination therapy—synthetic DMARDs, synthetic DMARDs with corticosteroids, or synthetic DMARDs with biologic DMARDs—all often in combination with the synthetic DMARD methotrexate. In addition, there is debate about how early in the disease process combination therapy should be initiated and whether patients will respond to a biologic agent if they have previously failed a different biologic agent. 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.

Historically, few trials have been conducted on patients with PsA, with only minimal research conducted before biologic agents were introduced; management options tended to be adapted from RA trial evidence. All the same issues noted for RA of short- and long-term risks and safety, as well as performance in population subgroups, have been only minimally addressed to date for PsA.

This report from the RTI-University of North Carolina Evidence-based Practice Center summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, synthetic DMARDs, and biologic DMARDs in the treatment of patients with either RA or PsA. The key questions (KQs) were developed through a public process in conjunction with the Scientific Resource Center at the Oregon Health and Science University. The KQs are as follows:

KQ 1. 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?

KQ 2. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?

KQ 3. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?

KQ 4. 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?

We identified 2,153 citations from our searches. Working from 619 articles retrieved for full review, we included 156 published articles reporting on 103 studies: 22 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 13 placebo-controlled trials, 10 meta-analyses or systematic reviews, 55 observational studies, and 2 poor-quality pooled data analyses on subgroups. Of the 103 included studies, 51 (50 percent) were supported by pharmaceutical companies, 21 (20 percent) were funded by governmental or independent funds, and 11 (11 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 20 studies (19 percent). One-quarter of the individual trials were rated good quality; most were found to be fair quality.

Conclusions

We present our major findings in this section by type of drug comparison and important outcomes (both benefits and harms). Summary Table A summarizes the information for RA. We limit our findings in the Executive Summary to RA because no comparative evidence exists on PsA for any drugs. We also have not presented findings from subpopulation analyses for RA because the strength of evidence for age, sex, and comorbidities is very weak.

Summary Table A. Summary of findings: rheumatoid arthritis

Key comparisons	Efficacy and strength of evidence	Harms and strength of evidence
	Monotherapy vs. Monotherapy	
Synthetic DMARDs		
Leflunomide vs. methotrexate	No differences in ACR 20 or radiographic responses: *Moderate* Greater improvement in functional status (HAQ-DI) and health-related quality of life (SF-36 physical component) for leflunomide: *Moderate* No differences in work productivity outcomes: *Moderate*	No differences in tolerability and discontinuation rates: *Moderate*
Leflunomide vs. sulfasalazine	Higher ACR 20 and ACR 50 response rates and greater improvement in functional capacity for leflunomide: *Low* No differences in radiographic changes: *Low*	No differences in tolerability and discontinuation rates: *Moderate*
Sulfasalazine vs. methotrexate	No differences in ACR 20 response, disease activity scores, functional capacity, and radiographic changes: *Moderate*	No differences in tolerability; more patients on methotrexate than sulfasalazine long term: *Moderate*
Biologic DMARDs		
Biologic DMARDs vs. biologic DMARDs		
Anti-TNF drugs (adalimumab, etanercept, infliximab) vs. anti-TNF drugs	No differences in ACR 20/50 response rates among anti-TNF drugs: *Moderate*	Insufficient evidence on the comparative risk of harms: *Low*
Biologic DMARDs vs. biologic DMARDs	Indirect comparisons consistently showed anakinra to have lower ACR 20 and ACR 50 response rates than anti-TNF drugs as a class: *Moderate*	Risk for injection site reactions apparently higher for anakinra than for adalimumab and etanercept: *Moderate*
Biologic DMARD vs. synthetic DMARD		
Anti-TNF drugs vs. methotrexate	In patients with early RA, no differences in clinical response, functional capacity, and quality of life between adalimumab or etanercept and methotrexate; better radiographic outcomes in patients on biologic DMARDs than in patients on synthetic DMARDs: *Moderate* In patients who had failed initial RA treatment, greater functional independence and remission for anti-TNF drugs as a class than synthetic DMARDs as a class: *Moderate*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence on differences in the risk for rare but severe adverse events: *Low*

Summary Table A. Summary of findings: rheumatoid arthritis (continued)

Key comparisons	Efficacy and strength of evidence	Harms and strength of evidence
Combination Therapy vs. Monotherapy		
Synthetic DMARDs vs. Synthetic DMARDs		
Sulfasalazine plus methotrexate vs. monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes: *Moderate* No differences in functional capacity in all patients: *Moderate* In patients with early RA, significantly better disease activity scores with combination therapy: *Low*	No differences in withdrawal rates attributable to adverse events: *Moderate*
1, 2, or 3 synthetic DMARDs (methotrexate, sulfasalazine, hydroxychloroquine) plus prednisone vs. 1 synthetic DMARD	In patients on 1, 2, or 3 synthetic DMARDs plus prednisone, improved ACR 50 response rates, disease activity scores, and less radiographic progression: *Moderate* In patients with early RA, significantly lower radiographic progression and fewer eroded joints: *Low* Better outcomes with the combination strategies for functional capacity: *Low* for each individual comparison, *Moderate* for combination therapy vs. monotherapy	No differences in discontinuation rates: *Moderate*
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional treatment effects from combination of etanercept plus anakinra compared with etanercept monotherapy: *Low*	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy: *Moderate*
Biologic DMARD plus methotrexate vs. biologic DMARD	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARD plus methotrexate than from monotherapy with biologics: *Moderate* In methotrexate-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group: *Low*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence on differences in the risk for rare but severe adverse events: *Low*
Biologic DMARDs plus synthetic DMARD other than methotrexate vs. biologic DMARD	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: *Low*

Summary Table A. Summary of findings: rheumatoid arthritis (continued)

Key comparisons	Efficacy and strength of evidence	Harms and strength of evidence
Biologic DMARD plus methotrexate vs. methotrexate	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and methotrexate than from methotrexate monotherapy: *Moderate*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence to make conclusion on differences in the risk for rare but severe adverse events: *Low*
Combination Therapy vs. Combination Therapy or Other Treatment Strategy		
Sulfasalazine plus methotrexate plus hydroxychloroquine vs. 2 drugs	In patients previously on monotherapy, higher ACR 20/50 response rates for triple therapy than for 2-drug combinations: *Moderate* In patients with no previous use of study drugs, higher ACR 20/50 response rates in the triple combination therapy group than in methotrexate plus sulfasalazine or methotrexate plus hydroxychloroquine: *Low*	No differences in withdrawal rates attributable to adverse events: *Moderate*
Sequential monotherapy starting with methotrexate 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 from initial combination therapy of methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus methotrexate than from sequential DMARD monotherapy or step-up combination therapy: *Low*	No differences in serious adverse events between groups: *Low*

Abbreviations: ACR=American College of Rheumatology; DMARD=disease-modifying antirheumatic drug; HAQ-DI= Health Assessment Questionnaire Disability Index; RA=rheumatoid arthritis; SF-36=Medical Outcomes Study Short Form 36; TNF=tumor necrosis factor.

Monotherapy vs. Monotherapy

Synthetic DMARDs. The data show no differences in radiographic outcomes over 2 years for leflunomide and methotrexate. One systematic review that included a meta-analysis of two RCTs suggested that higher proportions of patients on methotrexate than on leflunomide met the American College of Rheumatology (ACR) 20-percent improvement criteria at 1 year (odds ratio [OR], 1.43; 95-percent confidence interval [CI], 1.15-1.77, $P = 0.001$), but statistical significance was lost at 2 years (OR, 1.28; 95-percent CI, 0.98-1.67). However, patients on methotrexate had less improvement in functional status and health-related quality of life than patients taking leflunomide (Short Form [SF]-36 physical component: 4.6 vs. 7.6, $P < 0.01$; Health Assessment Questionnaire Disability Index [HAQ-DI]: -0.26 vs. -0.45, $P < 0.01$). Existing head-to-head evidence (three RCTs) supports no differences in efficacy between methotrexate and sulfasalazine by ACR 20, disease activity score (DAS), and functional capacity.

For leflunomide vs. sulfasalazine, data are limited to one RCT with 2-year followup that reported that leflunomide resulted in a higher proportion of patients reaching ACR 20-percent improvement and ACR 50-percent improvement criteria and greater improvement in functional

capacity (ACR 20: 82 percent vs. 60 percent, $P < 0.01$; ACR 50: 52 percent vs. 25 percent, $P < 0.01$; HAQ: -0.50 vs. -0.29, $P < 0.03$). Radiographic changes were not different for those treated with leflunomide and those treated with sulfasalazine.

No differences in tolerability were reported for leflunomide, methotrexate, and sulfasalazine in three efficacy trials and one meta-analysis of data up to 3 years. Similarly, discontinuation rates because of adverse events did not differ among leflunomide, methotrexate, or sulfasalazine. In the meta-analysis, 2-year withdrawals attributed to adverse events were not significantly different for leflunomide vs. methotrexate (relative risk [RR], 1.19; 95-percent CI, 0.89-1.6) or sulfasalazine (RR, 0.77; 95-percent CI, 0.45-1.33). However, in one meta-analysis of 71 RCTs and 88 observational studies, at 5 years the proportion of patients who were continuing to take methotrexate was higher than the proportion continuing to take sulfasalazine (36 percent vs. 22 percent, P = not reported [NR]).

Biologic DMARDs. We did not find any head-to-head RCTs that compared one biologic DMARD with another. No evidence exists on abatacept and rituximab compared with other biologic DMARDs.

Existing direct head-to-head evidence is limited to one nonrandomized, open-label effectiveness trial and two prospective cohort studies comparing etanercept with infliximab. In all three studies, patients on etanercept had a faster onset of action than patients on infliximab, although no differences in effectiveness were apparent between the two agents. The above findings are generally consistent with results from three adjusted indirect comparison models (adalimumab, etanercept, and infliximab) that reported no differences in efficacy among anti-TNF drugs.

Adjusted indirect comparisons also indicated that anakinra has lower efficacy than anti-TNF drugs. Although not all results reached statistical significance, anakinra had consistently lower response rates on ACR 20 (RR, 1.64; 95-percent CI, 1.04-2.56) and ACR 50 (RR, 1.89; 95-percent CI, 0.98-3.57) than anti-TNF drugs as a class.

Biologic DMARD vs. biologic DMARD. Biologic DMARDs were generally well tolerated in efficacy studies. Long-term extension studies of anti-TNF drugs indicated that the rate of adverse events does not increase over time. One nonrandomized, open-label trial directly compared the tolerability of two biologic DMARDs. This 12-month study did not report any differences in harms between etanercept and infliximab.

A good-quality systematic review reported that the mean crude incidence rates of injection site reactions in RCTs and observational studies were substantially higher in patients using anakinra (67.2 percent; 95-percent CI, 38.7-95.7) than in patients on adalimumab (17.5 percent; 95-percent CI, 7.1-27.9) or etanercept (22.4 percent; 95-percent CI, 8.5-36.3).

Otherwise, evidence from placebo-controlled trials and observational studies is insufficient to draw conclusions about the comparative tolerability and safety of biologic DMARDs. One prospective cohort study suggested that adalimumab, etanercept, and infliximab did not differ in the risk for serious infections. Three fair-quality observational studies, however, indicated that infliximab might have a higher risk of granulomatous infections than etanercept.

The evidence on comparative discontinuation rates is limited to three observational studies. In one large, retrospective cohort study, anakinra led to statistically significantly higher overall discontinuation rates (41 percent) than either etanercept (31 percent; $P = 0.004$) or infliximab (35 percent; $P = 0.03$).

Biologic DMARD vs. synthetic DMARD. Three RCTs compared the efficacy of two anti-TNF drugs (adalimumab or etanercept) with that of methotrexate. Two trials enrolled exclusively

methotrexate-naive patients with early RA; the third trial included a mixed population of methotrexate-naive patients and patients who had failed synthetic DMARDs other than methotrexate. In all three studies, results did not indicate substantial differences in clinical response, functional capacity, or quality of life between either adalimumab or etanercept and methotrexate. In the adalimumab study, 25 percent of patients achieved remission in each treatment group. Radiographic outcomes, however, were statistically significantly better in patients treated with biologic DMARDs than in those tapered with methotrexate. For example, in the ERA (Early Rheumatoid Arthritis) study, 72 percent of patients on etanercept and 60 percent of patients on methotrexate had no radiographic progression of the disease ($P = 0.007$). What implications such intermediate outcomes have on the long-term progression of the disease remains unclear. No studies comparing biologics with synthetic DMARDs other than methotrexate were available.

One prospective cohort study enrolled a population who failed initial RA treatment. After 12 months, patients on biologic DMARDs as a class had almost four times higher odds of achieving functional independence (OR, 3.88; 95-percent CI, 1.71-8.79) and almost two times higher odds of achieving remission (OR, 1.95; 95-percent CI, 1.20-3.19) than patients on synthetic DMARDs. In both groups, only half of patients who were in remission at 6 months achieved a sustained remission until 12 months.

In general, adverse events did not differ significantly between biologic and synthetic DMARDs. Studies were too small to assess reliably differences in rare but severe adverse events.

Combination Therapy vs. Monotherapy

Synthetic DMARDs. The data are limited by the number of supporting studies for each drug combination.

Sulfasalzine-methotrexate vs. monotherapy. In two trials lasting 4 years, ACR response rates and radiographic changes did not differ in patients with early RA. Findings of these studies are consistent and do not support a difference in functional capacity between combination therapy and monotherapy. One study in patients with early RA, however, reported improved DAS scores at 18 months with combination therapy (DAS score -0.67 combination, -0.30 sulfasalazine, -0.26 methotrexate; $P = 0.023$ for combination vs. methotrexate).

Synthetic DMARD-corticosteroid vs. monotherapy. Three RCTs examined combination strategies of one or more synthetic DMARDs with corticosteroids against synthetic DMARD monotherapy. These trials suggest better outcomes with the combination strategies, although each study used different outcome measures, including ACR, DAS, and radiographic scores. One RCT comparing a combination involving a synthetic DMARD (either methotrexate or sulfasalazine) and a corticosteroid with a synthetic DMARD monotherapy had a higher remission rate in the combination group than in the monotherapy group (remission defined by DAS 28 < 2.6: 55.5 percent vs. 43.8 percent; $P = 0.0005$). Patients with early RA had significantly lower radiographic progression and fewer eroded joints with the combination treatment than with monotherapy.

One open-label RCT compared synthetic DMARD use with and without prednisolone. It was found that the prednisolone group had a greater improvement in functional capacity. The investigators did not compare the results statistically, and the clinical relevance of the results is uncertain.

Combination studies involving two synthetic DMARDs, including sulfasalazine and methotrexate, vs. one DMARD showed no differences in withdrawal rates because of adverse

events. Combination studies including prednisone with one or more DMARDs also had no differences in discontinuation rates between groups.

Biologic DMARDs. The data are limited by the number of supporting studies for each drug combination.

Biologic combination vs. monotherapy. One RCT did not detect any synergistic effects of a combination treatment of etanercept and anakinra compared with etanercept monotherapy. The incidence of serious adverse events, however, was substantially higher with the combination treatment (14.8 percent vs. 2.5 percent; P = NR).

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. The evidence, however, is limited to combinations of anakinra plus etanercept and abatacept plus anakinra, adalimumab, etanercept, or infliximab.

Biologic combination with methotrexate vs. biologic DMARDs alone. Most of the other studies compared combinations of biologic DMARDs and methotrexate with monotherapies of these drugs. Overall, combination therapy of biologic DMARDs and methotrexate achieved better clinical response rates than monotherapies. For example, four RCTs and two prospective cohort studies suggested that a combination of adalimumab, etanercept, infliximab, or rituximab with methotrexate leads to statistically significantly greater improvements than monotherapy of biologic DMARDs. In one trial, significantly more patients on the combination therapy (adalimumab plus methotrexate) than patients on adalimumab monotherapy (59 percent vs. 37 percent; $P < 0.001$) exhibited responses on the ACR 50 after 2 years of treatment. Likewise, more patients on etanercept plus methotrexate than on etanercept monotherapy achieved remission (DAS < 1.6; 35 percent vs. 16 percent; $P < 0.0001$) during the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study. Both RCTs suggested that a combination of either adalimumab or etanercept with methotrexate led to statistically significantly greater improvements in functional capacity or health-related quality of life than monotherapy with a biologic DMARD. In methotrexate-naive patients with early, aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression were seen in the combination therapy group.

Biologic DMARD combinations with other synthetics vs. biologic DMARDs. Only one study used sulfasalazine as a synthetic DMARD in combination with a biologic DMARD. A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy. No differences in adverse events were found between combinations of biologic and synthetic DMARDs and biologic DMARD monotherapy.

Biologic DMARD combinations with methotrexate vs. methotrexate alone. Two trials found that a combination of either adalimumab plus methotrexate or infliximab plus methotrexate in patients with early, aggressive RA who were methotrexate naive led to better clinical and radiographic outcomes than methotrexate monotherapy. After 2 years of treatment, 59 percent of patients on adalimumab plus methotrexate met ACR 50 criteria, compared with 43 percent of patients on methotrexate monotherapy ($P < 0.001$). Likewise, significantly more patients in the infliximab plus methotrexate combination groups than in the methotrexate group exhibited remission rates in the ASPIRE (Active controlled Study of Patients receiving Infliximab for Rheumatoid arthritis of Early onset) retrial. Both RCTs and one prospective cohort study found greater improvements in functional capacity and quality of life with combination therapies (adalimumab, infliximab, or etanercept plus methotrexate) than with methotrexate alone.

In general, no statistically significant differences in adverse events existed between combinations of biologic and synthetic DMARDs and synthetic DMARD monotherapy. Studies, however, were too small to assess reliably differences in rare but severe adverse events. An exception was a study with high-dose infliximab plus methotrexate therapy, which led to a statistically significantly higher rate of serious infections than methotrexate monotherapy.

Combination Therapy Comparisons or Other Treatment Strategies

Evidence is insufficient to draw firm conclusions about whether one combination strategy is better than any other. Two RCTs reported more improved response rates at 2 years for the combination of sulfasalazine, methotrexate, and hydroxychloroquine than for one or two drugs in patients who had previously been on monotherapy. ACR 20 response rates were 78 percent for triple therapy, as contrasted with 60 percent for methotrexate and hydroxychloroquine ($P = 0.05$) and 49 percent for methotrexate and sulfasalazine ($P = 0.002$). Groups did not differ in withdrawal rates.

In patients with early RA, data are limited to one effectiveness trial. It reported less radiographic progression over 12 months with either (1) methotrexate, sulfasalazine, and high-dose tapered prednisone or (2) methotrexate and infliximab vs. (3) sequential DMARD therapy or (4) step-up combination therapy (median modified Sharp/van der Heijde score change: 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). Patients treated with initial combination therapy of methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab and methotrexate had statistically significantly better functional ability (Dutch version of the HAQ) at 12 months than those treated with sequential DMARD therapy starting with methotrexate. The magnitude of difference was small, however. The groups did not differ in serious adverse events.

Remaining Issues

Most of the trials were conducted in RA patients; data are limited for PsA patients. Common problems for both RA and PsA include the lack of effectiveness information—i.e., 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 about the performance of these drugs in subgroups of patients defined by health status, sociodemographics, or other variables is also needed.

To address problems with current literature, future studies should use designs of longer duration and followup, enroll patients representing key subgroups (or report on them when they are enrolled), and ensure that quality of life (or other patient-oriented outcomes) is measured in addition to clinician-oriented measures, such as joint erosion.

The gaps in information for specific RA therapies are substantial. With respect to comparative efficacy, future studies should focus on head-to-head trials assessing combination therapies involving synthetic DMARDs in comparison with those involving biologic DMARDs. Adequately powered, long-term RCTs must also examine different treatment strategies with and without corticosteroids, synthetic DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in patients with RA. Additionally, no head-to-head RCTs have compared one biologic DMARD with another; this is a significant hole in the literature that future research should fill. However, this is less likely to occur because of

the expense of biologic DMARDs. Investigators may find large registries helpful in identifying the same kinds of patients treated with different agents.

With respect to study design, 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 beneficial.

Minimal research was conducted on PsA before biologic DMARDs were introduced, so the gaps in this knowledge base are larger than those in RA. Going forward, head-to-head comparisons of any of the drug therapies to treat PsA are needed, probably with particular attention to biologic DMARDs. Issues similar to those for RA with respect to long-term outcomes and early initiation are also important for PsA.

Addendum

We updated our literature search in September 2007 and identified 243 new citations. We obtained the full text for 22 references and included 16 published articles on 10 new studies. We report relevant new data below but, overall, these studies do not change the conclusions of this report.

Rheumatoid Arthritis

Biologic comparisons. We found eight new studies on biologics that met our eligibility criteria;[1-8] five of these were observational studies assessing the safety of biologics.[4-8] Overall, these studies did not change our conclusions or any ratings of the strength of the evidence. Nevertheless, some studies added notable new evidence.

For example, one RCT compared the efficacy of rituximab monotherapy with a combination treatment of rituximab and methotrexate in patients with active RA despite ongoing methotrexate treatment.[3] To date, this is the first study comparing these treatment strategies. Results are similar to trials comparing adalimumab or etanercept monotherapies with combinations of these biologics and methotrexate. During the entire followup and after 2 years, the combination group experienced substantially greater response rates than the rituximab monotherapy group (ACR 50 at 2 years: 20 percent vs. 8 percent).

A prospective, population-based cohort study from Sweden, enrolling more than 1,100 patients, reported statistically significantly higher adherence rates for patients on etanercept and methotrexate than for those on infliximab and methotrexate.[1] After 5 years of treatment, 65 percent of patients on etanercept and 36 percent of patients on infliximab still adhered to therapy. Infliximab led to statistically significantly more withdrawals owing to adverse events than etanercept (data not reported; $P < 0.001$). To date, this study is the longest comparative assessment of two biologic treatments for RA.

Combination strategy comparisons. We found two articles[9,10] containing 2-year followup data for a previously reported RCT comparing complex combination strategies.[11] The 2-year data reinforce our conclusions that patients on initial combination therapy of methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with methotrexate and infliximab had less radiographic progression than sequential monotherapy and step-up combination therapy (median increase in total Sharp/van der Heijde score: 1.0, 1.0, 2.0, and 2.0, respectively). However, all arms had similar disease activity by disease activity score (DAS) values at 2 years regardless of which initial therapy they had received.

Psoriatic Arthritis

We identified six new articles published on studies concerning the treatment of PsA.[12-17] Two were new, formerly unreported studies;[12,13] four of the articles contained additional outcomes on studies previously reported.[14-17] Overall, these studies did not change our conclusions or any ratings of the strength of the evidence.

However, one of the studies added new evidence by comparing biologics with methotrexate, the conventional treatment of PsA.[12] In this prospectively planned observational study in Norway, 6 months of treatment with biologics and biologics plus methotrexate vs. methotrexate alone were compared in 1,022 patients. The group treated with biologics had poorer baseline characteristics than the methotrexate group; once statistical adjustments were made, the differences at 6 months were significantly in favor of the biologics group for the DAS-28 ($P < 0.001$) and other measures.

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Introduction

Background

Arthritis and other rheumatic conditions constitute the leading cause of disability among U.S. adults,[1] affecting more than 7 million persons. 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 RA and PsA—*the focus of this review*—the burden of disease is evidenced by decreased quality of life,[2-4] decreased employment rates,[5] and increased direct and indirect costs.[6-9] 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,[6] and most studies have reported indirect costs to be roughly twofold greater than direct costs.[10] Costs associated with PsA are not as well studied, although they are believed to be just slightly lower than those in RA.[8] Indirect costs are believed to increase over time; as the disease progresses so does the loss of function and inability to work.

Clinically, RA and PsA may present similarly. The most notable distinctions are the presence of serum rheumatoid factor in RA and accompanying skin presentations in PsA. Still, the two inflammatory conditions are unique, and they warrant independent descriptions.

Causes and Diagnosis

Rheumatoid Arthritis (RA)

RA is an autoimmune disease that affects 2.1 million adults in the United States. 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 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 has been described in certain populations.[11,12] Studies have shown the importance of T cells, B cells, and cytokines in the pathogenesis of RA.[13,14] 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.[14]

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.[15] Table 1 presents the diagnostic criteria for RA proposed by the American College of Rheumatology (ACR).[16] Patients are said to have RA if they meet four of the seven criteria in the table.[16]

Table 1. ACR criteria for the diagnosis of rheumatoid arthritis

Criteria
1. Morning stiffness lasting greater than 1 hour
2. Arthritis in 3 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.

Psoriatic Arthritis (PsA)

Psoriasis, a skin disease, affects 2.2 percent of U.S. adults; approximately 10 percent to 30 percent of patients with psoriasis develop PsA. Approximately 55,000 adults in the United States have PsA. PsA can develop at any age but most often appears between 30 and 50 years old. Unlike RA, PsA appears to affect men slightly more often than women.

The presentation is highly variable. In most cases, the psoriasis predates the onset of the PsA, although arthritis has been described as the initial manifestation of psoriatic disease. Common presentations include a symmetric small-joint polyarthritis (RA-like) and an axial arthritis with involvement of the sacroiliac joints, axial skeleton (spine), and large joints. In all cases, symptoms include pain and stiffness in the affected joint, enthesial areas (where tendons insert into bone) with joint line tenderness, swelling, and often loss of range of motion. Pitting of the fingernails often correlates with the extent and severity of the disease. Dactylitis—swelling of a whole digit—is a characteristic clinical finding, and inflammatory eye disease (iritis, uveitis) may occur. More than one-third of patients with PsA will develop dactylitis and enthesopathy (a disease process at the site where muscle tendons or ligaments insert into bones or joints).

The etiology and pathogenesis of psoriasis and PsA are not completely understood, but genetic, immunologic, and environmental factors are all likely to play a role.[17] Several classification systems have been proposed for the diagnosis of PsA,[18] but which one best represents true PsA remains unclear. Table 2 presents the CASPAR (ClASsification of Psoriatic ARthritis) as an example of one classification.[19]

Table 2. CASPAR criteria for the diagnosis of psoriatic arthritis

Inflammatory articular disease (joint, spine, or enthesial areas) with ≥ 3 points from the following	
1.	Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
2.	Typical psoriatic nail dystrophy including onycholysis, pitting, or hyperkeratosis
3.	Negative test result for the presence of rheumatoid factor
4.	Current dactylitis or history of dactylitis
5.	Radiographic evidence of juxtaarticular new bone formation

Source: Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.[19]

Treatment of Rheumatoid Arthritis and Psoriatic Arthritis

Overview

Treatment of patients with RA or PsA is aimed primarily at controlling pain and inflammation and, ultimately, at slowing or arresting the progression of joint destruction.

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 corticosteroids include betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone. The drugs differ in their relative potency and available modes of administration. Betamethasone and dexamethasone are the most potent of the corticosteroids, whereas cortisone and hydrocortisone are the least potent. Frequently used agents for oral administration are prednisone and methylprednisolone. Methylprednisolone, betamethasone, and triamcinolone are used for intra-articular therapy.

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. When used in PsA, corticosteroids are most often given as a joint injection rather than orally.

Synthetic disease-modifying antirheumatic drugs (DMARDs). Synthetic 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 synthetic 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 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.

Synthetic 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 synthetic DMARDs covered in this review can be given orally, although methotrexate can also be injected.

Biologic DMARDs. Biologic DMARDs—commonly referred to as biological response modifiers or simply biologics—are a relatively new category of DMARDs that differ from synthetic 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 five additional agents approved since that time: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), and rituximab (2006). Of the six agents, all are currently FDA approved for treating RA, but only adalimumab, etanercept, and infliximab are approved for treating PsA.

The biologic DMARDs work by selectively blocking mechanisms involved in the inflammatory and immune response. Adalimumab, etanercept, 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 and infliximab 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. Infliximab is a chimeric (i.e., made from human and mouse proteins) monoclonal antibody that binds specifically to human TNF. 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.

IL-1, another naturally occurring cytokine, has both immune and proinflammatory actions. Anakinra 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 in effect 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.

Tables 3 and 4 provide detailed information on agents used in the treatment of RA and PsA that we have included in this review. Table 3 documents names, manufacturers, and available dosage forms. Table 4 shows routes of administration, labeled uses, and usual (recommended) adult doses and frequency for RA and PsA.

Table 3. Pharmaceutical treatments for rheumatoid arthritis and psoriatic arthritis

Class	Generic Name	U.S. Trade Name(s)*	Manufacturer	How Supplied
Corticosteroids				
	Betamethasone	Celestone®, Soluspan®	Multiple	Injectable—3 mg/ml and 6 mg/ml Syrup—0.6 mg/5 ml Topical—cream, lotion, ointment (multiple strengths)
	Budesonide	Entocort® EC	AstraZeneca	Tabs—3 mg
	Cortisone	Cortone®	Multiple	Tabs—5 and 25 mg
	Dexamethasone	Decadron®, Maxidex®	Multiple	Injectable—4 and 10 mg/ml Solution—0.5 mg/5 ml, 1 mg/ml Tabs—0.5, 1.5, 2, and 4 mg
	Hydrocortisone	Cortef®, Solu-Cortef®	Multiple	Injectable—100, 250, 500, and 1,000 mg vials Tabs—5, 10, and 20 mg Topical—cream, foam, gel, lotion, ointment, solution (multiple strengths)
	Methylprednisolone	Medrol®, Depo-Medrol®, Solu-Medrol®	Multiple	Injectable (acetate)—20, 40, and 80 mg/ml Injectable (sodium succinate)—40, 125, and 500 mg, 1 and 2 g vials Tabs—2, 4, 8, 16, and 32 mg
	Prednisone	Deltasone®, Sterapred®, LiquiPred	Multiple	Solution—1 and 5 mg/ml Tabs—1, 2.5, 5, 10, 20, and 50 mg
	Prednisolone	Orapred®, Pediapred®, Prelone®, Delta-Cortef®, Econopred®	Multiple	Solution/Syrup—5, 6.7, 15, and 20 mg/5 ml Tabs—5 and 15 mg
	Triamcinolone	Aristospan®, Kenacort® Kenalog®	Multiple	Injectable (acetonide)—10 and 40 mg/ml Injectable (hexacetonide)—5 and 20 mg/ml Tabs—4 mg Topical—aerosol, cream, lotion, ointment, paste
Synthetic DMARDs				
	Hydroxychloroquine	Plaquenil®	Multiple	Tabs—200 mg
	Leflunomide	Arava®	Multiple	Tabs—10 and 20 mg
	Methotrexate	Trexall®, Folex®, Rheumatrex®	Multiple	Injectable—25 mg/ml, 20 mg and 1 g vials Tabs—2.5, 5, 7.5, 10, and 15 mg
	Sulfasalazine	Azulfidine®, EN-tabs®, Sulfazine®	Multiple	Suspension—250 mg/5 ml Tabs—500 mg
Biologic DMARDs				
	Abatacept	Orencia®	Bristol Myers Squibb	Injectable—250 mg vial
	Adalimumab	Humira®	Abbott	Injectable—40 mg/0.8 ml syringe
	Anakinra	Kineret®	Amgen	Injectable—100 mg/0.67 ml syringe
	Etanercept	Enbrel®	Amgen Wyeth Immunex	Injectable—50 mg/ml, 25 mg vial

Table 3. Pharmaceutical treatments for rheumatoid arthritis and psoriatic arthritis (continued)

Class	Generic Name	U.S. Trade Name(s)*	Manufacturer	How Supplied
	Infliximab	Remicade®	Centocor	Injectable—100 mg vial
	Rituximab	Rituxan®	Genentech IDEC	Injectable—10 mg/ml vial

DMARD, disease-modifying antirheumatic drug.
*Listed trade names are limited to commonly prescribed U.S. products when multiple are available.

Table 4. Route, labeled use, and usual dose of treatments for rheumatoid arthritis and psoriatic arthritis

Class	Generic Name	Route	Labeled Use*	Usual Adult Dose
Corticosteroids				
	Betamethasone	Injectable Oral Topical	NSA	IM—0.6 to 9 mg/day in 1 or 2 divided doses Intrabursal, intra-articular, intradermal, intralesional—0.25 to 2 ml Oral—2.4 to 4.8 mg/day in 2 to 4 divided doses Topical—1 to 2 times daily as needed
	Budesonide	Oral	Crohn's	Oral—9 mg once daily for up to 8 weeks
	Cortisone	Oral	NSA	Oral—25 to 300 mg/day in 1 or 2 divided doses
	Dexamethasone	Injectable Oral	NSA	IM, IV, oral—0.75 to 9 mg/day in 2 to 4 divided doses
	Hydrocortisone	Injectable Oral Topical	NSA	IM, IV, oral—15 to 240 mg/day in 2 divided doses Intralesional, intra-articular, soft tissue injection—10 to 37.5 mg Topical—2 to 4 times daily as needed
	Methylprednisolone	Injectable Oral	NSA	IM (acetate)—10 to 80 mg every 1 to 2 weeks IM (sodium succinate)—10 to 80 mg daily Intra-articular, intralesional (acetate)—4 to 80 mg every 1 to 5 weeks IV (sodium succinate)—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	Oral	NSA	Oral—Use lowest effective dose (≤ 7.5 mg/day)
	Prednisolone	Oral	NSA	Oral—Use lowest effective dose (5 to 7.5 mg/day)
	Triamcinolone	Injectable Oral Topical	NSA	IM—2.5 to 60 mg Intra-articular, intralesional, intradermal, intrasynovial—1 to 40 mg Oral—8 to 16 mg/day Topical—2 to 4 times daily as needed
Synthetic DMARDs				
	Hydroxychloroquine	Oral	RA	Oral—200 to 400† mg/day in 1 or 2 divided doses
	Leflunomide	Oral	RA	Oral—10 to 20 mg/day in a single dose
	Methotrexate	Injectable Oral	RA	IM, IV, oral—7.5 to 25 mg/week in a single dose
	Sulfasalazine	Oral	RA	Oral—500 to 3,000 mg/day in 2 to 4 divided doses

Table 4. Route, labeled use, and usual dose of treatments for rheumatoid arthritis and psoriatic arthritis (continued)

Class	Generic Name	Route	Labeled Use*	Usual Adult Dose
Biologic DMARDs				
	Abatacept	Injectable	RA	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
	Adalimumab	Injectable	PsA	SQ—40 mg every other week
			RA	SQ—40 mg every other week; may increase to 40 mg per week in patients not taking concomitant methotrexate
	Anakinra	Injectable	RA	SQ—100 mg/day; dose should be decreased to 100 mg every other day in renal insufficiency
	Etanercept	Injectable	PsA, RA	SQ—25 mg twice weekly or 50 mg once weekly
	Infliximab	Injectable	PsA	IV—5 mg/kg, with or without methotrexate, at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter
			RA	IV—3 mg/kg in combination with methotrexate 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	Injectable	RA	IV—1,000 mg on days 1 and 15 in combination with methotrexate

DMARD, disease-modifying antirheumatic drug; IM, intramuscular; IV, intravenous; NSA, nonspecific anti-inflammatory (or immunosuppressant) indication; PsA, psoriatic arthritis; SQ, subcutaneous; RA, rheumatoid arthritis.
*Labeled use limited to RA and PsA unless otherwise indicated.
† Initial dose is 400-600 mg/day for 4 to 12 weeks

Disease-Specific Treatments

Rheumatoid arthritis. In RA, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in early or mild disease, but they do not have any disease-modifying properties. For RA, the synthetic 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.

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.

There is debate as to 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). Additionally, uncertainty remains regarding risks and benefits of therapies in patient subgroups.

Two recent reports examined some of the biologic DMARDs in the treatment of RA. The first included a meta-analysis of the benefits and harms of three biologics (adalimumab,

etanercept, and infliximab).[20] It found that these three drugs were more efficacious than placebo for RA patients who are not well controlled by conventional DMARDs, specifically for improving control of symptoms, increasing physical function, and slowing radiographic changes in the joints. The second report used meta-regression techniques and found that anakinra was less effective than infliximab, etanercept, or adalimumab;[21] when the researchers accounted for disease duration and baseline quality-of-life scores, the three biologics appeared better than anakinra. These studies support the overall efficacy of biologics. Nonetheless, examining comparative efficacy and effectiveness with synthetic DMARDs and corticosteroids, as well as long-term outcomes and subpopulations, is warranted.

Psoriatic arthritis. Historically, few PsA trials have been conducted, and management has been adapted from RA trial data. With the introduction of biologic therapy, however, dedicated PsA trials have demonstrated efficacy in this distinct disease. The first line of treatment of PsA is NSAIDs, although in most cases DMARDs are necessary. MTX is particularly useful because it treats the psoriasis in addition to the arthropathy. Corticosteroids may be used to control inflammation, but they do not have much of a role in chronic disease management in psoriatic disease. The tapering or withdrawal of steroids in PsA has been associated with severe flares of skin disease. When chronic disease continues to be active despite the use of MTX, biologics are indicated. Biologics most often are given in combination with synthetic DMARDs (e.g., MTX).

Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and harms of corticosteroids, synthetic DMARDS, and biologic DMARDs in the treatment of patients with RA and PsA. We address the following four key questions (KQs):

KQ 1. For patients with rheumatoid 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?

KQ 2. For patients with rheumatoid or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?

KQ 3. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?

KQ 4. 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?

For each key question, we evaluated specific outcome measures as reported in Table 5. For efficacy and effectiveness, we focused on head-to-head trials and prospective observational studies comparing one drug to another. For biologic DMARDs, we also included placebo-controlled, double-blinded randomized controlled trials (RCTs). For safety and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and prospective and retrospective observational studies.

Because equipotency among the reviewed drugs is not well established, we assume that comparisons made within the recommended dosing ranges in Table 4 are appropriate. Dose comparisons made outside the recommended daily dosing range are not in our report.

Organization of the Report

The remainder of this comparative effectiveness review describes our methods to review and synthesize this literature, presents our results by key question (RA followed by PsA), and discusses the implications of those results for clinical applications and future research. Appendix A lists our peer reviewers; Appendix B describes our search strategy; Appendix C contains studies included in meta-analyses; Appendix D lists excluded studies; Appendix E presents evidence tables; Appendix F contains abstract-only studies; Appendix G presents the criteria for assessing the quality of individual studies; Appendix H provides characteristics of studies with poor internal validity; and Appendix I describes clinical assessment scales commonly used in arthritis trials.

Table 5. Outcome measures and study eligibility criteria

Key Questions, Outcomes of Interest, and Specific Measures	Study Eligibility Criteria
KQ 1 /KQ 2: Efficacy/effectiveness **KQ 1:** • Patient symptoms • Radiographic joint damage • Remission **KQ 2:** • Functional capacity • Quality of life	**Study Design** • Head-to-head double-blind RCTs • High-quality systematic reviews • Prospective, controlled observational studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA or PsA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100
KQ 3: Harms, tolerability, adherence, adverse effects	**Study Design** • Head-to-head double-blind RCTs • High-quality systematic reviews • Observational studies, prospective and retrospective **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA or PsA **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 • High-quality systematic reviews • Observational studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA or PsA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100

KQ, key question; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Methods

Topic Development

The topic of this report and preliminary key questions 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 International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) then refined the original questions, in consultation with AHRQ and the SRC through multiple conference calls, into the final set of key questions cited in the introduction.

Literature Search

To identify articles relevant to each key question we searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix B. 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 (rheumatoid arthritis [RA], psoriatic arthritis [PsA]), drug interactions, and adverse events with a list of nine corticosteroids (betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone), four synthetic disease-modifying antirheumatic drugs (DMARDs, including methotrexate [MTX], leflunomide, sulfasalazine, and hydroxychloroquine), and six biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab). We limited the electronic searches to "human" and "English language." Sources were searched from 1980 to September 2006 to capture literature relevant to the scope of our topic.

We used the National Library of Medicine (NLM) publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We also manually searched reference lists of pertinent review articles and letters to the editor. We imported all citations into an electronic database (EndNote 8.0). Additionally, we handsearched 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 Genetech).

Our searches found 1,957 citations, unduplicated across databases. Additionally, we identified 166 articles from manually reviewing the reference lists of pertinent review articles. Twenty-eight other studies came from pharmaceutical dossiers, and two additional studies came from peer review or public comments. The total number of citations in our database was 2,153.

Study Selection

We developed eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to medications inside our scope of interest. Table 5 in the introduction describes the criteria in more detail. Because multiple large RCTs had been conducted in this drug class, we adopted a minimum sample size requirement ($N \geq 100$) to be able to focus on the best available evidence.

Two persons independently reviewed abstracts. 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 to determine which, if any, to exclude at this stage. We did not include studies that met eligibility criteria but were reported as an abstract only. These studies are listed in Appendix F.

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 and an adult study population with a sample size of at least 100 participants were eligible for inclusion.

For harms (i.e., evidence pertaining to safety, tolerability, and adverse events), we examined data from both experimental and prospective and retrospective observational studies. We included RCTs and observational studies with large sample sizes (≥100 patients), lasting at least 3 months, that reported an outcome of interest.

Initially, we reviewed studies with health outcomes as primary outcome measures. Outcomes for efficacy or effectiveness, for example, were 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 overall and specific outcomes ranging in severity (e.g., serious infections, malignancies, hepatotoxicity, hematological adverse events, infusion and injection reactions, nausea), withdrawals attributable to adverse events, and drug interactions.

We included meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality.[22] We did not abstract individual studies if they had been used in an included meta-analysis; studies in this group that met eligibility criteria are cited in Appendix C. However, we reviewed them to determine whether any other outcomes of interest were reported. Appendix D summarizes reasons for exclusion of studies that were reviewed as full text articles but did not meet eligibility criteria.

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 and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating.

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 3.0, TrialStat™ Corporation. 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)[23] and the National Health Service Centre for Reviews and Dissemination.[24] 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 with missing values imputed), adequacy of blinding, and overall and differential loss to followup.

In general terms, a "good" study has the least bias and results are considered to be valid. A "fair" study is susceptible to some 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 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.[25] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting a third, independent party. Appendix G details the predefined criteria used for evaluating the quality of all included studies.

Studies that met all criteria were rated good quality. The majority of studies received a quality rating of fair. This category includes studies that presumably fulfilled all quality criteria but did not report their methods to an extent that answered all our questions. Time constraints precluded our contacting study authors for clarification of methodological questions. Thus, the fair-quality category includes studies with quite different strengths and weaknesses. Studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high probability of bias) in one or more categories were rated poor quality and, generally, excluded from our analyses. If no other evidence on an outcome of interest was available, we comment on findings from poor studies. Poor-quality studies and reasons for that rating are presented in Appendix H.

Applicability Assessment

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies.[26] We deemed studies that met at least six of seven predefined criteria to be effectiveness studies (Table 6). The results of effectiveness studies are more applicable to the spectrum of patients that will use a drug, have a test, or undergo a procedure than results from highly selected populations in efficacy studies.

Table 6. Criteria for effectiveness studies

Criteria	Relevance to Treatment of RA or PsA
Study population	Primary care population
Less stringent eligibility criteria	Determine case by case
Health outcomes	Response, remission, quality of life, functional capacity, hospitalization
Clinically relevant treatment modalities	> 8 week study duration; flexible dose design; physician-based diagnosis
Assessment of adverse events	Always
Adequate sample size to assess a minimally important difference from a patient perspective	N > 150
Intention-to-treat analysis	Always

PSA, psoriatic arthritis; RA, rheumatoid arthritis.

Rating Strength of a Body of Evidence

We rated the strength of the available evidence in a three-part hierarchy based on an approach devised by the GRADE working group.[27] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates four key elements: study design, study quality, consistency, and directness. It also considers the presence of imprecise or sparse data, high probability of publication bias, evidence of a dose gradient, and magnitude of the effect.

As shown in Table 7, we used three grades: high, moderate, and low (combining the GRADE category of very low with low).[28] Grades reflect the strength of the body of evidence to answer key questions on the comparative efficacy, effectiveness, and harms of drugs to treat RA and PsA. The critical element is the extent to which new evidence might alter the confidence we would have in our findings. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals.

Table 7. Definitions of the grades of overall strength of evidence

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.

Source: Adapted from the GRADE working group (Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill 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;4(1):38.)

This approach does not incorporate other factors, such as funding sources and comparable dosing, that might be relevant to assess reliably comparative efficacy, effectiveness, and harms. We have assessed these additional factors and highlighted issues that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

Data Synthesis

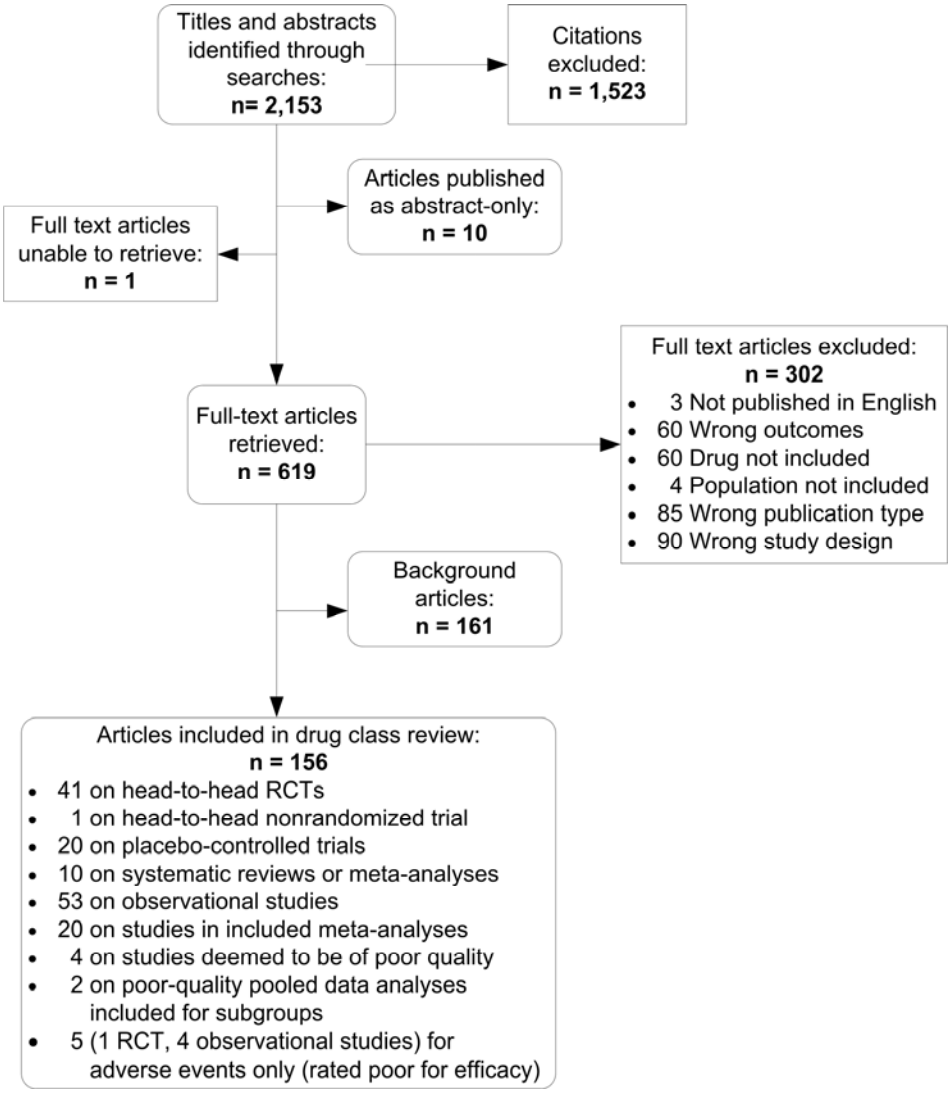
Throughout this report we synthesized the literature qualitatively. Comparisons of the drugs that had not yet been quantitatively analyzed in any of the meta-analyses or indirect comparisons that we included either were limited to fewer than three good or fair RCTs or had noncomparable study populations. Therefore, we did not attempt any quantitative analyses of such comparisons.

As is customary for all comparative effectiveness reviews done for AHRQ, the SRC requested review of this report from three outside rheumatology experts in the field. 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 key questions. Our peer reviewers (listed in Appendix A) 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 website (http://effectivehealthcare.ahrq.gov/) and compiled the comments for our review. Twenty-four public reviewers submitted comments. They represented advocacy groups, the pharmaceutical industry, and practicing physicians. Based on these comments, we revised the text where appropriate.

Results

We identified 2,153 citations from our searches (Appendix B). Figure 1 documents the results of the literature search. Working from 619 articles retrieved for full review, we included 161 for background and excluded 302 at this stage (Appendix D). We included 156 published articles reporting on 103 studies: 22 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 13 placebo-controlled trials, 10 meta-analyses or systematic reviews, and 55 observational studies. Our findings include studies rated good or fair, unless a particular study rated poor provides some unique information that we judged to be of interest. We included 2 poor-quality pooled data analyses on subgroups. 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. Results of literature search*



*Number of included articles differs from number of included studies because some studies have multiple publications.

We excluded articles based on eligibility criteria or methodological criteria (quality rating) as explained in Chapter 2. We excluded six studies that originally met eligibility (inclusion) criteria but were subsequently rated as poor quality after full review (Appendix H). The main reasons for poor ratings were high loss to followup and selection bias.

Of the 103 included studies, 51 (50 percent) were supported by pharmaceutical companies; 21 (20 percent) were funded by governmental or independent funds; and 11 (11 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 20 (19 percent) studies.

This chapter is organized by key question and, within each question, by disease (first rheumatoid arthritis [RA] and then psoriatic arthritis [PsA]). We then present findings in order by class of drugs, types of drugs, and combinations of drugs as appropriate to the condition and the particular key question. Generally, the chapter is organized using the following main analytic categories: corticosteroids vs. corticosteroids, synthetic disease-modifying antirheumatic drugs (DMARDs) vs. synthetic DMARDs, synthetic DMARD combinations (with or without corticosteroids) vs. synthetic DMARD combinations, biologics vs. biologics, biologics vs. corticosteroids, biologics vs. synthetic DMARDs, biologics plus synthetic DMARDs vs. biologics, and biologics plus synthetic DMARDs vs. synthetic DMARDs (see Table 3 in the introduction).

Across all key questions and both diseases, we have included head-to-head studies with either active or placebo controls (or both), observational studies, and other systematic reviews. When comparative evidence is available, we discuss it before presenting placebo-controlled trials. This occurs for RA only for KQ 3 and KQ 4 on harms and subgroups. PsA involves only placebo-controlled trials.

Table 8 below gives the numbers of trials or studies for drug class comparisons, only for RA, and reported only from *head-to-head trials or studies;* when some groupings have important subcomparisons, we note these in Table 8 as well. We do not, however, offer an exhaustive list of all *possible* comparisons among corticosteroids, synthetic DMARDs, and biologic DMARDs simply because of the sheer number of potential combinations of drugs within classes and across classes, which cannot be clearly and concisely presented here.

Table 8. Number of head-to-head trials or studies by drug comparison for rheumatoid arthritis

Drug Comparison	Number of Trials or Studies; Quality Rating
Corticosteroids vs. corticosteroids	1; 1 fair
Synthetic DMARDs vs. synthetic DMARDs	7; 1 good, 6 fair
Synthetic DMARD combinations	11; 5 good, 6 fair
Biologic DMARDs vs. biologic DMARDs	8; 2 good, 6 fair
Biologic DMARDs vs. synthetic DMARDs	4; 4 fair
Biologic DMARD + synthetic DMARD combinations	10; 2 good, 8 fair

DMARD, disease modifying anti-rheumatic drug.
*No head-to-head drug comparison studies were available for psoriatic arthritis; all were placebo-controlled studies.

Table 9 lists abbreviations and full names of diagnostic scales and health status or quality-of-life instruments encountered in these studies. For further details about such instruments and scales, see Appendix I**.**

Table 9. Diagnostic scales and quality-of-life instruments

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by
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
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 28	Disease Activity Score Short Form	0 to10	Decrease
EQ-5D*	EuroQol EQ-5D Quality of Life Questionnaire	0 to 1	Increase
HAQ* (D-HAQ)	Health Assessment Questionnaire (Dutch Version)	0 to 3	Decrease
HAQ-DI	Disability Index of the Heath Assessment Questionnaire	0 to 3	Decrease
Larsen Scale*	Larsen Scale for Grading Radiographs in Rheumatoid Arthritis	0 to 250	Decrease
PASI*	Psoriasis Area and Severity Index	0 to 72	Decrease
PsARC*	Psoriatic Arthritis Response Criteria	0 to 100 percent	Increase
SF-36*	Medical Outcomes Study Short Form 36 Health Survey	0 to 100	Increase
Sharp Scale	Sharp Scoring System for Radiographic Rheumatoid Arthritis	Erosion: 0 to 170 Narrowing: 0 to 144	Decrease
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
SOFI	Signals of Functional Impairment Scale	0 to 44	Decrease

* These key scales are defined in Appendix I.

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

This key question concerned three main topics for both diseases. Specifically, "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?" As noted earlier, we address first the evidence about RA and then the information about PsA. Tables 10 and 11 provide selected study-specific information on outcomes, broken out by primary outcomes in Table 10 and by radiologic outcomes in Table 11, for ease of comparison. Evidence Tables 1 (for head-to-head studies) and 2 (for systematic reviews and meta-analyses) in Appendix E document details about all these studies.

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Corticosteroids vs. Corticosteroids					
Kirwan et al., 2004[29]	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)	Fair
Synthetic DMARDs vs. Synthetic DMARDs					
Capell et al., 2007[30]	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)	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[31]	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
Emery et al., 2000[32]	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
Haagsma et al., 1997[33]	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
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week)	Lower ACR 20 responses for LEF vs. MTX at 12 months (OR, 1.43; 95% CI, 1.15-1.77; *P* = 0.001); no significant differences in ACR response rates at 2 years	Good

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Osiri et al., 2003 (cont'd)			LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	Higher ACR 20 and ACR 50 responses for LEF vs. SSZ at 24 months (ACR 20: OR, 0.35; 95% CI, 0.16-0.77; *P* = 0.009) (ACR 50: OR, 0.32; 95% CI, 0.15-0.67*; P* = 0.003); no significant differences in any ACR response rates at 6 and 12 months	
Smolen et al., 1999;[35] Larsen et al., 2001[36]	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
Strand, et al., 1999[37,38]	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* = 0.019)	Fair
Synthetic DMARD Combinations vs. Monotherapy or Combinations, With or Without Corticosteroids					
Boers et al., 1997;[39] Landewe et al., 2002[40] 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
Capell et al., 2007[30]	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

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Dougados et al., 1999[31] Maillefert et al., 2003[41]	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
Goekoop-Ruiterman et al., 2005[42] BeSt study	RCT 508 12 months	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1to 5); median duration of symptoms 23 weeks (IQR 14 to 53)	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/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	Good
Haagsma et al., 1997[33]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	MTX (7.5 to 15 mg/week) + SSZ (2 to 3 g/day) vs. SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR or DAS responses	Fair
Mottonen et al., 1999;[43] Korpela et al., 2004[44] FIN-RACo study	RCT 199 24 months (5 year follow-up)	Multicenter; early RA; mean disease duration 7.3 to 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
O'Dell et al., 2002[45]	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

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
O'Dell et al., 1996[46]	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 (7.5 to 17.5 mg/week) vs. 3: SSZ (1 g/day) + HCQ (400 mg/day)	50% improvement (defined by authors): 77%, 40%, 33% 1 vs. 3: $P < 0.001$ 1 vs. 2: $P = 0.003$	Good
Svensson et al., 2005[47]	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	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
Biologic DMARDs vs. Biologic DMARDs					
Clark et al., 2004[48]	Meta-analysis NR	Patients who have failed MTX treatment; mean disease duration varied	ANA vs. Anti-TNF as a class	Significantly lower ACR 20 response rates of anakinra than anti-TNF as a class. Risk difference: -0.21 (95% CI, -0.32-0.10)	Good
Gartlehner et al., 2006[49]	Meta-analysis 5,248	Patients who have failed MTX treatment; mean disease duration varied	ADA (40 mg every other week), ANA (100 mg/day), ETA (25 mg twice weekly), INF (3 to 10 mg every 8 weeks)	No difference in efficacy among anti-TNF drugs; greater efficacy of anti-TNF drugs than anakinra on ACR 20: RR, 0.61 (95% CI, 0.39-0.96)	Good
Geborek et al., 2002[50]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETA (25 mg twice weekly) vs. INF (3 mg/kg or higher)	Higher ACR 20 responses for ETA at 3 (data NR; $P < 0.02$) and 6 months (data NR; $P < 0.05$); no significant differences in ACR response rates at 12 months (data NR)	Fair
Hochberg et al., 2003[51]	Meta-analysis 1,053	Patients who have failed MTX treatment; mean disease duration varied	ADA (40 mg every other week), ETA (25 mg twice weekly), INF (3 to 10 mg every 8 weeks)	No difference in ACR 20 response rates among anti-TNF drugs	Fair
Kristensen et al., 2002[52]	Prospective cohort study 949 36 months	Inadequate response to at least 2 DMARDs	ETA (25 mg twice weekly) vs. INF (3 mg/kg or higher)	No difference in ACR 50 response at 36 months (data NR)	Fair
Wailoo et al., 2006[21]	Meta-analysis 6,694	Patients with RA; mean disease duration varied	INF, ETA, ANA, ADA	No difference in ACR 50 response rates among anti-TNF drugs	Fair
Weaver et al., 2006[53]	Prospective cohort study 1,371 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETA (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Higher mACR 20 response rates for ETA than INF (41% vs. 26%; P = NR)	Fair

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Biologic DMARDs vs. Synthetic DMARDs					
Bathon et al., 2000;[54] Genovese et al., 2002;[55] Genovese et al., 2005[56] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETA (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Significantly greater improvement of ACR-N for ETA 25 mg than for MTX (data NR; $P < 0.05$)	Fair
Breedveld et al., 2006 [57] 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
Geborek et al., 2002[50]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETA (25 mg twice weekly) vs. INF (3 mg/kg or higher) vs. LEF (20 mg/day)	Higher ACR 20/50 responses for ETA and INF at 3 months (data NR; $P < 0.05$) and for ETA at 6 months (data NR; $P < 0.05$); results for 12 months: NR	Fair
Listing et al., 2006[58]	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, ETA, INF; dose NR) vs. DMARDs as a class (dose NR)	Significantly higher chance of remission for biologics than DMARDs (OR, 1.95; 95% CI, 1.20-3.19)	Fair
Weaver et al., 2006[53]	Prospective cohort study 1,371 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETA (25 mg twice weekly) vs. INF (3.8 mg/kg or higher) vs. MTX (10 to 15 mg/week)	Higher mACR 20 response rates for ETA than INF (41% vs. 26%; P = NR)	Fair
Biologic DMARDs + Biologic DMARDs vs. Biologic DMARDs					
Genovese et al., 2004[59]	RCT 242 24 weeks	Inadequate control of disease with MTX; mean disease duration 9.9 years	ETA (25 mg twice weekly) + AKA (100 mg/day) vs. ETA (25 mg/week)	Higher ACR 50 response rates for ETA monotherapy (31% vs. 41%; P = 0.914)	Fair
Biologic DMARDs + Synthetic DMARDs vs. Biologic DMARDs					
Breedveld et al., 2006[57] 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

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Combe et al., 2006[60]	RCT 260 24 weeks	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETA (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. ETA (25 mg twice weekly)	Similar ACR 20 response rates between ETA + SSZ and ETA (74% vs. 74%; *P* = NR)	Fair
Edwards et al., 2004[61]	RCT 161 24 weeks	Active RA despite MTX treatment; mean disease duration 10.4 years	RIT (1,000 mg/days 1&15) + MTX (>10 mg/day) vs. RIT (1,000 mg/days 1&15) vs. MTX	Higher ACR 50 response rates for the RIT + MTX combination than for RIT monotherapy (43% vs. 33%; *P* = NR)	Fair
Hyrich et al., 2006[62]	Prospective cohort study 2,711 6 months	Population-based; patients with active RA who required change in therapy; mean disease duration 14.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly) + other DMARD (dose NR) vs. ETA (25 mg twice weekly) INF (3 mg/kg) + MTX (dose NR) vs. INF (3 mg/kg) + other DMARD (dose NR) vs. INF (3 mg/kg)	Significantly higher EULAR response rates for ETA + MTX than ETA (OR, 1.98; 1.45-2.71) Higher EULAR response rates for INF + MTX than INF (OR, 1.35; 0.92-2.00)	Good
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] 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	ETA (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 ETA + MTX than ETA (18.3%-years vs. 14.7%-years; *P* < 0.0001) at 24 weeks	Fair
Van Riel et al., 2006[66]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX; mean disease duration 10.9 years	ETA (25 mg twice weekly) + MTX (>12.5 mg/week) vs. ETA (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
Weaver et al., 2006[53]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly)	Similar mACR 20 response rates for ETA + MTX and ETA (43% vs. 41%; *P* = NR)	Fair
Zink et al., 2005[67]	Retrospective cohort study 1,523 1 year	Patients with RA who had a change in treatment regimen	ETA + MTX vs. ETA (dosages NR) INF + MTX vs. INF, (dosages NR)	Discontinuation due to lack of efficacy: Greater in ETA monotherapy vs. combination (ETA + MTX: 16.9%; ETA: 19.9%; *P* = NR) Greater in INF monotherapy than combination (INF + MTX: 17.9%, INF: 45%)	Good

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Biologic DMARDS + Synthetic DMARDs vs. Synthetic DMARDs					
Breedveld et al., 2006[57] 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
Combe et al., 2006[60]	RCT 260 24 weeks	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETA (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 ETA + SSZ and SSZ (74% vs. 28%; *P* = NR)	Fair
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] 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	ETA (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 ETA + MTX than MTX (18.3%-years vs. 12.2%-years; *P* < 0.0001) at 24 weeks	Fair
St Clair et al., 2004;[68] Smolen et al., 2006[69] 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)	Fair

ACR-N, American College of Rheumatology percent improvement from baseline to endpoint; ADA, adalimumab; ANA, anakinra; BUD, budesonide; CI, confidence interval; Combo, combination therapy; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; ETA, etanercept; EULAR, European League Against Rheumatism; HCQ, hydroxychloroquine; INF, infliximab; IQR, interquartile range; LEF, leflunomide; mACR, modified ACR; MACTAR, McMaster Toronto Arthritis Questionnaire; MTX, methotrexate; mg, milligram; NHS, National Health Service; NR, not reported; NS, not significant; OR, odds ratio; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; RIT, rituximab; SSZ, sulfasalazine; TNF, tumor necrosis factor; VAS, visual analog scale; vs., versus.

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Synthetic DMARDs vs. Synthetic DMARDs				
Capell et al., 2007[30]	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)

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Dougados et al., 1999[31]	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
Emery et al., 2000[32]	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
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	No	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week) LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	No differences in total Sharp score change or Larsen score change
Smolen et al., 1999;[35] Larsen, et. al., 2001[36]	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
Strand et al., 1999[37]	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)
Synthetic DMARD Combinations vs. Monotherapy or Combinations, With or Without Corticosteroids				
Boers et al., 1997;[39] Landewe et al., 2002[40] 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	Median modified Sharp/van der Heijde score change improved 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). [At 5 years mean modified Sharp/van der Heijde score change per year was lower for combo (5.6 vs. 8.6; *P*= 0.001)]
Capell et al., 2007[30]	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)

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Dougados et al., 1999;[31] Maillefert et al., 2003[41]	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
Goekoop-Ruiterman, 2005[42] BeST study	RCT 508 12 months	Yes	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-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
Mottonen et al., 1999; [43] Korpela et al., 2004[44] 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
Svensson et al., 2005[47]	Open-label 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
Biologic DMARDs vs. Synthetic DMARDs				
Bathon et al., 2000;[54] Genovese et al., 2002[55] Genovese et al., 2005[56] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Yes; MTX-naive patients with early, aggressive RA	ETA (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	At 1 year: Total modified Sharp score change: 1.00 vs. 1.59; *P* = 0.11 Erosion score change: 0.47 vs. 1.03; *P* = 0.002 Joint space narrowing score change: NR At 2 years: Total modified Sharp score change: 1.3 vs. 3.2; *P* = 0.001 Erosion score change: 0.7 vs. 1.9; *P* = 0.001 Joint space narrowing score change: NR

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Breedveld et al., 2006[57] 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
Klareskog et al., 2004[63] van der Heijde et al., 2006[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	No	ETA (25 mg twice weekly) + MTX (7.5 titrated to 20 mg/week) 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)
Biologic DMARDs + Synthetic DMARDs vs. Biologic DMARDs				
Breedveld et al., 2006[57] 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
Klareskog et al., 2004[63] van der Heijde et al., 2006[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 52 weeks	No	ETA (25 mg twice weekly) + MTX (20 mg/week) vs. ETA (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)
Biologic DMARDs + Synthetic DMARDs vs. Synthetic DMARDs				
Breedveld et al., 2006[57] 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

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
St Clair et al., 2004; [68] Smolen et al., 2006[69] ASPIRE study	RCT 1,049 54 weeks	Yes; MTX-naive patients with early, aggressive RA	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)	Modified Sharp/van der Heijde score change: 0.4 vs. 0.5 vs. 3.7; $P < 0.001$ Erosion score change: 0.3 vs. 0.1 vs. 3.0; $P < 0.001$ Joint space narrowing score change: 0.1 vs. 0.2 vs. 0.6; $P < 0.001$

ADA, adalimumab; Combo, combination therapy; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HCQ, hydroxychloroquine; INF, infliximab; LEF, leflunomide; MTX, methotrexate; PNL, prednisolone; PRED, prednisone; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine.

Rheumatoid Arthritis: Overview

A total of 21 RCTs, one nonrandomized controlled trial, five observational studies, and five systematic reviews or meta-analyses compared symptom response, radiographic joint damage, and remission. Details are found in Evidence Tables 1 and 2, Appendix E. 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. The main drug classes compared include corticosteroids, synthetic DMARDs, biologic DMARDs (also referred to simply as biologics), and various combined strategies.

Rheumatoid Arthritis: Key Points

Corticosteroids vs. corticosteroids. One head-to-head RCT found no significant differences between budesonide and prednisolone for outcomes assessed by the American College of Rheumatology (ACR) response criteria set for 20 percent improvement (ACR 20) or the disease activity score (DAS).[29] The strength of evidence is low.

Synthetic DMARDs vs. synthetic DMARDs. One systematic review and meta-analysis,[34] which included two RCTs, found methotrexate (MTX) resulted in higher ACR 20 responses at 1 year when compared with leflunomide (odds ratio [OR], 1.43; 95% CI, 1.15-1.77; $P = 0.001$), but statistical significance was lost at 2 years.[38] Radiographic changes were similar for both leflunomide and MTX. The results were limited by the few number of studies included for meta-analysis. The strength of the evidence is moderate.

Three RCTs found similar response rates for patients receiving sulfasalazine and for those receiving MTX on outcomes measured by ACR 20, DAS, and radiologic data.[30,31,33] The strength of evidence is moderate.

One RCT reported that leflunomide produced higher proportions of patients meeting ACR 20 and ACR 50 improvement criteria at 24 months than did sulfasalazine.[36] Radiographic changes were similar for leflunomide and sulfasalazine. The strength of the evidence is low.

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

Synthetic DMARD combinations. Studies of several different types of combination strategies favored, overall, combination strategies using two or three drugs over fewer drugs.

Of three RCTs,[30,31,33] one supported combination therapy with sulfasalazine and MTX vs. monotherapy with either drug; the changes in DAS scores were greater for combination therapy (-1.26 for combination, -1.15 for sulfasalazine, and -0.87 for MTX) ($P = 0.019$).[31] The other two trials reported no differences but focused on patients with early RA. The strength of evidence is moderate. All RCTs were funded by the makers of synthetic DMARDs.

Two RCTs found that, at 2 years, the combination of MTX, sulfasalazine, and hydroxychloroquine had better ACR 20 response rates than one or two drugs.[45,46] The strength of evidence is moderate. Both RCTs were funded by the makers of synthetic DMARDs.

One open-label effectiveness trial suggested that combining one synthetic DMARD (MTX or sulfasalazine) with prednisolone delayed radiographic progression more than a synthetic DMARD alone (25.9 percent vs. 39.3 percent progressed based on modified Sharp/van der Heijde score; $P = 0.033$).[47] One RCT[39] with a 5-year follow-up cohort[40] reported that combination therapy, which included two synthetic DMARDs (MTX and sulfasalazine) plus a stepped-down prednisolone treatment, demonstrated less radiographic progression than sulfasalazine alone (5-year mean change in Sharp Scale score, 5.6 vs. 8.6; $P = 0.001$). Another RCT[43] with a 5-year follow-up cohort[44] suggested that the combination of three synthetic DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone had less radiographic change than one synthetic DMARD (5-year median Larsen Scale score, 11 vs. 24; $P = 0.001$). Although the data are limited to one study for each comparison, we judged the strength of evidence to be moderate for these combinations.

One complex effectiveness trial compared several strategies.[42] The authors reported that 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) step-up combination therapy. The median increases in modified Sharp/van der Heijde scores were, respectively, 2.0, 2.5, 1.0, and 0.5 ($P = 0.003$ 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). The data are limited to one trial. The strength of evidence is low.

Biologic DMARDs. We did not find any head-to-head RCTs that compared one biologic DMARD with another. Existing direct head-to-head evidence is limited to a nonrandomized, open-label effectiveness trial[50] and two prospective cohort studies;[52,53] all compared etanercept with infliximab. These studies reported a faster onset of response for etanercept during the first months of therapy but no differences in efficacy thereafter. The faster onset of etanercept might be attributable partly to necessary dose adjustments for patients treated with infliximab. One study, however, attributed differences to lower rates of adherence among patients on infliximab than among those on etanercept. Generally, because of methodological limitations, findings of these studies must be interpreted cautiously.

Adjusted indirect comparisons, based on placebo-controlled RCTs, do not suggest any differences in efficacy among adalimumab, etanercept, and infliximab.[21,48,49,51] This is consistent with results from the open-label effectiveness trial[50] and two observational studies[52,53] mentioned above.

Anakinra, however, appears to have lower efficacy than adalimumab, etanercept, and infliximab.[48,49] Although not all results reached statistical significance, anakinra had consistently lower response rates on ACR 20 (relative risk [RR], 1.64; 95% CI, 1.04-2.56) and ACR 50 (RR, 1.89; 95% CI, 0.98-3.57) than anti-tumor necrosis factor (anti-TNF) drugs as a class (i.e.,

adalimumab, etanercept, and infliximab as a class). Individual comparisons of anakinra with adalimumab, etanercept, and infliximab consistently presented lower response rates for anakinra, but the confidence intervals were wide and the findings did not reach statistical significance.

The strength of evidence for these comparisons is moderate. No evidence from adjusted indirect comparisons exists for abatacept and rituximab. The strength of the evidence for the comparative effectiveness of biologics is low.

Biologic DMARD combinations. One RCT did not detect any synergistic effects of a combination treatment of etanercept and anakinra compared with etanercept monotherapy.[59] The strength of evidence is low.

Four RCTs[57,61,63,66] and two prospective cohort studies[53,62] suggested that a combination of MTX with adalimumab,[57] etanercept,[63-66] infliximab,[53,62] or rituximab[61] led to statistically significantly greater improvements with biologic DMARDs than with monotherapy. A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy.[60] For most of these comparisons, however, the evidence is limited to a single study. All RCTs were funded by the makers of the biologic DMARDs. Except for the PREMIER study on adalimumab,[57] none of these trials was conducted in patients with early RA. The strength of evidence is high for the comparison of etanercept with MTX and moderate for all the other comparisons. No evidence is available on abatacept, anakinra, rituximab, and combinations with synthetic DMARDs other than MTX and sulfasalazine.

Two studies found that a combination of adalimumab with MTX[57] and infliximab with MTX[68] in patients with early, aggressive (i.e., rapidly progressing) RA who were MTX-naive led to better clinical and radiographic outcomes than MTX monotherapy. Both RCTs were funded by the makers of the biologic DMARDs. The strength of the evidence supporting a greater efficacy of a combination treatment than monotherapy is moderate for the above comparisons.

The evidence on the comparative efficacy of biologic DMARDs and synthetic DMARDs is mixed. Population-based, observational evidence from prospective cohort studies indicated that biologic DMARDs as a class were more efficacious than synthetic DMARDs as a class. RCTs, however, did not indicate any substantial differences in clinical response between either adalimumab or etanercept and MTX.[54-57,63-65] Radiographic outcomes, however, were statistically significantly better in patients treated with biologic DMARDs than patients treated with MTX. How such intermediate outcomes translate to the long-term clinical progression of the disease remains unclear.

All RCTs were funded by the makers of the biologic DMARDs. No studies were available comparing biologics with either corticosteroids or with synthetic DMARDs other than MTX. The strength of the evidence for the available comparisons is moderate.

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 primary care population, therefore, remains unclear. The strength of evidence regarding comparative effectiveness is low.

One small study, which did not meet eligibility criteria, reported a higher efficacy of infliximab compared with pulse methylprednisolone. No other evidence comparing biologic DMARDs with corticosteroids was available.

Rheumatoid Arthritis: Detailed Analysis

Corticosteroids vs. corticosteroids. We found one head-to-head RCT (N = 143) comparing two corticosteroids.[29] 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.

Synthetic DMARDs vs. synthetic DMARDs. *Leflunomide vs. MTX.* We found two trials comparing leflunomide (20 mg/day) with MTX (studies ranging from 7.5 mg/week to 15 mg/week) and one systematic review with meta-analysis of leflunomide.[32,34,37] Given that the systematic review included only two trials comparing these two agents, 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.[37] Mean disease duration of RA across these groups was 6.5 years to 7 years. The proportions 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; $P = 0.05$).

A continuation study followed the same cohort for 2 years (leflunomide, n = 98; MTX, n = 101).[38] At 2 years, leflunomide was associated with higher proportions of patients meeting ACR 20 response criteria than MTX (79 percent vs. 67 percent; $P = 0.049$). The percentages 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).[32] 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 = NS, 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 this systematic review including two trials comparing leflumonide with MTX (n = 1,481) there were significantly more responders on the ACR 20 at 12 months favoring MTX (OR, 1.43; 95% CI, 1.15-1.77; $P = 0.001$); however, by 2 years, the statistically significant difference favoring MTX disappears (OR, 1.28; 95% CI, 0.98-1.67; $P = 0.07$). ACR 50 and ACR 70 responses did not differ between leflunomide and MTX, and the two drugs also did not differ in delaying bone erosions or joint damage assessed by total Sharp score.[34] This systematic review was limited by the small number of studies that the authors could use for meta-analysis.

Leflunomide and sulfasalazine. One study[35] with a 2-year followup[36] compared leflunomide with sulfasalazine. In addition, one systematic review did a meta-analysis of leflunomide against sulfasalazine.[34] Given that the systematic review included only one trial with this comparison, we describe it in detail first.[35] 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).[35] 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). ACR 50 response rates were also similar (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. In the follow-up study, patients who completed the first study could opt to continue on the 12- and 24-month double-blind extension.[36] 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 (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 meta-analysis compared leflunomide (10 to 20 mg/day) with sulfasalazine (2 g/day).[34] The analysis included the study described above.[35,36] 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, 0.35; 95% CI, 0.16-0.77; *P* = 0.009; ACR 50: OR, 0.32; 95% CI, 0.15-0.67; *P* = 0.003). The ACR 70 response was not different between groups at 6, 12, or 24 months. Leflunomide and SSZ 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.[35]

Sulfasalazine and MTX. Three RCTs examined the efficacy of sulfasalazine and MTX.[30,31,33] Overall, findings from these studies showed similar response rates between sulfasalazine and MTX for 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.[31,33] These trials also included a combination therapy arm, which we describe below (in the section on *Synthetic DMARD combinations vs. synthetic DMARD combinations or synthetic 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 (n = 68) for 52 weeks.[31] Mean disease duration for the groups ranged from 2.3 months to 3.4 months. The ACR 20 responses did not differ statistically (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 "*Synthetic DMARD combinations vs. synthetic DMARD combinations or synthetic DMARD monotherapy*"). Radiological scores at 5 years did not differ significantly; the mean total modified Sharp/van der Heijde scores were 8.5 for sulfasalazine and 7.5 for MTX (*P* = 0.7).

Another RCT, lasting 52 weeks (N = 105), also demonstrated similar ACR 20 and DAS results for sulfasalazine and MTX.[33] 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). ACR 20 response was 25 percent for sulfasalazine and 25 percent for MTX.

Finally, one trial included a population with a disease duration of up to 10 years.[30] 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 modified Sharp/van der Heijde score, total erosions, and joint space narrowing also did not differ significantly (data NR). However, 18 months is a short period for observing radiological outcomes, and this study was not powered to detect radiological progression.

Synthetic DMARD combinations vs. synthetic DMARD combinations or synthetic DMARD monotherapy. *Sulfasalazine plus MTX vs. sulfasalazine or MTX.* Three RCTs compared the efficacy of sulfasalazine and MTX vs. that of either sulfasalazine or MTX alone.[30,31,33] Findings from two of these randomized trials consistently reported no significant differences in ACR, DAS, or radiological outcomes.[31,33] 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.[31,33] 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.[30]

One 52-week trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine and 7.5 mg/week to 15 mg/week MTX (n = 68), sulfasalazine (n = 68), or MTX (n = 69).[31] ACR 20 responses were numerically higher in the combination group, but the groups did not differ statistically (ACR: 65 percent combination; 59 percent sulfasalazine; 59 percent MTX; *P* = NS, NR). The DAS change favored combination therapy (DAS change: -1.26 combination; -1.15 sulfasalazine; -0.87 MTX; *P* = 0.019). In a 5-year prospective followup of this cohort, however, when comparing combination therapy vs. monotherapy, the differences in DAS change scores became nonsignificant at year 5.[41] Additionally, radiological scores did not differ at 5 years; the total modified Sharp/van der Heijde score was 7.5 for combination therapy and 8.5 for single therapy (*P* = 0.7). A 52-week RCT (N = 105) also reported no significant differences in ACR or DAS results between combination and single therapy in this population.[33]

Finally, another trial included a population with a disease duration of up to 10 years (mean, 1.6 to 1.8 years).[30] It 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 plus MTX (n = 56), (2) sulfasalazine (n = 55), and (3) MTX (n = 54) (maximum dose, 25 mg/week). At 18 months, the DAS was significantly better in the combination arm than in either the sulfasalazine or MTX arms (DAS change scores: -0.67, -0.30, -0.26; combination vs. sulfasalazine*; P* = 0.039; combination vs. MTX*; P* = 0.023). The ACR 20, 50, and 70 responses were all higher in the combination arm, but they were not statistically different across the three arms. Additionally, the total modified Sharp/van der Heijde score, total erosions, and joint space narrowing also did not differ significantly across arms (data NR). However, 18 months is a short period for radiological outcomes, and this study was not powered for radiological progression.

MTX plus hydroxychloroquine plus sulfasalazine vs. one or two synthetic DMARDs. Two RCTs examined the combination of MTX, sulfasalazine, and hydroxychloroquine against either one or two drugs.[45,46] Both studies found that the combination of the three DMARDs was more effective than either one or two DMARDs.

The more recent study randomized 171 patients over 2 years to (1) MTX 7.5 mg/week titrated to 17.5 mg/week plus sulfasalazine 2 g/day plus hydroxychloroquine 400 mg/day, (2) MTX plus hydroxychloroquine, or (3) MTX plus sulfasalazine.[45] Mean disease duration across

groups was 5.8 to 7.9 years. After 2 years, patients receiving triple therapy had an ACR 20 of 78 percent; the figures were 60 percent for those treated with MTX and hydroxychloroquine ($P = 0.05$) and 49 percent for those treated with MTX and sulfasalazine ($P = 0.002$).

Synthetic DMARDs plus corticosteroid combinations vs. synthetic DMARDs. *One synthetic DMARD plus corticosteroid vs. synthetic DMARD.* One open-label RCT compared a combination therapy involving a synthetic DMARD (either MTX or sulfasalazine) and a corticosteroid with a synthetic DMARD only (N = 250).[47] This study suggested that, for patients with early RA, combining a synthetic DMARD with prednisolone may help slow radiographic progression and extend remission. This 2-year, multicenter Swedish study compared prednisolone 7.5 mg/day added to a DMARD (n = 119) with a DMARD only (n = 131) in patients with early RA. Patients were eligible if they had been diagnosed with RA (1987 ACR criteria) in the past year and had been started by their treating rheumatologist on their first DMARD. The choice of DMARD had been left to the patient's primary rheumatologist and included MTX (mean dose 10 mg/week) or sulfasalazine (2 g/day). The combination group had significantly less radiographic progression than the monotherapy group (25.9 percent vs. 39.3 percent based on modified Sharp/van der Heijde score; $P = 0.033$). Additionally, remission was higher in the combination group (DAS 28 < 2.6, 55.5 percent vs. 43.8 percent; $P = 0.0005$). This study can be considered an effectiveness trial based on design criteria.[26] However, the results should be interpreted cautiously, given the open-label design and potential for measurement bias.

Two synthetic DMARDs plus corticosteroid vs. synthetic DMARD. One multicenter RCT, known as COBRA (Combinatietherapie Bij Reumatoide Artritis), assessed differences in efficacy between a combination of step-down prednisolone, MTX, and sulfasalazine and sulfasalazine only.[39] 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).[40] 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; $P = 0.001$).[40]

Three synthetic DMARDs plus corticosteroid vs. synthetic DMARDs. 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.[43] 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 (37.9 percent vs. 18.4 percent; $P = 0.011$); the proportions achieving ACR 50 response criteria were higher but did not reach statistical significance (71 percent vs. 58 percent; $P = 0.058$). Larsen Scale radiographic scores had also improved at 2 years (Larsen Scale score increase 2 vs. 10; $P = 0.002$). Subsequently, patients in this trial were followed for 5 years.[44] 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 (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.

Other complex combination strategies. One good-quality RCT examined four different treatment strategies over 12 months.[42] 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) step-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 DAS44 > 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).

Biologic DMARDs vs. biologic DMARDs. We did not identify any head-to-head RCTs. The head-to-head evidence was limited to one nonrandomized, open-label effectiveness trial[50] and two fair-quality prospective cohort studies;[52,53] all compared etanercept with infliximab. All three studies were primary care based with minimal exclusion criteria, enrolling patients who were starting treatments with biologic DMARDs. Mean disease durations ranged from 7.7 years to 14.7 years, indicating that most patients suffered from advanced RA; the proportion of patients with early RA in these studies remains unclear. One study was conducted in the United States;[53] the other two were carried out in Sweden.[50,52] In addition to these studies evaluating biologic monotherapies, an RCT compared etanercept monotherapy to a combination treatment of etanercept and anakinra.[59]

The nonrandomized, open-label effectiveness study (N = 369) assessed the effectiveness and safety of etanercept (25 mg twice weekly), infliximab (3 mg/kg or higher every 8 weeks), and leflunomide (20 mg/day).[50] Study duration was 12 months. Comparisons of etanercept and infliximab with the leflunomide arm are reported in the section below comparing synthetic

DMARDs with biologic DMARDs. Etanercept had significantly greater ACR 20 response rates at 3 months ($P < 0.02$; data NR) and 6 months ($P < 0.05$; data NR) and greater ACR 50 response rates 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.

One prospective cohort study (N = 949) provided similar results. Etanercept treatments led to greater response rates than infliximab during the first months of treatment, but no differences were noted thereafter for up to 36 months.[52] 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.[53] Etanercept-treated patients had greater response rates 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 responses 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).

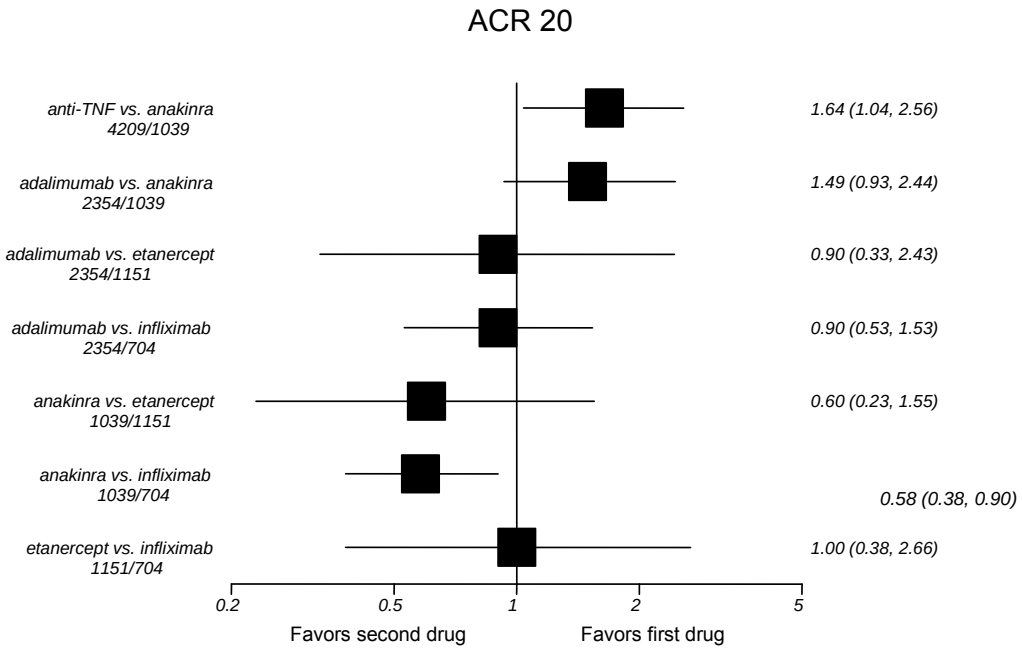
A well-conducted retrospective cohort study did not meet our eligibility criteria, but we present its findings here because it was the only study that examined radiographic progression for patients treated with etanercept or infliximab.[70] This population-based study determined erosion progression and joint space narrowing on 372 Swiss patients who were monitored through the Swiss Clinical Quality Management System. Combination therapies of infliximab and synthetic DMARDs or etanercept and synthetic DMARDs did not present statistically significant differences in progression of erosion (Ratingen score; data NR) after a mean followup of 1.7 years. The combination of infliximab and synthetic DMARDs led, however, to statistically significantly lower joint space narrowing than etanercept and synthetic DMARDs (data NR). This difference was not obvious when the analysis was limited to MTX as the concomitant DMARD. The combination of infliximab and MTX was statistically significantly more efficacious on all outcome measures than etanercept monotherapy (data NR).

Indirect head-to-head comparisons of biologic DMARDs. Multiple placebo-controlled RCTs and meta-analyses[20,71] provide evidence on the general efficacy of abatacept,[72-76] adalimumab,[77-83] anakinra,[48,84-89] etanercept,[63-65,90-97] infliximab,[90,98-107] and rituximab.[61,108] Most of these studies were conducted in patients who had failed synthetic DMARD treatment.

Using information from these placebo-controlled trials, four research groups did meta-analyses to produce adjusted indirect comparisons of biologic DMARDs.[21,48,49,51] The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[109] In the most recent analysis, findings suggested that efficacy does not differ substantially for adalimumab, etanercept, and infliximab (Figures 2 and 3).[49] However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty.

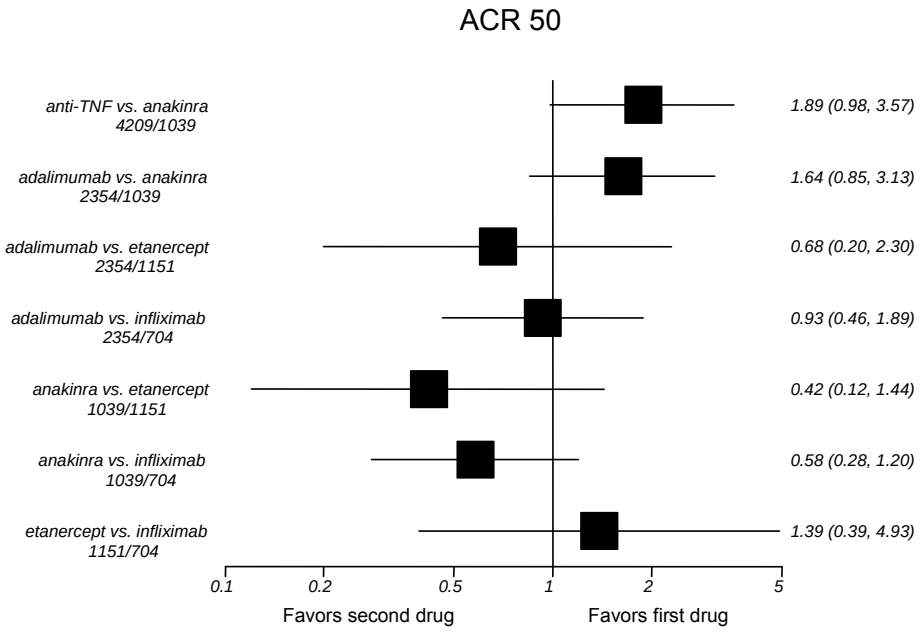
Compared with point estimates for anakinra, point estimates favored adalimumab, etanercept, and infliximab (Figures 2 and 3).[49] Not all differences reached statistical significance in adjusted indirect comparisons, which is likely attributable to a lack of power. Adjusted indirect comparisons of anti-TNF 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. Figures 2 and 3 summarize results of adjusted indirect comparisons of ACR 20 and ACR 50 responses.[49]

Figure 2. Adjusted indirect comparisons of biologic DMARDs for ACR 20 response rates



Adapted from Gartlehner et al., 2006[49]

Figure 3. Adjusted indirect comparisons of biologic DMARDs for ACR 50 response rates



Adapted from Gartlehner et al., 2006[49]

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 because of 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).[67]

No indirect comparisons were available of abatacept and rituximab with other biologic DMARDs.

Biologic DMARDs vs. corticosteroids. One RCT, which did not meet our eligibility criteria because of its small sample size (N = 28), compared the efficacy of infliximab (3 mg/kg at weeks 0, 2, and 6) and pulse methylprednisolone (1 g/single infusion).[110] We briefly summarize its findings here because it was the only study comparing these two treatments. Significantly higher proportions of patients treated with infliximab than with pulse methylprednisolone met ACR 20 criteria (67 percent vs. 8 percent; $P < 0.05$) and ACR 50 criteria (44 percent vs. 0 percent; $P < 0.05$). No quality-of-life measure improved with pulse methylprednisolone treatment.

Biologic DMARDs vs. synthetic DMARDs. Three RCTs, a nonrandomized trial, and a prospective cohort study determined the comparative efficacy and safety of various biologic and synthetic DMARDs. The RCTs compared adalimumab[57] and etanercept[54,63] with MTX; the nonrandomized trial compared etanercept and infliximab with leflunomide;[50] and the cohort study assessed differences in class effects.[58] No evidence exists on abatacept, anakinra, and rituximab or on synthetic DMARDs other than MTX and leflunomide.

Biologic DMARDs as a class vs. synthetic 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 DMARDs as a class (n = 265) in patients who had failed two previous DMARD treatments.[58] 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, 1.20-3.19). Likewise, patients treated with biologics had an almost four times higher likelihood of achieving functional independence than patients treated with synthetic DMARDs (OR, 3.88; 95% CI, 1.71-8.79). 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; synthetic DMARDs, 58 percent).

Adalimumab vs. MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA.[57] 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 adalimumab than for those on MTX monotherapy (37 percent vs. 43 percent; *P* = NR). Radiographic progression, by contrast, was statistically significantly lower in patients treated with adalimumab than with MTX (5.5 vs. 10.4 Sharp units; *P* < 0.001). No difference was apparent in clinical remission (DAS 28 < 2.6) between the two treatment groups (both 25 percent); discontinuation rates because of 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 DMARDs plus synthetic DMARDs vs. biologic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs.*

Etanercept vs. MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week) over 52 weeks.[54-56,63-65] The ERA (Early Rheumatoid Arthritis) study (N = 632) was conducted in patients with early RA who were MTX naive.[54-56] The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) trial[63-65] 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).[63-65] 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 response rates 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[55]and 5 years.[56]

Etanercept or infliximab vs. 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).[50] This study has been described in greater detail in the section (above) on *Biologic DMARDs vs. biologic DMARDs*. At 3 months and 6 months, patients on etanercept had significantly higher ACR 20 and ACR 50 response rates than those on leflunomide (data NR; $P < 0.05$). Patients on infliximab achieved higher ACR 20 and ACR 50 response rates at 3 months (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, no reduction with leflunomide was seen. 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.

Biologic combination strategies: Biologic DMARD plus biologic DMARD vs. 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.[59] 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).

Biologic DMARD plus synthetic DMARD vs. biologic DMARD. The majority of trials assessed a combination of a biologic DMARD and MTX against a monotherapy of the respective biologic DMARD.[53,57,61-63,66] Only one trial used sulfasalazine as a synthetic DMARD in combination with a biologic DMARD.[60] No evidence is available on combination treatments of abatacept or anakinra.

Adalimumab plus MTX vs. adalimumab. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA.[57] Details of this study are reported above in *Biologic DMARDs vs. synthetic DMARDs.* After 2 years, significantly more patients on the combination therapy exhibited responses 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 DMARDs vs. synthetic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs*.

Etanercept plus MTX vs. etanercept. Two RCTs (in four publications)[63-66] and two prospective cohort studies[53,62] 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 DMARDs vs. synthetic DMARDs)* 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, statistically significantly higher proportions 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.[64]

A German retrospective cohort study based on the RABBIT database did not find differences in discontinuation rates because of lack of efficacy between patients on etanercept monotherapy and those on an etanercept-MTX combination (20 percent vs. 17 percent; P = NR).[67]

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of findings from efficacy RCTs.[65] ACR response rates, 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),[66] a 12-month prospective cohort study,[53] and a 6-month prospective cohort study.[62] Their results were generally consistent with findings from the TEMPO trial. Both prospective cohort studies were population-based, one in the United States[53] and the other in the United Kingdom,[62] 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.[62] 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, 1.14-2.42).

Etanercept plus sulfasalazine vs. 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.[60] 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, DAS 28). 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.

Infliximab plus MTX vs. infliximab. No RCT examined the comparative efficacy and effectiveness of a combination of infliximab and MTX against infliximab monotherapy in patients with RA. The only comparative evidence comprises one U.S. and one U.K. prospective cohort study (already described).[53,62] Both studies indicated that European League Against Rheumatism (EULAR) and modified ACR response rates were better 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, 0.92-2.00).[62] At 12 months, mACR 20 responses were similar for U.S. patients in the combination and the monotherapy groups (OR, 0.96; 95% CI, 0.76-1.21; *P* = 0.72).[53]

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 with those on an infliximab-MTX combination regimen (45 percent vs. 18 percent; *P* = NR).[67] 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, 1.1-3.1).

Rituximab plus MTX vs. 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.[61] 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). Similar proportions of patients in both treatment groups achieved a good or moderate EULAR response (83 percent vs. 85 percent; *P* = NR). However, the proportions of patients meeting all three ACR response criteria were 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 had an ACR 50 response.

Biologic combination strategies: Biologic DMARD plus synthetic DMARD vs. synthetic DMARD. The evidence is limited to two studies comparing a combination regimen of adalimumab plus MTX[57]or a combination regimen of infliximab plus MTX[68] with MTX monotherapy. Both studies were conducted in patients with early, aggressive RA.

Adalimumab plus MTX vs. MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA[57] (see *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs).* 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).[57] 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 (DAS 28 < 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).

Infliximab plus MTX vs. 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.[68] 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] vs. 46.7 percent [6 mg infliximab plus MTX] vs. 26.4 percent [MTX]; $P < 0.001$); remission rates were 31 percent, 21 percent, and 15 percent, respectively. In addition, HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX group. Fewer patients in the combination groups than in the MTX monotherapy group withdrew because of lack of efficacy (1.9 percent vs. 3.3 percent vs. 9.6 percent; P = NR). More patients in the combination groups than in the placebo group had serious adverse events (14 percent vs. 11 percent; P = NR) and serious infections (5.6 percent [3 mg/kg infliximab] vs. 5.0 percent [6 mg/kg infliximab] vs. 2.1 percent [MTX]; $P = 0.02$ and $P = 0.04$). Patients on the combination treatment also had a higher probability of maintaining their employability than did those on MTX alone.[69]

Psoriatic Arthritis: Overview

Six RCTs and two systematic reviews examined symptom response, radiographic joint damage, and remission for psoriatic arthritis (PsA). Details are found in Evidence Tables 3 and 4 in Appendix E. Table 12 provides information on symptom response and quality ratings; Table 13 provides information on radiographic outcomes. The main drug classes examined include corticosteroids, synthetic DMARDs, biologic DMARDs, and combined strategies.

Table 12. Study characteristics, symptom response, and quality ratings of studies in adults with psoriatic arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Synthetic DMARDs vs. Placebo					
Jones et al., 2000[111]	Systematic review and meta-analysis 1,022	Active PsA; concomitant MTX NR	MTX vs. placebo SSZ vs. placebo	Change in pooled index: MTX 0.65 units (95% CI, 0.00-1.30) SSZ 0.38 units (95% CI, 0.21-0.54)	Good
Kaltwasser et al., 2004[112,113]	RCT 190 24 weeks	Active PsA; failed at least one DMARD; concomitant MTX 0%	LEF (100 mg/day 3 days then 20 mg/day) vs. placebo	PsARC at week 24: LEF 58.9% vs. placebo 29.7% ($P < 0.0001$)	Fair
Biologic DMARDs vs. Placebo					
Mease et al., 2005 ADEPT Trial[114]	RCT 313 24 weeks	Active PsA; failed at least one DMARD; concomitant MTX 51%	ADA (40 mg every other week) vs. placebo	ACR 20 at week 24: ADA 57% vs. placebo 15% ($P < 0.001$)	Fair

Table 12. Study characteristics, symptom response, and quality ratings of studies in adults with psoriatic arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Antoni et al., 2005 IMPACT Study[115,116]	RCT 104 50 weeks (16 blinded, 34 open-label)	Active PsA; failed at least one DMARD; concomitant MTX 56%	INF (5 mg/kg at weeks 0, 2, 6, 14 then every 8 weeks) vs. placebo 71% received a concomitant DMARD	ACR 20 at week 16: INF 65.4% vs. placebo 9.6% ($P < 0.001$)	Fair
Antoni et al., 2005 IMPACT 2 Study[117,118]	RCT 200 14 weeks (early escape at 16 weeks)	Active PsA; failed at least one DMARD; concomitant MTX 46%	INF (5 mg/kg at weeks 0, 2, 6, 14, 22) vs. placebo 46% received concomitant MTX	ACR 20 at week 14: INF 58% vs. placebo 11% ($P < 0.001$)	Fair
Mease et al., 2000[119]	RCT 60 12 weeks	Active PsA; failed at least one DMARD; concomitant MTX use 47%	ETA (25 mg twice a week) vs. placebo	PsARC at week 12: ETA 87% vs. placebo 23% ($P < 0.0001$)	Fair
Mease et al., 2004[120]	RCT 205 24 weeks (with additional 48 weeks open-label)	Active PsA; failed at least one DMARD; concomitant MTX 47%	ETA (25 mg twice a week) vs. placebo	ACR 20 at week 24: ETA 59% vs. placebo 15% ($P < 0.001$)	Fair
Woolacott et al., 2006[121]	Systematic review and meta-analysis 369	Adults with PsA; concomitant MTX 46% to 56%	ETA (25 mg twice a week) vs. placebo (two studies) INF (5 mg/kg) vs. placebo (one study)	ACR 20 at week 12: ETA 65% (RR, 4.19 [95% CI, 2.74-6.42] ACR 20 at week 16: INF 65% (RR, 6.80; 95% CI, 2.89-16.01)	Good

ACR 20, American College of Rheumatology 20 percent improvement from baseline to endpoint; ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, infliximab; LEF, leflunomide; mg, milligram; MTX, methotrexate; NR, not reported; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Scale; RCT, randomized controlled trial; RR, relative risk; SSZ, sulfasalazine; vs., versus.

Table 13. Study characteristics and radiographic joint damage in adults with psoriatic arthritis

Study	Study Design N Duration	Population with Early PsA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Biologic DMARDs vs. Placebo				
Mease et al., 2005 ADEPT Trial[114]	RCT 313 24 weeks	No	ADA (40 mg every other week) vs. placebo	Mean change in the modified total Sharp score at week 24: ADA -0.1 vs. placebo 1.0 ($P < 0.001$) Erosion scores (mean change): ADA 0.0 vs. placebo 0.6 Joint space narrowing scores (mean change): ADA -0.2 vs. placebo 0.4 ($P < 0.001$ for both)

Table 13. Study characteristics and radiographic joint damage in adults with psoriatic arthritis (continued)

Study	Study Design N Duration	Population with Early PsA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Mease et al., 2004[122]	RCT 205 72 weeks (24 blinded, 48 open-label)	No	ETA (25 mg twice a week) vs. placebo	Mean annualized rate of change over 1 year of treatment in modified Sharp score: ETA -0.03 unit vs. placebo 1.00 unit (*P* = 0.0001)

ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; mg, milligram; PsA, psoriatic arthritis.

Psoriatic Arthritis: Key Points

We did not find any head-to-head comparison for any of the drugs used to treat PsA. One systematic review found that, compared with placebo, parenteral high-dose MTX and sulfasalazine improved patient outcomes.[111] The strength of evidence is low.

Leflunomide patients had higher response rates and quality-of-life outcomes than those in the placebo arm.[112,113] The strength of evidence is moderate.

The use of three biologics—adalimumab, etanercept, and infliximab—led to better outcomes than did placebo.[114-120,122] The strength of evidence is moderate.

Psoriatic Arthritis: Detailed Analysis

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of synthetic and biologic DMARDs in the treatment of PsA. This, however, does not provide evidence on the comparative efficacy and tolerability of treatments for PsA.

Corticosteroids. We did not identify any studies that examined the use of corticosteroids in the treatment of PsA.

Synthetic DMARDs. One systematic review examined the efficacy of synthetic DMARDs used in placebo-controlled trials.[111] The investigators used data from 13 RCTs that included 1,022 adults with PsA in a meta-analysis that focused on comparisons of sulfasalazine, auranofin, etretinate, fumaric acid, intramuscular injection of gold, azathioprine, efamol marine, and MTX with placebo. Two drugs (MTX and sulfasalazine) are of interest for our report. The primary outcome measure included individual component variables validated by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) to create a pooled index; components used include acute phase reactants, disability, pain, patient global assessment, physician global assessment, swollen joint count, tender joint count, and radiographic changes of joints in any trial of 1 year or longer. The primary outcome was change in a pooled disease index.

MTX. In a systematic review, one study compared MTX with placebo; parenteral high-dose MTX (weekly dose of 7.5 mg to 15 mg) showed an overall improvement in the OMERACT index of 0.65 units (95% CI, 0.00-1.30), although the sample for this study was small (N = 37).

Sulfasalazine. The investigators pooled six trials involving comparisons of sulfasalazine (average dose of 2 g/day to 3 g/day) with placebo (N = 564). Sulfasalazine showed an improvement in the pooled index of 0.38 units (95% CI, 0.21-0.54).[111]

Leflunomide. One trial (two publications) evaluated the efficacy of leflunomide against placebo in 190 patients over 24 weeks;[112,113] PsA was defined as having at least three swollen joints and three tender or painful joints and psoriasis over at least 3 percent of the body surface area. In this study, almost 50 percent of the patients were DMARD naive. Patients who were not DMARD naive were required to discontinue all synthetic DMARDs as well as biologic agents and investigational drugs 28 days before baseline.

The leflunomide group saw significantly greater response rates on a modified ACR 20 (36.3 percent) than the placebo group (20 percent; $P = 0.014$). The PsARC (Psoriatic Arthritis Response Criteria) is a composite measure requiring improvement in two factors (at least one being a joint score) and worsening in none among the following four factors: patient and physician global assessments (improvement defined as decrease by ≥ 1 unit; worsening defined as increase by ≥ 1 unit); and tender and swollen joint scores (the sums of all joints scored; improvement defined as decrease by ≥ 30 percent; worsening defined as increase by ≥ 30 percent). The PsARC was achieved in 58.9 percent of those on leflunomide and 29.7 percent of those on placebo ($P = 0.0001$). PASI 75 (Psoriasis Area and Severity Index) is a composite score (range 0 to 72) used to evaluate the severity of psoriatic lesions by assessing the extent of skin involvement, erythema, plaque thickness, and degree of scaling; the PASI 75 indicates a 75 percent improvement in psoriasis activity from baseline. In this study, 17.4 percent of the leflunomide group and 7.8 percent of the placebo group reached the PASI threshold ($P = 0.048$).

Biologic DMARDs. Five trials (eight articles) and one systematic review examined the efficacy of biologics against placebo in treating patients with PsA.[114-122] One trial was of adalimumab, two of etanercept, and two of infliximab. All trials used a synthetic DMARD, usually MTX, as a base treatment in all patients. The systematic review examined etanercept and infliximab vs. placebo.[121] All showed that the use of biologics led to significantly better outcomes than placebo.

Adalimumab. One trial examined the use of adalimumab (40 mg every other week) in 313 patients suffering from moderate to severe PsA (defined as having at least three swollen joints and three tender or painful joints) who had an inadequate response or intolerance to nonsteroidal anti-inflammatory drug (NSAID) therapy.[114] Patients were allowed to continue current MTX therapy as long as the dose had been stable for 4 weeks. The double-blinded phase of the study lasted 24 weeks, but patients who failed to achieve at least a 20 percent decrease in both swollen and tender joint counts on two consecutive visits could receive rescue therapy with corticosteroids or synthetic DMARDs. A significantly higher percentage of the adalimumab group met ACR 20/50/70 response criteria than the placebo group (all $P < 0.001$). According to the PsARC, 60 percent of the adalimumab group and 23 percent of the placebo group responded (P = NR). PASI 75 was achieved by 59 percent of the adalimumab group and 1 percent of the placebo group ($P < 0.001$). At 24 weeks, the changes in the modified Sharp score, erosion score, and joint space narrowing score were significantly less in adalimumab-treated than placebo-treated patients ($P = 0.001$).

Etanercept. Two studies examined the efficacy of etanercept (25 mg twice weekly by subcutaneous injections) in 265 patients with active PsA who were not adequately responding to conventional DMARD therapies.[119,120] In both studies, patients were allowed to continue MTX therapy as long as the dose had been stable for 4 weeks before entry into the study. One study

lasted 12 weeks (N = 60);[119] the other (N = 205) was double-blinded for 24 weeks.[120] In both studies, the proportions of patients on etanercept meeting ACR 20 response criteria were significantly higher than those for patients on placebo. In the 12-week study, 87 percent of patients on etanercept and 23 percent of those on placebo achieved a PsARC response ($P < 0.0001$).[119] The 24-week study had similar results at 12 weeks: 72 percent of patients on etanercept and 31 percent of those on placebo achieved a PsARC response (P = NR).[120] PASI 75 criteria were met by a greater proportion of patients in the etanercept groups than the placebo groups in both studies. In the 12-week study, 26 percent of patients on etanercept met PASI 75 criteria vs. zero patients on placebo ($P = 0.015$); in the longer study, the figures were 23 percent on etanercept vs. 3 percent on placebo ($P < 0.001$). The longer study assessed the radiographic progression of disease at 24 weeks in 205 patients; the mean annualized change in the modified Sharp score was significantly lower in etanercept-treated patients (decrease of -0.03) than in placebo-treated patients (increase of 1.0; $P = 0.0001$).[122]

A recent systematic review pooled the 12-week data from these two studies; the ACR 20 threshold for improvement was achieved by 65 percent of the etanercept groups, with a pooled relative risk of 4.19 (95% CI, 2.74-6.42).[121] The ACR 50 and ACR 70 criteria were achieved by 45 percent and 12 percent, respectively. In addition, the PsARC was reached by almost 85 percent, with a pooled relative risk of 2.6 (95% CI, 1.96-3.45).[121]

Infliximab. Two studies of infliximab compared with placebo included 304 patients with active PsA who had not adequately responded to conventional DMARD therapies.[115,117] In both studies, patients were allowed to continue MTX therapy as long as the dose had been stable for 4 weeks before study entry. The earlier study (N = 104) was double-blinded for 16 weeks.[115] The later trial was double-blinded for 24 weeks (N = 200 patients with cross-over allowed at week 16 for nonresponders); the primary outcomes were evaluated at 14 weeks and before any crossover.[117] Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, and 14; the longer study had an additional injection at week 22. In both studies, the percentages meeting ACR 20 response criteria were significantly greater for infliximab than for placebo. In the earlier study, 86 percent of the patients on infliximab and 12 percent on placebo achieved a PsARC response ($P < 0.001$). The longer study had similar results in patients achieving a PsARC response at 14 weeks: 77 percent of the patients on infliximab and 27 percent on placebo ($P < 0.001$). PASI 75 was achieved by a greater proportion of patients in the infliximab groups than the placebo groups in both studies: for the 16-week study, 68 percent on infliximab vs. zero on placebo ($P < 0.01$) and, for the later study, 50 percent on infliximab vs. 1 percent on placebo ($P < 0.001$).

Key Question 2: Functional Capacity and Quality of Life

This question examined specifically the issue of whether, for patients with RA or PsA, drug therapies differed in their ability to improve functional capacity or quality of life. Findings are organized as for KQ 1: RA followed by PsA. Table 9 (above) lists the abbreviated and full names of all instruments and scales referred to in this section. Functional capacity, functional status, and functional ability are three concepts often used interchangeably to refer to similar capabilities. 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. For the purposes of this report we divided outcomes into functional capacity and health-related quality of life. We use the terms *functional capacity, functional status,* or *functional ability* to refer to

condition-specific measures, such as the Health Assessment Questionnaire (HAQ), developed to assess function in patients with RA or PsA. We use *health-related 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 quality of life in both healthy persons and those with different conditions. We also attempted to use terminology consistent with reporting from individual studies; if the authors used the term *functional ability* rather than *functional capacity,* we used the same term. Outcomes for functional capacity and health-related quality of life were sometimes secondary outcomes in these studies; that is, studies were not all designed to detect a difference between groups for these two types of outcomes.

Rheumatoid Arthritis: Overview

A total of 16 RCTS, two observational studies, and one systematic review compared functional capacity or quality-of-life outcomes between active drugs or between active drugs and placebo. Details are found in Evidence Tables 5 and 6 in Appendix E. Table 14 provides information on comparisons made, functional capacity, health-related quality of life, and quality ratings. The main drug classes compared include corticosteroids, synthetic DMARDs, biologic DMARDs, and combined strategies.

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Corticosteroids vs. Corticosteroids						
Kirwan et al., 2004[29]	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)	Better improvement in mean HAQ scores for PNL PNL 0.393 units better than BUD 3 mg; *P* < 0.001 PNL 0.276 units better than BUD 9 mg; *P* < 0.01	Better improvement in SF-36 physical component for PNL than for BUD (mean change 5.4 units better than BUD 3 mg, *P* < 0.01; 3.7 units better than BUD 9 mg, *P* < 0.05)	Fair
Synthetic DMARDs vs. Synthetic DMARDs						
Capell et al., 2007[30]	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
Dougados et al., 1999[31]	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

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Emery et al., 2000[32]	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)	Change in HAQ at 12 months, minimal quantitative (data NR) but significant ($P < 0.05$); at 24 months, difference NS	NR	Fair
Haagsma et al., 1997[33]	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
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week) LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	MHAQ scores improved significantly in LEF group compared with MTX at 6, 12, and 24 months; at both 12 and 24 months, no difference in improvement in HAQ At 6 and 24 months, LEF group had greater improvements in HAQ-DI than SSZ At one year there was no difference in work productivity in LEF vs. MTX weighted mean difference -2.3 points: 95% CI, 6.37-1.77	LEF showed better improvement than MTX in SF-36 physical component but not mental component	Good
Smolen et al., 1999[35] Scott et al., 2001[123]	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
Strand, et al., 1999[37] Cohen, et al., 2001[38]	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; $P \leq 0.01$) 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

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Synthetic DMARD Combinations						
Boers et al., 1997;[39] Landewe et al., 2002[40] 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
Capell et al., 2007[30]	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[31] Maillefert et al., 2003[41]	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

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Goekoop-Ruiterman et al., 2005 [42] BeSt study	RCT 508 12 months	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)	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/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)	Better functional ability after 12 months for patients treated with 3 or 4 than those treated with group (mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.5, and 0.5, respectively; $P < 0.05$ for 1 vs. 3 and 4, NS for other comparisons)	NR	Good
Haagsma et al., 1997[33]	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 - -0.26 vs. SSZ -0.32: 95% CI, -0.53 - -0.10 vs. MTX -0.46: 95% CI, -0.68 - -0.25; P = NR)	NR	Fair
Mottonen et al., 1999;[43] Korpela et al., 2004;[44] Puolakka et al., 2004[124] 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 (2 g/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
Svensson et al., 2005[47]	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

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Biologic DMARDs vs. Biologic DMARDs						
Weaver et al., 2006[53]	Prospective cohort study 1,371 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETA (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Greater mean percentage improvements in HAQ at 12 months in ETA than INF (17% vs. 1%; *P* = NR)	NR	Fair
Biologic DMARDs vs. Synthetic DMARDs						
Bathon et al., 2000;[54] Genovese et al., 2002;[55] Genovese et al, 2005;[56] Kosinski et al., 2002[125] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETA (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Better improvement in HAQ early in treatment (first 12 weeks) for ETA 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 ETA 25 mg than for either ETA 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 ETA group than the MTX group during first 12 weeks (*P* < 0.0001) No significant difference in weeks 16 to 52	Fair
Breedveld et al., 2006 [57] 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

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] 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	ETA (25 mg twice weekly) vs. MTX (20 mg/week)	Similar improvement in mean HAQ scores for MTX and ETA (scores fell from 1.7 to 1.1 and 1.7 to 1.0; *P* = 0.3751)	NR	Good
Listing et al., 2006[58]	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, ETA, 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, 1.7-8.8) Functional remission (≥ 83% of full function) more often achieved in biologic group than in DMARD group (OR, 2.18; 95% CI, 1.04-4.6)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Biologic DMARDs + Synthetic DMARDs vs. Biologic DMARDs						
Breedveld et al., 2006[57] 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
Combe et al., 2006[60]	RCT 260 24 weeks	Europe multicenter; active RA despite SSZ treatment; mean disease duration 6.6 years	ETA (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. ETA (25 mg twice weekly)	Mean percentage improvements in HAQ were similar for ETA + SSZ and ETA alone (40.2% vs. 35.3%, *P* = NS)	Mean percentage improvements in EuroQOL VAS were similar for ETA + SSZ and ETA alone (67.6% vs. 64.6%; *P* = NS)	Fair
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] TEMPO study	RCT 696 (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	ETA (25 mg twice weekly) + MTX (20 mg/week) vs. ETA (25 mg twice weekly)	At 52 weeks ETA + MTX was more likely to attain HAQ-DI scores similar to population norms (< 0.5) than ETA 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)	ETA + MTX patients reported better quality of life than ETA-only patients (mean EQ 5-D VAS 72.7 vs. 66.8; *P* < 0.05)	Good
Weaver et al., 2006[53]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly)	Patients treated with ETA + MTX had similar improvements in functional capacity to those treated with ETA only (mean percentage improvements in HAQ at 12 months: 17% vs. 17%; *P* = NR)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Biologic DMARDs + Synthetic DMARDs vs. Synthetic DMARDs						
Breedveld et al., 2006[57] 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)	At 1 year, ADA + MTX had greater improvements in HAQ-DI than MTX alone (mean -1.1 units vs. -0.8; $P < 0.001$). After 2 years, ADA + MTX remained statistically greater (-1.0 vs. -0.9; $P < 0.058$) After 2 years, more ADA + MTX patients had improvement of ≥ 0.22 in HAQ-DI than MTX patients (72% vs. 63%; $P < 0.05$). Had greater percentage with HAQ-DI scores of 0 (33% vs. 19%; $P < 0.001$)	NR	Fair
St Clair et al., 2004;[68] Smolen et al., 2006[69] 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)	Greater mean decrease in HAQ from weeks 30 to 54 for combination groups than MTX group (INF 3 mg + MTX and INF 6 mg + MTX vs. MTX: 0.80 and 0.88 vs. 0.68; $P = 0.03$; $P < 0.001$). Combination therapy was more effective for improving HAQ by at least 0.22 units (76.0% and 75.5% vs. 65.2%; $P = 0.003$; $P = 0.004$) Patients on combination treatment had a higher probability of improvement in employability than those on MTX alone ($P < 0.001$)	Significantly greater improvement in SF-36 physical component summary scores 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

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Weaver et al., 2006[53]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly)	Greater mean percentage improvements in HAQ at 12 months for ETA + 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

BUD, budesonide; combo, combination therapy; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETA, 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.

Rheumatoid Arthritis: Key Points

Corticosteroids vs. corticosteroids. Only one head-to-head RCT compared two corticosteroids, budesonide and prednisolone.[29] Prednisolone produced greater improvement in functional capacity and health-related quality of life than budesonide. The results are limited to one study. The strength of evidence is low.

Synthetic DMARDs vs. synthetic DMARDs. Two RCTs[32,37] and one systematic review with meta-analysis[34] compared leflunomide and MTX. Some results indicated greater improvement with leflunomide (mean improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI) at 12 months and 24 months and in the SF-36 (Medical Outcomes Study Short Form 36 Health Survey) physical component at 12 months; others showed no differences in work productivity or the SF-36 mental component. The strength of the evidence is moderate.

One RCT[35] with a 2-year followup[123] compared leflunomide and sulfasalazine. Leflunomide yielded greater improvements in functional capacity measured by HAQ scores at 24 weeks, 6 months, and 24 months. The results were limited to one study. The strength of the evidence is low.

Three RCTs compared sulfasalazine and MTX.[30,31,33] Results, consistent across the trials, did not support a difference in functional capacity between the medications. The strength of the evidence is moderate.

No fair or good evidence exists for comparing hydroxychloroquine to monotherapy with another synthetic DMARD.

Synthetic DMARD combinations. Three RCTs compared a combination of two synthetic DMARDs (sulfasalazine plus MTX) to monotherapy with either drug alone.[30,31,33] Findings do not support a difference in functional capacity between combination therapy and monotherapy. The strength of the evidence is moderate.

Three RCTs compared various combination strategies using corticosteroids and one or more synthetic DMARDs with synthetic DMARD monotherapy.[39,43,47] One open-label RCT compared the combination of a synthetic DMARD and prednisolone with synthetic DMARD monotherapy and found greater improvement in functional capacity for the combination group.[47] The functional capacity outcomes were not statistically evaluated for the two groups, and 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. Another RCT found that the combination of sulfasalazine, MTX, and prednisolone vs. sulfasalazine alone resulted in greater improvements in functional capacity at 28 weeks, but the difference was no longer statistically significant at 56 weeks.[39] The third RCT compared a combination of three synthetic DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone with synthetic DMARD monotherapy.[43] The combination therapy group had significantly less work disability than patients in the monotherapy group at 5-year followup.[124] Of note, the randomized treatments were carried out for 2 years and treatments were then at the discretion of the treating physician.

The data are limited to one study for each comparison. The strength of the evidence is low for each individual comparison. However, the strength of evidence is moderate favoring combination strategies using corticosteroids plus one or more synthetic DMARDs over synthetic DMARD monotherapy.

One RCT in patients with early RA found that patients treated with initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab and MTX had statistically significantly better functional ability than those treated with sequential DMARD therapy.[42] However, the magnitude of difference was small, and the clinical significance of this result is uncertain. The strength of the evidence is low.

Biologic DMARDs vs. biologic DMARDs. We did not find any head-to-head RCTs that compared one biologic DMARD with another. The evidence was limited to one prospective cohort study that compared etanercept with infliximab.[53] Patients treated with etanercept had better functional capacity at 12 months than did those treated with infliximab (mean percentage improvements in HAQ 17 percent vs. 1 percent; P = NR). However, direct statistical comparisons between etanercept and infliximab were not described. The strength of the evidence is low.

Biologic DMARDs vs. synthetic DMARDs. We found three RCTs[54,57,63] and one prospective cohort study[58] that included comparisons of monotherapy with a biologic DMARD to monotherapy with a synthetic DMARD. The evidence from these studies is mixed. Population-based, observational evidence from the cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than synthetic DMARDs as a class.[58] Two of the RCTs, however, found no differences when comparing either adalimumab[57] or etanercept[63] with MTX. The third RCT [54] found that etanercept resulted in better improvement of function and quality of life during the first 12 weeks of treatment, but it found no difference from week 16 to week 52. The study also reported that a greater percentage of patients treated with etanercept had significant improvements in functional capacity (≥ 0.5 unit HAQ-DI) at 24 months. All RCTs were funded by the makers of the biologic DMARDs. The strength of the evidence is moderate for biologics as a class compared to synthetics as a class.

No evidence exists on abatacept, anakinra, infliximab, and rituximab. No studies were available comparing biologics with synthetic DMARDs other than MTX.

Biologic DMARDS vs. corticosteroids. No studies meeting our quality criteria compared biologic DMARDs with corticosteroids.

Biologic DMARD combinations. Two RCTs suggested that a combination of adalimumab[57] or etanercept[63-65] with MTX led to statistically significantly greater improvements in functional capacity or health-related quality of life than monotherapy with biologic DMARDs. One other RCT found no difference between a combination of etanercept with sulfasalazine and etanercept monotherapy.[60] One prospective cohort study found no differences in these outcomes when comparing etanercept plus MTX to etanercept alone or infliximab plus MTX to infliximab alone.[53] The strength of the evidence is low for all comparisons.

For most individual medications in these comparisons, however, 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 synthetic DMARD vs. biologic DMARD) was available on abatacept, anakinra, rituximab, and combinations with synthetic DMARDs other than MTX and sulfasalazine.

Two RCTs found that a combination of adalimumab plus MTX[57] or infliximab plus MTX[68] in MTX-naive patients with early, aggressive RA led to better functional capacity and quality of life than MTX monotherapy. Both RCTs were funded by the makers of the biologic DMARDs. One prospective cohort study found the etanercept-MTX combination to be greater than MTX monotherapy for functional capacity, but it found no difference between the infliximab-MTX combination and MTX alone.[53] The strength of the evidence supporting a greater efficacy of combination treatment with a biologic DMARD plus MTX than with MTX monotherapy is moderate for the above comparisons.

Rheumatoid Arthritis: Detailed Analysis

Corticosteroids. *Corticosteroid vs. corticosteroid.* 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).[29] 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 (0.393 units better than budesonide 3 mg, $P < 0.001$; 0.276 units better than budesonide 9 mg, $P < 0.01$). A change of 0.22 units is generally considered the minimum clinically important difference.[126] Those treated with prednisolone also had better improvement in health-related quality of life as measured by the physical subscale of the SF-36 (difference in mean change of 5.4 units compared with budesonide 3 mg, $P < 0.01$; 3.7 compared with budesonide 9 mg, $P < 0.05$). 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.

Synthetic DMARD vs. synthetic DMARD. *Leflunomide vs. methotrexate.* We found two RCTs[32,37] comparing leflunomide (20 mg/day) with MTX (7.5 mg/week to 15 mg/week)[32,37] and one good systematic review with a meta-analysis of leflunomide.[34] The systematic review included only two trials comparing leflunomide with MTX and only one study for all but one of the functional capacity and quality-of-life outcomes. We describe the individual studies first.

The first trial randomized 482 patients to leflunomide (n = 182) or MTX (n = 182) over 12 months.[37,127] It is described in more detail in the KQ 1 section entitled *Synthetic DMARDs vs. synthetic DMARDs.* Patients receiving leflunomide reported greater mean improvement in the HAQ-DI (-0.45 vs. -0.26; $P \leq 0.01$), MHAQ (-0.29 vs. -0.15; $P < 0.01$), and the SF-36 physical component (7.6 vs. 4.6; $P < 0.01$) than those receiving MTX at 12 months. At 12 months, the

two groups did not differ significantly in improvement in the SF-36 mental summary score (1.5 vs. 0.9; *P* = NS) 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* ≤ 0.05) with leflunomide than with MTX.[38] 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.

One multinational trial comparing leflunomide and MTX was a 1-year RCT of 999 subjects with an optional second year.[32,128] Mean disease duration was 3.5 years to 3.8 years. At 12 months, a statistically significant but minimal quantitative difference (number not reported, shown in bar graph)[32] for change in the HAQ (*P* < 0.05) was reported between the two groups; at 24 months, however, the groups did not differ significantly.

The systematic review with meta-analysis included six trials (N = 2,044) comparing leflunomide (10 to 20 mg/day) with other synthetic DMARDs in patients with active RA.[34] It included two studies relevant to this section.[32,37] 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, -6.37-1.77). When comparing leflunomide with MTX, changes in SF-36 scores showed better improvement in the physical summary score (WMD, -3.0 points; 95% CI, -5.41 - -0.59) but not the mental summary score (WMD, -0.6 points; 95% CI, -3.01-1.81). 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, for which there were two studies.

Leflunomide vs. sulfasalazine. One RCT[35] with a 2-year followup[123] compared leflunomide (20 mg/day) with sulfasalazine (2 g/day); one systematic review included a meta-analysis of leflunomide.[34] The RCT was a multinational, multicenter study of 358 patients (leflunomide, n = 133; sulfasalazine, n = 133).[35] Baseline HAQ scores were similar for all groups. The leflunomide group had significantly greater improvement in HAQ scores at 24 weeks than the sulfasalazine group (-0.50 vs. -0.29; *P* < 0.03). The 2-year followup found that the leflunomide group had significantly greater improvements in HAQ scores than the sulfasalazine group at 6 and 24 months (-0.50 vs. -0.29 and -0.65 vs. -0.36; both *P* < 0.01).[123] The study was limited by only including 146 (leflunomide, n = 60; sulfasalazine, n = 60) 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.[34] For comparing leflunomide and sulfasalazine, the meta-analysis included one study (N = 229) with changes in HAQ at 6, 12, and 24 months.[123] 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 - -0.08; WMD -0.29 point; 95% CI, -0.57 - -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 vs. MTX. Three RCTs compared sulfasalazine with MTX.[30,31,33] Their findings are consistent and do not support a difference in functional capacity between the groups receiving these two pharmaceuticals. A multinational 52-week RCT of 209 DMARD-naive subjects found no statistically significant difference in change in the HAQ from baseline to 1

year (sulfasalazine -0.74; MTX -0.73; *P* = NS).[31] A 52-week RCT of 105 DMARD-naive subjects in academic and peripheral clinics in the Netherlands reported a change in HAQ scores from baseline to 52 weeks of -0.32 (95% CI, -0.53 - -0.10) for sulfasalazine and a change of -0.46 (95% CI, -0.68 - -0.25; *P* = NR) for MTX.[33] HAQ was a secondary outcome in this study; HAQ changes for the different groups were not compared statistically. An 18-month RCT of 165 subjects at eight sites in Scotland found no significant difference between the sulfasalazine and MTX groups on the HAQ between baseline and endpoint (-0.25 vs. -0.19; *P* = 0.99).[30]

Synthetic DMARD combinations. *MTX plus sulfasalazine vs. monotherapy with MTX or sulfasalazine.* Three RCTs (four publications) compared MTX plus sulfasalazine to either drug alone.[30,31,33,41] Two of the RCTs included patients with disease duration of less than 1 year;[31,33] the third included patients with RA of up to 10 years.[30] Findings of these studies do not support a difference in functional capacity between combination therapy and either monotherapy.

A multinational RCT of 209 DMARD-naive subjects compared sulfasalazine (2 g/day to 3 g/day; n = 68), MTX (7.5 mg/week to 15 mg/week; 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 (combination -0.70; sulfasalazine -0.74; MTX -0.73; *P* = NS).[31] A long-term followup comparing the combination therapy to monotherapy (combining the two monotherapy groups) found no significant difference in mean HAQ scores at 5 years (combination 0.6; monotherapy 0.6; *P* = 0.9).[41]

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 - -0.26) for the MTX-sulfasalazine combination therapy, a change of -0.32 (95% CI, -0.53 - -0.10; *P* = NR) for sulfasalazine, and a change of -0.46 (95% CI, -0.68 - -0.25; *P* = NR) for MTX.[33] The HAQ was a secondary outcome in this study; the authors did not attempt to explain these results or compare the values.

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 (combination -0.50; sulfasalazine -0.25; MTX -0.19; combination vs. sulfasalazine, *P* = 0.51; combination vs. MTX, *P* = 0.57).[30]

Synthetic DMARD plus corticosteroid combinations vs. synthetic DMARDs. *One synthetic DMARD plus corticosteroid vs. synthetic DMARD.* The evidence is limited to one open-label RCT that compared synthetic DMARD use with and without prednisolone in patients with active RA for 1 year or less.[47] This 2-year study compared prednisolone (7.5 mg/day) added to an initial DMARD (chosen by the treating physician) with a synthetic DMARD only in patients with early RA; it is described in greater detail in the Key Question 1 section entitled *One synthetic DMARD plus corticosteroid vs. synthetic DMARD.* The authors reported greater improvement in functional capacity for the prednisolone group than the nonprednisolone group. The DMARD plus prednisolone group had a decrease in HAQ scores from a mean of 1.0 at baseline to 0.4 at 1 year and 0.5 at 2 years. The corresponding values for the DMARD-only group were 1.0, 0.6, and 0.7 (*P* = NR). The DMARD plus prednisolone group also had greater improvement in the mean Signals of Functional Impairment (SOFI) index (mean decrease from 8 at baseline to 4 at 1 year and 4 after 2 years compared to values of 9, 6, and 7, respectively; *P* = NR). 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.

Two synthetic DMARDs plus corticosteroid vs. synthetic DMARD. The COBRA (Combinatietherapie Bij Reumatoide Artritis) study assessed differences in efficacy between a combination of sulfasalazine, MTX, and prednisolone and sulfasalazine only.[39] This RCT evaluated 155 patients with early RA over 56 weeks. Combination therapy included sulfasalazine (2 g/day), MTX (7.5 mg/week stopped after 40 weeks), and prednisolone treatment (60 mg/day tapered over 28 weeks). Compared with patients treated with sulfasalazine alone, patients treated with combination therapy had greater improvements in functional capacity at 28 weeks (mean change in HAQ of -1.1 vs. -0.6; $P < 0.0001$). The difference was no longer statistically significant at 56 weeks (mean change in HAQ, -0.8 vs. -0.6; $P < 0.06$).

Three synthetic DMARDs plus corticosteroid vs. synthetic DMARD. The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) RCT assessed the efficacy of a combination of MTX, sulfasalazine, hydroxychloroquine, and prednisolone against monotherapy with a DMARD with or without prednisolone.[43] This study randomized 199 patients with early RA to combination therapy or monotherapy. Combination therapy included sulfasalazine (2 g/day), MTX (7.5 mg/week to 10 mg/week), hydroxychloroquine (300 mg/day), and prednisolone (5 mg/day to 10 mg/day). 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 entitled *Three synthetic DMARDs plus corticosteroid vs. synthetic DMARDs*. 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 (median 12.4 days per patient-observation year vs. 32.2 days; $P = 0.008$, sex- and age-adjusted $P = 0.009$).[124] After 2 years, the drug treatment strategy was no longer restricted.

Other combination strategies. The BeSt RCT (Dutch acronym for Behandel Strategieen, "treatment strategies") examined four different treatment strategies over 12 months.[42] 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 (2 g/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. After 12 months of treatment, patients treated with strategy 3 or 4 had statistically significantly better functional ability than those treated with strategy 1; (mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.5, and 0.5, respectively; $P < 0.05$ for group 1 vs. groups 3 and 4, NS for other comparisons).

Biologic DMARD vs. biologic DMARD. We did not identify any head-to-head RCTs. The head-to-head evidence was limited to a prospective cohort study based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program that included etanercept and infliximab.[53]

Etanercept vs. infliximab. RADIUS was a primary care-based U.S. study that enrolled patients who were initiating any new DMARD at study entry. 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 greater mean percentage

improvements 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 greater mean percentage improvements in the HAQ at 12 months than infliximab-treated patients (22 percent vs. 4 percent; *P* = NR). However, direct statistical comparisons between etanercept and infliximab were not described. The study was designed to compare combinations of etanercept or infliximab with MTX to monotherapy with etanercept, infliximab, or MTX.

Biologic DMARDs vs. synthetic DMARDs. We found three RCTs and one prospective cohort study that included comparisons of biologic DMARD monotherapy with synthetic DMARD monotherapy. The RCTs compared etanercept with MTX[54,63] and adalimumab with MTX;[57] the cohort study assessed differences in class effects.[58] No head-to-head evidence exists on abatacept, anakinra, infliximab, and rituximab or on synthetic DMARDs other than MTX (although anakinra and infliximab were included in the prospective cohort study comparing biologics as a class to synthetic DMARDs as a class).

Biologic DMARDs as a class vs. synthetic DMARDs as a class. The prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab; n = 818) and synthetic DMARDs as a class (n = 265) in patients who had failed two previous DMARD treatments.[58] 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, defined as ≥ 67 percent of full function as measured by the Hanover Functional Status Questionnaire (FFbH, or Funktionsfragebogen Hannover), than controls on conventional synthetic DMARD therapy (OR, 3.88; 95% CI, 1.7-8.8). Functional remission (≥ 83 percent of full function) was more often achieved in patients receiving biologics than in controls (OR, 2.18; 95% CI, 1.04-4.6).

Adalimumab vs. 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.[57] Two treatment arms of this 2-year study were adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). Details of this study are reported in the KQ 1 section on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs.* After 1 year, the adalimumab and MTX monotherapy groups had similar improvements in functional status measured using the HAQ-DI (mean: -0.8; -0.8; *P* = NR). Improvements remained similar after 2 years (-0.9; -0.9; *P* = NR). After 2 years, 19 percent of patients in both monotherapy groups had HAQ-DI scores of zero. We report on results of the other comparisons of the PREMIER study for functional status outcomes in the respective KQ 2 sections on *Biologic DMARDS plus synthetic DMARDs vs. biologic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs*.

Etanercept vs. MTX. Two trials (seven publications) compared etanercept with MTX (20 mg/week) over 52 weeks.[54-56,63-65,125] The ERA (Early Rheumatoid Arthritis) study (N = 632) was conducted in patients with early RA who were MTX-naive.[54-56] The other study was the TEMPO trial (see KQ 1 section on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs).*[63-65] Patients had active RA and had failed at least one DMARD other than MTX. About 60 percent of the study population was MTX-naive.

ERA was a 52-week multicenter RCT of 632 patients with early RA in the United States that compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week).[54-56,125] 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 ($P = 0.021$).

The 52-week TEMPO RCT of RA patients who had failed previous DMARD therapy compared patients treated with etanercept (25 mg twice weekly) with those treated with MTX (20 mg/week) and those given combination therapy with both drugs.[63] 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 (mean HAQ scores fell from 1.7 to 1.1 and from 1.7 to 1.0, respectively; $P = 0.3751$). We report on comparisons of etanercept with the combination group in the KQ 2 section below on *Biologic DMARD plus synthetic DMARD vs. biologic DMARD*.

Biologic combination strategies: biologic DMARD plus synthetic DMARD vs. biologic DMARD. We found four studies, three RCTs[57,60,63] and one prospective cohort study,[53] comparing the combination of a biologic DMARD plus a synthetic DMARD with biologic DMARD monotherapy. The majority of these studies compared a combination of a biologic DMARD and MTX with monotherapy of the same biologic DMARD.[53,57,63] One trial used sulfasalazine as a synthetic DMARD in combination with a biologic DMARD.[60] We found no evidence on combination treatments of abatacept and anakinra.

Adalimumab plus MTX vs. adalimumab. The PREMIER study was conducted in MTX-naive patients with early (< 3 years), aggressive RA.[57] This 2-year multinational study randomized 799 patients 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). After 1 year, the combination group had greater improvements in HAQ-DI scores (mean: -1.1 units) than the adalimumab group (-0.8; $P = 0.002$). After 2 years, the combination group (-1.0) and the adalimumab-only group (-0.9) did not differ significantly ($P = 0.058$) for improvements in the HAQ-DI. More patients in the combination group (72 percent) had achieved improvement of ≥ 0.22 (considered the clinically relevant threshold) in HAQ-DI than the adalimumab group (58 percent; $P < 0.05$). 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 ($P < 0.001$). For functional capacity outcomes, we report on results of the other comparisons of the PREMIER study in the KQ 2 sections on *Biologic DMARDs vs. synthetic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs.*

Etanercept plus MTX vs. etanercept. One good-quality RCT (three publications)[63-65] and one prospective cohort study[53] assessed differences in efficacy between a combination of etanercept and MTX and etanercept monotherapy in patients with active, DMARD-resistant RA. The RCT

showed greater effectiveness for functional capacity and quality of life for combination therapy; the cohort study found no difference.

The 52-week TEMPO trial involved 696 patients with active RA who had failed previous DMARD therapy.[63-65,91] We focus here on results of the etanercept-MTX combination and the etanercept monotherapy arms; their baseline HAQ scores were similar. The combination therapy group had better improvement in functional status than the etanercept monotherapy group. 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 ($P < 0.05$). The combination group had greater improvement in functional capacity than the monotherapy group (mean HAQ changes from 1.8 to 0.8 vs. 1.7 to 1.0; $P < 0.001$; mean improvement from baseline HAQ 1.0 vs. 0.70; $P < 0.01$). In addition, those receiving combination therapy achieved better quality-of-life scores than etanercept monotherapy (mean European Quality of Life Health Status Visual Analogue Scale [EQ 5-D VAS] 72.7 vs. 66.8; $P < 0.05$).[64]

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings.[65] Improvement in disability (based on HAQ) remained statistically 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 prospective cohort study was based on the RADIUS program[53] (see *Biologic DMARD vs. 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 (17 percent vs. 17 percent; P = NR).

Etanercept plus sulfasalazine vs. etanercept. A 24-week multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy (25 mg twice weekly), sulfasalazine monotherapy (2, 2.5, or 3 g/day), and an etanercept-sulfasalazine combination (25 mg twice weekly plus 2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[60] This study is described in greater detail in the corresponding section for KQ 1. We focus on results of the etanercept monotherapy (n = 103) and the combination (n = 101) arms. 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 (40.2 percent) and the etanercept group (35.3 percent; P = NS). The mean percentage improvement for health-related quality of life measured by the EuroQOL VAS was also similar (67.6 percent vs. 64.6 percent; P = NS).

Infliximab plus MTX vs. 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 vs. etanercept*).[53] 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 combination strategies: biologic DMARD plus synthetic DMARD vs. synthetic DMARD. We found two RCTs[57,68] and one prospective cohort study[53] comparing a combination regimen of adalimumab plus MTX,[57] infliximab plus MTX,[53,68] or etanercept plus MTX[53] with MTX monotherapy. Both RCTs were conducted in patients with early, aggressive RA. The RCTs found greater improvement in functional capacity and quality of life with combination therapies than with MTX monotherapy. The prospective cohort study found the etanercept-MTX combination improved in functional capacity more than MTX monotherapy, but the infliximab-MTX group did not differ from the MTX-only group.[53]

Adalimumab plus MTX vs. 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[57] (see KQ 1 section on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs*). After 1 year, the combination group had greater improvements in HAQ-DI scores (mean: -1.1) than the methotrexate group (-0.8; $P < 0.001$). After 2 years, the combination (-1.0) was superior to MTX (-0.9; $P < 0.05$). More patients in the combination group (72 percent) had achieved improvement of ≥0.22 (considered the clinically relevant threshold) in the HAQ-DI than the MTX group (63 percent; $P < 0.05$). 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 ($P < 0.001$). We report on results of the other comparisons of the PREMIER study in the sections on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs* and *Biologic DMARDs vs. synthetic DMARDs.*

Infliximab plus MTX vs. 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.[68] This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or with a combination of MTX and infliximab (3 mg/kg or 6 mg/kg) over 52 weeks. HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX-only group. The mean decrease from baseline HAQ score from week 30 to week 54 was greater for the combination groups (0.80 for 3 mg/kg group and 0.88 for the 6 mg/kg group) than for the MTX-only group (0.68; $P = 0.03$ and $P < 0.001$, respectively). In addition, more patients in the combination groups (76.0 percent and 75.5 percent, respectively) improved their HAQ scores by at least 0.22 units than in the MTX-only group (65.2 percent; $P = 0.003$ and $P = 0.004$, respectively). 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.[69]

One prospective cohort study from the RADIUS program in the United States (described above in the *Etanercept plus MTX vs. etanercept section)* involved patients who were initiating any new DMARD.[53] The mean percentage improvements in the HAQ at 12 months were not statistically significantly different between patients treated with the infliximab-MTX combination and those treated with MTX monotherapy (3 percent vs. 7 percent; P = NS).

Etanercept plus MTX vs. MTX. Another prospective cohort study from the RADIUS program showed that patients treated with the etanercept-MTX combination had greater mean percentage improvements in HAQ scores at 12 months than those treated with MTX alone (17 percent vs. 7 percent; $P < 0.01$).[53]

Abatacept plus synthetic DMARD vs. synthetic DMARD. One RCT,[129] ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders), that did not meet our inclusion criteria for KQ 2 deserves mention here because it provides some support that combination therapy with a biologic DMARD plus a synthetic DMARD may lead to greater improvement in quality of life and functional capacity than synthetic DMARD monotherapy. It was excluded for study design because all patients were on some background synthetic DMARD and were randomized to a biologic DMARD or placebo, rather than being randomized to abatacept plus a synthetic DMARD or placebo plus a synthetic DMARD. The study enrolled adults with RA for more than 1 year who had inadequate response to 3 months of anti-TNF therapy. Patients treated with abatacept had greater improvements in quality of life (mean change on SF-36 physical

component: 6.5 vs. 1.0; $P < 0.0001$; SF-36 mental component: 5.4 vs. 1.7, $P = 0.0025$) and functional capacity (mean change on HAQ-DI: -0.5 vs. -0.1; $P < 0.0001$) than patients treated with placebo.

Psoriatic Arthritis: Overview

A total of six RCTS examined functional capacity or quality of life in patients being treated for psoriatic arthritis. Details are found in Evidence Table 7 in Appendix E. Table 15 provides information on comparisons made, quality-of-life outcomes, and quality ratings. The main drug classes compared include corticosteroids, synthetic DMARDs, biologic DMARDs, and combined strategies.

Table 15. Interventions, functional capacity, health-related quality of life and quality ratings of studies in adults with psoriatic arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	QOL outcomes (HAQ, SF-36)	Quality Rating
Synthetic DMARD vs. Placebo					
Kaltwasser et al., 2004[112,113]	RCT 190 24 weeks	Active PsA; failed at least one DMARD	LEF (100 mg/day 3 days then 20 mg/day) vs. placebo	Change in HAQ LEF significantly greater than placebo (-0.19 vs. -0.05; $P = 0.0267$)	Fair
Biologic DMARDs vs. Placebo					
Antoni et al., 2005[115,116] IMPACT study	RCT 104 50 weeks (16 blinded, 34 open-label)	Active PsA; failed at least one DMARD	INF (5 mg/kg at weeks 0, 2, 6, 14 then every 8 weeks) vs. placebo 71% received a concomitant DMARD	HAQ INF significantly better than placebo (49.8 vs. -1.6 ; $P < 0.001$)	Fair
Antoni et al., 2005[117,118,130] IMPACT2 study	RCT 200 14 to 24 weeks	Active PsA; failed at least one DMARD	INF (5 mg/kg at weeks 0, 2, 6, 14, 22) vs. placebo 46% received concomitant MTX	INF significantly better than placebo in HAQ improvement, At week 14: -18.4% vs. 48.6% ($P < 0.001$) SF-36 change from baseline, at week 24: -19.4 vs. 46 ($P < 0.001$) SF-36 PCS; change from baseline: to week 14: vs. 9.1 ($P < 0.001$) to week 24: 1.3 vs. 7.7 ($P < 0.001$) SF36 MCS; change from baseline to week 14: -1.2 vs. 3.8 ($P = 0.001$) to week 24: 0.4 vs. 3.9 ($P = 0.047$) No significant difference in percentage of missed workdays in past 4 weeks at 14 weeks: 13% vs. 3.7% ($P = 0.138$)	Fair

Table 15. Interventions, functional capacity, health-related quality of life and quality ratings of studies in adults with psoriatic arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	QOL outcomes (HAQ, SF-36)	Quality Rating
Mease et al., 2005[39]	RCT 313 24 weeks	Active PsA; failed at least one DMARD	ADA (40 mg every other week) vs. placebo 51% received concomitant MTX	SF-36 PCS; change from baseline: to week 12 and week 24 ADA 9.3 vs. placebo 1.4 ($P < 0.001$) SF-36 MCS; change from baseline; to week 12: 1.2 vs. 1.6 (P = NS) to week 24: 0.6 vs. 1.8 (P = NS) HAQ-DI change from baseline; to week 12 and week 24 ADA -0.4 ± 0.5 vs. placebo -0.1 ± 0.4 ($P < 0.001$)	Fair
Mease et al., 2000[40]	RCT 60 12 weeks	Active PsA; failed at least one DMARD	ETA (25 mg twice a week) vs. placebo 51% received concomitant MTX	Improvement in HAQ from baseline ETA 83% vs. placebo 3% ($P <$ 0.0001)	Fair
Mease et al., 2004[41,47]	RCT 205 72 weeks (24 blinded, 48 open-label)	Active PsA; failed at least one DMARD	ETA (25 mg twice a week) vs. placebo 41% received concomitant MTX	Improvement in HAQ from baseline ETA 54% vs. placebo 6% ($P <$ 0.0001)	Fair

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HAQ, Health Assessment Questionnaire; INF, infliximab; LEF, leflunomide; MTX-methotrexate; PsA, psoriatic arthritis.

Psoriatic Arthritis: Key Points

Conclusions are limited because no head-to-head comparisons have been done for any of the drugs used to treat PsA. The available studies are all placebo-controlled studies. Leflunomide patients had better quality-of-life outcomes than those in the placebo arm. The strength of evidence about leflunomide is low. The use of biologics—adalimumab, etanercept, and infliximab—led to better outcomes than did placebo. The strength of evidence about these three biologic DMARDs is moderate.

Psoriatic Arthritis: Detailed Analysis

Leflunomide. One 24-week trial (two publications) evaluated the efficacy of leflunomide against placebo in PsA patients.[112,113] The study included 190 patients; PsA was defined as having at least three swollen joints and three tender or painful joints and psoriasis over at least 3 percent of the body surface area. Almost 50 percent of the patients were DMARD naive. Those who were not were required to discontinue all synthetic DMARDs, biologic agents, and

investigational drugs 28 days before baseline measures were done. At 24 weeks, quality of life was significantly improved in the leflunomide group as measured by the change in HAQ scores (-0.19 vs. -0.05; $P = 0.0267$).

Adalimumab. One adalimumab trial (40 mg every other week) included 313 patients suffering from moderate to severe PsA, which was defined as having at least three swollen joints and three tender or painful joints, who had had an inadequate response or intolerance to nonsteroidal anti-inflammatory drug (NSAID) therapy.[114] Patients were allowed to continue current MTX therapy as long as the dose had been stable for 4 weeks. The double-blinded phase of the study was 24 weeks, but patients who failed to achieve at least a 20 percent decrease in both swollen and tender joint counts on two consecutive visits could receive rescue therapy with corticosteroids or DMARDs. Quality of life was significantly improved as measured by the greater change in HAQ scores in patients who took adalimumab than in those who received placebo (-0.4 vs. -0.1; $P < 0.001$).

Etanercept. Two studies that examined the efficacy of etanercept included 265 patients with active PsA who were not adequately responding to conventional DMARD therapies.[119,120] In both studies patients were allowed to continue MTX therapy as long as it had been stable for 4 weeks prior to enrollment. One of these trials lasted 12 weeks (N = 60);[119] the other was double-blinded for 24 weeks (N = 205).[120] Both studies had the same dosing regimen of 25 mg of etanercept twice weekly by subcutaneous injections. Quality of life improved significantly as measured by the HAQ in both studies. Mean improvements were 83 percent in etanercept-treated patients and three percent in placebo-treated patients in the 12-week study ($P < 0.0001$). In the longer study, at 24 weeks the mean improvements were 54 percent in the etanercept group and 6 percent in the placebo group ($P < 0.0001$).

Infliximab. Two studies on the use of infliximab IMPACT involved 304 patients with active PsA who were not adequately responding to conventional DMARD therapies.[115,117] Both studies permitted patients to continue MTX therapy as long as it had been stable for 4 weeks before enrollment. One trial was double-blinded for 16 weeks (N = 104);[115] the other was double-blinded for 24 weeks (N = 200), with crossover allowed at week 16 for nonresponders on the primary outcomes measured at the 14-week evaluation (i.e., before crossover).[117] Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, and 14; the longer study had an additional injection at week 22. Quality of life improved significantly as measured on the HAQ in both studies. Mean percentages of patients improving on the HAQ were 49.8 percent in infliximab and -1.6 percent in placebo-treated patients in the smaller study ($P < 0.001$). In the bigger study, at 14 weeks the mean percentages of patients improving were 48.6 percent in the infliximab group and -18.4 percent in the placebo group ($P < 0.001$). Additionally, the larger study found that, in the 4 weeks before week 14, 13 percent of the placebo group and 3.7 percent of the infliximab group missed work ($P = 0.138$).[130]

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

This key question examined overall harms for both diseases. Specifically, for patients with rheumatoid or psoriatic arthritis, do drug therapies differ in harms, tolerability, or adverse effects? We first address evidence on rheumatoid arthritis and then psoriatic arthritis. For each disease, we describe overall tolerability, then specific adverse events for each drug class,

followed by studies reporting on adherence for each disease. Evidence Tables 8 and 9 in Appendix E describe details about these studies, some of which were described for efficacy in KQ 1, above (i.e., Tables 10 and 11).

Rheumatoid Arthritis: Overview

A total of 28 randomized controlled trials (RCTs), one nonrandomized controlled trial, 48 observational studies, and four systematic reviews reported on tolerability, harms and adherence (see Evidence Tables 8 and 9 in Appendix E). Table 16 provides information on Food and Drug Administration (FDA) black box warnings and warnings in bold letters as well as toxicities requiring monitoring according to the American College of Rheumatology (ACR). A black box warning is a type of warning that the FDA requires on the labels of prescription drugs that may cause serious adverse effects, and it signifies that clinical studies have indicated that the drug carries a significant risk of serious or even life-threatening side effects. Its name comes from the black border that typically surrounds the text of the warning. A bold letter (or "bolded") warning is text prominently displayed on the main panel of the drug label that warns users about possible side effects and other cautions. Adding a bold-text warning is a lesser step than a black box warning, even if it does relate to the possibility of serious adverse effects.

Table 16. Drug toxicities and Food and Drug Administration warnings

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Corticosteroids	Hypertension, hyperglycemia, osteoporosis	No black box warnings[131-135]	Dosage requirements are variable and must be individualized on basis of disease under treatment and response of the patient[131-135]
Synthetic DMARDs			
Leflunomide	Diarrhea, alopecia, rash, headache, theoretical risk of immunosuppression infection	Pregnancy must be excluded before start of treatment; pregnancy must be avoided during treatment or prior to completion of treatment[136]	Hepatotoxicity; rare cases of severe liver injury, including cases with fatal outcome, have been reported[136]
Hydroxychloroquine	Macular damage	Physicians should be completely familiar with complete contents of package insert before prescribing[137]	No bold letter warnings[137]
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis	Bone marrow, liver, lung, and kidney toxicities; hepatotoxicity, fibrosis and cirrhosis; chronic interstitial pneumonitis; diarrhea and ulcerative stomatitis; malignant lymphomas; severe to fatal skin reactions; fatal opportunistic infections; fetal death and/or congenital anomalies[138]	No bold letter warnings[138]
Sulfasalazine	Myelosuppression	No black box warning[139]	No bold letter warnings[139]

Table 16. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Biologics DMARDs			
Abatacept	No ACR recommendations about monitoring	No black box warning[142]	No bold letter warnings[142]
Adalimumab	No ACR recommendations about monitoring	Risk of infections (TB, invasive fungal infections, other opportunistic infections); some infections have been fatal; patients should be evaluated for latent TB; patients should be monitored for signs of active TB during treatment[143]	Should not be initiated in patients with active infections (chronic or localized); patients who develop new infections during treatment should be monitored closely; physicians should exercise caution when considering treating patients with history of recurrent infection or underlying conditions which may predispose them to infections; serious infections observed in clinical studies with concurrent use of anakinra; concurrent use of anakinra is not recommended[143]
Anakinra	No ACR recommendations about monitoring	No black box warning[144]	Increased incidence of serious infections; discontinue if patient develops serious infection; should not be initiated in patients with active infections; safety and efficacy in immunosuppressed patients or patients with chronic infections have not been evaluated; concurrent therapy with etanercept is not recommended[144]
Etanercept	None recognized by ACR guidelines	No black box warning[145]	Serious infections and sepsis, including fatalities; TB; should not be taken by patients with active infections; malignancies; neurologic events; should be discontinued if patient develops serious infection or sepsis; exercise caution when considering prescribing to patients with history of recurring infections or with underlying conditions which may predispose patient to infection, such as advanced or poorly controlled diabetes; concurrent therapy with anakinra is not recommended[145]

Table 16. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities[†]	Warnings Black Box	Warnings Bold Letter
Infliximab	None recognized by ACR guidelines[‡]	Increased risk for infections, including progression to serious infections leading to hospitalization or death; these infections include bacterial sepsis, TB, invasive fungal and other opportunistic infections; increased risk for TB; patients should be closely monitored for signs and symptoms of infection during and after treatment; patients should be evaluated for TB risk factors and tested for latent TB prior to treatment; fatal hepatosplenic T-cell lymphoma reported in adolescent and young adult patients with Crohn's disease[146]	Some serious infections resulted in patients on concomitant immunosuppressive therapy; some patients were hospitalized or had fatal outcome from infections while treated with infliximab alone; should not be given to patients with clinically important, active infection; new infections should be closely monitored; treatment should be discontinued if patient develops serious infection; TB, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, other bacterial, mycobacterial and fungal infections observed; monitor patients for signs and symptoms of TB[146]
Rituximab	No ACR recommendations about monitoring	Fatal infusion reactions; these fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock; TLS—acute renal failure requiring dialysis; severe mucocutaneous reactions; PML—JC virus infection resulting in PML and death has been reported[147]	No bold label warnings[147]

[†]Toxicities requiring monitoring according to ACR guidelines, 2002.[140]
[‡]ACR issued a warning for hepatosplenic T-cell lymphoma with infliximab use.[141]
ACR: American College of Rheumatology; PML: progressive multifocal leukoencephalopathy; TB: tuberculosis; TLS: tumor lysis syndrome.

As with earlier KQs, the main drug classes examined are corticosteroids, synthetic DMARDs, and biologic DMARDs.

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 pre-specified 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,[148] 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 data were limited to one 3-month trial.[29] The strength of evidence is low.

Corticosteroid use significantly predicted the risk of serious infections, as compared with methotrexate (MTX), sulfasalazine, hydroxychloroquine, leflunomide, and etanercept, in one long-term retrospective study (hazard ratio [HR] 1.56; 95% CI, 1.20-2.04).[149] The strength of evidence is low.

Synthetic 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.[32,34,35,37] The strength of evidence is moderate.

The proportion of patients who stayed on MTX was higher than the proportion remaining on sulfasalazine at 5 years in one meta-analysis of 71 RCTs and 88 observational studies (36 percent vs. 22 percent, P = NR).[150] The strength of evidence is moderate.

Five studies involving combinations of two or three DMARDs, including sulfasalazine, MTX, hydroxychloroquine, and etanercept (a biologic DMARD), vs. one or two DMARDs have similar withdrawal rates attributable to adverse events.[30,31,33,46,151] 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.[31,33] The level of evidence is moderate.

Three studies of combinations including prednisone with one or more DMARDs indicated similar discontinuation rates between groups.[42,44,47] The level of evidence is moderate.

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.[152,153] Longer term evidence is lacking. 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 (RR, 1.9; 95% CI, 1.1-3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8-2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4-1.5).[154] The level of evidence is low.

In three cohort studies, infection risk was elevated in patients receiving prednisone and possibly MTX and leflunomide compared with the risk in patients receiving other DMARDs.[149,152,155] The level of evidence is low.

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.[156] Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR 1.28; P = 0.014).[157]

Biologic DMARDs. In efficacy studies, biologic DMARDs were generally well tolerated. Injection site reactions (adalimumab, anakinra, etanercept) and infusion reactions (abatacept, infliximab, rituximab) were the two most commonly and consistently reported adverse events. Some infusion reactions appeared to be more serious than injection site reactions. Overall, 0.5 percent of patients treated with infliximab had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions.[158] Fatal infusion reactions have also occurred with rituximab.[147] The strength of evidence is moderate.

One nonrandomized, open-label 12-month trial directly compared the tolerability of two biologic DMARDs.[159] It did not report any differences in harms between etanercept and

infliximab. Evidence from placebo-controlled trials and observational studies is insufficient to draw conclusions about the comparative tolerability and safety of biologic DMARDs. The strength of the evidence is low.

In efficacy trials, injection site reactions were the most common reason for discontinuation because of adverse events.[49] Incidence rates appeared to be significantly higher with anakinra than with anti-TNF drugs.[49] In a large retrospective cohort study, anakinra led to statistically significantly higher discontinuation rates (41 percent) than etanercept (31 percent; $P = 0.004$) and infliximab (35 percent; $P = 0.03$).[67] A prospective cohort study indicated that etanercept had statistically significantly lower discontinuation rates than infliximab during 60 months of follow-up (data NR; $P < 0.001$).[52] The strength of the evidence is moderate.

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.[59,160] 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,[83] anakinra,[85] etanercept,[161] and infliximab[101,162] 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.

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. One prospective cohort study suggested that risks do not differ for adalimumab, etanercept, and infliximab;[163] it showed that, compared with synthetic DMARDs as a class, anti-TNF drugs as a class did not lead to a higher overall risk for serious infections (incidence rate ratio [IRR], 1.03; 95% CI, 0.68-1.57). The strength of the evidence is low.

Two studies indicated that the general risk of biologic DMARDs for serious infections is dose dependent. The evidence, however, is limited to adalimumab[164] and infliximab.[107] The strength of the evidence is moderate.

Three observational studies indicated that infliximab might have a higher risk of granulomatous infections than etanercept.[165-167] The strength of the evidence is low.

Hepatotoxicity has been reported for infliximab but not for other biologic DMARDs. The strength of the evidence is low.[146]

Adherence. Few efficacy studies reported rates of adherence. 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.

A review of a large, managed care database suggested that infliximab might have greater adherence than etanercept or MTX.[168] In contrast, however, an observational study that suggested that etanercept had a better response rate than infliximab attributable to greater adherence.[52] However, as noted below, measurements of adherence are different between these two studies. Strength of evidence is low for efficacy and effectiveness studies.

Detailed Analysis

Tables 17, 18, and 19 provide information on harms for the three main categories of drugs covered in this review. We cover overall tolerability, then specific adverse events. When sufficient data are available, we break out specific events by type (e.g., hepatic or infection).

Corticosteroids: overall tolerability. Corticosteroids are associated with several well-known side effects (noted already in Table 16). 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.[131-135] Table 17 describes relevant studies for harms from corticosteroids.

Table 17. Comparative harms in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Corticosteroids Overall Tolerability					
Kirwan et al., 2004[29]	RCT 143 12 weeks	Active RA	BUD PNL	Similar in all groups	Fair
Corticosteroids Adverse Events					
Doran, et al., 2002[149]	Retrospective cohort 609 39 years	RA patients	Several synthetic DMARDs, corticosteroids	In patients hospitalized for infection, corticosteroid use increased risk (HR, 1.56; 95% CI, 1.20-2.04)	Fair
Saag et al., 1994[169]	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, 4.6-220) PRED 5 mg to 10 mg/day (OR, 4.5; 95% CI, 2.1-9.6) No increase in AE for PRED < 5 mg/day Fracture: OR, 3.9 (95% CI, 0.8-18.1; *P* < 0.09) First infection: OR, 8.0 (95% CI, 1.0-64.0; *P* < 0.05) First GI event: OR, 3.3 (95% CI, 0.9-12.1; *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.

Comparatively, the tolerability for corticosteroids appears to be similar between groups, although the information is limited by short study duration and the fact that only one study is available. One 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.[29] 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).

Corticosteroids: specific adverse events. We found no comparative study of corticosteroids directly assessing specific serious adverse events. One study of a retrospective 39-year cohort of 609 RA patients in Rochester, Minnesota, examined the predictors of serious infections requiring hospitalization.[149] Corticosteroids (intravenous [IV] or intramuscular [IM]), various synthetic DMARDS including MTX, sulfasalazine, hydroxychloroquine, and leflunomide, and etanercept (a biologic DMARD) were among the predictors examined. Of those patients requiring hospitalization for infection, only the use of corticosteroids was associated with an increased risk (HR 1.56; 95% CI, 1.20-2.04). Cumulative dose or duration of corticosteroids did not provide additional information beyond a history of corticosteroid use.

One retrospective cohort study of 224 RA patients directly assessed the toxicity of low-dose, long-term corticosteroid therapy (mean 4.9 years).[169] 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. Records were abstracted 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, myocardial infarction, 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, 4.6-220; *P* = 0.0004; adverse event at 5 to 10 mg/day: OR, 4.5; 95% CI, 2.1-9.6; *P* = 0.0001; and adverse event at 0 to 4 mg/day: OR, 1.9; 95% CI, 0.8-4.7; *P* = 0.15). Patients on long-term prednisone (any dose) were at higher risk for fracture (OR, 3.9; 95% CI, 0.8-18.1; *P* < 0.09), infection (OR, 8.0; 95% CI, 1.0-64; *P* < 0.09) and GI event (OR, 2.2; 95% CI, 0.9-12.1; *P* < 0.07).

Synthetic DMARDs: overall tolerability. MTX, sulfasalazine, hydroxychloroquine and leflunomide all can produce several well-known, and similar, reactions (Table 16). 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;[138]
- Sulfasalazine: stomatitis, nausea, dyspepsia, rash, headache, abdominal pain or vomiting, fever, dizziness, pruritus, and abnormal liver function tests.[139]
- Hydroxychloroquine: dizziness, headache, abdominal pain/nausea/vomiting/diarrhea, pruritus, weight loss, hair bleaching, and alopecia;[137] and
- Leflunomide: diarrhea, rash, elevated liver enzymes, and alopecia.[136]

Table 18 describes studies providing information on tolerability and various adverse events. Three trials[32,35,37] and one meta-analysis with up to 2 years of data,[34] 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. 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.[150] At 5 years, 36 percent of patients had remained on MTX to continue their treatment; 22 percent had remained on sulfasalazine. Patients on sulphasalazine were more likely to have withdrawn from medication than those on

MTX (RR, 1.68; $P < 0.0001$). Withdrawal rates did not differ between observational studies and RCTs.

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Synthetic DMARDs Overall Tolerability					
Cannon, et al., 2004[152]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	AE rates in LEF, LEF + MTX were lower than or similar to AE rates for MTX and other DMARDS	Fair
Emery et al., 2000[32]	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[150]	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., 2003[34]	Systematic review and meta-analysis 1,732 2 years	Active RA	LEF, MTX LEF, SSZ	Discontinuation rates from AEs were similar for LEF, MTX and SSZ	Good
Smolen et al., 1999[35]	RCT 358 24 weeks	Active RA	LEF, SSZ	Withdrawal due to AEs 14% vs. 19%	Fair
Strand, et al., 1999[37,38]	RCT 482 12 months (1 year continuation)	RA for at least 6 months, MTX-naive	LEF, MTX	AEs constant over time LEF and MTX 12 months: Higher discontinuation rate for LEF (22% vs. 10.4%, P = NR)	Fair
Synthetic DMARD Combinations Overall Tolerability					
Boer et al., 1997[39] COBRA study	RCT 155 56 weeks	Early RA, DMARD naive	PNL taper + MTZ + SSZ vs. SSZ	Lower withdrawal rate due to AEs (2.6% vs. 7.6%, P = NR)	Fair
Capell et al., 2007[30]	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 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Dougados et al., 1999[31]	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[42] 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 (MTZ, 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[33]	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[44] 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
O'Dell et al., 2006[151]	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[45]	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[46]	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
Svensson et al., 2005[47]	Open-label RCT 250 2 years	Early RA	DMARD + PNL vs. DMARD	Similar number of discontinuations between groups	Fair

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Svensson et al., 2003[170]	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
Synthetic DMARDs Adverse Events					
Hepatic Event					
Cannon et al., 2004[152]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Hepatic event: LEF 4.1/1,000PY, MTX 6.2/1,000PY, Other 4.2/1,000PY, LEF + MTX 4.6/1,000PY	Fair
Suissa et al., 2004[153]	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, 0.2-4.9), traditional DMARD: 2.3 (95% CI, 0.8-1.4), biologic DMARD: 5.5 (95% CI, 1.2-24.6)	Fair
Interstitial Lung Disease					
Suissa et al., 2006[154]	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 to other DMARDs: OR, 1.9 (95% CI, 1.1-3.6). No elevation noted in LEF pts with no history of MTX or no history of interstitial lung disease	Fair
Infection					
Cannon et al., 2004[152]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Respiratory infection: LEF 20/1,000PY, MTX 38.9/1,000PY, Other 36.9/1,000PY	Fair
Doran et al., 2002[149]	Retrospective cohort 609 39 years	RA pts	Several synthetic DMARDs, corticosteroids	Use of corticosteroids increased risk of hospitalization for infection (HR 1.56; 95% CI, 1.20-2.04)	Fair
Wolfe et al., 2006[155]	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, 1.5-2.0), LEF HR 1.2 (95% CI, 1.0-1.5). No significant differences for SSZ, MTX	Fair

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Malignancies					
Baecklund et al., 2006[156]	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[157]	Retrospective cohort 15,789 (RA) 4 years	RA pts	PRED, LEF, MTX	PRED was associated with increased risk for non melanoma skin cancer PRED: HR 1.28 (95% CI, 1.05-1.55, *P* = 0.014)	Fair

3x, three times; ADA, adalimumab; AEs, adverse events; AERS, adverse events reporting system; AKA, anakinra; CHF, congestive heart failure; CI, confidence interval; DAS; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GI, gastrointestinal; HCQ, hydroxychloroquine; HR, hazard ratio; INF, infliximab; LEF, leflunomide; LFT, liver function test; mg/kg, milligram/kilogram; MTX, methotrexate; N/A, not applicable; NR, not reported; OR, odds ratio; PNL, prednisolone; PRED, prednisone; Pts, patients PY, person years; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; SAEs, serious adverse events; SSZ, sulfasalazine; TB, tuberculosis; TNF, tumor necrosis factor; txt, treatment; vs., versus.

For combination therapies, five studies of DMARD combinations (one up to 5 years[31]) included MTX, sulfasalazine, hydroxychloroquine, and etanercept (described in detail under KQ 1). They had similar withdrawal rates attributed to adverse events.[30,31,33,45,46,151] Although discontinuation rates were similar, rates of adverse events were higher in two studies for sulfasalazine plus MTX vs. monotherapy (adverse events for combination therapy range from 53 percent to 91 percent; adverse events for monotherapy range from 50 percent to 75 percent).[31,33] Side effects included nausea, erythema, and elevated transaminases. Three RCTs of combination therapy including prednisone with one or more DMARDs (described in detail in KQ 1) showed similar discontinuation rates between groups.[42,44,47] 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).[39] 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).[170]

Synthetic DMARDS: specific adverse events. Synthetic DMARDs can produce several serious adverse events (Table 16). The package inserts for MTX give several warnings.[138] 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 NSAIDS. MTX-induced lung disease can occur in 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.[139] 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.[137] Potentially severe adverse

reactions for leflunomide include blood dyscrasias, hepatotoxicity, and hypersensitivity reactions including Stevens-Johnson syndrome.[136]

Hepatic events. Two retrospective cohorts examined hepatic events in patients with rheumatoid arthritis.[152,153] Both studies found similar hepatic event rates for leflunomide and MTX.

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).[152] The hepatic event rate for leflunomide was similar to that for other DMARDs (leflunomide, 4.1/1,000 person-years [95% CI, 2.4-7.0], MTX, 6.2/1,000 person-years [95% CI, 5.1-9.3]; other DMARDs, 4.2/1,000 person-years [95% CI, 3.3, 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).[153] Using MTX as the reference, they observed no higher rates in serious hepatic events for leflunomide (rate ratio 0.9; 95% CI, 0.2-4.9) or for traditional DMARDs (rate ratio 2.3; 95% CI, 0.8-6.5), but they did report higher rates for biologic DMARDs (rate ratio 5.5; 95% CI, 1.2-24.6).

Infection. Prednisone and possibly MTX and leflunomide increase the risk of infection compared with risks from other DMARDs. Two prospective cohort studies and one 39-year retrospective cohort study examined the risk of hospitalization for pneumonia infection.[149,152,155] One study examined 16,788 patients from U.S. rheumatology practices and followed up semi-annually with questionnaires for 3.5 years.[155] 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, 1.5-2.1; HR 1.3; 95% CI, 1.0-1.5); MTX, hydroxychloroquine, sulfasalazine, infliximab, etanercept, or adalimumab did not increase risks.

The 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).[152] 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 39-year population-based study of the Rochester, Minnesota, cohort examined potential risk factors for hospitalization for infection in RA patients (N = 609).[149] Outcomes were assessed by reviewing inpatient and outpatient community medical records. The use of corticosteroids increased hospitalization for infection (HR 1.56; 95% CI, 1.20-2.04). Compared with corticosteroids, other DMARDs including MTX, hydroxychloroquine, sulfasalazine, leflunomide, or etanercept had no increased risk of infection-related hospitalizations.

Interstitial Lung Disease. One 5-year retrospective cohort examined claims data from 62,734 patients with RA given a DMARD 1 year prior to the date of diagnosis of interstitial lung disease.[154] Patients were divided into four categories: leflunomide, methotrexate, 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 to patients prescribed other DMARDs (RR, 1.9; 95% CI, 1.1-3.6) but

not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8-2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4-1.5).[154]

Malignancies. One retrospective study examined 756 patients with RA to determine the risk of lymphoma over a 30-year period.[156] 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, 0.3-1.6) or sulfasalazine (OR, 0.6; 95% CI, 0.3-1.1).

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 semi-annual questionnaires over a 4-year period in which they reported any current malignancies.[157] 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.

Biologic DMARDs: overall tolerability. Table 19 describes studies providing information on tolerability and various adverse events. Table 16 presented the basic information about toxicities and FDA or other warnings. The prescription information for abatacept highlights precautions for hypersensitivity reactions,[142] and the prescription information of rituximab has a black box warning for fatal infusion reactions.[147]

Table 19. 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			
Bathon et al., 2000[54-56] 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 [57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive	ADA, MTX, ADA + MTX	No statistically significant differences in adverse events	Fair
Combe et al., 2006[60]	RCT 260 24 weeks	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%; $P < 0.05$)	Fair
Edwards et al., 2004[61]	RCT 161 24 weeks	Active RA despite MTX treatment	RIT,MTX, RIT+MTX, RIT+CYP	No significant differences in adverse events	Fair
Feltelius et al., 2005[161]	Case series 1,073 2 years	Pts with RA initiating ETA therapy	ETA	Incidence of serious adverse events remained constant over time	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Fleischmann et al., 2003[171]	RCT 1,414 6 months	Pts with active RA despite MTX treatment	AKA	Higher rates of injection site reactions with AKA than placebo. Otherwise no statistically significant differences in adverse events	Fair
Fleischmann et al., 2006[172]	Open-label extension of RCT 1,346 Up to 3 years	Pts with active RA despite MTX treatment	AKA	Incidence of serious adverse events remained constant over time	Fair
Flendrie et al., 2003[173]	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
Furst et al., 2003[80] STAR study	RCT 636 6 months	Pts with active RA despite MTX treatment	ADA	No statistically significant differences in adverse events	Fair
Gartlehner et al., 2006[49]	Meta-analysis 5,248 NA	Patients who have failed MTX treatment; mean disease duration: varied	ADA, AKA, ETA,INF	Higher rates of injection site reactions for AKA than ADA and ETA (56% vs. 19% vs. 25%)	Good
Geborek et al., 2002[50]	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[55]	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[59]	RCT 242 24 weeks	Inadequate control of disease with MTX	ETA, ETA+AKA	Significantly higher rates of serious adverse events in combination group	Fair
Genovese et al., 2005[56]	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

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Klareskog et al., 2004 [63-65] 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
Langer et al., 2003[174]	Post marketing surveillance 454 6 months	Pts with RA, initiating AKA treatment	AKA	Rate of adverse events was generally similar to those reported in efficacy trials; lower rates of injection site reactions than in clinical trials	Fair
Maini et al., 2004[101]	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
Moreland et al., 2006[162]	Open-label extension of clinical trials 714	Pts treated with ETA	ETA	Incidence of serious adverse events remained constant over time	Fair
Nuki et al., 2002[85]	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[151]	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
Schaible et al., 2000[158]	Retrospective 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

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Schiff et al., 2006[175]	Retrospective data analysis of clinical trials; post marketing surveillance 10,050 12,506 pt years	Pts treated with ADA	ADA	Incidence of serious adverse events remained constant over time	Fair
St. Clair et al., 2004 [68,69] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive	MTX, INF, INF+ MTX	Significantly more patients in the INF than in the MTX group had more than one serious infection (5.3 vs. 2.1%; $P < 0.05$)	Fair
Van Riel et al., 2006[66]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX	ETA, ETA+MTX	No statistically significant differences in adverse events	Fair
Wasserman et al., 2004 [176]	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
Weinblatt et al., 2006 [160] 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[83]	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 [107] 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
Zink et al., 2005[67]	Retrospective cohort study 1,523 1 year	Pts with RA who had a change in treatment regimen	AKA, ETA, INF, LEF	Significantly higher overall discontinuation rates for AKA than ETA and INF after 12 months; no differences in discontinuation rates due to adverse events	Good

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Biologic DMARDs Adverse Events					
Infectious Diseases					
Askling et al., 2005[177]	Retrospective cohort study 62,321 467,770 person-years	Pts with RA in daily clinical care in Sweden	ETA, INF	4-fold increase of risk for TB for ETA and INF compared with conventional DMARDs	Good
Bergstrom et al., 2004[178]	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 coccidioidmoycosis than pts on synthetic DMARDs	Fair
Bongartz et al., 2006[164]	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 (OR, 2.0; 95% CI, 1.3-3.1)	Fair
Dixon et al., 2006[163]	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 synthetic DMARDs	Fair
Gomez-Reino et al., 2003[179]	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 synthetic DMARDs	Fair
Keane et al., 2001[180]	Database analysis 70 cases of TB NA, AERS data	Pts treated with INF	INF	TB may develop soon after initiation of INF treatment	Fair
Lee et al., 2002[166]	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
Listing et al., 2005[181]	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
Mohan et al., 2004[182]	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

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Salliot et al., 2006[183]	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
Slifman et al., 2003[167]	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
Wallis et al., 2004[165]	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
Wolfe et al., 2004[184]	Prospective cohort study with historic control 17,242 3 years	Pts with RA in daily clinical care in U.S.	INF, synthetic DMARDs	TB was more common in pts treated with INF than with synthetic DMARDs	Fair
Wolfe et al., 2006[155]	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 to a historic control	Fair
Lymphoma and Other Malignancies					
Askling et al., 2005[185]	Retrospective cohort study 60,930 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, synthetic DMARDs	No increase in solid cancers for pts treated with anti-TNF drugs	Fair
Askling et al., 2005[186]	Retrospective cohort study 53,067 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, synthetic DMARDs	No increase in lymphoma for pts treated with anti-TNF drugs	Fair
Bongartz et al., 2006[164]	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 (OR, 3.3; 95% CI, 1.2-9.1)	Fair
Brown et al., 2002[187]	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

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Chakravarty et al., 2005[157]	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[159]	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 synthetic DMARDs	Fair
Lebwohl et al., 2005[188]	Post marketing 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
Setoguchi et al., 2006[189]	Retrospective cohort study 8,458 33,240 pt-years	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 synthetic DMARDs	Good
Wolfe et al., 2004[190]	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
Congestive Heart Failure					
Chung et al., 2003[191]	RCT 150 28 weeks	Pts with CHF	INF	INF (10 mg)-treated pts were more likely to die than placebo-treated pts	Fair
Jacobsson et al., 2005[192]	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
Kwon et al., 2003[193]	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

Table 19. Comparative harms 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., 2004[194]	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
Demyelination					
Mohan et al., 2001[195]	Database analysis AERS 19 cases of demye-lination NA, AERS data	Pts on anti-TNF therapy	ETA, INF	Discontinuation of therapy led to partial or complete resolution of all cases	Fair
Other Adverse Events					
De Bandt et al., 2005[196]	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[197]	Prospective cohort study with historic control 578 911 pt-years	Pts with RA starting anti-TNF therapy	ADA, ETA, INF	Higher rates of dermatological conditions in pts on anti-TNF drugs compared to DMARDs	Fair
Shin et al., 2006[198]	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

ABA, abatacept; ADA, adalimumab; AERS, adverse events reporting system; AKA, anakinra; CD, cardiovascular disease; CHF, congestive heart failure; CI, confidence interval; CYP, cyclophosphmide; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HCQ, hydroxychloroquine; HR, hazard ratio; INF, infliximab; LEF, leflunomide; mg/kg, milligram/kilogram; MTX, methotrexate; N/A, not applicable; NR, not reported; OR, odds ratio; Pts, patients; RA, rheumatoid arthritis; RCT, randomized controlled trial; RIT, rituximab; SSZ, sulfasalazine; TB, tuberculosis; TNF, tumor necrosis factor; US, United States.

In efficacy trials of biologic DMARDs, overall tolerability profiles appeared to be similar among biologic and synthetic DMARDs, or combinations of biologic and synthetic DMARDs. An exception was the combination of two biologic DMARDs. 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.[59] 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).[160]

One nonrandomized open-label trial determined the comparative harms among combinations of biologic DMARDs and synthetic DMARDs other than MTX.[151] No differences in adverse events could be detected between a combination of etanercept and either sulfasalazine or hydroxychloroquine.

The ERA (Early Rheumatoid Arthritis) study, described in more detail in KQ 1, had an open-label extension of up to 2 years,[55] and an uncontrolled extension with etanercept (25 mg twice weekly) of up to 5 years.[56] 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,[83] anakinra,[85,172] and infliximab.[101,162] Likewise, safety analyses of post marketing surveillance data showed that the incidence of adverse events did not rise over time in patients treated with adalimumab[175] and etanercept.[161]

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.[49] Injection site reactions (adalimumab, anakinra, etanercept) and infusion reactions (abatacept, infliximab, rituximab) were the more commonly and consistently reported adverse events. Most infusion reactions were nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever.

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.[158] In these trials, however, less than 2 percent of patients discontinued because of infusion reactions.[158] A prospective cohort study of infliximab in a Canadian clinical care setting reported substantially higher rates of events than did the clinical trials.[176] 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).

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, 7.1-27.9) for adalimumab, 22.4 percent (95% CI, 8.5-36.3) for etanercept, and 67.2 percent (95% CI, 38.7-95.7) for anakinra.[49] 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.[143-145] A German retrospective study based on post marketing surveillance data, however, reported a lower incidence of injection site reaction for anakinra than clinical trials (20 percent).[174]

The evidence on comparative discontinuation rates is limited to observational studies.[52,67,173] A Swedish population-based, prospective cohort study reported statistically significantly higher rates of overall discontinuation (data NR; $P < 0.001$), discontinuation because of adverse events (data NR; $P < 0.001$), and discontinuation because of lack of efficacy (data NR; $P < 0.018$) for patients on infliximab than for those on etanercept over 60 months of followup.[52] These findings are consistent with those from a German retrospective, population-based cohort study, based on the RABBIT (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) database. This study 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).[67] 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).

Four RCTs were designed to assess adverse events as primary outcomes.[80,107,160,171] Overall, adverse event rates were similar for abatacept,[160] adalimumab,[80] anakinra,[171] or infliximab[107] and placebo. All four studies, however, reported a trend toward higher rates of *severe* infections in patients treated with biologic DMARDs than in those receiving placebo. In general, these studies were too short and did not have enough power to detect such rare but severe adverse events.

Specific adverse events. Because the evidence on the comparative risk for rare but severe adverse events is lacking for biologic DMARDs, we summarize the evidence on the risk of individual drugs below.

Serious infections. Because of the immunosuppressive nature of biologic DMARDs, serious infections including tuberculosis, 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.[199] The available head-to-head evidence is insufficient to draw firm conclusions about the comparative risk of biologic DMARDs.

The best evidence stems from a prospective cohort study.[163] This study enrolled 8,973 patients with severe RA from the British Society for Rheumatology Biologics Register. Patients were treated with adalimumab (n = 1,190), etanercept (n = 3,596), infliximab (n = 2,878), or synthetic DMARDs (n = 1,354). The overall followup included 11,220 patient-years. Results indicated no differences in risks among anti-TNF drugs. Compared with synthetic DMARDs, anti-TNF drugs did not lead to a higher overall risk for serious infections (IRR, 1.03; 95% CI, 0.68-1.57). The frequency of serious skin infections, however, was fourfold higher in patients treated with anti-TNF drugs than with synthetic DMARDs (IRR, 4.28; 95% CI, 1.06-17.17). What proportion of patients treated with anti-TNF drugs were also on a background synthetic DMARD regimen remains unclear. Although the statistical analysis 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 synthetic 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).

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. 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).[171] 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.[107] 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, 0.3-3.1). 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% CI, 1.2-7.9). A fair meta-analysis of efficacy studies confirmed this finding and reported a similar dose-dependent risk for a combined population of adalimumab- and infliximab-treated patients.[164]

The higher risk of biologic DMARDs for serious infections was confirmed by a fair meta-analysis that pooled data of more than 5,000 RA patients from adalimumab and infliximab efficacy trials.[164] The pooled odds ratio for serious infections was 2.0 (95% CI, 1.3-3.1) relative to placebo. The number needed to harm (NNH) was 59 (95% CI, 39-125) within a treatment period of 3 months to 12 months.

Most long-term observational studies support these findings.[158,181,183,185] 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 patient-years) than rates reported in phase 3 efficacy trials (3 to 4 per 100 patient-years).[183]

The most common serious infections were cases of tuberculosis.[180] In addition, observational studies reported infections with coccidiomycosis,[178] histoplasmosis,[166] pneumocystis carinii,[200] and listeriosis[167] and candida.[180]

Six retrospective cohort studies determined the risk of tuberculosis or granulomatous infections during treatment with infliximab or etanercept.[165,177,179,180,182,184] All studies report a significant increase of risk attributable to anti-TNF therapy relative to placebo.

No evidence exists on the general risks of abatacept, adalimumab, anakinra, and rituximab. The best available evidence stems from three studies based on Spanish, Swedish, and U.S. databases that collected data on patients treated with biologic DMARDs.[177,179,184] These data were collected systematically from participating physicians, regardless of the occurrence of adverse events. By contrast, the adverse events reporting system (AERS) database of the FDA includes post marketing adverse events spontaneously reported from U.S. sources, serious and unlabeled spontaneous reports from non-U.S. sources, and serious, unlabeled post marketing clinical trial reports from all sources. Therefore, the AERS lacks an adequate denominator to draw inferences about causation and the comparative risks of any drugs. In addition, underreporting is likely.[201]

The U.S. study, using data from the National Data Bank of Rheumatic Diseases (NBI), reported an eightfold higher rate of tuberculosis in patients treated with infliximab than in patients in a historic control group who had been treated with synthetic DMARDs.[184] The analysis yielded rates of 6.2 cases per 100,000 patient-years in the control group and 52.5 cases per 100,000 patient-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)[179] and several Swedish databases.[177] Both studies analyzed data on infliximab and etanercept and indicated a substantially higher risk for tuberculosis in patients treated with etanercept or infliximab than in those on synthetic RA therapy. The Swedish study reported a fourfold increased risk of tuberculosis (RR, 4.0; 95% CI, 1.3-12) for patients on anti-TNF treatment compared with the risk for RA patients not exposed to etanercept or infliximab.[177] Three studies based on the AERS database provided similar results.[165,180,182]

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).[165] The rate of tuberculosis 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.[165]

Lymphoma and other malignancies. The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with RA compared with the general population.[202] 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.

A large prospective cohort study followed 18,572 RA patients in a registry for up to 3 years.[190] The risk of lymphomas was higher for patients on anti-TNF therapies than for those on synthetic 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, 0.9-3.2); infliximab, 2.6 (95% CI, 1.4-4.5); and etanercept, 3.8 (95% CI, 1.9-7.5).

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 synthetic DMARDs.[159,186,189] The largest study included 4,160 patients treated with anti-TNF drugs.[186] Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6-2.1) for anti-TNF patients relative to patients on synthetic DMARDs.

Results regarding an increased risk for overall malignancies in patients treated with biologic DMARDs relative to placebo are also mixed. The best evidence comes from a fair meta-analysis that pooled data of more than 5,000 RA patients from adalimumab and infliximab efficacy trials.[164] The pooled odds ratio for malignancies was 3.3 (95% CI, 1.2-9.1). The NNH was 154 (95% CI, 91-500) within a treatment period of 3 months to 12 months. Two large retrospective cohort studies, however, do not support such findings.[185,189] The larger 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.

A clinical trial database review did not detect a higher incidence of squamous cell carcinoma in 1,442 RA patients (4,257 patient-years) treated with etanercept (crude rate: 2.8 cases/1,000 patients) than for those on placebo;[188] 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; $P = 0.014$).[157]

Congestive heart failure. No direct evidence on the comparative risk of biologic DMARDs for congestive heart failure (CHF) exists. The evidence on the risk of CHF with anti-TNF therapy is mixed. Two observational studies reported lower rates of CHF[194] and cardiovascular events[192]for RA patients on anti-TNF therapy than for those on conventional RA therapies. 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, 0.25-0.85; $P = 0.013$). A large retrospective cohort study (N = 13,171) reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -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.[194] Confounding by indication, however, cannot entirely be ruled out with such study designs.

By contrast, an analysis of 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.[193] Indirect evidence comes from three trials, two on etanercept[203] and one on infliximab,[191] 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.[191] The package insert of infliximab issues a contraindication regarding use in patients with CHF; the package inserts of etanercept and adalimumab emphasize precaution.

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 AERS indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[175,195] Similar cases have been seen in regulatory trials of adalimumab.[143] All neurologic events partially or completely resolved after discontinuation of treatment.

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.[146,158,196,204] Lupus-like syndromes have also been reported for adalimumab.[175] Development of antinuclear, antidouble-stranded DNA, or antihistone antibodies have also been reported in regulatory trials of other anti-TNF-α drugs.[143,145] The infliximab package insert reports that 34 percent of patients treated with infliximab and MTX experienced transient elevations of liver function parameters.[146] Severe liver injury, including acute liver failure, has been reported. Owing to a lack of studies with the methodological strength to assess these rare events, conclusions should be drawn on other grounds, such as comorbidities, taking case reports into consideration.

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; $P < 0.0005$).[197]

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.[205] Given the lack of a clear definition, we use the term *adherence*. Table 20 summarizes included studies for adherence.

Table 20. Studies assessing adherence in patients with rheumatoid arthritis

Author, Year	Study Type and Interventions	N	Results
Boers et al., 1997[39]	RCT MTX + SSZ + prednisolone vs. SSZ	155	Compliance satisfactory in 85%
Emery et al., 2000[32]	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[171]	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[42]	RCT Four treatment strategies	508	24 (5%) were nonadherent
Haagsma et al., 1997[33]	RCT SSZ + MTX vs. SSZ or MTX	105	Percentage of tablets taken > 90% (pill count)
Harley et al., 2003[168]	Retrospective database analysis INF vs. ETA vs. MTX	2,662	INF more adherent than ETA or MTX ($P < 0.05$)
Hyearich et al., 2006[62]	Prospective observational study	2,711	Adherence at 6 months: ETA 80% vs. INF 79% ETA subgroups (22% monotherapy, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy, vs. 22% DMARD co-therapy)
Kremer et al., 2002[126]	RCT LEF + MTX vs. placebo + MTX	263	Overall, 98% adherent Adherence rates 80%-120% LEF, 87.7% placebo 90.2%
Kristensen et al., 2006[52]	Prospective observational study INF vs. ETA	949	ETA had better drug survival than INF ($P = 0.001$)
Strand et al., 1999[37]	RCT LEF vs. MTX vs. placebo	402	Nonadherence as the reason for withdrawal: LEF (1) MTX (1)

AKA, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; 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. Six published studies reported levels of adherence in RCTs.[32,33,39,42,126,171] 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.[39] Only three of the six RCTs reported adherence rates for different treatment arms.[32,126,171] None of these studies noted a significant difference in adherence. 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.[168] 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 at least 80 percent vs. 68 percent of the etanercept and 64 percent of the MTX patients ($P < 0.05$ for infliximab vs. both other drugs) over 1 year.

A 5-year observational study from March 1999 to January 2004 with 949 patients in Sweden prospectively evaluated the long-term efficacy and tolerability of treatment with infliximab and etanercept in adults with RA using the LUNDEX.[52] The LUNDEX, a new index combining the proportion of responders with the proportion of patients adhering to treatment, was designed to compare the efficacy of the different therapies based on continued adherence and continuation of treatment. The study found that the etanercept group had a greater LUNDEX value, attributable primarily to better treatment adherence or survival time in the active treatment group, than did the infliximab group (P = NR).

Psoriatic Arthritis: Overview

A total of six RCTS compared tolerability, harms, and adherence. Details are found in Evidence Table 10 in Appendix E. Table 14 provides information on common adverse events of included drugs and black box warnings. Table 21 provides information on studies primarily examining comparative efficacy and safety. The drugs examined in patients with active disease included one synthetic DMARD (leflunomide) and the three biologic DMARDs (adalimumab, etanercept, or infliximab), all in comparison with placebo.

Table 21. Studies assessing adverse events and discontinuation rates during blinded portion of studies of psoriatic arthritis

Study	Study Design Duration	Study Population	Drug	Results	Quality Rating
		Synthetic DMARDs			
Kaltwasser et al., 2004[112]	RCT 190 24 weeks	Patients with active PsA	LEF	Differences in rates of withdrawals because of adverse events, diarrhea, and clinically significant increases in ALT (for all, P = NR)	Fair
		Biologic DMARDs			
Mease et al., 2005[114]	RCT 313 24 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	ADA	No statistically significant differences in adverse events except for ISRs. ADA 6.6% vs. placebo 3.1% (P = NR)	Fair
Mease et al., 2000[119]	RCT 60 12 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	ETA	No statistically significant differences in adverse events except for ISRs. ETA 20% vs. placebo 3% (P = NS)	Fair

Table 21. Studies assessing adverse events and discontinuation rates during blinded portion of studies of psoriatic arthritis (continued)

Study	Study Design, Duration	Study Population	Drug	Results	Quality Rating
Mease et al., 2006[122]	RCT 205 72 weeks (24 blinded, 48 open-label)	Patients with active PsA despite background biologic or synthetic DMARD treatment	ETA	No statistically significant differences in adverse events except for ISRs. ETA 20% vs. placebo 9% ($P \leq 0.001$)	Fair
Antoni et al., 2005[115] IMPACT study	RCT 104 16 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	INF	No statistically significant differences in adverse events	Fair
Antoni et al., 2005[117] IMPACT2 study	RCT 200 24 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	INF	No statistically significant differences in adverse events	Fair

ADA, adalimumab; ALT, alanine aminotransferase; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; ISR, injection site reaction; LEF, leflunomide; NR, not reported; NS, not significant; PsA, psoriatic arthritis; RCT, randomized controlled trial.

Psoriatic Arthritis: Key Points

Very limited information is available for harms, tolerability, adverse events, and adherence for patients with psoriatic arthritis. The available studies include only placebo-controlled studies; there are no head-to-head studies. The strength of evidence is low.

Synthetic DMARDs. The use of leflunomide vs. placebo can increase the likelihood of diarrhea and clinically significant increases in alanine aminotransferase. The rates of adherence are similar for leflunomide and placebo. The strength of evidence is low.

Biologic DMARDs. Five placebo-controlled studies of biologics, including one in adalimumab and two each in etanercept and infliximab, provide indirect evidence on harms. When the individual drugs are compared with placebo, the authors reported no differences in the rate of adverse events with the exception of increased rates of injection site reactions with the use of adalimumab and etanercept. No study reported adherence rates. The strength of evidence is low.

Psoriatic Arthritis: Detailed Analysis

Synthetic DMARDs. *Overall tolerability.* One 24-week trial in 190 patients examined adverse events in the treatment of PsA using leflunomide vs. placebo. The overall rates of adverse events were the same in each group: 85.4 percent of both trial arms experienced an adverse event.[112]

Specific adverse events. This same trial showed some differences in specific adverse events, in particular diarrhea (leflunomide, 24 percent; placebo, 13 percent; P = NR) and increases in alanine aminotransferase (leflunomide, 13 percent; placebo, 13 percent; P = NR).[112]

Biologic DMARDs. *Overall tolerability.* In efficacy trials for patients with PsA, overall tolerability profiles appeared to be similar for biologic DMARDs (adalimumab, etanercept, infliximab) and placebo.[112,114,115,117,119,122] Injection site reactions, dizziness, headaches, and

upper respiratory tract infections were the most commonly reported individual adverse events. Of these, injection site reactions appear to occur more often in the active group than in the control group.

Specific adverse events. Adalimumab and etanercept used to treat PsA show some differences in injection-site reactions. In a 24-week RCT examining adalimumab vs. placebo, the adalimumab group experienced more injection site reactions (6.6 percent) than the placebo group (3.1 percent; *P* = NR).[114] Two other studies comparing etanercept to placebo also showed higher rates of injection site reactions in the active arms.[119,122] A 12-week RCT reported injection site reaction rates of 20 percent in the etanercept group and 3 percent in the placebo group; these results were not significant, probably owing to the small sample size (N = 60).[119] In an RCT with 205 patients, however, the difference between these two groups was statistically different.[122] In the 24-week blinded portion of this study, injection site reactions occurred in 36 percent of the etanercept patients and 9 percent of the placebo patients (*P* < 0.001).

Adherence. Only one study reported adherence in the treatment of PsA (Table 22).[112] This 24-week study found that treatment adherence of ≥ 80 percent to < 110 percent was reported by 85 percent of leflunomide patients and 78 percent of placebo patients and (*P* = NR). Additionally, one patient was withdrawn by the investigator from the placebo group because of poor adherence.

Table 22. Adherence in patients with psoriatic arthritis

Author, Year	Study Type and Interventions	N	Results
Kaltwasser et al., 2004[112]	RCT LEF vs. placebo	190	Compliance of ≥ 80% to <110%: LEF, 85%; placebo, 78%. One patient was withdrawn from placebo arm because of poor adherence

LEF, leflunomide; RCT, randomized controlled trial.

Key Question 4: Benefits and Harms for Selected Populations

This key question concerned two main topics. Specifically, what are the comparative benefits and harms of drug therapies for rheumatoid arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities? Stage of disease and history of prior therapy were addressed under KQ 1. We did not find any interventions that grouped subjects by early RA vs. more advanced RA, or those that compared MTX-naive RA groups with those with RA who were MTX-experienced.

We found no studies of adults with PsA that compared efficacy, effectiveness, or harms of drug therapies between subgroups and the general population. No studies conducted subgroup analyses or used subgroups as the study population.

Rheumatoid Arthritis: Overview

We did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups and the general population for treating RA patients. Our findings are limited to results from subgroup analyses, a weaker form of evidence. Overall, we included

11 studies in addressing this key question: one RCT, four subgroup analyses of multiple RCTs, one database analysis, four observational studies, and one systematic review.

We focused on groups defined by demographics (age, sex, race or ethnicity), concomitant therapies, comorbidities (any comorbidity, cardiovascular disease, osteoporosis, and renal disease) and pregnancy. Strength of evidence is low for comparative efficacy and effectiveness for age, concomitant therapies, comorbidities, and pregnancy.

We present key points and detailed analyses below for the population groups noted above. Details about included studies are presented by subgroup analysis in Tables 23 to 28 (listed alphabetically by drug comparison).

Key Points

Demographics. We found no studies that conducted comparisons by sex, race, or ethnicity, but we did include one trial that addressed age;[206] two other studies, both rated poor quality, also addressed age, and we discuss them here because of the sparseness of this part of the evidence base.[207,208] One study directly compared the efficacy of DMARDs in elderly RA patients (65 years of age or older) with younger RA patients (under 64 years of age and older than 18); however, the analysis was focused on outcomes within age groups, not the specific effects of age.[209] Comparisons were available for only two DMARDs: one synthetic (MTX) and one biologic (etanercept).

Table 23 presents the studies of adults with RA that conducted comparisons by age groups. One systematic review by the Rheumatoid Arthritis Clinical Trial Archive Group found an inverse relationship between age and major clinical improvement.[206] Of the three trials reviewed, the differences between the odds ratios was small.[206] Two meta-analyses (pooled analyses of original data), both rated poor quality, provided mixed evidence on differences in efficacy in the elderly compared with a younger population treated with MTX and etanercept.[207,208] In one, the investigators determined that patients in the elderly age groups had a lower response to treatment than those in the younger age groups,[207] but both meta-analyses reported no difference in efficacy or function.[207,208] Given that two of the studies are of poor quality, the level of evidence is low.

Table 23. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by age

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Bathon et al., 2006[207]	Subgroup analysis within 4 RCTs 1,353 12 months to 6 years	Adults with early DMARD resistance or late-stage RA Subgroups: elderly (≥ 65 years of age) and younger adults (< 65 years of age)	ETA 25 mg twice weekly + MTX vs. ETA 25 mg twice weekly	No significant difference found for improved efficacy or function between groups; elderly subjects had similar or less treatment response than younger subjects	Poor

Table 23. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by age (continued)

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Fleischmann et al., 2003[208]	Pooled data from RCTs 1,128 Varies	Adults with RA taking ETA continuously for 1 year Subgroups: elderly (≥ 65 years of age) and younger adults (< 65 years of age)	ETA twice weekly Dosage not reported	No significant difference between elderly and younger groups at 1 year	Poor
Rheumatoid Arthritis Clinical Trial Archive Group 1995[206]	Systematic review 496 ≥ 12 weeks	Adults with RA Subgroups: Under 60 years of age; 60 to 64 years; 65 to 69 years; and 70 years or above	MTX Dosages not reported	Adjusted analysis demonstrated that as age increases, the odds ratio for major clinical improvement decreases; no effect found on toxicity	Fair
Schiff et al., 2006[209]	Pooled data from RCTs 1,049 ≤4 years	Adults with RA Subgroups: elderly (≥ 65 years of age) and younger adults (< 65 years of age)	ETA (25 mg twice weekly)	No significant difference found between groups in functional status; both groups exhibited similar improvements	Fair

ETA, etanercept; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Concomitant Therapies. We found no evidence from head-to-head comparisons, placebo-controlled trials, or observational studies on other treatment therapies and the various RA treatments addressed in this report. An analysis of data from a 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.[210] The level of evidence is low.

Comorbidities. Table 24 presents the studies found 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.[211] Lower rates of either myocardial infarction[192] or CHF[194] in RA patients on anti-TNF therapy compared with those on other RA therapies were reported by two observational studies. Another retrospective cohort study of RA patients on anti-TNF medications found that half of those who developed new onset CHF had no identifiable risk factors for CHF.[193] A systematic review of 11 MTX trials of RA patients determined that greater renal impairment was associated with greater toxicity.[206] The level of evidence is low.

Table 24. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis and other conditions

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Schiff et al., 2004[211]	RCT 951 6 months	RA patients with high-risk comorbid conditions	AKA 100 mg vs. placebo	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
Jacobsson et al., 2005[192]	Case and comparison cohort study 983 7 years	RA patients treated with TNF blockers in a Swedish Arthritis Treatment Register compared to a non-exposed anti-TNF RA population from the same geographic area	TNF inhibitors	Treatment group had significantly lower incidence and RR for development of first time cardiovascular events (myocardial infarctions) than the community cohort not treated with anti-TNFs.	Fair
Kwon et al., 2003[193]	Database analysis AERS 47 cases of CHF NA	RA or other rheumatoid illness patients treated with ETA or INF	ETA, INF	Half of the patients who developed new onset CHF did not have any identifiable risk factors	Poor
Wolfe et al., 2004[194]	Retrospective cohort study 13,171 2 years	Patients with RA in daily clinical care in U.S.	ADA, ETA, INF	Absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -0.5; *P* = NR) for patients treated with anti-TNF medications compared with those not treated with anti-TNF medications over a 2-year period	Fair
Rheumatoid Arthritis Clinical Trial Archive Group, 1995[206]	Systematic review of 11 RCTs 496 NA	Adults with RA treated with MTX and having age and renal function data available	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

ADA, adalimumab; AERS, adverse events reporting system; AKA, anakinra; CHF, congestive heart failure; ETA, etanercept; INF, infliximab; MTX, methotrexate; NA, not applicable; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Pregnancy. The effects of DMARDs on pregnancy or neonatal outcomes are mixed. Table 25 presents the studies found that addressed neonatal or pregnancy outcomes for women with RA. Two observational studies[212,213] are presented. We included one poor-quality study due to the sparseness of evidence on pregnancy outcomes for women with RA. The level of evidence is low.

Table 25. Study characteristics, outcomes, and quality ratings of studies of pregnant women

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Chakravarty et al., 2003[213]	Case reports from mailed survey 65 NA	Women of childbearing age seen by responding rheumatologists	MTX, LEF, ETA, INF (no dose specified)	Rate of congenital abnormalities in women on MTX was 10%	Poor
Katz et al., 2004[212]	Retrospective analysis of drug safety database 146 NA	Pregnant women who either before or after conception were treated with INF or whose partners were treated with INF before conception	INF: 1 to 9 infusions vs. General population	No statistical differences in live births, miscarriages, or therapeutic terminations relative to rates in U.S. population of pregnant women	Fair

ETA, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; US, United States.

Detailed Analysis

Demographics. We identified three studies analyzing etanercept use in the elderly and two of MTX. 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.[206] 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, 0.7-2.6), 1.0 (95% CI, 0.5-2.2) for those 65 to 69 years of age, and 0.7 (95% CI, 0.3-1.7) for those 70 years of age or older (P = NR). As renal functioning declines, the odds for toxicity increased as much as four fold. Baseline renal function was found to be a significant predictor of toxicity, with the lower creatinine clearances ending up with greater toxicity ($P = 0.027$).[206]

In a post-hoc analysis of three controlled and open-label extension studies of RA patients treated with etanercept; outcomes for elderly and younger adult age groups were compared for all those treated with etanercept for at least 4 years.[209] Though the elderly group exhibited greater mean HAQ-DI improvements than those in the younger group (0.39 to 0.92 vs. 0.57 to 1.00), at baseline the elderly group was more disabled than the younger adults. Also, the proportion of elderly in each study was much smaller than the younger adult group, usually about 20 percent vs. 80 percent.[209] Both groups demonstrated similar rapid improvements in disability and pain during the first few months of the controlled phase of the trials, then stabilized, and improvements were maintained through the open-label portions of the trials.[209]

Another post-hoc analysis (poor quality) of original data from four RCTs evaluated treatment comparisons of etanercept, both in combination with MTX and as a monotherapy in adults with early DMARD resistance or late-stage RA.[207] Within each of the four trials, subset analysis was conducted comparing elderly subjects to younger adults (under 65 years of age). Each trial and extension exhibited similar or lower ACR responses for the elderly in comparison to the younger adult group in regard to functioning and progression (P = NR).

Another pooled analysis (poor quality) of nine RCTs found similar or less etanercept treatment response in elderly subjects than younger adults, although the difference was not significant for function and improved efficacy.[208]

Concomitant Therapies. One placebo-controlled trial of 1,399 adults with active RA disease examined safety profiles of those treated with 100 mg/day anakinra. No differences were found in the adverse event profiles of the subjects taking or not taking concomitant antihypertensive, antidiabetic, or statin pharmacotherapies. Even when the analysis was done comparing those treated with anakinra with those on placebo, no differences emerged (P = NR).[210]

Comorbidities. *Any comorbidity***.** We did not identify any study specifically designed to assess the comparative efficacy and risk of biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, or rituximab) 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, central nervous system-related events).[211] 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. The evidence on the risk of cardiovascular disease with anti-TNF therapy is mixed. A Swedish retrospective cohort study (N = 983), using data from population-based databases, reported a statistically significantly lower risk of cardiovascular events for patients treated with anti-TNF medications than for those on conventional therapy (age-sex adjusted rate ratio: 0.46/1,000 person-years; 95% CI, 0.25-0.85; P = 0.013).[192] A large retrospective cohort study (N = 13,171) based on the National Databank for Rheumatic Diseases reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -0.5; P = NR) for patients treated with anti-TNF therapy relative to the risk for those not treated with anti-TNF medications over a 2-year period.[194]

A MedWatch analysis of data from the AERS found that half of the patients who developed new onset CHF while being treated with etanercept or infliximab for RA or other rheumatoid illnesses did not have any identifiable risk factors.[193] These findings support the possible association between new onset cardiovascular harms for RA patients treated with etanercept or infliximab. However, package inserts for infliximab, etanercept, and adalimumab warn about a contraindication for patients already diagnosed with CHF. For infliximab that package insert warns about a contraindication regarding its use in patients with CHF;[147] the package inserts of etanercept and adalimumab express precautions in use of these agents in patients with CHF.[143,145]

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, 0.9-22.6) 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.[206]

Pregnancy. Two observational studies addressed pregnancy in women with RA.[212,213] A retrospective analysis of data from a U.S. and European drug safety database found no statistical differences in live births, miscarriages, or therapeutic terminations in the subpopulation studied. The focus was on pregnant RA patients who had been treated with between one to nine infliximab infusions either before or after conception and male patients treated with up to nine

infusions before their partners' conception. The authors also reported no increase in adverse events from infliximab exposure during pregnancy relative to the rate in the U.S. population of pregnant women.[212]

One poor-quality study, using case reports from survey responses from 175 rheumatologists, found 10.3 percent (4/39) of women exposed to MTX during their pregnancies resulted in congenital malformations.[213] This is a much higher rate than the 2 percent to 3 percent average reported in a California cohort of 1.6 million infants.[213] In all, 23 physicians (rheumatologists) reported on 65 pregnancies with their patients treated with DMARDs (MTX, 38 patients; leflunomide, 10; etanercept, 14; infliximab, 2; and MTX plus etanercept, 1). A majority of the survey respondents agreed that pregnancy was contraindicated for women being treated with DMARDs, especially with patients being treated with MTX (95 percent agreement) and leflunomide (92.7 percent agreement). For patients treated with etanercept, the percentage agreement dropped to 38.6 percent, and for infliximab to 46.5 percent. Two observational studies addressed pregnancy in women with RA.[212,213]

A retrospective cohort study using data from a U.S. and European drug safety database found no statistical differences in live births, miscarriages, or therapeutic terminations in the subpopulation studied. The focus was on pregnant RA patients who had been treated with between one to nine infliximab infusions either before or after conception and male patients treated with up to nine infusions before their partners' conception. The authors also reported no increase in adverse events from infliximab exposure during pregnancy vs. those in the U.S. population of pregnant women.[212]

Discussion

This report provides a comprehensive review of the comparative efficacy, effectiveness, and harms of members of three main classes of drugs used to treat adult patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA). These include corticosteroids, synthetic 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 26 and Table 27 (for RA and PsA, respectively) summarize our findings and the strength of evidence for the four key questions (KQs) addressed by this report. In brief, the KQs involved benefits of these drugs, alone or in combination, in terms of reducing patient-reported symptoms, slowing or limiting the progression of radiographic joint damage, and maintaining remission (KQ 1); improving functional capacity and quality of life (KQ 2); harms and risks of these drugs (KQ 3); and the benefits or harms in various patient subpopulations defined by sociodemographic characteristics or health states (KQ 4). Most of the evidence meeting inclusion criteria focuses on comparative efficacy. We highlight comparative effectiveness studies when available.

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Key Question 1: Comparative Efficacy and Effectiveness of Drug Therapies		
Corticosteroids vs. corticosteroids	**Comparative efficacy:** One RCT indicated no differences in efficacy between prednisolone and budesonide. No other head-to-head evidence was available.	Low
Synthetic DMARD vs. synthetic DMARD	**Comparative efficacy:** Two trials and a good-quality meta-analysis (of these two RCTs) reported no differences in efficacy at 2 years for leflunomide and MTX.	Moderate
	One RCT reported higher efficacy for leflunomide than for sulfasalazine at 2 years.	Low
	Six trials and one meta-analysis found no differences in radiographic changes up to 2 years for MTX, leflunomide, and sulfasalazine.	Moderate
	No evidence exists for hydroxychloroquine.	NA
Synthetic DMARD combinations	**Comparative efficacy:** One RCT supported higher efficacy for sulfasalazine + MTX vs. monotherapy. Two studies reporting no difference focused on patients with early RA.	Low
	Two trials supported higher efficacy at 2 years for triple combination MTX + sulfasalazine + hydroxychloroquine than for 1 or 2 drugs.	Moderate
	Three trials including prednisone with 1, 2 or 3 synthetic DMARDs (respectively (MTX + sulfasalazine + hydroxychloroquine) showed less radiographic progression than 1 synthetic DMARD alone.	Moderate
	Comparative effectiveness: One fair trial of early RA patients found that combination therapy with MTX + sulfasalazine + tapered high-dose prednisone or infliximab + MTX showed less radiographic change than sequential DMARD or step-up combination therapy.	Low

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Biologic DMARDs vs. placebo	**Comparative efficacy:** Head-to-head trials are not available. Adjusted indirect comparisons indicated no differences in efficacy among adalimumab, etanercept, and infliximab. Anakinra appeared to be less efficacious than anti-TNF drugs. No adjusted indirect comparisons are available on abatacept or rituximab.	Moderate
Biologic DMARD combinations vs. monotherapy	**Comparative efficacy:** Combination of biologic DMARDs did not yield additional treatment effects compared with monotherapy of the same drugs.	Low
	Comparative effectiveness: A nonrandomized effectiveness study and two prospective observational studies indicated a faster onset of response for etanercept than for infliximab during the first months of therapy but no differences in effectiveness thereafter.	Low
Biologic DMARDs vs. MTX (class effects)	**Comparative efficacy:** Three RCTs (two with early RA patients) indicated no significant differences in clinical outcomes between either adalimumab or etanercept and MTX. Adalimumab and etanercept led to statistically significantly better radiographic outcomes than MTX.	Moderate
Biologic DMARDs vs. synthetic DMARDs	**Comparative effectiveness:** One retrospective cohort study indicated significantly higher rates of remission for biologic DMARDs as a class than synthetic DMARDs.	Low
Biologic DMARDs + MTX vs. biologic DMARDs	**Comparative efficacy:** Multiple good (or fair) RCTs supported a higher efficacy of a combination treatment of adalimumab, etanercept, infliximab, or rituximab and MTX compared with a monotherapy of the respective biologic DMARD. Some comparisons are limited to single studies.	High for etanercept Moderate for adalimumab, infliximab, and rituximab
Biologic DMARDs + synthetic DMARD other than MTX vs. biologic DMARDs	**Comparative efficacy:** One RCT found no difference between a combination of etanercept with sulfasalazine and etanercept monotherapy.	Low
Biologic DMARD + MTX vs. MTX	**Comparative efficacy:** Two RCTs indicated a greater efficacy of combinations of adalimumab or infliximab and MTX compared with MTX monotherapy in patients with early RA.	Moderate
Key Question 2: Functional Capacity or Health-related Quality of Life		
Corticosteroids vs. corticosteroids	**Comparative efficacy:** In one head-to-head RCT, prednisolone improved functional capacity and health-related quality of life more than budesonide.	Low
Synthetic DMARDs vs. synthetic DMARDs	**Comparative efficacy:** Seven studies compared synthetic DMARDs head-to-head: leflunomide with MTX, leflunomide with sulfasalazine, and sulfasalazine with MTX. Three RCTs and one systematic review suggested that leflunomide led to greater improvement in functional status and/or health-related quality of life than either MTX or sulfasalazine.	Moderate
	Three RCTs did not support a difference in functional capacity between sulfasalazine and MTX.	Moderate
Two synthetic DMARDs vs. synthetic DMARD monotherapy	**Comparative efficacy:** Three RCTs compared a combination of MTX and sulfasalazine to monotherapy with either drug alone. These studies did not support a difference in functional capacity between combination therapy and monotherapy.	Moderate
Synthetic DMARD combinations vs. synthetic DMARD monotherapy	**Comparative efficacy:** Three RCTs examined combination strategies with corticosteroids and one or more synthetic DMARDs compared to synthetic DMARD monotherapy. Some suggested better outcomes with the combination strategies.	Low

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Biologic DMARDs vs. biologic DMARDs	**Comparative effectiveness:** Head-to-head evidence was limited to a prospective cohort study that compared etanercept and infliximab. Etanercept patients had greater improvements in functional capacity, but the groups were not compared statistically.	Low
Biologic DMARDs vs. MTX	**Comparative efficacy:** Three RCTs (one good quality) found no difference in endpoint outcomes comparing either adalimumab or etanercept with MTX. Two of the RCTs found no difference between groups; one found greater improvement during the first 12 weeks in functional capacity and health-related quality of life with etanercept than with MTX but no difference from weeks 16 to 52.	Moderate
Biologic DMARDs vs. other synthetic DMARDs (as class effects)	**Comparative effectiveness:** No head-to-head evidence is available. One prospective cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than synthetic DMARDs as a class.	NA
Biologic DMARDs + MTX vs. biologic DMARDs	**Comparative efficacy:** Evidence is mixed. Two RCTs found that a combination of adalimumab or etanercept with MTX led to statistically significantly greater improvements in functional capacity or health-related quality of life than monotherapy with the same biologic DMARDs. One prospective cohort study found no difference when comparing etanercept plus MTX with etanercept alone or infliximab plus MTX with infliximab alone. For most of these comparisons, the evidence is limited to a single study.	Low
Biologic DMARDs + synthetic DMARD other than MTX vs. biologic DMARDs	**Comparative efficacy:** One RCT found no difference between a combination of etanercept with sulfasalazine and etanercept monotherapy.	Low
Biologic DMARD + MTX vs. MTX	**Comparative efficacy:** Two RCTs found greater improvement in functional capacity and quality of life with combination therapies (adalimumab + MTX or infliximab + MTX) than with MTX alone. One prospective cohort study found, for functional capacity, the etanercept-MTX combination, but not the infliximab-MTX combination, to be better than MTX alone.	Moderate
Key Question 3: Comparative Tolerability and Safety of Drug Therapy		
General Tolerability		
Corticosteroids	Overall adverse events in one efficacy trial of prednisolone and budesonide were not different.	Low
Synthetic DMARDs	Three efficacy trials and one meta-analysis indicate no differences in tolerability for leflunomide, MTX, and sulfasalazine.	Moderate
Biologic DMARDs	**Overall adverse event profiles:** In efficacy trials, overall profiles did not differ among biologic DMARDs. Two fair RCTs suggested that the risk of serious adverse events is dose-dependent.	Moderate
	Injection site reactions: In efficacy trials, anakinra had substantially higher rates of injection site reactions than either adalimumab or etanercept.	Moderate
	Infusion reactions: The existing evidence is insufficient to draw conclusions about the comparative risk of abatacept, infliximab, and rituximab with respect to severe or fatal infusion reactions.	Low
Combination of two biologic DMARDs	Two RCTs indicated that the combination of two biologic DMARDs led to statistically significantly higher rates of serious adverse events than monotherapy.	Moderate

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Discontinuation Rates		
Synthetic DMARDs	Three trials and one meta-analysis indicate no differences in discontinuation rates for leflunomide, MTX, and sulfasalazine. However, one meta-analysis of studies up to 5 years indicated that the proportion of patients who discontinue MTX is lower than the proportion who discontinue sulfasalazine.	Moderate
Synthetic DMARD combinations	Five studies of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had no differences in withdrawal rates attributed to adverse events.	Moderate
	Three studies combining prednisone with one or more DMARDs reported no differences in discontinuation rates between groups.	
Biologic DMARDs	Two cohort studies indicated that infliximab has statistically significantly higher rates of discontinuation than etanercept.	Moderate
	One cohort study reported that anakinra had higher rates of discontinuation than etanercept and infliximab.	Low
Serious Infections		
Corticosteroids and synthetic DMARDs	Three cohort studies indicated elevated infection risk for prednisone and possibly MTX and leflunomide compared with other DMARDs.	Low
Biologic DMARDs	The existing evidence is insufficient to draw conclusions about the comparative risk of biologic DMARDs.	NA
Biologic DMARDs and synthetic DMARDs	One cohort study indicated that anti-TNF drugs as a class (adalimumab, etanercept, and infliximab) did not lead to a higher overall risk for serious infections compared with synthetic DMARDs as a class.	Low
Malignancies		
Synthetic DMARDs	The existing evidence is limited to retrospective cohort studies. No risk of lymphoma was found for MTX or sulfasalazine.	Low
Biologic DMARDs	The existing evidence is insufficient to draw conclusions about the comparative risk of biologic DMARDs with respect to lymphoma or other malignancies.	NA
Combinations	One study of prednisone and a biologic DMARD-MTX combination was associated with nonmelanoma skin cancer.	Low
Other Serious Adverse Events		
Synthetic or biologic DMARDs	The existing evidence is insufficient to draw conclusions about the comparative risk of synthetic or biologic DMARDs with respect to serious adverse events such as demyelinations, drug-induced lupus, hepatotoxicity, interstitial lung disease, or congestive heart failure.	Low
Key Question 4: Differences by Subgroups		
Demographics: Age		
Various drug comparisons	The evidence base is sparse and mixed. One pooled analysis found similar responses in patients ages 65 years and older versus patients under 65 treated with a biologic (etanercept). Two poor-quality studies of one synthetic (MTX) and one biologic (etanercept) found no difference between these groups in adverse events, infections, or malignancies. A systematic review of MTX also found an inverse relationship between age and major clinical improvement, and no difference in toxicity.	Low

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Concomitant Therapies: Chronic Disease		
Various drug comparisons	No evidence is available from head-to-head comparisons, or observational studies for these concomitant treatment therapies. One subgroup analysis from a placebo-controlled trial involving anakinra found that safety profiles did not differ in subjects receiving antidiabetic, antihypertensive, or statin medication treatments.	NA
Comorbidities		
Various drug comparisons	**High-risk comorbidities:** One placebo-controlled RCT of anakinra found no difference between groups in serious adverse events or infections for adults with RA and various high-risk conditions.	Low
	Cardiovascular: Evidence is limited for subpopulations with cardiovascular disease. Two observational studies reported lower rates of either myocardial infarction or congestive heart failure on anti-TNF therapy than on other RA therapies. One database analysis found that only half of those with new onset congestive heart failure had no identifiable risk factors for congestive heart failure.	Low
	Renal impairment: One systematic review reported that greater renal impairment was associated with worse toxicity.	Low
Pregnancy and Neonatal Outcomes		
Various drug comparisons	**Fetal abnormalities:** Evidence is very limited and mixed. One poor-quality study using case reports calculated a higher incidence of congenital abnormalities in pregnancies of women taking DMARDs than in the general population, but a fair-quality database analysis found no statistical difference in live births, miscarriages, or therapeutic terminations in mothers or fathers treated with infliximab and the general population of pregnant women.	Low

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NA, not applicable; PSA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor; vs., versus.
* Studies are of fair quality (see Methods) unless otherwise noted.
† Strength of evidence assessed according to a modified GRADE approach.[27]

Table 27. Summary of findings with strength of evidence: psoriatic arthritis

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Key Question 1: Comparative Efficacy and Effectiveness of Drug Therapies		
Synthetic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo in one fair study, leflunomide produced greater response rates.	NA
Biologic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. The current evidence is limited to placebo-controlled trials. Compared with placebo, adalimumab, etanercept, and infliximab produced greater response rates.	NA
Key Question 2: Functional Capacity or Health-related Quality of Life		
Synthetic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo in one study, leflunomide provided better improvement in functional capacity and health-related quality of life.	NA

Table 27. Summary of findings with strength of evidence: psoriatic arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Biologic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo, adalimumab, etanercept, and infliximab led to greater improvement in functional capacity and health-related quality of life.	NA
	Key Question 3: Comparative Tolerability and Safety of Drug Therapy	
Synthetic DMARDs	No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo, leflunomide led to higher rates of withdrawals because of adverse events, diarrhea, and clinically significant increases in alanine aminotransferase.	NA
Biologic DMARDs	No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled efficacy trials. In these, overall adverse event profiles appeared to be similar for biologic DMARDs and placebo. **Injection site reactions:** adalimumab and etanercept had more injection site reactions than placebo.	NA
	Key Question 4: Differences by Subgroups: No Evidence	

DMARD; disease-modifying antirheumatic drug; NA, not applicable.
* Findings are limited to placebo-controlled studies.
† No head-to-head studies that evaluated comparative effectiveness in psoriatic arthritis met the inclusion criteria.

Most of the trials were conducted in RA patients, and we can draw some conclusions regarding the comparative efficacy of drugs for RA. Data are quite limited for PsA patients, and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either synthetic or biologic DMARDs in this condition.

Key Findings

Rheumatoid Arthritis

Over the past few years, treatment strategies for RA have changed considerably. Early use of DMARDs is now considered crucial to avoid persistent and erosive arthritis. Clinicians frequently start treatment regimens with DMARD monotherapies and adjust dosages as appropriate to achieve a low disease activity.

Existing comparative evidence permits us to draw some conclusions for monotherapies of synthetic and biologic DMARDs. Overall, the evidence supports similar efficacy and effectiveness for methotrexate (MTX) and sulfasalazine, but it is insufficient to draw conclusions about efficacy and effectiveness for sulfasalazine and leflunomide relative to each other.[30,31,33] All three drugs have similar discontinuation rates attributed to adverse events in short-term efficacy trials up to 2 years.[32,34,35,37]

Although the evidence is insufficient to draw firm conclusions on the comparative efficacy, effectiveness, and harms of biologic DMARDs, adjusted indirect comparisons of placebo-controlled studies suggest that no differences exist among the set of anti-tumor necrosis factor (anti-TNF) drugs (namely, etanercept, infliximab, and adalimumab).[21,48,49,51] Results of adjusted indirect comparisons indicate, however, that anakinra is less efficacious than anti-TNF drugs for

patients with RA.[48,49] 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 a synthetic DMARD is mixed. Monotherapies of adalimumab[57] and etanercept[54,63] generally did not reveal a benefit relative to MTX monotherapy; the exception was for radiographic outcomes, which were statistically 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. Other biologic DMARDs have not been directly compared with MTX.

By contrast, population-based, observational evidence suggests that biologic DMARDs as a class resulted in better functional capacity than synthetic DMARDs as a class.[58] No evidence exists on abatacept, anakinra, infliximab, and rituximab. No studies were available comparing biologics with synthetic DMARDs other than MTX. All randomized controlled trials (RCTs) were funded by the makers of the biologic DMARDs.

Although a substantial percentage of patients responds well to DMARD monotherapy,[34,54,57,63-65] 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.[42] 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 synthetic DMARDs appear to be more efficacious than monotherapy of either drug.

The existing evidence supports combination strategies of up to three synthetic 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.[45,46]

Similarly, combination therapy of biologic DMARDs (adalimumab and etanercept) with MTX achieved better results in clinical outcomes, functional capacity, and quality of life than monotherapy with biologic DMARDs.[57,63-66] Whether these results can be extrapolated to combinations of biologic DMARDs with other synthetic DMARDs is uncertain. In clinical practice, patients often receive biologic DMARDs as an add-on therapy to an existing regimen of various synthetic 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 monotherapies (14.8 percent vs. 2.5 percent; P = NR).[59,160] Current evidence also suggests improved functional capacity[39,43,47,124] and less radiographic progression[39,40,43,44,47] for combination strategies with corticosteroids and one or more synthetic DMARDs compared with synthetic DMARD monotherapy. For most of these comparisons, the evidence is limited to a single study.

The evidence is insufficient to draw firm conclusions about whether one combination strategy is better than another. Data are limited to one effectiveness trial for patients with early RA; it reported less radiographic progression over 12 months with either (1) MTX, sulfasalazine, and high-dose tapered prednisone or (2) MTX and infliximab versus (3) sequential DMARD therapy or (4) step-up combination therapy.[42] Of note, after the report was in peer review, the 2-

year followup was published.[214] 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. However, all arms had similar functional ability by Health Assessment Questionnaire scores (HAQ), and similar disease activity by Disease Activity Score (DAS) values regardless of which initial therapy they received.

The therapeutic advantage of combination therapy compared with monotherapy does not seem to be outweighed by an increase in harms. Evidence of moderate strength suggests that combination studies of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had similar withdrawal rates attributable to adverse events. Combination studies including prednisone with one or more DMARDs had similar discontinuation rates between groups.

Similarly, combinations of biologic and synthetic DMARDs had similar rates of adverse events than monotherapies of either drugs. However, because biologic DMARDs are relatively new medications, solid 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. The evidence is particularly sparse on abatacept and rituximab. Furthermore, the pharmaceutical industry funded a large percentage of these studies, and selective reporting is conceivable, although we had no way to account for missing information.

The most obvious differences among biologic DMARDs that might be clinically decisive for choosing a particular drug involve 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.[146,147]

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 RA suggested that an early start of a biologic DMARD can prevent joint erosions and beneficially influence the clinical course of the disease. 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 synthetic DMARDs.[140,215]

A considerable limitation of our conclusions is that we have had to derive them primarily from efficacy trials. 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 reaction in, on average, 17 percent of patients.[158] A prospective cohort study in a Canadian clinical care setting, however, reported substantially higher percentages.[176] In this study (113 patients with 1,183 infusions), 53

percent of patients experienced at least one infusion reaction during their therapy (mean, 15 months).

Patients who were enrolled in efficacy trials usually suffered from more severe disease than the average patient in clinical practice.[216] For example, a recent study found that only small proportions 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;[54] 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;[100,216] 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.

Furthermore, with RA we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups and the general population. Several studies conducted subgroup analyses or used subgroups as the study population. Age subgroup analyses suggested no differences in adverse events, infections, or malignances in patients treated with MTX or etanercept.[207,208] For MTX, the odds for major clinical improvement dropped slightly as age increases in all clinical trial patients; age did not affect MTX efficacy or the rate of side effects.[206] The strength of this evidence is weak, and results have to be interpreted cautiously.

Psoriatic Arthritis

No head-to-head comparative evidence meeting inclusion criteria exists for any drugs in this review for treating patients with PsA. Parenteral high-dose MTX and sulfasalazine improved patient outcomes compared with placebo.[111] Additionally, patients taking leflunomide had higher response rates and quality of life outcomes than those taking placebo.[112,113]

Evidence supports the general efficacy of adalimumab, etanercept, and infliximab for the treatment of PsA.[114-122] However, evidence is insufficient to draw firm conclusions about the comparative efficacy, effectiveness, functional status, health-related quality of life, or tolerability of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab for the treatment of PsA.

Information is insufficient for the harms, tolerability, adverse events, and adherence for patients with psoriatic arthritis. The available studies include only placebo-controlled studies; no head-to-head studies meeting inclusion criteria have been published.

Future Research

We have identified several areas needing further research to help clinicians and researchers arrive at stronger conclusions on the comparative efficacy, effectiveness, quality of life, and harms of medications for both RA and PsA.

Rheumatoid Arthritis

Important areas that will influence clinical decisionmaking include three critical topics: (1) timing of initiation of therapies, (2) applicability of combination strategies and biologic DMARD therapy in community practice, and (3) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs. 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, synthetic 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 synthetic DMARDs in patients who currently do not qualify for a treatment with a biologic DMARD. Also still unclear is whether newer synthetic DMARDs such as leflunomide have a better, long-term adverse events profile than older synthetic DMARDs such as MTX. Additionally, although combination strategies with synthetic DMARDs with or without corticosteroids appear more effective, further research examining *which* combination strategy is more effective would be beneficial for medical treatment decisionmaking.

Moreover, head-to-head RCTs need to establish the comparative effectiveness and safety of biologic DMARDs. Currently, evidence from systematic reviews, placebo-controlled trials, and observational studies is insufficient to draw any firm conclusions. 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 a high rate of 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 because of 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.

Psoriatic Arthritis

For this condition, the available evidence is limited to placebo-controlled trials (six studies and two systematic reviews). The quality of studies on synthetic DMARDs is sparse and fraught with methodological issues.

Areas of future research are similar to the ones on RA outlined above. Head-to-head RCTs have to establish the comparative efficacy and safety of different treatment strategies with and

without corticosteroids, synthetic DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage.

Furthermore, head-to-head RCTs have to determine the comparative effectiveness and safety of biologic DMARDs for the treatment of PsA.

More generally, the issues of effectiveness, subgroups, and use in ordinary clinical settings highlighted for RA warrant attention for PsA as well.

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APPENDIXES

Appendix A: Peer Reviewers and Acknowledgments

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Appendix B: Search Strings

#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

2 were discarded as clearly out of scope, so PUBMED = 1403
Cochrane Reviews = 84 = 24 New, unduplicated
EMBASE =1808 = 469 New, unduplicated
Unduplicated = 1986

Appendix C: Studies in an Included Meta-Analysis

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Appendix D: Excluded Studies

Not Published in English

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Wrong Outcome

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Wrong Study Design

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Appendix E: Evidence Tables

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. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission

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, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study **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**:	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study (continued)				**ACR20,%** **D1:** 59 **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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Landewe et al., 2002 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)	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Landewe et al., 2002 COBRA study (continued)				**Sharp mean change:** **D1:** 2 **D2:** 6 (*P* < 0.004) **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**		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study	Inclusion and	Characteristics	Baseline Disease	Health Outcomes	Adverse	Analysis and

Characteristics	Exclusion Criteria	and Interventions	and Treatment Characteristics		Events, %	Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study				**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		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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)	**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)	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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• Pre-existing pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			**ACR70, %:** **D1:** 4 **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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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	**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	**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 ($P < 0.01$)	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• Presence of relevant comorbidity, including active infections		**Baseline DAS, mean:** **D1:** 5.0 **D2:** 5.1 **D3:** 5.2	**Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical advantage to use of ETA in combination with SSZ		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., 2003 **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:** **D1:** 2.2 (sd 1) **D2:** 2.2 (sd 1) **D3:** 2.2 (sd 1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., [1] 2003 (continued)			**Baseline DAS, mean:** **D1:** 4.23 **D2:** 4.13 **D3: 4.24** **RF positive, %:** **D1:** 75 **D2:** 62 **D3:** 71 **RAI:** **D1:** 17.6 **D2:** 16.5 **D3:** 18.9	**Median radiologic score** D2: 7.5 D3: 8.5: (*P* = 0.7)**D3:** 2.2 (sd 1.1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9) **Median radiologic score** D2: 7.5 D3: 8.5 (*P* = 0.7) Similar results with 3 groups (**D3** vs. **D2** vs. **D1**) instead of 2 groups (**D3** vs. **D2** or **D1**) when compared, but data not shown **Attrition rate**: 21%		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 **Country, Setting:** Multinational, multicenter (26 rheumatology centers) **Funding:** Roche **Research Objective:** To confirm role of B cells in RA by evaluating effect of RIT in pts with active RA according to ACR and EULAR criteria **Study Design:** RCT **Overall N:** 161 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 21 • Diagnosed according to 1987 ACR criteria • Failed previous MTX treatment • > MTX 10 mg/wk and active disease • RF-positive • NSAIDS at stable doses or Css at doses < 12.5 mg per d of PNL • All received 17-d txt with Css and a 10 mg dose of leucovorin **Exclusion Criteria:** • Autoimmune disorder other than RA (except Srjogen's) • Functional class IV • Active rheumatoid vasculitis • Systemic diseases associated with arthritis • CFS • Serious, uncontrolled diseases • Active infection	**Interventions, dose:** **D1:** MTX (≥10 mg/wk) **D2:** RIT (1000 mg on ds 1 and 15) **D3:** RIT (1000 mg on ds 1 and 15) + CYP (750 mg d 3,17) **D4:** RIT (1000 mg on ds 1 and 15) + MTX (≥10 mg/wk) **N:** **D1:** 40 **D2:** 40 **D3:** 41 **D4:** 40 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 53 **D4:** 54 **Sex, % female:** **D1:** 80 **D2:** 73 **D3:** 83 **D4:** 75 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 9 **D3:** 10 **D4:** 12 **TJC, mean:** **D1:** 32 **D2:** 34 **D3:** 33 **D4:** 32 **SJC, mean:** **D1:** 19 **D2:** 21 **D3:** 19 **D4:** 23 **DMARD use (#):** **D1:** 2.6+/- 1.3 **D2:** 2.5+/-1.6 **D3:** 2.6+/-1.4 **D4:** 2.5+/-1.4 **Corticosteroid use, %** NR **MTX naive, %:** 0 **Txt resistant, %:** 100 **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D2:** 65 **D4:** 73 (*P* = NR) **ACR50, %:** **D2:** 33 **D4:** 43 (*P* = NR) **ACR70, %:** **D2:** 15 **D4:** 23 (*P* = NR) **Rates of moderate or good EULAR responses, %:** **D2:** 85 **D4:** 83 (*P* = NR) **DAS:** **D2:** -2.2 **D4:** -2.6 **At 48 weeks** **ACR20, %:** **D2:** 33 **D4:** 65 (*P* = NR) **ACR50, %:** **D2:** 15 **D4:** 35 (*P* = NR) **ACR70, %:** **D2:** 10% **D4:** 15% (*P* = NR)	**Overall:** **D1:** 80 **D2:** 80 **D3:** 73 **D4:** 85 **SAEs:** **D1:** 8.0 **D2:** 5.0 **D3:** 4.9 **D4:** 8.0 **Infusion or injection reaction:** **D1:** 30 **D2:** 45 **D3:** 32 **D4:** 33 **Nausea:** **D1:** 3 **D2:** 5 **D3:** 10 **D4:** 0 **URTI:** **D1:** 15 **D2:** 10 **D3:** 5 **D4:** 10	**Overall Attrition Rate, %:** at 24 wks 6.2% at 48 wks 37.8% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 (continued)	• History of recurrent infection or recurrent bacterial infections with encapsulated organisms • Primary of secondary immunodeficiency • History of cancer		**Baseline DAS, mean:** **D1:** 6.9 **D2:** 6.8 **D3:** 6.9 **D4:** 6.8			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)			**Baseline DAS, mean:** NR **NSAIDS, %:** **D1:** 80 **D2:** 84.7 **D3:** 37.3 **D4:** 42.5 **Larsen score:** **D1:** 1.25 **D2:** 1.29 **D3:** 1.27 **D4:** 1.31	**HAQ improvement:** difference between groups in change from baseline HAQ, NS **Radiograph change, Larsen Scores:** No further increase in joint damage in pts txted with LEF and small improvement in MTX pts; small net result, but statistically significant difference with MTX better than LEF (overall scores and significance NR)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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	**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	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• Other meds allowed **Exclusion Criteria:** NR		**Baseline DAS, mean:** **D1:** 5.8 **D2:** 5.6 **D3:** 5.4 **HAQ:** **D1:** 1.55 **D2:** 1.47 **D3:** 1.46			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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	**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	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• Received any intraarticular or systemic corticosteroid injections within past 4 wks • Recent history of significant infection or other important concurrent illness		**MTX use, %:** Overall: 100 **HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.6			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 BeST Study **Country, Setting:** The Netherlands, 18 peripheral and 2 university hospitals **Funding:** Schering-Plough BV and Centocor Inc Dutch College of Health Insurances **Research Objective:** To compare clinical and radiographic outcomes of 4 different txt strategies in pts with early RA **Study Design:** RCT **Overall N:** 508 **Study Duration:** 12 mos	**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 with PRE **D4:** initial combination with INF **D5:** NR Overall: Totals **N:** **D1:** 126 **D2:** 121 **D3:** 133 **D4:** 128 Overall: 508 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 55 **D4:** 54 Overall: 54 **Sex, % female:** **D1:** 86 **D2:** 86 **D3:** 86 **D4:** 85 Overall: 86 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 23 wks **D2:** 26 wks **D3:** 23 wks **D4:** 23 wks **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.5 +/- 0.9 **D2:** 4.5 +/- 0.8 **D3:** 4.4 +/- 0.9 **D4:** 4.3 +/- 0.9	**At 12 months** **Mean D-HAQ scores:** **D1:** 0.7 +/- 0.7 **D2:** 0.7 +/- 0.6 **D3:** 0.5 +/- 0.5 **D4:** 0.5 +/- 0.5 (**D1** vs. **D3**; *P* < 0.05) (**D3** vs. **D4**; *P* = NS) All others NR **Median total SHS increases (0 to 448 scale) from baseline:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (**D1** vs. **D3**; *P* = 0.003) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.007) (**D2** vs. **D4**; *P* < 0.001) **Progression of total SHS, %:** **D1:** 67 **D2:** 73 **D3:** 87 **D4:** 93 (**D1** vs. **D3** and **D4**; *P* = 0.001) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.010) (**D2** vs. **D4**; *P* < 0.001)	**Overall:** **D1:** 43 **D2:** 47 **D3:** 37 **D4:** 39 **SAEs:** **D1:** 6.3 **D2:** 7.4 **D3:** 12.8 **D4:** 4.7 **Infections:** **D1:** 4 **D2:** 7 **D3:** 8 **D4:** 8 **Serious Infections:** **D1:** 2.4 (pneumonia, HSV encephalitis, and fever) **D2:** 0.8 (diffuse peritonitis) **D3:** 0.8 (oral HSV) **D4:** 2.3 (pneumonia, pneumonitis, and septic arthritis) **Infusion or injection reaction:** **D4:** (10/128) = 7.8%	**Overall Attrition Rate, %:** 3.3% (17/508) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 (continued)	• concomittant txt with an experimental drug • bone marrow hypoplasia • diabetes • alcohol or drug abuse • wish to conceive • inadequate contraception		**D-HAQ (0 to 3 scale):** **D1:** 1.4 +/-0.7 **D2:** 1.4 +/-0.6 **D3:** 1.4 +/-0.7 **D4:** 1.4 +/-0.7	**Sharp van der Heijde median increase:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (*P* < 0.001) **Sustain DAS44 ≤ 2.4, %:** **D1:** 53 **D2:** 64 **D3:** 71 **D4:** 74 (**D1** vs. **D3**; *P* = 0.004) (**D1** vs. **D4**; *P* < 0.001) (*P* = NS and NR for others) **Patients who progressed to erosive from nonerosive disease at baseline, %** **D1:** 29 (9/31) **D2:** 53 (18/34) **D3:** 38 (14/37) **D4:** 15 (5/34) D1 vs D2, *P* = 0.050 D2 vs D4, *P* = 0.028 D3 vs D4, *P* =NS, NR	**Cardiovascular Events:** **D1:** 2 (hypertension, TIA, PE) **D2:** 2 (peripheral bypass, pacemaker implantation) **D3:** 6 (3 MIs, heart failure **D4:** 2 (TIA, PE, peripheral vascular disease) **Malignancies:** **D2:** N:1 bladder **D3:** N:2 breast, lymphoma **Adherence** 24 (5%) non-adherent	

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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	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)	**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 **D2:** 20.0 **D3:** 27.8	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)			**HAQ:** **D1:** 0.97 **D2:** 0.92 **D3:** 1.20	**HAQ change from 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		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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., 2006 **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 **Race, % white:** NR	**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	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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., 2006 (continued) **Overall N:** 2711 **Study Duration:** 6 mos			**Baseline DAS, mean:** **D1:** 6.8 **D2:** 6.6 **D3:** 6.6 **D4:** 6.8 **D5:** 6.8 **D6:** 6.7			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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 Duration:** 12 wks	**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 • Local or systemic infection • Allergy to BUD or other glucocorticoids; txt w/ live viruses	**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 **Baseline DAS, mean:** 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* < 0.001)	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• (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		**HAQ:** **D1:** 1.61 **D2:** 1.57 **D3:** 1.51 **D4:** 1.52	**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) Diffrence: 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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; van der Heijde, 2006 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 **Overall N:** 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	**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 investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos	**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:** **D1:** 5.5 **D2:** 5.7 **D3:** 5.5	**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 norms (< 0.5) than monotherapy	**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) **D3:** 24 (29)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• Previous txt with MTX if pt experienced clinically toxic side effects or had no response		**Sharp:** **D1:** 26.8 **D2:** 21.8 **D3:** 21.8 **JSN:** **D1:** 13.3 **D2:** 11.5 **D3:** 10.3	**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** **D2:** 0.74 **D3**: 0.20; *P* = NS, NR		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** N/A **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)				**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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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, ETA, 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, %:** Overall: 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	NR	**Overall Attrition Rate, %:** 14% **ITT Analysis:** No **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)				**Pts in ARA Remission, %:** **D1:** 13.2 **D2:** 10.2 Approximately half of pts in remission at 6 mos relapsed until 12 mos, %: **D1:** 55 **D2:** 58 Patients with moderate disease acitvitiy (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		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Korpela, 2004; Puolakka, 2004 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	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Korpela, 2004; Puolakka, 2004 FIN-RACo Study (continued)				**Larsen Erosion Score:** **D1:** 11 **D2:** 24 (*P* = 0.001) **Median increase in Larsen 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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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	**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	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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	difficulties • Retinal disease • Macular degeneration • Active peptic ulcer disease		**Duration of morning stiffness (minutes):** **D1:** 190 **D2:** 156 **D3:** 135 **RF:** **D1:** 89% **D2:** 85% **D3:** 84%			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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	**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)	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)			**% RF positive:** **D1:** 88 **D2:** 88 **D3:** 89 **ESR:** **D1:** 28.5 +/- 20.3 **D2:** 34.1 +/- 26.5 **D3:** 30.1 +/- 21.0	**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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Smolen, 2006 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)	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Smolen, 2006 ASPIRE Trial (continued)	within past 5 yrs (excluding excised skin cancers)		**HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5	**ACR-N, %:** **D1:** 26.4 **D2:** 38.9 **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		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Smolen, 2006 ASPIRE Trial (continued)				**Modified Sharp/van der Heijde Score change:** **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		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Larsen 2001; Scott 2001 **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of novel DMARD leflunomide was compared to placebo and sulfasalazine **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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Cohen 2001; Strand, Tagwell 1999 **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) **Discontinuation rate, %:** **D1**: 22 **D2**: 10.4 (*P* = NR)	**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 **Adherence:** Non-adherence as the reason for reason for withdrawal **D1**: 1 **D2**: 1	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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; Cohen 2001; Strand, Tagwell 1999 (continued)				**At 2 yrs** **ACR 20, %** **D1:** 79 **D2:** 67 (*P* = 0.049) **ACR 50, %** **D1:** 34 **D2:** 28 **ACR70, %** **D1:** 17 **D2:** 12 **Sharp score change** **D1:** 1.6 (n= 71) **D2:** 1.2 (n= 66) **HAQ DI change** **D1:** -0.6 (n= 97) **D2:** 0.37 (n=101) **Discontinuation rate, %:** **D1**: 27 **D2**: 17	**At 24 months** **SAEs, %:** **D1:** 18.9 **D2:** 18.9	

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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 • Glucocorticoids, DMARDs • Contraindication for glucocorticoid therapy • Previous fragility fractures, pts < 65 years with T score < -2.5 on bone mineral densitometry	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)	• 65 or older with Z score ≤ 1			**Radiographic progression beyond smallest detectable difference, %** **D1:** 25.9 **D2:** 39.3 (*P* = 0.033) **Joint space narrowing score, median change** **D1:** 1 **D2:** 2 (*P* = 0.08)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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:** ETA (50 mg/wk) **D3:** ETA (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	**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	**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

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)		**Sex (% female** **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	**DMARD use, %:** **D1:** 25 **D2:** 75 **D3:** 96 **D4:** 85 **D5:** 96 **D6:** 75 **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	**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)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)			**RF factor positive:** **D1:** 72 **D2:** 65 **D3:** 69 **D4:** 68 **D5:** 69 **D6:** 75 **D7:** 73 **D8:** 71 **D9:** 71			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 **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 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

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 (continued)			**Txt resistant, %:** NR **Pts. with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.1 **D2:** 6 **D3:** 6.1 **D4:** 5.4 **D5:** 5.5 **D6:** 5.6 **MTX use:** **D1:** 91.2 **D2:** 92.1 **D3:** 78.6 **D4:** 68.7 **D5:** 94.2 **D6:** 90.7			

Evidence Table 2. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Clark, 2004, International: Europe, U.S., Canada, Australia, Health Technology Assessment Programme (U.K.) **Study Design:** Systematic review and meta 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 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	Adjusted indirect comparisons with anti TNF agents (ETA, 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. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Gartlehner et al., 2006 US **Study Design:** Metaanalysis (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 ETA: 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. Indirect 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 ETA (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. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Hochberg et al., 2003 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, ETA and ADA) to methotrexate in a "step-up" strategy	Indirect comparisons, Relative Risk (95% CI) • Etanercept 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) • Etanercept 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. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Osiri et al., 2002 Multinational Cochrane Collaboration **Study Design:** Systematic review of RCTs and CCTs **Aims of Review:** To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA Meta-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 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. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Wailoo et al., 2006 AHRQ **Study Design:** Decision analytic model and metaanalysis **Aims of the Review:** Cost effectiveness of ETA, 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/ETA 1.17 (0.68, 2.08) • ADA/ETA 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 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni et al., 2005; Kavanaugh et al., 2006 IMPACT Study **Country, Setting:** Multinational, 9 clinical sites **Funding:** NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network **Research Objective:** Efficacy and tolerability of INF for the articular and dermatologic manifestations of active PsA **Study Design:** RCT **Overall N:** 104 **Study Duration:** 50 wks (1-16 wks RCT 16-50 open, all treated with INF)	**Inclusion Criteria:** • Age ≥ 18 • Failure of 1 or more DMARD • Active peripheral polyarticular arthritis • MTX ≥ 15 mg/wk w/ folic acid supplementation • LEF, SSZ, HCQ, intramuscular gold, penicillamine, or azathioprine stable for 4 wks • oral corticosteroids (dosage of 10 mg PRE equivalent/d or less) • NSAIDs stable for at least 2 wks **Exclusion Criteria:** • Monoclonal antibody or fusion protein • History of TB: positive tests for RF or latent TB investigational drug within 3 mos	**Interventions:** **D1:** Placebo **D2:** INF (5mg/kg at wks 0,2,6,14, then every 8 wks) **N:** **D1:** 52 **D2:** 52 **Mean age, yrs:** **D1:** 45.2 **D2:** 45.7 **Sex, % female:** **D1:** 42.3 **D2:** 42.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 11.7 **TJC, mean:** **D1:** 20.4 **D2:** 23.7 **SJC, mean:** **D1:** 14.7 **D2:** 14.6 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.4 **D2:** 5.5 **Concomitant MTX, %:** **56**	• ACR50 Placebo 0/52 (0.0%) vs. INF 24/52 (46.2%) • ACR70 Placebo 0/52 (0.0%) vs. INF 15/52 (28.8%) • # of tender joints Placebo -23.6 vs. INF 55.2 • # of swollen joints Placebo -1.8 vs. INF 59.9 • DAS Placebo 2.8 vs. INF 45.5 $P < 0.001$ • HAQ Placebo -1.6 vs. INF 49.8 $P < 0.001$ • PsARC Placebo -12% vs. INF +86% $P < 0.001$ • ACR20 wk 16 Placebo 5/52 (9.6%) vs. INF 34/52 (65.4%) $P < 0.001$ • At 50 wks • Total modified vdH-S score, 85% and 84% in Placebo/INF and INF/INF groups had no worsening. • Change in erosion scores INF/INF 0.921, placebo/INF 0.536 ($P = 0.780$) • Change in JSN INF/INF -0.51, placebo/INF -0.47 ($P = 0.211$) • 16 wks-PsARC INF 75% vs. Placebo 21% ($P < 0.001$) • PASI75 INF 68% vs, placebo 0% ($P < 0.001$)	**Overall:** **D1:** 65 **D2:** 73 **D3:** 84 **Headache:** **D1:** 3 **D2:** 4 **URTI:** **D1:** 5 **D2:** 1	**Overall Attrition Rate (%):** 5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni, 2005; Kavanaugh et al., 2006 IMPACT2 study **Country, Setting:** Multinational 36 sites in clinics **Funding:** Centocor Inc and Schering-Plough **Research Objective:** Efficacy, health related quality of life and physical function in pts with PsA **Study Design:** RCT **Overall N:** 200 **Study Duration:** 14 to 24 wks (pts with inadequate response entered early escape at wk 16)	**Inclusion Criteria:** • Diagnosed with PsA • Diagnosed at least 6 mos before first infusion of study drug • Inadequate response to current or previous DMARDs or NSAIDs • Pts had to have active plaque psoriasis with at least 1 qualifying target lesion at least 2 cm in diameter • Negative test for RF in their serum • Stable doses of MTX, oral corticosteroids, NSAIDs **Exclusion Criteria:** • TNF α inhibitors; active or latent TB • Chronic or clinically significant infection, malignancy, or CHF	**Interventions:** **D1:** Placebo **D2:** INF (5 mg/kg at wks 0, 2, 6, 14, 22) **N:** **D1:** 100 **D2:** 100 **Mean age, yrs:** **D1:** 46.5 **D2:** 47.1 **Sex, % female:** **D1:** 49 **D2:** 29 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.5 **D2:** 8.4 **TJC, mean:** **D1:** 25.1 **D2:** 24.6 **SJC, mean:** **D1:** 14.4 **D2:** 13.9 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 10 **D2:** 15 **MTX naive, %:** NR **Txt resistant, %:Overall 100** **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX, %:** **D1:** 45 **D2:** 47 **PASI:** **D1:** 10.2 **D2:** 11.4	• Placebo vs. INF (%): • ACR 50 at wk 14 3 vs. 36 (P < 0.001) and wk 24 4 vs. 41 (P < 0.001) • ACR70 at wk 14 1 vs. 15 (P < 0.001) and wk 24 2 vs. 27 (P < 0.001) • PsARC at wk 14 27 vs. 77 (P < 0.001) and wk 24 32 vs. 70 (P < 0.001) • •HAQ improvement at wk 14 -18.4 vs. 48.6 (P < 0.001) and wk 24 -19.4 vs. 46 (P < 0.001) • •SF-36 (change from baseline) • Physical wk 14 1.1 vs. 9.1 (P < 0.001) and wk 24 1.3 vs. 7.7 (P < 0.001) • Mental wk 14-1.2 vs. 3.8 (P = 0.001) and wk 24 0.4 vs. 3.9 (P = 0.047) • ACR20 at Wk 14 11 vs. 58 (P < 0.001) and Wk 24 16 vs. 54 (P < 0.001) • PASI 50: wk 14: 9 vs. 82 (P <0.01), wk 24: 8 vs. 75 (P <75 (P<0.01); PASI 75 wk 14: 2 vs. 64 (P < 0.01), wk 24: 1 vs. 50 (P < 0.01); • improvement wk 14: 0 vs. 41 (P < 0.01), wk 24: 0 vs. 39 (P < 0.01) • median productivity at 14 wks 9.2% vs. 67.5% (P < 0.0001) • missed workdays at 14 wks 13% vs. 3.7% (P = 0.138)	**Overall:** **D1:** 67 **D2:** 67 **SAEs:** **D1:** 6 **D2:** 9 **Infusion or injection reaction:** **D1:** 6 **D2:** 7 **Dizziness:** **D1:** 5 **D2:** 4 **Headache:** **D1:** 5 **D2:** 6 **URTI:** **D1:** 14 **D2:** 10	**Overall:** **Attrition Rate (%):** Wk 14: NR Wk 24: 7.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Kaltwasser et al., 2004 and Nash et al., 2006 **Country, Setting:** Multinational, multicenter (31) **Funding:** Aventis **Research Objective:** Efficacy and safety of LEF versus placebo in pts with PsA and psoriasis **Study Design:** RCT **Overall: N:** 190 (ITT = 186) **Study Duration:** 24 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA • NSAIDs or Css (prednisone dose of 10 mg/day or steroid equivalent administered orally) • Discontinue DMARDs, biologics and systemic antipsoriatic txt 28 days **Exclusion Criteria:** • Pregnant or lactating; leflunomide • Impaired renal or hepatic system • Nonpsoriatic inflammatory joint disease or arthritis onset < 16 yrs • RH factor +, rheumatoid nodules, serious infections, malignancy, or CVD, HIV, hepatitis B or C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg • Impaired bone marrow function; history of drug or alcohol abuse	**Interventions:** **D1:** Placebo **D2:** LEF **N:** **D1:** 91 **D2:** 95 **Mean age, yrs:** Drug 1: 46.9 Drug 2: 48.6 Overall **Sex, % female:** **D1:** 37.4 **D2:** 42.1 **Race, % white:** **D1:** 95.6 **D2:** 97.9	**Mean disease duration, yrs:** **D1:** 10 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 49.5 **D2:** 61.1 **Corticosteroid use, %:** **D1:** 9.9 **D2:** 15.8 **DMARD naive, %:** **D1:** e 50.5 **D2:** 38.9 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX, %:** 0	• 56 of 95 leflunomide-treated pts (58.9%; 95% CI, 48.4-68.9) and 27 of 91 placebo-treated pts (29.7% [95% CI, 20.6-40.2]) were classified as responders by PsARC ($P < 0.0001$) Change in HAQ total score • Placebo (N:90) -0.05 ± 0.46 ($P = 0.0267$) • Leflunomide (N:94) -0.19 ± 0.51 Change in PASI score • Placebo (N:90) -0.6 ± 6.1 $P = 0.0030$ • Leflunomide (N:92) -2.1 ± 5.9 Change in DLQI total score • Placebo (N:89) -0.2 ± 5.1 $P = 0.0173$ • Leflunomide (N:90) -1.9 ± 5.1	**Overall:** **D1:** 76.1 **D2:** 85.4 **SAEs:** **D1:** 5.4 **D2:** 13.5 **Serious Infections:** **D1:** 0 **D2:** 0 **Diarrhea:** **D1:** 13.0 **D2:** 24.0 **Headache:** **D1:** 7.6 **D2:** 11.5 **Nausea:** **D1:** 8.7 **D2:** 9.4	**Overall Attrition Rate (%):** 47.9% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2000 **Country, Setting:** US, single center in Seattle **Funding:** Immunex Corp. **Research Objective:** To study the efficacy and safety of etanercept in pts with psoriatic arthritis and psoriasis **Study Design:** RCT **Overall N:** 60 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA according to: > 3 swollen, tender, or painful joints • Inadequate response to NSAIDs • Hepatic transasminase concentrations no greater than 2x upper limit of normal • Hemoglobin 85 g/L or higher • Platelet count 125,000 per mL or more and serum creatinine 152-4 mmol/L or below • MTX < 25 mg/wk and stable for 4 wks • Corticosteriods if the dose < 10 mg/d of PRE, stable for at least 2 wks and maintained at a constant dose throughout study **Exclusion Criteria:** • Evidence of skin conditions other than psoriasis	**Interventions:** **D1:** Placebo **D2:** ETA (25mg 2x wkly) **N:** **D1:** 30 **D2:** 30 **Mean age, yrs:** **D1:** 43.5 **D2:** 46 **Sex, % female:** **D1:** 40 **D2:** 47 **Race, % white:** **D1:** 83 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 40 **D2:** 20 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX:** **D1:** 47 **D2:** 47	• PsARC ETA 26 (87%) vs. Placebo 7 (23%) *P* < 0.0001 95% CI, 44-83; ACR50 ETA 15 (50%) vs. Placebo 1 (3%) *P* = 0.0001 95% CI, 28-66; • ACR70 ETA 4 (13%) vs. Placebo 0 (0%) *P* = 0.0403 95% CI, 1-26; • HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) *P* < 0.001 • •ACR20 was achieved by 73% ETA treated pts compared with 13% placebo treated pts (*P* < 0.0001) • Median % improvements in tender and swollen joint counts at 12 wks ETA 75% and 72% respectively vs. placebo 5% worsening and 19% improvement; disability according to HAQ significantly more improved in ETA than placebo (83% vs. 3%, *P* < 0.0001) • 26% of ETA vs. 0 of placebo pts achieved 75% improvement in PASI at 12 wks (*P* = 0.0154); similar differences between ETA and placebo also seen at 25% and 50% improvements in PASI scores	**SAEs:** **D1:** 0 **D2:** 3.3 **Infusion or injection reaction:** **D1:** 20 **D2:** 3 **Headache:** **D1:** 13 **D2:** 10 **URTI:** **D1:** 57 **D2:** 57	**Overall Attrition Rate (%):** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2004; Mease et al., 2006 (2nd yr outcomes) **Country, Setting:** US, 17 sites **Funding:** Immunex **Research Objective:** Safety, efficacy, and effect on radiographic progression of ETA in pts with PsA **Study Design:** RCT **Overall N:** 205 **Study Duration:** 24 wks (with 48 wk open-label phase)	**Inclusion Criteria:** • Age 18 70 • Diagnosed with PsA ≥ 3 swollen and 3 tender joimts • Inadequate response to NSAID • At least one of PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis • Stable plaque psoriasis with a qualifying lesion • MTX therapy (stable 2 mo ≤ 25 mg/wk) • Css (stable 4 wks ≤ 10 mg/d of prednisone) **Exclusion Criteria:** • Oral retinoids, topical vitamin A or D analog preparations, and anthralin	**Interventions:** **D1:** placebo **D2:** ETA (25 mg 2x wkly) **N:** **D1:** 104 **D2:** 101 **Mean age, yrs:** **D1:** 47.3 **D2:** 47.6 **Sex, % female:** **D1:** 55 **D2:** 43 **Race, % white:** **D1:** 91 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 15 **D2:** 19 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX use, %:** **D1:** 41 **D2:** 42 **Sharp:** **D1:** 18.3 **D2:** 25.89	• At 12 wks, 59% of ETA pts met ACR20 criteria compared with 15% placebo pts ($P < 0.0001$) • 23% of ETA pts eligible for psoriasis evaluation achieved at least 75% improvement in psoriasis area and severity index, compared with 3% of placebo pts ($P = 0.001$) • 12 mos; the mean annualized rate of change over one yr of txt in modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo ($P = 0.0001$) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group ($P < 0.0001$) • 72% & 70% of ETA achieved PsARC at 12 and 24 wks, respectively, compared with 31% and 23% of placebo pts	**SAEs:** **D1:** 3.9 **D2:** 4 **Infusion or injection reaction:** **D1:** 9 **D2:** 36 **Headache:** **D1:** 5 **D2:** 8 **URTI:** **D1:** 23 **D2:** 21 **UTI:** **D1:** 6 **D2:** 6	**Overall Attrition Rate (%):** 19.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2005 ADEPT Study **Country, Setting:** Multinational, multi-clinic (50) **Funding:** Abbott Laboratories **Research Objective:** Safety and efficacy of ADA compared with placebo in txt of active psoriatic arthritis **Study Design:** RCT **Overall N:** 313 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 18 • Moderate to severe PsA • Active psoriatic skin lesions or a documented history of psoriasis • Inadequate response or intolerance to NSAIDs • MTX ≥ 3 mos with stable dose 4 wks **Exclusion Criteria:** • CYP, tacrolimus, DMARDs, or oral retinoids (4 wks) • Topical txts for psoriasis within 2 wks, other than medicated shampoos or low-potency topical steroids • Anti-TNF • History of TB • Central nervous system demyelinating disease • Listeriosis, or severe infection within 30 ds or oral antibiotics within 14 ds	**Interventions:** **D1:** placebo **D2:** ADA (40mg every other wk) **N:** **D1:** 162 **D2:** 151 **Mean age, yrs:** **D1:** 49.2 **D2:** 48.6 **Sex, % female:** **D1:** 45.1 **D2:** 43.7 **Race, % white:** **D1:** 93.8 **D2:** 97.4	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9.8 **TJC, mean:** **D1:** 25.8 **D2:** 23.9 **SJC, mean:** **D1:** 14.3 **D2:** 14.3 **Mean number previous DMARDS:** **D1:** 1.5 **D2:** 1.5 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline PASI (mean):** **D1:** 8.3 **D2:** 7.4 **Concomitant MTX use, %:** **D1:** 50 **D2:** 51 **Baseline HAQ:** **D1:** 1.0 **D2:** 1.0	• PsARC ADA 60% wk. vs.placebo 23% • ACR50 ADA, 39% vs. placebo, 6% ($P < 0.001$) • ACR70 ADA, 23% vs. placebo, 1% ($P < 0.001$) • The PASI75 ADA 59% vs. placebo 1% ($P < 0.001$) (N:69 per group). • HAQ DI change placebo -0.1 ± 0.4 vs. ADA -0.4 ± 0.5 ($P < 0.001$) • ACR20 ADA 57% vs. placebo 15% (between-group difference 42%, 95% CI, 31-52%; $P < 0.001$). • Mmean change in modified total Sharp was -0.2 for ADA versus placebo ($P < 0.001$) • Erosion scores (mean change ADA 0.0 vs. placebo 0.6) and JSN scores (mean change ADA -0.2 vs. placebo 0.4) ($P < 0.001$ for both) • SF-36: SF-36 PCS; change in baseline to wk 12 for placebo vs ADA; 1.4 vs 9.3 ($P < 0.001$) • Change in baseline to wk 24; 1.4 vs 9.3 ($P < 0.001$) • SF-36 MCS • Change in baseline to wk 12 ; 1.2 vs 1.6 (P NS) • Change in baseline to wk 12; 0.6 vs 1.8 (P NS)	**Infusion or injection reaction:** **D1:** 3.1 **D2:** 6.6 **Headache:** **D1:** 8.6 **D2:** 6.0 **URTI:** **D1:** 14.8 **D2:** 12.6 **UTI:** NR	**Overall Attrition Rate (%):** 7.6 **ITT Analysis:** Yes **Quality Rating:** Fair.

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life

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, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study **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**:	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study (continued)				**ACR20,%** **D1:** 59 **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)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Landewe et al., 2002 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)	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Landewe et al., 2002 COBRA study (continued)				**Sharp mean change:** **D1:** 2 **D2:** 6 (*P* < 0.004) **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**		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study	Inclusion and	Characteristics	Baseline Disease	Health Outcomes	Adverse	Analysis and

Characteristics	Exclusion Criteria	and Interventions	and Treatment Characteristics		Events, %	Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study				**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		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 **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)	**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)	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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)	• Pre-existing pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			**ACR70, %:** **D1:** 4 **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)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 **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	**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	**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 ($P < 0.01$)	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)	• Presence of relevant comorbidity, including active infections		**Baseline DAS, mean:** **D1:** 5.0 **D2:** 5.1 **D3:** 5.2	**Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical advantage to use of ETA in combination with SSZ		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., 2003 **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:** **D1:** 2.2 (sd 1) **D2:** 2.2 (sd 1) **D3:** 2.2 (sd 1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., [1] 2003 (continued)			**Baseline DAS, mean:** **D1:** 4.23 **D2:** 4.13 **D3: 4.24** **RF positive, %:** **D1:** 75 **D2:** 62 **D3:** 71 **RAI:** **D1:** 17.6 **D2:** 16.5 **D3:** 18.9	**Median radiologic score** D2: 7.5 D3: 8.5: (*P* = 0.7)**D3:** 2.2 (sd 1.1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9) **Median radiologic score** D2: 7.5 D3: 8.5 (*P* = 0.7) Similar results with 3 groups (**D3** vs. **D2** vs. **D1**) instead of 2 groups (**D3** vs. **D2** or **D1**) when compared, but data not shown **Attrition rate**: 21%		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 **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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)			**Baseline DAS, mean:** NR **NSAIDS, %:** **D1:** 80 **D2:** 84.7 **D3:** 37.3 **D4:** 42.5 **Larsen score:** **D1:** 1.25 **D2:** 1.29 **D3:** 1.27 **D4:** 1.31	**HAQ improvement:** difference between groups in change from baseline HAQ, NS **Radiograph change, Larsen Scores:** No further increase in joint damage in pts txted with LEF and small improvement in MTX pts; small net result, but statistically significant difference with MTX better than LEF (overall scores and significance NR)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 BeST Study **Country, Setting:** The Netherlands, 18 peripheral and 2 university hospitals **Funding:** Schering-Plough BV and Centocor Inc Dutch College of Health Insurances **Research Objective:** To compare clinical and radiographic outcomes of 4 different txt strategies in pts with early RA **Study Design:** RCT **Overall N:** 508 **Study Duration:** 12 mos	**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 with PRE **D4:** initial combination with INF **D5:** NR Overall: Totals **N:** **D1:** 126 **D2:** 121 **D3:** 133 **D4:** 128 Overall: 508 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 55 **D4:** 54 Overall: 54 **Sex, % female:** **D1:** 86 **D2:** 86 **D3:** 86 **D4:** 85 Overall: 86 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 23 wks **D2:** 26 wks **D3:** 23 wks **D4:** 23 wks **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.5 +/- 0.9 **D2:** 4.5 +/- 0.8 **D3:** 4.4 +/- 0.9 **D4:** 4.3 +/- 0.9	**At 12 months** **Mean D-HAQ scores:** **D1:** 0.7 +/- 0.7 **D2:** 0.7 +/- 0.6 **D3:** 0.5 +/- 0.5 **D4:** 0.5 +/- 0.5 (**D1** vs. **D3**; *P* < 0.05) (**D3** vs. **D4**; *P* = NS) All others NR **Median total SHS increases (0 to 448 scale) from baseline:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (**D1** vs. **D3**; *P* = 0.003) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.007) (**D2** vs. **D4**; *P* < 0.001) **Progression of total SHS, %:** **D1:** 67 **D2:** 73 **D3:** 87 **D4:** 93 (**D1** vs. **D3** and **D4**; *P* = 0.001) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.010) (**D2** vs. **D4**; *P* < 0.001)	**Overall:** **D1:** 43 **D2:** 47 **D3:** 37 **D4:** 39 **SAEs:** **D1:** 6.3 **D2:** 7.4 **D3:** 12.8 **D4:** 4.7 **Infections:** **D1:** 4 **D2:** 7 **D3:** 8 **D4:** 8 **Serious Infections:** **D1:** 2.4 (pneumonia, HSV encephalitis, and fever) **D2:** 0.8 (diffuse peritonitis) **D3:** 0.8 (oral HSV) **D4:** 2.3 (pneumonia, pneumonitis, and septic arthritis) **Infusion or injection reaction:** **D4:** (10/128) = 7.8%	**Overall Attrition Rate, %:** 3.3% (17/508) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 (continued)	• concomittant txt with an experimental drug • bone marrow hypoplasia • diabetes • alcohol or drug abuse • wish to conceive • inadequate contraception		**D-HAQ (0 to 3 scale):** **D1:** 1.4 +/-0.7 **D2:** 1.4 +/-0.6 **D3:** 1.4 +/-0.7 **D4:** 1.4 +/-0.7	**Sharp van der Heijde median increase:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (*P* < 0.001) **Sustain DAS44 ≤ 2.4, %:** **D1:** 53 **D2:** 64 **D3:** 71 **D4:** 74 (**D1** vs. **D3**; *P* = 0.004) (**D1** vs. **D4**; *P* < 0.001) (*P* = NS and NR for others) **Patients who progressed to erosive from nonerosive disease at baseline, %** **D1:** 29 (9/31) **D2:** 53 (18/34) **D3:** 38 (14/37) **D4:** 15 (5/34) D1 vs D2, *P* = 0.050 D2 vs D4, *P* = 0.028 D3 vs D4, *P* =NS, NR	**Cardiovascular Events:** **D1:** 2 (hypertension, TIA, PE) **D2:** 2 (peripheral bypass, pacemaker implantation) **D3:** 6 (3 MIs, heart failure **D4:** 2 (TIA, PE, peripheral vascular disease) **Malignancies:** **D2:** N:1 bladder **D3:** N:2 breast, lymphoma **Adherence** 24 (5%) non-adherent	

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 **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	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)	**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 **D2:** 20.0 **D3:** 27.8	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)			**HAQ:** **D1:** 0.97 **D2:** 0.92 **D3:** 1.20	**HAQ change from 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		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; van der Heijde, 2006 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 **Overall N:** 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	**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 investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos	**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:** **D1:** 5.5 **D2:** 5.7 **D3:** 5.5	**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 norms (< 0.5) than monotherapy	**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) **D3:** 24 (29)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)	• Previous txt with MTX if pt experienced clinically toxic side effects or had no response		**Sharp:** **D1:** 26.8 **D2:** 21.8 **D3:** 21.8 **JSN:** **D1:** 13.3 **D2:** 11.5 **D3:** 10.3	**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** **D2:** 0.74 **D3**: 0.20; *P* = NS, NR		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Korpela, 2004; Puolakka, 2004 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	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Korpela, 2004; Puolakka, 2004 FIN-RACo Study (continued)				**Larsen Erosion Score:** **D1:** 11 **D2:** 24 (*P* = 0.001) **Median increase in Larsen 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)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Smolen, 2006 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)	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Smolen, 2006 ASPIRE Trial (continued)	within past 5 yrs (excluding excised skin cancers)		**HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5	**ACR-N, %:** **D1:** 26.4 **D2:** 38.9 **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		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Smolen, 2006 ASPIRE Trial (continued)				**Modified Sharp/van der Heijde Score change:** **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		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Larsen 2001; Scott 2001 **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of novel DMARD leflunomide was compared to placebo and sulfasalazine **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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Cohen 2001; Strand, Tagwell 1999 **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) **Discontinuation rate, %:** **D1**: 22 **D2**: 10.4 (*P* = NR)	**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 **Adherence:** Non-adherence as the reason for reason for withdrawal **D1**: 1 **D2**: 1	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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; Cohen 2001; Strand, Tagwell 1999 (continued)				**At 2 yrs** **ACR 20, %** **D1:** 79 **D2:** 67 (*P* = 0.049) **ACR 50, %** **D1:** 34 **D2:** 28 **ACR70, %** **D1:** 17 **D2:** 12 **Sharp score change** **D1:** 1.6 (n= 71) **D2:** 1.2 (n= 66) **HAQ DI change** **D1:** -0.6 (n= 97) **D2:** 0.37 (n=101) **Discontinuation rate, %:** **D1**: 27 **D2**: 17	**At 24 months** **SAEs, %:** **D1:** 18.9 **D2:** 18.9	

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 **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 • Glucocorticoids, DMARDs • Contraindication for glucocorticoid therapy • Previous fragility fractures, pts < 65 years with T score < -2.5 on bone mineral densitometry	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)	• 65 or older with Z score ≤ 1			**Radiographic progression beyond smallest detectable difference, %** **D1:** 25.9 **D2:** 39.3 (*P* = 0.033) **Joint space narrowing score, median change** **D1:** 1 **D2:** 2 (*P* = 0.08)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 **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:** ETA (50 mg/wk) **D3:** ETA (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	**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	**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

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)		**Sex (% female** **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	**DMARD use, %:** **D1:** 25 **D2:** 75 **D3:** 96 **D4:** 85 **D5:** 96 **D6:** 75 **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	**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)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

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 (continued)			**RF factor positive:** **D1:** 72 **D2:** 65 **D3:** 69 **D4:** 68 **D5:** 69 **D6:** 75 **D7:** 73 **D8:** 71 **D9:** 71			

Evidence Table 6. KQ 2. Rheumatoid arthritis systematic reviews: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Osiri et al., 2002 Multinational Cochrane Collaboration **Study Design:** Systematic review of RCTs and CCTs **Aims of Review:** To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA Meta-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 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 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni et al., 2005 and Kavanaugh et al., 2006 IMPACT Study **Country, Setting:** Multinational 9 clinical sites **Funding:** NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network **Research Objective:** Efficacy and tolerability of INF for the articular and dermatologic manifestations of active PsA **Study Design:** RCT **Overall N:** 104 **Study Duration:** 50 wks (1-16 wks RCT 16-50 open, all treated with INF)	**Inclusion Criteria:** • Age ≥ 18 • Failure of 1 or more DMARD • Active peripheral polyarticular arthritis • MTX ≥ 15 mg/wk w/ folic acid supplementation • LEF, SSZ, HCQ, intramuscular gold, penicillamine, or azathioprine stable for 4 wks • oral corticosteroids (dosage of 10 mg PRE equivalent/d or less) • NSAIDs stable for at least 2 wks **Exclusion Criteria:** • Monoclonal antibody or fusion protein • History of TB: positive tests for RF or latent TB investigational drug within 3 mos	**Interventions:** **D1:** Placebo **D2:** INF (5mg/kg at wks 0,2,6,14, then every 8 wks) **N:** **D1:** 52 **D2:** 52 **Mean age, yrs:** **D1:** 45.2 **D2:** 45.7 **Sex, % female:** **D1:** 42.3 **D2:** 42.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 11.7 **TJC, mean:** **D1:** 20.4 **D2:** 23.7 **SJC, mean:** **D1:** 14.7 **D2:** 14.6 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.4 **D2:** 5.5	• ACR50 Placebo 0/52 (0.0%) vs. INF 24/52 (46.2%) • ACR70 Placebo 0/52 (0.0%) vs. INF 15/52 (28.8%) • # of tender joints Placebo -23.6 vs. INF 55.2 • # of swollen joints Placebo -1.8 vs. INF 59.9 • DAS Placebo 2.8 vs. INF 45.5 $P < 0.001$ • HAQ Placebo -1.6 vs. INF 49.8 $P < 0.001$ • PsARC Placebo -12% vs. INF +86% $P < 0.001$ • ACR20 wk 16 Placebo 5/52 (9.6%) vs. INF 34/52 (65.4%) $P < 0.001$ • At 50 wks • Total modified vdH-S score, 85% and 84% in Placebo/INF and INF/INF groups had no worsening. • Change in erosion scores INF/INF 0.921, placebo/INF 0.536 ($P = 0.780$) • Change in JSN INF/INF -0.51, placebo/INF -0.47 ($P = 0.211$) • 16 wks-PsARC INF 75% vs. Placebo 21% ($P < 0.001$) • PASI75 INF 68% vs, placebo 0% ($P < 0.001$)	**Overall:** **D1:** 65 **D2:** 73 **D3:** 84 **Headache:** **D1:** 3 **D2:** 4 **URTI:** **D1:** 5 **D2:** 1	**Overall Attrition Rate (%):** 5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni, 2005 And Kavanaugh et al., 2006 **Country, Setting:** Multinational 36 sites in clinics IMPACT2 Study **Funding:** Centocor Inc and Schering-Plough **Research Objective:** Efficacy, health related quality of life and physical function in pts with PsA **Study Design:** RCT **Overall N:** 200 **Study Duration:** 14 to 24 wks (pts with inadequate response entered early escape at wk 16)	**Inclusion Criteria:** • Diagnosed with PsA • Diagnosed at least 6 mos before first infusion of study drug • Inadequate response to current or previous DMARDs or NSAIDs • Pts had to have active plaque psoriasis with at least 1 qualifying target lesion at least 2 cm in diameter • Negative test for RF in their serum • Stable doses of MTX, oral corticosteroids, NSAIDs **Exclusion Criteria:** • TNF α inhibitors; active or latent TB • Chronic or clinically significant infection, malignancy, or CHF	**Interventions:** **D1:** Placebo **D2:** INF (5 mg/kg at wks 0, 2, 6, 14, 22) **N:** **D1:** 100 **D2:** 100 **Mean age, yrs:** **D1:** 46.5 **D2:** 47.1 **Sex, % female:** **D1:** 49 **D2:** 29 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.5 **D2:** 8.4 **TJC, mean:** **D1:** 25.1 **D2:** 24.6 **SJC, mean:** **D1:** 14.4 **D2:** 13.9 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 10 **D2:** 15 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 45 **D2:** 47 **PASI:** **D1:** 10.2 **D2:** 11.4	• Placebo vs. INF (%): • ACR 50 at wk 14 3 vs. 36 (*P* < 0.001) and wk 24 4 vs. 41 (*P* < 0.001) • ACR70 at wk 14 1 vs. 15 (*P* < 0.001) and wk 24 2 vs. 27 (*P* < 0.001) • PsARC at wk 14 27 vs. 77 (*P* < 0.001) and wk 24 32 vs. 70 (*P* < 0.001) • •HAQ improvement at wk 14 - 18.4 vs. 48.6 (*P* < 0.001) and wk 24 -19.4 vs. 46 (*P* < 0.001) • •SF-36 (change from baseline) • Physical wk 14 1.1 vs. 9.1 (*P* < 0.001) and wk 24 1.3 vs. 7.7 (*P* < 0.001) • Mental wk 14-1.2 vs. 3.8 (*P* = 0.001) and wk 24 0.4 vs. 3.9 (*P* = 0.047) • ACR20 at Wk 14 11 vs. 58 (*P* < 0.001) and Wk 24 16 vs. 54 (*P* < 0.001) • PASI 50: wk 14: 9 vs. 82 (*P* <0.01), wk 24: 8 vs. 75 (*P* <75 (*P*<0.01); PASI 75 wk 14: 2 vs. 64 (*P* < 0.01), wk 24: 1 vs. 50 (*P* < 0.01); • improvement wk 14: 0 vs. 41 (*P* < 0.01), wk 24: 0 vs. 39 (*P* < 0.01) • median productivity at 14 wks 9.2% vs. 67.5% (*P* < 0.0001) • missed workdays at 14 wks 13% vs. 3.7% (*P* = 0.138)	**Overall:** **D1:** 67 **D2:** 67 **SAEs:** **D1:** 6 **D2:** 9 **Infusion or injection reaction:** **D1:** 6 **D2:** 7 **Dizziness:** **D1:** 5 **D2:** 4 **Headache:** **D1:** 5 **D2:** 6 **URTI:** **D1:** 14 **D2:** 10	**Overall:** **Attrition Rate (%):** Wk 14: NR Wk 24: 7.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Kaltwasser et al., 2004 and Nash et al., 2006 **Country, Setting:** Multinational Multi-center (31) **Funding:** Aventis **Research Objective:** Efficacy and safety of LEF versus placebo in pts with PsA and psoriasis **Study Design:** RCT **Overall: N:** 190 (ITT = 186) **Study Duration:** 24 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA • NSAIDs or Css (prednisone dose of 10 mg/day or steroid equivalent administered orally) • Discontinue DMARDs, biologics and systemic antipsoriatic txt 28 days **Exclusion Criteria:** • Pregnant or lactating; leflunomide • Impaired renal or hepatic system • Nonpsoriatic inflammatory joint disease or arthritis onset < 16 yrs • RH factor +, rheumatoid nodules, serious infections, malignancy, or CVD, HIV, hepatitis B or C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg • Impaired bone marrow function; history of drug or alcohol abuse	**Interventions:** **D1:** Placebo **D2:** LEF **N:** **D1:** 91 **D2:** 95 **Mean age, yrs:** Drug 1: 46.9 Drug 2: 48.6 Overall **Sex, % female:** **D1:** 37.4 **D2:** 42.1 **Race, % white:** **D1:** 95.6 **D2:** 97.9	**Mean disease duration, yrs:** **D1:** 10 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 49.5 **D2:** 61.1 **Corticosteroid use, %:** **D1:** 9.9 **D2:** 15.8 **DMARD naive, %:** **D1:** e 50.5 **D2:** 38.9 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• 56 of 95 leflunomide-treated pts (58.9%; 95% CI, 48.4-68.9) and 27 of 91 placebo-treated pts (29.7% [95% CI, 20.6-40.2]) were classified as responders by PsARC ($P < 0.0001$) Change in HAQ total score • Placebo (N:90) -0.05 ± 0.46 ($P = 0.0267$) • Leflunomide (N:94) -0.19 ± 0.51 Change in PASI score • Placebo (N:90) -0.6 ± 6.1 $P = 0.0030$ • Leflunomide (N:92) -2.1 ± 5.9 Change in DLQI total score • Placebo (N:89) -0.2 ± 5.1 $P = 0.0173$ • Leflunomide (N:90) -1.9 ± 5.1	**Overall:** **D1:** 76.1 **D2:** 85.4 **SAEs:** **D1:** 5.4 **D2:** 13.5 **Serious Infections:** **D1:** 0 **D2:** 0 **Diarrhea:** **D1:** 13.0 **D2:** 24.0 **Headache:** **D1:** 7.6 **D2:** 11.5 **Nausea:** **D1:** 8.7 **D2:** 9.4	**Overall Attrition Rate, %:** 47.9% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2000 **Country, Setting:** US Single center in Seattle **Funding:** Immunex Corp. **Research Objective:** To study the efficacy and safety of etanercept in pts with psoriatic arthritis and psoriasis **Study Design:** RCT **Overall N:** 60 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA according to: > 3 swollen, tender, or painful joints • Inadequate response to NSAIDs • Hepatic transasminase concentrations no greater than 2x upper limit of normal • Hemoglobin 85 g/L or higher • Platelet count 125,000 per mL or more and serum creatinine 152-4 mmol/L or below • MTX < 25 mg/wk and stable for 4 wks • Corticosteriods if the dose < 10 mg/d of PRE, stable for at least 2 wks and maintained at a constant dose throughout study **Exclusion Criteria:** • Evidence of skin conditions other than psoriasis	**Interventions:** **D1:** Placebo **D2:** ETA (25mg 2x wkly) **N:** **D1:** 30 **D2:** 30 **Mean age, yrs:** **D1:** 43.5 **D2:** 46 **Sex, % female:** **D1:** 40 **D2:** 47 **Race, % white:** **D1:** 83 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 40 **D2:** 20 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX:** **D1:** 47 **D2:** 47	• PsARC ETA 26 (87%) vs. Placebo 7 (23%) *P* < 0.0001 95% CI, 44-83; ACR50 ETA 15 (50%) vs. Placebo 1 (3%) *P* = 0.0001 95% CI, 28-66; • ACR70 ETA 4 (13%) vs. Placebo 0 (0%) *P* = 0.0403 95% CI, 1-26; • HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) *P* < 0.001 • •ACR20 was achieved by 73% ETA treated pts compared with 13% placebo treated pts (*P* < 0.0001) • Median % improvements in tender and swollen joint counts at 12 wks ETA 75% and 72% respectively vs. placebo 5% worsening and 19% improvement; disability according to HAQ significantly more improved in ETA than placebo (83% vs. 3%, *P* < 0.0001) • 26% of ETA vs. 0 of placebo pts achieved 75% improvement in PASI at 12 wks (*P* = 0.0154); similar differences between ETA and placebo also seen at 25% and 50% improvements in PASI scores	**SAEs:** **D1:** 0 **D2:** 3.3 **Infusion or injection reaction:** **D1:** 20 **D2:** 3 **Headache:** **D1:** 13 **D2:** 10 **URTI:** **D1:** 57 **D2:** 57	**Overall Attrition Rate, %:** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2004; Mease et al., 2006 (2nd yr outcomes) **Country, Setting:** US, 17 sites **Funding:** Immunex **Research Objective:** Safety, efficacy, and effect on radiographic progression of ETA in pts with PsA **Study Design:** RCT **Overall N:** 205 **Study Duration:** 24 wks (with 48 wk open-label phase)	**Inclusion Criteria:** • Age 18 70 • Diagnosed with PsA ≥ 3 swollen and 3 tender joimts • Inadequate response to NSAID • At least one of PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis • Stable plaque psoriasis with a qualifying lesion • MTX therapy (stable 2 mo ≤ 25 mg/wk) • Css (stable 4 wks ≤ 10 mg/d of prednisone) **Exclusion Criteria:** • Oral retinoids, topical vitamin A or D analog preparations, and anthralin	**Interventions:** **D1:** placebo **D2:** ETA (25 mg 2x wkly) **N:** **D1:** 104 **D2:** 101 **Mean age, yrs:** **D1:** 47.3 **D2:** 47.6 **Sex, % female:** **D1:** 55 **D2:** 43 **Race, % white:** **D1:** 91 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 15 **D2:** 19 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 41 **D2:** 42 **Sharp:** **D1:** 18.3 **D2:** 25.89	• At 12 wks, 59% of ETA pts met ACR20 criteria compared with 15% placebo pts (P < 0.0001) • 23% of ETA pts eligible for psoriasis evaluation achieved at least 75% improvement in psoriasis area and severity index, compared with 3% of placebo pts (P = 0.001) • 12 mos; the mean annualized rate of change over one yr of txt in modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo (P = 0.0001) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group (P < 0.0001) • 72% & 70% of ETA achieved PsARC at 12 and 24 wks, respectively, compared with 31% and 23% of placebo pts	**SAEs:** **D1:** 3.9 **D2:** 4 **Infusion or injection reaction:** **D1:** 9 **D2:** 36 **Headache:** **D1:** 5 **D2:** 8 **URTI:** **D1:** 23 **D2:** 21 **UTI:** **D1:** 6 **D2:** 6	**Overall Attrition Rate, %:** 19.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2005 **Country, Setting:** Multinational, multi-clinic (50) ADEPT Study **Funding:** Abbott Laboratories **Research Objective:** Safety and efficacy of ADA compared with placebo in txt of active psoriatic arthritis **Study Design:** RCT **Overall N:** 313 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 18 • Moderate to severe PsA • Active psoriatic skin lesions or a documented history of psoriasis • Inadequate response or intolerance to NSAIDs • MTX ≥ 3 mos with stable dose 4 wks **Exclusion Criteria:** • CYP, tacrolimus, DMARDs, or oral retinoids (4 wks) • Topical txts for psoriasis within 2 wks, other than medicated shampoos or low-potency topical steroids • Anti-TNF • History of TB • Central nervous system demyelinating disease • Listeriosis, or severe infection within 30 ds or oral antibiotics within 14 ds	**Interventions:** **D1:** placebo **D2:** ADA (40mg every other wk) **N:** **D1:** 162 **D2:** 151 **Mean age, yrs:** **D1:** 49.2 **D2:** 48.6 **Sex, % female:** **D1:** 45.1 **D2:** 43.7 **Race, % white:** **D1:** 93.8 **D2:** 97.4	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9.8 **TJC, mean:** **D1:** 25.8 **D2:** 23.9 **SJC, mean:** **D1:** 14.3 **D2:** 14.3 **Mean number previous DMARDS:** **D1:** 1.5 **D2:** 1.5 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline PASI (mean):** **D1:** 8.3 **D2:** 7.4 **MTX use:** **D1:** 50 **D2:** 51 **Baseline HAQ:** **D1:** 1.0 **D2:** 1.0	• PsARC ADA 60% wk. vs.placebo 23% • ACR50 ADA, 39% vs. placebo, 6% ($P < 0.001$) • ACR70 ADA, 23% vs. placebo, 1% ($P < 0.001$) • The PASI75 ADA 59% vs. placebo 1% ($P < 0.001$) (N:69 per group). • HAQ DI change placebo -0.1 ± 0.4 vs. ADA -0.4 ± 0.5 ($P < 0.001$) • ACR20 ADA 57% vs. placebo 15% (between-group difference 42%, 95% CI, 31-52%; $P < 0.001$). • Mmean change in modified total Sharp was -0.2 for ADA versus placebo ($P < 0.001$) • Erosion scores (mean change ADA 0.0 vs. placebo 0.6) and JSN scores (mean change ADA -0.2 vs. placebo 0.4) ($P < 0.001$ for both) • SF-36: SF-36 PCS; change in baseline to wk 12 for placebo vs ADA; 1.4 vs 9.3 ($P < 0.001$) • Change in baseline to wk 24; 1.4 vs 9.3 ($P < 0.001$) • SF-36 MCS • Change in baseline to wk 12 ; 1.2 vs 1.6 (P NS) • Change in baseline to wk 12; 0.6 vs 1.8 (P NS)	**Infusion or injection reaction:** **D1:** 3.1 **D2:** 6.6 **Headache:** **D1:** 8.6 **D2:** 6.0 **URTI:** **D1:** 14.8 **D2:** 12.6 **UTI:** NR	**Overall Attrition Rate, %:** 7.6 **ITT Analysis:** Yes **Quality Rating:** Fair.

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence

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 **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 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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 (SIR = 1.2 lung cancer (SIR = 1.8), breast cancer (SIR = 0.4), NMSC (SIR = 3.6)	NA	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA: retrospective cohort **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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:** Observational **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Landewe et al., 2002 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)	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Landewe et al., 2002 COBRA study (continued)				**Sharp mean change:** **D1:** 2 **D2:** 6 (*P* < 0.004) **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**		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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 **D2**E7) • 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	: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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**Pts with Early RA (≤3 yrs):** NR **Baseline DAS mean:** **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			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 PREMIER study				**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		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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)	**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)	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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)	• Pre-existing pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			**ACR70, %:** **D1:** 4 **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)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	**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	**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 ($P < 0.01$)	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)	• Presence of relevant comorbidity, including active infections		**Baseline DAS, mean:** **D1:** 5.0 **D2:** 5.1 **D3:** 5.2	**Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical advantage to use of ETA in combination with SSZ		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Doran et al., 2002 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., 2003 **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:** **D1:** 2.2 (sd 1) **D2:** 2.2 (sd 1) **D3:** 2.2 (sd 1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., [1] 2003 (continued)			**Baseline DAS, mean:** **D1:** 4.23 **D2:** 4.13 **D3: 4.24** **RF positive, %:** **D1:** 75 **D2:** 62 **D3:** 71 **RAI:** **D1:** 17.6 **D2:** 16.5 **D3:** 18.9	**Median radiologic score** D2: 7.5 D3: 8.5: (*P* = 0.7)**D3:** 2.2 (sd 1.1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9) **Median radiologic score** D2: 7.5 D3: 8.5 (*P* = 0.7) Similar results with 3 groups (**D3** vs. **D2** vs. **D1**) instead of 2 groups (**D3** vs. **D2** or **D1**) when compared, but data not shown **Attrition rate**: 21%		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 **Country, Setting:** Multinational, multicenter (26 rheumatology centers) **Funding:** Roche **Research Objective:** To confirm role of B cells in RA by evaluating effect of RIT in pts with active RA according to ACR and EULAR criteria **Study Design:** RCT **Overall N:** 161 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 21 • Diagnosed according to 1987 ACR criteria • Failed previous MTX treatment • > MTX 10 mg/wk and active disease • RF-positive • NSAIDS at stable doses or Css at doses < 12.5 mg per d of PNL • All received 17-d txt with Css and a 10 mg dose of leucovorin **Exclusion Criteria:** • Autoimmune disorder other than RA (except Srjogen's) • Functional class IV • Active rheumatoid vasculitis • Systemic diseases associated with arthritis • CFS • Serious, uncontrolled diseases • Active infection	**Interventions, dose:** **D1:** MTX (≥10 mg/wk) **D2:** RIT (1000 mg on ds 1 and 15) **D3:** RIT (1000 mg on ds 1 and 15) + CYP (750 mg d 3,17) **D4:** RIT (1000 mg on ds 1 and 15) + MTX (≥10 mg/wk) **N:** **D1:** 40 **D2:** 40 **D3:** 41 **D4:** 40 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 53 **D4:** 54 **Sex, % female:** **D1:** 80 **D2:** 73 **D3:** 83 **D4:** 75 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 9 **D3:** 10 **D4:** 12 **TJC, mean:** **D1:** 32 **D2:** 34 **D3:** 33 **D4:** 32 **SJC, mean:** **D1:** 19 **D2:** 21 **D3:** 19 **D4:** 23 **DMARD use (#):** **D1:** 2.6+/- 1.3 **D2:** 2.5+/-1.6 **D3:** 2.6+/-1.4 **D4:** 2.5+/-1.4 **Corticosteroid use, %** NR **MTX naive, %:** 0 **Txt resistant, %:** 100 **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D2:** 65 **D4:** 73 (*P* = NR) **ACR50, %:** **D2:** 33 **D4:** 43 (*P* = NR) **ACR70, %:** **D2:** 15 **D4:** 23 (*P* = NR) **Rates of moderate or good EULAR responses, %:** **D2:** 85 **D4:** 83 (*P* = NR) **DAS:** **D2:** -2.2 **D4:** -2.6 **At 48 weeks** **ACR20, %:** **D2:** 33 **D4:** 65 (*P* = NR) **ACR50, %:** **D2:** 15 **D4:** 35 (*P* = NR) **ACR70, %:** **D2:** 10% **D4:** 15% (*P* = NR)	**Overall:** **D1:** 80 **D2:** 80 **D3:** 73 **D4:** 85 **SAEs:** **D1:** 8.0 **D2:** 5.0 **D3:** 4.9 **D4:** 8.0 **Infusion or injection reaction:** **D1:** 30 **D2:** 45 **D3:** 32 **D4:** 33 **Nausea:** **D1:** 3 **D2:** 5 **D3:** 10 **D4:** 0 **URTI:** **D1:** 15 **D2:** 10 **D3:** 5 **D4:** 10	**Overall Attrition Rate, %:** at 24 wks 6.2% at 48 wks 37.8% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 (continued)	• History of recurrent infection or recurrent bacterial infections with encapsulated organisms • Primary of secondary immunodeficiency • History of cancer		**Baseline DAS, mean:** **D1:** 6.9 **D2:** 6.8 **D3:** 6.9 **D4:** 6.8			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**Baseline DAS, mean:** NR **NSAIDS, %:** **D1:** 80 **D2:** 84.7 **D3:** 37.3 **D4:** 42.5 **Larsen score:** **D1:** 1.25 **D2:** 1.29 **D3:** 1.27 **D4:** 1.31	**HAQ improvement:** difference between groups in change from baseline HAQ, NS **Radiograph change, Larsen Scores:** No further increase in joint damage in pts txted with LEF and small improvement in MTX pts; small net result, but statistically significant difference with MTX better than LEF (overall scores and significance NR)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Feltelius, 2005 **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	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 2003; 1478 and 1081 and 2008 **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	**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)	**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**	**Overall Attrition Rate, %:** 21 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 2003 Abstracted with 1478 and 1081 and 2008 (continued)	• Abnormal liver function test result • Hepatitis B or C			• 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 v 0.21 events/100 PY)	**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	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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., 2003 **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	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	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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., 2003 (continued)		**DMARD use, %:** **D1:** previous DMARD use, mean 4.5 **D2:** 4.1 **D3:** 3.3 **Corticosteroid use, %:** **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%				

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 et al., 2002 **Country, Setting:** US, NR **Funding:** Immunex **Research Objective:** To compare the clinical and radiographic outcomes in pts with RAwho received monotherapy with either ETA or MTX (MTX) for 2 yrs and to assess the safety of this therapy. After 2 yrs all pts received 25 mg of ETA for 3 additional yrs **Study Design:** Open-label extension of RCT **Overall N:** 632 (512) **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age ≥ 18; duration of condition: no more than 3 yrs • At least 3 bone erosions of hands, wrists, feet • At least 10 swolllen joints • At least 12 tender or painful joints • ESR 28 or higher • CRP more than 2 • Morning stiffness at least 45 minutes **Exclusion Criteria:** • Prior txt with: MTX	**Interventions, dose:** **D1:** MTX (ext) **D2:** ETA 10mg (ext) **D3: ETA 25mg (ext)** **N:** **D1:** 217(169) **D2:** 208(166) **D3:** 207(177) **Mean age, yrs:** **D1:** 49(49) **D2:** 50(50) **D3:** 51(50) **Sex, % female:** **D1:** 75(75) **D2:** 75(75) **D3:** 74(74) **Race, % white:** **D1:** 88(88) **D2:** 84(86) **D3:** 86(86)	**Mean disease duration, yrs:** **D1:** 12 mos (12) **D2:** 11 mos (11) **D3:** 12 mos (12) **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 41 (46) **D2:** 42 (37) **D3:** 39 (36) **MTX naive, %:** NR **Txt resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Erosion (mean):** **D1:** 7.5 (6.9) **D2:** 6.1 (5.7) **D3:** 6.4 (5.7) **Sharp (mean):** **D1:** 12.9 (11.3) **D2:** 11.2 (9.7) **D3:** 12.4 (10.8)	• Radiographic mean outcome changes at 2 yrs- • Mean changes in total Sharp score ETA25 1.3 vs. MTX 3.2 *P* = 0.001 • Erosion score ETA25 0.66 units vs. MTX 1.86 units *P* = 0.001 • No increase in total Sharp score ETA25 63% vrsus MTX 51% (*P* = 0.017) • No increase in erosions ETA25 70% vs. MTX 58% (*P* = 0.012) • Incidence of adverse events remained constant over time	**SAEs:** **D1:** (16.1) **D2:** (21.2) **D3:** (20.6) **Serious Infections:** **D1:** 4.1 (4.9) **D2:** 2.4 (6.3) **D3:** 3.4 (8.7) **Infusion or injection reaction:** **D1:** 9 **D2:** 32 **D3:** 39 **Abdominal Pain:** **D1:** 15 **D2:** 13 **D3:** 13 **Dizziness:** **D1:** 12 **D2:** 7 **D3:** 15 **Headache:** **D1:** 28 **D2:** 27 **D3:** 25 **Malignancies:** **D1:** (per p-y 0.003) **D2:** (per p-y 0.008) **D3:** (per p-y 0.014) **Nausea:** **D1:** 31 **D2:** 14 **D3:** 20	**Overall Attrition Rate, %:** 34.5% at two yrs and 54.7% at 5 yrs **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 et al., 2002 (continued)			**JSN (mean):** **D1:** 5.4 (4.4) **D2:** 5.0 (4.0) **D3:** 6.0 (5.1)			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence

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 **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	**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	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)	• Received any intraarticular or systemic corticosteroid injections within past 4 wks • Recent history of significant infection or other important concurrent illness		**MTX use, %:** Overall: 100 **HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.6			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 BeST Study **Country, Setting:** The Netherlands, 18 peripheral and 2 university hospitals **Funding:** Schering-Plough BV and Centocor Inc Dutch College of Health Insurances **Research Objective:** To compare clinical and radiographic outcomes of 4 different txt strategies in pts with early RA **Study Design:** RCT **Overall N:** 508 **Study Duration:** 12 mos	**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 with PRE **D4:** initial combination with INF **D5:** NR Overall: Totals **N:** **D1:** 126 **D2:** 121 **D3:** 133 **D4:** 128 Overall: 508 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 55 **D4:** 54 Overall: 54 **Sex, % female:** **D1:** 86 **D2:** 86 **D3:** 86 **D4:** 85 Overall: 86 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 23 wks **D2:** 26 wks **D3:** 23 wks **D4:** 23 wks **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.5 +/- 0.9 **D2:** 4.5 +/- 0.8 **D3:** 4.4 +/- 0.9 **D4:** 4.3 +/- 0.9	**At 12 months** **Mean D-HAQ scores:** **D1:** 0.7 +/- 0.7 **D2:** 0.7 +/- 0.6 **D3:** 0.5 +/- 0.5 **D4:** 0.5 +/- 0.5 (**D1** vs. **D3**; *P* < 0.05) (**D3** vs. **D4**; *P* = NS) All others NR **Median total SHS increases (0 to 448 scale) from baseline:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (**D1** vs. **D3**; *P* = 0.003) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.007) (**D2** vs. **D4**; *P* < 0.001) **Progression of total SHS, %:** **D1:** 67 **D2:** 73 **D3:** 87 **D4:** 93 (**D1** vs. **D3** and **D4**; *P* = 0.001) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.010) (**D2** vs. **D4**; *P* < 0.001)	**Overall:** **D1:** 43 **D2:** 47 **D3:** 37 **D4:** 39 **SAEs:** **D1:** 6.3 **D2:** 7.4 **D3:** 12.8 **D4:** 4.7 **Infections:** **D1:** 4 **D2:** 7 **D3:** 8 **D4:** 8 **Serious Infections:** **D1:** 2.4 (pneumonia, HSV encephalitis, and fever) **D2:** 0.8 (diffuse peritonitis) **D3:** 0.8 (oral HSV) **D4:** 2.3 (pneumonia, pneumonitis, and septic arthritis) **Infusion or injection reaction:** **D4:** (10/128) = 7.8%	**Overall Attrition Rate, %:** 3.3% (17/508) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 (continued)	• concomittant txt with an experimental drug • bone marrow hypoplasia • diabetes • alcohol or drug abuse • wish to conceive • inadequate contraception		**D-HAQ (0 to 3 scale):** **D1:** 1.4 +/-0.7 **D2:** 1.4 +/-0.6 **D3:** 1.4 +/-0.7 **D4:** 1.4 +/-0.7	**Sharp van der Heijde median increase:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (*P* < 0.001) **Sustain DAS44 ≤ 2.4, %:** **D1:** 53 **D2:** 64 **D3:** 71 **D4:** 74 (**D1** vs. **D3**; *P* = 0.004) (**D1** vs. **D4**; *P* < 0.001) (*P* = NS and NR for others) **Patients who progressed to erosive from nonerosive disease at baseline, %** **D1:** 29 (9/31) **D2:** 53 (18/34) **D3:** 38 (14/37) **D4:** 15 (5/34) D1 vs D2, *P* = 0.050 D2 vs D4, *P* = 0.028 D3 vs D4, *P* =NS, NR	**Cardiovascular Events:** **D1:** 2 (hypertension, TIA, PE) **D2:** 2 (peripheral bypass, pacemaker implantation) **D3:** 6 (3 MIs, heart failure **D4:** 2 (TIA, PE, peripheral vascular disease) **Malignancies:** **D2:** N:1 bladder **D3:** N:2 breast, lymphoma **Adherence** 24 (5%) non-adherent	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	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)	**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 **D2:** 20.0 **D3:** 27.8	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**HAQ:** **D1:** 0.97 **D2:** 0.92 **D3:** 1.20	**HAQ change from 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		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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., 2006 **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 **Race, % white:** NR	**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	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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., 2006 (continued) **Overall N:** 2711 **Study Duration:** 6 mos			**Baseline DAS, mean:** **D1:** 6.8 **D2:** 6.6 **D3:** 6.6 **D4:** 6.8 **D5:** 6.8 **D6:** 6.7			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 with van der Heijde, 2006 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 **Overall N:** 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	**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 investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos	**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:** **D1:** 5.5 **D2:** 5.7 **D3:** 5.5	**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 norms (< 0.5) than monotherapy	**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) **D3:** 24 (29)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)	• Previous txt with MTX if pt experienced clinically toxic side effects or had no response		**Sharp:** **D1:** 26.8 **D2:** 21.8 **D3:** 21.8 **JSN:** **D1:** 13.3 **D2:** 11.5 **D3:** 10.3	**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** **D2:** 0.74 **D3**: 0.20; *P* = NS, NR		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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 assessment median:** **D1:** 69 **D2:** 48	• 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 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)	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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 **Study Duration:** 1-52 wks	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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:** 24 wks	**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, elevated SrCR • Psoriatic Arthritis or other acute inflammatory joint disease not RA	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** N/A **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)				**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)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kwon, 2003 **Country, Setting:** USA, Multicenter (FDA's MedWatch program) **Funding:** US Food and Drug Administration **Research Objective:** To describe adverse event reports of heart failure after TNF antagonist therapy **Study Design:** Database analysis; AERS **Overall N:** 47 cases **Study Duration:** long-term therapy	**Inclusion Criteria:** • Pts who reported heart failure as an adverse event while taking ETA or INF therapy in US since licensure of drugs until February 2002 • New onset failure and exacerbation of preexisting heart failure included **Exclusion Criteria:** • Heart failure reports temporally associated with other heart failure-inciting events (such as myocardial infarction) were excluded	**Interventions, dose:** **D1:** New Onset Heart Failure without risk factors **D2:** New Onset Heart Failure with risk factors **D3:** Heart failure exacerbation ETA: any INF: any **N:** NR **Mean age, yrs:** **D1:** 59 **D2:** 67 **D3: 70** **Sex, % female:** **D1:** 74 **D2:** 42 **D3: 44** **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 8 **D2:** 10 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **%ETA:** **D1:** 12 **D2:** 14 **D3:** 3 **%INF:** **D1:** 7 **D2:** 5 **D3:** 6	• 38 pts (81%) developed new-onset heart failure • 9 (19%) experienced heart failure exacerbation of which: 19 pts had no documented risk factors, 10 pts were under age 50 • Of pts under 50, after cessation of TNF antagonist therapy 3 pts experienced complete resolution of heart failure, 6 pts showed improvement, and 1 patient died	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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 **D3:** 10.8	• 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%	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 **UTI:** **NR**	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** **Fair**

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)		**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	• Swollen joint count 44% vs. 52% • Global health by 33% vs. 26%			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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:

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	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 3**D4:** 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**Baseline DAS, mean:** **D1:** 6.1 **D2:** 6.0 **D3:** 6.1 **D4:** 5.4 **MTX use:** **D1:** 33 **D2:** 64.5 **D3:** 61.4 **D4:** 20.1			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Moreland et al., 2006 **Country, Setting:** Multinational, pooled retrospective analysis **Funding:** NR **Research Objective:** To evaluate safety and efficacy of long-term etanercept treatment in pts with DMARD refractory RA **Study Design:** RCT **Overall N:** 714 safety and 581 efficacy **Study Duration:** Up to 7 yrs	**Inclusion Criteria:** • Adult pts with DMARD-refractory RA involved in included Initial clinical trials and extension (7 trials, 3 of placebo-controlled, randomized, double-blind phase 2 or 3 trials; 2 were phase 1 randomized dose-finding trials, and 2 were open-label) **Exclusion Criteria:** NR	**Interventions:** **D1:** All pts **D2:** Patients in extension **N:** **D1:** 714 **D2:** 581 **Mean age yrs:** **D1:** 53 **D2:** 52 **Sex, % female:** **D1:** 79 **D2:** 80 **Race, % white:** **D1:** 90 **D2:** 90	**Mean disease duration, yrs:** **D1:** 12 **D2: 12** **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 65 **D2: 65** **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Overall rate of SAEs was 14.8/100 patient-yrs compared to initial trial rates 8 pts out of 152 reported SAE in placebo group (20.0 events/100 PY; 40 PY), and 17 pts out of 349 reported SAE in etanercept group (15.0 events/100 patient yrs; 117 PY). Incidence rates stayed the same over time • Serious adverse events overall rate = 14.8 events/100 PY • Serious infections overall rate = 4.2 events/100 PY); cancer (overall rate = 1.0 events/100 PY); deaths (overall rate = 0.7 events/100 PY) • Overall 13.7% withdrew because of AEs	See health outcomes	**Overall Attrition Rate, %:** 52% **ITT Analysis:** Not applicable **Quality Rating:** Fair for AEs

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Korpela, 2004; Puolakka, 2004 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	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Korpela, 2004; Puolakka, 2004 FIN-RACo Study (continued)				**Larsen Erosion Score:** **D1:** 11 **D2:** 24 (*P* = 0.001) **Median increase in Larsen 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)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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 C**D4** 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	**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	• 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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	• Concurrent or alternative rheumatic disorder • Bedridden status • Referral 2nd to a steroid complication		**Extra-articular disease** **D1:** 16.1% **D2:** 6.3%			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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:** Observational **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Larsen 2001; Scott 2001 **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of novel DMARD leflunomide was compared to placebo and sulfasalazine **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Smolen, 2006 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)	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Smolen, 2006 ASPIRE Trial (continued)	within past 5 yrs (excluding excised skin cancers)		**HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5	**ACR-N, %:** **D1:** 26.4 **D2:** 38.9 **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		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Smolen, 2006 ASPIRE Trial (continued)				**Modified Sharp/van der Heijde Score change:** **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		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Cohen 2001; Strand, Tagwell 1999 **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) **Discontinuation rate, %:** **D1**: 22 **D2**: 10.4 (*P* = NR)	**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 **Adherence:** Non-adherence as the reason for reason for withdrawal **D1**: 1 **D2**: 1	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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; Cohen 2001; Strand, Tagwell 1999 (continued)				**At 2 yrs** **ACR 20, %** **D1:** 79 **D2:** 67 (*P* = 0.049) **ACR 50, %** **D1:** 34 **D2:** 28 **ACR70, %** **D1:** 17 **D2:** 12 **Sharp score change** **D1:** 1.6 (n= 71) **D2:** 1.2 (n= 66) **HAQ DI change** **D1:** -0.6 (n= 97) **D2:** 0.37 (n=101) **Discontinuation rate, %:** **D1**: 27 **D2**: 17	**At 24 months** **SAEs, %:** **D1:** 18.9 **D2:** 18.9	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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:** Observational **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	**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)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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:** ETA (50 mg/wk) **D3:** ETA (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	**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	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)		**Sex (% female** **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	**DMARD use, %:** **D1:** 25 **D2:** 75 **D3:** 96 **D4:** 85 **D5:** 96 **D6:** 75 **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	**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)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**RF factor positive:** **D1:** 72 **D2:** 65 **D3:** 69 **D4:** 68 **D5:** 69 **D6:** 75 **D7:** 73 **D8:** 71 **D9:** 71			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **Country, Setting:** NR **Funding:** Abbott Labs **Research Objective:** To evaluate efficacy and safety of adalimumab plus MTX (MTX) given for up to 4 yrs in pts with active, longstanding rheumatoid arthritis **Study Design:** Uncontrolled open-label extension of ARMADA trial **Overall N:** 262 in extension **Study Duration:** up to 4 yrs (6 mos blinded)	**Inclusion Criteria:** • Age: ≥ 18 yrs • Diagnosed with RA according to ACR criteria • Previous use of DMARDs • MTX for at least 6 mos • 9 tender and 6 swollen joints **Exclusion Criteria:** NR	**Interventions, dose:** Adalimumab + MTX **N:** Overall: 262 **Mean age, yrs:** Overall: 55 **Sex, % female:** Overall: 76 **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	• Serious infections occurring during open label txt and blinded period were similar (2.03 vs. 2.30 events per 100 PY, respectively) • Rates of all other adverse events were similar between blinded and extension phases	**Serious Infections:** **D1:** 2.03/ 100 pts **CHF**: **D1:** 0.11/ 100 pts **Malignancies:** **D1:** 19 cancers: • 5 non-melanoma skin • 4 GI • 2 prostate	**Overall Attrition Rate, %:** • 38% • 162/262 used for analysis with a mean txt time of 3.4 yrs however 147 completed 4 yrs of txt **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 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	**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	**Overall Attrition Rate, %:** 17.1 **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**Median HAQ score:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5 **% RF positive:** **D1:** 80.7 **D2:** 82.8 **D3:** 76.8		**Malignancies:** **D1:** 1.7 **D2:** 4.2 **Nausea:** **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	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	• 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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**VAS QoL:** **D1:** 65.8 **D2:** 64.3 **D3:** 66.7 **D4:** 65.9 **Pain:** **D1:** 4.2 **D2:** 4.3 **D3:** 3.7 **D4:** 3.9			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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	**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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**MTX use:** **D1:** 67 **D2:** 76 **D3:** 44 **D4:** 47 **D5:** 56			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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, 2004 **Country, Setting:** Multinational, multicenter **Funding:** Centocor, Inc **Research Objective:** To determine baseline rate of TB in RA prior to introduction of INF and to determine rate of TB among those currently receiving INF **Study Design:** Prospective cohort study with historic control **Overall N:** 17,242 Study 1: 10,782 Study 2: 6,460 **Study Duration:** 3 yrs	**Inclusion Criteria:** • Diagnosed with RA according to ACR criteria • Use of INF **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** Study 1 **D2: Study 2** **INF:** varied **N:** **D1:** 10782 **D2:** 6640 **Mean age, yrs:** **D1:** 59.8 **D2:** 61.4 **Sex, % female:** **D1:** 76.9 **D2:** 73.5 **Race, % white:** **D1:** 90.9 **D2:** 94.4	**Mean disease duration, yrs:** **D1:** 13.2 **D2:** 14 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 54.6 **D2:** 50.4 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX:** **D1:** 47.9 **D2:** 74.6	• In pre-INF group, 1 case of TB developed during 16,173 PY of follow-up, yielding a rate of 6.2 cases (95% CI,1.6-34.4) per 100,000 patient yrs • In INF-group, TB incidence rate among pts was 61.9 cases per 100,000 patient yrs • None of TB pts had undergone a TB skin test and no cases of TB occurred in 44-59% that had received test	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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, %:** **D1**: 12.6% ETA+MTX 13.3 **D2**: 18.7 INF+MTX: 18.2 **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 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 (continued)			**Txt resistant, %:** NR **Pts. with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.1 **D2:** 6 **D3:** 6.1 **D4:** 5.4 **D5:** 5.5 **D6:** 5.6 **MTX use:** **D1:** 91.2 **D2:** 92.1 **D3:** 78.6 **D4:** 68.7 **D5:** 94.2 **D6:** 90.7			

Evidence Table 9. KQ3. Rheumatoid arthritis systematic reviews: harms, tolerability, adverse effects, or adherence

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, country, funding: Bongartz, 2006, multinational, Mayo foundation, Abbott & Centocor **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 9. KQ3. Rheumatoid arthritis systematic reviews: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, country, funding: Gartlehner et al., 2006 US **Study Design:** Metaanalysis (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 ETA: 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 ETA (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 9. KQ3. Rheumatoid arthritis systematic reviews: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, country, funding: Osiri et al., 2002 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 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 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 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Antoni et al., 2005; Kavanaugh et al., 2006 IMPACT Study **Country, Setting:** Multinational 9 clinical sites **Funding:** NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network **Research Objective:** Efficacy and tolerability of INF for the articular and dermatologic manifestations of active PsA **Study Design:** RCT **Overall N:** 104 **Study Duration:** 50 wks (1-16 wks RCT 16-50 open, all treated with INF)	**Inclusion Criteria:** • Age ≥ 18 • Failure of 1 or more DMARD • Active peripheral polyarticular arthritis • MTX ≥ 15 mg/wk w/ folic acid supplementation • LEF, SSZ, HCQ, intramuscular gold, penicillamine, or azathioprine stable for 4 wks • oral corticosteroids (dosage of 10 mg PRE equivalent/d or less) • NSAIDs stable for at least 2 wks **Exclusion Criteria:** • Monoclonal antibody or fusion protein • History of TB: positive tests for RF or latent TB • investigational drug within 3 mos	**Interventions:** **D1:** Placebo **D2:** INF (5mg/kg at wks 0,2,6,14, then every 8 wks) **N:** **D1:** 52 **D2:** 52 **Mean age, yrs:** **D1:** 45.2 **D2:** 45.7 **Sex, % female:** **D1:** 42.3 **D2:** 42.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 11.7 **TJC, mean:** **D1:** 20.4 **D2:** 23.7 **SJC, mean:** **D1:** 14.7 **D2:** 14.6 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.4 **D2:** 5.5	**ACR50** **D1**: 0/52 (0.0%) **D2**: 24/52 (46.2%) **ACR70** **D1**: 0/52 (0.0%) **D2**: 15/52 (28.8%) **Tender joints, number** **D1**: -23.6 **D2**: 55.2 **Swollen joints, number** **D1**: -1.8 **D2**: 59.9 **DAS** **D1**: 2.8 **D2**: 45.5 *P* < 0.001 **HAQ** **D1**: -1.6 **D2**: 49.8 *P* < 0.001 **PsARC, %** **D1**: -12 **D2**: +86 *P* < 0.001 **At week 16** **ACR20** **D1**: 5/52 (9.6%) **D2**: 34/52 (65.4%) *P* < 0.001	**Overall:** **D1:** 65 **D2:** 73 **D3:** 84 **Headache:** **D1:** 3 **D2:** 4 **URTI:** **D1:** 5 **D2:** 1	**Overall Attrition Rate (%):** 5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				PsARC, % **D1**: 21 **D2**: 75 *P* < 0.001 **PASI75, %** **D1**: 0 **D2**: 68 *P* < 0.001 **At 50 weeks** **Total modified vdH-S score sowing no worsening** **D1**: 85% (Placebo/INF) **D2**: 84% (INF/INF) **Change in erosion scores** **D1**: 0.536 (Placebo/INF) **D2**: 0.921 (INF/INF) (*P* = 0.780) **Change in JSN** **D1** :-0.47 **D2**: -0.51 (*P* = 0.211)		

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Antoni, 2005; Kavanaugh et al., 2006 **Country, Setting:** Multinational 36 sites in clinics IMPACT2 Study **Funding:** Centocor Inc and Schering-Plough **Research Objective:** Efficacy, health related quality of life and physical function in pts with PsA **Study Design:** RCT **Overall N:** 200 **Study Duration:** 14 to 24 wks (pts with inadequate response entered early escape at wk 16)	**Inclusion Criteria:** • Diagnosed with PsA • Diagnosed at least 6 mos before first infusion of study drug • Inadequate response to current or previous DMARDs or NSAIDs • Pts had to have active plaque psoriasis with at least 1 qualifying target lesion at least 2 cm in diameter • Negative test for RF in their serum • Stable doses of MTX, oral corticosteroids, NSAIDs **Exclusion Criteria:** • TNF α inhibitors; active or latent TB • Chronic or clinically significant infection, malignancy, or CHF	**Interventions:** **D1:** Placebo **D2:** INF (5 mg/kg at wks 0, 2, 6, 14, 22) **N:** **D1:** 100 **D2:** 100 **Mean age, yrs:** **D1:** 46.5 **D2:** 47.1 **Sex, % female:** **D1:** 49 **D2:** 29 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.5 **D2:** 8.4 **TJC, mean:** **D1:** 25.1 **D2:** 24.6 **SJC, mean:** **D1:** 14.4 **D2:** 13.9 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 10 **D2:** 15 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 45 **D2:** 47 **PASI:** **D1:** 10.2 **D2:** 11.4	• Placebo vs. INF (%): • ACR 50 at wk 14 3 vs. 36 (P < 0.001) and wk 24 4 vs. 41 (P < 0.001) • ACR70 at wk 14 1 vs. 15 (P < 0.001) and wk 24 2 vs. 27 (P < 0.001) • PsARC at wk 14 27 vs. 77 (P < 0.001) and wk 24 32 vs. 70 (P < 0.001) • •HAQ improvement at wk 14 - 18.4 vs. 48.6 (P < 0.001) and wk 24 -19.4 vs. 46 (P < 0.001) • •SF-36 (change from baseline) • Physical wk 14 1.1 vs. 9.1 (P < 0.001) and wk 24 1.3 vs. 7.7 (P < 0.001) • Mental wk 14-1.2 vs. 3.8 (P = 0.001) and wk 24 0.4 vs. 3.9 (P = 0.047) • ACR20 at Wk 14 11 vs. 58 (P < 0.001) and Wk 24 16 vs. 54 (P < 0.001) • PASI 50: wk 14: 9 vs. 82 (P <0.01), wk 24: 8 vs. 75 (P <75 (P<0.01); PASI 75 wk 14: 2 vs. 64 (P < 0.01), wk 24: 1 vs. 50 (P < 0.01); • improvement wk 14: 0 vs. 41 (P < 0.01), wk 24: 0 vs. 39 (P < 0.01) • median productivity at 14 wks 9.2% vs. 67.5% (P < 0.0001) • missed workdays at 14 wks 13% vs. 3.7% (P = 0.138)	**Overall:** **D1:** 67 **D2:** 67 **SAEs:** **D1:** 6 **D2:** 9 **Infusion or injection reaction:** **D1:** 6 **D2:** 7 **Dizziness:** **D1:** 5 **D2:** 4 **Headache:** **D1:** 5 **D2:** 6 **URTI:** **D1:** 14 **D2:** 10	**Overall:** **Attrition Rate (%):** Wk 14: NR Wk 24: 7.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kaltwasser et al., 2004 and Nash et al., 2006 **Country, Setting:** Multinational Multi-center (31) **Funding:** Aventis **Research Objective:** Efficacy and safety of LEF versus placebo in pts with PsA and psoriasis **Study Design:** RCT **Overall: N:** 190 (ITT = 186) **Study Duration:** 24 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA • NSAIDs or Css (prednisone dose of 10 mg/day or steroid equivalent administered orally) • Discontinue DMARDs, biologics and systemic antipsoriatic txt 28 days **Exclusion Criteria:** • Pregnant or lactating; leflunomide • Impaired renal or hepatic system • Nonpsoriatic inflammatory joint disease or arthritis onset < 16 yrs • RH factor +, rheumatoid nodules, serious infections, malignancy, or CVD, HIV, hepatitis B or C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg • Impaired bone marrow function; history of drug or alcohol abuse	**Interventions:** **D1:** Placebo **D2:** LEF **N:** **D1:** 91 **D2:** 95 **Mean age, yrs:** Drug 1: 46.9 Drug 2: 48.6 Overall **Sex, % female:** **D1:** 37.4 **D2:** 42.1 **Race, % white:** **D1:** 95.6 **D2:** 97.9	**Mean disease duration, yrs:** **D1:** 10 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 49.5 **D2:** 61.1 **Corticosteroid use, %:** **D1:** 9.9 **D2:** 15.8 **DMARD naive, %:** **D1:** e 50.5 **D2:** 38.9 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• 56 of 95 leflunomide-treated pts (58.9%; 95% CI, 48.4-68.9) and 27 of 91 placebo-treated pts (29.7% [95% CI, 20.6-40.2]) were classified as responders by PsARC (*P* < 0.0001) Change in HAQ total score • Placebo (N:90) -0.05 ± 0.46 (*P* = 0.0267) • Leflunomide (N:94) -0.19 ± 0.51 Change in PASI score • Placebo (N:90) -0.6 ± 6.1 *P* = 0.0030 • Leflunomide (N:92) -2.1 ± 5.9 Change in DLQI total score • Placebo (N:89) -0.2 ± 5.1 *P* = 0.0173 • Leflunomide (N:90) -1.9 ± 5.1	**Overall:** **D1:** 76.1 **D2:** 85.4 **SAEs:** **D1:** 5.4 **D2:** 13.5 **Serious Infections:** **D1:** 0 **D2:** 0 **Diarrhea:** **D1:** 13.0 **D2:** 24.0 **Headache:** **D1:** 7.6 **D2:** 11.5 **Nausea:** **D1:** 8.7 **D2:** 9.4	**Overall Attrition Rate (%):** 47.9% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mease et al., 2000 **Country, Setting:** US, single center in Seattle **Funding:** Immunex Corp. **Research Objective:** To study efficacy and safety of etanercept in pts with psoriatic arthritis and psoriasis **Study Design:** RCT **Overall N:** 60 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA according to: > 3 swollen, tender, or painful joints • Inadequate response to NSAIDs • Hepatic transasminase concentrations no greater than 2x upper limit of normal • Hemoglobin 85 g/L or higher • Platelet count 125,000 per mL or more and serum creatinine 152-4 mmol/L or below • MTX < 25 mg/wk and stable for 4 wks • Corticosteriods if the dose < 10 mg/d of PRE, stable for at least 2 wks and maintained at a constant dose throughout study **Exclusion Criteria:** • Evidence of skin conditions other than psoriasis	**Interventions:** **D1:** Placebo **D2:** ETA (25mg 2x wkly) **N:** **D1:** 30 **D2:** 30 **Mean age, yrs:** **D1:** 43.5 **D2:** 46 **Sex, % female:** **D1:** 40 **D2:** 47 **Race, % white:** **D1:** 83 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 40 **D2:** 20 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX:** **D1:** 47 **D2:** 47	• PsARC ETA 26 (87%) vs. Placebo 7 (23%) *P* < 0.0001 95% CI, 44-83; ACR50 ETA 15 (50%) vs. Placebo 1 (3%) *P* = 0.0001 95% CI, 28-66; • ACR70 ETA 4 (13%) vs. Placebo 0 (0%) *P* = 0.0403 95% CI, 1-26; • HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) *P* < 0.001 • •ACR20 was achieved by 73% ETA treated pts compared with 13% placebo treated pts (*P* < 0.0001) • Median % improvements in tender and swollen joint counts at 12 wks ETA 75% and 72% respectively vs. placebo 5% worsening and 19% improvement; disability according to HAQ significantly more improved in ETA than placebo (83% vs. 3%, *P* < 0.0001) • 26% of ETA vs. 0 of placebo pts achieved 75% improvement in PASI at 12 wks (*P* = 0.0154); similar differences between ETA and placebo also seen at 25% and 50% improvements in PASI scores	**SAEs:** **D1:** 0 **D2:** 3.3 **Infusion or injection reaction:** **D1:** 20 **D2:** 3 **Headache:** **D1:** 13 **D2:** 10 **URTI:** **D1:** 57 **D2:** 57	**Overall Attrition Rate (%):** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mease et al., 2004; Mease et al., 2006 **Country, Setting:** US 17 sites **Funding:** Immunex **Research Objective:** Safety, efficacy, and effect on radiographic progression of ETA in pts with PsA **Study Design:** RCT **Overall N:** 205 **Study Duration:** 24 wks (with 48 wk open-label phase)	**Inclusion Criteria:** • Age 18 70 • Diagnosed with PsA ≥ 3 swollen and 3 tender joimts • Inadequate response to NSAID • At least one of PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis • Stable plaque psoriasis with a qualifying lesion • MTX therapy (stable 2 mo ≤ 25 mg/wk) • Css (stable 4 wks ≤ 10 mg/d of prednisone) **Exclusion Criteria:** • Oral retinoids, topical vitamin A or D analog preparations, and anthralin	**Interventions:** **D1:** placebo **D2:** ETA (25 mg 2x wkly) **N:** **D1:** 104 **D2:** 101 **Mean age, yrs:** **D1:** 47.3 **D2:** 47.6 **Sex, % female:** **D1:** 55 **D2:** 43 **Race, % white:** **D1:** 91 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 15 **D2:** 19 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 41 **D2:** 42 **Sharp:** **D1:** 18.3 **D2:** 25.89	• At 12 wks, 59% of ETA pts met ACR20 criteria compared with 15% placebo pts (*P* < 0.0001) • 23% of ETA pts eligible for psoriasis evaluation achieved at least 75% improvement in psoriasis area and severity index, compared with 3% of placebo pts (*P* = 0.001) • 12 mos; the mean annualized rate of change over one yr of txt in modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo (*P* = 0.0001) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group (*P* < 0.0001) • 72% & 70% of ETA achieved PsARC at 12 and 24 wks, respectively, compared with 31% and 23% of placebo pts	**SAEs:** **D1:** 3.9 **D2:** 4 **Infusion or injection reaction:** **D1:** 9 **D2:** 36 **Headache:** **D1:** 5 **D2:** 8 **URTI:** **D1:** 23 **D2:** 21 **UTI:** **D1:** 6 **D2:** 6	**Overall Attrition Rate (%):** 19.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mease et al., 2005 **Country, Setting:** Multinational, multi-clinic (50) ADEPT Study **Funding:** Abbott Laboratories **Research Objective:** Safety and efficacy of ADA compared with placebo in txt of active psoriatic arthritis **Study Design:** RCT **Overall N:** 313 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 18 • Moderate to severe PsA • Active psoriatic skin lesions or a documented history of psoriasis • Inadequate response or intolerance to NSAIDs • MTX ≥ 3 mos with stable dose 4 wks **Exclusion Criteria:** • CYP, tacrolimus, DMARDs, or oral retinoids (4 wks) • Topical txts for psoriasis within 2 wks, other than medicated shampoos or low-potency topical steroids • Anti-TNF • History of TB • Central nervous system demyelinating disease • Listeriosis, or severe infection within 30 ds or oral antibiotics within 14 ds	**Interventions:** **D1:** placebo **D2:** ADA (40mg every other wk) **N:** **D1:** 162 **D2:** 151 **Mean age, yrs:** **D1:** 49.2 **D2:** 48.6 **Sex, % female:** **D1:** 45.1 **D2:** 43.7 **Race, % white:** **D1:** 93.8 **D2:** 97.4	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9.8 **TJC, mean:** **D1:** 25.8 **D2:** 23.9 **SJC, mean:** **D1:** 14.3 **D2:** 14.3 **Mean number previous DMARDS:** **D1:** 1.5 **D2:** 1.5 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline PASI (mean):** **D1:** 8.3 **D2:** 7.4 **MTX use:** **D1:** 50 **D2:** 51 **Baseline HAQ:** **D1:** 1.0 **D2:** 1.0	• PsARC ADA 60% wk. vs.placebo 23% • ACR50 ADA, 39% vs. placebo, 6% (*P* < 0.001) • ACR70 ADA, 23% vs. placebo, 1% (*P* < 0.001) • The PASI75 ADA 59% vs. placebo 1% (*P* < 0.001) (N:69 per group). • HAQ DI change placebo -0.1 ± 0.4 vs. ADA -0.4 ± 0.5 (*P* < 0.001) • ACR20 ADA 57% vs. placebo 15% (between-group difference 42%, 95% CI, 31-52%; *P* < 0.001). • Mmean change in modified total Sharp was -0.2 for ADA versus placebo (*P* < 0.001) • Erosion scores (mean change ADA 0.0 vs. placebo 0.6) and JSN scores (mean change ADA -0.2 vs. placebo 0.4) (*P* < 0.001 for both) • SF-36: SF-36 PCS; change in baseline to wk 12 for placebo vs ADA; 1.4 vs 9.3 (*P* < 0.001) • Change in baseline to wk 24; 1.4 vs 9.3 (*P* < 0.001) • SF-36 MCS • Change in baseline to wk 12 ; 1.2 vs 1.6 (*P* NS) • Change in baseline to wk 12; 0.6 vs 1.8 (*P* NS)	**Infusion or injection reaction:** **D1:** 3.1 **D2:** 6.6 **Headache:** **D1:** 8.6 **D2:** 6.0 **URTI:** **D1:** 14.8 **D2:** 12.6 **UTI:** NR	**Overall Attrition Rate (%):** 7.6 **ITT Analysis:** Yes **Quality Rating:** Fair.

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year: Chakravarty et al., 2003 **Country, Setting:** US, Rheumatology practices (175) **Funding:** Not reported **Research Objective:** To describe prescribing practices of rheumatologists with respect to treatment of RA in women of childbearing age and pregnancy outcomes **Study Design:** Case reports from Mail Survey to Rheumatologists **Overall N:** 175 (29%) physicians returned survey **Study Duration:** NR	**Inclusion Criteria:** • Age • Childbearing age • Women **Exclusion Criteria:**	**Interventions:** NR Methotrexate Leflunomide EtanerceptInfliximab **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 **Treatment resistant, %):** NR **Patients with Early RA (≤3 years):** NR **Baseline DAS, mean:** NR **Other:** NR	• 39 MTX • 10 LEF • 13 ETA • 2 INF MTX: • 21 full term healthy infants • 7 spontaneous abortions, including one in which fetus had congenital malformation • 8 elective abortions • 3 resulted in congenital malformations (2 live, 1 spontaneous abortion) • All attributed to MTX exposure Of 10 with LEF2 had been prescribed cholestyramine 6 with known outcomes: • 2 fullterm, healthy infants • 1 preterm delivery • 2 underwent elective abortions upon recommendation by their rheumatologist • 1 miscarriage 15 with ETA: Of 8 with known outcomes • 6 fullterm healthy infants, • 1 terminated • 1 patient took both ETA and MTX had a spontaneous abortion	NR	**Overall Attrition Rate, %:** N/A **ITT Analysis:** N/A: Observational study **Quality Rating:** Poor

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year: Chakravarty et al., 2003 (continued)				• Only 2 pregnancies reported in patients taking INF for RA-1 a fullterm healthy baby • Outcome of other not stated • Combined rate of congenital abnormalities in women on MTX was 17% according to answered questionaires compared to an average of 2 to 3% from a California cohort of 1.6 million infants		

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

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 **Country, Setting:** Sweden, population-based (2 Swedish registers) **Funding:** NR **Research Objective:** The 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 to 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 assessment median:** **D1:** 69 **D2:** 48	• 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 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)	**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

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Katz et al., 2004 **Country, Setting:** US and Europe, safety database **Funding:** NR- but data came from manufacturer **Research Objective:** To report first large evaluation of INF exposure during pregnancy **Study Design:** AERS database analaysis **Overall N:** 131 direct and 15 indirect exposure (partner) **Study Duration:** From 1 to 9 infusions	**Inclusion Criteria:** • Pts either were treated with INF or their partners • Other meds allowed: 5-aminosalicylate 6-mercaptopurine/ azathioprine, corticosteroids, metronidazole • MTX • Ciprofloxacin • NSAIDs • Proton pump inhibitors • H2 antagonists • Narcotics • Cyclosporine **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** INF direct **D2:** INF indirect **N:** **D1:** 131 **D2:** 15 **Mean age, yrs:** **D1:** 33 **D2:** 33 **Sex, % female:** **D1:** 100 **D2:** 100 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 31 **D2:** 40 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts. with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 8 **D2:** 20	• INF exposure during pregnancy results in outcomes which are not different than US population of pregnant women. No increase in adverse events was detected • Comparing the general population with INF treated, there is no statistical difference • Direct exposure- 67% (64/96) live births (95% CI: 56.3, 76.0), 15% (14/96) miscarriages (95% CI: 8.2, 23.2), and 19% (18/96) therapeutic terminations (95% CI: 11.5, 28.0) among the 96 women. (General population rates live births occurred in 67%, miscarriages in 17%, and therapeutic termination in 16%) • Indirect exposure resulted in 90% live births (9/10) and 10% miscarriage (1/10)	NR	**Overall Attrition Rate, %:** 27 **ITT Analysis:** N/A **Quality Rating:** Fair

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kwon, 2003 **Country, Setting:** USA, multicenter (FDA's MedWatch program) **Funding:** US Food and Drug Administration **Research Objective:** To describe adverse event reports of heart failure after TNF antagonist therapy **Study Design:** Database analysis; AERS **Overall N:** 47 cases **Study Duration:** long-term therapy	**Inclusion Criteria:** •Pts who reported heart failure as an adverse event while taking ETA or INF therapy in US since licensure of drugs until February 2002 •New onset failure and exacerbation of preexisting heart failure included **Exclusion Criteria:** • Heart failure reports temporally associated with other heart failure-inciting events (such as myocardial infarction) were excluded	**Interventions, dose:** **D1:** New Onset Heart Failure without risk factors **D2:** New Onset Heart Failure with risk factors **D3:** Heart failure exacerbation ETA: any INF: any **N:** NR **Mean age, yrs:** **D1:** 59 **D2:** 67 **D3: 70** **Sex, % female:** **D1:** 74 **D2:** 42 **D3: 44** **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 8 **D2:** 10 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **%ETA:** **D1:** 12 **D2:** 14 **D3:** 3 **%INF:** **D1:** 7 **D2:** 5 **D3:** 6	• 38 pts (81%) developed new-onset heart failure • 9 (19%) experienced heart failure exacerbation of which: 19 pts had no documented risk factors, 10 pts were under age 50 • Of pts under 50, after cessation of TNF antagonist therapy 3 pts experienced complete resolution of heart failure, 6 pts showed improvement, and 1 patient died	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

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 **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

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

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 **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:** 2 years	**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 ETA INF **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	• 461 cases of heart failure in 13,171 pts with RA (overall risk of 3.5%); after adjusting for demographic characteristics the risk was 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

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

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 (continued)			**MTX use:** **D1:** 67 **D2:** 76 **D3:** 44 **D4:** 47 **D5:** 56			

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Bathon et al., 2006 United States, supported by Immunex Corporation, wholly owned subsidiary of Amgen, Inc., and by Wyeth, Collegeville, PA, USA **Study Design:** Pooled analysis Aims of the Review: To evaluate safety and efficacy of ETA treatment in elderly (age 65 yrs) and younger adult subjects (age < 65 yrs) with RA Number of Pts: 1,353 2 longterm extensions (N = 1,049)	**Studies included:** • RCTs • Weinblatt et al., 1999 • Moreland et al., 1999 • Bathon et al., 2000 • Keystone et al., 2004 **Characteristics of included studies:** • 4 RCTs and 2 long-term observational extensions • Dosing arms included ETA 25 mg twice weekly vs placebo, MTX • Studies 1 and 2 were LRA extensions and conducted in DMARD-failure RA subjects and MTX-incomplete responders, respectively • Study 3, early study compared MTX and ETA therapy • Study 4 included subjects who had failed at least 1 DMARD other than MTX • Characteristics of included	• Elderly subjects had similar or less response to treatment than younger subjects (ACR 20, ACR 50, ACR 70) • Elderly ETA-treated subjects had similar or slightly lower, ACR responses compared with younger ETA treated subjects across all timepoints • ACR 20/50/70 responses after 6 mos of ETA treatment were 70%/45%/15% for elderly subjects and 65%/39%/15% in younger subjects • For LRA extension, ACR responses were similar between age groups • ACR 20/50/70 responses were 70%/47%/11% in elderly subjects and 75%/53%/29% in younger subjects after 72 mos ETA treatment in extension • Study 3, ACR responses tended to be lower in elderly group compared with younger group in both MTX and ETA treatment arms • After 24 mos ETA treatment, ACR 20/50/70 responses were 54%/22%/14% for elderly ERA subjects	• Rates of serious adverse events tended to be higher in elderly than younger subjects; however, rates of safety events observed in elderly ETA-treated subjects did not exceed rates in elderly placebo or MTX-treated subjects			

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		populations: • Adults with RA • 14% to 22% across treatment arms were elderly **Characteristics of interventions:** ETA (25 mg) twice weekly and comparison (placebo or MTX)	and 77%/54%/32% for younger subjects			

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Bathon et al., 2006 United States; Supported by Immunex Corporation, wholly owned subsidiary of Amgen, Inc., and by Wyeth, Collegeville, PA, USA (continued)		• In Study 3 extension, ACR 20/50/70 responses were 60%/40%/19% in elderly subjects and 79%/58%/40% in younger subjects after 48 mos of treatment in extension • In Study 4, elderly subjects had greater separation between efficacy responses achieved with ETA and MTX versus either monotherapy compared with younger subjects • After 12 mos treatment with combiation ETA and MTX, ACR 20/50/70 responses were 77%/68%/39% • For both age groups, treatment with ETA resulted in improved efficacy and function compared with control treatment, and combination therapy with ETA plux MTX resulted in greater efficacy than eitehr ETA or MTx used alone • Efficacy responses of elderly subjects were sustained for up to 6 yrs • Radiographic progression, M-SHS after 1 year of treatment was lower in subjects treated with both ETA and MTX compared with subjects treated with either agent used alone and this pattern was similar in both age groups				

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Fleischmann et al., 2003, multinational, Immunex corporation (last author, George Spencer-Green, is full-time employee at Immunex) **Study Design:** Pooled analysis **Aims of the Review:** To compare safety and efficacy of ETA in pts with RA who were ≥ 65 yrs to those < 65 yrs in open-label and RCTs **Number of Pts:** 1,128 Improvement in signs and symptoms was assessed for those who were able to receive ETA continuously for at least 1 yr (n=1059)	**Studies included:** All 9 are not clearly identified; 4 that are: • Moreland et al., 1997 • Weinblatt et al., 1999 • Moreland et al., 1999 • Bathon et al., 2000 **Characteristics of included studies:** • 4 double-blind RCT • 5 open-label trials • 8 trials evaluated pts with long-standing disease who failed previous DMARD therapy and 1 evaluated pts with recent onset RA (≤ 3 yrs) who never received MTX **Characteristics of included populations:** • Adults with RA • 83% < 65 yrs old • 17% > 65 • 8 trials evaluated pts with long-standing disease who failed previous DMARD therapy and 1 evaluated pts with recent onset RA (≤ 3 yrs) who never received MTX **Characteristics of interventions:** • ETA twice weekly for all pts	• 17% of pts were ≥65 yrs old at time of study entry At 1 yr: • 69% of pts < 65 and 66% of pts ≥ 65 met ACR20 (P = 0.480) • 40% of pts ≥ 65 met ACR50 and 17% met ACR70, compared to 44% and 20% for < 65 group, respectively (P values NR) • Subgroup analysis of those with early RA showed no difference in ACR20 response between those ≥ 65 and those < 65 (51% vs. 58%, P = 0.265) • Same for subgroup of those with late RA (58% vs. 63%, P = 0.321)	• Any infection (< 65 vs. ≥ 65: 1.56 events/PY vs. 1.36, P = 0.036) • Injection site reactions (4.31 events/PY vs. 1.47, P < 0.001), headaches (0.37 vs. 0.18, P < 0.001), and rhinitis (0.19 vs. 0.10, P = 0.006) occurred at higher rates in younger pts (< 65) • Rates of other AEs were comparable between 2 groups: rash, diarrhea, nausea, and abdominal pain	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** NR **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No **Quality Rating:** Poor		

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Rheumatoid Arthritis Clinical Trial Archive Group, 1995, 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 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Rheumatoid Arthritis Clinical Trial Archive Group, 1995 Multinational NIH grants (continued)		• Pts with renal impairment had worse toxicity scores and a higher overall rate of toxicity; mean worst toxicity scores were 2.2 (referent), 3.0 (*P* = < 0.05), 2.9 (*P* = < 0.05), and 3.3 (*P* = < 0.01) for ≥ 99.8 ml/min (referent), 78.6-99.9 ml/min, 62.6-78.6 ml/min, and < 62.6 ml/min. groups respectively; Rates of any toxicity were 55%, 64%, 65%, and 72% for groups respectively (*P* NR) • They report that pts with renal impairment were at higher risk of severe toxicity and for respiratory toxicity; however, 95% CI crosses 1 for all but 1 group; for severe toxicity odds for 4 groups were 1.0 (referent), 3.0 (0.7, 13.0), 5.7 (1.4, 23.6), and 4.5 (0.9, 22.6); for respiratory toxicity, 1.0 (referent), 5.9 (0.6, 57.0), 5.6 (0.5, 60.4), and 6.9 (0.5, 88.8)				

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Appendix G: Quality Criteria

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.

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?

Appendix H: Characteristics of Studies With Poor Internal Validity

Study	Design	Sample Size	Intervention	Reason for Exclusion
†Bathon et al., 2006[1]	Pooled data analysis	2,402	Etanercept	Selection bias
de Nijs et al., 2001[2]	Cross-sectional	410	Corticosteroids	Selection bias
Faarvang et al., 1993[3]	RCT	91	Hydroxychloroquine Sulfasalazine	No ITT analysis; high LTF
†Fleischmann et al., 2003[4]	Pooled data analysis	1128	Etanercept	Selection bias
‡Flendrie et al, 2003[5]	Retrospective cohort study	230	Adalimumab Etanercept Infliximab	High differential LTF; no ITT analysis
Flendrie et al., 2005[6]	Observational	162	Leflunomide infliximab	High LTF; selection bias
Hansen et al., 1999[7]	RCT	102	DMARDs Prednisolone	High attrition; no ITT analysis
‡Langer et al., 2003[8]	Post-marketing surveillance	454	Anakinra	No comparison group; no ITT analysis
‡Moreland et al., 2006[9]	Pooled retrospective analysis	714	Etanercept	High LTF; completers analysis only
‡O'Dell et al., 2006[10]	Prospective open-label study	119	Etanercept Hydroxychloroquine Sulfasalazine	Bias due to poor ITT design
‡Svensson et al, 2003[11]	Open-label RCT	245	Methotrexate Prednisolone Sulfasalazine	High post-randomization exclusions; high differential LTF

ITT, intention to treat; LTF, loss to followup; RCT, randomized controlled trial.
†Included for subgroups
‡Rated fair for adverse events

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Appendix I: 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.

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

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.[26] 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.[26]

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.[26] 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.

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.[27] 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.

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