Drug Class Review

Targeted Immune Modulators

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The literature on this topic is scanned periodically.

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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INTRODUCTION

Targeted immune modulators, commonly referred to as biological response modifiers or simply *biologics*, are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. The US Food and Drug Administration approved the first of the biologics (infliximab) in 1998 and approved 9 additional agents since that time for treating various rheumatic conditions and plaque psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), efalizumab (2003), abatacept (2005), rituximab (2006), natalizumab (2008), and certolizumab pegol (2008). Table 1 summarizes currently approved biologics in the United States, including trade name, manufacturer, route of administration, therapeutic mechanism of action, and approved (labeled) uses.

Table 1. Targeted immune modulators

Generic name	United States trade name	Manufacturer	Route	Half-life	Onset of action	Mechanism of action	Labeled uses
Abatacept	Orencia®	Bristol Myers Squibb	Intravenous	8-25 days	>12 days	CTLA 4-Ig	RA JIA
Adalimumab	Humira®	Abbott	Subcutaneous	10-20 days	1-14 days	TNF inhibitor	RA JIA PsA AS Crohn's disease Plaque psoriasis
Alefacept	Amevive®	Astellas	Intramuscular	11-12 days	30-60 days	CD2 antagonist	Plaque psoriasis
Anakinra	Kineret®	Amgen	Subcutaneous	7-8 hours	7-21 days	IL-1 receptor antagonist	RA
Certolizumab pegol	Cimzia®	UCB, Inc	Subcutaneous	14 days	2-4 weeks	TNF inhibitor	RA Crohn's Disease
Efalizumab[a]	Raptiva®	Genentech	Subcutaneous	6.2 days	14 days	CD11a inhibitor	Plaque Psoriasis
Etanercept	Enbrel®	Amgen Wyeth Immunex	Subcutaneous	4.3 days	1-28 days	TNF inhibitor	RA JIA PsA AS Plaque psoriasis
Infliximab	Remicade®	Centocor	Intravenous	9.8 days	2-14 days	TNF inhibitor	RA Crohn's disease PsA AS Ulcerative colitis Plaque psoriasis
Natalizumab	Tysabri®	Biogen-Idec	Intravenous	7-15 days	2-4 weeks	Anti-IgG4	Crohn's disease
Rituximab	Rituxan®	Genentech IDEC	Intravenous	19 days	30-60 days[b]	Anti-CD 20a	RA

AS, ankylosing spondylitis; IgG, immunoglobulin G; IL, interleukin; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor.
[a] This drug was voluntarily withdrawn from the market since June 2009.
[b] American College of Rheumatology 20 response at 56 days in product labeling.

Targeted immune modulators work by selectively blocking mechanisms involved in the inflammatory and immune response. Tumor necrosis factor inhibitors block specific proinflammatory mediators known as cytokines. Adalimumab, certolizumab pegol, etanercept, and infliximab target tumor necrosis factor alpha. Adalimumab is a fully human monoclonal antibody that binds specifically to tumor necrosis factor alpha, blocking its interaction with both the p55 and p75 cell surface tumor necrosis factor receptor. Certolizumab pegol is a recombinant, humanized antibody FAB' fragment with specificity for human tumor necrosis factor alpha. Etanercept is a soluble dimeric form of the p75 tumor necrosis factor alpha receptor linked to the Fc portion of human immunoglobulin G1. It exerts its action by binding circulating tumor necrosis factor alpha and lymphotoxin-α and preventing it from interacting with a cell surface receptor. Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor alpha antibody that binds both the circulating and transmembrane forms of tumor necrosis factor alpha, thereby preventing binding with the receptor; infliximab does not neutralize lymphotoxin alpha.

Interleukin-1, another naturally occurring cytokine, has both immune and pro-inflammatory actions. Anakinra is a human recombinant protein and the therapeutic version of a naturally occurring cytokine that competitively blocks the interleukin-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agents abatacept, alefacept, and efalizumab exert their immune regulation 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 immunoglobulin G1. Alefacept is a dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen (LFA-3) and the Fc portion of human immunoglobulin G1. Efalizumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that binds to human CD11a and inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1).

Genentech, the manufacturer of efalizumab (Raptiva®) has voluntarily withdrawn the drug from the United States market because of an increased risk of progressive multifocal leukoencephalopathy. Progressive multifocal leukoencephalopathy is a rapidly progressive, viral infection of the central nervous system that leads to death or severe disability. Because it is unclear whether efalizumab will be reintroduced to the United States market, we will not discuss the use of efalizumab in this report any further.

Natalizumab is a recombinant, huminized immunoglobulin G4 antibody that binds to the alpha 4 subunit of all leukocytes except neutrophils. The specific mechanisms by which natalizumab exerts its effect in Crohn's disease has not been fully defined. Because of an increased risk of progressive multifocal leukoencephalopathy, natalizumab is only available through a specialized restricted distribution program called TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program only prescribers, infusion centers and pharmacies registered with the program are able to prescribe, distribute, and infuse the product.

Rituximab, a chimeric murine/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes. B-cells are believed to play a role in autoimmune and inflammatory processes, such as those involved in rheumatoid arthritis.

Table 2 summarizes dosages and administration for different indications.

Table 2. Recommended dosage and administration

Generic name	Indication	Dosage and administration
Abatacept	RA	Intravenous infusion dosed according to body weight (< 60kg = 500mg; 60-100kg = 750mg; > 100kg = 1000mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter
	JIA	10mg/kg for patients <75kg; adults schedule for patients >75kg on weeks 0, 2, and 4 and then every 4 weeks thereafter
Adalimumab	RA	40 mg every other week as subcutaneous injection; may increase to 40 mg per week for adalimumab monotherapy
	PsA Ankylosing spondylitis	40 mg every other week as subcutaneous injection
	JIA (4 yrs of age & older)	15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week ≥ 30 kg (66 lbs): 40 mg every other week
	Crohn's Disease	Initial subcutaneous dose (Day 1) is 160 mg (four 40 mg injections in 1 day or two 40 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week
	Plaque psoriasis	80 mg initial subcutaneous dose, followed by 40 mg every other week starting 1 week after initial dose
Alefacept	Plaque psoriasis	15 mg given once weekly as an intramuscular injection, or 7.5 mg given for intravenous injection. Treatment should be continued for 12 weeks; re-treatment with an additional 12 week course may be initiated provided that CD4+ T lymphocytes counts are > 250 cells/μL and a 12-week interval has passed since the end of the initial treatment cycle
Anakinra	RA	100 mg daily as subcutaneous injection; dose should be decreased to 100 mg every other day in renal insufficiency
Certolizumab pegol	RA	400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered
	Crohn's Disease	400 mg subcutaneous injection initially and at weeks 2 and 4. If response occurs 400 mg subcutaneously every 4 weeks
Efalizumab	Plaque psoriasis	Single 0.7 mg/kg subcutaneous conditioning dose followed by weekly subcutaneous doses of 1 mg/kg (maximum single dose not to exceed a total of 200 mg)
Etanercept	RA, PsA Ankylosing spondylitis	25 mg twice weekly as subcutaneous injections or 50 once weekly as subcutaneous injection
	JIA (patients 4-17 years)	0.8 mg/kg per week (maximum 50 mg per week) given as 1 or 2 subcutaneous injections
	Plaque psoriasis	50 mg given twice weekly (administered 3 or 4 days apart) as a subcutaneous injection for 3 months, followed by 50 mg weekly
Infliximab	RA	*Adult:* 3 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg every 4 weeks
	Crohn's Disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to 10 mg/kg *Pediatric (6-17 years):* 5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks
	PsA	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter
	Ankylosing spondylitis	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 6 weeks thereafter
	Active UC	5 mg/kg induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter
	Plaque Psoriasis	5 mg/kg induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter
Natalizumab	Crohn's Disease	300 mg intravenous infusion every 4 weeks
Rituximab	RA	1000 mg intravenous infusion on days 1 and 15 in combination with methotrexate

JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

In this report, we review the comparative effectiveness, safety, and tolerability of targeted immune modulators. Our review covers the use of these drugs in adult patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, plaque psoriasis, and pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. The next section briefly describes the epidemiology and pathophysiology of these conditions, as well as clinical features, assessment methods, management goals, and treatment strategies. Furthermore, we review the role of the targeted immune modulators in treating patients with these diseases.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease that affects about 1% of the population worldwide. The exact etiology of rheumatoid arthritis is not completely understood, but genetic susceptibility factors have been described in certain populations. The hallmarks of the disease are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and disability in most cases. Studies have shown the importance of CD4+ T cells, B cells, and cytokines in the pathogenesis of rheumatoid arthritis. Tumor necrosis factor alpha plays a central role in the pathobiology of rheumatoid arthritis. It is an important regulator of other pro-inflammatory 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 localized mass of tissue that causes localized joint destruction.[1]

The diagnosis of rheumatoid arthritis is primarily a clinical one. Constitutional symptoms, such as fatigue and low grade fevers, 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. In a subset of patients, rheumatoid arthritis can be a devastating disease with numerous extra-articular manifestations. Severe disease may be complicated by involvement of the eyes, lungs, nerves, and the cardiovascular system.

A serum rheumatoid factor is present in up to 75% of patients with rheumatoid arthritis but is frequently negative in early disease. A more specific marker, anti-cyclic citrullinated peptide antibody, has recently been described and may be a useful marker in patients with early disease.[2] Table 3 presents the classification criteria for rheumatoid arthritis proposed by the American College of Rheumatology. These criteria were developed for use in clinical trials, but may be relatively insensitive in early disease.

Treatment is aimed at controlling pain and inflammation and ultimately, slowing or arresting the progression of joint destruction. The key to successful management of rheumatoid arthritis is the early identification of the disease and the rapid institution of effective therapies. [3] Methotrexate is the cornerstone of most rheumatoid arthritis treatment regimens as it has demonstrated good disease control and tolerability. However, methotrexate toxicity may limit the use of methotrexate, and many patients do not adequately respond to methotrexate monotherapy. In patients with persistent disease despite aggressive management with oral agents, biologic agents, often in combination with methotrexate, are now considered the standard of care. Lifelong therapy is usually necessary.

Table 3. Criteria for the classification of rheumatoid arthritis[a] (revised 1987)

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

[a] Patients are said to have rheumatoid arthritis if they meet 4 of 7 criteria.[4]

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis is a form of arthritis that, by definition, lasts at least 6 weeks in a child under the age of 16. It is a systemic disease with a variable presentation and has 3 established subtypes: pauciarticular (<5 joints involved), polyarticular (≥5 joints involved), and systemic (arthritis with fever and a rash).[5]

Joint pain, stiffness, and swelling are the hallmarks of juvenile idiopathic arthritis. Children with systemic disease often present with constitutional symptoms such as fever or rash. Similar findings may be seen in polyarticular disease but are rare with pauciarticular presentation. Uveitis, an inflammatory disease of the eye, is common. Children with the most severe forms of juvenile idiopathic arthritis may have significant disability from progressive destructive arthritis. Long-term consequences of the disease include growth disturbances, deformity of the joints, and blindness.

Initial therapeutic strategies are aimed at decreasing pain and swelling and improving the child's functional status. Non-steroidal anti-inflammatory drugs are first line therapy and are usually fairly well tolerated in children. Systemic steroids are usually avoided, if possible, because of adverse effects on bone growth. However, intra-articular steroid injections can be an effective strategy, particularly if only a few joints are afflicted with active disease. As in rheumatoid arthritis, oral disease-modifying antirheumatic drugs are used next, with methotrexate being the most widely used. When the disease is resistant to oral therapies, biologic agents are indicated.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory arthritis with primary involvement of the axial skeleton and prominent involvement of the spine and sacroiliac joints. Peripheral joint disease can occur and may be destructive in some cases. The peak age of onset is in the 20s, and men are affected more frequently than women by a ratio of about 3 to 1. The onset is indolent with prominent stiffness in the low back, which is characteristically worse at night and in the early morning. The sacroiliac joints are usually the first joints involved, and the disease is characterized by progressive involvement of the spine. Enthesitis, inflammation of the insertion of ligaments and tendons on bones, is one of the hallmarks of the disease.

Existing diagnostic criteria are relatively insensitive and have limited utility in clinical practice. Ankylosing spondylitis usually presents with inflammatory back pain and stiffness in a young adult, although 20% present with peripheral joint involvement and more than 50% have joints other than the spine affected at some stage. Radiographs of the sacroiliac joints, when abnormal, can be useful in assessing the presence of ankylosing spondylitis; however, they are

frequently normal in early disease. Over time, patients with ankylosing spondylitis develop progressive fusion of the spine with resultant deformity and disability.

For years non-steroidal anti-inflammatory drugs were the standard of care for the treatment of ankylosing spondylitis, as they are effective in treating pain and stiffness. However, they do not have any effect on disease progression. Traditional disease-modifying antirheumatic drugs have been used, mostly because a lack of other more effective therapies, although they are usually ineffective in treating spinal arthritis. As tumor necrosis factor has been implicated in the pathophysiology of ankylosing spondylitis, biologic agents targeting tumor necrosis factor have become a standard treatment approach.[6] Studies are under way to assess whether treatment with these agents affects the natural history of ankylosing spondylitis.

Psoriatic Arthritis

Psoriatic arthritis is a chronic inflammatory arthritis associated with the skin disease psoriasis. In most cases, the psoriasis predates the onset of the psoriatic arthritis. The presentation, however, is highly variable. In all cases, symptoms include pain and stiffness in the affected joint as well as joint line tenderness, swelling, and sometimes loss of range of motion. Pitting of the fingernails often correlates with the extent and severity of the disease.[7] Dactylitis, swelling of a whole digit, is a characteristic clinical finding. Enthesitis, spondylitis, sacroiliitis, and inflammatory eye disease (iritis, uveitis) may occur.

The etiology and pathogenesis of psoriasis and psoriatic arthritis are not completely understood, but genetic, immunologic, and environmental factors are all likely to play a role.[8] The first line of treatment is non-steroidal anti-inflammatory drugs, although in most cases disease-modifying antirheumatic drugs are necessary. Corticosteroids may be used but do not have much of a role in chronic disease management in psoriatic disease. If disease continues to be active despite the use of non-steroidal anti-inflammatory drugs, methotrexate, or other oral disease-modifying antirheumatic drugs, biologics may be indicated.[9, 10]

Crohn's Disease

Crohn's disease is a condition of the bowel causing inflammation involving the full thickness of the bowel wall. This may occur at any point from the mouth to the anus. This chronic inflammation leads to fibrosis and obstructive symptoms with sinus tracts and fistulae. Fistulizing disease is a serious complication of Crohn's disease; it is basically abnormal communication between the gut and the skin or other internal organs, with small bowel or colonic contents draining to the skin or other organs. Abdominal pain and diarrhea, with or without bleeding, are characteristic of the disease. Constitutional symptoms are very common, predominantly fatigue and weight loss. Nonspecific digestive symptoms may predate the onset of clinically overt disease. Extra-intestinal symptoms may occur and include inflammatory eye disease, arthritis, and sclerosing cholangitis. Clinical diagnosis is made on the basis of history and physical examination and is confirmed on endoscopy and biopsy of the involved segment of the GI tract. Patients with aggressive or poorly controlled disease may suffer numerous complications; these include severe hemorrhage, intestinal obstruction, perforation, development of fistulae and abscess formation, malabsorption with nutritional deficiencies, and rarely, malignancy.

Treatment is aimed at controlling the inflammation and preventing complications. Mild disease may be controlled with 5-aminosalicylate drugs or antibiotics. If the disease is resistant

to these interventions or is more severe, corticosteroids are frequently used. If symptoms persist despite steroids or if the disease flares on tapering the steroids, immunomodulatory agents (azathioprine, 6-mercaptopurine, and methotrexate) often are instituted. Biologics may be warranted in patients with moderate to severe active Crohn's disease who have had inadequate response to conventional therapy. It is recommended that medical therapy be exhausted before surgical therapy is considered, except in cases of catastrophic complications such as acute colonic obstruction, massive hemorrhage, or bowel perforation.

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory bowel disease that is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain and limited to the colon and rectal areas, unlike Crohn's disease which causes inflammation deeper within the intestinal wall and can occur in other parts of the digestive system including the small intestine, mouth, esophagus, and stomach. The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Clinical diagnosis is most accurately made with colonoscopy or sigmoidoscopy.

Treatment is aimed at reducing and maintaining remission of symptoms and inflammation.[11] Mild disease may be controlled with oral and/or topical 5-aminosalicylate drugs. If the disease is resistant to these interventions or is more severe, corticosteroids are frequently used. In addition, infliximab has been approved by the US Food and Drug Administration for treatment of moderate to severe ulcerative colitis. Indications for surgery include excessive bleeding, perforation, carcinoma and toxic colitis. About 25% to 40% of ulcerative colitis patients must eventually have their colons removed.

Plaque Psoriasis

Plaque psoriasis is a chronically recurring, debilitating inflammatory disease that affects the skin, scalp, and joints. It is characterized by erythrosquamous skin lesions and ranges in severity from mild to severe. Patients with moderate to severe disease experience significant deterioration of quality of life.[12] The exact pathogenesis of plaque psoriasis is still unknown; however, pathophysiological evidence suggests that an overproduction of proinflammatory cytokines plays an important role.[13, 14] In particular, tumor necrosis factor levels are increased in psoriatic lesions compared with healthy skin.

The severity of plaque psoriasis is most commonly classified based on the percentage of body surface area involved. Severe psoriasis is generally defined as more than 10% body surface area affected.[12]

The goal of plaque psoriasis treatment is to gain control of the disease process, decrease the percentage of body surface involved, and achieve and maintain long-term remission.[15] Conventional therapy includes topical treatments (e.g. topical corticosteroids, calcipotriene, tazarotene), phototherapy (e.g. broadband ultraviolet B light, narrow band ultraviolet B light, psoralen plus ultraviolet A light), and systemic therapy (e.g., methotrexate, cyclosporine, acitretin). In addition, biologic agents such as adalimumab, alefacept, efalizumab, etanercept, and infliximab have been approved by the US Food and Drug Administration for the treatment of moderate to severe plaque psoriasis.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well-conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also

often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an

evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of targeted immune modulators. We compare the efficacy, effectiveness, and safety (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, infliximab, natalizumab, and rituximab in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. The Oregon Evidence-based Practice Center initially prepared preliminary key questions identifying the populations, interventions, and outcomes of interest, and we based the eligibility criteria for studies on these preliminary questions. Representatives of organizations participating in the Drug Effectiveness Review Project, in conjunction with experts in the fields of health policy, rheumatology, pharmacotherapy, and research methods reviewed, revised, and approved the questions and outcome measures. The participating organizations approved the following key questions:

1. How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis?

2. What are the comparative incidence and severity of complications associated with the use of these drugs?

3. Do the included drugs differ in effectiveness or adverse events in different age, sex, or ethnic groups, or in patients taking other commonly prescribed drugs?

The first key question addresses the issue of efficacy and effectiveness: do the biologics differ in their effects under real-life circumstances? This report addresses both efficacy (i.e., whether biologics differ in their effects under ideal or highly controlled circumstances) and effectiveness. We distinguish between *efficacy* (*explanatory*) studies and *effectiveness (pragmatic)* studies by using a validated tool proposed by the RTI (Research Triangle Institute-International)-UNC (University of North Carolina) Evidence-based Practice Center.[16] Studies conducted in community-based settings that use less stringent eligibility criteria (i.e., broad range of population characteristics and disease severity), have long follow-up periods (i.e., greater than one year), and assess health outcomes are characterized as *effectiveness* studies. Studies conducted in more highly selected populations over shorter periods of time are characterized as

efficacy studies. We summarize the results of efficacy and effectiveness studies separately as the results of effectiveness studies are more generalizable than results from highly selected populations (i.e., efficacy studies). However, effectiveness studies may have lower internal validity because of a higher risk of bias.

For assessing efficacy, effectiveness, and safety our review includes methodologically valid controlled clinical trials, placebo-controlled trials, fair- or good-quality systematic reviews, and fair- or good-quality observational studies. Table 4 summarizes outcome measures and study eligibility criteria.

Table 4. Outcome measures and study eligibility criteria

Outcome	Outcome measures	Study eligibility criteria
Efficacy / Effectiveness	• Health outcomes: o Quality of Life o Functional capacity o Pain o Reduction in the number of swollen or tender joints o Response o Remission o Reduction of affected body surface area o Hospitalizations o Mortality o Steroid withdrawal • If no studies with health outcomes were available, we included intermediate outcomes: o Radiological outcomes	• Outpatient study population • Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM to another o Good or fair quality o ≥ 3 months study duration o N ≥ 30 • When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials o Good or fair quality o ≥ 3 months study duration o N ≥ 100 • Head-to-head observational studies were reviewed for quality of life, functional capacity, hospitalizations and mortality - outcome measures rarely assessed in controlled trials o Good or fair quality o ≥ 3 months study duration o N ≥ 100
Safety/ Tolerability	• Overall adverse events • Withdrawals because of adverse events • Serious adverse events • Specific adverse events, including: o Serious infectious diseases o Lymphoma o CHF o Autoimmunity	• Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM drug to another o Good or fair quality o ≥ 3 months study duration o N ≥ 30 • When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials o Good or fair quality o ≥ 3 months study duration o N ≥ 100 • Observational studies o Good or fair quality o ≥ 6 months study duration o N ≥ 1000

CHF, congestive heart failure; TIM, targeted immune modulator.

As equipotency among the reviewed biologics is not well established, we assume that comparisons made within the recommended dosing range are appropriate (Table 2). Dose comparisons made outside the recommended daily dosing range are acknowledged in our report, but we do not use them to determine the quality of the evidence.

The primary focus of this review will be health outcomes (see Table 4). For head-to-head studies, however, we will also include radiographic outcomes. Many clinicians view radiographic changes as important parameters of treatment success or failure. To date, however, the exact relationship between radiographic progression and incapacitating joint destruction remains unclear. Several instruments for scoring radiological changes exist, using plain radiographs of hands and feet. The most widely used methods are the modified Sharp and the Larsen scores. Both methods determine joint damage and the progression of radiological damage on continuous scales. Currently, no consensus exists on how much progression constitutes a clinically important progression that would have an effect on health outcomes.

A re-analysis of published data of 185 patients with early rheumatoid arthritis assessed changes on the modified Sharp score and their association with functional disability (Health Assessment Questionnaire Disability Index).[17] Results indicated that the relation between Sharp score and Health Assessment Questionnaire Disability Index was dependent on the amount of damage (suggesting a threshold effect) and on patients' age. With lower age, no effect of radiographic joint damage on functional capacity could be demonstrated. With higher age, however, the effect is obvious. Overall a progression of 6 points on the Sharp score was associated with an increase of 0.2 points on the Health Assessment Questionnaire Disability Index. An increase in 0.2 points on the Health Assessment Questionnaire Disability Index represents a minimal clinically relevant difference from a patient perspective.[18, 19]

An international expert panel assessed the minimal clinically important difference in joint damage (from a clinician's perspective). They used hand and foot radiographs to correlate their findings with the smallest detectable difference on the Sharp/van der Heijde and the Larson/Scott methods.[20] Results suggested that the smallest detectable difference on the Sharp/van der Heijde score reflected a minimal clinically important difference, while the Larson/Scott method was too insensitive to determine relevant changes. This study, however, did not take minimal important differences from a patient perspective into consideration.

METHODS

Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts; 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, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, plaque psoriasis), drug interactions, and adverse events with a list of 10 specific targeted immune modulators (abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, efalizumab, etanercept, infliximab, natalizumab, rituximab). We limited the electronic searches to "human" and "English language"; we searched sources from 1980 to 2009 (April) to delimit literature relevant to the scope of our topic.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials, and meta-analyses; we also manually searched reference lists of pertinent review articles and letters to the editor. All citations were imported into an electronic database (EndNote, version X). Additionally, we hand-searched the Center for Drug Evaluation and Research database to identify unpublished research submitted to the US Food and Drug Administration.

Further, the Center for Evidence-based Policy at the Oregon Health and Science University contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol available at www.ohsu.edu/drugeffectiveness. We received dossiers from 8 pharmaceutical companies (Abbott Laboratories, Amgen Pharmaceuticals, Astellas Pharmaceuticals, Biogen, Bristol Myers Squibb, Centocor, Genentech, UCB Inc., and Wyeth/Amgen Pharmaceuticals).

Our searches found 3451 citations, unduplicated across databases; we found an additional 12 articles from manually reviewing the reference lists of pertinent review articles and an additional 3 articles in the pharmaceutical dossiers. The total number of citations included in the database was 236. For further details on the search strategy, see Appendix B.

Study Selection

Two people independently reviewed abstracts; if both reviewers agreed that the study did not meet eligibility criteria, it was excluded. We obtained the full text of all remaining articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest.

With respect to study design we took a "best evidence" approach for this review. Results from well-conducted, head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events; head-to-head trials were defined as those comparing one targeted immune modulator with another. Randomized controlled trials of at least 3 months' duration having an outpatient study population with a total sample size greater than 30 participants were eligible for inclusion.

In addition, we reviewed well-conducted, head-to-head observational studies with a follow-up of at least 3 months to augment findings from experimental studies. Long-term observational studies can provide evidence on outcomes that may be difficult to observe in randomized controlled trials due to limitations in sample sizes and study durations. Furthermore, observational data can provide information whether treatment effects observed in randomized controlled trials can be translated to less selected populations.[21] Nevertheless, the strength of evidence of these results for comparing different drugs must be rated lower than results from the most preferred type of trial.

If no head-to-head evidence was published, we reviewed placebo-controlled trials for indications of interest. We reviewed all placebo-controlled trials to provide an overview of efficacy without taking drug equivalency into account. We compared results of approved dosing ranges, but no evidence on exact comparative dosing is currently available. Study populations, disease severity, and concomitant treatments can differ considerably across placebo-controlled trials. Comparisons of treatment effects across trials must, therefore, be made with caution.

We included meta-analyses in the evidence report if they were relevant to a key question and of good or fair methodological quality.[22] We did not summarize individual studies in

evidence tables if they were included in a high-quality meta-analysis (listed in Appendix C). We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We checked our database to guarantee that our literature search had detected trials included in any meta-analyses that we discarded and obtained any missing articles.

For adverse events we included both experimental and observational studies. For observational studies we included those with large sample sizes ($\geq$ 1000 patients) that lasted at least 6 months and reported an included outcome.

We initially reviewed studies with health outcomes as the primary outcome measures. Outcomes were, among others, quality of life, functional capacity, alleviation of symptoms, hospitalizations, or mortality. For head-to-head studies we also included radiological changes. Safety outcomes included overall and specific adverse events (e.g., serious infections, lymphoma, autoimmunity), withdrawals attributable to adverse events or lack of efficacy, and drug interactions.

Data Abstraction

We designed and used a structured data abstraction form to ensure consistency in 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 trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, loss to follow-up, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat results if available.

Validity Assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix D) developed by the United States Preventive Services Task Force (ratings: good-fair-poor)[23] and the National Health Service Centre for Reviews and Dissemination.[24] External validity (generalizability) was assessed and reported but did not influence quality ratings. We did not rate the quality of pooled data-analyses.

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third, independent party. Elements of internal validity assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis, and overall and differential loss to follow-up.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study,[25] independent of the reason and the use of intention-to-treat analysis. We adopted no formal cut-off point of loss to follow-up since many studies defined withdrawals due to acute worsening of the disease as an outcome measure.

Trials that had a fatal flaw in 1 or more categories were rated poor quality and not included in the analysis of the evidence report; trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methods to an extent that answered all of our

questions. Therefore, the "fair quality" category includes trials with quite different strengths and weaknesses and a range of validity.

Data Synthesis

Throughout this report we synthesized the literature qualitatively. If data were sufficient, we augmented findings with quantitative analyses. Because only limited head-to-head evidence on targeted immune modulators was available, we conducted adjusted indirect comparisons when data was sufficient and trials were of similar design, conducted in similar settings with a comparable patient population. We based these analyses on the method proposed by Bucher et al.[26] Evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials.[27, 28] Nevertheless, findings must be interpreted cautiously.

To conduct indirect comparisons we employed random effects meta-analyses of data from placebo-controlled trials that were fairly homogenous in study populations and outcome assessments. Our outcome measure of choice for rheumatoid arthritis was the relative risk of achieving an American College of Rheumatology 20/50/70 response (numbers refer to percentage improvement [see Appendix E for a summary of different scales]). We did not find sufficient data to pool results of the Health Assessment Questionnaire or other measures of health-related quality of life. We chose the American College of Rheumatology 50 outcome measure because response to treatment can be viewed as a close proxy to health outcomes. Therefore, such an outcome measure has more clinical significance than a comparison of mean changes of scores on rating scales. A 50% improvement on the American College of Rheumatology scale is commonly viewed as a clinically significant response.

For each meta-analysis, we conducted a test of heterogeneity (I^2 statistic) and applied both a random and a fixed effects model.

We assessed publication bias using funnel plots and Kendell's tests. However, given the small number of component studies in our meta-analyses, results of these tests must be viewed cautiously. All statistical analyses were conducted using StatsDirect, version 2.6.6.

Rating the Strength of the Evidence

We rated the strength of the available head-to-head evidence in a 3-part hierarchy based on an approach devised by the GRADE working group.[29] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates 4 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 5, we used 3 grades: high, moderate, and low (combining the GRADE category of very low with low).[30] Grades reflect the strength of the body of evidence to answer key questions on the comparative efficacy, effectiveness, and harms of targeted immune modulators. 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.

This approach does not incorporate other factors, such as funding sources and comparable dosing, which 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.

Table 5. 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.

Adapted from the GRADE working group.[29]

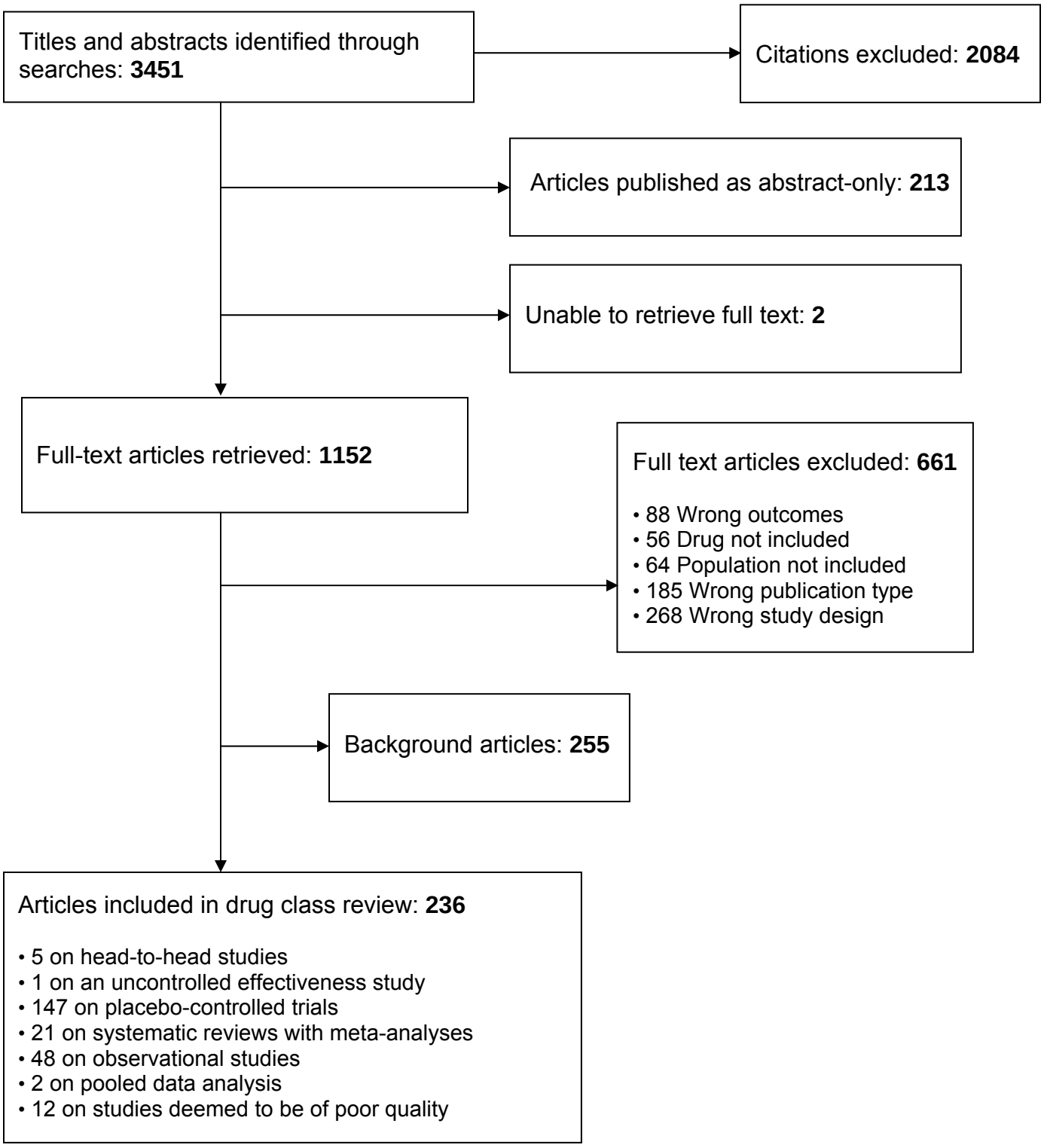
RESULTS

We identified 236 citations from searches and reviews of reference lists. In total we included 113 studies: 41 randomized controlled trials, 24 systematic reviews with meta-analyses, 45 observational studies, and 3 studies of other design (pooled data analysis). Furthermore, we retrieved 255 articles for background information.

Reasons for exclusions were based on eligibility or methodological criteria (Figure 1). We excluded 3 studies that originally met eligibility criteria but were later rated as poor quality for internal validity (Appendix H).

Of the 237 included studies, 70% were financially supported by pharmaceutical companies, 15% were funded by governmental agencies or independent funds, and 2% received both pharmaceutical and government funding. We could not determine a funding source for 13% of the included studies.

Figure 1. Disposition of articles (QUORUM tree)[a]



[a] Number of included articles differs from number of included studies due to the fact that some studies have multiple publications.

Key Question 1. Efficacy and Effectiveness

How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, or plaque psoriasis?

Rheumatoid Arthritis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, infliximab, and rituximab.

We included 16 randomized controlled trials, 16 meta-analyses, and 7 observational studies. Only 1 randomized controlled trial was a head-to-head trial.[31] One study was characterized as an effectiveness trial.[32] Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up.

Summary of findings

The only double-blinded head-to-head trial was a fair randomized controlled trial that compared abatacept with infliximab in patients with inadequate response to methotrexate.[31] At 6 months, no differences in efficacy were apparent. After 1 year, abatacept was statistically significantly more efficacious on most outcome measures than infliximab (American College of Rheumatology 20 response 72.4 compared with 55.8%; $P<0.001$; American College of Rheumatology 50 response 45.5 compared with 36.4%; $P<0.001$). It has to be noted though, that infliximab was administered at a fixed dose throughout the entire study. Infliximab efficacy trials have shown that up to 30% of patients require dose increases.

The second study with a randomized allocation of interventions was a fair, small (n=32) open-label randomized controlled trial that compared etanercept with infliximab.[33] Results indicated greater response rates of patients treated with etanercept than with infliximab (74.4% compared with 60% after 54 weeks; P=NR). Four head-to-head observational studies and 1 non-randomized trial reported similar results.[32, 34-36] The overall grade of evidence for this comparison is low.

Other head-to-head comparisons based on observational studies were limited to adalimumab compared with etanercept and infliximab. These comparisons, however, all stem from 1 prospective cohort study based on a Dutch register.[36] After 12 months of follow-up patients on adalimumab and etanercept had similar improvements of the DAS28 (disease activity score28; -1.8 compared with -1.8) and the Health Assessment Questionnaire (-0.42 compared with -0.35) but better scores than patients on infliximab (-1.2 and -0.26, respectively).

Adjusted indirect comparisons of placebo-controlled randomized controlled trials suggest that no substantial differences exist among the efficacy of adalimumab, etanercept, and infliximab. Point estimates favor adalimumab, etanercept, and infliximab over anakinra. However, differences do not reach statistical significance in adjusted indirect comparisons which is likely attributable to a lack of power. We could not find any direct or indirect evidence of the efficacy of certolizumab pegol and rituximab compared with other targeted immune modulators. Furthermore, for none of the comparisons is any evidence on radiographic progression available.

No synergistic effects of combination treatments of etanercept with abatacept or anakinra could be detected.[37, 38] The frequency of serious adverse events, however, was substantially higher in the combination groups.

Good to fair evidence exists from meta-analyses and large randomized controlled trials that abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, infliximab, and rituximab are significantly more efficacious than placebo for the treatment of rheumatoid arthritis. Treatment effects are large and consistent across studies. (See Table 6).

Table 6. Evidence profile of comparisons of targeted immune modulators for the treatment of rheumatoid arthritis

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall Grade of the evidence
Abatacept compared with Infliximab							
Outcome: Health outcomes							
1/ 431	RCT	Fair	NA	Direct evidence	Similar efficacy at 6 month ACR 50 response at 1 year: 45% vs. 36%	No dose increases for infliximab allowed	Moderate
Outcome: Radiographic progression							
No evidence							
Adalimumab compared with Etanercept							
Outcome: Health outcomes							
Direct: 1 / 356 Indirect: 4 /~ 2500	Prospective cohort study Meta-analyses and indirect comparisons of placebo-controlled trials	Good	Consistency between direct and indirect estimates	Mixed	Similar effects for ADA and ETA EULAR response: 78% vs. 80%	none	Low
Outcome: Radiographic progression							
No evidence							
Adalimumab compared with Infliximab							
Outcome: Health outcomes							
Direct: 1 / 418 Indirect: 4 / ~ 2500	Prospective cohort study Meta-analyses and indirect comparisons of placebo-controlled trials	Good	Inconsistent results between direct and indirect evidence	Mixed	Direct: EULAR response: 78% vs. 61% Indirect: no differences	none	Low
Outcome: Radiographic progression							
No evidence							
Anakinra compared with Adalimumab							
Outcome: Health outcomes							
Direct: 0	Meta-analyses and	Good	Yes	Indirect	ACR 50 response:	none	Low

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall Grade of the evidence
Indirect: 3 / ~ 2000	indirect comparisons of placebo-controlled trials			evidence	RR 0.64 (0.36-1.14)		
Outcome: Radiographic progression							
No evidence							
Anakinra compared with Etanercept							
Outcome: Health outcomes							
Direct: 0 Indirect: 3 / ~ 2000	Meta-analyses and indirect comparisons of placebo-controlled trials	Good	Yes	Indirect evidence	ACR 50 response: RR 0.41 (0.13-1.31)	none	Low
Outcome: Radiographic progression							
No evidence							
Anakinra compared with Infliximab							
Outcome: Health outcomes							
Direct: 0 Indirect: 3 / ~ 2000	Meta-analyses and indirect comparisons of placebo-controlled trials	Good	Yes	Indirect evidence	ACR 50 response: 0.69 (0.41-1.18)	none	Low
Outcome: Radiographic progression							
No evidence							
Etanercept compared with Infliximab							
Outcome: Health outcomes							
Direct 6 / 8435 Indirect: 5 / ~ 2500	1 open-label RCT 1 non-randomized controlled trial 4 prospective cohort studies	Good	Yes	Yes	ACR 20 response 74% vs. 60% HAQ improvements: -32.3 vs. -21.6	none	Moderate
Outcome: Radiographic progression							
ALL OTHER COMPARISONS							
No evidence							

ADA, adalimumab; ETA, etanercept; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; NA, not applicable; RCT, randomized controlled trial; RR, relative risk.

Study populations and outcome measures

All patients suffered from active rheumatoid arthritis and most randomized controlled trials employed the American College of Rheumatology criteria[4, 39] to classify the diagnosis of rheumatoid arthritis. Some trials, however, used stricter eligibility criteria. Disease duration and concomitant treatments also varied across studies. Most patients used non-steroidal anti-inflammatory drugs or oral corticosteroids in addition to the study medication. The majority of trials enrolled patients who had failed at least 1 disease-modifying antirheumatic drug treatment or were on a stable dose of methotrexate with unsatisfactory response.
Patients with an autoimmune disease other than rheumatoid arthritis, a history of active listeriosis or mycobacterial infection, or recent antibiotic treatment were generally excluded from studies.

All trials assessed response rates as defined by the American College of Rheumatology or by the European League Against Rheumatism. These scales (American College of Rheumatology 20/50/70, Disease Activity Score 28) combine measures of global disease activity with counts of tender and swollen joints and acute phase laboratory parameters (see Appendix E). In addition, most studies evaluated health outcomes such as quality of life, functional capacity (e.g., Short Form 36 Health Survey, Health Assessment Questionnaire, arthritis-specific health index), or discontinuation rates due to disease worsening.

Various observational studies enrolled primary care patients who started on targeted immune modulators treatment. Because these studies included unselected populations, findings are probably more applicable to the average rheumatoid arthritis patient than results from efficacy trials. Limitations with respect to internal validity have to be kept in mind though.

Sponsorship

All studies, except the non-randomized trial, 10 meta-analyses, and 5 cohort studies were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on comparative effectiveness

Overall we included 7 head-to-head studies comparing one targeted immune modulator to another.[31-36, 40]These direct comparisons, however, were limited to abatacept compared with infliximab, adalimumab and etanercept compared with infliximab, and adalimumab compared with etanercept. We could not find any head-to-head evidence for any of the other drugs. Included studies are summarized in Table 7.

Abatacept compared with infliximab

The only double-blinded head-to-head trial, the ATTEST (Abatacept or infliximab compared with placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis) study, was a fair randomized controlled trial that compared abatacept with infliximab in patients with inadequate response to methotrexate.[31] This study enrolled 431 patients and randomized them to abatacept (10 mg/kg every 4 weeks+ methotrexate), infliximab (3mg/kg every 8 weeks +methotrexate), or placebo. The primary outcome was assessed at 6 months followed by a double-blinded extension phase up to 1 year. No differences in efficacy were obvious between treatments at 6 months (DAS 28: abatacept -2.53, infliximab -2.25; *P*=NR) At 1 year, however, abatacept was statistically significantly more efficacious on most outcome measures than infliximab. For example, significantly more patients on abatacept than on infliximab achieved American College of Rheumatology 20/50 responses (American College of Rheumatology 20

response 72.4 compared with 55.8%; $P<0.001$; American College of Rheumatology 50 response 45.5 compared with 36.4%; $P<0.001$). Likewise, health related quality of life measures (Health Assessment Questionnaire Disability Index, Short Form 36 Health Survey) improved statistically significantly more with abatacept than with infliximab treatment. It has to be noted though, that infliximab was administered at a fixed dose regimen throughout the entire study. Infliximab efficacy trials have shown that up to 30% of patients require dose increases.

Adalimumab compared with etanercept

The evidence on the comparative effectiveness of adalimumab and etanercept is limited to 1 good observational study.[36] In a prospective cohort study based on the Dutch Rheumatoid Arthritis Monitoring (DREAM) register, investigators compared the effectiveness of adalimumab with etanercept for the treatment of rheumatoid arthritis in a primary care based population.[36] Eleven rheumatology centers in the Netherlands enrolled all rheumatoid arthritis patients who had at least moderate disease activity, had failed at least 1 conventional disease-modifying antirheumatic drug and started on an anti-tumor necrosis factor drug. The choice of the treatment and dosing was at the discretion of the treating rheumatologist. The primary outcome was the DAS28 course over a 12 months follow-up, as analyzed on an intention to treat basis. Overall, 916 patients were included, 707 (77%) patients had at least 1 year follow-up.

Discontinuation rates were similar in patients on adalimumab and etanercept (22% compared with 21%; P=NR). At study endpoint patients on adalimumab and etanercept had similar improvements of the DAS28 (-1.8 compared with -1.8; P=NR) and the Health Assessment Questionnaire (-0.42 compared with -0.35; P=NR).

Adalimumab compared with infliximab

The same prospective cohort study based on the Dutch DREAM register described above also compared the effectiveness of adalimumab with infliximab.[36] During the 1 year follow-up discontinuation rates were significantly higher in patients on infliximab than on adalimumab (31% compared with 22%; $P<0.049$). At study endpoint, patients treated with adalimumab had statistically significantly better improvements on the DAS28 (-1.8 compared with -1.2; $P < 0.05$) and the Health Assessment Questionnaire (-0.42 compared with -0.26; $P< 0.05$).

Etanercept compared with infliximab

The only study for this comparisons with a randomized allocation of interventions was a fair, small (n=32) open-label randomized controlled trial that compared etanercept (25mg twice weekly) with infliximab (3mg/kg, weeks 0, 2, 6 and every 2 months).[33] Patients in this trial had confirmed rheumatoid arthritis for longer than 2 years, did not respond adequately to disease-modifying antirheumatic drugs, and were on a stable dose of methotrexate (10-12 mg/week). Although infliximab had a faster onset of action than etanercept, more patients on etanercept achieved American College of Rheumatology 20 response after 54 weeks (74.4% compared with 60%; P=NR). The same pattern existed for Health Assessment Questionnaire (-32.3 compared with -21.6: P=NR). The study did not assess discontinuation rates or adverse events and did not report data on American College of Rheumatology 50 or American College of Rheumatology 70. Because the sample size of this trial was small, chance findings are likely.

In addition we identified 4 observational studies[34-36, 40] and 1 non-randomized trial.[32] With respect to the comparative efficacy of etanercept and infliximab, these studies reported similar findings as the head-to-head trial mentioned above.

For example, in the non-randomized, open-label trial, a Swedish population-based study that assessed the efficacy and safety of etanercept (n = 166), infliximab (n = 135), and leflunomide (n = 103), etanercept had significantly greater American College of Rheumatology 20 response rates at 3 months (data NR; $P<0.02$) and 6 months (data NR; $P<0.05$), and greater American College of Rheumatology 50 response rates at 6 months (data NR; $P<0.005$) than infliximab.[32] Comparisons at other time points, generally favored etanercept over infliximab although most differences failed to achieve statistical significance, which is probably primarily attributable to a lack of power.

The four observational studies were based on data collected for registries in the Netherlands,[36] Sweden,[35] the United Kingdom,[40] and the United States.[34] These studies, therefore, reflect populations that are treated in daily clinical practice. Overall, results were consistent with findings mentioned above. In all of these studies etanercept led to numerically greater response rates than infliximab after up to 3 years of follow-up. One study reported that steroid withdrawal rates did not differ between etanercept and infliximab.[35]

The largest of these observational studies was a prospective cohort study based on the Rheumatoid Arthritis DMARD (disease-modifying antirheumatic drug) Intervention and Utilization Study program.[34] This multicenter (509 rheumatology practices in the United States) registry enrolled patients who required changes in their rheumatoid arthritis treatment regimens. Data on 3034 patients on etanercept and 660 patients on infliximab were available for analysis after 12 months of follow up. Etanercept-treated patients had numerically greater response rates on the modified American College of Rheumatology 20 (the modified American College of Rheumatology 20 omits erythrocyte sedimentation rate and C-reactive protein because they are infrequently measured in clinical practice) than infliximab-treated patients (etanercept + methotrexate: 43%; etanercept monotherapy: 41%; infliximab + methotrexate: 35%; infliximab monotherapy: 26%; P=NR).

A well-conducted retrospective cohort study did not meet our eligibility criteria; nevertheless we are presenting findings because this study was the only one that compared radiographic progression between etanercept and infliximab.[41] 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 disease-modifying antirheumatic drugs and etanercept and disease-modifying antirheumatic drugs did not present statistically significant differences in progression of erosion (Ratingen score; data NR; $P=0.07$) after a mean follow-up of 1.7 years. The combination of infliximab and disease-modifying antirheumatic drugs led to statistically significantly lower joint space narrowing than etanercept and disease-modifying antirheumatic drugs (data NR; $P<0.001$). This difference, however, was not obvious when the analysis was limited to methotrexate as the concomitant disease-modifying antirheumatic drug.

Targeted immune modulators combination strategies

Two trials determined the potential for additive or synergistic effects of combination therapy of 2 targeted immune modulators.[37, 38] The largest study, a 24-week randomized controlled trial, 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.[37] Overall, 242 patients who were on stable doses of methotrexate 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%

for 50 mg etanercept plus anakinra, 4.9% for 25 mg etanercept plus anakinra, and 2.5% for etanercept only; *P*=NR). Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6% compared with 7.4%; *P*=NR).

The second study, examining a combination of abatacept (2 mg/kg) and etanercept (25mg twice weekly) compared with abatacept (2mg/kg) monotherapy reached similar conclusions.[38] The combination was associated with increased serious adverse events but only limited additional clinical benefit

Table 7. Summary of head-to-head studies in adult patients with rheumatoid arthritis

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Abatacept compared with infliximab									
Schiff et al., 2008[31]	RCT	431	12 months	ABA vs. INF	DAS 28	ACR 20/50/70, HAQ, SF-36	Active RA for at least 1 year; had failed MTX treatment; mean disease duration: 7.9 yrs.	Greater response rates with ABA than with INF at study endpoint	Fair
Adalimumab compared with infliximab									
Kievit et al., 2008[36]	Prospective cohort study	418	12 months	ADA vs. INF	DAS 28	SF-36	Population-based; active RA; started a biologic; mean disease duration: 6.5 yrs.	Improvements on DAS 28 and SF-36 physical component statistically significantly better for ADA than for INF	Good
Adalimumab compared with etanercept									
Kievit et al., 2008[36]	Prospective cohort study	556	12 months	ETA vs. INF	DAS 28	SF-36	Population-based; active RA; started a biologic; mean disease duration: 6.5 yrs.	DAS 28 and SF-36 physical component statistically similar between ADA and ETA	Good
Etanercept compared with infliximab									
De Fillipis et al, 2006[33]	Open-label randomized controlled trial	32	12 months	ETA vs. INF	ACR 20	ACR 50/70, HAQ	Active RA for at least 2 years; had failed MTX treatment; mean disease duration: NR.	ACR response rates and HAQ higher for ETA than for INF at 12 months	Fair
Geborek et al. 2002[32]	Non-randomized trial	301	12 months	ETA vs. INF	ACR 20/50	DAS28	Population-based; active RA; had failed at least 1 DMARD treatment; mean disease duration: 14.5 yrs.	ACR 20 response rates significantly greater for ETA than for INF at 3 months (P<0.02) and 6 months (P<0.05); no differences at 12 months	Fair
Hyrich et al, 2006[40]	Prospective cohort study	3694	6 months	ETA vs. INF	EULAR	DAS 28	Population-based; active RA; started a biologic; mean disease duration: 14.6 yrs.	EULAR response rates numerically greater for ETA than for INF at 6 months	Fair
Kievit et al., 2008[36]	Prospective cohort study	440	12 months	ETA vs. INF	DAS 28	SF-36	Population-based; active RA; started a biologic; mean disease duration: 6.5 yrs.	DAS 28 and SF-36 physical component statistically significantly better for ETA than INF (P<0.001)	Good
Kristensen et al. 2006[35]	Prospective cohort study	949	3 years	ETA vs. , INF	EULAR	ACR 20/50/70	Population-based; active RA; started a biologic; mean disease duration: 13.4 yrs.	Moderate EULAR and ACR response rates numerically greater for ETA than for INF at 3 years	Fair

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Weaver et al. 2006[34]	Prospective cohort study	3694	12 months	ETA vs. INF	mACR 20	HAQ	Primary-care based; active RA; patients who needed change in treatment regimen; mean disease duration: NR	mACR 20 response rates numerically greater for ETA than for INF at 12 months	Fair
Combination strategies									
Genovese et al., 2004[37]	RCT	242	24 weeks	ETA+MTX vs. ETA+ANA+MTX	ACR 50	ACR 20/70, SF-36	> 6 months history of active RA; stable MTX regimen; mean disease duration: 10 yrs.	No additional benefit from ETA-ANA combination therapy; Adverse events rates significantly higher in combination than in ETA group	Fair
Weinblatt et al., 2007[38]	RCT	121	6 months	ABA +ETA vs. ETA	ACR 20	ACR 50/70, HAQ	Chronic RA: on ETA for at least 3 months; mean disease duration: 12.9 yrs	No additional benefit from ABA-ETA combination therapy; Adverse events rates significantly higher in combination than in ABA group	Fair

ABA, abatacept; ACR 20/50/70, American College of Rheumatology, numbers refer to percentage improvement; ADA, adalimumab; ASHI, arthritis-specific health index; DAS28, disease activity score28; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; INF, infliximab; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Short Form 36 Health Survey.

Detailed assessment: Indirect evidence on the comparative effectiveness

Because of the lack of direct head-to-head evidence for most comparisons, we conducted adjusted indirect comparisons based on meta-analyses of placebo-controlled trials to compare the treatment effects of individual targeted immune modulators. We included data from published studies or from the Center for Drug Evaluation Research website. For all analyses we used only data derived from study arms at or near the recommended dosage. Appendix F summarizes studies included for indirect comparisons.

We chose American College of Rheumatology 50 as the outcome measure because a 50% improvement is likely to translate to a clinically significant improvement in health-related quality of life. For example, a patient with 12 swollen and 8 tender joints at baseline would need to have fewer than 6 swollen and 4 tender joints at the trial endpoint. This would be accompanied by at least a 50% improvement in at least 3 of the following 5 measures: the patient's assessment of pain, the patient's assessment of global disease activity, the physician's assessment of global disease activity, the Health Assessment Questionnaire Disability Index, and either a C-reactive protein or sedimentation rate (Westergren erythrocyte sedimentation rate).

The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[26] Included targeted immune modulator-studies primarily differ in study duration, disease duration, concomitant treatments, and some other baseline characteristics. Differences in study durations did not appear to be a factor altering the effect size. We included only studies of more than 3 months of study duration, however we did not limit by sample size. Most randomized controlled trials reported the onset of significant responses between 4 and 8 weeks. Treatment responses were sustained up to 2 years in open-label extension studies. Sensitivity analyses based on different study durations did not substantially change the point estimates of the treatment effect. Likewise, sensitivity analyses excluding studies without concomitant methotrexate treatment, or studies on patients with early rheumatoid arthritis, did not substantially change the point estimate. One exception was the sensitivity analysis of infliximab where removing a study on patients with early rheumatoid arthritis[42] substantially changed the effect size. However, it was unclear if this effect was attributable to true heterogeneity or to a lesser influence of random error in this large trial. Results presented below exclude this study. Overall, diagnostic criteria and eligibility criteria appeared to be sufficiently similar to make adjusted indirect comparisons a reasonable approach. However, given the small number of studies and the subsequent lack of precision, results should still be interpreted cautiously.

Results of adjusted indirect comparisons are depicted in Table 8; corresponding forest plots for meta-analyses are presented in Appendix F. Findings suggest that no substantial differences exist among the efficacy of adalimumab, etanercept, and infliximab. However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty. Confidence intervals encompass differences that would be clinically significant. More data is needed to increase the precision of these estimates.

Point estimates favor adalimumab, etanercept, and infliximab over anakinra. However, differences do not reach statistical significance in adjusted indirect comparisons which is likely attributable to a lack of power. Figure 2 depicts results of adjusted indirect comparisons of anakinra with adalimumab, etanercept, infliximab, and anti-tumor necrosis factor drugs as a class.

The evidence on abatacept, certolizumab pegol, and rituximab was insufficient or too heterogeneous to be included for indirect comparisons. Using information from placebo-

controlled trials, 5 research groups used various statistical models to produce indirect comparisons of treatment effects of targeted immune modulators.[43-47] Overall, all but 1 study[44] concluded that anti-tumor necrosis factor drugs have similar efficacy and that anakinra is less effective than adalimumab, etanercept, and infliximab. Table 9 summarizes studies that conducted indirect comparisons.

Figure 2. Adjusted indirect comparisons of anakinra with anti-tumor necrosis factor drugs for American College of Rheumatology 50 response

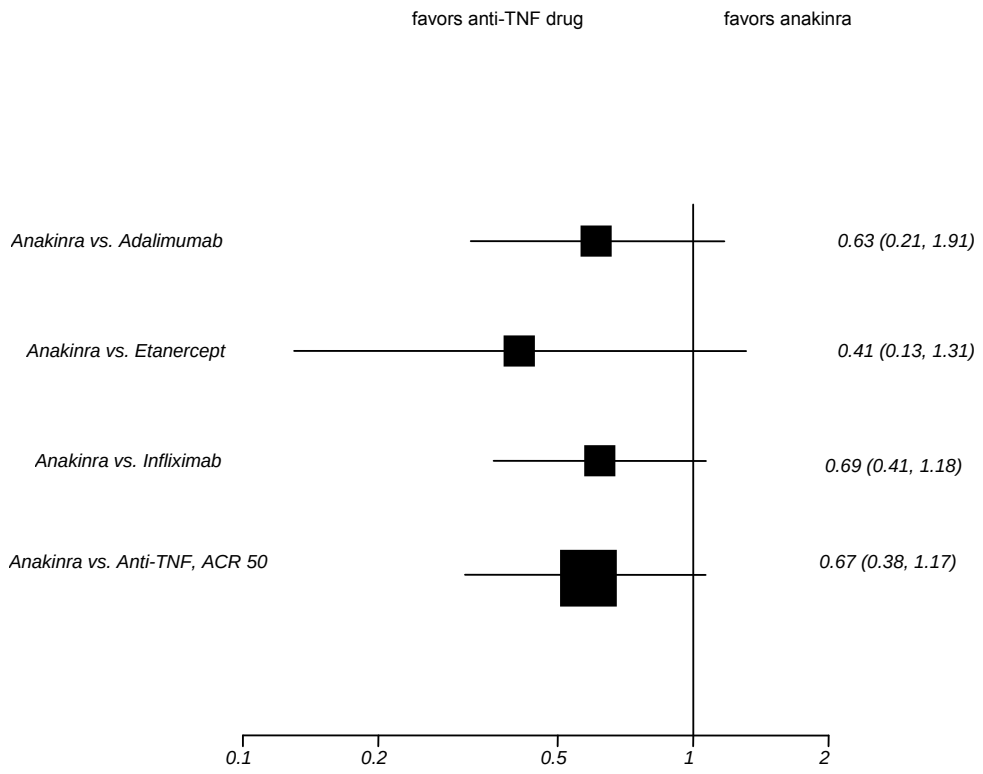


Table 8. Adjusted indirect comparisons of targeted immune modulators for the treatment of rheumatoid arthritis

Comparison	Relative risk (95% CI) for American College of Rheumatology 50 response
Adalimumab vs. etanercept	0.63 (0.21 to 1.91)
Adalimumab vs. infliximab	1.07 (0.73 to 1.58)
Anakinra vs. adalimumab	0.64 (0.36 to 1.14)
Anakinra vs. etanercept	0.41 (0.13 to 1.31)
Anakinra vs. infliximab	0.69 (0.41 to 1.18)
Etanercept vs. infliximab	1.69 (0.57 to 5.01)

Table 9. Characteristics and results of studies conducting indirect comparisons

Author Year	Comparisons	Primary outcome	Conclusion	Rating
Clark et al. 2004[47]	AKA, ETA, INF	ACR 20/50/70	Anakinra is less effective than etanercept and infliximab	Good
Hochberg et al. 2003[46]	ADA, ETA, INF	ACR 20/50	Anakinra is the least effective therapy. No differences among anti-tumor necrosis factor drug in efficacy	Fair
Lee et al. 2008[44]	ADA, ETA, INF	ACR 20/50,70, withdrawal	Adalimumab and infliximab are more efficacious than etanercept	Fair
Nixon et al. 2007[43]	ADA, AKA, ETA, INF	ACR 20/50, HAQ	Anakinra is the least effective therapy. No differences among anti-tumor necrosis factor drug in efficacy	Fair
Wailoo et al. 2006[45]	ADA, AKA, ETA, INF	ACR 20/50, HAQ	Anakinra is the least effective therapy. No differences among anti-tumor necrosis factor drug in efficacy	Good

ACR 20/50/70; ADA, adalimumab; AKA, Anakinra; INF, infliximab; ETA, etanercept.

Detailed assessment: Evidence on the general efficacy

Multiple placebo-controlled randomized controlled trials and meta-analyses provide evidence on the general efficacy of abatacept,[48-55] adalimumab,[56-67] anakinra,[47, 68-73] certolizumab pegol,[74] etanercept,[40, 56, 57, 75-90] infliximab,[42, 56, 57, 76, 77, 91-101 102, 103] and rituximab.[104-110] Most of these studies were conducted in patients who had failed synthetic disease-modifying antirheumatic drug treatment.

We have summarized evidence on the general efficacy of targeted immune modulators in the treatment of rheumatoid arthritis. This, however, does not provide evidence on the comparative efficacy and tolerability of targeted immune modulators. If we identified high quality meta-analyses, we report the pooled estimates but do not describe the results of individual component studies, except when outcome measures of interest are reported (e.g., quality of life, functional capacity) that were not quantitatively analyzed in a meta-analysis. Table 10 summarizes studies included for general efficacy.

Abatacept

Five trials examined the efficacy of abatacept in patients with rheumatoid arthritis (8 publications).[48-55, 111] The largest study was a good multi-national trial enrolling 652 patients with

methotrexate-resistant rheumatoid arthritis.[51] After 1 year of follow-up, abatacept (10 mg/kg) led to statistically significant improvements on all outcome measures (American College of Rheumatology 20/50/70, Health Assessment Questionnaire Disability Index, DAS28, Short Form 36 Health Survey, Genant modified Sharp scores). At 1 year, 48.3% of abatacept- and 18.2% of placebo-treated patients achieved an American College of Rheumatology 50 response ($P<0.001$), 28.8% compared with 6.1% achieved an American College of Rheumatology 70 response ($P<0.001$). Abatacept-treated patients showed statistically significant slowing of structural damage progression on the Genant modified Sharp score compared with those on placebo (0.0 compared with 0.27; 0.029). Two phase II studies[48-50, 53] and a phase III study[111] reported similar findings.

A good 6-month trial was conducted in patients with an inadequate response to anti-tumor necrosis factor treatment (etanercept or infliximab).[54] After 6 months of treatment, abatacept led to statistically significant improvement on all outcome measures compared to placebo (American College of Rheumatology 20/50/70, DAS28, Health Assessment Questionnaire, Short Form 36 Health Survey).

Adalimumab

Three well-conducted meta-analyses examined the efficacy of adalimumab in patients with rheumatoid arthritis.[56-58] Overall these studies included data on 2390 patients. Pooled results presented statistically significantly greater improvements of adalimumab- than placebo-treated patients on all outcome measures (American College of Rheumatology 20/50/70, DAS 28). The numbers needed to treat to achieve 1 additional responder on American College of Rheumatology 20/50/70 were 3, 4, and 6, respectively.[58]

Two placebo-controlled trials in Asian patients, not included in the meta-analyses mentioned above reported similar findings.[66, 67]

Anakinra

We identified 2 high quality meta-analyses on the general efficacy of anakinra.[47, 69] The more recent study included information on 2876 patients.[69] Pooled results presented statistically significantly greater improvements of anakinra- than placebo-treated patients on all outcome measures (American College of Rheumatology 20/50/70, Health Assessment Questionnaire, Patient Global Assessment). The numbers needed to treat to achieve 1 additional responder on American College of Rheumatology 20/50/70 were 8, 9, and 22, respectively.

Certolizumab pegol

The RAPID (Rheumatoid Arthritis Prevention of Structural Damage) 1 trial, examined the general efficacy of certolizumab pegol for the treatment of rheumatoid arthritis.[74] This trial randomized 982 patients with active rheumatoid arthritis despite methotrexate treatment to certolizumab pegol (200mg or 400mg) and methotrexate or placebo and methotrexate. In consideration of the disease severity in these patients, the protocol determined that all patients who did not achieve an American College of Rheumatology 20 response between weeks 12 to 14 were determined treatment failures and had to withdraw from the study at week 16. Consequently, 62.8% of placebo-treated patients withdrew because of lack of efficacy compared with 21.1% and 17.4% of patients in the groups receiving certolizumab pegol 200mg and 400mg, respectively. At week 12 significantly more patients on the certolizumab pegol regimens achieved American College of Rheumatology 20/50/70 responses than patients on placebo (data not reported). Because of the high withdrawal rates (overall 58%) any subsequent data analyses

must be interpreted cautiously because selection bias is very likely to occur with such high drop-out rates. At week 24, using non-responder imputation, the American College of Rheumatology 20 response rates were 58.8%, 60.8%, and 13.6% for patients treated with certolizumab pegol 200mg, certolizumab pegol 400mg, and placebo, respectively. Likewise, patients on certolizumab pegol had greater DAS-28 improvements, physical function and Health Assessment Questionnaire Disability Index values than patients on placebo.

Two additional placebo-controlled trials on the efficacy and safety of certolizumab pegol have been published since our final literature search. The RAPID 2[112] and the FAST4WARD (for efficacy and safety of certolizumab pegol – 400mg Q4 weeks as monotherapy)[113] trials are not included in this report but both confirm the general efficacy and safety of certolizumab pegol for the treatment of rheumatoid arthritis.

Etanercept

Four well-conducted meta-analyses examined the efficacy of etanercept in patients with rheumatoid arthritis.[56, 75-77] All studies reported significantly greater improvements for etanercept-treated patients at study endpoint. Pooled results indicated that 39% of patients treated with the recommended dose of 50 mg etanercept per week reached an American College of Rheumatology 50 response, compared to 4% of patients on placebo (relative risk, 8.89; 95% CI, 3.61 to 21.89).[75] The number needed to treat to achieve 1 additional American College of Rheumatology 50 response was 3.

One trial compared etanercept to methotrexate over 52 weeks in patients with early active disease.[83] Although the study failed to show statistically significant differences between etanercept (25 mg twice weekly) and methotrexate (20 mg/week) in health outcome measures (Short Form 36 Health Survey, Health Assessment Questionnaire, arthritis-specific health index), and American College of Rheumatology response rates at study endpoints (52 weeks), radiographic outcomes were significantly better in patients on etanercept than on methotrexate. Improved radiographic outcomes were maintained during an extension of the Early Rheumatoid Arthritis trial to 24 months.[84]

Infliximab

Four well-conducted meta-analyses determined the general efficacy of infliximab in rheumatoid arthritis.[56, 57, 76, 93] Pooled results of all 4 studies report significantly greater improvements of patients on infliximab than on placebo for all outcome measures. For 10 mg infliximab every 8 weeks, the American College of Rheumatology 50 response rate was 30% compared to 5% for placebo. The number needed to treat to achieve 1 additional response was 4. Two recent randomized controlled trials not included in the meta-analyses provide similar results.[97, 103]

Rituximab

Three fair, 24-week studies assessed the general efficacy of rituximab for the treatment of patients with disease-modifying antirheumatic drug resistant rheumatoid arthritis.[104, 106, 108-110] All 3 trials reported statistically significantly greater response rates for rituximab- than for placebo treated patients. In the largest trial (n = 520), rituximab regimens (2 x 1000 mg) led to statistically significantly greater response rates on American College of Rheumatology 20 than placebo (51% compared with 18%; $P<0.0001$).[108-110] Likewise, patients on rituximab achieved statistically significantly greater responses on American College of Rheumatology 50 (27% compared with 5%; $P<0.001$) and American College of Rheumatology 70 (12% compared with 1%; $P<0.001$) Furthermore, patients treated with rituximab had greater and statistically

significant improvements in patient-reported outcomes (Health Assessment Questionnaire Disability Index, Short Form 36 Health Survey, Functional Assessment of Chronic Illness Therapy – Fatigue Subscale) than patients on placebo.

Table 10. Studies included for general efficacy in rheumatoid arthritis

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ABATACEPT									
Genovese et al. 2005[54, 55]	RCT	391	6 months	ABA + DMARD vs. Placebo + DMARD	ACR 20, HAQ	DAS28, ACR 50/70 SF-36	Patients who had an inadequate response to etanercept or infliximab; mean disease duration: 11.9 yrs.	Statistically significantly greater improvements on all outcome measures for ABA	Good
Kremer et al. 2006[51, 52]	RCT	652	12 months	ABA + MTX vs. Placebo + MTX	ACR 20	HAQ-DI, ACR 50/70, radiographic evaluation	Active RA for at least 1 year; had failed MTX treatment; mean disease duration: 8.7 yrs.	Statistically significantly greater improvements on all outcome measures for ABA	Fair
Kremer et al. 2005[48-50]	RCT	339	12 months	ABA + MTX vs. Placebo + MTX	ACR 20	ACR 50/70 DAS28, HAQ	Active RA for at least 6 months with a stable dose of MTX; mean disease duration: 9.4 yrs.	Statistically significantly greater improvements on all outcome measures for ABA	Fair
ADALIMUMAB									
Alonso-Ruiz et al. 2008[57]	MA	2869	varying	ADA+MTX vs. Placebo+MTX	ACR 20/50/70	Withdrawals	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with ADA than with placebo	Good
Chen et al. 2006[56]	MA	9869	varying	ADA+MTX vs. Placebo+MTX	ACR 20/50/70	Cost effectiveness	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with ADA than with placebo	Good

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Kim et al. 2007[66]	RCT	128	24 weeks	ADA+MTX vs. Placebo+MTX	ACR 20	ACR 50/70	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 6.9 yrs.	ACR 20/50/70 response rates significantly greater with ADA than with placebo	Fair
Miyasaka et al. 2008[67]	RCT	352	24 weeks	ADA vs. Placebo	ACR 20	ACR 50/70, HAQ	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 9.5 yrs.	ACR 20/50/70 response rates significantly greater with ADA than with placebo	Fair
Navarro-Sarabaia et al. 2006[58]	MA	2390	52 weeks	ADA+MTX vs. Placebo+MTX	ACR 20/50/70	DAS 28, safety	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 9.5 yrs.	ACR 20/50/70 response rates significantly greater with ADA than with placebo	Good
ANAKINRA									
Clark et al. 2004[47]	MA	1007	6 mo	AKA + MTX vs. Placebo+MTX	ACR 20/50/ 70	HAQ	Adults with RA	ACR 20/50/70 response rates significantly greater with AKA than with placebo;	Good
Mertens et al. 2009[69]	MA	2876	6 mo	AKA + MTX vs. Placebo+MTX	ACR 20/50/ 70	HAQ, withdrawals	Adults with RA	ACR 20/50/70 response rates significantly greater with AKA than with placebo;	Good
CERTOLIZUMAB PEGOL									
Keystone et al. 2008(RAPID 1)[74]	RCT	982	52 weeks	CER +MTX vs. Placebo+ MTX	ACR 20	ACR 50/70, HAQ, DAS-28	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with CER than with placebo	Fair

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT									
Alonso-Ruiz et al. 2008[57]	MA	1637	varying	ETA+MTX vs. Placebo+MTX	ACR 20/50/70	Withdrawals	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with ETA than with placebo	Good
Bathon et al. 2000[83-85]	RCT	632	52 weeks	ETA vs. MTX	ACR 20/50/ 70	SF-36, HAQ, ACR-N, modified Sharp	early, active RA; mean disease duration: 1 yr.	Up to 6 months significantly higher ACR 50/70 response rates for ETA than for MTX; no differences after. At 12 months no differences in ACR 20 but less joint erosion for ETA; no significant differences in SF-36, HAQ, and ASHI scores	Fair
Blumenauer et al. 2003[75]	MA	955	> 6 mo	ETA+MTX vs. Placebo+MTX	ACR 20/50/ 70	Safety	Adults with RA	ACR 20/50/70 response rates significantly greater with ETA than with placebo	Good
Chen et al. 2006[56]	MA	3717	varying	ETA+MTX vs. Placebo+MTX	ACR 20/50/ 70	Cost effectiveness	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with ETA than with placebo	Good
Suarez-Almazor et al. 2007[77]	MA	1521	varying	ETA + MTX vs. Placebo + MTX	ACR 20/50/ 70	Safety	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with ETA than with placebo	Good
INFLIXIMAB									
Abe et al. 2006[97]	RCT	147	14 weeks	INF+MTX vs.Placebo+MTX	ACR 20/50/ 70	Safety	> 6 months history of active RA; stable MTX regimen; mean dis. duration: 7.9 yrs.	ACR 20/50/70 response rates at 14 weeks significantly greater with INF than with placebo	Fair

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Alonso-Ruiz et al. 2008[57]	MA	2581	varying	INF+MTX vs. Placebo+MTX	ACR 20/50/70	Withdrawals	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with INF than with placebo	Good
Blumenauer et al. 2002[93]	MA	529	6mo	INF+MTX vs. Placebo	ACR 20/50/ 70	Withdrawals, safety	Adults with RA	ACR 20/50/70 response rates significantly greater with INF than with placebo	Good
Suarez-Almazor et al. 2007[77]	MA	IFX (1,113 IFX, 408 control)	varying	IFX + MTX vs. MTX	ACR 20/50/ 70	NR	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates significantly greater with INF than with placebo	Good
Zhang et al. 2006[103]	RCT	173	18 weeks	INF + MTX vs. Placebo+MTX	ACR 20/50/70	NR	Adult outpatients with active RA and insufficient response to standard antirheumatic therapy	ACR 20/50/70 response rates were significantly greater with INF+MTX than with MTX	Fair
RITUXIMAB									
Cohen et al. 2006 (REFLEX)[108-110]	RCT	520	24 weeks	RIT + MTX vs. Placebo+ MTX	ACR 20	ACR 50/70, DAS 28, HAQ SF-36	Active RA; had failed anti-tumor necrosis factor therapy; mean disease duration: 11.9 yrs.	ACR 20/50/70 response rates and DAS-28 scores were significantly greater with RIT+MTX than with MTX	Fair
Edwards et al. 2004[104, 105]	RCT	161	24 weeks	RIT + MTX vs. RIT + placebo vs. RIT+ cyclophosphamide vs. MTX + placebo	ACR 50	ACR 20/70, DAS28	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 10.5	ACR 20/50/70 response rates and DAS28scores were significantly greater with RIT+MTX than with MTX + placebo	Fair

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
							yrs.		
Emery et al. 2006 (DANCER)[106]	RCT	465	24 weeks	RIT (500mg)+ MTX vs. RIT (1000mg) + MTX vs. MTX + placebo	ACR 50	ACR 20/70, DAS28	Active RA; had failed at least 1 DMARD or biologic treatment; RF-positive; mean disease duration: 10.4 yrs.	ACR 20/50/70 response rates and DAS28 scores were significantly greater with RIT+MTX than with MTX+ placebo	Fair

ABA, abatacept; ACR 20/50/70, American College of Rheumatology, numbers refer to percentage improvement; ACR-N, numeric index of the American College of Rheumatology response; ADA, adalimumab; AKA, anakinra; ASHI, arthritis-specific health index; CER, certolizumab pegol; DAS28, disease activity score; DMARD, disease-modifying antirheumatic drug ; ETA, etanercept; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; INF, infliximab; MA, meta-analysis; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; RIT, rituximab; RF, rheumatoid factor; SF-36, Medical Outcomes Study Short Form 36 Health Survey.

Juvenile Idiopathic Arthritis

Currently abatacept, adalimumab and etanercept are approved by the US Food and Drug Administration for the treatment of juvenile idiopathic arthritis.

Summary of findings

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of juvenile idiopathic arthritis exists (Table 11). Four randomized controlled trials provide fair evidence that abatacept,[114] adalimumab,[115] etanercept,[116] and infliximab[117] are more efficacious than placebo for the treatment of juvenile idiopathic arthritis. Except for the infliximab trial, however, the highly selected study populations are likely to compromise the external validity of these studies. Some of these studies did not meet our formal eligibility criteria. Because these studies are the only available randomized controlled evidence on some drugs, we are still presenting main findings. Included studies are presented in Table 12.

Table 11. Evidence profile of comparisons of targeted immune modulators for the treatment of juvenile idiopathic arthritis

Number of studies/patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							
Outcome: Radiographic progression							
No evidence							
Outcome: Safety							
No evidence							

Study populations and outcome measures

Patients suffered from active polyarticular juvenile idiopathic arthritis and were between 4 and 17 years of age. They had active disease despite treatment with corticosteroids and methotrexate. Patients with concurrent medical conditions or systemic juvenile idiopathic arthritis were excluded from trials. Except for the infliximab trial, all studies used withdrawal designs. After a run-in period with the active drug, only patients who responded, adhered to treatment, and had no intolerable adverse events were randomized to continuing active treatment or placebo. The primary outcome measure in the randomized controlled trials was the number of patients with disease flare. Disease flare was defined as a worsening of 30% or more in at least 3 of the 6 criteria of the American College of Rheumatology Pediatric scale or the Giannini criteria. Additional outcome measures were the articular severity score, duration of morning stiffness, degree of pain, and C-reactive protein.

Sponsorship

All studies were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on the comparative effectiveness

We did not find any head-to-head trials for the treatment of juvenile idiopathic arthritis.

Detailed assessment: Indirect evidence on the comparative effectiveness

We did not find any studies indirectly comparing the effectiveness of targeted immune modulators for the treatment of juvenile idiopathic arthritis.

Detailed assessment: Evidence on the general efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. In the following sections we have summarized evidence on the general efficacy of targeted immune modulators for the treatment of juvenile idiopathic arthritis.

Abatacept

A fair withdrawal study enrolled 190 patients with active juvenile idiopathic arthritis who had failed at least 1 disease-modifying antirheumatic drug or an anti-tumor necrosis factor drug (adalimumab, etanercept, or infliximab).[114] After 4 months of an open-label run-in phase with abatacept 10mg/kg, 122 patients were randomized to continuing abatacept treatment or placebo. Patients who did not respond or adhere to treatment or who had intolerable adverse events (45% of the original population) were excluded from the randomized trial phase, which will likely compromise the applicability of findings. The primary outcome measure was time to flare of arthritis. Flare was defined as a worsening of 30% or more in at least 3 of 6 core response variables. After 6 months significantly fewer children on abatacept than on placebo had experienced disease flares. Overall, 53% of patients on placebo and 20% of patients on abatacept experienced a flare (P=0.0003).

Adalimumab

One randomized controlled trial, employing the same withdrawal design as described for the abatacept study, randomized 133 patients with juvenile idiopathic arthritis to adalimumab (24 mg per square meter of body surface every other week) or placebo.[115] After the run-in phase 22% of patients were excluded from proceeding to the randomized phase. The primary outcome measure during the double-blinded randomized phase was disease flare during a follow-up period of 32 weeks. Among patients not receiving methotrexate, 43% on adalimumab and 71% on placebo experienced a disease flare within 16 weeks (P=0.03). Among patients receiving methotrexate, flares occurred in 37% of those on adalimumab and in 65% of those receiving placebo (P=0.02).

Etanercept

One fair withdrawal study randomized 51 patients to etanercept (0.4 mg/kg twice weekly) or placebo.[116] After 4 months, significantly more patients on placebo than on etanercept experienced a disease flare (81% compared with 28%; P<0.003). The median time to flare was 116 days for etanercept- and 28 days for placebo- treated patients (P<0.001). As stated above, the randomized trial was preceded by an active run-in phase. Only patients who adhered and responded to treatment, and had no intolerable adverse events entered the randomized phase. The applicability of results of this highly selected population to the average patient with juvenile idiopathic arthritis is likely to be low.

During the 3-month open-label run-in phase, 64% of patients achieved a 50% improvement of symptoms based on the Gianinni criteria. Nevertheless, the response rates of patients during the open-label run-in phase were comparable with those of patients from a retrospective analysis of data of 322 patients treated with etanercept from a German registry.[118] In this study, which did not meet our eligibility criteria, 61% had a 50% improvement of symptoms at 3 months and 72% at 6 months. However, patients in this analysis were not limited to polyarticular juvenile idiopathic arthritis. The mean length of treatment in this study was 13.4 months. At 1 year, 82% of the non-systemic patients presented a 50% improvement. Subgroup analysis showed markedly lower response rates in patients with systemic arthritis.

Infliximab

One fair randomized controlled trial randomized 122 patients with polyarticular juvenile idiopathic arthritis to infliximab (3mg/kg) + methotrexate and placebo + methotrexate.[117] This was the only study conducted in pediatric patients that did not use a withdrawal design. After 14 weeks numerically more patients on infliximab than on placebo achieved the American College of Rheumatology Pediatric Scale 30 criteria for improvement, which was the primary outcome measure of this study (64% compared with 39%). This difference, however, did not achieve statistical significance (P=0.12). Similarly, patients on infliximab had numerically greater American College of Rheumatology Pediatric Scale 50/70 responses than patients on placebo, without statistical significance.

Table 12. Summary of efficacy trials in patients with juvenile idiopathic arthritis

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality Rating
ABATACEPT									
Ruperto et al. 2008[114]	Withdrawal RCT	122	6 months	ABA vs. placebo	Disease flare	Safety	Active juvenile idiopathic arthritis; had failed at least 1 DMARD or anti-tumor necrosis factor drug; mean disease duration: NR	Significantly fewer patients on ABA than on placebo experienced disease flare	Fair
ADALIMUMAB									
Lovell et al. 2008[115]	Withdrawal RCT	133	4 months	ADA vs. placebo	Disease flare	ACR Pedi 30/50/70	Active juvenile idiopathic arthritis; had failed at least 1 DMARD; mean disease duration: 3.8 yrs	Significantly fewer patients on ADA than on placebo experienced disease flare	Fair
ETANERCEPT									
Lovell et al. 2000[116]	Withdrawal RCT	51	4 months	ETA vs. Placebo	Response based on Gianinni criteria; number of patients with disease flare	Articular severity score, pain, CRP	Active polyarticular JRA; had failed corticosteroid and MTX treatment; mean disease duration: 5.8 yrs.	Significantly fewer patients on ETA than on placebo experienced disease flare	Fair
INFLIXIMAB									
Ruperto; et al. 2007[117]	RCT	122	3.5 months	INF + MTX vs. Placebo + MTX	Response based on ACR Pedi 30	ACR Pedi 50/ 70, safety	Active juvenile idiopathic arthritis; had failed at least 1 DMARD; mean disease duration: 4 yrs	Numerically greater response for patients on INF than on placebo; no statistical significance	Fair

ABA, abatacept; ACR Pedi, American College of Rheumatology Pediatric criteria; ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; MTX, methotrexate

Ankylosing Spondylitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ankylosing spondylitis: adalimumab, etanercept, and infliximab. We found 2 placebo-controlled trials; 1 trial assessed the efficacy of adalimumab[119-121] and 1 trial assessed the efficacy of etanercept.[122, 123] There is a systematic review and meta-analysis that examines adalimumab, etanercept, and infliximab compared with placebo and also completes indirect comparisons of the same 3 treatments.[124] We did not detect any studies on abatacept, alefacept, anakinra, certolizumab pegol, natalizumab, and rituximab. Included studies are presented in Table 14.

Summary of the findings

No direct evidence on the comparative effectiveness of targeted immune modulators for the treatment of ankylosing spondylitis exists. The best available evidence on the comparative effectiveness stems from a meta-analysis with indirect comparisons of placebo-controlled trials.[124] This study indicated that the any of the 3 drugs were more effective than placebo but did not show any differences among the active treatments.

Additional good to fair evidence from 2 randomized controlled trials and 1 systematic review is presented that adalimumab,[119-121] etanercept,[122, 123] and infliximab are significantly more efficacious than placebo for the treatment of ankylosing spondylitis. Treatment effects are large and consistent across studies.

Table 13. Evidence profile of comparisons of targeted immune modulators for the treatment of ankylosing spondylitis in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							
Outcome: Radiographic progression							
No evidence							
Outcome: Safety							
No evidence							

Study populations and outcome measures

All patients suffered from active ankylosing spondylitis and were diagnosed based on the modified New York criteria.[125] Disease duration and concomitant treatments varied across studies. Most patients used non-steroidal anti-inflammatory drugs in addition to the study medication. The etanercept and adalimumab trials allowed corticosteroids and disease-modifying antirheumatic drugs as concomitant treatments.[120-123, 126-128] Patients in the infliximab trials were permitted to take only non-steroidal anti-inflammatory drugs in addition to the study drug.[129, 130] One study examined the efficacy of infliximab in patients with severe ankylosing spondylitis.[130]

Patients with an autoimmune disease other than ankylosing spondylitis, spinal fusion, a history of active listeriosis or mycobacterial infection, or recent antibiotic treatment were generally excluded from studies.

Most trials assessed response rates as defined by the Assessments in Ankylosing Spondylitis Working Group.[131] This scale combines measures of global disease activity with functional capacity, pain, and acute phase laboratory parameters (see Appendix E). In addition, the Bath Ankylosing Spondylitis Disease Activity Index was frequently assessed. Two studies evaluated health outcomes.[127, 130]

Sponsorship

All trials, except for the systematic review, were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on the comparative effectiveness

We did not find any head-to-head trials for the treatment of ankylosing spondylitis.

Detailed assessment: Indirect evidence on the comparative effectiveness

One systematic review attempts to provide indirect evidence on the comparative effectiveness of adalimumab, etanercept, and infliximab for adults with ankylosing spondylitis.[124] The analysis used results from 1611 patients with ankylosing spondylitis comparing adalimumab, etanercept or infliximab compared with placebo. However, due to the heterogeneity amongst the component studies the analysis is of poor quality so was excluded.

Detailed assessment: Evidence on the general efficacy

Due to the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of targeted immune modulators in the treatment of ankylosing spondylitis, see table 14. This, however, does not provide evidence on the comparative efficacy and tolerability of targeted immune modulators.

Adalimumab

We identified 1 high quality meta-analysis on the general efficacy of adalimumab.[124] The study included information on 2 trials of adult patients with ankylosing spondylitis. Pooled results presented statistically significantly greater improvements of adalimumab- than placebo-treated patients on outcome measures at 12 weeks (all $P<0.001$). Assessment in Ankylosing Spondylitis 20% improvement is achieved more frequently in adalimumab patients than placebo (relative risk, 2.43; 95% CI, 1.76 to 3.35), as is the Assessment in Ankylosing Spondylitis 70% improvement (relative risk, 5.47; 95% CI, 2.43 to 12.31). Indirect comparisons did not show that adalimumab was better or worse than infliximab or etanercept.

An additional fair study, published in 3 journal articles[119-121] evaluated the safety and efficacy of adalimumab (40 mg every other week) for the treatment of ankylosing spondylitis. The study lasted for 24 weeks and included 315 patients. The study was conducted in patients with moderate to severe ankylosing spondylitis and allowed concomitant treatment with disease-modifying antirheumatic drugs and corticosteroids. Results of the trial reported that significantly more patients receiving adalimumab than placebo presented clinical improvements on outcome measures at study endpoint, for example the Assessment in Ankylosing Spondylitis 20% improvement 58.2% compared with 20.6% ($P<0.001$).

Etanercept

We identified 1 high quality meta-analysis on the general efficacy of etanercept.[124] The study included information on 5 trials of adult patients with ankylosing spondylitis. Pooled results presented statistically significantly greater improvements of etanercept- than placebo-treated patients, for example Assessment in Ankylosing Spondylitis 20% improvement is achieved more frequently in etanercept patients than placebo (relative risk, 2.13; 95% CI, 1.73 to 2.63) as is the Assessment in Ankylosing Spondylitis 70% improvement (relative risk, 3.38; 95% CI, 2.10 to 5.45). Indirect comparisons did not show that adalimumab was better or worse than infliximab or etanercept.

An additional study not included in the meta-analysis was conducted in 356 patients over 12 weeks,[122, 123] evaluated the safety and efficacy of etanercept (50 mg once weekly or 25 mg twice weekly) for the treatment of ankylosing spondylitis. The study was conducted in patients with moderate to severe ankylosing spondylitis and allowed concomitant treatment with disease-modifying antirheumatic drugs and corticosteroids. Results of the trial reported that significantly more patients receiving etanercept than placebo presented clinical improvements on outcome measures at study endpoint. For example the primary end point, Assessment in Ankylosing Spondylitis 20% improvement response rate at week 12, was achieved by significantly more patients receiving etanercept 50 mg once weekly (74.2%) or 25 mg twice weekly (71.3%) than those receiving placebo (37.3%; $P<0.001$).

Infliximab

We identified 1 high quality meta-analysis on the general efficacy of infliximab.[124]The study included information on 2 trials of adult patients with ankylosing spondylitis. Pooled results presented statistically significantly greater improvements of etanercept- than placebo-treated patients on the Assessment in Ankylosing Spondylitis 20% improvement. The chances of achieving Assessment in Ankylosing Spondylitis 20% improvement at 12 weeks (relative risk, 4.11; 95% CI, 2.62 to 6.44) and Assessment in Ankylosing Spondylitis 20% improvement at 24 weeks (relative risk, 3.18; 95% CI, 1.99 to 5.08) was significantly better in the infliximab treated group ($P<0.00001$).

Table 14. Summary of efficacy trials in adult patients with ankylosing spondylitis

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB									
McLeod et al. 2007[124]	SR and MA	397	Various		ASAS 20% improvement at 12 weeks	ASAS 50/70, BASDAI	Adults with AS	Response rates on ASAS 20/50/70 were significantly greater for ADA than for placebo	Good
van der Heijde et al. 2006[119] Davis et al.[120] Revicki et al.[121]	RCT	315	24 weeks	ADA+standard treatment vs. Placebo+standard treatment	ASAS 20% improvement	ASAS 50/70,	Active, moderate to severe AS; mean disease duration: 12.5 yrs.	Response rates on ASAS 20 /50/70 were significantly greater for ADA than for placebo	Fair
ETANERCEPT									
McLeod et al. 2007[124]	SR and MA	434	Various		ASAS 20% improvement at 12 weeks	ASAS 50/70, BASDAI	Adults with AS	Response rates on ASAS 20/50/70 were significantly greater for ADA than for placebo	Good
van der Heijde et al. 2006[122] Braun et al. 2007[123]	RCT	356	12 weeks	ETA (50 mg once weekly or 25 mg twice weekly) +standard treatment vs. Placebo+standard treatment	Assessment in Ankylosing Spondylitis 20% improvement	ASAS 50/70, BASDAI	Active, moderate to severe AS; mean disease duration: 9 yrs.	Response rates on ASAS 20 /50/70 were significantly greater for ADA than for placebo	Fair
INFLIXIMAB									
McLeod et al. 2007[124]	SR and MA	349	Various		ASAS 20% improvement at 12 weeks	ASAS 50/70, BASDAI	Adults with AS	Response rates on ASAS 20//50/70 were significantly greater for ADA than for placebo	Good

ADA, adalimumab; AS, ankylosing spondylitis; ASAS 20/50/70, Assessment in Ankylosing Spondylitis 20/50/70% improvement; BASDAI, Bath AS Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ETA, etanercept; INF, infliximab; MA, Meta-analysis; RCT, randomized controlled trial, SR; Systematic Review.

Psoriatic Arthritis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of psoriatic arthritis: adalimumab, etanercept, and infliximab.

We included a systematic review and meta-analysis that analyses adalimumab, etanercept and infliximab, directly to placebo and indirectly to each other.[132] Additionally, we include 6 placebo-controlled trials assessing the efficacy of adalimumab,[133] alefacept,[134] etanercept,[135, 136] and infliximab.[137-140] The studies ranged in duration from 12 to 50 weeks. We did not find any studies on abatacept, anakinra, certolizumab pegol, natalizumab, and rituximab. Included studies are presented in Table 18.

Summary of findings

No direct evidence on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in adults or children exists.

There is an inclusive systematic review and meta-analysis that conducts indirect comparisons of adalimumab, etanercept and infliximab for the treatment of psoriatic arthritis in adults. It illustrates that the 3 treatments are more efficacious than placebo but indirect comparisons amongst the 3 do not show any differences.

For adults, fair evidence from 1 randomized controlled trial provides evidence that adalimumab is more effective than placebo. Fair evidence from 1 phase II study indicates that alefacept combined with methotrexate is more efficacious than methotrexate alone. Two randomized controlled trials exists that etanercept is significantly more efficacious than placebo for the treatment of psoriatic arthritis and 2 randomized controlled trials provide fair evidence on the general efficacy of infliximab. Treatment effects are large and consistent across studies. (See Table 15).

At this time there are no studies, placebo or head to head, that evaluates the use of targeted immune modulators in children with psoriatic arthritis. (See Table 16).

Table 15. Evidence profile of comparisons of targeted immune modulators for the treatment of psoriatic arthritis in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
Adalimumab compared with etanercept							
Outcome: Health outcomes							
Indirect: 1 N ≈ 678	MA with indirect comparison of placebo trials	Fair	NA	Indirect	ACR 20 RR (95% CI) 0.63 (0.22, 1.81) PsARC RR (95% CI) 1.35 (0.67, 2.73)	None	Insufficient
Adalimumab compared with infliximab							
Outcome: Health outcomes							
Indirect: 1 N ≈ 717	MA with indirect comparison of placebo trials	Fair	NA	Indirect	ACR 20 RR (95% CI) 0.60 (0.30, 1.20) PsARC RR (95% CI) 0.77 (0.53, 1.13)	None	Insufficient
Etanercept compared with infliximab							
Outcome: Health outcomes							
Indirect: 1 N ≈ 569	MA with indirect comparison of placebo trials	Fair	NA	Indirect	ACR 20 RR (95% CI) 0.96 (0.33, 2.76) PsARC RR (95% CI) 0.57 (0.28, 1.17)	None	Insufficient

ACR 20/50/70, American College of Rheumatology, numbers refer to percentage improvement; MA, meta-analysis; NA, not applicable; PsARC, Psoriatic Arthritis Response Criteria; RR, relative risk.

Table 16. Evidence profile of comparisons of targeted immune modulators for the treatment of psoriatic arthritis in children

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Study populations and outcome measures

All patients suffered from active psoriatic arthritis. However, the definition of active disease varied across studies. Three trials enrolled patients with at least 3 swollen and 3 tender joints at screening;[133-135] 2 other studies included patients with at least 5 swollen and 5 tender joints,[138, 139] and the third study employed additional criteria, which utilized clinical sub-types of psoriatic arthritis to establish the presence of psoriatic arthritis.[136] All 5 trials consisted of patients who had previously failed disease-modifying antirheumatic drug and/or methotrexate therapies.

All trials assessed response rates as defined by the American College of Rheumatology. In addition, all 6 studies used the disease specific Psoriatic Arthritic Response Criteria which is composed of a patient global self-assessment, a physician global assessment, a swollen joint score, and a tender joint score. Further details of this scale are presented in Appendix E. In addition, the Psoriasis Area and Severity Index were used in 5 studies to measure improvements in both the amount of psoriatic plaque, as well as the severity of the disease. The Short Form 36 Health Survey and Health Assessment Questionnaire were used to assess quality of life. Additionally, 1 study used a modified Sharp score to assess disease progression.[136]

Sponsorship

All trials, except the systematic review and meta-analysis, were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on the comparative effectiveness

We did not find any head-to-head trials for the treatment of psoriatic arthritis.

Detailed assessment: Indirect evidence on the comparative effectiveness

One systematic review provides indirect evidence on the comparative effectiveness of adalimumab, etanercept, and infliximab for adults with moderate to severe plaque psoriatic arthritis.[132] The analysis used results from 1611 patients in with psoriatic arthritis comparing adalimumab, etanercept or infliximab compared with placebo. There were no statistical difference in the relative risk of patients achieving an American College of Rheumatology 20% response for adalimumab, etanercept, or infliximab treated patients (Adalimumab compared with etanercept [RR, 0.63; 95% CI, 0.22 to 1.81], adalimumab compared with infliximab [RR, 0.60; 95% CI, 0.30 to 1.20], and etanercept compared with infliximab [RR, 0.96; 95% CI, 0.33 to 2.76]). Table 17 summarizes the study conducting indirect comparisons.

Table 17. Characteristics and results of studies conducting indirect comparisons

Author, year	Comparisons	Primary outcome	Conclusion	Quality
Saad et al., 2008[132]	ADA, ETA, INF	ACR and PsARC	No significant differences between TIMs	Good

ADA, adalimumab; ACR, American College of Rheumatology; ETA, etanercept; INF, infliximab; PsARC, psoriatic arthritis response criteria; TIM, targeted immune modulator.

Detailed assessment: Evidence on the general efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of targeted immune modulators in the treatment of psoriatic arthritis. This, however, does not provide evidence on the comparative efficacy and tolerability of targeted immune modulators.

Adalimumab

We identified 1 high quality meta-analysis on the general efficacy of adalimumab.[132]The study included information on 982 adult patients with psoriatic arthritis, of which 413 were present in adalimumab compared with placebo trials. Pooled results presented statistically significantly greater improvements of adalimumab- than placebo-treated patients on all included outcome measures. Patients on adalimumab were more likely to achieve the Psoriatic Arthritis Response Criteria (RR, 2.33; 95% CI, 1.80 to 3.01) compared with placebo ($P>0.05$). In like fashion the adalimumab treated patients were more likely to achieve an American College of Rheumatology 20 response, (RR, 3.42; 95% CI, 2.08 to 5.63), American College of Rheumatology 50, (RR, 8.71; 95% CI, 4.30 to 17.66), or American College of Rheumatology 70 (RR, 15.75; 95% CI, 4.44 to 55.82) than the placebo treated patients (all $P<0.05$).

Alefacept

One phase II trial has been reported on in the literature on the use of alefacept in psoriatic arthritis.[134] The study included 185 patients suffering from moderate to severe psoriatic arthritis, which was defined as having at least 3 swollen joints and 3 tender or painful joints, who had an inadequate response to methotrexate therapy. Patients continued current methotrexate therapy and the dose had been stable for 4 weeks. The double-blinded phase of the study was 24 weeks, 12 weeks of treatment followed by 12 weeks of observation during which methotrexate treatment was continued in all participants. The dose was 15 mg every week. The alefacept group saw significantly greater response rates on American College of Rheumatology 20 than the placebo group, 54% compared with 23% ($P<0.001$). There were no significant differences in the other outcomes which included American College of Rheumatology 50/70, Psoriasis Area and Severity Index and Physician Global Assessment, though there was a trend that favored alefacept. For example, American College of Rheumatology 50/70 was achieved by 17% and 7% of the alefacept group compared with 10% and 2%, respectively, of the placebo group. Similarly, the Psoriasis Area and Severity Index 50 and a Physician Global Assessment of clear or almost clear were reported in 45% and 31% of the alefacept group compared with 31% and 24% in the placebo group.

Etanercept

We identified 1 high quality meta-analysis on the general efficacy of etanercept.[132]The study included information on 265 adult patients with psoriatic arthritis in the 2 included etanercept trials. Pooled results presented statistically significantly greater improvements of etanercept- than placebo-treated patients on all outcome measures included. At 12 weeks the relative risk for achieving the Psoriatic Arthritis Response Criteria was 2.68 (95% CI, 1.78 to 4.04) for etanercept compared with placebo ($P<0.05$). Similarly, the etanercept treated patients were much more likely to reach an American College of Rheumatology 50 or 70 (RR, 10.68; 95% CI, 4.40 to 25.89 and RR, 14.75; 95% CI, 1.97 to 110.51, respectively) than the placebo treated patients (all $P<0.05$).

Additional outcomes can be found in the individual studies of etanercept in patients with psoriatic arthritis.[135, 136] In both fair studies patients were allowed to continue methotrexate therapy as long as it had been stable for 4 weeks prior. One study lasted 12 weeks;[135] the other trial was double-blinded for 24 weeks.[136] Both studies had the same dosing regimen of 25 mg of etanercept twice-weekly subcutaneous injections. Quality of life was significantly improved as measured by the Health Assessment Questionnaire in both studies. Mean improvements were 83% in etanercept- compared to 3% in placebo-treated patients in the 12 week study ($P<0.0001$). In the longer study, at 24 weeks the mean improvement was 54% in the etanercept group and 6% in the placebo group ($P<0.0001$).

Infliximab

We identified 1 high quality meta-analysis on the general efficacy of infliximab.[132] The study included information on 982 adult patients with psoriatic arthritis of which 304 were present in infliximab compared with placebo trials. Pooled results presented statistically significantly greater improvements of infliximab- than placebo-treated patients on all included outcome measures. The relative risk for achieving the Psoriatic Arthritis Response Criteria was 3.03 (95% CI, 2.27 to 4.04) for infliximab compared with placebo ($P>0.05$). In like fashion the infliximab treated patients were more likely to achieve an American College of Rheumatology 20, (RR, 5.71; 95% CI, 3.53 to 9.25); American College of Rheumatology 50, (RR, 14.73; 95% CI, 5.11 to 42.43); or American College of Rheumatology 70, (RR, 19.21; 95% CI, 3.77 to 97.87) than placebo treated patients (all $P<0.05$).

Additional outcomes were in the individual two fair studies on the use of infliximab in patients with psoriatic arthritis.[137-140] In both studies patients were allowed to continue methotrexate therapy as long as it had been stable for 4 weeks prior. The earlier study was double-blinded for 16 weeks;[137] the other trial was double-blinded for 24 weeks with cross-over allowed at week 16 for non-responders.[138] Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, 14 and the longer study had an additional injection at week 22. Quality of life was significantly improved as measured by the Health Assessment Questionnaire in both studies. Mean improvements were 49.8% in infliximab compared to -1.6% in placebo-treated patients in the smaller study ($P<0.001$). In the bigger study, at 14 weeks the mean improvement was 48.6% in the infliximab group and an 18.4% loss in the placebo group ($P<0.001$).

Psoriatic Arthritis in Children

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in children exists. In addition, no placebo-controlled trials on children with psoriatic arthritis are evident in the literature.

Table 18. Summary of efficacy trials in adult patients with psoriatic arthritis

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB									
Genovese et al. 2007[141]	RCT	100	12 weeks	ADA + DMARD vs. Placebo + DMARD	ACR 20	ACR 50/70, PsARC, PASI, SF-36, HAQ, DLQI	Active PsA; failed at least 1 DMARD; mean disease duration: 7.4 years	ADA had significantly better outcomes than placebo	Fair
Mease et al. 2005[133]	RCT	313	24 weeks	ADA + MTX vs. Placebo + MTX	ACR 20, change in modified Sharps score	ACR 50/70, HAQ, PsARC, SF-36	Active PsA; failed at least 1 DMARD; mean disease duration: 9.5 years	ADA had significantly better outcomes than placebo	Fair
Saad et al. 2008[132]	SR and MA	413	12-24 weeks	ADA + MTX vs. Placebo + MTX	ACR 20/50/70 PsARC	PASI 50/75/90 SF-36, HAQ-DI	Adults with PsA	ADA had significantly better outcomes than placebo	Good
ALEFACEPT									
Mease et al. 2006[134]	RCT	185	24 weeks (12 weeks treatment, 12 weeks observation)	ALE + MTX vs. Placebo + MTX	ACR 20	ACR 50/70, PASI, PGA	Active PsA; failed at least 1 DMARD; mean disease duration: NR	ALE had significantly better ACR 20 than placebo	Fair
ETANERCEPT									
Saad et al. 2008[132]	SR and MA	265	12-24 weeks	ETA + MTX vs. MTX + Placebo	ACR 20/50/70 PsARC	PASI 50/75/90	Adults with PsA	ETA had significantly better outcomes than placebo	Good
INFLIXIMAB									
Antoni et al. IMPACT Study 2005[137, 140]	RCT	104	50 weeks	INF vs. Placebo (71% received a concomitant DMARD)	ACR 20 and PASI	ACR 50/70 DAS; HAQ; ratings of enthesitis and dactylitis; PSARC.	Active PsA; failed at least 1 DMARD; mean disease duration 11.4 years	INF had significantly better outcomes than placebo	Fair

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Antoni et al. IMPACT 2[138] van der Heijde et al.[142] Kavanaugh et al.[139, 143, 144]	RCT	200	24 weeks	INF vs. Placebo (46% received concomitant MTX)	ACR 20; HAQ; SF-36; employability	ACR 50/70; PsARC; PASI; dactylitis and enthesopathy; time lost from work	Active PsA; failed at least 1 DMARD; mean disease duration 8 years	INF had significantly better outcomes than placebo	Fair
Saad et al. 2008[132]	SR and MA	304	12-24 weeks	INF + MTX vs. Placebo + MTX	ACR 20/50/70 PsARC	PASI 50/75/90	Adults with PsA	INF had significantly better outcomes than placebo	Good

ACR, American College of Rheumatology; ADA, adalimumab; ALE, alefacept; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; INF, infliximab; MA, meta-analysis; MTX, methotrexate; NR, not reported; PASI, Psoriasis Arthritis Severity Index; PGA, Physician Global Assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36 Health Survey; SR, systematic review.

Crohn's Disease

The following drugs are currently approved by the US Food and Drug Administration for the treatment of Crohn's disease: adalimumab, certolizumab pegol, infliximab, and natalizumab.

Summary of the evidence

Overall, the strength of evidence on the comparative effectiveness of targeted immune modulators for the treatment Crohn's disease is insufficient (Tables 19 and 20). We did not find any head-to-head randomized controlled trials or observational studies comparing one targeted immune modulator to another, and evidence was insufficient to make indirect comparisons. We included 2 systematic reviews with meta-analyses and 8 placebo-controlled trials. (Some component studies from included systematic reviews/meta-analyses did not report additional outcomes and are therefore not described.) Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up.

Fair to good evidence from 1 meta-analysis and 4 randomized controlled trials shows that infliximab is significantly more efficacious than placebo for initial (i.e., patients with refractory Crohn's disease that had not received a targeted immune modulator during the previous 12 weeks) and maintenance treatment of Crohn's disease in adults. Treatment effects are large and evident within 1 to 2 weeks. Maintenance treatment with infliximab maintains a response significantly longer than placebo, although infections and infusion-related reactions are more common with long-term treatment. Infliximab is also more efficacious than placebo in fistulizing Crohn's disease (a serious complication of Crohn's disease characterized by abnormal communication between the gut and the skin, with small bowel or colonic contents draining to the skin surface).

Adalimumab and certolizumab pegol had only 1 fair trial each assessing general efficacy. Two trials and 1 meta-analysis assessed the general efficacy of natalizumab. All 3 drugs were superior to placebo for the treatment of active Crohn's

We did not find any evidence on the general efficacy of abatacept, alefacept, anakinra, etanercept or rituximab for the treatment of Crohn's disease.

Although some studies allowed stable doses of other immunomodulatory agents, no conclusive evidence exists to determine whether combination treatment of etanercept and infliximab with other agents (azathioprine, 6-mercaptopurine or methotrexate) leads to clinically and statistically greater improvements than monotherapy.

We found no studies that met our eligibility criteria assessing the comparative or general efficacy of any targeted immune modulator in pediatric populations.

Table 19. Evidence profile of comparisons of targeted immune modulators for the treatment of Crohn's disease in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Table 20. Evidence profile of comparisons of targeted immune modulators for the treatment of Crohn's disease in children

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Study populations and outcome measures

All patients suffered from active Crohn's disease of at least 3 months' duration. Some patients also had abdominal or perianal fistulas. Most studies included patients with a Crohn's Disease Activity Index (CDAI) score between 220 and 400. However, some trials included patients with CDAI scores as high as 450 (i.e., more severe disease). Disease duration and concomitant treatments varied across studies. On average, disease duration ranged from 8 to 12 years. Many studies allowed concomitant treatment with 5-aminosalicylate, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, or methotrexate.

Most studies utilized the CDAI to characterize disease severity. The CDAI assesses 8 related variables (e.g., number of liquid or soft stools per day, severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of abdominal mass, the use or nonuse of antidiarrheal drugs, the hematocrit, and body weight; see Appendix E) to yield a composite score between 0 and 600; scores below 150 indicate remission while scores above 450 indicate severe illness. Response commonly was characterized by a CDAI reduction greater than or equal to 70 points. Several studies utilized the Inflammatory Bowel Disease Questionnaire. This questionnaire identifies 32 individual items categorized within 4 major quality of life domains (primary bowel symptoms, systemic symptoms, social impairment, and altered emotional function). Some studies assessed C-reactive protein concentrations as an intermediate marker for inflammation. In studies specifically designed to assess fistulizing disease, outcomes included 50% reduction in the number of draining fistulas or a complete absence in draining fistulas.

Sponsorship

All of the randomized controlled trials received funding from the pharmaceutical industry. Neither of the meta-analyses were funded by pharmaceutical companies. Several studies also received funding from the National Institutes of Health or the US Food and Drug Administration.

Detailed assessment: Direct evidence on the comparative effectiveness

We did not identify any head-to-head studies for the treatment of Crohn's disease.

Detailed assessment: Indirect evidence on the comparative effectiveness

We did not identify any indirect comparisons of targeted immune modulators for the treatment of Crohn's disease. Included placebo-controlled trials were too heterogeneous to conduct adjusted indirect comparisons.

Detailed assessment: Evidence on the general efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. Table 21 summarizes studies included for general efficacy.

Adalimumab

The Crohn's Trial of the Fully Human Antibody for Remission Maintenance (CHARM) compared adalimumab to placebo.[145-148] In this fair study,884 patients with moderately to severely active Crohn's disease (CDAI ≥ 220 and ≤ 450) enrolled in the trial for an induction period of four weeks of which 778 were randomized to placebo, adalimumab 40 mg every second week or adalimumab 40 mg/week. At week 56, a significantly greater percentage of patients achieved remission in both adalimumab groups compared with placebo (36% and 41% compared with 12%; $P<0.001$).[145]

All-cause hospitalization risk was lower in the combined adalimumab group than the placebo group at 3 months (5.1% compared with 13.1%, $P<0.01$) and 12 months (12.6% compared with 25.2%, $P<0.01$).[146] The hazard ratio for all-cause hospitalization was 0.40 (95% CI, 0.26 to 0.62; $P<0.001$) for the combined adalimumab group compared with the placebo group; the hazard ratio for hospitalization related to Crohn's disease was 0.42 (95% CI, 0.24 to 0.72; $P=0.002$).

Health reported quality of life (determined by Inflammatory Bowel Disease Questionnaire and Short Form 36 Health Survey) was better in adalimumab-treated patients.[147] Differences in mean Inflammatory Bowel Disease Questionnaire scores between adalimumab and placebo were statistically significant at all visits after week 4 ($P<0.001$ for adalimumab every other week and $P<0.05$ for adalimumab weekly). At week 56, the mean Inflammatory Bowel Disease Questionnaire score for the adalimumab groups was greater than placebo (18 points and 16 points greater for each active arm). Similar results were seen in Short Form 36 Health Survey scores across all subdomains. A subgroup analysis of 117 patients with fistulas (70 adalimumab- and 47 placebo-treated patients) showed a lower mean number of draining fistulas per day in adalimumab- than in placebo-treated patients (0.88 compared with 1.34, $P=0.043$).[148]

Certolizumab pegol

Three trials comparing certolizumab pegol with placebo met our eligibility criteria.[149-152] However, two were determined to be poor of quality primarily due to high rates of attrition. Overall attrition in the Pegylated antibody fRagment Evaluation in Crohn's disease Safety and Efficacy (PRECISE) 1 trial[149] was 42% (39% for certolizumab pegol and 46% for placebo). The PRECISE 2 trial[150] was of poor quality due to high overall attrition (40%) and high differential attrition (30% for certolizumab pegol and 49% for placebo). The high rates of attrition were primarily due to lack of improvement or worsening of disease.

The fair trial[151, 152] randomized 292 patients with moderate-to-severe active Crohn's disease to certolizumab pegol (100, 200, or 400 mg) or placebo for 20 weeks. All doses of certolizumab pegol were superior to placebo for all outcomes. At all time points, certolizumab pegol produced higher response rates (≥ 100 point CDAI decrease) than placebo. Response rates for certolizumab pegol 400 mg at week 12 were 44 percent versus35.6 percent for placebo ($P=NS$).[151]

A post hoc analysis of 290 patients assessed health-related quality of life data.[152] The percentage of patients achieving remission on the Inflammatory Bowel Disease Questionnaire

(defined as a score > 170 points) at week 12 was greater for all certolizumab pegol doses (100-, 200-, 400 mg) compared with placebo (38.4%, 23.6%, 38.9% compared with 23.4%, $P<0.05$).

Infliximab

One fair systematic review with meta-analyses[153] and 4 randomized controlled trials compared infliximab to placebo.[154-157] One of these trials addressed patients with multiple draining abdominal or perianal fistulas.[155]

The systematic review focused on the maintenance of remission in Crohn's disease patients treated with infliximab.[153] Three studies were included in the analysis. Pooled data showed that infliximab was more effective than placebo in maintenance of remission (relative risk, 2.50; 95% CI, 1.64 to 3.80; $P<0.001$). Infliximab-treated patients also demonstrated better clinical response (relative risk, 2.19; 95% CI, 1.27 to 3.75; $P=0.005$). Infliximab was also superior for corticosteroid-sparing effects (relative risk, 3.13; 95% CI, 1.25 to 7.81; $P=0.01$) and for complete healing of perianal and enterocutaneous fistulas (relative risk, 1.87; 95% CI, 1.15 to 3.04; $P=0.01$).

Two of the component trials included in the above meta-analysis reported outcomes not discussed in that analysis.[154, 155] We therefore present those studies and the relevant outcomes.

To assess the ability of infliximab to maintain treatment response, maintenance infusions of infliximab were compared to placebo in the A Crohn's disease Clinical study Evaluating infliximab in a New long term Treatment regimen (ACCENT) I trial (multiple articles).[154] In this trial, 335 patients responding (CDAI ≥ 70 points) at 2 weeks to an initial infliximab infusion of 5 mg/kg were randomized to repeat infusions of placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at week 2 and 6 and then every 8 weeks thereafter until week 46. Primary outcome measures included time to loss of response (CDAI ≥ 175) and the proportion of week 2 responders in remission (CDAI < 150) at week 30. Compared to placebo, infliximab-treated patients had a significantly longer time to loss of response (46 weeks compared with 19 weeks, $P=0.0002$) and the odds of being in remission at week 30 were nearly 3 times greater infliximab-treated patients also had better endoscopic healing, fewer hospitalizations, fewer surgeries, decreased corticosteroid use, fewer hours lost from work, and better quality of life scores ($P<0.05$ for all).[158-160] Additional analyses found scheduled maintenance treatment with infliximab to have better mucosal healing than episodic treatment ($P=0.007$).[161]

The second trial compared the efficacy of infliximab to placebo in patients with enterocutaneous or perianal fistulas, a serious complication of Crohn's disease characterized by abnormal communication between the gut and the skin with small bowel or colonic contents draining to the skin surface.[155] In this trial (ACCENT II),[155] 195 patients with Crohn's disease and 1 or more draining abdominal or perianal fistulas who responded to 3 open-label 5 mg/kg infusions of infliximab were randomized to maintenance treatment with 8-week infusions of infliximab 5 mg/kg or placebo. Patients that did not respond to open-label treatment (n = 87) also were followed for safety. The primary outcome was defined as time to loss of response. On average, patients randomized to infliximab maintenance therapy maintained their response for more than 26 weeks longer than placebo ($P<0.001$). At week 54, 36% of infliximab-treated patients had a complete absence of draining fistulas compared to 19% of placebo-treated patients ($P=0.009$). At 6 weeks, infliximab also was more efficacious than placebo in a subgroup of women with rectovaginal fistulas (fistula closure 61% and 45%, respectively).[162] Compared to placebo, infliximab-treated patients had fewer hospitalizations (11 compared with 31; $P<0.05$), fewer mean hospitalization days (0.5 compared with 2.5 days/100; $P<0.05$), and fewer surgeries

and procedures (65 compared with 126; $P<0.05$).[163] No differences between active treatment and placebo were found in the number of fistula-related abscesses.[164]

Two fair trials were not included in the above meta-analyses. One trial examined the efficacy of a single infusion of infliximab at doses of 5, 10, and 20 mg/kg in Crohn's disease (CDAI scores between 220 and 400).[156] Randomized patients were refractory to corticosteroids, mesalamine, 6-mercaptopurine, or azathioprine. This trial demonstrated significantly better efficacy of a single infusion of infliximab compared to placebo. In the 12 week multinational trial,[156] 108 patients randomized to infliximab 5, 10, or 20 mg/kg or placebo were assessed at 2, 4, and 12 weeks. Responders were characterized as having a CDAI reduction of 70 points or more. Quality of life with respect to bowel function (Inflammatory Bowel Disease Questionnaire) and C-reactive protein concentrations also were assessed. At 4 weeks, compared to placebo, significantly more infliximab-treated patients were characterized as CDAI responders ($P<0.005$). Quality of life scores and C-reactive protein concentrations also were significantly better than placebo in patients treated with infliximab ($P<0.05$ and $P<0.01$, respectively).[165]

The second trial evaluated the efficacy of infliximab compared with azathioprine or 6-mercaptopurine in steroid-dependent Crohn's disease patients.[157] Patients with active Crohn's diseased despite prednisone treatment for more than 6 months were stratified and randomized to infliximab (5 mg/kg) or placebo at weeks 0, 2, and 6. Success rate (defined as percentage with CDAI < 150 and off steroids) at week 24 was superior in infliximab group (57% compared with 29%; odds ratio, 3.3; 95% CI, 1.5 to 7.4; $P=0.003$). Patients were stratified based on whether or not they were azathioprine/6-mercaptopurine failed or naive. There was no significant interaction between treatment and stratum. Steroid resistance was less common in the infliximab group (5% compared with 23%; odds ratio, 5.1; 95% CI, 1.3 to 19.2; $P=0.01$).

Natalizumab

One systematic review with meta-analysis[166] and 3 randomized controlled trials met our eligibility criteria.[167-169] Of the component studies in the systematic review, 1 provided no additional outcomes and is not presented here, and a second presented additional outcomes on quality of life and is discussed briefly.[168] We include an additional study not included in the systematic review and present findings in full.[169]

The systematic review included four 12-week trials and assessed efficacy of 1, 2, or 3 infusions of natalizumab (300 mg or 3 to 4 mg/kg) with placebo.[166] Positive responses were seen with 1 injection of natalizumab. Furthermore, analyses suggested a trend toward increased benefits with additional injections. After 12 weeks, 3 infusions of natalizumab (4 mg/kg) compared with placebo indicated the relative risk of failure to induce remission with natalizumab was statistically significantly reduced (0.87; 95% CI, 0.78 to 0.98), as was the relative risk of failure to induce clinical response (0.85; 95% CI, 0.67 to 0.95).

One component study in the systematic review assessed quality of life.[168] This trial randomly assigned 248 patients to 1 of 4 treatment arms: 1 or 2 infusions of 3 mg/kg natalizumab, 2 infusions of 6 mg/kg natalizumab, or placebo. At week 6, all 3 natalizumab groups had significant improvement in mean Inflammatory Bowel Disease Questionnaire scores (155, 163, 155) compared with 145 for placebo (compared with placebo, P values were 0. 008, <0.001, and 0.001, respectively). However, at week 12, only the 2-infusion natalizumab group was significantly better than placebo ($P=0.021$).

One randomized controlled trial (not included in the above meta-analysis) showed consistent results.[169] This trial, the Efficacy of Natalizumab in Crohn's disease Response and

Remission (ENCORE), evaluated the efficacy of natalizumab induction therapy in patients with moderate-to-severe active Crohn's disease (CDAI ≥ 220 and ≤ 450). In the ENCORE trial, 309 patients were randomized to natalizumab or placebo. The primary endpoint (response at week 8 sustained through week 12) was realized in more natalizumab than placebo patients (48% compared with 32%, $P<0.001$). Natalizumab showed significantly greater improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire score improvement at week 12 (+32.34 compared with +28.97, $P<0.001$).

Table 21. Summary of studies in adult patients with Crohn's disease

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB									
Colombel et al., 2007[145] Feagan et al., 2008[146] Loftus et al., 2008[147] Colombel et al. 2009[148] CHARM	RCT	778	2 week active run-in plus 54 weeks	Induction ADA 2 weeks then ADA vs. Placebo	Clinical remission (CDAI <150) at weeks 26 and 56; response		Moderate-to-severe active CD (CDAI ≥ 220 and ≤ 450)	ADA superior for all outcomes	Fair
CERTOLIZUMAB PEGOL									
Schreiber et al., 2005[151] and Rutgeerts et al., 2007[152]	RCT	292	20 weeks	CER vs. Placebo	Response CDAI response (≥ 100 point decrease) at week 12	Remission (CDAI score ≤ 150), HRQOL at 12 weeks using IBDQ	Adults with moderate-to-severe CD (CDAI score 220-450) who had initial response or remission or were unable to wean corticosteroids	CER at all doses better than placebo for all outcomes	Fair
INFLIXIMAB									
Behm and Bickston, 2008[153]	MA	952	12 weeks	INF vs. Placebo	Maintenance of remission	Maintenance of clinical response	Adults with active CD	INF superior to placebo for maintenance of remission, clinical response, corticosteroid-sparing effects, and complete healing of perineal and enterocutaneous fistulas	Fair
Hanauer et al., 2002[154, 158-161] ACCENT I	RCT	573	54 weeks	INF vs. Placebo	Proportion of week 2 responders in remission at week 30; time to loss of	Employment status/work loss, surgeries, SF-36, IBDQ, hospitalizations, corticosteroid	> 3 month history of moderate to severe Crohn's disease and CDAI response at 2 weeks to single	Better quality of life, better endoscopic healing, fewer surgeries and hospitalizations, and less work loss in INF	Fair

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
					response	discontinuation , endoscopic healing	dose 5mg/kg INF		
Lemann et al., 2006[157]	RCT	115	24 weeks with planned follow-up to week 52	INF vs. Placebo	Remission (CDAI < 150) and off steroids at week 24		Adults with active CD despite prednisone for > 6 months	INF superior to placebo	Fair
Sands et al., 2004[155, 162-164] ACCENT II	RCT	282	54 weeks	INF vs. Placebo	Time to loss of response after randomization (week 14)	CDAI, IBDQ, hospitalizations, hospitalization days, surgeries	> 3 month history of active CD with multiple draining fistulas and 14 week response (≥ 50% closure) to 3 open label doses of INF 5mg/kg	Significantly longer time to loss of response, fewer draining fistulas, greater improvement in CDAI and IBDQ, fewer hospitalizations, hospitalization days, and surgeries for INF compared to placebo; no difference in fistula-related abscesses for maintenance	Good
Targan et al., 1997[156] and Lichtenstein et al., 2002[165]	RCT	108	12 weeks	INF vs. Placebo	Response at 4 weeks (≥ 70 point reduction in CDAI)	IBDQ, CRP	> 6 month history of moderate to severe CD refractory to corticosteroids, mesalamine, 6-mercaptopurine, or azathioprine	Significantly more responders and greater improvement in IBDQ and CRP for INF compared to placebo	Fair
NATALIZUMAB									
MacDonald and McDonald, 2008[166]	MA	1692	12 weeks	NAT vs. Placebo	Remission (CDAI < 150)	Clinical response, mean CDAI	Adults with moderate to severe CD, CDAI > 150	NAT (1, 2, or 3 injections) greater in response & remission	Fair
Ghosh et al., 2003[168]	RCT	248	12 weeks	NAT vs. Placebo	Remission (CDAI< 150) at 6 weeks	IBDQ	Adults with moderate-to-severe CD (CDAI ≥ 220)	Significant improvement in IBDQ at week 6 for all NAT groups vs. placebo; improvement	Good

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
								significant for 2 infusion NAT group at week 12	
Targan et al., 2007[169] ENCORE Trial	RCT	509	12 weeks	NAT vs. Placebo	Response (≥70 point CDAI decrease) at weeks 8 and 12	Response, remission at week 12; IBDQ, SF-36	Adults with moderate-to-severe active CD	INF significantly greater in improvement for all outcomes	Fair

ADA, adalimumab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CER, certolizumab pegol; CRP, C-reactive protein; ETA, etanercept; IBDQ, Inflammatory Bowel Disease Questionnaire; INF, infliximab; MA, meta-analysis; NAT, natalizumab; RCT, randomized controlled trial; SF-36, Short Form 36 Health Survey

Crohn's Disease in Children

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease in children exists. In addition, no placebo-controlled trials on children with Crohn's disease met our eligibility criteria.

We identified 1 randomized controlled trial ("A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNFα chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease" ortho REACH study) comparing 2 different dosing regimens of infliximab.[170] We briefly describe the REACH study because it is the only study we found that included children. In this study, 112 patients with a Pediatric CDAI score greater than 30 were treated with 5 mg/kg of infliximab at weeks 0, 2, and 6. At week 10, patients who responded to treatment (88.4% of treated patients) were randomized to 5 mg/kg every 8 or 12 weeks through week 46. Pediatric patients were more likely to be in clinical response and remission at week 54 when given infliximab every 8 weeks rather than every 12 weeks.

Ulcerative Colitis

Infliximab is the only drug currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis.

Summary of findings

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of ulcerative colitis exists. (See Tables 22 and 23) The only evidence found was in 2 studies of poor quality, primarily due to withdrawal rates of almost or more than 40% and differential rates of greater than 15 between the active and placebo groups. These studies will be briefly described as they are the only evidence to date.

Table 22. Evidence profile of comparisons of targeted immune modulators for the treatment of ulcerative colitis in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Table 23. Evidence profile of comparisons of targeted immune modulators for the treatment of ulcerative colitis in children

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Study populations and outcome measures

All patients suffered from active ulcerative colitis. Two poor studies, reported in the same article, included patients with moderate to severe ulcerative colitis based on stool frequency, rectal bleeding, endoscopy and physician's assessment.[171] Both trials consisted of patients who had previously failed 5-aminosalicylate and steroid treatments.

Sponsorship

All trials were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on the comparative effectiveness

We did not find any head-to-head trials for the treatment of ulcerative colitis.

Detailed assessment: Indirect evidence on the comparative effectiveness

We did not find any studies indirectly comparing the effectiveness of targeted immune modulators for the treatment of ulcerative colitis.

Detailed assessment: Evidence on the general efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of targeted immune modulators in the treatment of ulcerative colitis. This, however, does not provide evidence on the comparative efficacy and tolerability of targeted immune modulators.

Infliximab

We found 2 poor trials on the use of infliximab in patients with ulcerative colitis.[171, 172] These 2 studies, Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and 2) had dosing regimens of 5 or 10 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. Concomitant medications were continued except for corticosteroids which were tapered down by 5 mg per week until a dose of 20 mg was reached and then additional reductions occurred at a rate of 2.5 mg per week. ACT 1 and 2 showed clinical responses, defined as a decrease in the Mayo score of 3 or more points, decrease of at least 1 in the subscore for rectal bleeding, at 8 weeks that were significantly better in the infliximab groups. In ACT 1, at 8 weeks, 69% of patients receiving 5 mg/kg and 62% receiving 10 mg/kg responded compared with 37% placebo patients (for both $P<0.001$). Similarly in ACT2, at 8 weeks 65% patients receiving 5 mg/ kg and 69% receiving 10 mg/kg responded compared with 29% placebo patients (for both, $P<0.001$). However, attrition rates were very

high at the study endpoints of 30 and 54 weeks and not reported at 8 weeks when the primary outcome was evaluated. ACT 1 had attrition of 37% in patients receiving 5 mg/kg and 40% receiving 10 mg/kg responded compared with 61% placebo patients and ACT 2 had attrition of 19% in patients receiving 5 mg/kg and 22% receiving 10 mg/kg responded compared with 46% placebo patients. No reasons were presented to explain the high attrition rates by the authors.

In a systematic review that contains a meta-analysis of the above studies,[173] the effect of infliximab was greater than placebo. It was found that Peto odds ratio was 3.40 (95% CI, 2.52 to 4.59) for a response and for remission was 2.72 (95% CI, 1.92 to 3.86).

Ulcerative Colitis in Children

No targeted immune modulators are currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in children. There are no trials in the pediatric population of patients with ulcerative colitis at the time of our searches.

Plaque Psoriasis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of plaque psoriasis: adalimumab, alefacept, etanercept, and infliximab. We did not review trials of efalizumab because it was withdrawn from the market.

Summary of findings

We did not find any head-to-head trials directly comparing the efficacy and safety of one targeted immune modulator to another for the treatment of plaque psoriasis.

Fair to good evidence from multiple placebo-controlled randomized controlled trials and meta-analyses exists on the general efficacy of adalimumab, alefacept, etanercept, and infliximab for the treatment of adults with plaque psoriasis. Specifically, we located 11 placebo-controlled trials that assessed the efficacy and safety of targeted immune modulators for the treatment of plaque psoriasis: 3 of adalimumab,[174-176] 3 on alefacept,[177-179] 4 on etanercept,[180-183] and 1 on infliximab.[184] These studies on alefacept and etanercept have been pooled in meta-analyses.[185, 186] We did not find any studies on other targeted immune modulators. In addition, 1 study assessed the efficacy of etanercept in children and adolescents.[187] Significantly more children in the etanercept group than in the placebo group experienced a response. Included studies are presented in Table 26.

Table 24. Evidence profile of comparisons of targeted immune modulators for the treatment of plaque psoriasis (adults)

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							
Outcome: Quality of life							
No evidence							
Outcome: Safety							
No evidence							

Table 25. Evidence profile of comparisons of targeted immune modulators for the treatment of plaque psoriasis (children)

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							
Outcome: Safety							
No evidence							

Study populations and outcome measures

In general, studies enrolled patients who had a history of plaque psoriasis for more than 6 months, with more than 5% to 10% of body surface area involved. Minimum Psoriasis Area and Severity Index scores to meet inclusion criteria ranged from 10 to 12. Most patients had had previous systemic treatments for plaque psoriasis or were candidates for systemic treatment. Patients were excluded if they had clinically significant disease flares at screening or enrollment, major concomitant illnesses, immune disorders, malignancies, or organ dysfunction. Prior therapy with biologic agents was an exclusion criterion for most studies.

All studies assessed Psoriasis Area and Severity Index 50 or Psoriasis Area and Severity Index 75 as 1 of the primary outcome measures (see Appendix E). The physician global assessment was also a common outcome measure. In addition, most trials included some measure of health-related quality of life or functional capacity such as the Dermatology Life Quality Index, Dermatology Quality of Life Scale, the itching visual analogue scale, the European Quality of Life – 5 Dimensions, or the Short Form 36 Health Survey.

The methodological quality of studies was generally good and some of the "fair" ratings are probably more attributable to inadequate reporting than methodological flaws. Randomization methods and blinding were generally adequate; all studies used a double-dummy

design (i.e., using 0.1% human serum albumin placebo in an identical container to active treatment) to guarantee blinding; method of allocation concealment was rarely reported.

Sponsorship

All of the included studies were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on the comparative effectiveness

We did not find any head-to-head trials for the treatment of plaque psoriasis.

Detailed assessment: Indirect evidence on the comparative effectiveness

We did not find any indirect evidence on the comparative effectiveness of the targeted immune modulators for plaque psoriasis.

Detailed assessment: Evidence on the general efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We summarized evidence on the general efficacy of targeted immune modulators in the treatment of plaque psoriasis; however, this does not provide evidence on the comparative efficacy and tolerability of targeted immune modulators.

Adalimumab

Two good[175, 176] and 1 fair[174] studies provide evidence on the general efficacy of adalimumab for the treatment of moderate to severe plaque psoriasis in adult patients. All 3 trials lasted between 12 and 16 weeks and included 1 arm where patients received an initial dose of 80mg adalimumab subcutaneously followed by 40mg adalimumab every other week (adalimumab EOW). Furthermore, 1 trial included methotrexate as a comparison arm,[175] and 1 trial also included a dose of adalimumab that is higher then the approved dose for plaque psoriasis (80mg initial dose followed by 40mg weekly: adalimumab weekly).[174] All results consistently demonstrated that adalimumab is more efficacious than placebo for Psoriasis Area and Severity Index, Physician Global Assessment, Dermatology Life Quality Index and health-related quality of life outcomes. Between 53% and 80% of patients in the adalimumab EOW arms achieved a Psoriasis Area and Severity Index 75 response compared with 4% to 19% of placebo-treated patients. Likewise, patients receiving adalimumab consistently achieved significantly more improvement in Physician Global Assessment, Dermatology Life Quality Index, the health-related quality of life indices, European Quality of Life – 5 Dimensions, and Short Form 36 Health Survey than those receiving placebo.

Specifically, in the largest trial 1212 patients were randomized to adalimumab EOW or placebo for 16 weeks.[176] Results at week 16 favored adalimumab over placebo for all outcome measures: 71% of patients receiving adalimumab achieved a Psoriasis Area and Severity Index 75 response compared with 7% of placebo patients; similarly, patients receiving adalimumab demonstrated significantly greater improvement in Physician Global Assessment, Dermatology Life Quality Index and health-related quality of life measures. In the smallest, fair-quality trial 147 patients were randomized to adalimumab EOW, adalimumab weekly or placebo. Fifty-three percent of the adalimumab EOW arm achieved a Psoriasis Area and Severity Index 75 response compared with 80% or the adalimumab weekly arm and 4% of placebo patients.[174] These patients also achieved significantly greater improvements in Dermatology Life Quality Index and

health-related quality of life. Again, the results from the good trial of 271 patients randomized to adalimumab EOW, methotrexate, or placebo for 16 weeks showed the superiority of adalimumab compared with placebo for Psoriasis Area and Severity Index 75 (79.6% compared with 18.9%) and Dermatology Life Quality Index, Physician Global Assessment, and health-related quality of life.[175]

Alefacept

Two fair-quality systematic reviews[185, 186] included 3 trials[177-179] of alefacept compared with placebo for patients with plaque psoriasis in meta-analyses. Overall, the studies included data on 1289 patients with plaque psoriasis. The pooled relative risk for a Psoriasis Area and Severity Index 75 response was 3.37 (95% CI, 2.18 to 5.23) and for a Psoriasis Area and Severity Index 50 response 2.57 (95% CI, 2.03 to 3.25) after 12 weeks of follow-up.[185] The number needed to treat for a Psoriasis Area and Severity Index 75 response for alefacept was 8 (95% CI, 5.05 to 12.20).[186] In addition, alefacept had a beneficial effect on health-related quality of life compared with placebo. The pooled mean difference in the Dermatology Life Quality Index compared with placebo was 1.65 (95% CI, 1.23 to 2.01).[185]

Etanercept

Two fair meta-analyses examined the efficacy of etanercept in approximately 2000 patients with plaque psoriasis.[185, 186] Pooled results from 4 placebo-controlled trials[180-183, 188, 189] showed a relative risk of a Psoriasis Area and Severity Index 75 response of 11.92 (95% CI, 8.17 to 17.39) and for a Psoriasis Area and Severity Index 50 response 5.85 (95% CI, 4.77 to 7.17) over a follow-up period of 12 weeks.[185] The number needed to treat for a Psoriasis Area and Severity Index 75 response was 3 (95% CI, 2.07 to 2.49).[186] The pooled analysis of the effect of etanercept on health-related quality of life (Dermatology Life Quality Index scores) showed a mean difference of 6.07 (95% CI, 3.99 to 8.16) compared with placebo.[185]

Infliximab

One good randomized controlled trial assessed the efficacy and safety of infliximab for 378 patients randomized to 24 weeks of infliximab (5mg/kg) or placebo for treatment of plaque psoriasis.[184] At week 24, 82% of patients on infliximab and 4% of patients on placebo achieved a Psoriasis Area and Severity Index 75 response ($P<0.001$). In addition, the infliximab group had statistically significantly greater improvements on Short Form 36 Health Survey, Dermatology Life Quality Index,[190] nail psoriasis and severity index, and Physician Global Assessment.[184]

Children

No biologics are approved for the treatment of plaque psoriasis in children. We did not find direct or indirect evidence on the comparative effectiveness of targeted immune modulators for treating children or adolescents with plaque psoriasis.

We found 1 fair quality randomized controlled trial of etanercept in children.[187] We did not locate any other trials of targeted immune modulators for children or adolescents. In the initial phase of this trial, 211 children and adolescents aged between 4 and 17 with moderate to severe plaque psoriasis of at least 6 months duration were randomized to etanercept 0.8mg/kg/week or placebo for 12 weeks. Children receiving etanercept achieved consistently better improvement on Psoriasis Area and Severity Index, Physician Global Assessment, and the children's Dermatology Life Quality Index than those receiving placebo after 12 weeks. For

example, after 12 weeks 57% of the children in the etanercept group demonstrated a Psoriasis Area and Severity Index 75 improvement compared with 11% in the placebo group ($P<0.001$). Patients who experienced a worsening of their disease during the initial double-blinded phase of the trial were eligible for "escape" to open-label etanercept. Twenty-six percent of children in the placebo group and 5% of etanercept-treated patients escaped during the first 12 weeks. One patient in the etanercept group withdrew in the first 12 weeks due to an adverse event. Table 27 summarizes efficacy trials in children with plaque psoriasis.

Table 26. Summary of efficacy trials in patients with plaque psoriasis

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB									
Gordon et al., 2006[174] Shikiar, 2007[191]	RCT	147	12 weeks	ADA / placebo	PASI 75, DLQI	PGA, SF-36, EQ-5D	Adult patients with plaque psoriasis (of at least 1 year duration and involving >5% body surface area)	Significant improvement in PASI, DLQI, and HQL scores for ADA compared with placebo	Fair
Saurat et al., 2008[175] Revicki, 2008[192]	RCT	271	16 weeks	ADA / MTX / placebo	PASI 75, DLQI	PASI 50, 90, & 100, PGA, EQ-5D	Adult patients with moderate to severe plaque psoriasis	Significant improvement in PASI and DLQI for ADA compared with both MTX and placebo. Significant improvement in HQL for ADA compared with placebo	Good
Menter et al., 2008[176] Revicki, 2007[193] Revicki, 2008[194]	RCT	1212	16 weeks	ADA / placebo	PASI 75, DLQI	PASI 90 & 100, PGA, SF-36	Adult patients with moderate to severe plaque psoriasis	Significant improvement in PASI, DLQI, PGA, HQL in ADA compared with placebo	Good
ALEFACEPT									
Reich et al. 2008[185]	MA	1289	12 weeks	3 RCTs of ALE/placebo	PASI	DLQI	Adult patients with plaque psoriasis without any systemic treatment	RR for PASI 75 response 3.37 (95% CI 2.18 to 5.23)	Fair
Brimhall et al 2008[186]	MA	1289	12 weeks	3 RCTs of ALE/placebo	PASI	None	Adult patients with plaque psoriasis without any systemic treatment	NNT for PASI 75 response 8 (95% CI 5.05 to 12.20) HQL	Fair
ETANERCEPT									
Reich et al.[185]	MA	1965	12 - 24 weeks	4 RCTs of ETA/placebo	PASI	DLQI	Adult patients with plaque psoriasis without any systemic treatment	RR for PASI 75 response 11.92 (95% CI 8.17 to 17.39)	Fair
Brimhall et al	MA	2017	12 - 24 weeks	4 RCTs of	PASI	None	Adult patients with	NNT for PASI 75	Fair

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
2008[186]				ETA/placebo			plaque psoriasis without any systemic treatment	response 3 (95% CI 2.07 to 2.49)	
INFLIXIMAB									
Reich et al., 2005[184] Reich et al., 2006[190] Reich et al., 2007[195]	RCT	378	24 weeks (double-blind placebo cross-over to INF at week 24, to week 46)	INF / placebo	PASI	PGA, NAPSI, DLQI, SF-36	Adult patients with plaque psoriasis without any systemic treatment	Significantly greater improvement on all outcome measures for INF than for placebo	Good

ALE, alefacept; DLQI, Dermatology Life Quality Index; EFA, efalizumab; ETA, etanercept; EFA, efalizumab; EQ-5D, European Quality of Life – 5 Dimensions; HQL, health-related quality of life; INF, infliximab; MA, meta-analysis; NAPSI, Nail Psoriasis and Severity Index; NNT, number needed to treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36 Health Survey; VAS, Visual Analogue Scale

Table 27. Summary of efficacy trials in children with plaque psoriasis

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT									
Paller et al., 2008[187]	RCT	211	12 weeks	ETA / placebo	PASI 75	PASI 50 & 90, PGA, children's DLQI	Children and adolescents with moderate to severe plaque psoriasis	Significant improvement in PASI, PGA and CDQLI in ETA compared with placebo	Fair

CDQLI: Children's Dermatology Quality of Life Index; DLQI, Dermatology Life Quality Index; ETA, etanercept; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; RCT, randomized controlled trial

Key Question 2. Adverse Events

What are the comparative incidence and severity of complications associated with the use of these drugs?

Summary of Findings

Only 3 head-to-head studies provide direct evidence on the comparative risk of adverse events.[31, 32, 35] These comparisons, however, are limited to abatacept compared with infliximab and etanercept compared with infliximab.

The only double-blinded head-to-head randomized controlled trial, the ATTEST study, indicated that abatacept had a better adverse events profile than infliximab in patients with rheumatoid arthritis.[31] Serious infections occurred more frequently in patients treated with infliximab than with abatacept (8.5% compared with 1.9%; *P*=NR). Likewise, more patients on infliximab than on abatacept suffered from serious adverse events (18.2% compared with 9.6%; *P*=NR). The evidence on the comparative safety of targeted immune modulators is summarized in tables 28 and 29.

A non-randomized effectiveness trial[32] and a prospective observational study[35] reported no significant differences in adverse events between etanercept and infliximab.

In efficacy studies targeted immune modulators generally appeared to have a good tolerability profile. Long-term, rare but serious adverse events such as malignancies, serious infections, or autoimmunity are a cause of concern for all drugs and could not be assessed reliably in efficacy trials. [196-203] Injection site or infusion reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events. In efficacy studies up to 97% of patients experienced at least 1 adverse event during the course of the study.

Discontinuation rates because of adverse events in patients treated with targeted immune modulators ranged from 3% to 16% and generally did not differ significantly from those in patients treated with placebo.

Long-term extension studies of randomized controlled trials and safety analyses of post-marketing surveillance reported that the incidence of adverse events did not increase over time.[86, 99, 102, 204-207]

Injection site reactions (adalimumab, alefacept, anakinra, certolizumab pegol, etanercept) and infusion reactions (abatacept, infliximab, natalizumab, rituximab) were the most commonly and consistently reported adverse events. Except for certolizumab pegol, injection site reactions were also the most common reason for discontinuation due to adverse events. Incidence rates appeared to be significantly higher with anakinra than with anti-tumor necrosis factor drugs. Rituximab appeared to have the highest rate of infusion reactions, some of which were fatal.

The combination of 2 targeted immune modulators substantially increased the frequency of serious adverse events.

Little evidence besides efficacy trials is available on targeted immune modulators that have been approved recently such as alefacept, certolizumab pegol, natalizumab, or rituximab.

Little evidence is also available on the safety of targeted immune modulators in children.

Table 28. Evidence profile of comparisons of targeted immune modulators for adverse events in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
Abatacept compared with Infliximab							
Outcome: Adverse events							
1/ 431	RCT	Fair	N/A	Direct evidence	Higher rates of serious infections with INF than ABA (8.5% vs. 1.9%; *P*=NR) Higher rates of serious adverse events with INF than ABA (18.2% vs. 9.6%)	none	Moderate
Etanercept compared with Infliximab							
Outcome: Health outcomes							
2 / 1353	1 open-label RCT 1 prospective cohort study	Good	Yes	Yes	No difference in adverse events	none	Low
All other comparisons							
No evidence							

ABA, abatacept; INF, Infliximab; N/A, not applicable; RCT, randomized controlled trial.

Table 29. Evidence profile of comparisons of targeted immune modulators for adverse events in children

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
All comparisons							
Outcome: Adverse events							
No evidence							

Study Populations and Outcome Measures

The vast majority of studies assessing adverse events were conducted in patients with rheumatoid arthritis. Few studies used objective scales such as the Utvalg for Kliniske Undersogelser Side Effect Scale or the adverse reaction terminology from the World Health Organization. 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. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events. See Table 30 for all included studies in this section.

Sponsorship

More than 70% of studies included for this key question were funded by the pharmaceutical industry.

Detailed Assessment: Direct Evidence on the Comparative Safety

Not all studies that provided data on the comparative efficacy and effectiveness of targeted immune modulators also reported on the comparative safety. Of the 7 head-head studies included for this report only 3 provided findings on adverse events.[31, 32, 35] The available evidence is limited to comparisons of abatacept compared with infliximab and etanercept compared with infliximab. Details about these studies are described in the chapter on the comparative effectiveness.

Abatacept compared with infliximab

The only double-blinded head-to-head trial, the ATTEST study, also assessed the comparative safety of abatacept and infliximab.[31] During 1 year of follow-up abatacept generally had a better adverse events profile than infliximab. The most frequently reported adverse events in both treatment groups were infections and infusion reactions (abatacept: 59.6%, infliximab: 68.5%; *P*=NR). Serious infections occurred more frequently in patients treated with infliximab than with abatacept (8.5% compared with 1.9%; *P*=NR). Likewise, more patients on infliximab than on abatacept suffered from serious adverse events (18.2% compared with 9.6%; *P*=NR). In the infliximab group 24.8% of patients experienced infusional events compared with 7.1% treated with abatacept. Overall, numerically more patients discontinued treatment in the infliximab than in the abatacept group (7.3% compared with 3.2%; *P*=NR).

Etanercept compared with infliximab

A non-randomized effectiveness trial[32] and a prospective observational study[35] provide information on the comparative safety of etanercept and infliximab. The non-randomized trial used the adverse reaction terminology from the World Health Organization to determine adverse events.[32] Overall, no significant differences in adverse events were reported between etanercept and infliximab. The overall discontinuation rates at 20 months were also similar (etanercept 21%; infliximab 25%). In both studies, however, infliximab treated patients had higher rates of withdrawal due to adverse events than patients on etanercept (data NR). Nevertheless, the

evidence is insufficient to draw firm conclusions about the comparative safety of etanercept and infliximab.

Detailed Assessment: Evidence on the General Tolerability and Safety

Monotherapies

Most studies that examined the general efficacy of targeted immune modulators also determined their tolerability. In addition, some randomized controlled trials had open-label extension phases of up to 3 years.[60, 102, 116, 204, 208, 209]

Overall, targeted immune modulators appeared to have a good tolerability profile, although some rare but serious adverse events such as serious infections, lymphoma, leucopenia, malignancies, or demyelinations are of concern.[196-203] Appendix G summarizes black box warnings, precautions, and bold letter warnings issued by the US Food and Drug Administration for individual targeted immune modulators.

Injection site or infusion reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events. In efficacy studies up to 97% of patients experienced at least 1 adverse event during the course of the study.

Discontinuation rates because of adverse events in patients treated with targeted immune modulators ranged from 3% to 16% and generally did not differ significantly from those in patients treated with placebo. A German retrospective, population-based cohort study reported that discontinuation rates because of adverse events, after 12 months of treatment were 16% for anakinra, 13% for etanercept, and 19% for infliximab.[210] Similarly, an uncontrolled effectiveness study including more than 6000 rheumatoid arthritis patients treated with adalimumab reported that 10.3% of patients withdrew because of adverse events over a time period of 60 weeks.[196]

Injection site reactions (adalimumab, alefacept, anakinra, certolizumab pegol, etanercept) and infusion reactions (abatacept, infliximab, natalizumab, rituximab) were the most commonly and consistently reported adverse events. A small proportion of infusion reactions resembled anaphylactic reactions or led to convulsions and has to be considered serious adverse events. In efficacy trials of rituximab up to 32% of patients experienced infusion reactions during the first infusion. According to the US Food and Drug Administration prescription information, fatal infusion reactions have been reported for rituximab.[211]

In clinical trials of infliximab, 17% of patients experienced infusion reactions. These were mostly non-specific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. Nevertheless in 0.5% of all infusions severe reactions occurred.[201] Less than 2% of patients in clinical trials discontinued because of infusion reactions. Similarly, 10% of rheumatoid arthritis patients in a Japanese post-marketing surveillance of 5000 patients reported infusion reaction.[203] The rates of infusion reactions reported in abatacept and natalizumab studies were 9% and 11%, respectively.

In contrast, injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity. Except for certolizumab pegol, injection site reactions were the most common reason for discontinuation due to adverse events. The mean, crude incidence of injection site reactions in randomized controlled trials and observational studies reviewed for this report was 17.5% (95% CI, 7.1 to 27.9) for adalimumab, 2.2 % (95% CI, 0.4 to 3.9) for certolizumab pegol, 22.4% (95% CI, 8.5 to 36.3) for etanercept, but 67.2% (95% CI, 38.7 to 95.7) for anakinra. The higher incidence of injection site reactions for anakinra than for

adalimumab and etanercept is consistent with numbers reported in the respective package inserts.[212-214] The prescription information of alefacept reported injection site reactions in 16% of patients.[215]

One large, multinational randomized controlled trial was designed primarily to evaluate the safety of anakinra over 6 months.[198-200] A total of 1414 patients were randomized to anakinra (100 mg) or placebo. After 6 months the rate of adverse events did not differ significantly between anakinra and placebo, except for injection site reactions (72.6% compared with 32.9%; *P* value not reported). Overall discontinuation rates (anakinra 21.6%; placebo 18.7%) and the rate of serious adverse events (anakinra 7.7%; placebo 7.8%) were also similar. However, a trend towards an increased risk of serious infections in anakinra-treated patients was apparent (2.1% compared with 0.4%; *P*=0.068). A 3-year uncontrolled extension of this study confirmed the higher rates of serious infections in patients treated with anakinra, compared with the controls during the blinded phase.[208]

The STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) study determined the safety of adalimumab in combination with standard rheumatoid therapy.[62] At 22 weeks, there were no significant differences between adalimumab and placebo with respect to adverse events.

Long-term extension studies of randomized controlled trials and safety analyses of post-marketing surveillance reported that the incidence of adverse events does not increase over time.[86, 99, 102, 204-207] A population-based post-marketing cohort study from Sweden reported that in 27% of patients treated with etanercept, at least 1 adverse event was reported.[216]

Combination strategies

The combination of 2 targeted immune modulators substantially increased the frequency of serious adverse events. For example, a combination of anakinra and etanercept led to a substantially higher rate of serious adverse events than etanercept monotherapy (14.8% for 50 mg etanercept plus anakinra, 4.9% for 25 mg etanercept plus anakinra, and 2.5% for etanercept only; *P*=NR).[37] Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6% compared with 7.4%; *P*=NR).

Similarly, 2 studies examining a combination of abatacept (2 mg/kg) and etanercept (25 mg twice weekly) compared with abatacept (2 mg/kg) monotherapy revealed that the combination was associated with a substantial increase in serious adverse events (16.5% compared with 2.8%).[38, 111]

Detailed Assessment: Evidence on Specific Adverse Events

Serious infections

Because of the immunosuppressive nature of targeted immune modulators, serious infections including tuberculosis, pneumonia, osteomyelitis, sepsis, or progressive multifocal leukoencephalopathy are of special concern.

In June 2009, the manufacturer of efalizumab has voluntarily withdrawn the drug from the United States market because of an increased risk of progressive multifocal leukoencephalopathy. Progressive multifocal leukoencephalopathy is a rapidly progressive, viral infection of the central nervous system that leads to death or severe disability. A case series of more than 3000 patients treated with natalizumab for various indications did not meet our formal inclusion criteria. This study, however, estimated the risk of progressive multifocal leukoencephalopathy of roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9

months.[217] No evidence is available about the risk for progressive multifocal leukoencephalopathy for any of the other targeted immune modulators.

The US Food and Drug Administration has issued black box warnings or cautions in bold letters about an increased risk of infections for all targeted immune modulators.

An Italian retrospective cohort study of 1064 rheumatoid arthritis patients treated with adalimumab, etanercept, and infliximab estimated the incidence rate of infections as 35.9 per 1000 patient years.[218] Most infections were lower respiratory tract infections (34%) or skin and soft tissue infections (21%).

In efficacy trials, the incidence of serious infections was consistently higher in targeted immune modulators than in placebo-treated patients although clinically relevant differences rarely reached statistical significance due to lack of power. For example, in a large safety randomized controlled trial (n = 1414), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1% compared with 0.4%; P=0.068).[198-200] Similarly, a fair, uncontrolled effectiveness study of more than 6600 patients treated with adalimumab reported that 3.2% of patients suffered from serious infections during up to 60 weeks of follow-up.[196] Likewise, a fair meta-analysis of efficacy trials of abatacept, anakinra, and rituximab indicated an increased risk of serious infections without reaching statistical significance.[219] A good meta-analysis pooled data of more than 5000 rheumatoid arthritis patients from adalimumab and infliximab efficacy trials.[220] The pooled odds ratio for serious infections was 2.0 (95% CI, 1.3 to 3.1). The number needed to harm was 59 (95% CI, 39 to 125) within a treatment period of 3 to 12 months.

The START (Trial for Rheumatoid Arthritis with Remicade) study was a good randomized controlled trial (N=1084) conducted to assess the risk of serious infections during infliximab treatment for rheumatoid arthritis.[94] After 22 weeks of treatment patients on 3mg/kg infliximab had similar rates of serious infections as patients on placebo (relative risk, 1.0; 95% CI, 0.3 to 3.1). Patients treated with 10mg/kg infliximab had a significantly higher rate of serious infections than patients on placebo (relative risk, 3.1; 95% CI, 1.2 to 7.9).

Most long-term observational studies support these findings.[197, 201, 221-226] The most common serious opportunistic infections were cases of tuberculosis. Other observational studies, some of which did not meet eligibility criteria for this review, reported infections with candida,[227] coccidiomycosis,[228, 229] Herpes Zoster,[230] histoplasmosis,[231] listeriosis,[232] and pneumocystis carinii.[233]

Three retrospective database analyses[222, 234, 235] and a prospective cohort study with a historic control group[236] specifically determined the risk of tuberculosis or granulomatous infections during treatment with infliximab and etanercept. All studies reported a significant increase of risk attributable to anti-tumor necrosis factor therapy. A study of patients from the National Data Bank for Rheumatic Diseases (NDP) reported an incidence 52.5 cases per 100,000 patients years.[236] Two other database analyses used the Spanish BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia)[235] and different Swedish databases[222] which included data on infliximab and etanercept. Both reports indicated a substantially increased risk for tuberculosis in patients treated with etanercept or infliximab. The Swedish study reported a 4-fold increased risk of tuberculosis (relative risk, 4.0; 95% CI, 1.3 to 12) for patients on anti-tumor necrosis factor treatment compared with rheumatoid arthritis patients not exposed to etanercept or infliximab.[222]

Lymphoma and other malignancies

The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with rheumatoid arthritis.[237] Data from controlled trials do not provide sufficient evidence concerning a further increase of risk attributable to targeted immune modulators or a combination of targeted immune modulators and methotrexate. A good meta-analysis pooled data of more than 5000 rheumatoid arthritis patients from adalimumab and infliximab placebo-controlled efficacy trials.[220] The pooled odds ratio for malignancies was 3.3 (95% CI, 1.2 to 9.1). The number needed to harm was 154 (95% CI, 91 to 500) within a treatment period of 6 to 12 months. In this cohort authors identified 10 lymphomas in 3493 anti-tumor necrosis factor-treated patients compared with no lymphomas in 1512 patients treated with conventional rheumatoid arthritis therapy.

Several large retrospective cohort studies, using data from population-based databases, assessed the risk of malignancies during targeted immune modulators therapy. The only study that partially supported findings from the meta-analysis mentioned above was a Swedish retrospective cohort study of 1557 patients.[238] Although results did not reach statistical significance, findings revealed a substantially increased relative risk of lymphoma for patients treated with anti-tumor necrosis factor drugs compared with those on non-anti-tumor necrosis factor medications (hazard ratio, 4.9; 95% CI, 0.9 to 26.2)

Various large retrospective cohort studies and a meta-analysis of individual patient data from etanercept trials[239] did not detect an increased risk of hematopoietic malignancies[240-243] or solid tumors.[241 243-245] For example, a large retrospective Swedish cohort study, based on data of more than 60000 rheumatoid arthritis patients, found similar standardized incidence ratios for solid cancers (standard incidence ratio, 0.8; 95% CI, 0.4 to 1.8)[244] and hematopoietic malignancies (relative risk, 1.1; 95% CI, 0.6 to 2.1)[242] between rheumatoid arthritis patients treated with anti-tumor necrosis factor medications and those on conventional therapy using both a contemporary and a historic control.

Two fair retrospective cohort studies, however detected an increased risk of skin cancers in patients treated with anti-tumor necrosis factor drugs.[241, 246] The larger study (N=15789), reported a statistically significant association of a combination of anti-tumor necrosis factor treatment and methotrexate and non-melanoma skin cancer (hazard ratio, 1.28; 95% CI, NR; P=0.014).[246]

These findings, however, were not supported by a smaller retrospective cohort study that did not detect an increased incidence of squamous cell carcinoma in 1442 rheumatoid arthritis patients (4257 patient years) treated with etanercept (crude rate: 2.8 cases per 1000 patients).[247]

Cardiovascular events and congestive heart failure

No direct evidence on the comparative risk of targeted immune modulators for congestive heart failure exists. The existing evidence on the risk of cardiovascular events and congestive heart failure with anti-tumor necrosis factor therapy is mixed. A large retrospective cohort study (N=13,171) based on the National Databank for Rheumatic Diseases reported an absolute risk reduction for congestive heart failure of 1.2% (95% CI, -1.9 to -0.5; P=NR) for patients treated with anti-tumor necrosis factor therapy compared with those not treated with anti-tumor necrosis factor medications over a 2 year period.[248] A retrospective cohort study based on the British Society for Rheumatology Biologics Register found that the risk for myocardial infarction is substantially reduced in patients responding to anti-tumor necrosis factor therapy after 6 months compared with non-responders (3.5 events per 1000 patient years compared with 9.4 events per

1000 patient years).[249] Confounding by indication, however, cannot entirely be ruled out with such study designs.

By contrast, 2 retrospective cohort studies based on Medicare data reported a statistically significantly higher risk for hospitalization due to congestive heart failure in rheumatoid arthritis patients treated with anti-tumor necrosis factor drugs compared with those on methotrexate (hazard ratio, 1.70; 95% CI, 1.07 to 2.69).[250] Similarly, a MedWatch analysis reports that half of the patients who developed new onset congestive heart failure under etanercept or infliximab treatment did not have any identifiable risk factors.[251]

Indirect evidences comes from 3 trials, 2 on etanercept[252] and 1 on infliximab,[253] that evaluated the efficacy of these drugs for the treatment of congestive heart failure. Information on the 2 etanercept studies, however, is limited to a review article.[252] The studies have not been published otherwise. We did not include this review article because it was not based on a systematic literature review. Nevertheless, we are briefly summarizing the findings.

Populations of these studies did not have any rheumatoid illnesses and, therefore, provide only indirect evidence. One of the 2 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.[253] The package insert of infliximab issues a contraindication regarding the use in patients with congestive heart failure; the package inserts of etanercept and adalimumab emphasize precaution.

Finally, 5 retrospective cohort studies could not detect statistically significant differences supporting an increased or a decreased risk for cardiovascular events or congestive heart failure between anti-tumor necrosis factor treatment and conventional rheumatoid arthritis[249, 254-257] or Crohn's disease treatment.[256]

Other adverse events

Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but serious adverse events such as autoimmunity, demyelination, hepatotoxicity, and pancytopenia.

Reports of autoimmunity based on data from MedWatch (which did not meet our inclusion criteria) have not been confirmed in controlled trials and observational studies. Case reports, however, suggest an association between infliximab and drug induced lupus and other autoimmune diseases.[197, 201, 258, 259] Lupus-like syndromes have also been reported for adalimumab.[205] A prospective cohort study of 125 consecutive Crohn's disease patients treated with infliximab reported a cumulative incidence of antinuclear antibodies of 56.8% after 24 months.[260] Development of anti-nuclear, anti-double-stranded DNA, or anti-histone antibodies have also been reported in regulatory trials of other anti-tumor necrosis factor alpha drugs.[213, 215] A retrospective cohort study indicated an increased risk of new onset psoriasis in rheumatoid arthritis patients treated with anti-tumor necrosis factor drugs.[261]

Similarly, reports from MedWatch indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[205, 262] Similar cases have been seen in regulatory trials of adalimumab.[213] All neurologic events partially or completely resolved after discontinuation of treatment.

The infliximab package insert reports that 34% of patients treated with infliximab and methotrexate experienced transient elevations of liver function parameters.[263] Severe liver injury, including acute liver failure has been reported. A retrospective cohort study based on more than

1400 patients treated with either etanercept or infliximab also reported a substantially increased risk of serious hepatic events with targeted immune modulators (relative risk, 5.5; 95% CI, 1.2 to 24.6).[264] The wide confidence intervals, however, indicate the uncertainty of these results.

Table 30. Summary of studies assessing adverse events in adult patients

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
Overall tolerability							
Braun et al. 2005[130, 204, 265-267]	Open-label extension of RCT	70	3 years	INF	Patients with AS	INF is a well tolerated treatment	Fair
Burmester et al., 2007[196]	Uncontrolled effectiveness trial	6610	Up to 60 weeks	ADA	Patients with RA	10.3% discontinued because of adverse events. 3% of patients had serious infections	Fair
Feltelius et al, 2005[216]	Retrospective cohort study	1073	≥2 years	ETA	Patients with RA	27% of patients experienced at least 1 adverse event. The incidence of serious adverse events remained constant over time.	NA
Fleischmann et al. 2006[198-200, 208]	Open-label extension of RCT	1,414	3 years	AKA	Patients with RA	Higher rates of infections and serious adverse events for AKA than for controls during blinded phase	Fair
Genovese et al., 2004[37]	RCT	242	24 weeks	ETA+MTX / ETA+ANA+MTX	Patients with RA	Adverse events rates significantly higher in combination than in ETA group	Fair
Genovese et al.[86]	Open-label extension of RCT	201	5 years	ETA	Patients with RA	Higher rates of lymphoma compared to general population	Fair
Maini et al. 2004[99, 102]	Open-label extension of RCT	259	2 years	INF	Patients with RA	Rate of severe adverse events was similar in INF and placebo	Fair
Nuki et al.2002[207]	Uncontrolled extension of RCT	309	76 weeks	AKA	Patients with RA	AKA was well tolerated at all dose levels for up to 76 weeks	NA
Schiff et al. 2006[205]	Postmarketing surveillance	10,050	12, 506 patient years	ADA	Patients with RA	Long-term ADA treatment was generally safe	NA
Takeuchi et al., 2008[203]	Postmarketing surveillance	5000	6 months	INF	Patients with RA	Infusion reaction occurred in 10%, serious adverse events in 6% of patients	NA
Weinblatt et al., 2006[111]	RCT	121	24 weeks	ABA +ETA / ETA	Patients with RA	Adverse events rates significantly higher in combination than in ABA group	Fair
Weinblatt et al., 2006[60]	Open-label extension of RCT	162	3.4 years	ADA	Patients with RA	2.03 serious infections / 100patient-years	Fair
Zink et al, 2005[210]	Retrospective cohort study	1523	12 months	AKA, ETA,	Patients with RA	Similar discontinuation rates because of adverse events among AKA, ETA and	Fair

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
				INF		INF	
Infectious diseases							
Askling et al. 2007[224]	Retrospective cohort study	44946	NR	ADA, ETA, INF	Patients with rheumatic diseases; primary care-based cohort	Treatment with anti-TNF drugs is associated with an increased risk of hospitalization due to infection	Good
Askling et al., 2005[222]	Database analysis, Sweden	62,321	467,770 person years	ETA, INF	Patients with RA	4-fold increase of risk for tuberculosis for ETA and INF	NA
Bongartz et al. 2006[220]	Meta-analysis	5014	3 to 12 months	ADA, INF	Patients with RA	Statistically significantly higher risk of serious infections for ADA and INF compared with placebo (*P*=NR)	Good
Brassard et al., 2006[234]	Retrospective cohort study	112,300	NR	ANA, ETA, INF	Patients with rheumatic diseases; primary care-based cohort	Treatment with anti-TNF drugs is associated with an increased risk of tuberculosis	Fair
Curtis et al., 2007[226]	Retrospective cohort study	6287	8740 person years	ADA, ETA, INF	Patients with rheumatic diseases; primary care-based cohort	Treatment with anti-TNF drugs is associated with an increased risk of infections	Fair
Favalli et al., 2009[218]	Retrospective cohort study	1,064	NR	ADA, ETA, INF	Patients with rheumatic diseases; primary care-based cohort	Treatment with anti-TNF drugs is associated with an increased risk of infections	Fair
Gomez-Reino et al. 2003[235]	Retrospective cohort study	1540	Any duration	ETA, INF	Patients treated with INF or ETA	TB is more common in patients treated with INF or ETA	Fair
Lichtenstein et al., 2006[268]	Prospective cohort study	6290	Mean 1.9 years	INF / Other Crohn's therapies	Patients treated with INF	Mortality rates and serious infections between INF and other therapies were similar	Fair
Listing et al. 2005[223]	Prospective cohort study	1529	Up to 12 months	AKA, ETA, INF	Patients with RA	Higher risk of infections for AKA, ETA, INF compared with DMARDS	Fair

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
Salliot et al., 2009[219]	Meta-analysis	6879	12-48 weeks	AKA, ABA, RIT	Patients with RA	Numerically higher rates of serious infections for ABA, AKA, and RIT than for placebo	Fair
Schneeweis et al., 2007[225]	Retrospective cohort study	15,597	NR	ABA, ETA, INF	Elderly patients with RA	Compared with MTX no higher rates of serious bacterial infections	Good
Strangfeld et al, 2009[230]	Retrospective cohort study	5040	NR	ADA, ETA, INF	Patients with RA	Numerically increased risk of Herpes Zoster for patients on anti-TNF drugs	Good
Westhovens et al., 2006 (START)[94]	RCT	1084	22 weeks	INF + MTX / MTX	Outpatients with active RA and insufficient response to standard antirheumatic therapy	The risk of serious infections was similar between placebo and 3mg/kg infliximab. 10mg/kg infliximab led to increased risk of serious infections.	Good
Wolfe et al. 2004[236]	Prospective cohort study	17,242	3 years	INF	Patients treated with INF	TB is more common in patients treated with INF	Fair
Wolfe et al., 2006[269]	Prospective cohort study	16,788	3.5 years	ADA, ETA, INF	Patients with RA	No increased risk for hospitalization for pneumonia foe ADA, ETA, and INF	Fair
Lymphoma and other malignancies							
Askling et al., 2005[244]	Retrospective cohort study	60,930	NR	Anti-TNF	Patients with RA	No increase in solid cancers for patients treated with anti-TNF drugs	Fair
Askling et al., 2005[242]	Retrospective cohort study	60,930	NR	Anti-TNF	Patients with RA	No increase in lymphoma for patients treated with anti-TNF drugs	Fair
Bongartz et al. 2006[220]	Meta-analysis	5014	3 to 12 months	ADA, INF	Patients with RA	Statistically significantly higher risk of malignancies for ADA and INF compared with placebo	Good
Bongartz et al. 2009[239]	Meta-analysis	3316	12 weeks or longer	ETA	Patients with RA	No statistically significant difference in risk for malignancies between ETA and placebo	Good
Chakravarty et al., 2005[246]	Retrospective cohort study	15,789	NR	ETA, INF	Patients with RA	Statistically significant association between anti-TNF+MTX use and non-melanoma skin cancer	Fair
Geborek et al., 2005[238]	Retrospective cohort study	1557	5551 patient years	ETA, INF	Patients with RA	Higher risk of lymphoma for anti-TNF drugs	NA
Lebwohl et al.	Database review	1,442	3.7 years	ETA	Patients with RA	ETA does not seem to be associated	NA

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
2005[247]						with an increase in the incidence of cutaneous squamous cell carcinoma	
Setoguchi et al., 2006[243]	Retrospective cohort study	8,458	30,300 patient years	ADA, ANA, ETA, INF	Patients with RA	No increased risk of cancer in patients treated with TIMs	Fair
Simon et al., 2008[245 5670]	Retrospective cohort study	4134	NR	ABA	Patients with RA	No increased risk of cancer in patients treated with ABA	Fair
Wolfe et al. 2007[241]	Retrospective cohort study	13,001	49,000 patient years	ETA, INF	Patients with RA	Increased risk of skin cancers but not of solid tumors or lymphoproliferative malignancies in patients treated with ETA or INF	Good
Wolfe et al. 2007[240]	Retrospective cohort study	19,591	89,710 patient years	ETA, INF	Patients with RA	No increased risk of lymphoma in patients treated with ETA or INF	Good
Congestive heart failure							
Chung et al. 2003[253]	RCT	150	28 weeks	INF	Patients with CHF	INF (10mg) –treated patients were more likely to die or have heart failure than placebo-treated patients	Fair
Curtis et al., 2007[256]	Retrospective cohort study	4018	NR	ETA, INF	Patients with RA or CD	No significant difference for the risk of heart failure between anti-TNF or conventional treatment	Fair
Dixon et al., 2007[249]	Retrospective cohort study	10840	16126 person years	ADA, ETA, INF	Patients with RA	Significantly reduced risk of myocardial infarction in responders to anti-TNF treatment compared with non-responders	Good
Listing et al., 2008[257]	Retrospective cohort study	4248	5 years	ADA, ETA, INF	Patients with RA	No significant difference for the risk of heart failure between anti-TNF or conventional treatment	Good
Setoguchi et al., 2008[250]	Retrospective cohort study	6595	12303 person years	ADA, ETA, INF	Patients with RA older than 65 years	Significantly higher risk of hospitalization due to heart failure for patients treated with anti-TNF than with MTX	Good
Solomon et al., 2006[255]	Nested case control study	3501	22-24 months	ADA, ETA, INF	Patients with RA older than 65 years	No difference in cardiovascular events between anti-TNF drugs and MTX	Fair
Suissa et al., 2006[254]	Retrospective cohort study,	6,138	NR	ANA, ETA,	Patients with RA	No difference in cardiovascular events between anti-TNF drugs and no use of	Fair

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
	nested case control study			INF		DMARDs	
Wolfe et al.2004[248]	Retrospective cohort study	13,171	2 years	Retrospective cohort study	Patients with RA	Patients on anti-TNF treatment had a lower rate of congestive heart failure than patients on traditional RA therapy	Fair
Other adverse events							
Harrison et al., 2009[261 5772]	Retrospective cohort study	12,706	NR	ADA, ETA, INF	Patients with RA	Incidence of psoriasis is increased in patients with anti-TNF treatment	Fair
Suissa et al., 2004[264 4984]	Retrospective cohort study	1402	NR	ETA, INF	Patients with RA	Fivefold increase of risk for serious hepatic events	Fair

ABA, abatacept; ADA, adalimumab; AKA, anakinra; AS, ankylosing spondylitis; CD, Crohn's disease; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; IBS, irritable bowel disease; INF, infliximab; JRA, juvenile rheumatoid arthritis; MTX, methotrexate; NA, not applicable; RA, rheumatoid arthritis; RCT, randomized controlled trial; RIT, rituximab; TB, tuberculosis; TNF, tumor necrosis factor, TIM, targeted immune modulator.

Tolerability in Children

No evidence on the comparative safety of targeted immune modulators in children exists (Table 29). Furthermore, no study met our eligibility criteria for general safety. In the following paragraphs we summarize the scarce evidence that exists on the safety of targeted immune modulators in pediatric populations (presented in table 31). Overall, various methodological issues limit the quality and applicability of this body of evidence.

A major limitation was that all studies had small sample sizes and lacked power to detect rare but potentially serious adverse events. Furthermore, except for the infliximab trial,[117] all studies used withdrawal designs, which seriously compromise the external validity of findings. After a run-in period with the active drug, only patients who responded, adhered to treatment, and had no intolerable adverse events were randomized to continuing active treatment or placebo. Therefore, all findings presented in the following paragraphs are subject to considerable uncertainty and should be interpreted accordingly. To provide a more realistic picture of the frequency of adverse events we focus on numbers from the open-label run-in phases that still included a less selected population than the randomized phases.

The 4 randomized controlled trials summarized in the chapter on juvenile idiopathic arthritis also provided information on the general tolerability and safety of abatacept,[114] adalimumab,[115] etanercept,[116] and infliximab.[117] Generally, adverse events profiles in children were similar to those observed in adult populations. For example, in the adalimumab trial the most common adverse events were infections and injection site reactions,[115] which were also the most commonly reported adverse events in adult populations. During the open-label run-in phase of the adalimumab and methotrexate arm (n = 85) the rate of any adverse event was 15.5 per patient year. The rate of serious adverse events was 0.1 per patient year.

Similarly, injection site reactions (39% of patients) and upper respiratory tract infections were the most commonly reported adverse events during the run-in phase of the etanercept study.[116] Nine patients (15%) had to be hospitalized because of serious adverse events during the 2-year extension phase.[116, 209] Fifty% of the patients received etanercept up to 4 years.[270] The rate of serious adverse events in children treated over 4 years was 0.04 per patient-year.[270]

In an uncontrolled trial of etanercept (n=60), 20% of patients withdrew over a 12-months period because of adverse events including severe infections, pancytopenia, and cutaneous vasculitis.[271] In a case series based on data from a registry of children treated with etanercept in Austria and Germany (n = 322) withdrawal rates because of adverse events were substantially lower than in the trial.[118] Overall, 3.4% of etanercept-treated patients withdrew because of adverse events. Given the voluntary nature of this registry, under reporting of adverse events is possible.

Abatacept and infliximab are both administered intravenously and acute infusion reactions are a concern for both drugs. The rate of infusion reactions appeared to be greater in the infliximab study than in the abatacept study. Overall, 18% to 35% of patients treated with infliximab experienced acute infusion reactions.[117] A case series of patients (n = 11) with Crohn's disease or ulcerative colitis reported infusion reactions in 8.1% of patients.[272] By comparison, only 4% of patients on abatacept reported acute infusion reactions.[114] With respect to other adverse events, the profiles and frequencies were similar as in subcutaneously administered drugs.

On August 4th the US Food and Drug Administration issued a warning about an increased risk of cancer in children and adolescents who receive anti-TNF drugs (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm). The warning is based on an investigation of cancer cases (n = 48) reported in children and adolescents with juvenile idiopathic arthritis, Crohn's disease, or other inflammatory diseases who were treated with anti-TNF drugs. About half of the cancers were lymphomas, some of which were highly malignant hepato-splenic T-cell lymphomas. Some of the malignancies were fatal. The analysis showed that an increased risk occurred after an average of 30 months of anti-TNF treatment. The Food and Drug Administration will add the new safety information as boxed warnings to the prescription information.

Table 31. Summary of studies assessing adverse events in pediatric patients[a]

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
Overall tolerability							
Friesen et al., 2004[272]	Case series	111	19.9 months	INF	Pediatric patients with Crohn's disease or UC	8.1% had infusion reactions	NA
Horneff et al., 2004[118]	Case series	322	NR	ETA	Pediatric patients with polyarticular-JIA	3.4% withdrew because of adverse events	NA
Lovell et al.[116, 209] 2003	Open-label extension of RCT	58	up to 2 years	ETA	Pediatric patients with polyarticular-JIA	16% of patients experienced serious adverse events	NA
Lovell et al. 2006[270]	Open-label extension of RCT	34	up to 4 years	ETA	Pediatric patients with polyarticular-JIA	Overall the rate of serious adverse events was 0.13 per patient-year	NA
Quartier et al., 2003.[271]	Uncontrolled trial	60	NR	ETA	Pediatric patients with polyarticular-JIA	20% withdrew because of adverse events	NA

ETA, etanercept; JIA, juvenile idiopathic arthritis; INF, infliximab; NA, not applicable; NR, not reported; RCT, randomized controlled trial; UC, ulcerative colitis.
[a] None of these studies met eligibility critria.

Key Question 3. Subgroups

Do the included drugs differ in their effectiveness or adverse events in the following subgroups: racial groups, genders, or age groups; or in patients taking other commonly prescribed drugs?

Summary of Findings

Overall, the strength of evidence to determine differences in effectiveness or adverse events among subgroups was low or insufficient. The majority of the studies were not specifically designed to compare the effectiveness and safety of targeted immune modulators in one subgroup of patients compared to another or compared to the general population. Subgroup analyses and indirect evidence from placebo-controlled trials provide evidence for some targeted immune modulator drugs in certain subpopulations.

Evidence on the effect of age is mixed. Indirect evidence exists from 3 studies[273-275] that age is not associated with greater or lesser clinical response rates or adverse events in ankylosing spondylitis, rheumatoid arthritis psoriatic arthritis, or plaque psoriasis.

No studies were identified addressing the differences in effectiveness or safety based on race. The evidence on differences between men and women is sparse: 1 study reported on efficacy and 1 study reported on adverse events. A pooled analysis of 9 efficacy studies of alefacept did not detect any differences in efficacy and safety for obese or diabetic patients with plaque psoriasis.[275]

Findings in studies evaluating effectiveness and safety in patients with comorbid conditions (respiratory disease, diabetes, cardiovascular disease) are mixed. Two studies reported no differences in adverse events in patients with comorbidities[200, 275] while 3 studies reported an increased risk of the occurrence of adverse events.[111, 203, 276]

All studies shown in Table 32, below.

Detailed Assessment

Age

Overall, the evidence of the effect of age on the effectiveness and safety of targeted immune modulators is mixed. For plaque psoriasis a pooled data analysis of 9 efficacy studies of alefacept did not show any differences in efficacy and safety in patients older than 65 years compared to younger patients during 12 weeks of treatment.[275]

This finding is supported by a pooled data analysis of 18 rheumatoid arthritis trials, 2 psoriatic arthritis trials, and 2 ankylosing spondylitis trials.[273] This analysis detected no significant differences in adverse events between elderly and younger (under 65) patients. In addition, a retrospective cohort study found no differences in discontinuation rates or mean DAS28 scores at 2 years between anti-tumor necrosis factor treated patients older than and younger than 65 years.[274]

In contrast, a prospective cohort study[34] (N=3694), indicated that response to treatment in rheumatoid arthritis patients treated with etanercept and infliximab was better in those younger than 65 years.[34] A post-marketing surveillance of 5000 rheumatoid arthritis patients reported a difference in adverse events in older patients.[203] Risk factor for bacterial pneumonia in infliximab-treated patients was significantly higher in patients aged 70 years and older compared with patients in their 50's (odds ratio, 2.57; 95% CI, 1.48 to 4.46; $P<0.001$).

Racial groups

We did not identify any study specifically designed to compare the effect of targeted immune modulators in one racial group compared to another. In general, trials were conducted predominantly in white populations. No indirect evidence suggests that effectiveness or adverse events differ among races.

Gender

We did not identify any study specifically designed to compare the effects of targeted immune modulators in females compared to males. On average, study populations comprised more females than males; this fact reflects population and disease demographics and does not provide insight into treatment differences.

The available evidence is of low methodological quality and findings are mixed. One prospective observational study of rheumatoid arthritis patients treated with anti-tumor necrosis factor drugs found no significant differences in treatment response between men and women at 3 and 6 months of follow-up.[277]. The Japanese post-marketing surveillance study of infliximab (described above),[203] reported that men were significantly more susceptible than women for bacterial pneumonia (odds ratio, 1.94; 95% CI, 1.29 to 2.93; P=0.001).

No other indirect evidence suggests that effectiveness or adverse events differ between females and males.

Comorbidities

Overall, the evidence of the effect of certain comorbid conditions on the efficacy and safety of targeted immune modulators is mixed. Three studies reported on rheumatoid arthritis patients with comorbid respiratory disease.[111, 203, 276] One randomized controlled trial assigned rheumatoid arthritis patients with asthma or chronic obstructive pulmonary disease to 16 weeks of treatment with etanercept or placebo.[276] Etanercept was associated with small increases in the incidence of serious adverse events in patients with chronic obstructive pulmonary disease; however, the relative risk was not significantly elevated (1.58; 95% CI, 0.65 to 3.87). A postmarketing surveillance of the safety of infliximab in rheumatoid arthritis patients reported a significantly higher risk factor for bacterial pneumonia in patients with comorbid respiratory disease (odds ratio, 3.90; 95% CI, 2.32 to 6.47; P<0.001).[203] A subgroup analyses from 1 randomized controlled trial found that more adverse events were reported in rheumatoid arthritis patients with chronic obstructive pulmonary disease taking abatacept compared with placebo.[111] This was also the case for adverse events involving the respiratory system (43.2% compared with 23.5%) and serious adverse events (27% compared with 5.9%).

Three studies reported on patients with comorbid diabetes, 2 in rheumatoid arthritis patients[111, 276] and 1 in plaque psoriasis.[275] One trial stratified randomization of 535 rheumatoid arthritis patients by diagnosis of diabetes (with or without another comorbidity).[276] Subjects were treated with etanercept (25 mg twice/week) or placebo for 16 weeks and to evaluate the occurrence of infections and serious adverse events. Etanercept was associated with small increases in the incidence of serious adverse events compared with placebo in patients with diabetes; however, the relative risk was not significantly elevated (1.34; 95% CI, 0.59 to 3.08).

These findings are supported by a subgroup analysis of 1 randomized controlled trial of rheumatoid arthritis patients with diabetes treated with abatacept.[111] Results indicated a slightly higher incidence of overall adverse events in diabetic patients taking abatacept compared with

diabetic patients taking placebo (93.8% [n=65] compared with 90.3% [n=31]).[111] Rates of serious adverse events were higher in the abatacept group (21.5% compared with placebo 12.9%).

Results from a pooled analysis of 9 efficacy studies of alefacept for the treatment of plaque psoriasis indicated that alefacept has similar efficacy and safety in obese and diabetic patients compared to patients without these comorbidities.[275]

A post hoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, central nervous system-related events).[198, 200] Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

No direct evidence on the comparative risk of targeted immune modulators in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, or plaque psoriasis and congestive heart failure exists. The existing evidence on the risk of cardiovascular events and congestive heart failure with anti-tumor necrosis factor therapy is mixed. A large retrospective cohort study (N=13 171) based on the National Databank for Rheumatic Diseases reported an absolute risk reduction for congestive heart failure of 1.2% (95% CI, -1.9 to -0.5; *P*=NR) for patients treated with anti-tumor necrosis factor therapy compared with those not treated with anti-tumor necrosis factor medications over a 2 year period.[248] A retrospective cohort study based on the British Society for Rheumatology Biologics Register found that the risk for myocardial infarction is substantially reduced in patients responding to anti-tumor necrosis factor therapy after 6 months compared with non-responders (3.5 events/1000 patient years compared with 9.4 events/1000 patient years).[249]

By contrast, indirect evidence exists regarding an increased risk of worsening heart failure and mortality during anti-tumor necrosis factor alpha therapy. One trial[253] evaluated efficacy of infliximab for the treatment of congestive heart failure. Infliximab was associated with higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.[253] This evidence on congestive heart failure is presented in greater detail in Key Question 2.

Other subgroups

We found 1 study, a case series of 131 pregnant women exposed to infliximab; however, this study did not meet our eligibility criteria.[278] We describe it briefly because it is the only study addressing pregnant women. This study did not detect an increased risk of adverse pregnancy outcomes compared to the general population. However, the sample size of this study was small and limitations of case series must be kept in mind. In addition, 27% of patients were lost to follow-up.

Other commonly prescribed medications

No formal drug interaction studies have been performed with any targeted immune modulators. Concurrent administration of anakinra with tumor necrosis factor-blocking agents (i.e., adalimumab, etanercept, infliximab) may be associated with an increased risk of serious infections, an increased risk of neutropenia, and no additional benefit compared to monotherapy. This evidence comes from a 24 week trial comparing concurrent treatment with anakinra and etanercept to etanercept monotherapy in patients with rheumatoid arthritis.[37] Patients treated with both anakinra and etanercept had a 7% rate of serious infections, compared to no infections observed in patients treated with etanercept alone. Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia. Because adalimumab and infliximab have a

similar mechanism of action to etanercept, similar risks are believed to be associated with concurrent treatment with anakinra, although no formal evidence exists.

Because the majority of patients included in clinical studies received 1 or more concomitant medications (e.g., 5-aminosalicylates, antibiotics, antivirals, azathioprine, corticosteroids, folic acid, narcotics, nonsteroidal anti-inflammatory agents, and 6-mercaptopurine) with no identifiable differences in safety or tolerability, concomitant treatment with such agents is believed to be safe. One analysis of data from the first 6 months of a large, blinded, placebo-controlled safety trial of anakinra provides evidence for the risk of infections or other serious adverse events for some concomitant medications.[199] In this trial, no statistically significant differences were noted in the risk of infection or other serious adverse events between placebo- and anakinra-treated patients concurrently taking methotrexate or other disease-modifying antirheumatic drugs. Two patients taking anakinra and azathioprine developed serious infections compared to no patients taking azathioprine and placebo, although the number of patients taking azathioprine was deemed to be too small to draw any definitive conclusions. The adverse event profiles were similar for anakinra and placebo for patients who were or were not taking concomitant antihypertensive, antidiabetic, or statin drugs.

Concomitant administration of adalimumab and methotrexate has demonstrated a 29% to 44% reduction in the clearance of adalimumab. However, data do not suggest the need for dose adjustment of either methotrexate or adalimumab.[279] Studies evaluating concomitant administration of methotrexate with anakinra or etanercept have not demonstrated changes in the clearance either drug. Although no formal studies have evaluated drug interactions between methotrexate and alefacept, or infliximab, concomitant administration of these agents is believed to be safe.

Table 32. Summary of studies assessing subgroups

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
Age							
Fleischmann et al. 2005[273]	Pooled safety data from RCTs	4322	NR	Anti-TNF	Patients with RA, AS, PsA	No differences in adverse events between patients older and younger than 65 years	Fair
Genevay et al. 2007[274]	Retrospective cohort	1571	Median 3 yrs	Anti-TNF	Patients with RA	No differences in discontinuation rates or change in DAS28 between patients older and younger than 65	Fair
Gottlieb et al. 2005[275]	Pooled analysis of efficacy trials	NR	12 weeks	ALE	Patients with plaque psoriasis	No differences in efficacy and adverse events between patients older and younger than 65 years	Fair
Takeuchi et al. 2008[203]	Postmarketing surveillance	5000	6 months	INF	Patients with RA	Significantly higher risk factor for bacterial pneumonia in patients older than 70 vs. patients in their 50s	NA
Weaver et al. 2006[34]	Prospective cohort study	3694	52 weeks	ETA, INF	Patients with RA	Patients younger than 65 years had better response	Fair
Comorbidities							
Chung et al. 2003[253]	RCT	150	28 weeks	INF	Patients with CHF	INF-treated (10mg) patients were more likely to die or have heart failure than placebo-treated patients	Fair
Gottlieb et al. 2005[275]	Pooled analysis of efficacy trials	NR	12 weeks	ALE	Patients with plaque psoriasis	No differences in efficacy and adverse events in diabetic and obese patients compared to the general study population	Fair
Dixon et al. 2007[249]	Retrospective cohort study	10840	16126 person years	ADA, ETA, INF	Patients with RA	Significantly reduced risk of myocardial infarction in responders to anti-TNF treatment compared with non-responders	Good
Schiff et al. 2004[198, 200]	Subgroup analyses of RCT	1,414	6 months	AKA	Patients with RA	Incidence rates of adverse events similar in patients with comorbidities	Fair
Takeuchi et al. 2008[203]	Postmarketing surveillance	5000	6 months	INF	Patients with RA	Significantly higher risk factor for bacterial pneumonia in patients with comorbid respiratory disease	NA
Weinblatt et al. 2006[111]	Subgroup analyses of RCT	NR	52 weeks	ABA vs. placebo	Patients with RA	More SAEs in ABA-treated patients with COPD or DM	Fair
Weisman et al. 2007[276]	RCT	535	16 weeks	ETA vs. placebo	Patients with RA and ≥ 1 comorbidity	ETA associated with small increases in incidence of SAEs in patients with diabetes and COPD	Fair

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
Wolfe et al. 2004[248]	Retrospective cohort study	13,171	2 years	Anti-TNF	Patients with RA	Patients on anti-TNF treatment had a lower rate of CHF than patients on traditional RA therapy	Fair
Concomitant medications							
Genovese et al. 2004[37]	RCT	242	24 weeks	AKA + ETA, ETA	Patients with RA	Patients treated with both AKA and ETA had a 7% rate of serious infection, compared to no infections observed with ETA alone.	Fair
Tesser et al. 2004[199]	RCT	1399	6 months	AKA	Patients with RA	The adverse event profiles were similar for anakinra and placebo for patients who were or were not taking concomitant antihypertensives, antidiabetic, or statin drugs.	Fair
Gender							
Kristensen 2008[277]	Prospective observational study	1565	3 months	Anti-TNF	Patients with RA	Gender did not influence treatment response	Fair
Takeuchi et al. 2008[203]	Postmarketing surveillance	5000	6 months	INF	Patients with RA	Significantly higher risk factor for bacterial pneumonia in men vs. women	NA

ABA, abatacept; AKA, anakinra; ALE, alefacept; AS, ankylosing spondylitis; CD, Crohn's disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ETA, etanercept; INF, infliximab; MTX, methotrexate; NA, not applicable; NR, not reported; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor

SUMMARY

Our conclusions are based on the review of 3451 abstracts and the inclusion of 236 studies. The large majority of these studies was funded by the pharmaceutical industry and could be classified as efficacy trials with highly selected patients. Few studies existed that enrolled less selected, primary care based populations. Overall, however, results between efficacy trials and more generalizable effectiveness studies appear to be consistent with only small variations in the magnitude of effects. (See Table 33)

In summary, insufficient evidence exists for most comparisons about the efficacy, effectiveness, and safety of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, infliximab, natalizumab, and rituximab for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

The most obvious differences that might be clinically decisive for choosing a targeted immune modulator involve dosage and administration. Abatacept, infliximab, natalizumab, and rituximab require intravenous administration at different intervals and present the danger of rare but severe infusion reactions. Adalimumab, anakinra, certolizumab pegol, and etanercept can be administered subcutaneously by the patient. Alefacept requires an intramuscular injection. Furthermore, administration intervals differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, etanercept once a week, and certolizumab pegol every other week.

Key Question 1. Comparative Effectiveness

Rheumatoid Arthritis

One fair quality, double-blinded head-to head trial provides evidence of moderate strength that abatacept and infliximab do not differ in efficacy for the treatment of rheumatoid arthritis up to 6 months. The safety profile, however, appeared to be better for abatacept than for infliximab with fewer serious adverse events (9.6% compared with 18.2%) and fewer serious infections (1.9% compared with 8.5%).

Other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis are limited to 1 small randomized controlled trial and multiple observational studies rendering evidence of low strength. These studies indicated no differences in efficacy and safety between adalimumab and etanercept but greater response rates for adalimumab and etanercept compared with infliximab. No differences in safety were obvious in these studies. All of the observational studies were population-based and have high applicability. None of these studies provided any evidence on radiographic outcomes.

Adjusted indirect comparisons suggested greater efficacy for adalimumab, etanercept, and infliximab compared with anakinra for the treatment of rheumatoid arthritis.

The general efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, infliximab, and rituximab for the treatment of rheumatoid arthritis is well established by multiple good to fair randomized controlled trials and meta-analyses. Effect sizes are large and consistent across studies.

Juvenile Idiopathic Arthritis

No head-to-head trial comparing the efficacy and safety of targeted immune modulators for the treatment juvenile idiopathic arthritis are available. The general efficacy of abatacept, adalimumab, etanercept, and infliximab for the treatment of juvenile idiopathic arthritis is supported by 1 randomized controlled trial for each drug. Sample sizes of these studies, however, were small (overall data on only 369 patients) and active run-in periods limit the applicability of results. In efficacy trials significantly fewer patients on targeted immune modulators (20% to 37%) experienced disease flares than children treated with placebo (53% to 81%).

Ankylosing Spondylitis

No head-to-head trials provide direct evidence on the comparative efficacy of biologics for ankylosing spondylitis. One study conducted indirect comparisons and summarized the comparative efficacy quantitatively. The authors reported no significant differences in treatment response among adalimumab, etanercept, and infliximab. The general efficacy of adalimumab, etanercept, and infliximab for the treatment of moderate to severe ankylosing spondylitis is supported by several good to fair randomized controlled trials and 1 meta-analysis. In efficacy trials 57% to 80% of patients treated with targeted immune modulators achieved an Assessment in Ankylosing Spondylitis 20% improvement, compared with 20% to 30% of patients on placebo.

Psoriatic Arthritis

No head-to-head trials provided evidence on the comparative efficacy of biologics for psoriatic arthritis. One study conducted indirect comparisons and summarized the comparative efficacy quantitatively. The authors report no significant differences between adalimumab, etanercept, and infliximab. The general efficacy of adalimumab, alefacept, etanercept, and infliximab for the treatment of active psoriatic arthritis is supported by several good to fair randomized controlled trials and 1 meta-analysis. In efficacy trials 39% to 50% of patients treated with US Food and Drug Administration approved targeted immune modulators achieved an American College of Rheumatology 50, compared with 0% to 10% of patients on placebo.

No studies on the efficacy and safety of targeted immune modulators for the treatment of psoriatic arthritis in children are available.

Crohn's Disease

No head-to-head trials provide evidence on the comparative efficacy of biologics for Crohn's disease. The general efficacy of adalimumab, certolizumab pegol, infliximab and natalizumab for the treatment of moderate to severe Crohn's disease is supported by several good to fair randomized controlled trials and meta-analyses. In efficacy trials 26% to 57% of patients treated with targeted immune modulators achieved a Crohn's Disease Activity Index remission (CDAI <150), compared with 12% to 30% of patients on placebo.

The only study in a pediatric population with Crohn's disease was a dose ranging study without placebo arm that did not meet our eligibility criteria. In the active run-in phase (10 weeks) 88% of children achieved remission.

Ulcerative Colitis

No head-to-head trials provide evidence on the comparative efficacy of biologics for ulcerative colitis. The general efficacy of infliximab for the treatment of active ulcerative colitis is supported by 2 poor randomized controlled trials and 1 meta-analysis. In efficacy trials 25% to 35% of patients treated with targeted immune modulators achieved clinical remission from ulcerative colitis, compared with 10% to 16% of patients on placebo

No studies on the efficacy and safety of targeted immune modulators for the treatment of ulcerative colitis in children are available.

Plaque Psoriasis

No head-to-head trials provide evidence on the comparative efficacy of biologics for plaque psoriasis. The general efficacy of adalimumab, alefacept, etanercept, and infliximab for the treatment of moderate to severe plaque psoriasis is supported by several good to fair randomized controlled trials and 2 meta-analyses. In efficacy trials 50% to 80% of patients treated with targeted immune modulators achieved a Psoriasis Area and Severity Index 75 response, compared with 5% to 20% of patients on placebo.

One study assessed the efficacy of etanercept for plaque psoriasis in children and adolescents. Significantly more children in the etanercept group than in the placebo group experienced a response.

Key Question 2. Comparative Safety

The evidence on the comparative safety of targeted immune modulators is sparse. One randomized controlled trial provides moderate strength evidence that infliximab leads to higher rates of serious adverse events (18.2% compared with 9.6%) and serious infections (8.5% compared with 1.9%) than abatacept.

Based on 1 non-randomized trial and 1 prospective cohort study rendering evidence of low strength, no differences in adverse events between etanercept and infliximab could be detected.

The combination of 2 targeted immune modulators substantially increased the frequency of serious adverse events (15% compared with 3%) without any additional yield in benefits.

Regarding the general tolerability and safety, in placebo-controlled efficacy studies targeted immune modulators generally appeared to have a good tolerability profile, although some rare but serious adverse events such as serious infections, lymphoma, leucopenia, malignancies, or demyelinations are of concern for all targeted immune modulators. The evidence, however, is currently insufficient to draw any conclusions about the comparative risk for serious adverse events.

Injection site or infusion reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events. More than 90% of patients in efficacy trials experienced at least 1 adverse event. Incidence rates of injection site reactions appeared to be significantly higher with anakinra than with anti-tumor necrosis factor drugs (67% compared with 3% to 22% for other subcutaneous targeted immune modulators). Rituximab appeared to have the highest rate of infusion reactions (77% compared with 9% to 17% for other intravenous targeted immune modulators), some of which were fatal.

Discontinuation rates because of adverse events in patients treated with targeted immune modulators ranged from 3% to 20% and generally did not differ significantly from those in patients treated with placebo.

For newer targeted immune modulators such as abatacept, certolizumab pegol, natalizumab, or rituximab long-term safety data are generally missing.

Key Question 3. Subgroups

The overall grade of the evidence on efficacy and tolerability in subgroups is low. We did not identify any study specifically designed to compare the effect of targeted immune modulators in 1 subgroup of patients compared to another. Subgroup analyses and indirect evidence from placebo-controlled trials provide evidence for some drugs.

Indirect evidence exists from 2 pooled analyses and a retrospective cohort that age is not associated with greater clinical response rates or safety in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. In contrast to this, a separate study found the response to treatment with etanercept and infliximab for rheumatoid arthritis was better in patients younger than 65 years. No differences in adverse events between patients with ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis older than 65 years and those younger were reported with the exception of bacterial pneumonia which was more common in older patients in their 70s than those in their 50s. The same report also showed that bacterial pneumonia was more common in women than men and those with respiratory conditions when treated with infliximab.

Evidence is mixed whether patients with congestive heart failure have a higher risk of hospitalization and mortality when treated with etanercept and infliximab. Additionally there is low evidence to show that commonly prescribed concomitant medications such as statins or antihypertensives appear to have little or no increase in adverse events.

CONCLUSIONS

Overall, targeted immune modulators are highly effective medications for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis that substantially improve the burden of disease and are generally safe for short-term treatment. The evidence is currently insufficient to reliably determine the comparative effectiveness and safety for most comparisons. In addition, for many drugs the balance between benefits and risks cannot be reliably assessed without sound long-term data on safety.

Table 33. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
1. Comparative efficacy for rheumatoid arthritis	Moderate	Based on 1 randomized controlled trial, no difference in efficacy between *abatacept* and infliximab
	Low	Based on indirect comparisons and 1 observational study, no difference in effectiveness between adalimumab and etanercept
	Insufficient	Based on indirect comparisons and 1 observational study, conflicting evidence on the comparative effectiveness of adalimumab and infliximab
	Moderate	Based on 2 trials and 4 observational studies, greater effectiveness of etanercept than infliximab
	Low	Based on indirect comparisons, greater effectiveness of adalimumab, etanercept, and infliximab compared with anakinra
	Insufficient	No evidence available for all other comparisons
1. Comparative effectiveness for juvenile idiopathic arthritis	Insufficient	No comparative evidence available
1. Comparative effectiveness for ankylosing spondylitis	Low	Based on indirect comparisons, no difference in effectiveness between adalimumab, etanercept and/or infliximab
1. Comparative effectiveness for psoriatic arthritis	Low	Based on indirect comparisons, no difference in effectiveness between adalimumab, etanercept and/or infliximab
1. Comparative effectiveness for Crohn's disease	Insufficient	No comparative evidence available
1. Comparative effectiveness for ulcerative colitis	Insufficient	No comparative evidence available
1. Comparative effectiveness for plaque psoriasis	Insufficient	No comparative evidence available
2. Comparative safety	Moderate	Based on 1 randomized controlled trial, higher rates of serious adverse events and serious infections for infliximab than for abatacept
	Low	Based on 1 trial and 1 observational study, no differences between etanercept and infliximab
	Insufficient	No evidence available for all other comparisons
	High	Based on 2 randomized controlled trials, substantially higher rates of serious adverse

Key question	Strength of evidence	Conclusion
		events for combination therapies of anakinra with etanercept and abatacept with etanercept than for monotherapies
3. Subgroups - age	Insufficient	The evidence on the effect of age is contradicting and insufficient to draw conclusions
3. Subgroups - sex	Insufficient	The evidence is mixed and insufficient to draw conclusions
3. Subgroups - ethnicity	Insufficient	The evidence is mixed and insufficient to draw conclusions
3. Subgroups - comorbidities	Insufficient	The evidence is mixed and insufficient to draw conclusions

ADDENDUM

On April 24, 2009 the US Food and Drug Administration approved golimumab (*Simponi*; Centocor Ortho Biotech) for the treatment of moderate to severe rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis in adult patients. Because this approval took place after finalizing the key questions, we were unable to integrate data on golimumab into this report.

Golimumab is a monthly, self-injectable anti-tumor necrosis factor alpha drug which should be used in combination with methotrexate. The US Food and Drug Administration approval was based on 3 multicenter randomized controlled trials for rheumatoid arthritis (with more than 1500 patients),[280-282] 1 randomized controlled trial (n = 405) for psoriatic arthritis,[283] and 1 randomized controlled trial (n = 356) on ankylosing spondylitis.[284]

As with other anti-tumor necrosis factor drugs, the US Food and Drug Administration issued a black box warning about the risk of serious infections that can lead to hospitalizations or death. Furthermore, the US Food and Drug Administration cautions about an increased risk of reactivation of hepatitis B, malignancies, and worsening or new onset of heart failure.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategies

Initial PubMed Search took place in June 2008:

#1	Search "Arthritis, Rheumatoid"[MeSH] OR ankylosing arthritis	62269
#2	Search "Arthritis, Rheumatoid"[MeSH] OR ankylosing arthritis Limits: **All Adult: 19+ years**	33489
#3	Search "Arthritis, Psoriatic"[MeSH] OR "Crohn Disease"[MeSH] OR "Colitis, Ulcerative"[MeSH] OR plaque psoriasis OR "Arthritis, Juvenile Rheumatoid"[Mesh] OR juvenile idiopathic arthritis	36828
#4	Search "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR "Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Multicenter Study "[Publication Type] OR "Evaluation Studies "[Publication Type] OR "Longitudinal Studies"[MeSH] OR "Prospective Studies"[MeSH] OR "Validation Studies"[Publication Type] OR observational studies OR evaluation studies [pt] OR systematic [sb] OR (MEDLINE[Title/Abstract] OR systematic[Title/Abstract] AND review[Title/Abstract] OR meta-analysis[Publication Type])	1495185
#5	Search "Treatment Outcome"[Mesh] OR outcome OR efficacy OR effectiveness OR adverse OR safety OR withdrawal* OR harm OR mortality OR morbidity OR function* OR toxicity	4247399
#6	Search #3 OR #2	68280
#7	Search #6 AND #5 AND #4	11340
#8	Search "adalimumab"[Substance Name] OR humira OR "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR enbrel OR "CDP870"[Substance Name] OR certolizumab OR cimzia OR "infliximab"[Substance Name] OR remicade OR "interleukin 1 receptor antagonist protein"[Substance Name] OR kineret OR anakinra OR "efalizumab"[Substance Name] OR raptiva OR "alefacept"[Substance Name] OR amevive OR "abatacept "[Substance Name] OR orencia OR "rituximab"[Substance Name] OR rituxan OR "natalizumab"[Substance Name] OR tysabri	15102
#9	Search #8 AND #6 AND #5 AND #4 Limits: **Publication Date from 1980, English**	2802

PubMed: 2802

Analogous search terms were used in other databases yielding the following results:

EMBASE: 117

IPA: 80

Cochrane: 5

Analogous search terms were used to conduct an update search in April 2009 yielding the following results:

PubMed: 51
EMBASE: 56
CINAHL: 38
IPA: 4
Cochrane: 4

Appendix C. Component studies of included systematic reviews

The following full-text publications were included in this report but were not described fully if outcomes were well-described in an included systematic review.

Rheumatoid Arthritis - Adalimumab

1. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.
2. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30(12):2563-71.
3. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50(5):1400-11.
4. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63(5):508-16.
5. van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis 2003;62(12):1168-77.
6. Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 2006;65(6):753-9.
7. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48(1):35-45.

Rheumatoid Arthritis - Anakinra

1. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41(12):2196-204.
2. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46(3):614-24.

3. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis 2004;63(9):1062-8.
4. Cohen SB, Woolley JM, Chan W. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol 2003;30(2):225-31.
5. Jiang Y, Genant HK, Watt I, Cobby M, Bresnihan B, Aitchison R, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 2000;43(5):1001-9.

Rheumatoid Arthritis - Etanercept

1. Genovese MC, Bathon JM, Fleischmann RM, Moreland LW, Martin RW, Whitmore JB, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol 2005;32(7):1232-42.
2. Hyrich KL, Symmons DP, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54(6):1786-1794.
3. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363(9410):675-81.
4. Lan JL, Chou SJ, Chen DY, Chen YH, Hsieh TY, Young MJ. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc 2004;103(8):618-23.
5. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther 2000;22(1):128-39.
6. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130(6):478-86.
7. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337(3):141-7.
8. Van Der Heijde D, Klareskog L, Landewe R, Bruyn GAW, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis and Rheumatism 2007;56(12):3928-3939.
9. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the

treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54(4):1063-74.
10. van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis 2006;65(3):328-34.
11. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340(4):253-9.

Rheumatoid Arthritis - Infliximab

1. Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63(2):149-55.
2. Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol 2000;27(4):841-50.
3. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343(22):1594-602.
4. 34. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41(9):1552-63.
5. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354(9194):1932-9.
6. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004;50(4):1051-65.
7. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52(4):1020-30.
8. Smolen JS, Han C, van der Heijde D, Emery P, Bathon JM, Keystone E, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006;54(3):716-22.
9. St. Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50(11):3432-43.
10. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid

arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006;54(4):1075-86.

Rheumatoid Arthritis – Rituximab

1. Mease PJ, Revicki DA, Szechinski J, Greenwald M, Kivitz A, Barile-Fabris L, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol 2008;35(1):20-30.

Plaque Psoriasis - Alefacept

1. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001;345(4):248-55.
2. Ellis CN, Mordin MM, Adler EY. Effects of alefacept on health-related quality of life in patients with psoriasis: results from a randomized, placebo-controlled phase II trial. Am J Clin Dermatol 2003;4(2):131-9.
3. Finlay AY, Salek MS, Haney J. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. Dermatology 2003;206(4):307-15.
4. Gordon KB, Langley RG. Remittive effects of intramuscular alefacept in psoriasis. J Drugs Dermatol 2003;2(6):624-8.
5. Gordon KB, Vaishnaw AK, O'Gorman J, Haney J, Menter A. Treatment of psoriasis with alefacept: correlation of clinical improvement with reductions of memory T-cell counts. Arch Dermatol 2003;139(12):1563-70.
6. Feldman SR, Menter A, Koo JY. Improved health-related quality of life following a randomized controlled trial of alefacept treatment in patients with chronic plaque psoriasis. Br J Dermatol 2004;150(2):317-26.
7. Krueger GG. Clinical response to alefacept: results of a phase 3 study of intravenous administration of alefacept in patients with chronic plaque psoriasis. J Eur Acad Dermatol Venereol 2003;17 Suppl 2:17-24.
8. Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. Br J Dermatol 2003;148(4):784-8.
9. Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. J Am Acad Dermatol 2002;47(6):821-33.
10. Lebwohl M, Christophers E, Langley R, Ortonne JP, Roberts J, Griffiths CE. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. Arch Dermatol 2003;139(6):719-27.
11. Ortonne JP. Clinical response to alefacept: results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis. J Eur Acad Dermatol Venereol 2003;17 Suppl 2:12-6.

Plaque Psoriasis - Etanercept

1. Feldman SR, Kimball AB, Krueger GG, Woolley JM, Lalla D, Jahreis A. Etanercept improves the health-related quality of life of patients with psoriasis: results of a phase III randomized clinical trial. J Am Acad Dermatol 2005;53(5):887-9.

2. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003;139(12):1627-32; discussion 1632.
3. Krueger GG, Langley RG, Finlay AY, Griffiths CE, Woolley JM, Lalla D, et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. Br J Dermatol 2005;153(6):1192-9.
4. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349(21):2014-22.
5. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152(6):1304-12.
6. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367(9504):29-35.

Psoriatic Arthritis

1. Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis 2007;66(2):163-8.

Crohn's Disease

1. Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, et al. Natalizumab for active Crohn's disease. N Engl J Med 2003;348(1):24-32.

Appendix D. Quality assessment for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria. This appendix lists questions that are posed for each included study in order to assess study quality. These quality-assessment questions differ for systematic reviews, controlled trials, and nonrandomized trials.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria that may indicate the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies?
   A good-quality review should focus on a well-defined question or set of questions. These questions ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design: indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
   If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, dates, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only Medline was searched for a review looking at proton pump inhibitors then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?
   A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors

may use a published checklist or scale or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
   The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample sizes, patient characteristics, interventions, settings, outcome measures, follow-up periods, drop-out rates (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?
   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis). For reviews that provide a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual studies should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of internal validity

1. Was the assignment to treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random-numbers table

   Inferior approaches to sequence generation:
   - Use of alternation, case record number, birth date, or day of week

   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

   Inferior approaches to concealment of randomization:
   - Use of alternation, case record number, birth date, or day of week
   - Open random-numbers list

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 (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 (giving numbers for each group)?

Assessment of external validity (applicability)

1. How similar is the population to the population to which 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 follow-up? (Give numbers at each stage of attrition.

Nonrandomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion unbiased? In other words, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of external validity

1. Was the description of the population adequate?

2. How similar is the population to the population to which the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

References:

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Appendix E. Instruments used to measure outcomes in trials involving targeted immune modulators

Abbreviation	Name	Condition(s) used in	General description	Range and direction
ACR 20/50/70	American College of Rheumatology, numbers refer to percentage improvement	RA, JIA, PsA	Improvement is defined by at least 20% improvement in TJC and in SJC, and at least 20% improvement in 3 of the 5 measures: ESR or CRP PhGA of disease activity PtGA of disease activity Patient assessment of pain Disability	0-100, higher is better
ACR Pedi	American College of Rheumatology Pediatric scale	JIA	See above – adapted for children	0-100, higher is better
ASAS 20/50/70	ASsessment in Ankylosing Spondylitis, numbers refer to percentage improvement	AS	Improvement of 20% or more and absolute improvement of 10 units (on a scale of 0-100) in 3 of the following 4 domains: Patient global assessment - pain – function – inflammation Absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of 20% and net worsening of 10 units (on a scale of 0-100)	0-100, higher is better
BASDAI	Bath AS Disease Activity Index	AS	Six 10 cm horizontal visual analog scales to measure severity of fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative)	0-10, lower is better
BASFI	Ankylosing Spondylitis Functional Index	AS	Defining and monitoring functional ability in patients with AS	0-10, higher is better
BASMI	Bath Ankylosing Spondylitis Metrology Index	AS	Measures axial status using: cervical rotation, tragus to wall distance, lateral flexion, modified Schober's, and intermalleolar distance.	Lower is better
CAHP	Childhood Arthritis Health Profile	JIA	Three modules – the CHQ, JIA specific scales and patients characteristics	
CDAI	Crohn's Disease Activity Index	CD	Eight clinical factors, each summed after adjustment with a weighting factor. These include, Number of liquid or soft stools each day for 7 days x 2, Abdominal pain (graded from 0-3 on severity) each day for 7 days x 5, General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days x 7, Presence of complications* x 20, Taking Lomitil or opiates for diarrhea x 30, Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite) x 10, Absolute deviation of Hematocrit from 47% in men and 42% in women x 6, Percentage deviation from standard weight x 1	Lower numbers are better, values of 150 and less equal minimal disease; values above 150 equal active disease, and values above 450 equal extremely severe disease.
CDEIS	Crohn's Disease Endoscopy	CD	Segment score averaged over segments on which data were available, ulcerated stenosis in any segment, and nonulcerated stenosis in any	0-44, lower is better

Abbreviation	Name	Condition(s) used in	General description	Range and direction
	Index of Severity		segment.	
CHAQ	Childhood Health Assessment Questionnaire	JIA	Five generic patient-centered health dimensions: (1) to avoid disability; (2) to be free of pain and discomfort; (3) to avoid adverse treatment effects; (4) to keep dollar costs of treatment low; and (5) to postpone death adopted for children	For DI 0-3 lower is better
CHQ	Childhood Health Questionnaire	JIA	measure physical functioning, role/social-emotional/behavioural, role/social-physical, bodily pain (bodily pain), behaviour, mental health, self-esteem, general health, parental impact – emotional, parental impact – time, family activities and family cohesion	0-100 for each subscale (there are 8), higher is better
DLQI	Dermatology Life Quality Index	PP and PsA	10-item questionnaire covering 6 dimensions (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) that assesses the overall impact of skin disorders and current treatments on the patient's functioning and well-being	0-30, lower is better
DQOLS	Dermatology Quality of Life Scales	PP	psychosocial, activities and symptoms scale consisting, respectively, of 17 psychosocial items grouped into 4 categories (embarrassment, despair, irritability and distress); 12 activity items in 4 categories (everyday activities, summer activities, social activities and sexual activity); and a 12-item symptom scale including redness, itching, scarring, flaking, rawness, change in skin colour, pain, tiredness, swelling, bleeding, aching and burning.	0-100, lower is better
ESR	Eyrthrocyte sedimentation rate	all	Rate at which red blood cells precipitate in a period of 1 hour.	Ranges from 10 – 25 or more, lower is better
EULAR response	European League Against Rheumatism	RA	A good response is defined as reaching a DAS 2.4 or a DAS28 3.2 ("low" disease activity) in combination with an improvement >1.2 (twice the measurement error) in DAS or DAS28. A non-response is defined as an improvement 0.6, and also as an improvement 1.2 with a DAS>3.7 or DAS28>5.1 ("high" disease activity). All other possibilities are defined as a moderate response.	Lower is better
EQ-5D	European Quality of Life-5 Dimensions	all	Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take 1 of 3 responses. The responses record 3 levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension.	0-1, higher is better
HAQ	Health Assessment Questionnaire	all	Five generic patient-centered health dimensions: (1) to avoid disability; (2) to be free of pain and discomfort; (3) to avoid adverse treatment effects; (4) to keep dollar costs of treatment low; and (5) to postpone death.	For DI, 0-3, lower is better
HAQ-DI	Disability Index of the Health Assessment Questionnaire	all	Patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a	

Abbreviation	Name	Condition(s) used in	General description	Range and direction
			comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities.	
IBDQ	Inflammatory-bowel-disease questionnaire	CD and UC	32 questions grouped into 4 domains: bowel symptoms, systemic symptoms, emotional functioning (EF), and social functioning	0-7, higher is better
NAPSI	Nail psoriasis and severity index	PP	The nail plate - including nail pitting, leukonychia, red spots in the lunula, and crumbling in each quadrant of the nail. Nail bed psoriasis - including onycholysis, oil drop (salmon patch) dyschromia, splinter hemorrhages, and nail bed hyperkeratosis in each quadrant of the nail. 0 if the findings are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail. Thus each nail has a matrix score (0-4) and a nail bed score (0-4), and the total nail score is the sum of those 2 (0-8).	0-8, lower is better
PASI	Psoriasis Area and Severity Index	PP and PsA	Based on the extent of the skin-surface area involved and the severity of erythema, desquamation, and plaque induration,	0 - 72, lower score is better
PDAI	Pouchitis Disease Activity Index	CD	Measures clinical findings and the endoscopic and histologic features of acute inflammation	0-6, lower is better
PGPA	Patient's Global Psoriasis Assessment	PP and PsA	Single self-explanatory item to be completed by the patient, evaluating overall cutaneous disease at a specific point in time	0-10, lower is better
PsARC	Psoriatic Arthritis Response Criteria	PsA	Response is defined by improvement in at least 2 of the 4 following measures, 1 of which must be joint swelling or tenderness, and no worsening in any of the 4 measures: PtGA of articular disease (1–5) and PhGA of articular disease (1–5): improvement = decrease by 1 category, worsening = increase by 1 category. Joint pain/tenderness score and joint swelling score: improvement = decrease by 30%, worsening = increase by 30%.	0-100, higher is better
SF – 36 MOS	Medical Outcomes Study Short Form 36 Health Survey	all	Measures the general level of wellbeing, consists of 8 domains reflecting 8 dimensions of life: PF – Physical Functioning, RP – Role Physical, BP – Bodily Pain, GH – General Health, VT – Vitality, SF – Social Functioning, RE – Role Emotional, MH – Mental Health..	0-100, higher is better

ACR, American College of Rheumatology; AS, ankylosing spondylitis; CD, Crohn's disease; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; EULAR; JIA, juvenile idiopathic arthritis; PhGA, physician global assessment; PP, plaque psoriasis; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; PtGA, patient global assessment; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; UC, ulcerative colitis

Appendix F. Study characteristics, pooled relative risks and forest plots of meta-analyses

Adalimumab

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Furst et al. 2003[62]	RCT	636	24 weeks	ADA +Standard RA therapy / Placebo + Standard RA therapy	safety	Active RA for at least 3 months; DMARD naïve/or on stable regimen; mean disease duration: 10.5 yrs.
Keystone et al. 2004[63]	RCT	619	52 weeks	ADA +MTX / Placebo + MTX	Sharp, ACR 20, HAQ	Active RA; on stable MTX regimen; mean disease duration: 11 yrs.
Kim et al., 2007[66]	RCT	128	24 weeks	ADA+MTX/ MTX	ACR 20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 6.9 yrs.
Miyasaka et al., 2008[67]	RCT	352	24 weeks	ADA/Placebo	ACR 20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 9.5 yrs.
Van de Putte et al. 2003[64]	RCT	284	12 weeks	ADA / Placebo	ACR 20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 10 yrs.
Van de Putte et al. 2004[65]	RCT	544	26 weeks	ADA / Placebo	ACR20	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 11 yrs.
Weinblatt et al. 2003[59]	RCT	271	24 weeks	ADA+MTX / MTX + Placebo	ACR20, HAQ	Active RA; stable MTX regimen; had failed at least 1 other DMARD; mean disease duration: 12 yrs.

Relative risk meta-analysis: ACR-50

Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	2.552833	1.80314	3.63624	38.187149	27.528725	Furst 2003
2	4.17033	2.711696	6.522056	27.284858	22.80811	Keystone 2004
3	3.015385	1.597745	5.893943	9.695956	14.404515	Kim 2007
4	4.206593	1.74703	10.401544	5.422957	8.916726	Miyasaka 2008
5	16.527778	2.954667	96.371194	1.075694	2.307069	Van de Putte 2003
6	2.607407	1.365527	5.10824	12.824043	14.173745	Van de Putte 2004
7	6.847761	3.047254	16.177401	5.509343	9.861109	Weinblatt 2003

Non-combinability of studies

Cochran Q = 9.446885 (df = 6) $P = 0.15$

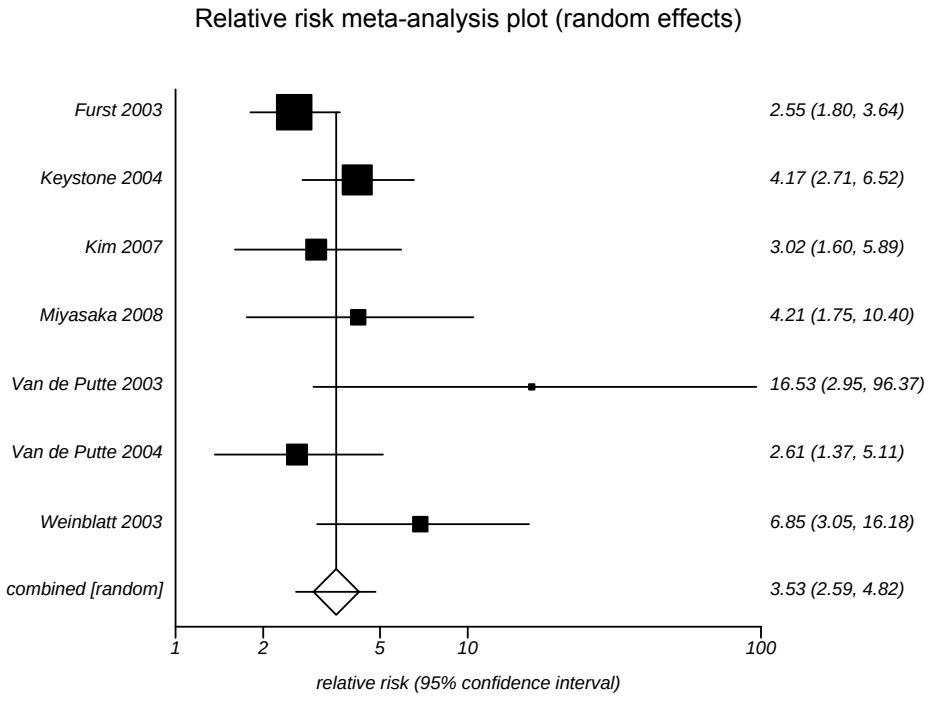
Moment-based estimate of between studies variance = 0.058945

I^2 (inconsistency) = 36.5% (95% CI = 0% to 72.2%)

Random effects (DerSimonian-Laird)

Pooled relative risk = 3.529151 (95% CI = 2.586505 to 4.815342)

Chi^2 (test relative risk differs from 1) = 63.262225 (df = 1) $P < 0.0001$



Anakinra

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Bresnihan et al. 1998[71]	RCT	472	24 weeks	AKA / Placebo	ACR-N	> 6 months active RA <8 years; mean disease duration: 3.7-4.3 years
Cohen et al. 2002[72]	RCT	419	24 weeks	AKA+MTX / MTX+ Placebo	ACR 20	> 6 months active RA < 12 years; stable MTX regimen; mean disease duration: 6.3-8.8 years
Cohen et al. 2004[70]	RCT	501	24 weeks	AKA+MTX / MTX+ Placebo	ACR 20	> 6 months active RA; stable MTX regimen; mean disease duration: 10.5 yrs.

Relative risk meta-analysis: ACR-50

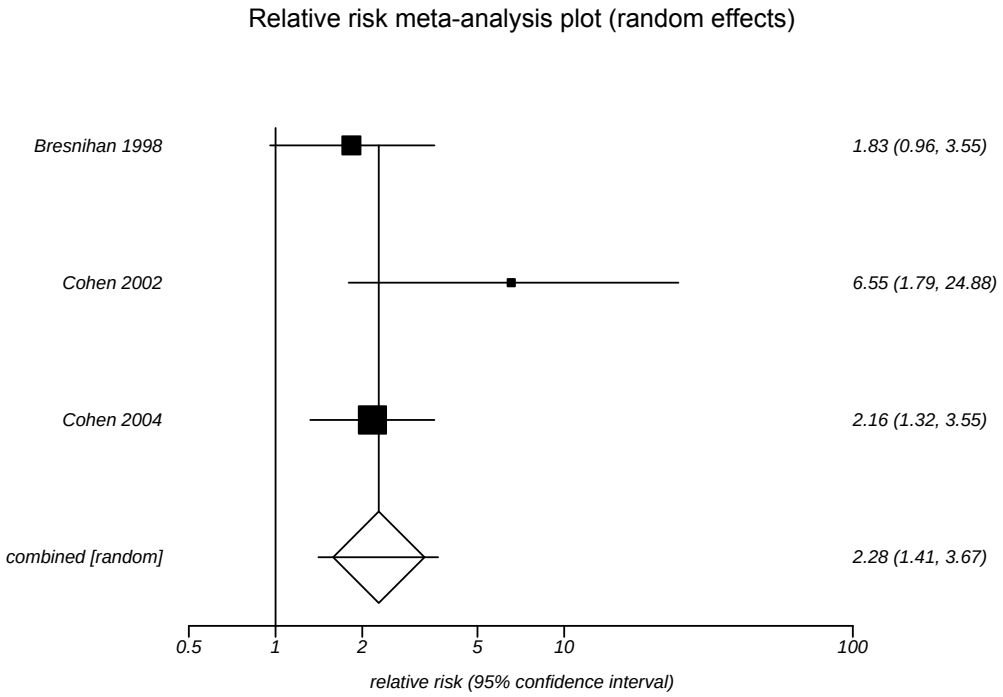
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.825431	0.958312	3.546318	6.572238	Bresnihan 1998
2	6.548673	1.790818	24.879122	1.208556	Cohen 2002
3	2.1586	1.318936	3.55346	9.98004	Cohen 2004

M-H pooled estimate (Rothman-Boice) of relative risk = 2.334041
Robins-Greenland approximate 95% CI = 1.590173 to 3.425885

Chi-square (for pooled relative risk) = 18.739732 (df = 1) $P < 0.0001$

Q ("non-combinability" for relative risk) = 2.631496 (df = 2) $P = 0.2683$

I^2 : 23.99%



Etanercept

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Klareskog et al. 2004[80]	RCT	682	52 weeks	ETA / MTX / MTX + ETA	Sharp	> 6 months active RA; ACR functional class I-III; unsatisfactory response to at least 1 DMARD other than MTX; mean disease duration: 6.5 yrs.
Lan et al. 2004[88]	RCT	58	12 weeks	ETA+ MTX / Placebo + MTX	Number of swollen/ tender joints	Active RA > 1 year; stable MTX for 4 weeks; mean disease duration: NR
Moreland et al. 1997[89]	RCT	180	12 weeks	ETA / Placebo	Number of swollen/ tender joints	Active RA; failed 1 to 4 DMARD treatments; mean disease duration: NR
Moreland et al. 1999[78, 79]	RCT	234	12 weeks	ETA / Placebo	ACR 20/50	Active RA; failed 1 to 4 DMARD treatments other than MTX; mean disease duration: 12 yrs.
Weinblatt et al. 1999[90]	RCT	89	24 weeks	ETA+ MTX / Placebo + MTX	ACR 20	Active RA; > 6 months MTX, stable >1 month; mean disease duration: 13 years

Relative risk meta-analysis: ACR-50

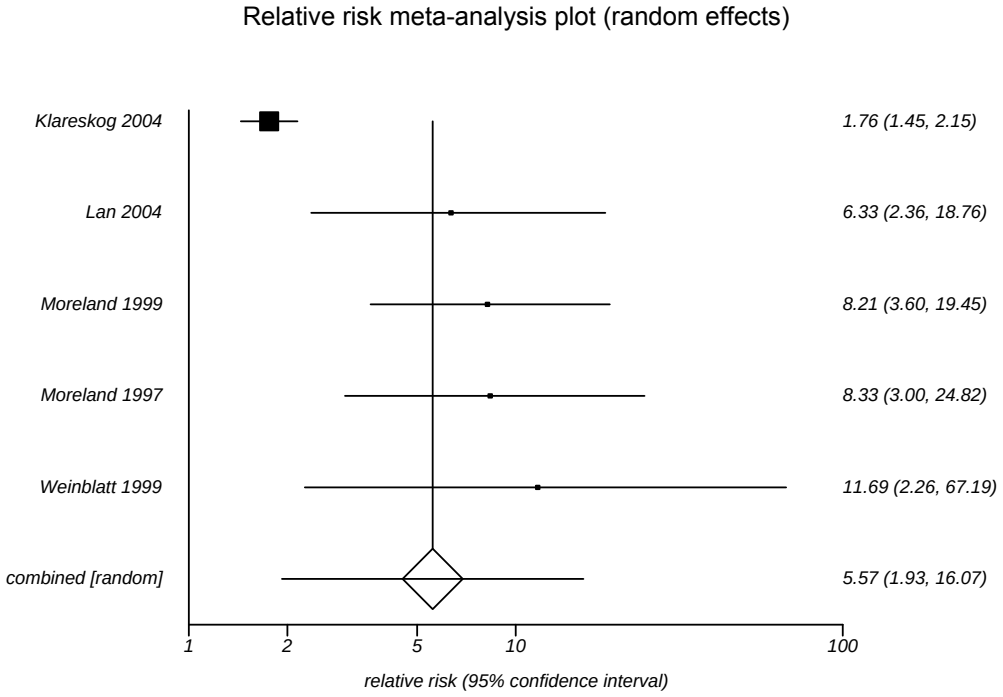
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.757365	1.446	2.153791	41.267974	Klareskog 2004
2	6.333333	2.362599	18.757771	1.5	Lan 2004
3	8.205128	3.598388	19.451313	2.468354	Moreland 1999
4	8.333333	2.998444	24.815338	1.5	Moreland 1997
5	11.694915	2.26005	67.188802	0.662921	Weinblatt 1999

M-H pooled estimate (Rothman-Boice) of relative risk = 2.585038
Robins-Greenland approximate 95% CI = 2.130037 to 3.137232

Chi-square (for pooled relative risk) = 92.446788 (df = 1) $P < 0.0001$

Q ("non-combinability" for relative risk) = 30.10553 (df = 4) $P < 0.0001$

I^2: 87%



Infliximab

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Abe et al., 2006[97]	RCT	147	14 weeks	INF+ MTX / Placebo + MTX	ACR 20	> 6 months history of active RA; mean disease duration 7.9 yrs.
Kavanaugh et al. 2000[100]	RCT	28	12 weeks	INF+ MTX / Placebo + MTX	ACR 20	RA < 15 years; MTX > 3 months; mean disease duration 4.9 – 7.5 years
Maini et al. 1998[98]	RCT	43	26 weeks	INF+ MTX / Placebo + MTX	Paulus 20	MTX > 6 months; mean disease duration 7.6 – 114.3 years
Maini et al. 1999[99]	RCT	428	30 weeks	INF+MTX / Placebo + MTX	ACR 20	MTX stable > 4 weeks; mean disease duration 7.2 – 9.0 years
Westhovens et al., 2006[94]	RCT	1084	22 weeks	INF+ MTX / Placebo + MTX	ACR 20	Active RA despite MTX treatment; median disease duration: 15 yrs
Zhang et al., 2006[103]	RCT	173	18 weeks	INF + MTX / MTX	ACR 20/50/70	Adult outpatients with active RA and insufficient response to standard antirheumatic therapy

Relative risk meta-analysis: ACR-50, St. Clair et al.

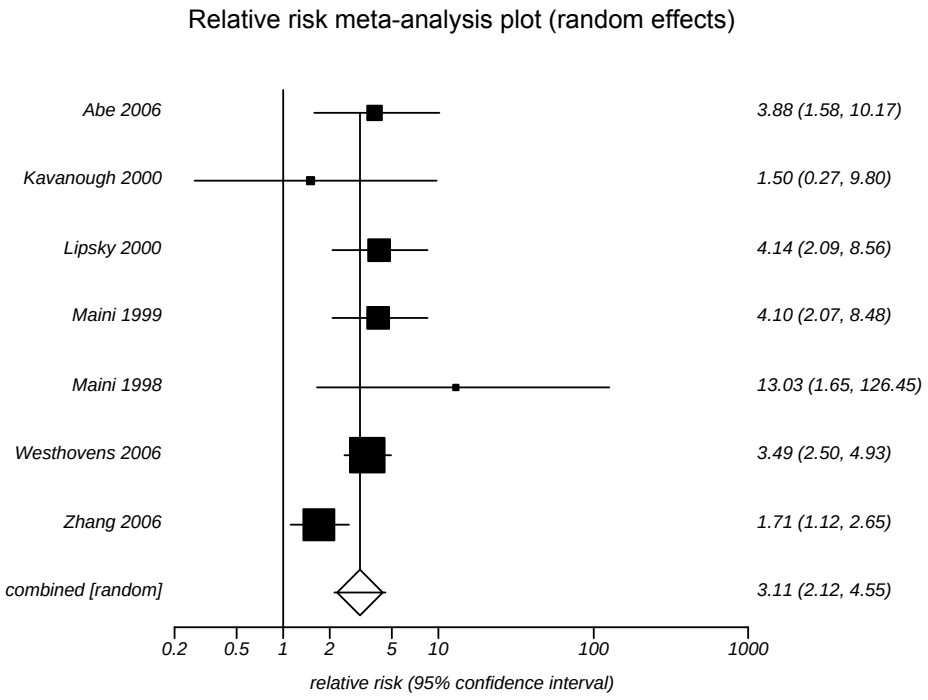
Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	3.8775	1.576166	10.168522	5.685599	10.727026	Abe 2006
2	1.5	0.269401	9.804675	1.392972	3.095502	Kavanough 2000
3	4.141176	2.085196	8.555213	11.618948	15.684713	Lipsky 2000
4	4.104202	2.066097	8.480455	11.618948	15.679487	Maini 1999
5	13.034483	1.645997	126.445188	0.704585	1.826972	Maini 1998
6	3.493759	2.497169	4.931648	45.862057	28.166294	Westhovens 2006
7	1.707419	1.11932	2.646191	23.116892	24.820005	Zhang 2006

Non-combinability of studies

Cochran Q = 11.31666 (df = 6) P = 0.0791
Moment-based estimate of between studies variance = 0.103872
I^2 (inconsistency) = 47% (95% CI = 0% to 75.9%)

Random effects (DerSimonian-Laird)

Pooled relative risk = 3.108816 (95% CI = 2.123152 to 4.55207)
Chi^2 (test relative risk differs from 1) = 33.984613 (df = 1) P < 0.0001



ANTI-TNF-combined

Relative risk meta-analysis: ACR-50

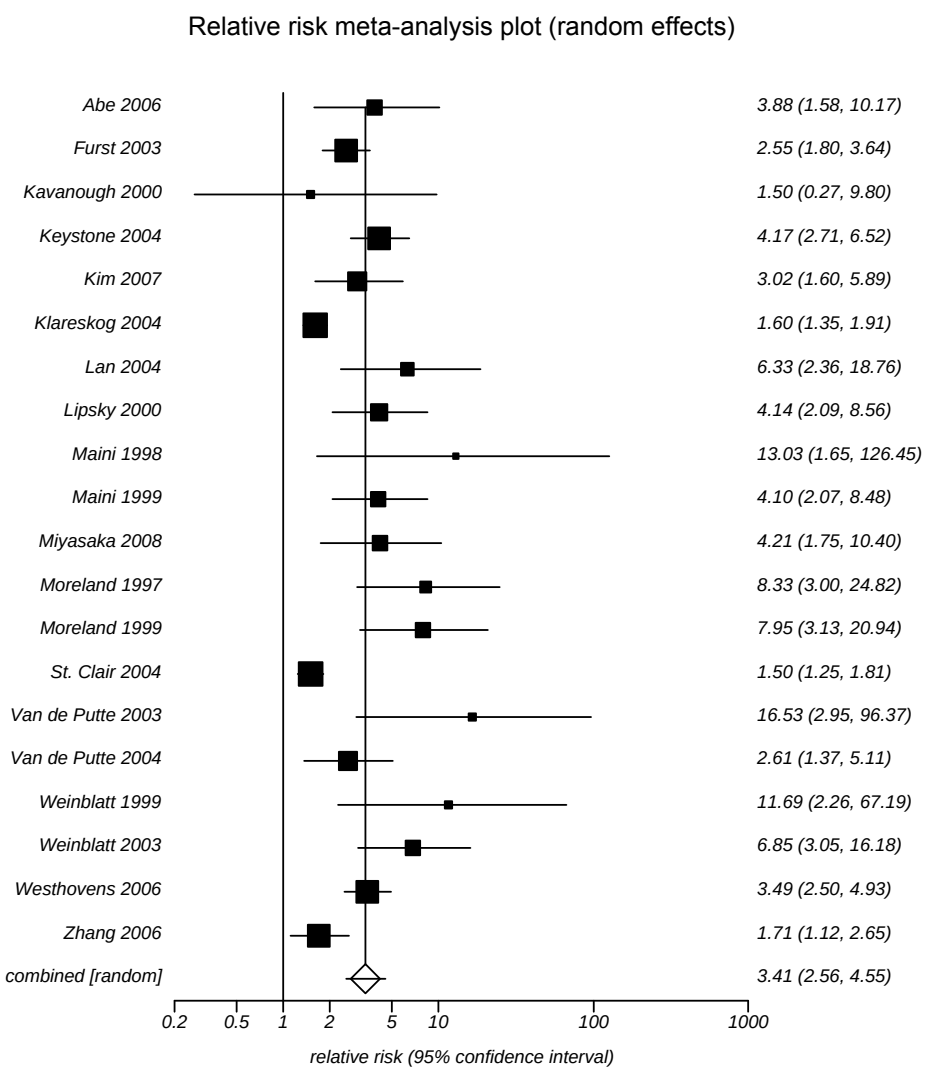
Stratum	Relative risk	95% CI (Koopman)		% Weights (fixed, random)		
1	3.8775	1.576166	10.168522	1.275414	4.290628	Abe 2006
2	2.552833	1.80314	3.63624	8.436866	7.579343	Furst 2003
3	1.5	0.269401	9.804675	0.312477	1.564542	Kavanough 2000
4	4.17033	2.711696	6.522056	6.028172	7.104331	Keystone 2004
5	3.015385	1.597745	5.893943	2.142173	5.855767	Kim 2007
6	1.601378	1.352304	1.911821	23.117135	8.301569	Klareskog 2004
7	6.333333	2.362599	18.757771	0.703072	3.776524	Lan 2004
8	4.141176	2.085196	8.555213	2.606405	5.524856	Lipsky 2000
9	13.034483	1.645997	126.445188	0.158055	0.965713	Maini 1998
10	4.104202	2.066097	8.480455	2.606405	5.52371	Maini 1999
11	4.206593	1.74703	10.401544	1.198119	4.526845	Miyasaka 2008
12	8.333333	2.998444	24.815338	0.703072	3.705462	Moreland 1997
13	7.948718	3.130217	20.937153	0.925563	4.223708	Moreland 1999
14	1.495075	1.245348	1.81407	29.714604	8.254582	St. Clair 2004
15	16.527778	2.954667	96.371194	0.237658	1.672513	Van de Putte 2003
16	2.607407	1.365527	5.10824	2.833276	5.810641	Van de Putte 2004
17	11.694915	2.26005	67.188805	0.310721	1.722888	Weinblatt 1999
18	6.847761	3.047254	16.177401	1.217205	4.800716	Weinblatt 2003
19	3.493759	2.497169	4.931648	10.287943	7.629047	Westhovens 2006
20	1.707419	1.11932	2.646191	5.185665	7.166616	Zhang 2006

Random effects (DerSimonian-Laird)

Pooled relative risk = 3.411549 (95% CI = 2.56072 to 4.545077)
Chi² (test relative risk differs from 1) = 70.292422 (df = 1) $P < 0.0001$

Non-combinability of studies

Cochran Q = 99.20585 (df = 19) $P < 0.0001$
Moment-based estimate of between studies variance = 0.250292
I^2 (inconsistency) = 80.8% (95% CI = 70.7% to 86.3%)


Relative risk meta-analysis plot (random effects)
Abe 2006
Furst 2003
Kavanough 2000
Keystone 2004
Kim 2007
Klareskog 2004
Lan 2004
Lipsky 2000
Maini 1998
Maini 1999
Miyasaka 2008
Moreland 1997
Moreland 1999
St. Clair 2004
Van de Putte 2003
Van de Putte 2004
Weinblatt 1999
Weinblatt 2003
Westhovens 2006
Zhang 2006
combined [random]
3.88 (1.58, 10.17)
2.55 (1.80, 3.64)
1.50 (0.27, 9.80)
4.17 (2.71, 6.52)
3.02 (1.60, 5.89)
1.60 (1.35, 1.91)
6.33 (2.36, 18.76)
4.14 (2.09, 8.56)
13.03 (1.65, 126.45)
4.10 (2.07, 8.48)
4.21 (1.75, 10.40)
8.33 (3.00, 24.82)
7.95 (3.13, 20.94)
1.50 (1.25, 1.81)
16.53 (2.95, 96.37)
2.61 (1.37, 5.11)
11.69 (2.26, 67.19)
6.85 (3.05, 16.18)
3.49 (2.50, 4.93)
1.71 (1.12, 2.65)
3.41 (2.56, 4.55)
0.2
0.5
1
2
5
10
100
1000
relative risk (95% confidence interval)

Appendix G. Black box warnings of drugs approved by the US Food and Drug Administration

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Orencia® (abatacept)	None listed
Humira® (adalimumab)	**Boxed Warning** Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving HUMIRA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with HUMIRA. However, active tuberculosis has developed in patients receiving HUMIRA whose screening for latent tuberculosis infection was negative. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating HUMIRA and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.
Amevive® (alefacept)	None listed
Kineret® (anakinra)	None listed
Cimzia® (certolizumab pegol)	**Boxed Warning** Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving CIMZIA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with TNF blockers such as CIMZIA. However, active tuberculosis has developed in patients receiving CIMZIA whose tuberculin test was negative. Evaluate patients for tuberculosis risk factors and test for latent tuberculosis infection prior to initiating CIMZIA and during therapy. Initiate treatment of latent tuberculosis infection prior to therapy with CIMZIA. Monitor patients receiving CIMZIA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.
Enbrel® (etanercept)	**Boxed Warning** Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL®. Infections have included bacterial sepsis and tuberculosis. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with ENBREL®. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, ENBREL® should be discontinued. Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. Data from clinical trials and preclinical studies suggest that the risk of

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating ENBREL® and during treatment. Treatment of latent tuberculosis infection should be initiated prior to therapy with ENBREL®. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers. Some patients who tested negative for latent tuberculosis prior to receiving ENBREL® have developed active tuberculosis. Physicians should monitor patients receiving ENBREL® for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.
Remicade® (Infliximab)	**Boxed Warning** Patients treated with REMICADE are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. REMICADE should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: • Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy. Treatment for latent infection should be initiated prior to REMICADE use. • Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. • Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. HEPATOSPLENIC T-CELL LYMPHOMAS Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis.
Tysabri® (natalizumab)	**Boxed Warning** TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking TYSABRI who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI as monotherapy. • Because of the risk of PML, TYSABRI is available only through a special restricted

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program. • Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.
Rituxan® (Rituximab)	Infusion Reactions: Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue Rituxan infusion and provide medical treatment for Grade 3 or 4 infusion reactions. Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with Rituxan. Severe Mucocutaneous Reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan. Progressive Multifocal Leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving Rituxan.

Appendix H. Excluded studies

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

1. Infliximab (Remicade) for Crohn's disease. Med Lett Drugs Ther 1999;41(1047):19-20. **WRONG PUBLICATION TYPE**
2. Controlling childhood Crohn's disease requires a multipronged approach. Drugs & Therapy Perspectives 2001;17(7):5-8. **WRONG PUBLICATION TYPE**
3. Etanercept and infliximab for rheumatoid arthritis. Drug Ther Bull 2001;39(7):49-52. **WRONG PUBLICATION TYPE**
4. Drug update. Revised labeling reflects fatalities linked to arthritis drug. RN 2004;67(12):72-72. **WRONG PUBLICATION TYPE**
5. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha--California, 2002-2003. MMWR. Morbidity and mortality weekly report 2004;53(30):683-686. **WRONG PUBLICATION TYPE**
6. Peacekeeping in Crohn's disease: maintenance of remission. Drugs & Therapy Perspectives 2005;21(3):7-9. **WRONG PUBLICATION TYPE**
7. Consult stat. Patients on this Crohn's med are prone to infections. RN 2006;69(2):51, 53, 2p. **WRONG PUBLICATION TYPE**
8. Natalizumab (Tysabri) for Crohn's disease. Obstetrics & Gynecology 2008;112(3):693-694. **WRONG PUBLICATION TYPE**
9. Aboulafia DM, Bundow D, Wilske K, Ochs UI. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. Mayo Clin Proc 2000;75(10):1093-8. **WRONG DESIGN**
10. Abramovits W, Arrazola P, Gupta AK. Enbrel (etanercept). Skinmed 2004;3(6):333-5. **WRONG PUBLICATION TYPE**
11. Ackermann C, Kavanaugh A. Economic burden of psoriatic arthritis. PharmacoEconomics (New Zealand) 2008;26:121. **WRONG OUTCOME**
12. Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2004(1):CD003574. **WRONG PUBLICATION TYPE**
13. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56(10):3226-35. **WRONG OUTCOME**
14. Ali Y, Shah S. Infliximab-induced systemic lupus erythematosus. Ann Intern Med 2002;137(7):625-6. **WRONG PUBLICATION TYPE**
15. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkmans BA. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 2006;24(6 Suppl 43):S-77-82. **DRUG NOT INDLUCED**
16. Alldred A. Etanercept in rheumatoid arthritis. Expert Opin Pharmacother 2001;2(7):1137-48. **WRONG DESIGN**
17. Allison C. Abatacept as add-on therapy for rheumatoid arthritis (Structured abstract). Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2005:4-4. **WRONG PUBLICATION TYPE**

18. Amezcua-Guerra LM, Hernandez-Martinez B, Pineda C, Bojalil R. Ulcerative colitis during CTLA-4Ig therapy in a patient with rheumatoid arthritis. Gut 2006;55(7):1059-60. **WRONG DESIGN**
19. Anandacoomarasamy A, Kannangara S, Barnsley L. Cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis. Intern Med J 2005;35(10):638-40. **WRONG PUBLICATION TYPE**
20. Anders DL. TNF inhibitors: a new age in rheumatoid arthritis treatment. American Journal of Nursing 2004;104(2):60-69. **WRONG PUBLICATION TYPE**
21. Anderson JJ, O'Neill A, Woodworth T, Haddad J, Sewell KL, Moreland LW. Health status response of rheumatoid arthritis to treatment with DAB486IL2. Arthritis Care & Research 1996;9(2):112-9. **DRUG NOT INDLUCED**
22. Ang DC, Paulus HE, Louie JS. Patient's ethnicity does not influence utilization of effective therapies in rheumatoid arthritis. J Rheumatol 2006;33(5):870-8. **WRONG OUTCOME**
23. Angelucci E, Cocco A, Viscido A, Caprilli R. Safe use of infliximab for the treatment of fistulizing Crohn's disease during pregnancy within 3 months of conception. Inflamm Bowel Dis 2008;14(3):435-6. **WRONG PUBLICATION TYPE**
24. Angus JE, Andriolo R, Bigby M, Goodman S, Jobling R, Williams H. Biologics for chronic plaque psoriasis. Cochrane Database of Systematic Reviews 2006(4). **WRONG POPULATION**
25. Anonymous. Anakinra and combination therapy. WHO Drug Information (Switzerland) 2002;16:291. **WRONG PUBLICATION TYPE**
26. Anonymous. Adverse effects have most influence on choice of rheumatic drug for older people. Pharmaceutical Journal 2004;273:590. **WRONG PUBLICATION TYPE**
27. Anonymous. Anakinra - Weakly effective in rheumatoid arthritis. Prescrire International (France) 2004;13:43-5. **WRONG PUBLICATION TYPE**
28. Anonymous. Natalizumab - AN 100226, anti-4alpha integrin monoclonal antibody. Drugs in R and D 2004;5:102-107. **WRONG PUBLICATION TYPE**
29. Anonymous. Crohn's disease: certolizumab, adalimumab demonstrate efficacy in prior users of infliximab. Formulary (USA) 2007;42:58-9. **WRONG PUBLICATION TYPE**
30. Anonymous. Infliximab. Prescrire International (France) 2007;16:194. **WRONG PUBLICATION TYPE**
31. Anonymous. New indication - Humira - Adalimumab. Formulary (USA) 2007;42:216-17. **WRONG PUBLICATION TYPE**
32. Anonymous. No differences in efficacy of anti-rheumatic drugs. Australian Journal of Pharmacy 2008;89:92. **WRONG PUBLICATION TYPE**
33. Antoni C, Kalden JR. Combination therapy of the chimeric monoclonal anti-tumor necrosis factor alpha antibody (infliximab) with methotrexate in patients with rheumatoid arthritis. Clinical and Experimental Rheumatology 1999;17(Suppl 18):S73-S77. **WRONG PUBLICATION TYPE**
34. Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol 2008;35(5):869-76. **WRONG POPULATION**
35. Antoniou C, Dessinioti C, Katsambas A, Stratigos AJ. Elevated triglyceride and cholesterol levels after intravenous antitumour necrosis factor-<it>alpha</it> therapy in a patient

with psoriatic arthritis and psoriasis vulgaris. British Journal of Dermatology (England) 2007;156:1090-91. **WRONG PUBLICATION TYPE**
36. Aratari A, Papi C, Clemente V, Moretti A, Luchetti R, Koch M, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. Dig Liver Dis 2008;40(10):821-6. **WRONG DESIGN**
37. Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs 2005;65(16):2253-2286. **WRONG PUBLICATION TYPE**
38. Arend LJ, Nadasdy T. Emerging therapy-related kidney disease. Archives of Pathology & Laboratory Medicine 2009;133(2):268-278. **WRONG PUBLICATION TYPE**
39. Ariza-Ariza R, Navarro-Sarabia F, Hernandez-Cruz B, Rodriguez-Arboleya L, Toyos J, et al. Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. Rheumatology 2007;46:529. **WRONG OUTCOME**
40. Armuzzi A, De Pascalis B, Lupascu A, Fedeli P, Leo D, Mentella MC, et al. Infliximab in the treatment of steroid-dependent ulcerative colitis. Eur Rev Med Pharmacol Sci 2004;8(5):231-3. **WRONG DESIGN**
41. Asch-Goodkin J. Eye on Washington. Contemporary Pediatrics 2006;23(7):14-14. **WRONG PUBLICATION TYPE**
42. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005;52(7):1986-92. **WRONG DESIGN**
43. Aslanidis S, Pyrpasopoulou A, Douma S, Petidis K. Is it safe to readminister tumor necrosis factor (alpha) antagonists following tuberculosis flare? Arthritis and Rheumatism 2008;58(1):327-328. **WRONG PUBLICATION TYPE**
44. Asrani NS. Disseminated histoplasmosis associated with the treatment of rheumatoid arthritis with anticytokine therapy. Annals of Internal Medicine 2008;149(8):594-595. **WRONG PUBLICATION TYPE**
45. Bacquet-Deschryver H, Jouen F, Quillard M, Menard JF, Goeb V, Lequerre T, et al. Impact of three anti-TNFalpha biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients. J Clin Immunol 2008;28(5):445-55. **WRONG POPULATION**
46. Baert F, Norman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. New England Journal of Medicine 2003;348(7):601-608. **WRONG OUTCOME**
47. Baeten D, Kruithof E, Van den Bosch F, Van den Bossche N, Herssens A, Mielants H, et al. Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? Ann Rheum Dis 2003;62(9):829-34. **WRONG DESIGN**
48. Bal A, Gurcay E, Aydog E, Umay E, Tatlican S, Cakci A. Onset of psoriasis induced by infliximab. Journal of Clinical Rheumatology 2008;14(2):128-129. **WRONG PUBLICATION TYPE**
49. Bal A, Gurcay E, Aydog E, Unlu E, Umay E, Cakci A. Neuralgic amyotrophy due to rheumatoid arthritis or etanercept: Causal association or coincidence? Indian Journal of Medical Research 2008;127(1):89-90. **WRONG PUBLICATION TYPE**
50. Balandraud N, Guis S, Meynard JB, Auger I, Roudier J, Roudier C. Long-term treatment with methotrexate or tumor necrosis factor (alpha) inhibitors does not increase Epstein-

Barr virus load in patients with rheumatoid arthritis. Arthritis Care and Research 2007;57(5):762-767. **WRONG OUTCOME**

51. Baldassano R, Braegger CP, Escher JC, DeWoody K, Hendricks DF, Keenan GF, et al. Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. Am J Gastroenterol 2003;98(4):833-8. **WRONG POPULATION**
52. Bankhurst AD. Etanercept and methotrexate combination therapy. Clin Exp Rheumatol 1999;17(6 Suppl 18):S69-72. **WRONG PUBLICATION TYPE**
53. Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum 2005;52(4):1216-23. **WRONG OUTCOME**
54. Baraliakos X, Listing J, Rudwaleit M, Brandt J, Sieper J, Braun J. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. Ann Rheum Dis 2005;64(10):1462-6. **WRONG DESIGN**
55. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess 2004;8(11):iii, 1-91. **WRONG DESIGN**
56. Belkhou A, Younsi R, El Bouchti I, El Hassani S. Rituximab as a treatment alternative in sarcoidosis. Joint Bone Spine 2008;75(4):511-512. **WRONG PUBLICATION TYPE**
57. Bennett AN, Peterson P, Zain A, Grumley J, Panayi G, Kirkham B. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. Rheumatology (Oxford) 2005;44(8):1026-31. **WRONG DESIGN**
58. Benucci M, Manfredi M, Demoly P, Campi P. Injection site reactions to TNF-(alpha) blocking agents with positive skin tests. Allergy: European Journal of Allergy and Clinical Immunology 2008;63(1):138-139. **WRONG PUBLICATION TYPE**
59. Berger JR. Natalizumab. Drugs of Today (Spain) 2006;42:639-55. **WRONG PUBLICATION TYPE**
60. Berger JR, Koralnik IJ. Progressive multifocal leukoencephalopathy and natalizumab -- unforseen consequences. New England Journal of Medicine 2005;353(4):414-416. **WRONG PUBLICATION TYPE**
61. Bergstrom L, Yocum DE, Ampel NM, Villanueva I, Lisse J, Gluck O, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum 2004;50(6):1959-66. **WRONG DESIGN**
62. Bernstein CN. Ulcerative colitis with low-grade dysplasia. Gastroenterology 2004;127(3):950-6. **WRONG DESIGN**
63. Berthelot JM, Varin S, Cormier G, Tortellier L, Guillot P, Glemarec J, et al. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy. Joint Bone Spine 2007;74(2):144-7. **WRONG DESIGN**
64. Biancone L, Cretella M, Tosti C, Palmieri G, Petruzziello C, Geremia A, et al. Local injection of infliximab in the postoperative recurrence of Crohn's disease. Gastrointest Endosc 2006;63(3):486-92. **WRONG POPULATION**

65. Biancone L, Orlando A, Kohn A, Colombo E, Sostegni R, Angelucci E, et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. Gut 2006;55(2):228-33. **WRONG DESIGN**
66. Bickston SJ, Lichtenstein GR, Arseneau KO, Cohen RB, Cominelli F. The relationship between infliximab treatment and lymphoma in Crohn's disease. Gastroenterology 1999;117(6):1433-7. **WRONG DESIGN**
67. Blick SK, Curran MP. Certolizumab pegol in Crohn's disease. BioDrugs (New Zealand) 2007;21:195-201. **WRONG PUBLICATION TYPE**
68. Bobbio-Pallavicini F, Caporali R, Alpini C, Avalle S, Epis OM, Klersy C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. Ann Rheum Dis 2007;66(3):302-7. **WRONG PUBLICATION TYPE**
69. Bombardieri S, Ruiz AA, Fardellone P, Geusens P, McKenna F, Unnebrink K, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology (Oxford) 2007;46(7):1191-9. **WRONG PUBLICATION TYPE**
70. Bondeson J, Maini RN. Tumour necrosis factor as a therapeutic target in rheumatoid arthritis and other chronic inflammatory diseases: the clinical experience with infliximab (REMICADE). Int J Clin Pract 2001;55(3):211-6. **WRONG DESIGN**
71. Boonen A, Patel V, Traina S, Chiou CF, Maetzel A, Tsuji W. Rapid and sustained improvement in health-related quality of life and utility for 72 weeks in patients with ankylosing spondylitis receiving etanercept. J Rheumatol 2008;35(4):662-7. **WRONG DESIGN**
72. Bosch RI, Amo NDVD, Manteca CF, Cortina EL, Polo RG, Courel LG. Psoriasis induced by anti-TNF probably not so uncommon. Journal of Clinical Rheumatology 2008;14(2):128. **WRONG PUBLICATION TYPE**
73. Botsios C, Sfriso P, Ostuni PA, Todesco S, Punzi L. Efficacy of the IL-1 receptor antagonist, anakinra, for the treatment of diffuse anterior scleritis in rheumatoid arthritis. Report of two cases [8]. Rheumatology 2007;46(6):1042-1043. **WRONG PUBLICATION TYPE**
74. Brandt J, Haibel H, Sieper J, Reddig J, Braun J. Infliximab treatment of severe ankylosing spondylitis: one-year followup. Arthritis Rheum 2001;44(12):2936-7. **WRONG PUBLICATION TYPE**
75. Brandt J, Khariouzov A, Listing J, Haibel H, Sorensen H, Grassnickel L, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48(6):1667-75. **WRONG DESIGN**
76. Braun J, Baraliakos X, Listing J, Davis J, van der Heijde D, Haibel H, et al. Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor alpha agents. Arthritis Rheum 2007;57(4):639-47. **WRONG DESIGN**
77. Braun J, Landewe R, Hermann KG, Han J, Yan S, Williamson P, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: Results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum 2006;54(5):1646-52. **WRONG OUTCOME**

78. Breedveld F, Agarwal S, Yin M, Ren S, Li NF, Shaw TM, et al. Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. J Clin Pharmacol 2007;47(9):1119-28. **WRONG OUTCOME**
79. Breedveld FC, Han C, Bala M, van der Heijde D, Baker D, Kavanaugh AF, et al. Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Annals of the Rheumatic Diseases 2005(1):52; 5-52; 5. **WRONG OUTCOME**
80. Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol 2004;31(6):1103-11. **WRONG DESIGN**
81. Bridges Jr SL, Hughes LB, Mikuls TR, Howard G, Tiwari HK, Alarcon GS, et al. Early rheumatoid arthritis in African-Americans: The CLEAR registry. Clinical and Experimental Rheumatology 2003;21(5 SUPPL. 31):S138-S145. **WRONG PUBLICATION TYPE**
82. Briot K, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-(alpha) treatment. Journal of Rheumatology 2008;35(5):855-861. **WRONG DESIGN**
83. Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, et al. TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 2007;74(2):148-54. **WRONG DESIGN**
84. Brodszky V, Pentek M, Gulacsi L. Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR50 response after 24 weeks of treatment. Scandinavian Journal of Rheumatology 2008;37(5):399-400. **WRONG PUBLICATION TYPE**
85. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002;46(12):3151-8. **WRONG DESIGN**
86. Buch MH, Bingham SJ, Bryer D, Emery P. Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. Rheumatology (Oxford) 2007;46(7):1153-6. **WRONG DESIGN**
87. Bujanover Y, Weiss B. Anti-tumor necrosis factor therapy for pediatric inflammatory bowel diseases. Israel Medical Association Journal 2008;10(9):634-639. **WRONG PUBLICATION TYPE**
88. Burke JP, Kelleher B, Ramadan S, Quinlan M, Sugrue D, O'Donovan MA. Pericarditis as a complication of infliximab therapy in Crohn's disease. Inflamm Bowel Dis 2008;14(3):428-9. **WRONG PUBLICATION TYPE**
89. Burmester GR, Ferraccioli G, Flipo RM, Monteagudo-Saez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum 2008;59(1):32-41. **WRONG DESIGN**
90. Burr ML, Malaviya AP, Gaston JH, Carmichael AJ, Ostor AJK. Rituximab in rheumatoid arthritis following anti-TNF-associated tuberculosis. Rheumatology 2008;47(5):738-739. **WRONG PUBLICATION TYPE**
91. Cacace E, Anedda C, Ruggiero V, Fornasier D, Denotti A, Perpignano G. Etanercept in rheumatoid arthritis: Long term anti-inflammatory efficacy in clinical practice. European Journal of Inflammation 2006;4(3):171-176. **WRONG PUBLICATION TYPE**

92. Cada DJ, Levien T, Baker DE. Natalizumab. Hospital Pharmacy (USA) 2005;40:336-43. **WRONG PUBLICATION TYPE**
93. Cairns AP, Duncan MK, Hinder AE, Taggart AJ. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis 2002;61(11):1031-2. **WRONG DESIGN**
94. Calabrese LH. Anakinra treatment of patients with rheumatoid arthritis. Ann Pharmacother 2002;36(7-8):1204-9. **WRONG PUBLICATION TYPE**
95. Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1Ra Arthritis Study Group. Arthritis Rheum 1996;39(7):1092-101. **WRONG DESIGN**
96. Canadian Coordinating Office for Health Technology Assessment. Infliximab (Remicade (R)) for the treatment of ankylosing spondylitis (Structured abstract). Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2004. **WRONG PUBLICATION TYPE**
97. Cantini F, Niccoli L, Benucci M, Chindamo D, Nannini C, Olivieri I, et al. Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. Arthritis Rheum 2006;55(5):812-6. **WRONG POPULATION**
98. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology 2008;47(6):872-876. **WRONG DESIGN**
99. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003;30(7):1436-9. **WRONG OUTCOME**
100. Cartwright MW. Methotrexate, Laboratory testing and risk of serious illness: analyses in 20,000 patients. Johns Hopkins Arthritis ACR Highlights on Rheumatoid Arthritis Treatments 2003. **DRUG NOT INDLUCED**
101. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. J Rheumatol 2006;33(7):1452-6. **WRONG OUTCOME**
102. Cauza E, Hanusch-Enserer U, Frischmuth K, Fabian B, Dunky A, Kostner K. Short-term infliximab therapy improves symptoms of psoriatic arthritis and decreases concentrations of cartilage oligomeric matrix protein. Journal of Clinical Pharmacy & Therapeutics 2006;31(2):149-152. **WRONG POPULATION**
103. Caviglia R, Ribolsi M, Rizzi M, Emerenziani S, Annunziata ML, Cicala M. Maintenance of remission with infliximab in inflammatory bowel disease: efficacy and safety long-term follow-up. World J Gastroenterol 2007;13(39):5238-44. **WRONG POPULATION**
104. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 2005;32(5):811-9. **WRONG OUTCOME**
105. Centre for Reviews and Dissemination. Systematic review of the clinical effectiveness, safety, tolerability and cost effectiveness of etanercept for the treatment of active and progressive psoriatic arthritis - systematic review (project) (Brief record). York: Centre for Reviews and Dissemination (CRD) 2008. **WRONG PUBLICATION TYPE**

106. Cezard JP, Nouaili N, Talbotec C, Hugot JP, Gobert JG, Schmitz J, et al. A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe pediatric crohn disease. J Pediatr Gastroenterol Nutr 2003;36(5):632-6. **WRONG DESIGN**
107. Chahine LM, Patrick R, Tavee J. Complex Regional Pain Syndrome After Infliximab Infusion. Journal of Pain and Symptom Management 2008;36(3):e2-e4. **WRONG PUBLICATION TYPE**
108. Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: A survey of practice patterns and pregnancy outcomes. Journal of Rheumatology 2003;30(2):241-246. **WRONG DESIGN**
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656. Yelin E, Trupin L, Katz P, Lubeck D, Rush S, Wanke L. Association Between Etanercept Use and Employment Outcomes Among Patients With Rheumatoid Arthritis. Arthritis and Rheumatism 2003;48(11):3046-3054. **WRONG DESIGN**
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Appendix I. Characteristics of studies with poor internal validity

Study	Design	Sample size	Intervention	Reason for poor rating
Bathon et al., 2006[285]	Pooled data analysis	2402	Etanercept	Non-systematic pooling
Bejarano et al., [286]	RCT	148	Adalimumab	High LTF, high differential LTF
Carmona et al., 2007[287]	Retrospective cohort	5248	Various	Bias
Fleischmann et al., 2003[288]	Pooled data analysis	1128	Etanercept	Non-systematic pooling
Gerloni et al.[289]	Open label prospective trial	24	Infliximab	High LTF
Menter et al., 2008[290]	Retrospective data analysis	1373	Infliximab	Non-systematic pooling
Moreland et al., 2006[291]	Pooled retrospective analysis	714	Etanercept	High LTF; no ITT analysis
Sandborn et al., 2007[149]	RCT	662	Certoluzimab	High LTF
Schreiber et al., 2007[150]	RCT	428	Certoluzimab	High LTF
Seong et al., 2007[292]	Retrospective data analysis	193	Infliximab and etanercept	Inadequate design
Venkateshan, et al., 2009[293]	Systematic review	25 studies	Various	No dual review; no critical appraisal or component studies
Wolfe et al., 2007[294]	Retrospective data analysis	17598	Infliximab and etanercept	Inadequate analysis of a case control study

ITT, intention to treat; LTF, loss to follow-up; RCT, randomized controlled trial.

Drug Class Review

Targeted Immune Modulators

Final Report
Update 2
Evidence Tables

November 2009

Update 1: January 2007
Original Report: December 2005

The literature on this topic is scanned periodically.

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Abe et al.**[1] **Year: 2006** **Country:** Japan		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab in Japanese patients with RA already taking MTX.		
DESIGN:	**Study design:** Placebo controlled **Setting:** Multi-center **Sample size:** 147		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF (3 mg/kg)** 3 mg/kg (weeks 0,2,6) 14 weeks 47	**INF (10 mg/kg)** 10 mg/kg (weeks 0,2,6) 14 weeks 49	**placebo** N/A 14 weeks 51
INCLUSION CRITERIA:	20–75 years of age; met ARA diagnostic criteria for RA of at least 6 months prior to enrollment; Had ≥ 6 tender joints (of 68 counted) and ≥ 6 swollen joints (of 66 counted), plus at least 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate ≥ 28 mm/h, or CRP ≥ 2 mg/dl, despite treatment with MTX for more than 3 months; MTX dosage must have been stable 6 mg/week or more during the last 4 weeks. Patients receiving oral or suppository NSAIDs folic acid, oral or suppository corticosteroid (10 mg/day or less prednisolone equivalent) must have been taking a stable dose for 4 weeks prior to entry.		
EXCLUSION CRITERIA:	Use of DMARD, immunosuppressive drugs other than MTX, intraarticular, intramuscular, intravenous or epidural corticosteroids, to have arthrocentesis and plasma exchange (for 4 wks prior to entry), or use alkylating agents (for 5 yrs prior to entry); Functional class IV using Steinbrocker's criteria: Any other systemic rheumatic diseases except Sjögren's syndrome; Serious infections; Opportunistic infections (within the previous 3 mo); TB (within the previous 3 yrs); Infections of artificial joints (within the previous 5 yrs); Human immunodeficiency virus infection; Malignancies (within the previous 5 yrs); History of known allergies to human/murine chimeric antibodies; Pregnancy; Hemoglobin < 8.5 g/dl; leukocyte count < 3500 × 106/l; neutrophil count < 1500 × 106/l; platelet count < 10 × 104/µl; serum creatinine level > 1.5 mg/dl; and alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, and alkaline phosphatase (ALP) levels greater than twice the normal upper limit.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; NSAID; folic acid, corticosteroids		

<table>
<tr><td colspan="4">Authors: Abe et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 7.9 years)</td></tr>
<tr><td></td><td><u>INF (3 mg/kg)</u></td><td><u>INF (10 mg/kg)</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>55.2</td><td>56.8</td><td>55.1</td></tr>
<tr><td>Sex (% female):</td><td>81.6</td><td>78.4</td><td>74.5</td></tr>
<tr><td>Ethnicity:</td><td>Japanese</td><td>Japanese</td><td>Japanese</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>19</td><td>18.7</td><td>17.8</td></tr>
<tr><td>• SJC</td><td>15.1</td><td>13.2</td><td>13.5</td></tr>
<tr><td>• Mean disease duration (yrs)</td><td>9.1</td><td>7.1</td><td>7.5</td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>85.7</td><td>92.2</td><td>89.4</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR20 at Week 14.

Secondary Outcome Measures: ACR50 and ACR70 and individual measurements of the ACR core set

Timing of assessments: Weeks 0, 2, 6, 10, and 14</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• ACR20 response rates at Week 14 were 23.4%, 61.2%, and 52.9% in the placebo, 3 mg/kg, and 10 mg/kg groups, respectively. Showing significantly higher response in the combined INF groups than in the placebo group ($P < 0.001$).*
• A significantly greater percentage of patients in both INF groups than in the placebo group achieved improvement of ACR20 and ACR50 at all evaluation points.
• There was not a significant difference in any outcome measure between INF groups.

Intermediate Outcome Measures:
• N/A</td></tr>
</table>

Authors: Abe et al. **Year: 2006**			
ADVERSE EVENTS:	**INF (3 mg/kg)**	**INF (10 mg/kg)**	**placebo**
Overall adverse effects reported (%):	73.5	72.5	68.1
• Infections	44.9	49	36.2
• Cold	18.4	25.5	8.5
• Fever	18.4	15.7	19.1
• Diarrhea	12.2	13.7	4.3
• Cough	6.1	13.7	10.6
• Headache	14.3	5.9	12.8
• Sputum	6.1	5.9	8.5
• Rash	8.2	5.9	0
• Pneumonia	2	5.9	0
• Hot flushes	0	5.9	2.1
• Pruritus	6.1	3.9	0
• Pain, pharynx	6.1	2	6.4
• Stomatitis	8.2	0	6.4
• Epigastralgia	6.1	0	0
Significant differences in adverse events:	None reported. Statistics not given on individual adverse events.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** yes		
ADEQUATE RANDOMIZATION:	Method NR.		
ADEQUATE ALLOCATION CONCEALMENT:	Method NR.		
BLINDING OF OUTCOME ASSESSORS:	NR.		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14 (4 dropped out prior to first dose) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**INF (combined)**	**placebo**	
Loss to follow-up:	5 (5.2%)	5 (9.8%)	
Withdrawals due to adverse events:	5 (5.2%)	1 (1.9%)	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Alonso-Ruiz et al.**[2] **Year: 2008** **Country:** Multinational
FUNDING:	Authors declare that they have no competing interests; no external funding reported
DESIGN:	**Study design:** Systematic review & meta-analysis **Number of patients:** 7,098
AIMS OF REVIEW:	To analyze available evidence on the efficacy and safety of anti-TNFα drugs (INF, ETA and ADA) for treating RA.
STUDIES INCLUDED IN META-ANALYSIS	13 trials (7,098 patients) ADA (5 trials) Weinblatt (ARMADA) 2003; van de Putte 2004; Furst (STAR) 2003; Keystone 2004; Breedveld (PREMIER) 2006 ETA (4 trials) Moreland 1999; Weinblatt 1999; Bathon 2000; van der Heijde (TEMPO) 2006; INF (4 trials) Lipsky 2000; St. Clair 2004; Quinn 2005; Westhovens 2006
TIME PERIOD COVERED:	Up to October 2006
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs of INF, ETA or ADA for treatment of RA; trial duration ≥ 6 months with efficacy measured by ACR response; trials were excluded if they either used administration routes other than recommended or included no treatment arm with recommended doses. Only information published in the trial reports was assessed.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients had to meet ACR criteria for diagnosis of RA

Authors: Alonso-Ruiz et al. **Year: 2008**	
CHARACTERISTICS OF INTERVENTIONS:	ADA 10-40 mg/wk, ETA 20-50 mg/wk, or INF 7.5 -20mg/wk; compared with and/or MTX
MAIN RESULTS:	• Global comparison of ACR20 efficacy of any dose of any anti-TNFα drug with any control treatment showed a combined effect of 1.81 (95% CI 1.43–2.29) with an NNT of 6 (5–7). • Combined effects were 1.89 (1.30–2.75) for ADA, 1.71 (1.11–2.63) for ETA and 1.82 (1.19–2.77) for INF. • ACR50 efficacy showed a combined effect of 2.46 (95% CI 1.75-3.45) • ACR70 showed combined effect of 2.77 (95% CI 1.85-4.15) • Analysis of this set of 13 trials provided evidence of relevant and statistically significant heterogeneity (Q = 157.7; $P < 0.001$; I^2 92%). • ACR20 effect of anti-TNF in MTX-naive patients: 1.10 (0.96-1.26) • ACR20 effect of ant-TNF in patients with previous insufficient response to MTX: 2.32 (1.99-2.72); NNT of 4 (3-5)
ADVERSE EVENTS:	• No significant overall difference between experimental and control groups in withdrawals due to adverse events: pooled RR = 1.25 (0.65-2.39) • ETA-treated patients less likely to withdraw from AEs than controls • INF- and ADA-treated patients more likely to withdraw from AEs than controls • More adverse events in anti-TNF patients: RR 1.02 (1.00–1.04); $P = 0.021$) • INF patients showed a higher frequency of serious adverse events ($P = 0.048$) and infections ($P = 0.004$), but the combined estimates for all three anti-TNFα drugs and safety outcomes were not significant. • No significant increases in risk detected in anti-TN patients in severe infections, malignancies and deaths vs. controls
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes; Trials were searched in scientific journals and congress conference proceedings. Information from the MEDLINE, EMBASE and Cochrane Library databases up to October 2006 was checked using a high-sensitivity strategy. The computerized search was completed with a manual search of reference lists.
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Bathon et al.,[3] Genovese et al.,[4, 5] and Kosinski et al.[6]** **Year: 2000, 2002 and 2005** **Country:** US		
FUNDING:	Immunex Corporation		
RESEARCH OBJECTIVE:	To compare etanercept and methrotrexate in patients with early RA		
DESIGN:	**Study design:** RCT **Setting:** Clinics **Sample size:** 632		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** 20mg/week 12 months 217	**ETA10** 10 mg 2x week 12 months 208	**ETA25** 25 mg 2x week 12 months 207
INCLUSION CRITERIA:	At least 18 years of age; RA < 3 years; positive serum test for RF or at least 3 bone erosions evident on radiographs of the hands, wrists, or feet; at least 10 swollen joints and at least 12 tender or painful joints; erythrocyte sedimentation rate of at least 28 mm per hour; a serum CRP concentration of at least 2.0 mg per deciliter, or morning stiffness that lasted at least 45 minutes		
EXCLUSION CRITERIA:	Prior treatment with MTX; no other important concurrent illnesses		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of NSAIDs and prednisone (≤ 10 mg daily)		

Authors: Bathon et al., Genovese et al., and Kosinski et al. **Year: 2000, 2002 and 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Early RA (mean disease duration 1 year)		
	MTX	**ETA 10mg**	**ETA 25mg**
Mean age (years):	49	50	51
Sex (% female):	75	75	74
Ethnicity (% white):	88	84	86
Other germane population qualities:			
• TJC	30	31	31
• SJC	24	24	24
• DMARD use (%)	46	25	23
• MTX use (%)	N/A	N/A	N/A
• Corticosteroids use (%)	41	42	39
• Total Sharp score	12.9	11.2	12.4
• Mean disease duration (mo)	12	11	12
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR-N/20/50/70; radiographic progression - Sharp score **Secondary Outcome Measures:** CRP **Timing of assessments:** Base line, 2 weeks, 1, 6, 8, 10, and 12 months		

Authors: Bathon et al., Genovese et al., and Kosinski et al. **Year: 2000 and 2002**	
RESULTS:	**Health Outcome Measures:** • Up to 6 months significantly more patients on ETA 25mg than on MTX achieved ACR50 and ACR70 responses ($P < 0.05$); thereafter no significant difference existed between ETA 25mg and MTX. **Intermediate Outcome Measures:** • At 12 months no significant differences existed in ACR 20 response rates: 72% ETA 25mg vs. 65% MTX ($P = 0.16$). • Compared to MTX, ETA acted more quickly to decrease symptoms and slow joint damage in patients with early active RA. The area under the curve was significantly greater for ETA 25mg throughout the study ($P < 0.05$) • At 12 months there was less joint erosion in the ETA 25mg than in the MTX group; mean increase in Sharp score ETA 25mg 0.47 vs. MTX 1.03 ($P = 0.002$). **24 months open-label extension:** • Significantly more patients on ETA 25 mg than on MTX achieved ACR 20 response at 24 months (72% vs. 59%; $P = 0.005$) • No significant differences for ACR50 (49% vs. 42%) and ACR 70 (29% vs. 24%) responses. • Significantly more patients on ETA 25mg than on MTX had a HAQ improvement of at least 0.5 units (55% vs. 37%; $P < 0.001$)

<table>
<tr><td colspan="4">Authors: Bathon et al., Genovese et al., and Kosinski et al.
Year: 2000, 2002 and 2005</td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">Yes - number of infections per patient year in both ETA10mg and 25mg 1.5 vs. MTX 1.9 events per patient-year P = 0.006
24 months open-label extension:
• No significant differences in sever adverse events between MTX and ETA
5 year extension
Observed number of malignancies were within expected rates of the general population; lymphoma, however, was increased: SIR: 3.3</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: NR</td></tr>
<tr><td>ADEQUATE RANDOMIZATION:</td><td colspan="3">Yes</td></tr>
<tr><td>ADEQUATE ALLOCATION CONCEALMENT:</td><td colspan="3">NR</td></tr>
<tr><td>BLINDING OF OUTCOME ASSESSORS:</td><td colspan="3">Yes</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 19% (118)
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>MTX</u></td><td><u>ETA10</u></td><td><u>ETA25</u></td></tr>
<tr><td>Loss to follow-up:</td><td>45(21%)</td><td>42(20%)</td><td>31(15%)</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>24(11%)</td><td>12(6%)</td><td>11(5%)</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Blumenauer et al.**[7] **Year: 2002** **Country:** US
FUNDING:	Institute of Population Health, Canada and other sources listed on the CMSG scope
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 529
AIMS OF REVIEW:	To assess the efficacy and safety of infliximab for the treatment of RA.
STUDIES INCLUDED IN META-ANALYSIS	Lipsky PE et al., 2000, Maini RN et al., 1998, and Maini RN et al. 1999
TIME PERIOD COVERED:	1966- March 2002
CHARACTERISTICS OF INCLUDED STUDIES:	RCT or controlled trials comparing INF and MTX to MTX alone or comparing INF alone to placebo; at least 6 months study duration; patients could also be taking other DMARDs or corticosteroids provided they were on stable doses and were randomly allocated to treatment with INF or to treatment without INF
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients were 16 years of age or older; met the ACR 1987 revised criteria for RA; Had evidence of active disease as demonstrated by at least two of the following symptoms: TJC, SJC, early morning stiffness greater than 30 minutes, and acute phase reactants.

Authors: Blumenauer et al. **Year:** 2002 **Country:** US	
CHARACTERISTICS OF INTERVENTIONS:	Treatment with INF (3mg/kg every 4 weeks and 10mg/kg every 4 weeks) and MTX versus MTX or INF (3mg/kg every 4 weeks and 10mg/kg every 4 weeks) alone versus placebo; minimum trial duration of 6 months.
MAIN RESULTS:	• **ACR 20** response was significantly improved in all INF doses compared to control at 6 months: INF 3mg/kg/8 weeks: 53% vs. 20% (controls); NNT: 3.03 INF 3mg/kg/4 weeks: 49% vs. 19% (controls); NNT: 3.33 INF 10mg/kg/8 weeks: 53% vs. 20% (controls); NNT: 3.13 INF 10mg/kg/4 weeks: 55% vs. 19% (controls); NNT: 2.78 • **ACR 50** response was significantly improved in all INF doses compared to control at 6 months: INF 3mg/kg/8 weeks: 26% vs. 5% (controls); NNT: 4.76 INF 3mg/kg/4 weeks: 32% vs. 4% (controls); NNT: 3.57 INF 10mg/kg/8 weeks: 30% vs. 5% (controls); NNT: 4 INF 10mg/kg/4 weeks: 28% vs. 4% (controls); NNT: 4.17 • **ACR 70** response was significantly improved in all INF doses compared to control at 6 months: INF 3mg/kg/8 weeks: 8% vs. 0% (controls); NNT: 12.5 INF 3mg/kg/4 weeks: 10% vs. 0% (controls); NNT: 10 INF 10mg/kg/8 weeks: 17% vs. 0% (controls); NNT: 5.88 INF 10mg/kg/4 weeks: 11% vs. 0% (controls); NNT: 9.09 • **ACR 20** response was significantly improved in all INF doses compared to control at 12 months INF 3mg/kg/8 weeks: 42% vs. 17% (controls); NNT: 4 INF 3mg/kg/4 weeks: 48% vs. 17% (controls); NNT: 3.23 INF 10mg/kg/8 weeks: 59% vs. 17% (controls); NNT: 2.38 INF 10mg/kg/4 weeks: 59% vs. 17% (controls); NNT: 2.38 Significantly more patients in the control groups withdrew than in the INF groups, RR 0.42; 95% CI 0.31-0.56

Authors: Blumenauer et al. **Year:** 2002 **Country:** US	
ADVERSE EVENTS:	• Withdrawals due to adverse events were not statistically significantly different between groups: RR 0.96; 95% CI 0.43-2.14 • 6 months, infections requiring antibiotics 31% of INF patients versus 21% of controls (not statistically different) • At 12 months, serious adverse events (WHO definition) were statistically different between INF and placebo for any dose. RR: 0.8;95% CI: 0.5 – 1.29; serious infections were not statistically different, RR 0.76; 95% CI 0.33-1.73
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Blumenauer et al.**[8] **Year:** 2003 **Country:** US
FUNDING:	Institute of Population Health, Canada and other sources listed on the CMSG scope
DESIGN:	**Study design:** Meta-analysis **Number of patients: 955**
AIMS OF REVIEW:	To assess the efficacy and safety of etanercept for the treatment of RA.
STUDIES INCLUDED IN META-ANALYSIS	Bathon et al. 2000, Moreland et al., 1999, and Weinblatt et al. 1999.
TIME PERIOD COVERED:	1966 to February 2003
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs or controlled clinical trials comparing ETA to placebo, ETA to MTX, or ETA plus MTX to MTX alone; at least 6 months duration; patients could be on other DMARDS, NSAIDs or corticosteroids.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients were 16 years of age or older; met the ACR 1987 revised criteria for RA; evidence of active disease as demonstrated by at least two of the following symptoms: TJC, SJC, early morning stiffness greater than 30 minutes, and acute phase reactants.
CHARACTERISTICS OF INTERVENTIONS:	Treatment with: 1. ETA (10 or 25 mg twice weekly) versus placebo (Moreland) 2. ETA (25 mg subcutaneously twice weekly) plus MTX versus MTX alone (Weinblatt) 3. ETA (10 or 25 mg twice weekly) versus MTX (Bathon) Subcutaneous injections; minimum trial duration of 6 months.

Authors: Blumenauer et al. **Year:** 2003 **Country:** US	
MAIN RESULTS:	**6 Month Efficacy (pooled results from treatments 1 & 2)** • **ACR 20** response was significantly improved in both ETA doses compared to control at 6 months ETA 10 mg/twice weekly: 51% vs. 11% (controls); RR: 4.6 (95% CI 2.4-8.8); NNT: 3 ETA 25 mg/twice weekly: 64% vs. 15% (controls); RR: 3.8 (95% CI 2.5-6.0); NNT: 2 • **ACR 50** response was significantly improved in both ETA doses compared to control at 6 months ETA 10 mg/twice weekly: 24% vs. 5%(controls); RR 4.74 (95% CI 1.68-13.36); NNT: 5 ETA 25 mg/twice weekly: 39% vs. 4% (controls); RR 8.89 (95% CI 3.61-21.89); NNT: 3 • **ACR 70** response was significantly improved in the ETA 25 mg dose, but not with the 10 mg dose at 6 months ETA 10 mg/twice weekly: RR: 7.37 C.I.: 0.93-58.49 ETA 25 mg/twice weekly: 15% vs. 1% (controls); RR 11.31 (95% CI 2.19-58.30); NNT: 7 **6 Month Efficacy (results from treatment 3)** • **ACR 20, ACR 50, and ACR 70** response rates at 6 months were not statistically different between patients taking ETA and patients taking MTX. (no statistics given) **12 Month Efficacy (results from treatment 3)** • **ACR 20** response was not statistically different between patients taking ETA and patients taking MTX at 12 months ETA 10 mg/twice weekly: RR: 0.93 C.I.: 0.79-1.10 ETA 25 mg/twice weekly: RR: 1.12 C.I.: 0.96-1.29 • **ACR 50** response was statistically significantly greater with the 10 mg dose of ETA ($P = 0.04$), but not the 25 mg dose of ETA versus MTX at 12 months ETA 10 mg/twice weekly: RR: 0.75 C.I.: 0.58-0.98 ETA 25 mg/twice weekly: RR: 1.17 C.I.: 0.93-1.46 • **ACR 70** response was not statistically different between patients taking ETA and patients taking MTX at 12 months ETA 10 mg/twice weekly: RR: 0.74 C.I.: 0.49-1.12 ETA 25 mg/twice weekly: RR: 1.16 C.I.: 0.93-1.67 • Significantly more patients in the control groups (33%) withdrew than in the ETA 25 mg dose group (15%). RR 0.43; 95% CI 0.24-0.77 • No significant difference in withdrawal was observed between the control groups and the 10 mg dose group RR: 0.65; CI 0.34-1.26

Authors: Blumenauer et al. **Year:** 2003 **Country:** US	
ADVERSE EVENTS:	• Withdrawals due to adverse events were not statistically significantly different between the 10 mg ETA group and controls RR 0.59; 95% CI 0.31-1.10 • Fewer withdrawals due to adverse events occurred in the 25 mg ETA group versus controls RR 0.50; 95% CI 0.27-0.94 • The risk of ISR was increased in patients taking 10 mg ETA versus controls RR 3.86; 95% CI 2.59-5.77 • The risk of ISR was increased in patients taking 25 mg ETA versus controls RR 4.77; 95% CI 3.26-6.97
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Breedveld et al.**[9] **Year: 2006** **Country:** Multinational (Europe, North America, Australia)		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	To compare the efficacy and safety of adalimumab plus methotrexate versus methortrexate monotherapy or adalimumab monotherapy in patients with early, aggressive RA who had not previously received MTX treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (133) **Sample size:** 799		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** 20 mg/week 2 years 257	**ADA** 40 mg biweekly 2 years 274	**ADA plus MTX** 40 mg biweekly and 20 mg/week 2 years 268
INCLUSION CRITERIA:	18 years of age or older; Fulfilled ACR 1987 revised criteria for the classification of RA; Disease duration of 3 years; ≥8 swollen joints, ≥ 10 tender joints, and an erythrocyte sedimentation rate of ≥ 28 mm/hour or CRP concentration of ≥ 1.5 mg/dl; Had to either be RF positive or have had at least 1 joint erosion.		
EXCLUSION CRITERIA:	Patients who had received treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or 2 other DMARDs were excluded.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Folic acid		

Authors: Breedveld et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** severe (mean disease duration 0.7 years)		
	MTX	**ADA**	**ADA plus MTX**
Mean age (years):	52	52.1	51.9
Sex (% female):	73.9	77.4	72.0
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• TJC	32.3	31.8	30.7
• SJC	22.1	21.8	21.1
• Mean disease duration	.8	.7	.7
• previous DMARD use (%)	31.5	33.2	32.5
• Corticosteroids use (%)	35.4	36.5	35.8
• DAS score	6.3	6.4	6.3
• HAQ score	1.5	1.6	1.5
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Percentage of patients in whom an ACR50 response was achieved; Mean change from baseline in the modified total Sharp score comparing the combination therapy group versus the MTX monotherapy group. **Secondary Outcome Measures:** Percentage of patients in whom clinical remission was achieved (defined as a DAS28 of < 2.6); Improvement in physical function (as measured by the change from baseline in the HAQ DI); % of patients with ACR20, ACR50, ACR70, or ACR90 response at year 2; Change from baseline in the modified total Sharp score at year 2; Maintained clinical response through 104 weeks, defined as an ACR70 response for ≥6 continuous months **Timing of assessments:** NR		
RESULTS:	**Health Outcome Measures:** • At 1 year, ACR50 response had been achieved in 62% ADA + MTX, 41% ADA, and 46% MTX monotherapy ($P \leq 0.001$ for both comparison treatments versus combination therapy).* • 2year: clinical remission had been attained statistically significantly more in combination therapy than with either drug alone: ADA + MTX: 49%; ADA 25%; MTX: 25% (both $P \leq 0.001$). **Intermediate Outcome Measures:** • At 2 years, 49% ADA + MTX achieved remission (DAS20 < 2.6), compared with 23 % on ADA and 21% on MTX ($P < 0.001$). • ADA + MTX had significantly less progression on the modified Sharp score than either drug alone (1.9 vs 5.5 vs. 10.4 Sharp units; $P < 0.002$)		

Authors: Breedveld et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported (events/ 100 patient-years):**	**MTX**	**ADA**	**ADA plus MTX**
• Serious adverse events	18.5	21.1	15.9
• Infectious adverse events	123	110	119
• Serious infections	2.9	0.7	1.6
• TB	0.2	0	0
• Malignancies	0.4	0.9	0.9
• Lymphoma	0	0	0.2
• Demyelination	0	0	0
Significant differences in adverse events:	Significantly more serious infections occurred in the MTX alone group than in the ADA alone group ($P < 0.05$).		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Unable to determine		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 260 (32%) **Loss to follow-up differential high:** Yes (Significantly more patients in the ADA + MTX group completed treatment than in the MTX or ADA group $P \leq 0.05$)		
Loss to follow-up:	**MTX**: 88 (34.2%)	**ADA**: 107 (39%)	**ADA plus MTX**: 65 (24.3%)
Withdrawals due to adverse events:	19 (7.4%)	26 (9.5%)	32 (11.9%)
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Chen et al.**[10] **Year: 2006** **Country:** Multinational
FUNDING:	Health Technology Assessment Programme on behalf of NICE
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 9939 (9869 actually treated)
AIMS OF REVIEW:	To review the clinical effectiveness and cost-effectiveness of ADA, ETA and INF when used in the treatment of RA in adults.
STUDIES INCLUDED IN META-ANALYSIS	29 RCTs (9 on ADA, 11 on ETA, 9 on INF)
TIME PERIOD COVERED:	1994 to February 2005
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs comparing ADA, ETA or INF with MTX or placebo
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults with RA

Authors: Chen et al. **Year: 2006**	
CHARACTERISTICS OF INTERVENTIONS:	ADA (40 mg every other week or 20 mg every week), ETA (25 mg twice weekly, 50 mg once weekly, or 16 mg m^{-2} twice weekly), INF 3 mg kg^{-1} at 0, 2, and 6 weeks then every 8 weeks, or placebo
MAIN RESULTS:	Effect size (95% CI), *denotes $P < 0.05$ <u>ACR20/50/70 responder:</u> ADA vs. placebo: 2.11 (1.84, 2.42)*/3.58 (2.81, 4.58)*/5.22 (3.45, 7.89)* ETA vs. placebo: 3.59 (2.89, 4.46))*/5.72 (3.93, 8.34)*/9.44 (3.98, 22.38)* INF vs. placebo: 2.30 (1.90, 2.78)*/3.20 (2.30, 4.44)*/3.16 (1.89, 5.27)* <u>Swollen Joint Count</u> ADA vs. placebo: -5.14 (-6.07, -4.21)* [mean change from baseline] ETA vs. placebo: -6.75 (-8.95, -4.56)* [end of study result] INF vs. placebo: -5.08 (-6.23, -3.94)* [mean change from baseline] <u>HAQ</u> ADA vs. placebo: -0.31 (-0.36, -0.26)* [mean change from baseline] ETA vs. placebo: -0.50 (-0.59, -0.42)* [end of study result] INF vs. placebo: -0.27 (-0.35, -0.19)* [mean change from baseline] <u>DAS28</u> ADA vs. placebo: -1.12 (-1.37, -0.26)* ETA vs. placebo: -1.50 (-1.89, -1.11)* INF vs. placebo: No data available <u>Modified van de Heijde-Sharp score, mean change from baseline</u> ADA vs. placebo: -2.20 (-3.33, -1.07)* ETA vs. placebo: No data available INF vs. placebo: -5.70 (-8.58, -2.82)* <u>NNT (95% CI) required to produce ACR20/50/70 response</u> ADA vs. placebo: 3.6 (3.1, 4.2)/4.2 (3.7, 5.0)/7.7 (5.9, 11.1) ETA vs. placebo: 2.1 (1.9, 2.4)/3.1 (2.7, 3.6)/7.7 (6.3, 10.0) INF vs. placebo: 3.2 (2.7, 4.0)/5.0 (3.8, 6.7)/11.1 (7.7, 20.0
ADVERSE EVENTS:	Effect size (95% CI), * denotes $P < 0.05$ <u>Withdrawals due to AEs</u> ADA vs. placebo: 1.37 (0.87, 2.16) ETA vs. placebo: 0.80 (0.49, 1.30) INF vs. placebo: 1.55 (0.82, 2.93) <u>SAEs</u> ADA vs. placebo: 1.05 (0.78, 1.41) ETA vs. placebo: 1.25 (0.75, 2.08) INF vs. placebo: 0.84 (0.56, 1.26)

	Malignancy ADA vs. placebo: 2.92 (0.50, 17.13) ETA vs. placebo: 0.44 (0.11, 1.68) INF vs. placebo: 2.48 (0.49, 12.70) Serious infection ADA vs. placebo: 2.35 (1.00, 5.53) ETA vs. placebo: 0.78 (0.37, 1.62) INF vs. placebo: 0.61 (0.26, 1.46)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes: Searches of Cochrane Library, MEDLINE, EMBASE, Science Citation Index, National Research Register, FDA and EMEA websites, manufacturers' submissions to NICE, citation lists
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Clark, et al.**[11] **Year:** 2004 **Country:** International: Europe, US, Canada, Australia
FUNDING:	Health Technology Assessment Programme (UK)
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 1007
AIMS OF REVIEW:	To review the evidence on the clinical benefits and hazards of using anakinra in adult RA patients.
STUDIES INCLUDED IN META-ANALYSIS	• ***Efficacy Trials*** ▪ Bresnihan (1998); Cohen (2001); Cohen (2002); Unpublished report by Amgen (2001; STN 103950 Clinical Review; low-dose for 3 months) • ***Safety Trial*** ▪ Fleischmann (2001) Efficacy data not released to authors with the statement that as the trial was not designed to evaluate efficacy and the varied patient population it enrolled, "it would be inappropriate and misleading to draw any conclusions from any efficacy assessments taken from this study." (p. 30)
TIME PERIOD COVERED:	Through 2002.
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized placebo-controlled (except 1) trials of AKA or AKA plus MTX in patients with highly active RA. Fleischmann study control arm consisted of placebo plus current DMARD treatment.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Mean ages in the 50s; duration of disease from 6 months to over 10 years; majority had failed at least one DMARD and some were taking MTX up to trial start; majority of patients were taking low-dose steroids and NSAIDs.

Authors: Clark et al. **Year:** 2004 **Country:** International: Europe, US, Canada, Australia	
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
MAIN RESULTS:	• Combined Data at 6 months (N = 1007): measure AKA 100mg/d versus control (95% CI); significantly greater response rates for AKA- than placebo-treated patients: ▪ ACR20: RR 1.61 (1.31 to 1.97); RD 0.14 (0.09 to 0.20); NNT 7.1 ▪ ACR50: RR 2.26 (1.53 to 3.32); RD 0.09 (0.05 to 0.13); NNT 11.1 ▪ ACR70: RR 3.06 (1.28 to 7.33); RD 0.03 (0.01 to 0.05); NNT 33.3 ▪ HAQ: -0.18 (-0.24 to -0.12) ▪ Patient Global Assessment: -10.37 (-14.41 to -6.33) ▪ SJC: -1.53 (-2.68 to -0.38) • 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- -0.10).
ADVERSE EVENTS:	• Withdrawals due to adverse events: Control: 4.1% to 9%; AKA: 5% to 13% • Specific adverse events ▪ Serious adverse events: Control: 3.2% to 11.6%; AKA: 4.4% to 12.8% ▪ Malignancy: Control: 0% to 1.8%; AKA: 0% to 1.1% ▪ ISRs: 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%
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Cohen et al.**[12] **Year: 2004** **Country:** Multinational		
FUNDING:	Amgen, Thousand Oaks, CA, US		
RESEARCH OBJECTIVE:	To evaluate effects of anakinra 100 mg injection daily vs. placebo injection in combination with methotrexate in patients with persistent RA activity after treatment with methotrexate alone.		
DESIGN:	**Study design**: RCT **Setting:** Multicenter, university clinic **Sample size:** 501		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/day 24 weeks 250	**Placebo** N/A 24 weeks 251	
INCLUSION CRITERIA:	At least 18 years old; diagnosis of RA according to ACR criteria; disease duration of at least 24 weeks before study entry; radiographic evidence of bone erosion in the hands, wrists, or feet; currently active RA. (Active RA defined as six or more swollen joints, nine or more tender of painful joints, and either a C reactive protein level of at least 15 mg/l or an ESR of at least 28 mm/1st hour. Must also be treated with stable dosing of either MTX 10-25 mg/week for at least 24 consecutive weeks or MTX 25-50 mg/every other week for at least 24 weeks.		
EXCLUSION CRITERIA:	Presence of significant systemic disease or autoimmune disease other than RA; serious infection; leukopenia; allergy to products derived from Eschericia coli; were being considered for surgery to their hands, wrists, or feet; treated with intra-articular or systemic corticosteroid injections within 4 weeks before the study; being treated with DMARDs other than MTX (60 day washout period required before randomization); requiring narcotic analgesics for pain; or previous treatment with IL1 receptor antagonist.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX, NSAIDs, or oral corticosteroids (≤ 10 mg/day of prednisone equivalent) if the dose has been stable for at least 4 weeks before randomization.		

Authors: Cohen et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** moderate		
	AKA	**Placebo**	
Mean age (years):	56	57	
Sex (% female):	79	75	
Ethnicity:			
Caucasian	86	87	
African American	5	6	
Latino	6	4	
Other	3	2	
Other germane population qualities:			
• Corticosteroid Use (%)	53	52	
• MTX dose (mg/week), mean	16	16	
• SJC (0-66)	20.1	20.0	
• Tender/painful joint count (0-68)	26.8	24.5	
• Physician's assessment of disease severity (0-100)	53.2	52.3	
• Patient's assessment of pain (0-100)	59.2	55.7	
• HAQ score (0-3)	1.4	1.3	

Authors: Cohen et al. **Year: 2004**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Proportion of subjects who attained an ACR20 response at week 24. **Secondary Outcome Measures:** Change from baseline in individual ACR components, including patient's assessment of disease activity, patient's assessment of pain, HAQ score, plasma CRP level, and ESR; ACR50 and ACR70 responses; and sustainability of the ACR20 responses (response for minimum of 4 out of 6 months). **Timing of assessments:** One week after randomization (evaluation of tolerability and adverse events) and every 4 weeks after randomization through week 24
RESULTS:	**Health Outcome Measures: (AKA compared to placebo)** • ACR50 response at week 24: 17% vs. 8%, OR (95% CI) 2.61 (1.46, 4.84) ($P < 0.01$) • ACR70 response at week 24: 6% vs. 2%, OR (95% CI) 3.14 (1.16, 10.06) ($P < 0.05$) • Sustained ACR20 response: 27% vs. 12%, OR (95% CI) 3.43 (2.05, 5.90) ($P < 0.001$) • Change from baseline at week 24: o Patient's assessment of disease activity: -17.7 vs. -8.9 ($P < 0.001$) o Patient's assessment of pain: -19.0 vs. -11.7 ($P < 0.01$) o HAQ: -0.29 vs. -0.18 ($P < 0.05$) • SJC: -6.8 vs. -6.5 (not statistically significant) • Tender or painful joint count: -12.0 vs. -8.7 ($P < 0.01$) • Physician's assessment of disease activity: -25.2 vs. -20.1 ($P < 0.05$) **Intermediate Outcome Measures: (AKA compared to placebo)** • ACR20 response at week 24: 38% vs. 22%, OR (95% CI) 2.36 (1.55, 3.62); $P < 0.001$ • Log transformed CRP: -5 vs. -1 ($P < 0.001$) • ESR: -16.2 vs. – 6.0 ($P < 0.001$)

Authors: Cohen et al. **Year: 2004**			
ADVERSE EVENTS:	**AKA**	**Placebo**	
Overall adverse events reported:	90	81	
• ISRs, %	65	24	
○ withdrawals	8.4	0.8	
• Serious adverse events, %	4	3	
○ withdrawals	0.8	1	
• Infectious events, %	33	26	
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (AKA: 3; Placebo: 2)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 23% **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*):	**AKA**	**Placebo**	
Loss to follow-up:	NR	NR	
Withdrawals due to adverse events:	9.2%	1.8%	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Cohen et al.**[13] **and Keystone et al.**[14] [15] **Year: 2005, 2008, 2009** **Country:** Multinational (US, Europe, Canada, Israel) **Trial Name:** REFLEX		
FUNDING:	Hoffmann-La Roche, Biogen Idec, and Genentech.		
RESEARCH OBJECTIVE:	efficacy and safety of treatment with RIT plus MTX in patients with active RA who had an inadequate response to anti–tumor necrosis factor (anti-TNF)		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 520		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**RIT +MTX** 2 infusions of 1,000 mg days 1 and 15 24 weeks 311	**Placebo +MTX** N/A 24 weeks 209	
INCLUSION CRITERIA:	adult patients, active RA and an inadequate response to 1 or more anti-TNF agents (INF (≥3 mg/kg; at least 4 infusions)), ADA (40 mg every other week for ≥3 months), or ETA (25 mg twice weekly for ≥3 months), or intolerant to at least 1administration of these agents + MTX (10–25 mg/week) for at least 12 weeks.		
EXCLUSION CRITERIA:	rheumatic autoimmune disease other than RA (except secondary Sjögren's syndrome), significant systemic involvement secondary to RA (vasculitis, pulmonary fibrosis, or Felty's syndrome), or ACR functional class IV disease.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	glucocorticoids (≤10 mg/day of prednisone or equivalent)		

Authors: Cohen et al. and Keystone et al. **Year: 2005, 2008, 2009**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** moderate-refractory		
	RIT +MTX	**Placebo +MTX**	
Mean age (years):	52.2 ± 12.2	52.8 ± 12.6	
Sex (% female):	251 (81)	169 (81)	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Active joint count	NR	NR	
• Swollen joint count	23.4	22.9	
• Mean disease duration	12.1	11.7	
• DMARD use (%)	2.6 +- 1.8	2.4 +- 1.8	
• Weekly dose of MTX	16.4 +- 8.8	16.7+- 9.9	
• Corticosteroids use (%)	200 (65)	127 (61)	
• DAS score	6.9	6.8	
• HAQ DI score	1.86 +- 0.58	1.91 +- 0.54	
• VAS-pain	64.08 +- 22.28	64.46 +- 21.32	
• FACIT-F	30.40 +- 10.75	30.24 +- 11.75	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 response at week 24, **Secondary Outcome Measures:** Physician's global assessment of disease activity; patient's global assessment of disease activity, patient's assessment of pain, patient's assessment of physical function, and either the CRP level or the ESR ACR50 and ACR70, DAS28, EULAR response criteria, swollen joint count, tender joint count, patient's and physician's global assessments of disease activity, patient's assessment of pain, HAQ DI, the CRP level, and the ESR, Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score, the Short Form 36 (SF-36), Genant-modified Sharp radiographic score **Timing of assessments:** at screening, on day 1, and every 4 weeks through week 24. After week 24, up to 18 months posttreatment.		
RESULTS:	**Health Outcome Measures:** • proportion of patients ACR20 response at 24 weeks rituximab 51% versus placebo 18% • proportion of patients ACR50 response at 24 weeks rituximab 27% versus placebo 5% • proportion of patients ACR70 response at 24 weeks rituximab 12% versus placebo 1% Mean changes from baseline in individual parameters of the ACR improvement criteria at week 24:		

	• Swollen joint count RIT -10.4 + - 13.0 vs. placebo -2.6 + - 10.4 • Tender joint count RIT -14.4 + - 17.5 vs. placebo -2.7 + - 15.5 • Patient's global assessment of disease activity, mm (0–100-mm VAS) RIT -26.0 + -30.0 vs. placebo -5.3 +- 22.9 • Physician's global assessment of disease activity, mm (0–100-mm VAS) RIT -29.5 + - 27.4 vs. placebo -6.2 + - 27.1 • Health Assessment Questionnaire Disability Index RIT -0.4 + - 0.6 vs. placebo -0.1 + - 0.5 • Patient's assessment of pain, mm (0–100-mm VAS) RIT -23.4 + - 29.4 vs. placebo -2.5 + - 23.3 **Unadjusted mean changes (baseline to week 24) in patient-reported outcomes** SF-36 PCS RIT + MTX 6.64 +- 8.74 versus placebo 1.48 +- 7.32 **(*P* < 0.0001).** SF-36 MCS RIT + MTX 5.32 +- 12.41 versus placebo 2.25 +- 12.23 **(*P* = 0.0269)** VAS-pain RIT + MTX -23.37 +- 29.35 versus placebo -2.50 +- 23.30 FACIT-F RIT + MTX -9.14 +- 11.31 versus placebo -0.54 +- 9.84 HAQ DI RIT + MTX -0.44 +- 0.60 versus placebo -0.07 +- 0.45

Authors: Cohen et al. and Keystone et al. **Year: 2005, 2008, 2009**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Severe adverse event	**RIT +MTX** 261 (85%) - 55 (18%)	**Placebo+MTX** 183 (88%) - 49 (23%)	
Significant differences in adverse events:	UTI RIT 3% vs. placebo 8% nausea RIT 7% vs. placebo 2%		
ANALYSIS:	**ITT:** Yes, but 21 excluded **Post randomization exclusions:** Yes, 3		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 29% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**RIT +MTX** 18% 3%	**Placebo+MTX** 46% <1%	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: De Fillipis**[16] **Year: 2006** **Country:** Italy		
FUNDING:	None reported		
RESEARCH OBJECTIVE:	Comparison of INF and ETA		
DESIGN:	**Study design:** Open label randomized trial **Setting:** Rheumatology clinic **Sample size:** 32		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg 2x a week 52 weeks 16	**INF** 3 mg/kg 0,2,6 wks then every 2 months 52 weeks 16	
INCLUSION CRITERIA:	Ages 20-60, met 1987 ACR criteria; symptom duration more than 2 yrs; active disease; not responding to DMARDS for more than 6 months including stable dose of MTX		
EXCLUSION CRITERIA:	Early onset disease; hospitalization in last 6 months for important medical problems or infections; hepatic or renal failure; positive ANA; heart failure; positive TBC; more than 10 mg of prednisone		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Cox-2 or NSAIDS, MTX		

Authors: De Fillipis **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	ETA	**INF**	
Mean age (years):	44.7	46.79	
Sex (% female):	NR	NR	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	22.4	20.93	
• Swollen joint count	16.87	14.73	
• Mean disease duration	NR	NR	
• DMARD use (%)	100	100	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	NR	NR	
• DAS score	1.89	1.67	
• HAQ score			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20/50/70 **Secondary Outcome Measures:** HAQ **Timing of assessments:** Baseline weeks 14, 22 and 54		
RESULTS:	**Health Outcome Measures: INF vs. ETA** • HAQ 14 wks -14.08 vs. -12.7 *P* = NS 22 wks -16.2 vs. -17.5 *P* = NS 54 wks -21.6 vs.-32.3 *P* = NS • ACR responders 14 wks 74.4% vs. 54.4% 22 wks 60% vs. 60% 54 wks 60% vs. 74.4% • Most data reported in graphs		

Authors: De Fillipis **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ETA** NR	**INF** NR	**drug 3**
Significant differences in adverse events:	None reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes – 2, 1 from each group		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	No		
ATTRITION (*overall*):	**Overall attrition:** 2- 6% **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**ETA** 1 0	**INF** 1 0	**drug 3**
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Edwards et al.[17] and Strand et al.[18]** **Year: 2004 and 2006** **Country:** Multinational			
FUNDING:	Roche			
RESEARCH OBJECTIVE:	To confirm the role of B cells in RA by evaluating the effect of RIT in patients with active RA.			
DESIGN:	**Study design:** RCT, double-blind **Setting:** Multicenter (26 rheumatology centers) **Sample size:** 161			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** ≥ 10 mg/wk up to 2 yrs 40	**RIT** 1000 mg days 1 and 15 up to 2 yrs 40	**RIT + Cyclophosphamide** 1000 mg days 1 and 15 + 750 mg days 3 and 17 up to 2 yrs 41	**RIT + MTX** 1000 mg days 1 and 15 + ≥ 10 mg/wk up to 2 yrs 40
INCLUSION CRITERIA:	Age ≥ 21 years; fulfillment of revised 1987 American Rheumatism Association criteria; active disease (defined as ≥ 8 swollen & 8 tender joints and at least 2 of the following: a serum CRP level ≥ 15mg/l, ESR ≥ 28mm/hr, or morning stiffness lasting longer than 45 minutes) despite treatment with ≥ 10mg of MTX per week; RF ≥ 20 IU per ml.; failed at least 1 DMARD.			
EXCLUSION CRITERIA:	Autoimmune disorder other than RA (except concurrent Srjogen's); American Rheumatism Association functional class IV disease; active rheumatoid vasculitis; a history of systemic diseases associated with arthritis; chronic fatigue syndrome; serious & uncontrolled coexisting diseases; active infection; a history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms; primary of secondary immunodeficiency; or a history of cancer (except basal cell carcinoma of the skin that had been excised).			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS at stable doses or corticosteroids at doses ≤ 12.5 mg per day of prednisolone (or the equivalent); all groups, including control, also received a 17-day course of treatment with corticosteroids and a single 10mg dose of leucovorin.			

Authors: Edwards et al. and Strand et al. **Year: 2004 and 2006**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** "highly active" (mean disease duration 10.5 years)			
	MTX	**RIT**	**RIT + Cyclophosphamide**	**RIT + MTX**
Mean age (years):	54	54	53	54
Sex (% female):	80	73	83	75
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• TJC	32	34	33	32
• SJC	19	21	19	23
• Mean disease duration	11	9	10	12
• DMARD use (no.)	2.6+/- 1.3	2.5+/-1.6	2.6+/-1.4	2.5+/-1.4
• DAS score	6.9	6.8	6.9	6.8
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR50 response at week 24. **Secondary Outcome Measures:** ACR20 & ACR70 responses; change in DAS; response according to EULAR **Timing of assessments:** Clinical assessments at baseline and at weeks 12, 16, 20, & 24; lab assessments at screening (3 weeks before baseline), on days 1, 3, 15, 17, and at weeks 4, 8, 12, 16, 20, and 24.			
RESULTS:	**Health Outcome Measures:** at 24 weeks n (%) MTX vs. RIT vs. RIT + CTX + RIT + MTX ACR20 15 (38) vs. 26 (65)* vs. 31 (76)** vs. 29 (73)** ACR50 5 (13) vs. 13 (33) vs. 17 (41)** vs. 17 (43)** ACR70 2 (5) vs. 6 (15) vs. 6 (15) vs. 9 (23)* *$P < 0.05$, **$P < 0.01$ • %patients with improved HAQ-DI at 26 weeks 45 vs. 68 vs. 59 vs. 63 At week 24, mean change from baseline in DAS score showed significant improvement over MTX alone in all RIT groups ($P \leq 0.002$): -1.3 +/- 1.2 (MTX), -2.2 +/- 1.4 (RIT), -2.6 +/- 1.5 (RIT + CYP), -2.6 +/- 1.3 (RIT + MTX) • At 24 weeks, 20-24% RIT groups had a good EULAR response; MTX group (5%) . • Moderate or good EULAR response (P value for comparison with MTX group) 50% (MTX), 85% (RIT; $P = 0.002$), 85% (RIT + CYP; $P = 0.001$), 83% (RIT + MTX; $P = 0.004$) **Intermediate Outcome Measures:** • RIT treatment was associated with a large, rapid, & sustained decrease in RF levels; conversely, treatment with MTX alone resulted in modest decreases that returned to baseline by week 24.			

Authors: Edwards et al. and Strand et al. **Year: 2004 and 2006**				
ADVERSE EVENTS: **Overall adverse effects reported at 24 weeks:** • Hypotension • RA exacerbation • Hypertension • Nasopharyngitis • Arthralgia • Rash • Back pain • Cough • Pruritis • Nausea • Dyspnea	**MTX** 80% 18 40 15 15 8 3 5 0 0 3 0	**RIT** 80% 30 15 15 10 8 10 10 13 10 5 10	**RIT + Cyclophosphamide** 73% 29 15 7 5 2 10 7 2 10 10 0	**RIT + MTX** 85% 18 5 25 10 10 3 0 5 0 0 0
Significant differences in adverse events:	NR			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	Method not described			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** 6.2% at 24 weeks (19% at 48 weeks) **Loss to follow-up differential high:** No			
ATTRITION (*treatment specific*): **Loss to follow-up (24 weeks):** **Withdrawals due to adverse events:**	**MTX** 7.5% 1	**RIT** 5% 2	**RIT + Cyclophosphamide** 9.8% 2	**RIT + MTX** 2.5% 1
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Emery et al.**[19] **Year: 2006** **Country:** Multinational		
FUNDING:	Roche, Genentech, Inc.		
RESEARCH OBJECTIVE:	To examine the safety & efficacy of different RIT doses plus MTX, with or without gkucocorticoids, in patients with active RA resistant to DMARDs.		
DESIGN:	**Study design:** RCT, double blind, placebo-controlled **Setting:** Multicenter, outpatient **Sample size:** 465		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A Days 1 and 15; 24 weeks 149	**RIT 500mg** Two 500mg infusions Days 1 and 15; 24 weeks 124	**RIT 1,000mg** Two 1,000mg infusions Days 1 and 15; 24 weeks 192
INCLUSION CRITERIA:	Outpatients between 18 & 80 years old; ≥ 6 month history of moderate to severe RA (diagnosed according to ACR) despite ongoing with MTX (10-25 mg/week) for at least 12 weeks before randomization, with stable dosage during the last 4 weeks; active disease defined as swollen and TJC ≥ 8 and either an ESR ≥ 28mm/hour or a CRP level ≥ 1.5 mg/dl; failed prior treatment with 1-5 DMARDs; patients on glucocorticoids included if oral dosage stable > 4 weeks or parenteral / intraarticular dosage given > 4 weeks before screening.		
EXCLUSION CRITERIA:	Significant systemic involvement secondary to RA; evidence of significant other illnesses, recurrent infections, or lab abnormalities; history of severe allergic / anaphylactic reactions to humanized or murine monoclonal antibodies; previous treatment with RIT or any lymphocyte-depleting therapies.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, if the dosage had been stable at least 2 weeks prior to entry		

Authors: Emery et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate to severe (mean disease duration 10.4 years)		
	Placebo	**RIT 500mg**	**RIT 1,000mg**
Mean age (years):	51.1	51.4	51.1
Sex (% female):	80	83	80
Ethnicity (% white):	NR	NR	NR
Other germane population qualities:			
• TJC	35	33	32
• SJC	21	22	22
• Mean disease duration (years)	9.3	11.1	10.8
• DMARD use (mean no.)	2.2	2.5	2.5
• DAS score	6.8	6.8	6.7
• HAQ score	1.7	1.8	1.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 response **Secondary Outcome Measures:** ACR50, ACR70, DAS28, and EULAR responses; fatigue measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale; HAQ-DI, SF-36 **Timing of assessments:** baseline , every 4 weeks to 24 weeks		

RESULTS:	**Health Outcome Measures:** The primary ITT efficacy population was 367 RF-positive patients.
	• ACR20 response ($P < 0.0001$): 55% of RIT 500mg group, 54% of RIT 1000mg group, and 28% of placebo group. RIT groups vs. placebo ACR50 response (both $P \leq 0.001$) and an ACR70 response ($P = 0.029$ for 500mg; $P \leq 0.001$ for 1000mg)
	• Compared with placebo, moderate or good EULAR responses occurred in more RIT-treated patients ($P < 0.0001$ in both groups)
	• Changes in mean HAQ-DI scores = -0.43 (RIT 500mg), -0.49 (1,000mg), and -0.16 (placebo)
	• Percent improvement in FACIT-F = 20% (RIT 500mg), 28% (RIT 1000mg), and 4% (placebo)
	  • SF-36 PCS (mean, SE): Placebo + MTX 2.36 (0.78) vs. RIT 500mg + MTX 7.08 (0.77) vs. RIT 1000mg + MTX 7.40 (0.78)
	  • SF-36 MCS (mean, SE): Placebo + MTX 1.88 (1.00) vs. RIT 500mg + MTX 4.49 (1.22) vs. RIT 1000mg + MTX 3.03 (1.11)		

Authors: Emery et al. **Year: 2006**			
ADVERSE EVENTS (%):	**Placebo**	**RIT 500mg**	**RIT 1,000mg**
Overall adverse effects reported:	70	81	85
• Severe events	18	17	18
• RA exacerbation	30	17	14
• Headache	13	11	11
• Nausea	9	6	10
• Upper respiratory infection	6	8	6
• Nasopharyngitis	5	6	5
• Arthralgia	3	4	6
• Diarrhea	5	6	3
• Fatigue	5	4	4
• Hypertension	3	4	6
• Rigors	2	4	7
• Dizziness	4	3	5
• Serious infections	1	0	2
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (13)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 19.4% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**Placebo**	**RIT 500mg**	**RIT 1,000mg**
Loss to follow-up:	35%	9%	14%
Withdrawals due to adverse events:	0	3 (2%)	6 (3%)
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Finckh et al.**[20] **Year: 2006** **Country:** Switzerland		
FUNDING:	Swiss Health Authorities; Swiss Academy for Medical Sciences; Abbott; Essex; Wyeth; Aventis; Bristol-Mayers; Mepha; Merck; Novartis; Roche; Swiss National Science Foundation; Geneva University Hospital; Kirkland Scholars Fellowship; NIH; Grant Number: P60-AR-47782; Kirkland Scholars Fellowship; NIH; Grant Number: AR-047605; NIH; Grant Number: AR-47782; Kirkland Scholar Award; Lupus Clinical Trials Consortium; Faculty of Medicine, Northwestern University, Chicago, Illinois		
RESEARCH OBJECTIVE:	To compare the effectiveness of DMARDs + infliximab vs. DMARDs + etanercept vs. etanercept in preventing progressive joint damage, in a population-based cohort.		
DESIGN:	**Study design:** Observational (prospective and retrospective) **Setting:** Swiss Clinical Quality Management System **Sample size:** 372		
INTERVENTION: **Dose (median mg/week):** **Duration (years):** **Sample size:**	**ETA** 50 1.76 110	**ETA + DMARD** 50 1.73 130	**INF + DMARD** 3.3 mg/kg every 8 wks 1.63 132
INCLUSION CRITERIA:	Patients with RA; anti-TNF treatment > 10 months.		
EXCLUSION CRITERIA:	Did not have complete serial radiographs of the hands and feet; previous treatment failure with other anti-TNF agents; interruption in therapy within 10 months of treatment initiation because of side effects or treatment ineffectiveness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes, at physicians discretion		

Authors: Finckh et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes but ETA group seems a little more severe **Disease severity:** Mild-moderate-severe		
	ETA	**ETA + DMARD**	**INF + DMARD**
Mean age (years):	53.6	54.4	53.2
Sex (% female):	79	74	82
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• TJC	6	4	3
• SJC	8	7.5	8
• Median disease duration	10.9	9.0	10.6
• DMARD use (%)	0	100	100
• MTX use (%)	0	70	92
• Corticosteroids use (%)	29	36	35
• DAS score	4.7	4.3	4.3
• HAQ score	1.46	1.29	1.40
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Radiographic disease progression with Ratingen score (JSN; assessed prospectively) **Secondary Outcome Measures:** Cartilage destruction, via progressive narrowing of the joint space width (assessed retrospectively) **Timing of assessments:** < 4 months before therapy started and < 4months after treatment cessation.		
RESULTS:	**Health Outcome Measures:** • No statistically significant differences between groups in functional disability measured with the HAQ (data NR). **Intermediate Outcome Measures:** • Progression of erosions: No significant differences between INF + DMARDs and ETA + DMARDs (Data NR; $P = 0.07$). • Joint space narrowing (JSN): INF plus DMARDs was statistically significantly better than ETA plus DMARDs (data NR; $P = 0.02$). No difference, however, was obvious when comparison was limited to INF + MTX and ETA + MTX (data NR; P = NR) • INF + DMARDs was significantly more effective than ETA in all outcome measures (data NR).		

Authors: Finckh et al. **Year: 2006**			
ADVERSE EVENTS:	**ETA** NR	**ETA + DMARD** NR	**INF + DMARD** NR
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14% **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**N/A**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Furst et al.**[21] **Year: 2003** **Study name: STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis)** **Country:** US and Canada		
FUNDING:	Abbott Laboratories, Abbot Park, Il		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of adalimumab when given with standard anti-rheumatic therapy in patients with active RA not adequately responding to standard therapies.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (69 sites) **Sample size:** 636		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 40 mg subcutaneously every other week 24 weeks 318	**Placebo** N/A 24 weeks 318	
INCLUSION CRITERIA:	18 years of age or older; active RA at screening and baseline as defined by at least 6 swollen joints and 9 tender joints; met the 1987 revised ACR criteria for diagnosis of RA for at least 3 months		
EXCLUSION CRITERIA:	Those who participated in other trials of other biologic DMARD in RA; patients treated with Anti-CD4 therapy or biologic DMARD; history of an active inflammatory arthritide other than RA; history of active listeriosis or mycobacterial infection; major episode of infection requiring hospitalization; treatment with IV antibiotics within 30 days of screening; oral antibiotics within 14 days of screening; any uncontrolled medical condition		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with standard antirheumatic therapy which included traditional DMARD, low dose corticosteroids, NSAID, or analgesics		

Authors: Furst et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	ADA	**Placebo**	
Mean age (years):	55.0	55.8	
Sex (% female):	79.6	79.2	
Ethnicity (%):			
White:	89	85.8	
Other:	11	14.2	
Other germane population qualities:			
• TJC	27.3	27.6	
• SJC	20.9	21.3	
• DMARD use (%)	82.1	84.9	
• MTX use (%)	56.0	62.6	
• Corticosteroids use (%)	50.9	54.4	
• DAS score	NR	NR	
• HAQ score	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (adverse events, physical examination findings, standard laboratory results) **Secondary Outcome Measures:** ACR20; ACR50; ACR70 **Timing of assessments:** Baseline and weeks 2,4,8,12,16,20, and 24		
RESULTS:	**Health Outcome Measures:** • At endpoint, significantly more ADA (28.9%) patients achieved an ACR50 response than placebo patients (11.3%) ($P \leq 0.001$) • At endpoint, significantly more ADA (14.8%) patients achieved an ACR70 response than placebo patients (3.5%) ($P \leq 0.001$) **Intermediate Outcome Measures:** • At endpoint, significantly more ADA (52.8%) patients achieved an ACR20 response than placebo patients (34.9%) ($P \leq 0.001$)		

Authors: Furst et al. **Year: 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA**	**Placebo**	
• URTI	19.8%	15.1%	
• UTI	9.1%	5.7%	
• ISR	19.5%	11.6%	
• Rash	10.7%	6.0%	
• Back pain	5.3%	1.6%	
Significant differences in adverse events:	• Significantly more ADA patients reported ISR than placebo patients 19.5% vs. 11.6% ($P \leq 0.01$) • Significantly more ADA patients reported rash than placebo patients 10.7% vs. 6.0% ($P \leq 0.05$) • Significantly more ADA patients reported back pain than placebo patients 5.3% vs. 1.6% ($P \leq 0.01$) • No significant differences between ADA and placebo in overall adverse events 86.5% vs. 82.7% ($P > 0.05$) and serious infections 1.3% vs. 1.9% ($P > 0.05$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions**: No		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 58 (9%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**ADA**	**Placebo**	
Loss to follow-up:	28 (9%)	30 (9%)	
Withdrawals due to adverse events:	9 (3%)	8 (3%)	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Geborek et al.**[22] **Year: 2002** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess the efficacy and safety of etanercept, infliximab, and leflunomide in a population-based setting		
DESIGN:	**Study design:** Non-randomized, open-label trial **Setting:** Primary care clinics; university clinic **Sample size:** 369 (33 patients tried two different treatments and one tried all three; 404 treatments)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** Varied 12 months 166	**INF** Varied 12 months 135	**Leflunomide** Varied 12 months 103
INCLUSION CRITERIA:	Diagnosis of RA according to the clinical judgment of the treating doctor. All patients included were required to have failed to respond to or not tolerated at least two DMARDs, including MTX. The patients were selected on the basis of current disease activity and/or unacceptable steroid requirement as judged by the treating doctor, but had different backgrounds concerning previous treatment, concomitant diseases, and functional impairment and disability		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Geborek et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Disease severity:** Mild-moderate-severe (mean disease duration 14.5 years)		
	ETA	**INF**	**Leflunomide**
Mean age (years):	54.0	55.4	61.3
Sex (% female):	78	79	82
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Mean disease duration	14.9	14.1	14.9
• DMARD use (%)	NR	NR	NR
• MTX use (%)	NR	NR	NR
• Corticosteroids use (%)	83	81	73
• DAS score	5.8	5.6	5.4
• HAQ score	1.55	1.47	1.46
• CRP	43.7	44.4	37.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20/50/70 **Secondary Outcome Measures:** DAS28 **Timing of assessments:** At months 0, 3 ,6, 12 and then every 3 or 6 months		
RESULTS:	**Health Outcome Measures:** • The ETA and INF performed significantly better than leflunomide • ACR 20-ETA significantly better than INF at three months ($P < 0.02$) and six months ($P < 0.05$) • ETA and INF significant decreases in prednisolone use after 2 weeks ($P < 0.001$) • ETA had a significantly higher ACR response rate than INF at 3 and 6 months (data NR; $P < 0.02$; $P < 0.05$) • ETA had a significantly higher ACR50 response rate at 3 months (data NR; $P < 0.05$) • Response rates of ETA and INF as monotherapies were not significantly better than MTX monotherapy		

Authors: Gerborek et al. **Year: 2002**			
ADVERSE EVENTS:	**ETA**	**INF**	**Leflunomide**
Overall adverse effects reported:	120	107	55
• Fatal	3	0	0
• Life threatening	0	3	0
• Serious	15	11	4
• Moderate	36	34	20
• Mild	61	59	22
• Not graded	5	0	9
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	No, outcome assessors not blinded		
STATISTICAL ANALYSIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Genovese et al.**[23] **Year: 2004** **Country:** US		
FUNDING:	Amgen, Inc., Thousand Oaks, CA		
RESEARCH OBJECTIVE:	To determine the potential for additive or synergistic effects of combination therapy with the selective anti-TNF-α agent etanercept and the anti-IL1 agent anakinra.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 242		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg *twice* per week 24 weeks 80	**½ ETA + AKA** 25 mg *once* per week; 100 mg/day 24 weeks 81	**ETA + AKA** 25 mg *twice* per week; 100 mg/day 24 weeks 81
INCLUSION CRITERIA:	Age 18 or greater; greater than 6-month history of RA diagnosed by ACR criteria; 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, received MTX for at least 16 weeks, with a stable dose in the range of 10-25 mg/week for at least 8 weeks.		
EXCLUSION CRITERIA:	Any DMARD other than MTX within the past 4 weeks; treatment with AKA or any protein-based TNF-alpha inhibitor; received any intraarticular or systemic corticosteroid injections within past 4 weeks; or, had a recent history of significant infection or other important concurrent illness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with stable doses of MTX and other stable medications, such as corticosteroids.		

<table>
<tr><td colspan="4">Authors: Genovese, et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes, but there is a slight overall trend to more severe disease in full ETA + AKA group.
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>½ ETA + AKA</u></td><td><u>ETA + AKA</u></td></tr>
<tr><td>Mean age (years):</td><td>54.4</td><td>53.8</td><td>55.7</td></tr>
<tr><td>Sex (% female):</td><td>82.5</td><td>71.6</td><td>77.8</td></tr>
<tr><td>Ethnicity (% white race):</td><td>86.3</td><td>77.8</td><td>75.3</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>31.0</td><td>31.0</td><td>35.9</td></tr>
<tr><td>• SJC</td><td>21.4</td><td>19.8</td><td>23.4</td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>48.8</td><td>54.3</td><td>44.4</td></tr>
<tr><td>• HAQ score</td><td>1.5</td><td>1.5</td><td>1.6</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR50 at week 24.
Secondary Outcome Measures: ACR20 and ACR70 at week 24; sustained ACR20 response (“response for at least 4 monthly measurements, not necessarily consecutive, with 1 occurring at month 6”); good or moderate EULAR response at week 24; improvement in the ACR core criteria components; duration of morning stiffness; the DAS; and the SF-36; plasma AKA and ETA concentrations and anti-AKA and anti-ETA antibody concentrations.
Timing of assessments: Baseline and weeks 2, 4, 8, 12, 16, 20, and 24; plasma concentrations at weeks 4, 12, and 24; antibody concentrations at weeks 12 and 24.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures (<u>ETA</u> v. <u>½ ETA + AKA</u> v. <u>ETA + AKA</u>), measure (95% CI):
• At week 24 there were no significant differences in outcomes between the treatment groups
ACR50 at week 24: 41% v. 39% v. 31% (P = 0.914, by 1-tailed t-test)
o OR (ETA + AKA v. ETA alone) 0.64 (90% CI: 0.37 to 1.09)
o Sensitivity analysis yielded similar results.
• ACR20 at week 24:
o 68% v. 51% v. 62% Only significant difference is between ETA alone and the ½ ETA + AKA group (P = 0.037).
• ACR70 at week 24: 21% v. 24% v. 14% (P-value NR)
• Sustained ACR20 response: between 43% and 54% of subjects in each group (specifics NR).
• EULAR response at week 24: 79% v. 66% v. 73% (P-value NR)
• Mean % reduction in DAS: 39% v. 41% v. 40% (P-value NR)</td></tr>
</table>

Authors: Genovese et al. **Year: 2004**			
ADVERSE EVENTS:	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Overall adverse effects reported, %:	90.0	95.1	93.8
• Infections	40.0	37.0	46.9
• URTI	20.0	11.1	13.6
• ISR	40.0	67.9	70.4
• Any serious adverse event	2.5	4.9	14.8
• Serious infection	0.0	3.7	7.4
Significant differences in adverse events:	Patients receiving ETA (any dosage) + AKA experienced more ISRs and serious adverse events than patients receiving ETA alone. *P*-values NR.		
ANALYSIS:	**ITT:** YES **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	**YES**		
ADEQUATE ALLOCATION CONCEALMENT:	Unknown		
BLINDING OF OUTCOME ASSESSORS:	YES		
ATTRITION (*overall*):	**Overall loss to follow-up:** 15.7% **Loss to follow-up differential high:** 15% between ETA alone and ½ ETA + AKA		
ATTRITION (*treatment specific*):	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Loss to follow-up:	7%	22%	20%
Withdrawals due to adverse events:	0%	8.6%	7.4%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Genovese et al.[24] and Westhovens**[25] **Year: 2005 and 2006** **Country:** US	
FUNDING:	Bristol-Myers Squibb; the National Center for Research Resources, National Institutes of Health	
RESEARCH OBJECTIVE:	To evaluate efficacy and safety of ABA in patients with active RA and an inadequate response to at least 3 months of anti-TNF α therapy.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 391 (393 randomized)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA** 10mg/kg 6 months 258	**Placebo** N/A 6 months 133
INCLUSION CRITERIA:	Age ≥ 18 years; RA for ≥ 1 year; inadequate response to anti-TNF α therapy with ETA, INF, or both at the approved dose after ≥ 3 months of treatment; also included patients who had adverse events while on anti-TNF α therapy but who discontinued primarily due to lack of efficacy; at randomization, presence of at least 10 swollen and 12 tender joints, and CRP levels of at least 1 mg per deciliter; taking oral DMARD or AKA for ≥ 3 months with stable dose for ≥ 28 days.	
EXCLUSION CRITERIA:	NR	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (≤ 10 mg of prednisone or its equivalent per day) if the dose had been stable for at least 28 days	

Authors: Genovese et al. and Westhovens **Year: 2005 and 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR	
	ABA	**Placebo**
Mean age (years):	53.4	52.7
Sex (% female):	77.1	79.7
Ethnicity:		
% White / % Black	96.1 / 3.5	93.2 / 3.8
Other germane population qualities:		
• NSAID use (%)	70.2	71.4
• MTX use (%)	75.6	82.0
• Corticosteroids use (%)	70.2	64.7
• DAS28 score	6.5	6.5
• HAQ score	1.8	1.8
• SJC	22.3	22.0
• TJC	31.2	32.8
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 response; HAQ disability index response (improvement of at least 0.3 from baseline) and SF-36 **Secondary Outcome Measures:** ACR50 and ACR70 at 6 months; DAS28; SF-36 at 6 months; **Timing of assessments:** NR	
RESULTS:	**Health Outcome Measures: 6 months** • ACR20 response was (ABA vs. placebo) 50.4% vs. 19.5% ($P < 0.001$) • ACR50 and ACR70 response were significantly higher in the ABA group than placebo group (ACR50, 20.3% vs. 3.8%, $P < 0.001$; ACR70, 10.2% vs. 1.5%, $P = 0.003$) • Rates of remission (via DAS28) were 10.0% in ABA group vs. 0.8% in placebo group. ($P < 0.001$) • Patients (%) with clinically meaningful improvement in physical function (via HAQ) were 47.3% (ABA) vs. 23.3% (placebo) ($P < 0.001$) • ABA group had significantly greater improvements from baseline in scores for all 8 physical and mental subscales of the SF-36. • ABA vs. placebo on change from baseline SF-36 PCS: 6.5 (9.6) vs. 1.0 (7.7) $P < 0.0001$ MCS: 5.4 (11.7) vs.1.7 (10.2) $P = 0.0025$ HAQ-DI: -0.5 (0.6) vs. -0.1 (0.4) $P < 0.0001$ Fatigue VAS: -22.1 (28.6) vs. -5.3 (27.4) $P < 0.0001$	

Authors: Genovese et al. and Westhovens **Year: 2005 and 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Serious adverse events • Serious infections • Headache	**ABA** 79.5 10.5 2.3 12.4	**Placebo** 71.4 11.3 2.3 5.3	
Significant differences in adverse events:	Headache ($P = 0.03$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 17.6% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ABA** 13.6% 3.5%	**Placebo** 25.6% 3.8%	
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators-Rheumatoid Arthritis

STUDY:	**Authors: Hyrich et al.**[26] **Year: 2006** **Country:** Great Britain					
FUNDING:	British Society for Rheumatology Biologics Register					
RESEARCH OBJECTIVE:	Compare outcome at 6 months in unselected "real-world" patients with RA treated with etanercept or infliximab as either monotherapy, or cotherapy with methotrexate or another DMARD					
DESIGN:	**Study design:** Prospective cohort study **Setting:** Multi-clinic **Sample size:** 2711					
INTERVENTION:	**ETA**	**ETA+DMARD**	**ETA+MTX**	**INF**	**INF+DMARD**	**INF+MTX**
Dose:	25 mg 2x wk	Not specified	Not specified	3mg/kg wks 0,2,6 then every 8wks	Not specified	Not specified
Duration:	6 months	6 months	6 months	6 months	6 months	6 months
Sample size:	763	245	250	128	121	1204
INCLUSION CRITERIA:	16 years and older; starting either ETA or INF as their first biologic drug; 1987 ACR criteria for RA.					
EXCLUSION CRITERIA:	None reported					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes					

Authors: Hyrich et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe (mean disease duration 14.6 years)

	ETA	ETA+DMARD	ETA+MTX	INF	INF+DMARD	INF+MTX
Mean age (years):	58	55	54	59	58	55
Sex (% female):	80	79	76	79	74	77
Ethnicity:	NR	NR	NR	NR	NR	NR
Other germane population qualities:						
• Mean disease duration	16	15	13	16	14	14
• Corticosteroids use (%)	54	51	44	69	59	48
• DAS score	6.8	6.6	6.6	6.8	6.8	6.7
• HAQ score	2.2	2.1	2.1	2.1	2.1	2.2

OUTCOME ASSESSMENT:

Primary Outcome Measures: EULAR response

Secondary Outcome Measures: mean improvement in the DAS28

Timing of assessments: monthly

RESULTS:

Health Outcome Measures:

EULAR response at 6 months

- ETA+MTX had an increased EULAR response compared to ETA (OR 2.0, 95% CI 1.5-2.7) or ETA+DMARD vs. ETA (OR 1.2, 95% CI 0.9-1.6)
- EULAR response rates numerically greater for ETA than for INF at 6 months (64% vs. 53%)
- A better EULAR response in both the 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 the INF monotherapy

DAS28 at 6 months

- ETA 4.8 $\pm$ 1.4; ETA+MTX 4.3 $\pm$ 1.5; ETA+DMARD 4.6 $\pm$ 1.5
- INF 5.0 $\pm$ 1.6; INF+MTX 4.6 $\pm$ 1.6; INF+DMARD 4.9 $\pm$ 1.6

Authors: Hyrich et al. **Year:2006**						
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	NR					
Significant differences in adverse events:	NR					
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A					
ARE GROUPS COMPARABLE AT BASELINE:	Yes					
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes					
STATISTICAL ANALYIS ADEQUATE:	Yes					
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 21% **Loss to follow-up differential high:**					
	ETA	**ETA+DMARD**	**ETA+MTX**	**INF**	**INF+DMARD**	**INF+MTX**
Loss to follow-up (%):	22	19	16	30	22	21
Withdrawals due to adverse events (%):	11	9	7	16	12	10
QUALITY RATING:	**Fair**					

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Keystone et al.**[27] **Year: 2004** **Country:** US and Canada		
FUNDING:	Abbott Laboratories, Abbott Park, Illinois		
RESEARCH OBJECTIVE:	To investigate the ability of adalimumab to inhibit the progression of structural joint damage, reduce the signs and symptoms, and improve physical function in patients with RA receiving concomitant methotrexate treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (89 sites) **Sample size:** 619		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA 40 mg biweekly** 40 mg every other week 52 weeks 207	**ADA 20 mg weekly** 20 mg weekly 52 weeks 212	**Placebo** N/A 52 weeks 200
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria; 9 or greater tender joints; 6 or greater swollen joints; CRP concentration $\geq$ 1 mg/dl; either RF positivity or at least 1 joint erosion on hand and feet radiographs; required to be on stable MTX therapy for 3 or more months		
EXCLUSION CRITERIA:	Prior use of anti-CD4 antibody therapy or TNF antagonists; active inflammatory arthritide other than RA; active listeriosis or mycobacterial infection; lymphoma or leukemia; major episode of infection; pregnant or lactating; uncontrolled medical condition		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Constant doses of concomitant RA therapies allowed (e.g. MTX, corticosteroids, NSAIDs)		

Authors: Keystone et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate to severe		
	ADA 40 mg biweekly	**ADA 20 mg weekly**	**Placebo**
Mean age (years):	56.1	57.3	56.1
Sex (% female):	76.3	75.5	73.0
Ethnicity: (% White)	83.6	85.4	83.0
Other germane population qualities:			
• TJC	27.3	27.9	28.1
• SJC	19.3	19.6	19.0
• DMARD use (%)	NR	NR	NR
• MTX use (%)	100	100	100
• Corticosteroids use (%)	NR	NR	NR
• Physician's assessment of disease activity	62.0	61.6	613.
• Patient's assessment of disease activity	52.7	51.9	54.3
• HAQ score	1.45	1.44	1.48
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Radiographic progression (Sharp score); ACR20; HAQ **Secondary Outcome Measures:** ACR50; ACR70; SF-36 **Timing of assessments:** Radiographs performed at baseline, week 24, and week 52; ACR responses and HAQ assessed at weeks 2, 4, 8, 12, 16, 20 ,24, 32, 40, 48, and 52;		
RESULTS:	**Health Outcome Measures at 52 weeks:** • ACR 50 response was significantly improved in ADA groups compared to placebo ($P \leq 0.001$; ADA 40 mg biweekly: 41.5%, ADA 20 mg weekly: 37.7%, placebo: 9.5%) • ACR 70 response was significantly improved in ADA groups compared to placebo ($P \leq 0.001$; ADA 40 mg biweekly: 23.2%, ADA 20 mg weekly: 20.8%, placebo: 4.5%) • Improvements in HAQ function scores were significantly better in ADA treated groups compared to placebo ($P \leq 0.001$) **Intermediate Outcome Measures at 52 weeks:** • Radiographic progression was significantly less in ADA treated groups compared to placebo. ($P \leq 0.001$) • ACR 20 response was significantly improved in both ADA groups compared to placebo ($P \leq 0.001$; ADA 40 mg biweekly: 58.9%, ADA 20 mg weekly: 54.7%, placebo: 24.0%)		

Authors: Keystone et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA 40 mg biweekly**	**ADA 20 mg weekly**	**Placebo**
• Serious infections	5.3%	2.4%	0.5%
• ISR	26.1%	22.2%	24.0%
• URTI	19.8%	19.3%	13.5%
• Rhinitis	16.4%	17.5%	16.5%
• Sinusitis	15.9%	14.6%	13.0%
• Accidental injury	14.0%	13.2%	12.0%
Significant differences in adverse events:	• Serious infections were significantly greater in the ADA 40 mg biweekly group than placebo. ($P \leq 0.01$). • ADA was associated with statistically significant decreases ($P \leq 0.05$ compared with baseline) in mean white blood cell count, platelet count, and neutrophil percentage, and statistically significant increases ($P \leq 0.05$ compared to baseline) in the mean hemoglobin concentration, hematocrit, and lymphocyte percentage.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 152/619 (25%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**ADA 40 mg biweekly**	**ADA 20 mg weekly**	**Placebo**
Loss to follow-up:	48 (23%)	44 (21%)	60 (30%)
Withdrawals due to adverse events:	26 (13%)	16 (7.5%)	13 (6.5%)
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Keystone et al.**[28] **Year: 2008** **Country:** Multinational		
FUNDING:	UCB Inc		
RESEARCH OBJECTIVE:	Efficacy and safety of 2 dosage regimens of certolizumab pegol as adjunctive therapy to MTX in patients with active RA with an inadequate response to MTX therapy alone.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 982		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 52 weeks w/early escape at 16 weeks 199	**CZP 200** 200 mg 52 weeks 393	**CZP 400** 400 mg 52 weeks 390
INCLUSION CRITERIA:	at least 18 years; diagnosis of RA, 6 months prior to screening but <15 years.; required to have received MTX for 6 months, with a stable dosage of 10 mg/week for 2 months prior to baseline.		
EXCLUSION CRITERIA:	Diagnoses of any other inflammatory arthritis or a secondary noninflammatory arthritis that could have interfered with our evaluation of the effects of certolizumab pegol on RA; history of TB or a chest radiograph showing active or latent TB; positive findings on a purified protein derivative (PPD) skin test were excluded, unless the PPD positivity was associated with previous vaccination with BCG (PPD positive by local standard); at a high risk of infection; a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease; received any biologic therapy within 6 months (or had received ETA and/or ANA within 3 months) of baseline and/or any previous biologic therapy that resulted in a severe hypersensitivity or anaphylactic reaction were excluded, as were patients who had previously failed to respond to treatment with an anti-TNF agent.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (≤10 mg/day of prednisone or equivalent, with a stable dosage NSAIDs/cox- 2 inhibitors, and analgesics		

Authors: Keystone et al.
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe

	Placebo	CZP 200	CZP 400
Mean age (years):	52.2	51.4	52.4
Sex (% female):	83.9	82.4	83.6
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Tender joint count	28.8	30.8	31.1
• Swollen joint count	21.2	21.7	21.5
• Mean disease duration	6.2	6.1	6.2
• DMARD use (# used)	1.4	1.3	1.3
• MTX use (%)	100	100	100
• Corticosteroids use (%)	NR	NR	NR
• DAS score	7.0	6.9	6.9
• HAQ score	1.7	1.7	1.7

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR20 and mean change in modified TSS
Secondary Outcome Measures: HAQ DI, ACR50 and 70
Timing of assessments: Baseline, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 then every 4 weeks until week 52 or withdrawal

RESULTS:

Health Outcome Measures:

Measure	Placebo	CZP 200	CZP 400
ACR20 at 52 wks	13.6%	58.8% ($P < 0.001$ vs. placebo)	60.8% ($P < 0.001$ vs. placebo)
ACR50 at 52 wks	7.6%	37.1% ($P < 0.001$ vs. placebo)	39.9% ($P < 0.001$ vs. placebo)
ACR70 at 52 wks	3.0%	21.4% ($P < 0.001$ vs. placebo)	20.6% ($P < 0.001$ vs. placebo)
HAQ DI change from baseline at 12 weeks	-8.2	-30.4 ($P < 0.001$ vs. placebo)	-27.6 ($P < 0.001$ vs. placebo)

Authors: Keystone et al. **Year: 2008**			
ADVERSE EVENTS incidence/100 pys:	**Placebo**	**CZP 200**	**CZP 400**
Overall adverse effects reported:	125.9	96.6	94.5
• infections	56.9	56.4	56.2
• Serious infections	2.2	14.8	15.2
• Headache	12	7.3	5.7
• Hypertension	2.2	8.2	10.2
• Back pain	2.2	5.6	6.4
• Malignancy	1.1	2.3	1.3
• Urinary tract infection	14.2	7.6	10.5
• Nasopharyngitis	3.3	6.9	9.5
• URTI	5.5	7.9	6.7
Significant differences in adverse events:	see headaches and hypertension		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 58% **Attrition differential high:** Yes		
ATTRITION (*treatment specific*):	**Placebo**	**CZP 200**	**CZP 400**
Attrition overall (16 weeks for lack of efficacy):	78.4% (62.8%)	35.1% (21.1%)	29.7% (17.4%)
Attrition due to adverse events:	1.5%	4.3%	5.7%
QUALITY RATING:	**Fair for first 12 weeks of data**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Kievit**[29] **Year: 2008** **Country:** The Netherlands		
FUNDING:	Dutch National Health Insurance Board and the Dutch affiliations of Wyeth Pharmaceuticals, Abbott Pharmaceuticals and Roche Pharmaceuticals enabled the data collection for the DREAM cohort.		
RESEARCH OBJECTIVE:	To evaluate the effects of ADA, ETA and INF on disease activity, functional ability and quality of life and the medication costs in a naturalistic design		
DESIGN:	**Study design:** prospective cohort study **Setting:** The Netherlands RA Register (DREAM) **Sample size:** 707		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 40 mg per 2 weeks N/A 267	**ETA** 25 mg twice weekly N/A 289	**INF** 3 mg/kg every 8 weeks after a loading dose 151
INCLUSION CRITERIA:	DAS28 > 3.2 and failed on at least two DMARDs including MTX at an optimal dose of 25 mg/week.		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	a DMARD, corticosteroids or other treatment		

<table>
<tr><td colspan="4">Authors: Kievit
Year: 2008</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline:
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>ADA,</u> 40 mg per 2 weeks</td><td><u>ETA,</u> 25 mg twice weekly</td><td><u>INF,</u> 3 mg/kg every 8 weeks</td></tr>
<tr><td>Mean age (years):</td><td>55.1 (12.6)</td><td>54.6 (14.2)</td><td>57.8 (13.4)</td></tr>
<tr><td>Sex (% female):</td><td>70.0%</td><td>68.9%</td><td>70.2%</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Tender joint count</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Swollen joint count</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Mean disease duration</td><td>7.7</td><td>6.0</td><td>7.7</td></tr>
<tr><td>• DMARD use (%)</td><td>87%</td><td>78%</td><td>85%</td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>41%</td><td>57%</td><td>48%</td></tr>
<tr><td>• DAS score</td><td>5.3 (1.3)</td><td>5.5 (1.2)</td><td>5.2 (1.3)</td></tr>
<tr><td>• HAQ score</td><td>1.3 (0.7)</td><td>1.4 (0.7)</td><td>1.4 (0.7)</td></tr>
<tr><td>• RF</td><td>81.0%</td><td>71.1%</td><td>77.7%</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
course of the DAS28 over the 12 months follow-up.

Secondary Outcome Measures: HAQ, EQ-5D, SF-36

Timing of assessments: every 3 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Decrease in DAS28: ADA -1.8 (1.5) vs. ETA -1.8 (1.4) vs. INF -1.2 (1.4)

Intermediate Outcome Measures:
• SF-36 PCS “ADA and ETA patients improved after baseline and the course over 12 months was significantly better (P = 0.001) than the course of INF patients”
• HAQ: ADA -0.42 (0.6) vs. ETA -0.35 (0.6) vs. INF -0.26 (0.5)</td></tr>
</table>

Authors: Kievit **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA,** 40 mg per 2 weeks NR	**ETA,** 25 mg twice weekly NR	**INF,** 3 mg/kg every 8 weeks NR
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** N/A (22.8% patients in database not included)		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 4.7% **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**ADA,** 40 mg per 2 weeks	**ETA,** 25 mg twice weekly	**INF,** 3 mg/kg every 8 weeks
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Kim et al.**[30] **Year: 2007** **Country:** Korea		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	Compare the efficacy and safety of 40mg ADA (sc) injections every other week versus placebo, both in conjunction with continued MTX treatment, in patients with RA.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 128		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Washout phase** Not reported Up-to 6 weeks 128	**ADA** 40mg (SC) EOW Up-to 24 weeks 65	**Placebo** N/A Up-to 24 weeks 63
INCLUSION CRITERIA:	Patients 18 yrs or older; meeting ACR criteria for diagnosis of active RA; ≥ 6 swollen joints and ≥ 9 tender joints at screening and baseline; received at least one prior DMARD other than MTX with no more than 4 prior efficacy failures to std DMARDs other than MTX; treatment with MTX for at least 6 months and have been receiving a stable dose for at least 4 weeks prior to screening.		
EXCLUSION CRITERIA:	Acute inflammatory joint diseases other than RA; active listeria; tuberculosis; positive serology for HIV antibody; hepatitis B surface antigen; hepatitis C antibody; calcified granuloma and/or pleural scarring; positive RT23 2TU (> 5mm) skin test unless receiving prophylactic isoniazid 300 mg daily at least 3 weeks prior to baseline.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX		

Authors: Kim **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** yes **Disease severity:** not specified		
	ADA	**Placebo**	
Mean age (years):	48.5	49.8	
Sex (% female):	62 (95.4)	54 (85.7)	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	19.2	20.3	
• Swollen joint count	12.2	12.8	
• Mean disease duration	6.8	6.9	
• DMARD use (%)	86.2	79.3	
• MTX use (%)	16.6	16.3	
(mg/mean)	NR	NR	
• Pt /Phy (mmVAS):	59.7 / 63.7	63.2 / 64.0	
• KHAQ score	1.4	1.3	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 at 24 weeks **Secondary Outcome Measures:** ACR 50/70, ACR core components including tender joint count, swollen joint count, the physicians global assessment disease activity, , patients global assessment pain, Korean HAQ; % reporting morning stiffness. **Timing of assessments:** screening, baseline on study day 1, efficacy and safety at weeks 2, 4, 6, 8, 12, 16, 20, 24.		
RESULTS:	**Health outcome measures:**	**ADA**	**Placebo**
	ACR20*	61.5%	36.5%
	ACR50 / 70	43.1% / 21.5%	14.3% / 7.9%
	Morning stiffness	38.5%	17.5%
	ACR Core components (change at 24 weeks)		
	Tender joint count	-9.5 ± 9.61	-3.4 ± 11.5
	Swollen joint count	-7.9 ± 6.78	-2.0 ± 7.17
	Physician's global assess of disease activity	-29.2 ± 27.48	-9.6 ± 26.47
	Patient's global assess of disease activity	-23.7 ± 26.54	-10.7 ± 24.85
	Patient's global assess of pain	-23.7 ± 22.86	-7.3 ± 27.50
	KHAQ	-0.5 ± 0.55	-0.2 ± 0.50

Authors: Kim **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA**	**Placebo**	
• Infections	84.6%	82.%	
• URTI	36.9%	34.9%	
• cough	27.7%	28.6%	
• rhinorrhea	10.8%	3.2%	
• fatigue	9.2%	1.6%	
• pruritus	7.7%	4.8%	
• headache	6.2%	1.6%	
• hypercholesterolemia	6.2%	4.8%	
• injection site pain	6.2%	0%	
• rhuematoid arthritis flare-up	3.1%	7.9%	
• Death (n)	0% 1	6.3% 0	
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes 1 patient tested positive for Hep C and discontinued after 2 weeks		
ADEQUATE RANDOMIZATION:	Yes but method not reported		
ADEQUATE ALLOCATION CONCEALMENT:	Not reported		
BLINDING OF OUTCOME ASSESSORS:	Not reported		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall attrition:** 21.5% of ADA and 36.5% of placebo (this excludes patients who switched from the double blinded treatment to the open-label rescue) **Attrition differential high:** Yes		
Attrition overall: **Attrition due to adverse events:** Attrition due to lost to follow-up or violation of exclusion criteria	**ADA** 6.2% 3%	**Placebo** 6.3% 0%	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Klareskog et al.**[31] **and van der Heijde et al.**[32-34] **Study name:** TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) **Year: 2004, 2006, 2007** **Country:** Multinational (Europe)		
FUNDING:	Wyeth Research		
RESEARCH OBJECTIVE:	To compare safety, efficacy and patient reported outcomes of the combination of ETA and MTX with the monotherapies in patients with RA who had failed previous DMARD treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 682		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** 20 mg per week 52 weeks (2 yrs) (3 yrs) 228	**ETA** 25 mg twice per week 52 weeks (2 yrs) (3 yrs) 223	**MTX + ETA** Same MTX + ETA doses 52 weeks (2 yrs) (3 yrs) 231
INCLUSION CRITERIA:	Aged 18 years or older; disease duration of 6 months to 20 years; active, adult-onset RA (ACR functional class I-III), defined as 10 or more swollen and 12 or more painful joints and at least one of: ESR $\geq$ 28 mm/h, plasma CRP $\geq$ 20 mg/L, or morning stiffness for $\geq$ 45 minutes; less than satisfactory response at the discretion of the investigator, to at least one DMARD other than MTX.		
EXCLUSION CRITERIA:	Previous treatment with MTX if patient experienced clinically toxic side effects or had no response; treatment with MTX within 6 months; previous treatment with ETA or other TNF antagonist; previous treatment with immunosuppressive drugs within 6 months of screening; use of any investigational drug or biological agent within 3 months of screening; any other DMARD or corticosteroid injection within 4 months of the baseline visit; and presence of relevant comorbidity, including active infections.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Folic acid 5 mg twice per week; NSAIDs		

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe (mean disease duration 6.6 years)		
	MTX	**ETA**	**Combination**
Mean age (years):	53.0	53.2	52.5
Sex (% female):	79	77	74
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Disease duration, years	6.8	6.3	6.8
• RF positive, %	71	75	76
• Corticosteroid use, %	64	57	62
• Total Sharp score, median	26.8	21.8	21.8
• Number of tender joints	33.1	35.0	34.2
• Number of swollen joints	22.6	23.0	22.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Efficacy: ACR-N AUC over the first 24 weeks; radiographic: change from baseline in total joint damage score (modified total Sharp score) over 52 weeks; EQ5D-Vas; HAQ. **Secondary Outcome Measures:** ACR20, ACR50, ACR70 responses; DAS, remission (DAS < 1.6); and HAQ **Timing of assessments:** Baseline, 24 weeks, and 53 weeks and 100 weeks for primary and secondary end points; unspecified frequency of "patient visits throughout the study" for assessment of vital signs, blood work, and adverse events.		

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**	

RESULTS:	**Health Outcome Measures: (combination vs. ETA v. MTX) (95% CI)**
	• Overall, combination treatment achieved significantly better results on most outcome measures than ETA and MTX, separately
	• ACR-N AUC at 24 weeks was significantly greater for combination and ETA than for MTX: 18.3%-years (17.1-19.6) vs. 14.7%-years (13.5-16.0) vs. 12.2%-years (11.0-13.4)
	• ACR-N AUC at 24 weeks, mean differences:
	  • Combination vs. MTX: 6.1 (4.5-7.8) ($P < 0.0001$)
	  • ETA vs. MTX: 2.5 (0.8-4.2) ($P = 0.0034$)
	  • Combination vs. ETA: reported as "greater" ($P < 0.0001$)
	• ACR20/50/70 response rates at 52 weeks were significantly greater for combination than for ETA and MTX; No statistically significant difference between ETA and MTX
	  • ACR20: 85% (80-89) vs. 76% (70-81) vs. 75% (69-80); combination vs. ETA: $P = 0.0151$; combination vs. MTX: $P = 0.0091$
	  • ACR50: 69% (63-75) vs. 48% (42-55) vs. 43% (36-49); combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$
	  • ACR70: 43% (36-50) vs. 24% (19-30) vs. 19% (14-25); combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$
	• Proportion in remission at 52 weeks (DAS < 1.6): 35% (29-41) vs. 16% (11-21) vs. 13% (9-18) (combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$; ETA vs. MTX: $P = 0.5031$)
	• HAQ, mean decline at 52 weeks: 1.0 vs. 0.7 vs. 0.6 (CIs NR) (combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$; ETA vs. MTX: $P = 0.3751$)
	• EQ-5D VAS mean (SD) 72.7 (3.1) 63.7 (3.2), 66.8 (3.2), 63.7 (3.2) (CIs NR)
	Health Outcome Measures at 100 weeks: (combination vs. ETA or MTX)
	▪ ACR20 86% vs. 75% or 71% $P < 0.01$ for combination vs. ETA or MTX
	▪ ACR50 71% vs. 54% or 42% $P < 0.01$ for combination vs. ETA or MTX
	▪ ACR70 49% vs. 27% or 21% $P < 0.01$ for combination vs. ETA or MTX
	▪ DAS 2.2 vs. 2.9 or 3.0 $P < 0.01$ for combination vs. ETA or MTX
	▪ Remission (DAS < 1.6) 40.7% vs. 23.3% vs. 18.9% $P < 0.01$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$
	Health Outcome Measures at 3 years: (combination vs. ETA or MTX)
	▪ ACR20 85.3% vs. 70.9% or 70.2% $P < 0.01$ for combination vs. ETA or MTX
	▪ ACR50 67.1% vs. 45.7% or 43.9% $P < 0.01$ for combination vs. ETA or MTX

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**	
RESULTS (continued):	▪ ACR70 47.2% vs. 26.0% or 21.1% $P < 0.01$ for combination vs. ETA or MTX ▪ Remission (DAS < 1.6) 40.7% vs. 21.5% vs. 17.5% $P < 0.01$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$ **Intermediate Outcome Measures (combination v. ETA v. MTX) (95% CI)** • DAS, mean, at 52 weeks: 2.3 (2.1-2.5) vs. 3.0 (2.8-3.1) vs. 3.0 (2.8-3.2) o (combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$) • Total Sharp score, mean difference at 52 weeks: Combination vs. MTX: -3.34 (-4.86 - -1.81), $P < 0.0001$ ETA vs. MTX: -2.27 (-3.81 - -0.74), $P < 0.0001$ • Proportion of patients without progression (total Sharp score $\leq$ 0.5): 80% (74-85) vs. 68% (61-74) vs. 57% (50-64) o (combination v. ETA: $P = 0.0043$; combination vs. MTX: $P < 0.0001$; ETA vs. MTX: $P = 0.0213$) **Intermediate Outcome Measures at 100 weeks (combination v. ETA or MTX (95% CI)** ▪ Total Sharp score -0.56 (-1.05, -0.06) vs. 1.10 (0.13, 2.07) or 3.34 (1.18, 5.50) $P < 0.05$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$ ▪ Erosion score -0.76 (-1.113, -0.38) vs. 0.36 (-0.25, 0.97) or 2.12 (0.66, 3.57) $P < 0.05$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$ ▪ JSN score 0.20 (-0.03, 0.44) vs. 0.74 (0.25, 1.23) or 1.23 (0.39, 2.60) $P < 0.05$ for combination vs. MTX **Intermediate Outcome Measures at 3 years (combination v. ETA or MTX (95% CI)** ▪ Total Sharp score –0.14 (–1.07, 0.78) vs. 1.61 (0.41, 2.81) or 5.95 (2.96, 8.94) $P < 0.01$ for combination vs. ETA or MTX ▪ Erosion score –0.67 (–1.05, –0.28) vs. 0.39; (–0.44, 1.22) or 3.25 (1.50, 5.01)) $P < 0.01$ ▪ JSN score –0.67 (–1.05, –0.28) vs. 1.22 (0.59, 1.84) or 2.70 (1.26, 4.13) $P < 0.01$ for combination vs. MTX or ETA

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**			
ADVERSE EVENTS (2 yrs):	**MTX**	**ETA**	**MTX + ETA**
Overall adverse effects reported:	185 (199)	192 (206)	187 (199)
• **Abdominal Pain, %**	18 (22)	12 (17)	18 (22)
• **Diarrhea, %**	9 (11)	10 (11)	8 (11)
• **Nausea**	32 (39)	10 (13)	24 (29)
• **Vomiting, %**	11 (14)	3 (4)	5 (9)
• **Headache, %**	14 (16)	15 (17)	15 (17)
• **ISR, %**	2 (2)	21 (22)	10 (11)
• **Rash, %**	9 (12)	7 (8)	10 (12)
Infections, number (%) (2 yrs %)	147 (64) (75)	131 (59) (71)	154 (67) (76)
• **Serious**	10 (4) (7)(8.3 3 yrs)	10 (4) (6)(6.7 3 yrs)	10 (4) (6)(7.4 3 yrs)
Significant differences in adverse events:	• ISR: ETA (21%) v. MTX (2%), $P < 0.0001$ • Nausea: ETA (10%) v. MTX (32%), $P < 0.0001$; • Vomiting: ETA (3%) v. MTX (11%), $P = 0.0009$ • At 2 yrs Nausea and ISR Combination vs. MTX or ETA $P < 0.01$ and ETA vs. MTX $P < 0.01$		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 23% (160/682) (2 yrs 38%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**MTX**	**ETA**	**MTX + ETA**
Loss to follow-up:	NR (2 yrs 48%)	NR (2 yrs 39%)	NR (2 yrs 29%)
Withdrawals due to adverse events:	14.0% (2 yrs 21%)	11.2% (2 yrs 16%)	10.4% (2 yrs 17%)
Lack of Efficacy	9.2% (2 yrs 14%)	7.2% (2 yrs 13%)	2.6% (2 yrs 4%)
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Kremer et al.**[35, 36] **and Emery et al.**[37] **Year: 2003, 2005, and 2006** **Country:** Multinational		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To investigate effectiveness of cytotoxic T-lymphocyte-associated antigen 4-IgG1 (abatacept) therapy in patients with RA who had an inadequate response to methotrexate.		
DESIGN:	**Study design:** RCT, double blind, placebo-controlled **Setting:** multicenter **Sample size:** 339		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo/MTX** Mean 15mg/wk 6 months/12 months 119	**ABA2/MTX** 2mg/kg 6 months/12 months 105	**ABA10/MTX** 10mg/kg 6 months/12 months 115
INCLUSION CRITERIA:	Age 18-65 years; meeting ACR criteria for RA and in functional class I, II, or III; active disease, characterized by ≥ 10 swollen and 12 tender joints, and CRP levels of at least 1 mg per deciliter; Treatment with MTX (10-30 mg/week) for at least 6 months and have a stable dose for 28 days before enrollment;		
EXCLUSION CRITERIA:	Nursing or pregnant women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; stable low dose corticosteroids (≤ 10 mg / day); NSAIDS		

<table>
<tr><td colspan="4">Authors: Kremer et al. and Emery et al.
Year: 2003 and 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 9.4 years)</td></tr>
<tr><td></td><td><u>Placebo/MTX</u></td><td><u>ABA2/MTX</u></td><td><u>ABA10/MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>54.7</td><td>54.4</td><td>55.8</td></tr>
<tr><td>Sex (% female):</td><td>66</td><td>63</td><td>75</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>% White</td><td>87</td><td>87</td><td>87</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• SJC</td><td>21.8</td><td>20.2</td><td>21.3</td></tr>
<tr><td>• TJC</td><td>29.2</td><td>28.2</td><td>30.8</td></tr>
<tr><td>• Physician global assessment</td><td>63.3</td><td>61.0</td><td>62.1</td></tr>
<tr><td>• Pain score</td><td>65.2</td><td>65.2</td><td>62.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR 20 response at 6 months, HRQOL at 1 year
Secondary Outcome Measures: ACR 50 and ACR 70 at 6 months; Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36)
Timing of assessments: ACRs on day 1, 15, and 30 and then monthly; SF-36 at baseline, 90 days then 180 days.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At 6 months, rate of ACR20 was significantly higher in the ABA 10mg group than placebo group: ACR 20 was 35.3% (placebo/MTX), 41.9% (ABA 2mg/MTX), and 60.0% (ABA 10mg/MTX; $P < 0.001$ vs. placebo).
• At 6 months, rates of ACR50 and ACR70 response were significantly higher in both ABA group than placebo group: ACR 50: 11.8% (placebo/MTX), 22.9% (ABA 2mg/MTX; $P < 0.05$ vs. placebo), and 36.5% (ABA 10mg/MTX; $P < 0.001$ vs. placebo). ACR 70: 1.7% (placebo/MTX), 10.5% (ABA 2mg/MTX; $P < 0.05$ vs. placebo), and 16.5% (ABA 10mg/MTX; $P < 0.001$ vs. placebo).
• Patients in ABA 10mg/MTX group had significant and clinically meaningful improvements from baseline scores in all 8 subscales of the SF-36, with the greatest effect in the physical-health, pain, vitality, and social function domains.
• One year HRQOL ABA10 vs. MTX (MANOVA F = 4.71, $P < 0.001$) and ABA2 vs. MTX MANOVA F = 1.97, $P = 0.05$</td></tr>
</table>

Authors: Kremer et al. and Emery et al. **Year: 2003 and 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:**	**Placebo/MTX**	**ABA2/MTX**	**ABA10/MTX**
• Serious adverse events	10.1	11.4	2.6
• Headache	12.6	14.3	10.4
• URTI	10.1	12.4	13.0
• Musculoskeletal pain	12.6	14.1	7.0
• Nausea and vomiting	11.8	6.7	13.9
• Fatigue	8.4	9.5	5.2
• Cough	8.4	5.7	10.4
• Diarrhea	5.9	6.7	9.6
• Pharyngitis	5.9	4.8	10.4
Significant differences in adverse events:	*P* = 0.03 for serious adverse events in ABA 10mg/MTX group vs. placebo.		
ANALYSIS:	**ITT:** Yes (LOCF) **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Safety assessments unblinded.		
ATTRITION (*overall*):	**Overall loss to follow-up:** 38.9% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo/MTX**	**ABA2/MTX**	**ABA10/MTX**
Loss to follow-up:	34.5%	21.9%	13.9%
Withdrawals due to adverse events:	7	7	2
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Kremer et al.**[38] **and Russell**[39] **Year: 2006 and 2007** **Country:** Multinational	
FUNDING:	Bristol-Myers Squibb	
RESEARCH OBJECTIVE:	To evaluate effects of ABA in patients with persistent, active RA despite MTX treatment.	
DESIGN:	**Study design:** RCT (double-blind, placebo-controlled) **Setting:** Multicenter **Sample size:** 652	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA + MTX** 10mg/kg per month 1 year 433	**Placebo + MTX** N/A 1 year 219
INCLUSION CRITERIA:	Age ≥ 18 years; RA (based on ACR criteria) for ≥ 1 year that was persistent and active despite MTX treatment; treatment with MTX (≥ 15 mg/wk) for 3+ months, with a stable dose for 28 days before enrollment; and completion of 28-day DMARD washout period. At randomization, required ≥ 10 swollen or 12 tender joints; CRP ≥ 10.0 mg/L while receiving MTX.	
EXCLUSION CRITERIA:	Positive tuberculin skin test, unless patient had completed treatment for latent TB before enrollment.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroid use, with dosages ≤ 10 mg/day of prednisone, stabilized for 25 days before randomization & stable doses of NSAIDS.	

Authors: Kremer et al. and Russell **Year: 2006 and 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR (mean disease duration 8.7 years)	
	ABA + MTX	**Placebo + MTX**
Mean age (years):	51.5	50.4
Sex (% female):	77.8	81.7
Ethnicity (% White):	87.5	88.1
Other germane population qualities:		
• TJC (No.)	31.0	32.3
• SJC (No.)	21.4	22.1
• Mean disease duration (yrs)	8.5	8.9
• DMARD use (%)	12.2	8.7
• MTX use (%)	100	100
• Corticosteroids use (%)	72.1	68.5
• HAQ-DI score	1.7	1.7
• DAS28	6.4	6.4
• SF-36 MCS	41.8	40.8
• SF-36 PCS	30.6	30.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20 at 6 months; clinically meaningful improvements (≥0.3 units) in HAQ-DI at 1 year; change from baseline in joint erosion score (Genant-modified Sharp score) at 1 year. Change in HQL (SF-36) **Secondary Outcome Measures:** ACR50/ACR70 at 6 months; all ACR scores at 1 year; DAS28; SF-36. **Timing of assessments:** At enrollment & at every visit before treatment administration on days 1, 15, 29; every 28 days up to & including day 169 (6 months); and days 225, 281, and 365 (1 year).	
RESULTS:	**Health Outcome Measures:** • 6-month ACR 20 = 67.9% (ABA) vs. 39.7% (placebo) (difference, 28.2% [95% CI, 19.8 to 36.7]); 6-month ACR 50 = 39.9% (ABA) vs. 16.8% (placebo) (difference, 23.0% [95% CI, 15.0 to 31.1]); 6-month ACR 70 = 19.8% (ABA) vs. 6.5% (placebo) (difference, 13.3% [95% CI, 7.0 to 19.5]) • 1-year ACR 20 = 73.1% (ABA) vs. 39.7% (placebo) (difference, 33.4% [95% CI, 25.1 to 41.7]); 1-year ACR 50 = 48.3% (ABA) vs. 18.2% (placebo) (difference, 30.1% [95% CI, 21.8 to 38.5]); 1-year ACR 70 = 28.8% (ABA) vs. 6.1% (placebo) (difference, 22.7% [95% CI, 15.6 to 29.8]). All $P < 0.001$ • At 1 year, physical function improved in 63.7% (ABA) vs. 39.3% (placebo) ($P < 0.001$; difference 24.4% [95% CI, 15.9 to 32.9]). • 1 year, ABA-treated patients showed statistically significant slowing of structural damage progression:	

	median change from baseline erosion score was 0.0 (25^{th} & 75^{th} percentiles, 0.0 and 1.0, respectively) for ABA vs. 0.27 (25^{th} & 75^{th} percentiles, 0.0 and 1.3, respectively) for placebo ($P = 0.029$) • DAS28 $\leq$ 3.2 achieved in 30.1% (6-month) & 42.5% (1-year) of ABA group vs. 10.0% (6-month) & 9.9% (1-year) of placebo group ($P < 0.001$). • Change in SF 36 was greater in ABA vs. placebo (data in graph) PCS $P < 0.001$ MCS $P < 0.05$.

Authors: Kremer et al. and Russell **Year: 2006 and 2007**		
ADVERSE EVENTS:	**ABA + MTX**	**Placebo + MTX**
Overall adverse effects reported(%):	87.3	84.0
• Headache	17.6	11.9
• Nasopharyngitis	15.2	11.4
• Nausea	12.0	11.0
• Diarrhea	10.9	9.6
• Upper respiratory infection	10.9	9.6
• Dizziness	9.2	7.3
• Back pain	9.2	5.5
• Hypertension	5.5	1.4
• Fatigue	5.3	6.8
Significant differences in adverse events:	NR	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (n= 14; 1 study center was excluded because of poor adherence)	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 16.1% **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**ABA + MTX**	**Placebo + MTX**
Loss to follow-up:	11%	26%
Withdrawals due to adverse events:	4.2%	1.8%
QUALITY RATING:	**Fair**	

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Kristensen et al.**[40] **Year: 2006** **Country:** Sweden	
FUNDING:	Supported by the Osterlund and Kock Foundations, Inc; the 80-year Fund of King Gustav V, and Reumatikerforbundet	
RESEARCH OBJECTIVE:	To describe the use of the LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA patients treated in clinical practice.	
DESIGN:	**Study design:** Observational **Setting:** Multicenter **Sample size:** 949	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg SQ, twice weekly 3 years 309	**INF** 3 mg/kg at 0,2,6,& 12 weeks and then every 8 weeks 3 years 640
INCLUSION CRITERIA:	Patients diagnosed with RA according to clinical judgment of the treating physician; treated at 8 centers in Southern Sweden during the period March 1999 through January 2004; unsuccessful treatment with ≥ 2 DMARDs, including MTX;	
EXCLUSION CRITERIA:	Previous treatment with biologic therapy	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

<table>
<tr><td colspan="4">Authors: Kristensen et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: NR (mean disease duration 13.4 years)</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>55.1</td><td>56.2</td><td></td></tr>
<tr><td>Sex (% female):</td><td>82</td><td>75</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean disease duration (years)</td><td>14.7</td><td>12.7</td><td></td></tr>
<tr><td>• DMARD use (No.)</td><td>4.2</td><td>3.6</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>31</td><td>73</td><td></td></tr>
<tr><td>• DAS28 score</td><td>5.9</td><td>5.6</td><td></td></tr>
<tr><td>• HAQ score</td><td>1.6</td><td>1.4</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: LUNDEX = (fraction of starters still in the study at time T) x (fraction responding at time T)
Secondary Outcome Measures: HAQ; VAS for pain and general health; physician’s global assessment of disease activity (Evalglobal); 28-joint TJC & SJCs; ESR; CRP; ACR20; ACR50; ACR70; EULAR.
Timing of assessments: 0,3,6, & 12 months, then every 3-6 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• ETA had the highest overall LUNDEX values; ~55% of these patients fulfilled ACR20 response criteria at 12 months (~40% after 3 years).
• ~45% of patients started on INF fulfilled ACR20 response criteria at 12 months (~30% at 3 years)
• ACR 20: % response at 36 months = 63 (ETA) vs. 61 (INF) (P = NS)
• % response at 24 months = 65 (ETA) vs. 56 (INF) (P = NS)
• % response at 12 months = 69 (ETA) vs. 53 (INF) (P = 0.001)
• % response at 6 months = 61 (ETA) vs. 47 (INF) (P = NS)
• % response at 36 months = 63 (ETA) vs. 45 (INF) (P < 0.001)
• 36 months- ACR50: 39 (ETA) vs. 39 (INF) (P = NS),ACR 70: 16 (ETA) vs. 18 (INF) (P = NS)
• EULAR (moderate): % response at 36 months = 46 (ETA) vs. 29 (INF) (P = NS)
• EULAR (good): % response at 36 months = 36 (ETA) vs. 45 (INF) (P = NS)
Intermediate Outcome Measures:
• INF had significantly lower adherence compared to ETA (P < 0.001); study cites this as possible reason for lower response rates for INF</td></tr>
</table>

Authors: Kristensen et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** •	**ETA** NR	**INF** NR	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** NR	**INF** NR	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Mertens and Singh**[41] **Year: 2009** **Country:** Multinational
FUNDING:	Cochrane
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 2876
AIMS OF REVIEW:	To evaluate the clinical effectiveness and safety of AKA in adult patients with rheumatoid arthritis
STUDIES INCLUDED IN META-ANALYSIS:	Bresnihan 1998, Cohen 2002, Cohen 2004, Fleischman 2003, Genovese 2004
TIME PERIOD COVERED:	1950 to 4th week January 2008
CHARACTERISTICS OF INCLUDED STUDIES:	All randomized controlled trials (RCTs) comparing AKA alone or in combination with DMARDs or biologics to placebo or other DMARDs or biologics in patients with rheumatoid arthritis
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults aged 18 years and above meeting the ACR 1987 revised criteria for rheumatoid arthritis

Authors: Mertens and Singh **Year: 2009**	
CHARACTERISTICS OF INTERVENTIONS:	AKA alone or in combination with other drugs.
MAIN RESULTS:	ACR 20 at 24 weeks AKA 50-150 mg/day 38% vs. placebo 23%, (RR 1.61; 95% CI 1.32 to 1.98). The absolute treatment benefit for AKA 50 to 150mg/day 15%with NNTB 8 ACR20 at 24 weeks AKA < 50 mg/day 33% vs. placebo 26% RR of 1.38 (95% CI 1.01 to 1.89), ACR50 at 24 weeks AKA 50-150 18% vs. placebo 7% (RR 2.51; 95%CI 1.56 to 4.03). The absolute treatment benefit for AKA 50-150 11% and NNTB- 9 ACR70 at 24 weeks AKA 50-150 7% vs. placebo 2% (RR3.71; 95% CI 1.44 to 9.57) The absolute treatment benefit for AKA50-150 was 5% and NNTB was 22 HAQ scores AKA vs. placebo MD of -0.19 (95% CI -0.30 to -0.09)
ADVERSE EVENTS:	Withdrawals AKA50-150 22% vs. placebo 22% (RR 1.04; 95% CI 0.86 to 1.27) Adverse events AKA 92% vs. placebo 87% (RR 1.05; 95%CI 0.94 to 1.17) AKA(w/o MTX) vs. Placebo(w/o MTX) RR1.00; 95% CI 0.96 to 1.04 AKA + MTX vs. placebo +MTX subgroup, (RR 1.11; 95% CI 1.03 to 1.20) ISRs AKA50-150 71% vs. placebo 28% RR 2.45; 95% CI 2.17 to 2.77 SAEs AKA50-150 7%vs. placebo 6%, RR 1.04; 95% CI 0.70 to 1.56 Infections AKA50-150 40% vs. placebo 35% RR 1.08; 95%CI 0.80 to 1.45
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Good

Evidence Table 1. Targeted Immune Modulators -- Rheumatoid Arthritis

STUDY:	**Authors: Miyasaka**[42] **Year: 2008** **Country:** Japan			
FUNDING:	Abbott Japan Co., Ltd., Osaka, Japan, and Eisai Co., Ltd., Tokyo, Japan			
RESEARCH OBJECTIVE:	Effects of three doses of ADA 20, 40, 80 every other week (eow) versus placebo in Japanese patients with rheumatoid arthritis			
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 352			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 wks 87	**ADA 20** 20 mg eow 24 wks 87	**ADA 40** 40 mg eow 24 wks 91	**ADA 80** 80 mg eow 24 wks 87
INCLUSION CRITERIA:	20 years or older; met the ACR criteria for active RA, had failed treatment with at least one prior DMARD, 10 or more swollen joints and 12 or more tender joints (excluding distal interphalangeal joints) and a C-reactive protein (CRP) concentration 2 mg/dl or more			
EXCLUSION CRITERIA:	Acute inflammatory joint diseases other than RA, active Listeria or tuberculosis, lymphoma, or leukemia, or any malignancy except for successfully treated nonmetastatic basal-cell carcinoma of the skin. HIV, hepatitis B virus surface antigen, or anti-hepatitis C virus antibody, ongoing or active infection, advanced or poorly controlled diabetes, or CNS demyelinating disorders; pregnancy			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR			

Authors: Miyasaka
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: yes
Disease severity: Mild-moderate-severe

	Placebo	ADA 20	ADA 40	ADA 80
Mean age (years):	53.4	54.8	56.9	54.3
Sex (% female):	77	79.3	79.1	82.8
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Tender joint count	23.7	24.6	24.4	24.9
• Swollen joint count	19.3	19.2	19.1	20.8
• Mean disease duration	8.4	10.0	9.9	9.5
• HAQ score	1.39	1.57	1.64	1.77

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR20 at 24 weeks
Secondary Outcome Measures: ACR20/50/70 at 12 and 24 weeks, SJC and TJC, HAQ DI, ACR20 AUC
Timing of assessments: 12 and 24 weeks

RESULTS:

Health Outcome Measures:
Placebo vs. ADA20 vs. ADA40 vs. ADA80
ACR20 - Week 12 11 (12.6) vs. 39 (44.8)* vs. 39 (42.9)* vs. 47 (54.0)*
Week 24 12 (13.8) vs. 25 (28.7)a vs. 40 (44.0)** vs. 44 (50.6)**
ACR50 - Week 12 3 (3.4) vs. 16 (18.4)* vs. 19 (20.9)* vs. 23 (26.4)*
Week 24 5 (5.7) vs. 14 (16.1) vs. 22 (24.2)* vs. 28 (32.2)*
ACR70 - Week 12 1 (1.1) vs. 6 (6.9) vs. 15 (16.5)* vs. 10 (11.5)*
Week 24 1 (1.1) vs. 9 (10.3)* vs. 11 (12.1)* vs. 13 (14.9)*
TJC Study week 24 -0.5 ± 10.9 vs. -6.6 ± 11.4 vs. -10.7 ± 12.3* vs.-10.0 ± 13.3*
SJC Study week 24 -1.8 ± 7.4 vs. -5.9 ± 7.6* vs. -8.2 ± 8.8* vs. -8.7 ± 9.4*
HAQ DI Study week 24 0.1 ± 0.6 vs. -0.2 ± 0.5 vs. -0.2 ± 0.6 vs. -0.4 ± 0.6
* $P < 0.05$ versus placebo
* $P < 0.0001$ versus placebo

Authors: Miyasaka **Year: 2008**				
ADVERSE EVENTS:	**Placebo**	**ADA 20**	**ADA 40**	**ADA 80**
Overall adverse effects reported:	81.6	92.0	98.9*	93.1*
• Serious AEs	9.2	11.5	18.7	9.2
• Severe AE	5.7	3.4	4.4	5.7
• Infectious AE	36.8	34.5	45.1	42.5
• Serious infectious AE	1.1	4.6	6.6	3.4
• ISR	2.3	31.0*	30.8*	33.3*
Significant differences in adverse events:	* $P < 0.05$ compared to placebo			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR			
ADEQUATE RANDOMIZATION:	NR			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall attrition:** 34 (9.7%) **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Placebo**	**ADA 20**	**ADA 40**	**ADA 80**
Attrition overall:	7	7	16	4
Attrition due to adverse events:	4.6	5.7	13.2	3.4
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Moreland et al.**[43] **and Mathias et al.**[44] **Year: 1999 and 2000** **Country:** North America		
FUNDING:	Immunex Corporation, Seattle, Washington		
RESEARCH OBJECTIVE:	To compare the functional status and well-being of patients with RA who were randomized to placebo, etanercept 10 mg, or etanercept 25 mg over a 26-week period; embedded in a phase III, double-blind clinical trial (Moreland, 1999)		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 234		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 26 weeks 80	**ETA (low dose)** 10 mg twice per week 26 weeks 76	**ETA (high dose)** 25 mg twice per week 26 weeks 78
INCLUSION CRITERIA:	Adults at least 18 years old; meet ACR criteria for RA and fall into functional class I, II, or III; discontinuation of one to four DMARDs due to lack of effect; have currently active disease defined as 12 or more tender joints, 10 or more swollen joints, and at least one of the following: ESR $\geq$ 28 mm/h, CRP $\geq$ 20 mg/dl, or morning stiffness $\geq$ 45 minutes; aminotransferase levels $\leq$ twice the upper limit of normal; hemoglobin level of $\geq$ 85 g/dl; leukocyte count of $\geq$ 125,000 cells/mm3; a serum creatinine of $\leq$ 2 mg/dl; and, no DMARDs within one month of enrollment. (From Moreland 1999.)		
EXCLUSION CRITERIA:	Intra-articular corticosteroid steroid injections within 4 weeks of enrollment; corticosteroid doses over the equivalent of 10 mg of prednisone per day; and, NSAID dosages exceeding manufacturer recommended dosing (From Moreland 1999).		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of corticosteroids and NSAIDs; however, no analgesics within 24 hours preceding a joint examination; no concurrent DMARDs allowed during the study.		

Authors: Moreland et al. and Mathias et al. **Year: 1999 and 2000**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Placebo	**ETA (low dose)**	**ETA (high dose)**
Mean age (years):	51	53	53
Sex (% female):	76	84	74
Ethnicity (% white):	89	96	94
Other germane population qualities:			
• TJC	35	34	33
• SJC	25	25	25
• Prior DMARD use (%)	100	100	100
• Prior DMARDs, mean	3.0	3.4	3.3
• MTX use prior to study (%)	90	92	87
• Corticosteroids use (%)	58	66	81
• DAS score	N/A	N/A	N/A
• HAQ score	1.66	1.77	1.63
• Feeling Thermometer	47	44	48
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20/50, Paulus Index **Secondary Outcome Measures:** SF-36, HAQ, feeling thermometer **Timing of assessments:** Baseline and at weeks 2, 3, 4, 8, 12, 16, 21, and 26.		

Authors: Moreland et al. and Mathias et al. **Year: 1999 and 2000**	

RESULTS:	**Health Outcome Measures: (placebo v. ETA 10 mg v. ETA 25 mg)**
	• Significantly more patients in the ETA groups than in the placebo group achieved ACR50 response (24% vs. 40% vs. 5%; $P < 0.001$ for each ETA group compared to placebo)
	• Patients receiving ETA achieved statistically significant improvements on a variety of quality-of-life measures, including the HAQ, compared to placebo after 6 months of therapy.
	• **HAQ:**
	  • Data NR
	  • Placebo v. ETA 10 mg and placebo v. ETA 25 mg: $P < 0.05$
	• **SF-36: PCS-36 (n = 48)**
	  • Data NR
	  • At months 3 and 6, ETA groups performed significantly ($P \leq 0.01$) better than the placebo group
	• **SF-36: MCS-36 (n = 48)**
	  • Data NR
	  • At month 6, ETA groups performed significantly ($P < 0.02$) better than the placebo group
	• **MOS**
	  • Energy/Vitality: At month 6: 4.74 v. 17.38 v. 16.35 ($P < 0.01$)
	  • Mental Health: At month 6: 4.41 v. 12.95 v. 13.88 ($P < 0.01$)
	• **Feeling Thermometer:**
	  • 8.15 v. 19.97 v. 18.19
	  • ETA 10 mg v. placebo: $P = 0.019$; ETA 25 mg v. placebo: $P = 0.054$
	
	Intermediate outcome measures
	• Significantly more patients in the ETA groups than in the placebo group achieved ACR20 response (51% vs. 59% vs. 11%; $P < 0.001$ for each ETA group compared to placebo)

Authors: Moreland et al. and Mathias et al. **Year: 1999 and 2000**			
ADVERSE EVENTS: %	**Placebo**	**ETA (low dose)**	**ETA (high dose)**
Overall adverse effects reported:	NR	NR	NR
• Injection-site reaction	13	43	49
• URTI	16	29	33
• Headache	10	20	14
• Sinusitis	11	11	12
• Rhinitis	11	12	10
• Diarrhea	6	11	5
Significant differences in adverse events:	ISRs- each treatment groups vs. placebo ($P < 0.001$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (12/246)		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 41.5% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**Placebo**	**ETA (low dose)**	**ETA (high dose)**
Loss to follow-up:	67.5%	31.6%	24.4%
Withdrawals due to adverse events:	3.8%	6.6%	2.6%
Withdrawals due to lack of efficacy:	52.5%	21.1%	15.4%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Moreland et al.**[45] **Year: 2002** **Country:** Multinational			
FUNDING:	Bristol-Myers Squibb			
RESEARCH OBJECTIVE:	To investigate determine safety and preliminary efficacy of costimulatory blockade using CTLA-4Ig (abatacept) and LEA29Y in RA patients who have been treated unsuccessfully with at least 1 DMARD.			
DESIGN:	**Study design:** RCT, double blind, placebo-controlled **Setting:** multicenter **Sample size:** 214 (only 122 of which were of interest to this study)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 85 days 32	**ABA 0.5** 0.5 mg/kg 85 days 26	**ABA 2** 2 mg/kg 85 days 32	**ABA 10** 10 mg/kg 85 days 32
INCLUSION CRITERIA:	Age 18-65 years; meeting ACR criteria for RA and in functional class I, II, or III; disease duration < 7 years; ≥ 10 swollen and 12 tender joints at study entry; Westergren ESR ≥ 28 mm/hour or morning stiffness of ≥ 45 minutes; unsuccessful treatment with at least 1 classic DMARD; negative result of purified protein derivative (PPD) tuberculin skin test, or if there was history of positive PPD, either bacillus Calmette-Guerin immunization or completion of adequate course of chemoprophylaxis for TB; hemoglobin level ≥ 8.5 gm/dl; platelet count ≥ 125,000/mm3; white blood cell count ≥ 3,000/mm3; serum creatinine not more than twice the upper limit of normal.			
EXCLUSION CRITERIA:	NR			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable dose of low-dose corticosteroids (≤ 10 mg / day) or NSAIDS			

Authors: Moreland et al.
Year: 2002

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 3.4 years)

	Placebo	ABA 0.5	ABA 2	ABA 10
Mean age (years):	48.3	46.9	46.2	51.5
Sex (% female):	81	85	72	69
Ethnicity: % White	94	88	94	94
Other germane population qualities:				
• MTX use (%)	72	85	81	75
• Corticosteroids	97	100	91	84
• NSAIDS	84	73	94	84
• Other DMARDS	88	88	78	81
• TJC	32.10	32.87	32.13	29.53
• SJC	24.21	18.78	26.94	23.27
• Pain score	3.55	3.48	3.50	3.47
• Physician global assessment	3.62	3.52	3.50	3.70

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR20 and ACR70 responses at day 85; individual components of the ACR core data set
Secondary Outcome Measures: NR
Timing of assessments: day 15, 29, 43, 57, 71, and 85

RESULTS:

Health Outcome Measures:

- A dose response was noted for the primary outcome.
- ABA was associated with numeric improvements in ACR20 compared to placebo.
- On day 85, 100% improvement in both swollen and tender joints had occurred in 0%, 16%, and 9%, respectively of the patients who had received ABA at 0.5, 2, and 10mg/kg.
- Mean % improvement in TJC at day 85 = 29.3% (placebo) vs. 26.1%, 49.0%, and 54.6% (ABA at 0.5, 2, and 10mg/kg, respectively).
- Mean % improvement in SJC at day 85 = 32.1%(placebo) vs. 15.4%, 41.6%, and 40.7% (ABA at 0.5, 2, and 10mg/kg, respectively).
- Mean % improvement in pain score at day 85 = 4.6% (placebo) vs. 5.1%, 25.6%, and 28.1% (ABA at 0.5, 2, and 10mg/kg, respectively).
- Mean % improvement in function score at day 85 = 5.1% (placebo) vs. 0.7%, 11.8%, and 20.3% (ABA at 0.5, 2, and 10mg/kg, respectively).

Authors: Moreland et al. **Year: 2002**				
ADVERSE EVENTS (%):	**Placebo**	**ABA (all doses)**		
Overall adverse effects reported:	75	81.1		
• Serious adverse events	12.5	4.4		
• Headache	3.1	8.9		
• Nausea and vomiting	6.3	5.6		
• Fatigue	3.1	4.4		
• Arthritis	9.4	4.4		
• Hypotension	6.3	3.3		
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 2			
ADEQUATE RANDOMIZATION:	No			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR; Data safety monitoring board was unblinded			
ATTRITION (*overall*):	**Overall loss to follow-up:** 25% (day 169; 19% at day 85) **Loss to follow-up differential high:** Cannot tell; (combined attrition =22.2% for ABA all doses)			
ATTRITION (*treatment specific*):	**Placebo**	**ABA 0.5**	**ABA 2**	**ABA 10**
Loss to follow-up:	37.5	NR	NR	NR
Withdrawals due to adverse events:	NR	2	2	1
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Navarro-Sarabia**[46] **Year: 2006** **Country:** Multinational
FUNDING:	Cochrane
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 2390
AIMS OF REVIEW:	**Efficacy and safety of ADA in RA**
STUDIES INCLUDED IN META-ANALYSIS:	6 – Furst 2003, Keystone 2004, Rau 2004, Van de Putte 2003, Van de Putte 2004, Weinblatt 2003
TIME PERIOD COVERED:	Up until August 2004
CHARACTERISTICS OF INCLUDED STUDIES:	All controlled clinical trials comparing ADA alone or in combination to placebo or other DMARD
CHARACTERISTICS OF INCLUDED POPULATIONS:	Confirmed active RA

Authors: Navarro-Sarabia **Year: 2006**	
CHARACTERISTICS OF INTERVENTIONS:	ADA 20, 40, and 80 mg every or every other week , alone or in combination versus placebo or DMARD
MAIN RESULTS:	**ADA 40 mg (every other week) + MTX (or DMARD) vs. placebo + MTX (or DMARD). ACR 50/70 response at 24 weeks** (Furst 2003, Weinblatt 2003, Keystone 2004) ACR50 ADA 36.44% control 10.52% RR (95% CI) 3.73 (2.21–6.29) NNT (95% CI) 4.0 (3.0–8.0) ACR70 ADA 18.31% control 3.38% RR (95% CI) 5.14 (3.14–8.41) NNT (95% CI) 7.0 (5.0–13.0) **ADA 40 mg (every other week) vs. placebo ACR 20/50/70 response 24/26 weeks** (van de Putte 2004, Furst) ACR20 ADA 47.05% placebo 23.41% RR 1.91 (95% CI 1.17–3.10) NNT = 5.0 (95% CI 3.0–9.0). ACR50 ADA 23.53% placebo 8.22% RR 2.84 (95% CI 1.58–5.12) NNT = 7.0 (95% CI 4.0–20.0). ACR70 ADA 14.11% placebo 1.89%. RR 7.33 (95% CI 2.25–23.90) NNT = 9.0 (95% CI 3.0–38.0) **ADA 40 mg (every other week) + MTX (or DMARD) vs. placebo + MTX (or DMARD). Components of ACR response** WMD (95% CI) at 24 weeks (Weinblatt 2003, Keystone 2004) Tender joints -6.68 (-9.02 to -4.34) Swollen joints -5.86 (-7.90 to -3.82) Patient pain assessment -15.79 (-20.27 to -11.32) Patient global -17.01 (-21.71 to -12.31) Physician global -19.42 (-27.19 to -11.65) HAQ -0.33 (-0.42 to -0.20) CRP -1.21 (-2.09 to -0.33)
ADVERSE EVENTS:	ADA in combination Serious infections (Furst 2003) ADA 1.53% Control 2.22% RD NS RR (95% CI) 0.69 (0.20-2.42) NNH NA (Keystone 2004) ADA 3.81% Control 0.5% RD (95%CI) 0.03 (0.01-0.05) RR (95% CI) 7.64 (1.02-57.18) NNH 30.2 ADA in monotherapy pooled data ADA 1.98% Placebo 0% RD NS RR NS NNH NA
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Good

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Schiff**[47] **Year: 2008** **Country:** International		
FUNDING:	Bristol-Myers Squibb, Princeton, New Jersey, USA		
RESEARCH OBJECTIVE:	To evaluate the mean change from baseline in Disease Activity Score (based on erythrocyte sedimentation rates; DAS28 (ESR)) for the ABA vs. placebo groups at day 197		
DESIGN:	**Study design:** RCT **Setting:** International, Multi-center **Sample size:** 431		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA** 500-1000mg, days 1, 15, 29, and every 28 days thereafter 365 days (12 months) 156	**Placebo** N/A 197 days (6 months) 110	**INF** 3mg/kg, days 1, 15, 43, 85, and every 56 days thereafter 365 days (12 months) 165
INCLUSION CRITERIA:	(ACR) criteria for RA, age ≥ 18, RA ≥ 1 year, inadequate response to MTX, as demonstrated by ongoing active disease (at randomization SJC >10, TJC >12, and CRP >1 mg/dl. All patients had received MTX >15 mg/week for >3 months prior to randomization (stable for at least 28 days) and washed out all DMARDs (>28 days prior) except for MTX. Anti-TNF-therapy naïve.		
EXCLUSION CRITERIA:	All patients were screened for TB by purified protein derivative (PPD) testing and chest x ray.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids ((10 mg of prednisone or equivalent daily (stable for >25 out of 28 days prior to randomization)), and/or stable NSAIDs (including acetyl salicylic acid, and analgesics not containing aspirin or NSAIDs). No MTX dose adjustments were permitted except in the occurrence of adverse events (AEs). Between days 198–365, dose modification was permitted for MTX ((25 mg weekly) and oral corticosteroids ((10 mg prednisone or equivalent daily); hydroxychloroquine, sulfasalazine, gold, or azathioprine were also permitted. Premedication prior to infusions of study drug was left at the discretion of the investigator (not required by protocol).		

<table>
<tr><td colspan="4">Authors: Schiff
Year: 2008</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>ABA</u></td><td><u>Placebo</u></td><td><u>INF</u></td></tr>
<tr><td>Mean age (years):</td><td>49.0 (12.5)</td><td>49.4 (11.5)</td><td>49.1 (12.0)</td></tr>
<tr><td>Sex (% female):</td><td>83.3%</td><td>87.3%</td><td>82.4%</td></tr>
<tr><td>Ethnicity:</td><td>80.8% caucasian</td><td>76.4% caucasian</td><td>80.6% caucasian</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Tender joint count (SD)</td><td>31.3 (13.9)</td><td>30.3 (11.7)</td><td>31.7 (14.5)</td></tr>
<tr><td>• Swollen joint count (SD)</td><td>21.3 (8.6)</td><td>20.1 (7.0)</td><td>20.3 (8.0)</td></tr>
<tr><td>• Mean disease duration (SD)</td><td>7.9 (8.5)</td><td>8.4 (8.6)</td><td>7.3 (6.2)</td></tr>
<tr><td>• DMARD use (%)</td><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td>• MTX use (%)</td><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>75.6%</td><td>70.0%</td><td>71.5%</td></tr>
<tr><td>• DAS28 (ESR) score</td><td>6.9</td><td>6.8</td><td>6.8</td></tr>
<tr><td>• HAQ-DI score</td><td>1.8 (0.6)</td><td>1.8 (0.7)</td><td>1.7 (0.7)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
reduction in disease activity, measured by DAS28 (ESR), with ABA vs. placebo at 6 months
Secondary Outcome Measures:
Mean reduction in DAS28 (ESR) with INF vs. placebo at 6 months.
6 months & 1 year: ABA vs. INF mean reduction in DAS28 (ESR); DAS28 (ESR) EULAR responses; low disease activity score (LDAS; DAS28 (ESR) ≤ 3.2); DAS28 (ESR)-defined remission (DAS28 (ESR), < 2.6); ACR 20, 50, 70 responses; HAQ-DI response rates (>0.3 improvement from baseline); SF-36: mean changes in PCS, MCS, & 8 subscales.
Tertiary endpoints: comparative safety at 1 year ABA vs. INF.
Timing of assessments: Baseline, 6 months, 1 year</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Primary Health Outcome Measures (6 months):
• reduction in DAS28 (ESR), ABA vs. placebo (–2.53 vs. –1.48, P < 0.001)
• ABA vs. placebo ACR20: 66.7 vs. 41.8%, P < 0.001, ACR50: 40.4 vs. 20.0%, P < 0.001; and ACR70: 20.5 vs. 9.1%, P = 0.019.
• INF vs. placebo ACR20: 59.4 vs. 41.8%, P = 0.006; ACR 50: 37.0 vs. 20.0%, P = 0.004; and ACR70: 24.2 vs. 9.1%, P = 0.002.</td></tr>
</table>

	Health Outcome Measures (head-to-head, day 365): • a greater reduction in DAS28 (ESR) was observed with ABA than with INF –2.88 vs. –2.25; estimate of difference (95% CI) = –0.62 (–0.96, –0.29). **Intermediate (Secondary) Outcome Measures (head-to-head, day 365):** • proportion of patients achieving a good EULAR response (ABA 32.0 vs. INF 18.5%, estimate of difference (95% CI) = 13.5% (3.6, 23.3)), • LDAS (ABA 35.3 vs. INF 22.4%, estimate of difference (95% CI) = 12.9 (2.1, 23.7)), • DAS28 (ESR)-defined remission (ABA 18.7 vs. INF 12.2%, estimate of difference (95% CI) = 18.7 (–2.2, 15.2)) • ACR20 responses were higher with ABA than with INF (ACR20: 72.4 vs. 55.8%, difference of 16.7, 95% CI = 5.5, 27.8). • percentages of ACR50 and 70 responders were numerically higher with ABA vs. INF treatment (with overlapping 95% CIs for the estimate of difference for ACR50: 45.5 vs. 36.4%, estimate of difference (95% CI) = 9.1 (–2.2, 20.5); ACR70: 26.3 vs. 20.6%, estimate of difference (95% CI) = 5.7 (–4.2, 15.6), respectively) • HAQDI responses were maintained in the ABA and INF groups (57.7 and 52.7%, respectively, estimate of difference (95% CI) = 5.0 (–6.5, 16.5)) • greater improvements from baseline in the PCS were observed with ABA vs. INF (difference of 1.93, 95% CI = 0.02, 3.84). Improvements in the MCS (difference of 1.92, 95% CI = –0.30, 4.15) and in all eight subscales were also numerically higher with ABA vs. INF

Authors: Schiff **Year: 2008**			
ADVERSE EVENTS:	**ABA (365 days)**	**Placebo (6 months)**	**INF (365 days)**
Overall adverse effects reported:	89.1%	83.6%	93.3%
• Serious infections	1.9%	4.2%	8.5%
• Serious AEs	9.6%	11.5%	18.2%
• Acute infusional AEs	7.1%	10.0%	24.8%
• Infections and infestations	1.9%	2.7%	8.5%
Significant differences in adverse events:	a higher proportion of patients in the INF group compared with the placebo group reported related SAEs (4.8 vs. 2.7%), discontinued due to AEs (4.8 vs. 0.9%), and discontinued due to SAEs (2.4 vs. 0%). The higher frequency of SAEs in the INF vs. placebo groups was largely due to an increase in serious infections (4.2 vs. 2.7%, respectively)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 11% **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**ABA**	**Placebo**	**INF**
Attrition overall:	10.9%	5.4%	14.5%
Attrition due to adverse events:	2.6%	0.9%	7.3%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: St. Clair et al.**[48] **and Smolen et al.**[49, 50] **Year: 2004 and 2006** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To compare the benefits of initiating treatment with methotrexate and infliximab with those of methotrexate treatment alone in patients with RA of ≤ 3 years duration and to identify disease characteristics which lead to progression of joint damage and the impact of treatment on patient employment status.		
DESIGN:	**Study design:** RCT **Setting:** University hospitals **Sample size:** 1049		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** N/A 54 weeks 298	**MTX-INF 3** 3 mg/kg 54 weeks 373	**MTX-INF 6** 6 mg/kg 54 weeks 378
INCLUSION CRITERIA:	At least 18years old but not older than 75 years, met the 1987 revised criteria of the ACR for the classification of RA, and had persistent synovitis for ≥ 3 months and ≤ 3 years; ≥ 10 swollen joints, and ≥ 12 tender joints; one or more of the following: a positive test result for serum RF, radiographic erosions of the hands or feet, or a serum CRP level of ≥ 2.0 mg/dl		
EXCLUSION CRITERIA:	Prior treatment with MTX; received other DMARDs within 4 weeks of entry; used ETA, INF, ADA or other anti-TNF-α agent; infection with HIV, hepatitis B or C virus; history of active or past TB, CHF, or lymphoma or other malignancy within the past 5 years (excluding excised skin cancers)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids; NSAIDS; 20 mg MTX		

Authors: St Clair et al. and Smolen et al. **Year: 2004 and 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Early RA with moderate to severe disease activity (mean disease duration 0.9 years)		
	MTX	**MTX-INF 3**	**MTX-INF 6**
Mean age (years):	50	51	50
Sex (% female):	75	71	68
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Tender joint count	34	32	33
• SJC	22	21	22
• DMARD naïve (%)	65	71	68
• MTX use (%)	100	100	100
• Glucocortiod use (%)	38	37	39
• HAQ score	1.5	1.5	1.5
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR-N; HAQ, SF-36, vdH-Sharp score; employment rates **Secondary Outcome Measures:** ACR20; ACR50; ACR 70, DAS28, **Timing of assessments:** weeks 0, 2, 4, 6, and every 8 weeks thereafter through week 46		

Authors: St Clair et al. and Smolen et al. **Year: 2004 and 2006**	
RESULTS:	**Health Outcome Measures:** • HAQ scores improved significantly more from weeks 30-54 in the MTX-3mg/kg and MTX-6mg/kg INF groups than in the MTX group: 0.80 and 0.88 vs. 0.68; $P = 0.03$; $P < 0.001$ • From baseline to weeks 54 significantly more patients in the MTX-3mg/kg and MTX-6mg/kg INF groups than in the MTX group improved HAQ by more than 0.22 (minimum level for clinical significance): 76.0% and 75.5% vs. 65.2%; $P = 0.003$; $P = 0.004$ • ACR20/50/70 were significantly higher in the MTX-INF 3mg and 6mg groups than in the MTX group: o ACR20: 62.4% and 66.2% vs. 53.6%; $P = 0.028$; P = 0.001 o ACR50: 45.6% and 50.4% vs. 32.1%; $P < 0.001$; $P < 0.001$ o ACR70: 32.5% and 37.2% vs. 21.2%; $P = 0.002$; $P < 0.001$ • Change (loss) in actual employment between patients receiving MTX plus INF and those receiving MTX plus placebo 0.5% versus 1.3%; $P > 0.5$ (NS). • Proportion of patients whose status changed from employable at baseline to unemployable at week 54 MTX 8% versus MTX + INF 14%; $P = 0.05$. **Intermediate Outcome Measures:** • ACR-N was significantly higher for MTX-INF 3mg/kg and 6 mg/kg vs. MTX: 38.9% and 46.7% vs 26.4%; $P < 0.001$ • ACR20/50/70 were significantly higher in the MTX-INF 3mg and 6mg groups than in the MTX-placebo group: o ACR20: 62.4% and 66.2% vs. 53.6%; $P = 0.028$; $P = 0.001$ o ACR50: 45.6% and 50.4% vs. 32.1%; $P < 0.001$; $P < 0.001$ o ACR70: 32.5% and 37.2% vs. 21.2%; $P = 0.002$; $P < 0.001$ • MTX-INF 3 and 6 mg/kg groups showed significantly less radiographic progression than MTX (mean +/-SD changes in van der Heijde modification of the total Sharp score at week 54: 0.4+/-5.8 and 0.5+/-5.6 versus 3.7+/-9.6 ; $P < 0.001$ • Change in modified Sharp/van der Heijde score from baseline to week 52 MTX-3mg vs. MTX-6mg INF vs MTX group mean ± SD 0.4 ± 5.8, 0.5 ± 5.6 and 3.7 ± 9.6, respectively; $P < 0.001$ for each comparison. • High CRP level, high ESR, or persistent disease activity was associated with greater radiographic progression in the group taking MTX alone, while little radiographic progression was seen in patients receiving both MTX and INF, regardless of the abnormal levels of these traditional predictors.

Authors: St. Clair et al. and Smolen et al. **Year:2004 and 2006**			
ADVERSE EVENTS: **Overall adverse effects reported** • URTIs (%) • Nausea (%) • Sinusitis (%) • Pneumonia (%) • TB (%) • Sepsis (%) • Infusion reaction	**MTX** NR 21 18 8 0.7 0 0 0	**MTX-INF 3** NR 25 20 12 2 0.8 0.5 0.5	**MTX-INF 6** NR 28 17 10 3 0.3 0.3 0.5
Significant differences in adverse events:	• Serious infections were significantly more common in the MTX-3mg and MTX-6mg INF groups than in the MTX group: 5.6% and 5.0% vs. 2.1%; $P = 0.02$; $P = 0.04$		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14.9% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**MTX** 17.8% 3.2%	**MTX-INF 3 mg** 13.4% 9.5%	**MTX-INF 6 mg** 14% 9.6%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Suarez-Almazor**[51] **Year: 2007** **Country:** Multinational
FUNDING:	CATH
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients: IFX (**1,113 IFX, 408 control), **ETN** (869 ETN and 445 controls)
AIMS OF REVIEW:	long-term effectiveness and safety of IFX and ETN for RA
STUDIES INCLUDED IN META-ANALYSIS	IFX: 4 (5 publications) Lipsky 2000 (ATTRACT) Maini 2004 (ATTRACT), St Clair 2004 (ASPIRE), Taylor2004, Quinn 2005 ETN: 2 (4 publications) ERA (Bathon 2000, Kosinski 2002, Genovese 2002), Klareskog 2004 (TEMPO)
TIME PERIOD COVERED:	up until September 2005
CHARACTERISTICS OF INCLUDED STUDIES:	RCTS. Long-term effectiveness : comparator placebo or other therapies, duration of therapy and follow-up ≥1 year
CHARACTERISTICS OF INCLUDED POPULATIONS:	Confirmed active RA

Authors: Suarez-Almazor **Year: 2007**	
CHARACTERISTICS OF INTERVENTIONS:	IFX dose of 3 mg/kg q8wk, 5 mg/kg q8wk, 3 mg/kg q4wk, 10 mg/kg q8wk, 10 mg/kg q4wk, 6 mg/kg q8wk plus MTX vs. MTX ETA and/versus MTX, ETN 25 mg subcutaneous (SC) biw, 10 mg SC biw
MAIN RESULTS:	**IFX 3 mg/kg q8wk+MTX versus MTX (Lipsky 2000, St Clair 2004, Taylor2004, Quinn 2005) ACR50 ACR70 response at 1 year** ACR 50 Relative Benefit (95% CI) 1.52 (1.25, 1.85) NNT 7.1 ACR 70 Relative Benefit (95% CI) 1.63 (1.26, 2.12) NNT 9.1 **IFX 3 mg/kg q4wk+MTX versus MTX Lipsky 2000 ACR50 ACR70 response at 1 year** ACR 50 Relative Benefit (95% CI) 4.24 (1.96, 9.16) NNT 3.8 ACR 70 Relative Benefit (95% CI) 7.67 (1.81, 32.56) NNT 6.7 **IFX 5 to 6 mg/kg q8wk+MTX versus MTX (St Clair 2004, Taylor2004) ACR50 response at 1 year** ACR 50 Relative Benefit (95% CI) 1.59 (1.30, 1.94) NNT 3.2 **IFX 10 mg/kg q8wk+MTX versus MTX Lipsky 2000 ACR50 ACR70 response at 1 year** ACR 50 Relative Benefit (95% CI) 4.91 (2.30, 10.48) NNT 3,2 ACR 70 Relative Benefit (95% CI) 11.13 (2.70, 45.89) NNT 4.3 **IFX 10 mg/kg q4wk+MTX versus MTX Lipsky 2000 ACR50 ACR70 response at 1 year** ACR 50 Relative Benefit (95% CI) 4.81 (2.24, 10.32) NNT 3,3 ACR 70 Relative Benefit (95% CI) 8.15 (1.92, 34.54) NNT 6,2 **IFX 3 mg/kg q8wk+MTX versus MTX Maini 2004 Quinn 2005 ACR50 ACR70 response at 2 years** ACR 50 Relative Benefit (95% CI) 1.97 (0.94, 4.13) NNT 6.2 ACR 70 Relative Benefit (95% CI) 1.43 (0.61, 3.37) NNT 16.7 **IFX 3 mg/kg q4wk+MTX versus MTX Maini 2004 ACR50 ACR70 response at 2 years** ACR 50 Relative Benefit (95% CI) 4.18 (1.04, 16.82) NNT 4.3 ACR 70 Relative Benefit (95% CI) 5.89 (0.81, 43.09)NNT 5.9 **IFX 10 mg/kg q8wk+MTX versus MTX Maini 2004 ACR50 ACR70 response at 2 years**

	ACR 50 Relative Benefit (95% CI) 5.03 (1.27, 19.90) NNT 3,4 ACR 70 Relative Benefit (95% CI) 5.69 (0.78, 41.39) NNT 5,9 **IFX 10 mg/kg q4wk+MTX versus MTX Maini 2004 ACR50 ACR70 response at 2 years** ACR 50 Relative Benefit (95% CI) 2.80 (0.67, 11.77) NNT 7.7 ACR 70 Relative Benefit (95% CI) 3.05 (0.39, 24.15) NNT 14.3 **IFX 3 mg/kg q8wk+MTX versus MTX St Clair 2004 Quinn 2005) DAS28 responses at 54 weeks** Mean change from baseline WMD (random) −1.26 (−2.82, 0.31), SMD (random) −1.19 (−3.14, 0.76) **IFX 5mg/kg to 6 mg/kg q8wk+MTX versus MTX St Clair 2004 Taylor2004 DAS28 responses at 54 weeks** Mean change from baseline WMD (random) −1.37 (−2.43, −0.30), SMD (random) −1.03 (−2.25, 0.18) **IFX 3 mg/kg q8wk+MTX versus MTX (Lipsky 2000, St Clair 2004 Quinn 2005) functional status (HAQ and SF-36) at 1 year** HAQ Mean change from baseline WMD (fixed) 0.13 (0.05, 0.22) SMD (fixed) 0.21 (0.08, 0.35) SF-36 Mean change from baseline WMD (fixed) 1.77 (0.19, 3.36) SMD (fixed) 0.15 (0.02, 0.29) **IFX 3 mg/kg q8wk+MTX versus MTX (Maini 2004 Quinn 2005) functional status (HAQ) at 2 years** HAQ Mean change from baseline WMD (fixed) 0.32 (0.15, 0.50)SMD (fixed) 0.53 (0.25, 0.82) **IFX 3 mg/kg q8wk+MTX versus MTX radiological outcomes at 1 year Lipsky 2000 St Clair 2004** Total Score Mean change from baseline WMD −3.69 (−4.85, −2.53) Erosion Mean change from baseline WMD −2.93 (−3.85, −2.00) Joint Space Narrowing Mean change from baseline WMD −0.55 (−0.84, −0.26) Other Radiological outcome RR 0.32 (0.20, 0.53) **IFX 5 mg/kg to 6 mg/kg q8wk + MTX versus MTX radiological outcomes at 1 year St Clair 2004 Taylor2004** Total Score Mean change from baseline WMD -3.44 (-4.67, -2.20) **ETN 10 mg biw versus MTX ACR50 ACR70 response (Bathon 2000) at 1 year** ACR 50 Relative Benefit (95% CI) 0.75 (0.58, 0.97) NNT [9.1] favours MTX ACR 70 Relative Benefit (95% CI 0.72 (0.48, 1.07) NNT [16.7] beneficial effect of ETN **ETN 25 mg biw 20.0 versus MTX ACR50 ACR70 response (Bathon 2000 Klareskog 2004) at 1 year** ACR 50 Relative Benefit NNT ACR 70 Relative Benefit 1.13 (0.97, 1.30) NNT 20.0 ACR 70 Relative Benefit NNT ACR 70 Relative Benefit) 1.21 (0.94, 1.54) NNT 25.0

	ETN 25 mg biw versus MTX HAQ at 1 year (Kosinski 2002, Klareskog 2004) Mean change from baseline POOLED WMD (fixed) −0.03 (−0.04, −0.02)* POOLED WMD (random) 0.02 (−0.11, 0.14) POOLED SMD (fixed) -0.21 (−0.35, −0.08)* POOLED WMD (random) −0.23 (−0.95, 0.48) **25 mg biw versus MTX radiological outcomes (Bathon 2000 Klareskog 2004) at 1 year** Total Score Mean change from baseline POOLED WMD −1.78 (−3.32, −0.25)* POOLED SMD −0.14 (−0.27, 0.00) Erosion Mean change from baseline POOLED WMD −1.20 (−2.15, −0.25)* POOLED SMD −0.15 (−0.29, −0.02)* Joint Space Narrowing Mean change from baseline POOLED WMD −0.67 (−1.38, 0.05) POOLED SMD −0.11 (−0.25, 0.02) **ETN 25 mg biw drug discontinuations (Bathon 2000 Klareskog 2004) POOLED** All RR (versus control MTX) 0.76 (0.59, 0.97)* Lack of efficacy RR (versus control MTX) 0.92 (0.55, 1.54) Toxicity RR (versus control MTX) 0.66 (0.45, 0.99)* Others RR (versus control MTX) 0.78(0.46, 1.34)
ADVERSE EVENTS:	IFX at 1 year: **Serious AE** 1.03 (0.72, 1.46) IFX 3 mg/kg q8wk (Lipsky 2000 St Clair 2004) **Serious infusion reactions** 3.91 (0.19, 81.22) IFX 3 mg/kg q8wk (Lipsky 2000 St Clair 2004) **Non-serious infusion reactions** 3.09 (1.95, 4.90) IFX 3 mg/kg q8wk (St Clair 2004 Quinn 2005) **Serious infections** 1.48 (0.74,2.93) IFX 3 mg/kg q8wk (Lipsky 2000 St Clair 2004) at 2 years: **Serious AE IFX 3 mg/kg q8wk** 29/88 (33%) **3 mg/kg q4wk** 20/86 (23%) **10 mg/kg q8wk** 25/87 (29%) **10 mg/kg q4wk** 26/81 (32%) **MTX** 28/86 (33%) Maini 2004 **Serious infections IFX 3 mg/kg q8wk** 10/88 (11%) **3 mg/kg q4wk** 11/86 (13%) **10 mg/kg q8wk** 11/87 (13%) **10 mg/kg q4wk** 8/81(10%) **MTX** 11/86 (13%) Maini 2004

	Serious infusion reactions IFX 3 mg/kg q8wk 0/88 3 mg/kg q4wk 1/86 (1%) 10 mg/kg q8wk 0/87 10 mg/kg q4wk 0/81 MTX 0/88 Maini 2004 **Death** IFX 3 mg/kg q8wk 3/88 (3%) 3 mg/kg q4wk 2/86 (2%) 10 mg/kg q8wk 1/87 (1%) 10 mg/kg q4wk 1/81 (1%) MTX 4/86 (5%) Maini 2004 **Malignancies** IFX 3 mg/kg q8wk 1/88 (1%) 10/88 3 mg/kg q4wk 0/86 10 mg/kg q8wk 3/87 (3%) 10 mg/kg q4wk 5/81 (6%) MTX 1/86 (1%) Maini 2004
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Good

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: van de Putte et al.**[52] **Year: 2003** **Country:** Multinational (Europe)			
FUNDING:	Abbott Laboratories			
RESEARCH OBJECTIVE:	To evaluate efficacy, dose response, safety, and tolerability of adalimumab in DMARD refractory patients with longstanding, active RA			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (25 sites) **Sample size:** 284			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 20 mg 12 weeks 72	**ADA** 40 mg 12 weeks 70	**ADA** 80 mg 12 weeks 72	**Placebo** N/A 12 weeks 70
INCLUSION CRITERIA:	Patients 18 years of age or older; a diagnosis of RA according to the revised 1987 American College of Rheumatology (ACR) criteria and active inflammatory synovitis, defined by a TJC of ≥ 12 and SJC of ≥10 based on an examination of 68 and 66 assessed joints, respectively; either an erythrocyte sedimentation rate (ESR) of ≥28 mm/1st h or a serum CRP level ≥20 mg/l; patients for whom treatment had failed with at least one traditional DMARD were eligible.			
EXCLUSION CRITERIA:	Joint surgery within two months before screening or an episode of infection requiring admission to hospital within 30 days before study entry; treatment with either intra-articular or intramuscular corticosteroids within four weeks of prescreening or an investigational chemical or biological drug within two or six months, respectively, of prescreening; patients with impaired renal or hepatic function or an abnormal serum profile; patients' body weight could not exceed 100 kg; women of childbearing potential required a negative pregnancy test; the use of a reliable contraceptive method was mandatory.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs; oral corticosteroids; propoxyphene; codeine; acetaminophen plus codeine; and aspirin			

Authors: van de Putte et al. **Year: 2003**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Severe			
	ADA 20	**ADA 40**	**ADA 80**	**Placebo**
Mean age (years):	53.7	52.6	53.2	50.2
Sex (% female):	85	81	69	81
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• TJC	31.7	31.0	32.5	30.9
• SJC	19.64	18.7	19.3	20.2
• Corticosteroids use (%)	76	70	75	77
• HAQ score (Disability Index)	1.79	1.74	1.66	1.63
• DAS score	7.0	7.1	7.0	7.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 **Secondary Outcome Measures:** ACR50; ACR70; TJC; SJC; DAS28; disability index of the HAQ. **Timing of assessments:** 2 and 12 weeks			

Authors: van de Putte et al. **Year: 2003**	
RESULTS:	**Health Outcome Measures: Week 12** • The ADA treatment groups all had significantly better ACR50 than placebo. ADA20 vs. Placebo 17 (23.9%) vs. 1 (1.4%) ($P \leq 0.001$) ADA40 vs. Placebo 19 (27.1%) vs. 1 (1.4%) ($P \leq 0.001$) ADA80 vs. Placebo 14 (19.4 %) vs. 1 (1.4%) ($P \leq 0.001$) • The ADA treatment groups all had significantly better ACR70 than placebo. ADA20 vs. Placebo 8 (11.3%) vs. 0 (0%) ($P \leq 0.05$) ADA40 vs. Placebo 7 (10.0%) vs. 0 (0%) ($P \leq 0.05$) ADA80 vs. Placebo 6 (8.3 %) vs. 0 (0%) ($P \leq 0.05$) • All ADA treatment groups improved significantly for both TJC and SJC. TJC changes from baseline ADA20 vs. Placebo -14 (44.2%) vs. -5.1 ($P \leq 0.001$) ADA40 vs. Placebo -15.3 (49.4%) vs. -5.1 ($P \leq 0.001$) ADA80 vs. Placebo -15.2 (46.8%) vs. -5.1 ($P \leq 0.001$) SJC changes from baseline ADA20 vs. Placebo -8.1 (41.3%) vs. -2.8 (13.9%) ($P \leq 0.001$) ADA40 vs. Placebo -9.6 (51.3%) vs. -2.8 (13.9%) ($P \leq 0.001$) ADA80 vs. Placebo -10.7 (54.6%) vs. -2.8 (13.9%) ($P \leq 0.001$) • All ADA treatment groups improved significantly on the HAQ Disability Index. ADA20 vs. Placebo 0.45 vs. 0.04 ($P \leq 0.001$) ADA40 vs. Placebo 0.47 vs. 0.04) ($P \leq 0.001$) ADA80 vs. Placebo 0.48 vs. 0.04 ($P \leq 0.001$) • All ADA treatment groups improved significantly on the DAS28. ADA20 vs. Placebo -1.8 vs. -0.5 ($P \leq 0.001$) ADA40 vs. Placebo -2.1 vs. -0.5 ($P \leq 0.001$) ADA80 vs. Placebo -2.0 vs. -0.5 ($P \leq 0.001$) **Intermediate Outcomes** • The ADA treatment groups all had significantly better ACR20, than placebo. ADA20 vs. Placebo 36 (50.7%) vs. 7 (10%) ($P \leq 0.001$) ADA40 vs. Placebo 40 (57.1%) vs. 7 (10%) ($P \leq 0.001$) ADA80 vs. Placebo 39 (54.2 %) vs. 7 (10%) ($P \leq 0.001$)

Authors: van de Putte **Year: 2003**				
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious AE • Serious or intractable AE • Serious infections • ISRs • Hyperlipidamea	**ADA 20** NR 3 11 0 29 25	**ADA 40** NR 7 16 3 23 31	**ADA 80** NR 13 19 3 29 31	**Placebo** NR 10 27 0 6 19
Significant differences in adverse events:	Yes In all doses vs. placebo- Severe or intractable AE 15 vs.27 ($P \leq 0.05$) ISRs 27 vs. 6 ($P \leq 0.01$) Proteinuria 7 vs. 0 ($P \leq 0.05$)			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** yes-one with Felty Syndrome			
ADEQUATE RANDOMIZATION:	**Yes**			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** 18% **Loss to follow-up differential high:** No **ADA 20** 6 0	 **ADA 40** 4 4	 **ADA 80** 1 3	 **Placebo** 1 1
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: van de Putte et al.**[53] **Year: 2004** **Country:** Multinational (3)				
FUNDING:	Abbott				
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of monotherapy with adalimumab in patients with RA for whom previous DMARD treatment failed				
DESIGN:	**Study design:** RCT **Setting:** Multicenter (52) **Sample size:** 544				
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 26 weeks 110	**ADA** 20 mg biweekly (BW) 26 weeks 106	**ADA** 20 mg week (W) 26 weeks 112	**ADA** 40 mg week 26 weeks 113	**ADA** 40 mg biweekly 26 weeks 103
INCLUSION CRITERIA:	18 years or older who met criteria for RA established by ACR; treatment with at least one DMARD had previously failed; had active disease defined as ≥12 tender joints based on a 68 joint assessment, ≥10 swollen joints based on a 66 joint evaluation, and either an ESR ≥28 mm/1st hr or a serum CRP concentration ≥20 mg/l; negative pregnancy test and the use of a reliable contraceptive method were mandatory in women of childbearing potential				
EXCLUSION CRITERIA:	Joint surgery within 2 months before screening or infection requiring admission to hospital or treatment with intravenous antibiotics within 1 month before screening; intra-articular or intramuscular corticosteriod within 1 month before the study or an investigational small molecule drug or biological agent within 2 months or 6 months before screening; patients with impaired renal or hepatic function or a history of TB as shown by radiographic				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Propoxyphene, aspirin, codeine				

Authors: van de Putte et al. **Year: 2004**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Severe				
	Placebo	**ADA20BW**	**ADA20W**	**ADA40W**	**ADA 40BW**
Mean age (years):	53.5	53.1	54.4	52.7	51.8
Sex (% female):	77.3	79.2	72.3	79.6	78.6
Ethnicity:	NR	NR	NR	NR	NR
Other germane population qualities:					
• TJC	35.5	33.9	35.3	33.7	33.8
• SJC	19.8	19.6	19.8	20.5	19.3
• DMARD use	0	0	0	0	0
• MTX treatment failure (%)	86.4	88.7	93.8	92.9	87.4
• Corticosteroids use (%)	74	76	77	84	74
• DAS score	7.09	7.08	7.09	7.02	7.09
• HAQ score	1.88	1.88	1.88	1.83	1.84
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 response **Secondary Outcome Measures:** ACR50 and ACR70 response rates, improvements in ACR core components, HAQ-DI, DAS 28, EULAR response **Timing of assessments:** Baseline, biweekly during the first month, monthly thereafter, and at week 26				
RESULTS:	**Health Outcome Measures at 26 weeks (only observed values reported) :** • Patients treated with ADA 20 mg biweekly, 20 mg per week, 40 mg/wk , 40 mg biweekly achieved better improvement in mean HAQ-DI vs. those receiving placebo (-0.29, -0.39, -0.38, -.049 vs. –0.07; $P \leq 0.01$) • ACR70 response rates for ADA 40 mg biweekly were significantly better at all evaluation points and for ADA 40 mg weekly at most evaluation points compared with placebo ($P \leq 0.05$) • No significant difference in good EULAR responders between ADA regimens and placebo except for ADA 40 mg weekly (13.6% vs. 3.6%; $P < 0.01$) **Intermediate Outcome Measures at 26 weeks (only observed values reported):** • ACR20 response rates were 35.8%, 39.3%, 46.0%, and 53.4% with ADA 20 mg biweekly, 20 mg per week, 40 mg biweekly, 40 mg per week versus 19.1% with placebo ($P \leq 0.01$) • Significantly more moderate EULAR responders for ADA groups than for placebo group ($P < 0.001$)				

Authors: van de Putte et al. **Year:2004**					
ADVERSE EVENTS: **Overall adverse effects reported [%]:**	**Placebo** NR	**ADA20BW** NR	**ADA20W** NR	**ADA40W** NR	**ADA40BW** NR
• Clinical flare reaction	21.8	23.6	19.6	15.9	15.5
• Rhinitis	10.9	10.4	18.8	18.6	21.4
• Headache	10.0	20.8	17.9	21.2	20.4
• Rash	5.5	14.2	16.1	20.4	11.7
• ISR	0.9	4.7	11.6	9.7	16.5
• Sore throat	6.4	13.2	3.6	9.7	4.9
• Gastrointestinal pain	4.5	12.3	4.5	6.2	6.0
• Pruritus	0.9	10.4	7.1	11.5	8.7
Significant differences in adverse events:	• Placebo vs. all ADA : Headache (20% vs. 10%), rash (15.7% vs. 5.5%), ISRs (10.6% vs. 0.9%), and pruritus (9.4% vs. 0.9%) occurred significantly more often in ADA patients (all $P < 0.05$).				
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Yes [8]				
ADEQUATE RANDOMIZATION:	Yes				
ADEQUATE ALLOCATION CONCEALMENT:	Yes				
BLINDING OF OUTCOME ASSESSORS:	Yes				
ATTRITION (*overall*):	**Overall loss to follow-up:** 33% **Loss to follow-up differential high:** yes				
ATTRITION (*treatment specific*):	**Placebo**			**Adalimumab**	
Loss to follow-up:	56.4%			27.2%	
Withdrawals due to adverse events:	0.9%			3.7%	
QUALITY RATING:	**Fair**				

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Weaver et al.**[54] **Year: 2006** **Country:** US				
FUNDING:	Immunex Corporation				
RESEARCH OBJECTIVE:	To evaluate the effectiveness of select biologics, methotrexate, and DMARDs in the management of adult RA in routine clinical practice.				
DESIGN:	**Study design:** Prospective observational **Setting:** 509 rheumatology practices **Sample size:** 5397 (includes 762 patients whose treatment strategies were not of interest to this review)				
INTERVENTION: **Dose (median wkly at baseline):** **Duration:** **Sample size:**	**MTX** 10 mg 12 months 941	**ETA** 50 mg 12 months 1251	**INF** 3.8 mg/kg every 8 wks 12 months 120	**ETA+MTX** 50 mg+15 mg 12 months 1783	**INF+MTX** 3.8mg/kg every 8 wks+15mg 12 months 540
INCLUSION CRITERIA:	Patients requiring a change in their existing RA treatment: ≥ 18 years; met ACR criteria for RA.				
EXCLUSION CRITERIA:	Active infection; pregnancy; concurrent enrollment in a clinical trial				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes				

Authors: Weaver et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: No
Disease severity: Mild-moderate-severe

	MTX	ETA	INF	ETA+MTX	INF+MTX
Mean age (years):	56.8	53.2	60.2	52.6	58.5
Sex (% female):	75	75	71	79	77
Ethnicity:	77	81	78	81	81
Other germane population qualities:					
• TJC	13.0	13.4	10.6	13.3	13.9
• SJC	11.3	11.1	14.8	11.5	12.0
• Mean disease duration	3.5	9.2	10.6	7.7	9.5
• DMARD naive (%)	75	65	15	4	4
• Corticosteroids use (%)	NR	NR	NR	NR	NR
• DAS score	N/A	N/A	N/A	N/A	N/A
• HAQ score	1.3	1.4	1.5	1.3	1.4

OUTCOME ASSESSMENT:

Primary Outcome Measures: Modified ACR 20 (doesn't include ESR or CRP)
Secondary Outcome Measures: HAQ, patient global and pain assessments, physician global assessment and 28-count swollen and tender joints
Timing of assessments: 12 months (± 1 month)

RESULTS:

Health Outcome Measures:

- Unadjusted mACR20 ETA+MTX 43% ETA 41% INF+MTX 35% INF 26% MTX 37%
- After adjusting for baseline covariates, ETA + MTX vs MTX OR 1.29, 95% CI 1.09-1.52; $P < 0.01$
- ETA vs. MTX OR 1.23, 95% CI 1.02-1.47; $P < 0.05$
- Significant differences were not observed between patients receiving MTX vs. INF + MTX (OR 0.96 CI 0.76-1.21 $P = 0.72$) or INF monotherapy (OR 0.66 95% CI 0.43-1.02 $P = 0.06$)
- Percent improvement on HAQ (vs MTX) MTX 7% (N/A) ETA 17% ($P < 0.001$) INF 1% (P =NS)ETA+MTX 17% ($P < 0.0001$) INF+MTX 3% (P = NS)

Authors: Weaver et al. **Year: 2006**					
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**MTX** NR	**ETA**	**INF**	**ETA+MTX**	**INF+MTX**
Significant differences in adverse events:	NR				
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A				
ARE GROUPS COMPARABLE AT BASELINE:	No				
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes				
STATISTICAL ANALYIS ADEQUATE:	Yes				
ATTRITION (*overall*):	**Overall loss to follow-up:** No **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*):	**MTX**	**ETA**	**INF**	**ETA+MTX**	**INF+MTX**
Loss to follow-up:	23%	31%	33%	39%	29%
Withdrawals due to adverse events:	4%	6%	11%	8%	9%
QUALITY RATING:	**Fair**				

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Weinblatt et al.**[55, 56] **Year: 2003 and 2006** **Country:** US and Canada			
FUNDING:	Abbott Labs and Knoll Pharmaceuticals			
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of adalimumab administered subcutaneously every other week to patients with active RA despite long term therapy with methotrexate and long-term safety and efficacy in a 4 year extended study.			
DESIGN:	**Study design:** RCT and open label extension **Setting:** Multicenter (35 sites) **Sample size:** 271 (262 in extension)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 20 mg every 2 weeks 24 weeks 69	**ADA** 40 mg every 2 weeks 24 weeks 67	**ADA** 80 mg every 2 weeks 24 weeks 73	**Placebo** N/A 24 weeks 62
INCLUSION CRITERIA:	18 years of age or older; Active RA as defined by 9 tender joints and 6 swollen joints according to ACR; treated with MTX for at least 6 months at a weekly dosage of 12.5-25 mg or 10 mg (if intolerant to higher doses) for at least 4 weeks before entering the study; must have failed treatment with at least 1 DMARD besides MTX, but no more than 4 DMARD's			
EXCLUSION CRITERIA:	Standard exclusion criteria used in trials of other biologics in patients with RA; previous treatment with anti-CD4 therapy or TNFα antagonists; history of active listeriosis or mycobacterial infection; major episode of infection requiring hospitalization; treatment with intravenous antibiotics within 30 days: oral antibiotics within 14days prior to screening			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with MTX, salicylates, NSAIDS, and corticosteroids			

Authors: Weinblatt et al. **Year: 2003 and 2006**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate				
		Placebo	**ADA20**	**ADA40**	**ADA80**
Mean age (years):		56	53.5	57.2	55.5
Sex (% female):		82.3	75.4	74.6	75.3
Ethnicity:		NR	NR	NR	NR
Other germane population qualities:					
• TJC		28.7	28.5	28.0	30.3
• SJC		16.9	17.6	17.3	17.0
• Previous # DMARDs used, mean		3.0	3.0	2.9	3.1
• MTX use dosage, mg/week		16.5	16.9	16.4	17.2
• Corticosteroids use (%)		NR	NR	NR	NR
• DAS score		58.9	60.5	58.7	62.6
• HAQ score		1.64	1.52	1.55	1.55

Authors: Weinblatt et al. **Year: 2003 and 2006**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20; And improvements in TJC, SJC, patients assessment of pain, patients global assessment of disease activity, physicians global assessment of disease activity, HAQ and serum levels of CRP. **Secondary Outcome Measures:** ACR50; ACR70; SF36 score and FACIT **Timing of assessments:** Efficacy: baseline, weekly during the first month, every other week during the second month, and monthly thereafter. Antibody assessments: baseline and weeks 4, 12, and 24
RESULTS:	**Health Outcome Measures:** • ACR50 response rates with the 20, 40, 80 mg ADA dosages (31.9%, 55.2%, 42.5%) were significantly greater than that with placebo (8.1%) ($P = 0.003$, $P < 0.001$, and $P < 0.001$) • 40 and 80 mg doses of ADA were associated with an ACR70 response (26.9%, 19.2%) that was statistically significantly greater than with placebo (4.8%) ($P < 0.001$ and $P = 0.020$) • SF-36 scores at 24 weeks compared with baseline: o ADA: statistically significant increases ($P \leq 0.05$) were achieved on 7 of 8 domains, 8 of 8 domains, and 8 of 8 domains by patients receiving 20 mg, 40 mg, and 80 mg, respectively. o Placebo: statistically significant increases ($P \leq 0.05$) were achieved on only 4 of 8 domains. o After 24 weeks, all ADA treatment groups achieved a minimum clinically important mean increase over baseline (≥10 points) in 6 of 8 domains. In contrast, placebo treated patients achieved a minimally clinically important response in only 2 of 8 domains. • FACIT fatigue scale scores at 24 weeks compared with baseline: o Statistically significant improvements over baseline were observed for the ADA 40mg (8.5 points) and 80 mg (9.5 points) groups versus placebo (3.0 points) ($P = 0.001$ and $P < 0.001$) At 4 year open label extension • 147 patients completers ACR 20/50/70, 78%, 57%, and 31%; clinical remission (DAS28 <2.6) 43%; no physical function abnormalities (HAQ = 0) 22% • Serious infection rates 24 weeks vs. 4 years, 2.03 vs. 2.3 per 100 patient years **Intermediate Outcome Measures:** • ACR20 response at week 24 was achieved by a significantly greater proportion of patients in the 20, 40, 60 mg ADA plus MTX groups (47.8%, 67.2%, 65.8%) than in the placebo plus MTX group (14.5%) ($P < 0.001$)

Authors: Weinblatt et al., **Year: 2003**				
ADVERSE EVENTS:	**ADA20**	**ADA40**	**ADA80**	**Placebo**
Overall adverse effects reported (%):	NR	NR	NR	NR
• Nausea	18.8	4.5	9.6	6.5
• Injection site pain	8.7	10.4	11.0	3.2
• ISR	4.3	1.5	11.0	0
• Dizziness	11.6	3.0	1.4	1.6
Significant differences in adverse events:	• ISRs occurred more frequently in the ADA 80 mg group compared with placebo ($P \leq 0.05$) • Dizziness and nausea occurred more frequently in the ADA 20 mg group (11.6% and 18.8%) compared with placebo (1.6% and 6.5%) ($P \leq 0.05$)			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes			
ADEQUATE RANDOMIZATION:	Yes (block size 8, stratified by center)			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall loss to follow-up:** 110/271 (40.6%) at 4 years LTF was 36% **Loss to follow-up differential high:** Yes			
ATTRITION (*treatment specific*):	**ADA**	**4 yr extension**	**Placebo**	***loss to follow was NR in treatment specific fashion only as overall
Loss to follow-up:	NR	36	NR	
Withdrawals due to adverse events:	2	8	5	
Withdrawals due to lack of efficacy	23,27,27	12	35	
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Weinblatt et al.**[57] **Year: 2007** **Country:** Multicenter US		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	Efficacy and safety of ABA in combination with ETA in active RA		
DESIGN:	**Study design:** RCT with an open-label long-term extension (LTE) phase **Setting:** Multicenter (40 centers in the US) **Sample size:** 121(2:1 ratio), LTE 80		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA + ETN 25 mg twice wkly** 2 mg/kg intravenously on days 1, 15, 30, every 4 weeks 6 months 85	**Placebo + ETN 25 mg twice wkly** 6 months 36	LTE **ETN 25 mg twice wkly+abatacept 10 mg/kg** 80
INCLUSION CRITERIA:	>18 years of age and met the criteria of the American College of Rheumatology (ACR) for RA, functional class I, II or III. Patients must have received ETA 25 mg twice weekly for >3 months, >8 swollen joints (66-joint count) and >10 tender joints (68-joint count).		
EXCLUSION CRITERIA:	Active or latent infection, recent opportunist infection, TB requiring treatment within the previous 3 years, history of cancer within the previous 5 years or history of drug or alcohol misuse. Pregnant and nursing women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low-dose corticosteroids (≤10 mg/day) or NSAIDs stable during the study (6mo). hydroxychloroquine, sulfasalazine, leflunomide or MTX was allowed after 6 months (LTE)		

Authors: Weinblatt et al. **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** active RA		
	ABA	**Placebo**	
Mean age (years):	49.8 (23–73) 1	54.3 (28–71)	
Sex (% female):	78	72	
Ethnicity/Caucasian%:	94	100	
Other germane population qualities:			
• Tender joint count	28.7 (14)	29.2 (13.2)	
• Swollen joint count	19.6 (9.4)	20.1 (10.5)	
Mean disease duration years	13 (10.1)	12.8 (8.6)	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** of the double-blind phase: modified ACR20 response rate at 6 months. of the of the LTE: safety and tolerability of abatacept in combination with ETA during long-term administration **Secondary Outcome Measures:** double-blind phase: modified ACR 50 response at 6 months **Timing of assessments: RCT** at 6 mo, LTE at 1 year		
RESULTS:	**Health Outcome Measures:** ABA 2 mg/ kg and ETA vs. placebo and ETA at 6 mo ACR 20 48.2% vs. 30.6%; *P* = 0.072 ACR 50 25.9% vs. 19.4% *P* = 0.448 ACR 70 10.6% vs. 0% *P* = 0.042 ABA 2 mg/ kg and ETA vs. placebo and ETA at 1 year ACR 20 48.2% vs. 30.6% ACR 50 28.2% vs. 16.7% ACR 70 9.4% vs. 5.6% *P* = 0.481 Modified HAQ response Change (from baseline to 1 year) abatacept 2 mg/ kg and ETA vs. placebo and ETA - 0.3 (0.5) vs - 0.2 (0.4)		

Authors: Weinblatt et al. **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • URTI • Serious infections • Discontinuations due to AEs • Deaths	**ABA** 79 (92.9) 20 (23.5) 3 (3.5) 10 (11.8) 0	**Placebo** 32 (88.9) 5 (13.9) 0 1 (2.8) 0	**LTE** 78 (97.5) 23 (28.8) 1 (1.3) 8 (10) 1 (1.3)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1 pt.		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 34 **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ABA** 20 6	**Placebo** 14 1	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Westhovens et al.**[58] **Year: 2006** **Country:** Multinational		
FUNDING:	Centocor Research and Development, Inc		
RESEARCH OBJECTIVE:	To assess the risk of serious infections following 22 weeks of infliximab therapy		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1084		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo + MTX** N/A 22 weeks 363	**INF 3 + MTX** 3 mg/kg wks 0,2,6,14 22 weeks 360	**INF 10 + MTX** 10 mg/kg wks 0,2,6,14 22 weeks 361
INCLUSION CRITERIA:	Diagnosis of RA according to the ACR: had active disease despite receiving MTX; patients may or may not have been treated with other concomitant DMARDs.		
EXCLUSION CRITERIA:	opportunistic infections; serious infections during the 2 months prior to screening; known HIV, active, latent or history of TB with inadequate documentation of treatment; an inability to receive prophylaxis with isoniazid; history of lymphoproliferative disease or malignancy; CHF.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Chloroquine, azathioprine, penicillamine, oral or intramuscular gold, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, oral corticosteroids, or NSAIDs		

Authors: Westhovens et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes - except for median disease duration but not statistically significant ($P = 0.083$) **Disease severity:** Moderate-severe		
	Placebo + MTX	**INF 3 + MTX**	**INF 10 + MTX**
Mean age (years):	52.0	53.0	52.0
Sex (% female):	83.2	80.0	77.8
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• TJC	22	22	22
• SJC	15	15	15
• Median disease duration	8.4	7.8	6.3
• DMARD use (%)	100	100	100
• MTX use (%)	100	100	100
• Corticosteroids use (%)	59.2	59.2	59.0
• DAS score	NR	NR	NR
• HAQ score	1.5	1.5	1.5
• Concomitant conditions predisposing to infection, no. (%)	29 (8.0)	29 (8.1)	20 (5.5)
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Rate of serious infections **Secondary Outcome Measures:** ACR 20/50/70; DAS28 **Timing of assessments:** Weeks 0,2,6,14,22		
RESULTS:	**Health Outcome Measures:** Week 22 • ACR20 INF3 58% INF10 61% MTX 26% • ACR50 INF3 32.1% INF10 35.4% MTX 9.7% • ACR70 INF3 14.0% INF10 16.1% MTX 4.7% • DAS28 response (mean) INF3 3.5 INF10 3.3 MTX 4.4 • All INF 3 or INF 10 vs. MTX had a statistical significance of $P < 0.001$		

Authors: Westhovens **Year: 2006**			
ADVERSE EVENTS (%):	**Placebo + MTX**	**INF 3 + MTX**	**INF 10 + MTX**
Overall adverse effects reported:	66.2	69.7	72.3
• Serious infections	1.7	1.7	5.0
• Pneumonia	0	0.8	1.1
• Serious AEs	7.5	7.8	7.5
• Rash	1.7	4.7	4.4
Significant differences in adverse events:	Rate of serious infections was significantly higher in the 10mg/kg group compared to placebo: RR: 3.1 95% CI 1.2 – 7.9 No significant differences in serious infections in the 3 mg/kg group: RR 1.0 95% CI 0.3 – 3.1		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 18 from efficacy analysis		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7.6 % **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo + MTX**	**INF 3 + MTX**	**INF 10 + MTX**
Loss to follow-up:	6.3	7.2	8.9
Withdrawals due to adverse events:	2.2	5.0	5.5
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Zhang et al.**[59] **Year: 2006** **Country:** China	
FUNDING:	Not reported	
RESEARCH OBJECTIVE:	Examine the safety and, side-effect profile and efficacy of INF plus MTX combination therapy in Chinese patients with RA	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 173	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 3mg/kg 14 weeks 87	**Placebo** NR 14 weeks 86
INCLUSION CRITERIA:	Diagnosis of RA by ACR criteria, and active disease at screening despite treatment with MTX for ≥3 months at a stable dose (7.5–20 mg/week) for at least 4 weeks.	
EXCLUSION CRITERIA:	Positive tuberculin skin test (induration = 15 mm); hepatitis; acquired immunodeficiency syndrome; tumour, infections, congestive heart failure; commencement of other DMARDs within 4 weeks prior to screening; treatment with thalidomide or other TNF antagonists within 3 months of entry to study; glucocorticosteroid exceeding 10 mg/day of prednisone or equivalent.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX, Other DMARD's commenced > 4 weeks prior to screening, glucocorticosteroids < 10mg day	

Authors: Zhang et al. **Year: 2006**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Not specified			
	INF	**Placebo**		
Mean age (years):	47.9 ± 10.1	48.9 ± 8.0		
Sex (% female):	85.1	84.9		
Ethnicity:	Chinese	Chinese		
Other germane population qualities:				
• Tender joint count	NR	NR		
• Swollen joint count	NR	NR		
• Mean disease duration (mts)	85.6 ± 74	96 ± 74.6		
• Drugs other than MTX used (%)	55.2	64%		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20,50,70 **Secondary Outcome Measures:** HAQ, ESR, duration of morning stiffness, adverse events **Timing of assessments:** weeks 0, 2, 6, 14, 18			
RESULTS:	**Health Outcome Measures:**	**INF**	**Placebo**	***P* value**
	Week 18			
	ACR20 (%)	75.86	48.84	0.0003
	ACR50 (%)	43.68	25.58	0.011
	ACR70 (%)	22.99	13.95	0.137
	HAQ (decrease from baseline)	0.76	0.45	0.0016
	Improvement in the number of swollen joint counts, tender joint counts, duration of morning stiffness, and ESR	NR	NR	<0.05

Authors: Zhang et al. **Year: 2006**		
ADVERSE EVENTS:	**INF**	**Placebo**
• **Overall adverse effects reported (#):**	57	48
• AE thought to be related to trial drug	40	
• Infections		
o Urinary tract	0	1
• Involved organ		
o Respiratory (%)	13.79	13.95
o Liver (%)	11.49	8.14
o Skin (%)	10.34	4.65
o Urinary (%)	8.05	6.96
o Hematological (%)	8.05	2.33
• TB (cases)	1	NR
• Demyelinating disease (cases)	0	0
• Lupus-like syndrome (cases)	0	0
• Hear failure (cases)	0	0
• Tumor (cases)	0	0
• Abdominal pain (cases)	1	0
Significant differences in adverse events:	None	
ANALYSIS:	**ITT:** NR **Post randomization exclusions:** NR	
ADEQUATE RANDOMIZATION:	Method not reported	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Method NR	
ATTRITION (*overall*):	**Overall attrition (#):** 24 **Attrition differential high:** No	
ATTRITION (*treatment specific*):	**INF**	**Placebo**
Attrition overall (%):	10.34	17.44
Attrition due to adverse events (#):	6	4
QUALITY RATING:	Fair	

Evidence Table 2. Targeted Immune Modulators – Juvenile Rheumatoid Arthritis

STUDY:	**Authors: Lovell et al.**[60-62] **Year: 2000, 2003, and 2006** **Country:** US		
FUNDING:	Immunex Corporation, Children's Hospital Foundation of Cincinnati, NIH		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of etanercept in children with PJRA		
DESIGN:	**Study design:** RCT and open label extension **Setting:** Academic medical centers (children's hospitals) **Sample size:** 51 and 58		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 4 months 26	**ETA** 0.4 mg/kg body weight/2x weekly 4 months 25	**Extension** 0.4 mg/kg body weight/2x weekly up to 2 years/4 years 58/34
INCLUSION CRITERIA:	Ages 4-17 with active PJRA; active disease despite treatments with NSAIDs and MTX at doses of at least 10 mg/sq meter of body surface area per week; normal or nearly normal platelet, white cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal function tests		
EXCLUSION CRITERIA:	Pregnant and lactating patients were excluded along with patients with major concurrent medical conditions		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, low doses of corticosteroids (≤.2 mg of prednisone /kg/day with a max of 10 mg/day) or bother were permitted		

Authors: Lovell et al.
Year: 2000, 2003, 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease characteristic: Polyarticular (mean disease duration 5.8 years)

	Placebo	ETA	Extension 2 years	Extension 4 years
Mean age (years):	12.2	8.9	10	10.6
Sex (% female):	58	76	67	81
Ethnicity: white (%)	88	56	74	84
Other germane population qualities:				
• Disease duration mean (years)	6.4	5.3	5.9	5.9
• TJC	NR	NR	NR	NR
• SJC	NR	NR	NR	NR
• DMARD use (%)	73	64	74	100
• MTX use (%)	69	64	72	100
• Corticosteroids use (%)	50	24	38	41
• DAS score	NR	NR	NR	NR
• HAQ score	NR	NR	NR	NR

OUTCOME ASSESSMENT:

Primary Outcome Measures: Number of patients with disease flare (disease flare is based on worsening of 30% of more in 3 or 6 response variables and a minimum of 2 active joints)
Secondary Outcome Measures: Articular severity score, duration of morning stiffness, degree of pain, and CRP
Timing of assessments: day 1, day 15, and at the end of each month

RESULTS:

Health Outcome Measures:

- Significantly more in placebo group (81%) than patients in ETA group (28%) had disease flare ($P = 0.003$)
- Rates of flare were constant and significantly lower in ETA group ($P < 0.001$) after adjustment for baseline effects
- At study endpoint , 72% of ETA group and 23% of placebo group met definition of 50% improvement (P = NR)
- Over 4 years the rate of serious adverse events 0.13 per patient year; the rate of serious infections 0.04 per patient-year.

Authors: Lovell et al. **Year: 2000; 2003; 2006**				
ADVERSE EVENTS:	**Open label**	**Double-blind portion**	**Extension 2 years**	**Extension 4 years**
Overall adverse effects reported:	NR	NR	NR	NR
▪ **Serious adverse events requiring hospitalization**	3%	NR	16% NR	NR NR
• ISR	39%	4%	NR	NR
• URTI	35%	NR	NR	NR
• Headache	20%	NR	NR	NR
• Abdominal pain	16%	NR	NR	NR
• Vomiting	14%	NR	NR	NR
• Rash	10%	NR	NR	NR
• Varicella-Zoster virus	NR	NR	5% requiring hospitalization	NR
Significant differences in adverse events:	Unable to determine- NR			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes			
ATTRITION (*treatment specific*):	**Open label**	**ETA**	**Placebo**	**Extension 2 years**	**Extension 4 years**
Loss to follow-up:	5	6 (24%)	19 (63%)	10 (17%)	24 (42%)
Withdrawals due to adverse events:	1	6- Disease flare	18-Disease flare	2-Adverse events 7-lack of efficacy	4-Adverse events 6-lack of efficacy
QUALITY RATING:	**Fair**				

Evidence Table 2. Targeted Immune Modulators – Juvenile Rheumatoid Arthritis

STUDY:	**Authors: Lovell et al.**[63] **Year: 2008** **Country:** Multinational					
FUNDING:	Abbott Labs					
RESEARCH OBJECTIVE:	Efficacy and safety of ADA, in children with polyarticular-course juvenile rheumatoid arthritis					
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 171					
INTERVENTION:	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Dose:	24 mg/m eow	24 mg/m eow	N/A	24 mg/m eow	N/A	24 mg/m eow
Duration:	16 wks	16 wks	32 wks	32 wks	32 wks	32 wks
Sample size:	85	86	37	38	28	30
INCLUSION CRITERIA:	4 to 17 years of age with polyarticular-course juvenile rheumatoid arthritis who had active disease (at least five swollen joints and at least three joints with limitation of motion) that had not responded adequately to treatment with NSAIDs					
EXCLUSION CRITERIA:	Clinically significant deviations in hematologic, hepatic, or renal indicators; ongoing infection or had recently had a major infection requiring hospitalization or intravenous antibiotics; recent live or attenuated vaccines; previously treated with other biologic agents at any time or recently treated with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered by the intraarticular, intramuscular, or intravenous route.					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable dosages of NSAIDs and low-dose corticosteroids, pain medications were also allowed except for the 12 hours preceding an assessment of the joints.					

Authors: Lovell et al.
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Moderate-severe

	Open MTX	Open No	MTX Pla	MTX ADA	No Pla	No ADA
Mean age (years):	11.4	11.1	10.8	11.7	11.3	11.1
Sex (% female):	80	78	81	79	71	77
Ethnicity (% Caucasian):	95	88	97	95	96	87
Other germane population qualities:						
• Mean disease duration	4.0	3.6	4.0	4.3	2.9	3.6
• DMARD use (%)	9	9	19	3	11	13
• MTX use (%)	100	21	100	100	14	27
• Corticosteroids use (%)	5	2	5	5	4	0
•						

OUTCOME ASSESSMENT:

Primary Outcome Measures: percentage of patients not receiving MTX who had a disease flare during the double-blind phase of the study (weeks 16 to 48).

Secondary Outcome Measures: ACR Pedi 30, 50, 70, 90, 100

Timing of assessments: screening, at baseline (day 1), between days 2 and 10, at weeks 2 and 4, and every 4 weeks through week 48 or withdrawal from the study.

RESULTS:

Health Outcome Measures:

- Open label portion
- ACR Pedi at week 16 ADA ACR PEDI 30 74% ACR PEDI 50 64% ACR Pedi 70 46% ACR Pedi 90 26%
- ACR Pedi at week 16 ADA+MTX ACR PEDI 30 94% ACR PEDI 50 91%ACR Pedi 70 71% ACR Pedi 90 28%

- 48 weeks (Double blinded portion)
- No MTX disease flares ADA 13 of 30 [43%] vs. placebo 20 of 28 [71%], *P*=0.03
- MTX disease flares, ADA 14 of 38 (37%) vs. placebo 24 of 37 (65%) (*P*=0.02)

Authors: Lovell et al. **Year: 2008**						
ADVERSE EVENTS per pt yr of exposure:	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Overall adverse effects reported:	15.5	15.3	10.3	12.8	14.4	11.9
• ISR	5.2	5.7	3.8	4.0	1.9	4.9
• Contusion	0.5	0.2	0.5	0.7	0.5	0.1
• Nasopharyngitis	0.2	0.1	0.4	0.3	0.5	0
• URTI	0.3	0.4	0.3	0.3	0.6	0.4
• Viral infection	0.3	0.3	0.2	0.4	0.4	0.6
• Vomiting	0.2	0.1	0.1	0.2	0.1	0
• Excoriation	0.2	0.2	0.1	0.6	0.2	0.4
Significant differences in adverse events:	NR					
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR					
ADEQUATE RANDOMIZATION:	NR					
ADEQUATE ALLOCATION CONCEALMENT:	NR					
BLINDING OF OUTCOME ASSESSORS:	Yes					
ATTRITION (*overall*):	**Overall attrition:** 25% overall 6% open label **Attrition differential high:**					
ATTRITION (*treatment specific*):	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Attrition overall:	2%	10%	3%	8%	0	3%
Attrition due to adverse events:	1%	2%	0	0	0	0
QUALITY RATING:	**Fair**					

Evidence Table 2. Targeted Immune Modulators – Juvenile Rheumatoid Arthritis

STUDY:	**Authors: Ruperto**[64] **Year: 2007** **Country:**	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of INF in the treatment of juvenile rheumatoid arthritis (JRA).	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 122	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF + MTX** 3 mg/kg 14 weeks 62	**Placebo + MTX** N/A 14 weeks 60
INCLUSION CRITERIA:	At least 4 years but no more than 18 years old, a diagnosis of JRA, suboptimal response to MTX after 3 months, at least 5 active joints, and no active systemic symptoms.	
EXCLUSION CRITERIA:	Active uveitis, serious infection including tuberculosis, malignancy, or prior treatment with any TNF inhibitor.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX and intraarticular corticosteroid injections, low-dose corticosteroids , 1 NSAID, 1 analgesic that was not an NSAID, folic acid prophylaxis (required for all patients taking MTX), and narcotic or opioid analgesics	

Authors: Ruperto **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe	
	INF + MTX	**Placebo + MTX**
Mean age (years):	11.3	11.1
Sex (% female):	88.3	79.0
Ethnicity:	86.2	88.3
Other germane population qualities:		
• Tender joint count	NR	NR
• Swollen joint count	NR	NR
• Mean disease duration	4.2	3.6
• DMARD use (other than MTX) (%)	40	31.1
• MTX use (%)	100	100
• Corticosteroids use (%)	43.3	34.4
• DAS score	NR	NR
• C-HAQ score	1.2	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR Pedi 30 **Secondary Outcome Measures:** ACR Pedi 50 and ACR Pedi 70 and # patients with 0 joints with active arthritis **Timing of assessments:** "… recorded throughout the study"	
RESULTS:	**Health Outcome Measures:** ACR Pedi 30 - INF 37 of 58 [63.8%] versus placebo 29 of 59 [49.2%] $P = 0.12$ ACR Pedi 50 - INF 29 of 58 [50%] versus placebo 20 of 59 [33.9%]; $P = 0.078$ ACR Pedi 70 - INF 13 of 58 [22.4%] versus placebo 7 of 59 [11.9%]; $P = 0.130$ Number of joints with active arthritis INF vs. placebo $P = 0.016$	

Authors: Ruperto **Year: 2007**		
ADVERSE EVENTS: **Overall adverse effects reported:** • **Serious adverse events** • Infections • Serious infections • Infusion reactions	**INF + MTX (0-52 weeks)** 96.7% 31.7% 68.3% 8.3% 9.1%	**Placebo + MTX (0-14 weeks)** 81.7% 5.0% 46.7% 3.3% 3.4%
Significant differences in adverse events:	N/A- denominators are different	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 5	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	Method NR	
BLINDING OF OUTCOME ASSESSORS:	Method NR	
ATTRITION (*overall*):	**Overall attrition:** 4% at 14 weeks, 19% at 52 weeks **Attrition differential high:** No	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**INF + MTX** 3% at 14 weeks 0 at 14 weeks	**Placebo + MTX** 5% at 14 weeks 0 at 14 weeks
QUALITY RATING:	**Fair**	

Evidence Table 2. Targeted Immune Modulators – Juvenile Rheumatoid Arthritis

STUDY:	**Authors: Ruperto et al.**[65] **Year: 2008** **Country:** Europe, Latin America and USA		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To assess the safety and efficacy of ABA, in children with juvenile idiopathic arthritis who had failed previous treatments.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 190 run- in phase; and 122 RCT		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Open label run-in** 10 mg/kg days 1,15,29,57,85 4 months 190	**ABA** 10 mg/kg every 28 days 6 months 60	**Placebo** NA 6 months 62
INCLUSION CRITERIA:	Age 6 – 17 years; $\geq$ 5 active joints (those with swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness) and active disease (at least two active joints and two joints with a limited range of motion)patients with inadequate response or intolerance to at least one DMARD, including biological agents		
EXCLUSION CRITERIA:	Active uveitis, major concurrent medical conditions; pregnant or lactating.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable MTX and folinic acid or folic acid.		

Authors: Ruperto et al.
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe

	Open label	ABA	Placebo
Mean age (years):	12.4	12.6	12.0
Sex (% female):	72	72	73
Ethnicity:	77% white, 8% black, 15% other	77% white, 8% black, 15% other	79% white, 7% black, 15% other
Other germane population qualities:			
• Active joint count	12.7	12.6	12.0
• Swollen joint count	NR	NR	NR
• Mean disease duration	4.4	3.8	3.9
• DMARD use (%)	NR	NR	NR
• MTX use (%)	74	80	74
• Corticosteroids use (%)	NR	NR	NR
• DAS score	NR	NR	NR
• HAQ score	CHAQ 1.3	1.3	1.2

OUTCOME ASSESSMENT:

Primary Outcome Measures:
Time to flare of juvenile idiopathic arthritis
Secondary Outcome Measures:
Proportion of patients who had disease flare; the changes from baseline in each of the six ACR core variables; and assessment of safety and tolerability.
Timing of assessments: screening, baseline, and at each dosing visit in the 4-month open-label lead-in period (days 1, 15, 29, 57, 85, 113) and the 6-month double-blind period (days 29, 57, 85, 113, 141, 169).

RESULTS:

Health Outcome Measures: ABA versus placebo at end of 6 month double blind period

- **Time to flare** - insufficient events to analyze *
- Proportion of patients having flare - 12 (20%) vs. 33 (53%) *P* = NR
- 30% or greater improvement at end, 49 (82%) vs. 43 (69%) *P* = 0.1712
- 50% or greater improvement at end, 46 (77%) vs. 32 (52%) *P* = 0.0071
- 70% or greater improvement at end, 32 (52%) vs. 19 (31%) *P* = 0.0185
- 90% or greater improvement at end, 24 (40%) vs. 10 (16%) *P* = 0.0062
- Inactive disease status 18 (30%) vs. 7 (11%) *P* = 0.0195

Authors: Ruperto et al. **Year: 2008**			
ADVERSE EVENTS:	**Open label**	**ABA**	**Placebo**
Overall adverse effects reported:	70%	62%	55%
• Infections	36%	45%	44%
• Nausea	10%	3%	7%
• Headache	13%	5%	2%
• Cough	9%	0	3%
• Diarrhea	9%	2%	2%
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** none		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 11% in open label run-in phase, 34% in RCT **Attrition differential high:** Yes		
ATTRITION (*treatment specific*):	**Open label**	**ABA**	**Placebo**
Overall attrition:	11%	18.3%	50%
Attrition due to adverse events:	0.5%	0	0
QUALITY RATING:	**Fair**		

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: Braun et al.**[66-69], **Listing et al.**[70] **Year: 2002, 2003, 2004, 2005** **Country:** Multinational		
FUNDING:	Schering-Plough		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab treatment of AS		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 70		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 12 weeks 35	**Placebo** N/A 12 weeks 35	
INCLUSION CRITERIA:	AS that was clinically classified as active based on a score of ≥4 on the BASDAI and a score of ≥4 on a 10-cm visual analog scale for pain in the spine		
EXCLUSION CRITERIA:	Comorbidity; insufficient disease activity; complete ankylosis; incorrect diagnosis; DMARD therapy; active TB within the previous 3 years; specific changes in the radiograph of the chest at baseline; serious infections within the previous 2 months or a history of lymphoproliferative disease or other malignant diseases in the past 5 years; signs or symptoms of severe renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, but the dosage could not be increased over the baseline level during the course of the trial		

Authors: Braun et al. and Listing et al. **Year: 2002, 2004, 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Severe (mean disease duration 15.6 years)		
	INF	**Placebo**	
Mean age (years):	40.6	39.0	
Sex (% female):	32	37	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Mean disease duration (years)	16.4	14.9	
• BASDAI score (mean)	6.5	6.3	
• BASFI score (mean)	5.4	5.1	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** BASDAI **Secondary Outcome Measures:** BASFI, BASMI, SF-36, CRP **Timing of assessments:** 0, 2, 12 weeks		
RESULTS:	**Health Outcome Measures:** • More patients given INF (53%, 95% CI: 37-69) achieved a 50% improvement in BASDAI at week 12 than did controls (9%, 3-22) • Function and quality of life improved significantly on INF but not on placebo ($P < 0.0001$ and $P < 0.0001$, respectively) • BASDAI improved significantly to 3.3 at 12 weeks in the INF group, whereas little change was recorded in controls (5.7; difference 2.1 (1.6-3.7); $P < 0.0001$) • The BASFI changed to 3.4 in the INF group ($P < 0.0001$) and to 5.0 in the placebo group ($P = 0.54$) • In a 2 year open-label extension hospital admissions for INF patients were significantly reduced compared to the 12 months before the start of the trial (10% vs. 41%). A reduction of the mean inpatient days from 11.1 days before INF treatment to 2.9 days after 2 years of treatment • Treatment effects could be sustained in the third year of extension • Overall 16% of participants discontinued treatment because of adverse events during 3 years **Intermediate Outcome Measures:** • CRP and ESR dropped significantly from baseline to endpoint in the INF group ($P < 0.001$); no significant changes were seen in the placebo group ($P = 0.77$)		

Authors: Braun et al. and Listing et al. **Year: 2002, 2004, 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Serious events	**INF** NR 18 3	**Placebo** NR 12 0	
Significant differences in adverse events:	Yes-three patients on INF had serious events and were withdrawn from the study, compared with one on placebo ($P = 0.239$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 4.2% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF** 0 3	**Placebo** 2 0	
QUALITY RATING:	**Fair**		

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: Davis et al.**[71] **Year: 2003** **Country:** Multinational	
FUNDING:	Immunex Corporation, Seattle, WA	
RESEARCH OBJECTIVE:	To determine the safety and efficacy of etanercept in adults with moderate to severe active AS.	
DESIGN:	**Study design:** RCT, placebo-controlled, parallel-group **Setting:** Multicenter **Sample size:** 277	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg twice weekly 24 weeks 138	**Placebo** N/A 24 weeks 139
INCLUSION CRITERIA:	Men and women aged 18 to 70 years who satisfied the NY criteria for AS and active AS defined as: a score of ≥ 30 mm for morning stiffness on a 100-mm VAS analyzing duration or intensity; and scores of ≥ 30 mm for 2 of the following 3 parameters: patient's global assessment of disease activity, back pain, and the BASFI (all based on a 100-mm VAS).	
EXCLUSION CRITERIA:	Complete ankylosis of the spine based on radiographic assessment; previous TNF inhibitor therapy; had a serious infection (infection requiring hospitalization or intravenous antibiotics) within 4 week period prior to screening; use of DMARDs other than hydroxychloroquine, sulfasalazine, or MTX within 4 weeks of baseline evaluation.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Hydroxychloroquine, sulfasalazine, and MTX at doses stable prior to enrollment; NSAIDs and prednisone (up to 10 mg/day) if stable for 2 weeks prior to enrollment. Other analgesics (acetaminophen, codeine, hydrocodone, oxycodone, and tramadol) were permitted in standard dosages.	

<table>
<tr><td colspan="3">Authors: Davis et al.
Year: 2003</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes
Disease severity: Severe (mean disease duration 10.3 years)</td></tr>
<tr><td><u>ETA</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity (% white):
Other germane population qualities:
• DMARD use (%)
• MTX use (%)
• Corticosteroids use (%)
• BASDAI score (mean)
• BASFI score (mean)</td><td>42.1
24
94

32
11
13
58.1
51.7</td><td>41.9
24
91

31
12
14
59.6
56.3</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Efficacy Outcome Measures:
▪ ASAS20 at 12 and 24 weeks
Secondary Efficacy Outcome Measures:
ASAS50/70; BASDAI; spinal mobility (using the modified Schober test, chest expansion score, and occiput-to-wall measurements), tender and SJCs, acute-phase reactants (ESR and CRP), and assessor's global assessments (measured on a 100-mm VAS) over time.
Timing of assessments:
Efficacy: 2, 4, 8, 12, and 24 weeks. Testing for antibody to ETA occurred at baseline and week 24.</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures: (ETA v. placebo)
• Partial remission at 24 weeks: 17% v. 4%. (P-value NR)
• At weeks 12 and 24, patients receiving ETA achieved significant improvements over those receiving placebo on the individual components of the ASAS criteria, ESR, CRP, and the BASDAI (all P-values < 0.0001). Statistically significant differences were also observed for the spinal mobility measures at 12 and 24 weeks (P-values ≤ 0.0014).
Intermediate Outcome Measures
• ASAS20 at 12 weeks: 59% v. 28% (P < 0.0001) ASAS20 at 24 weeks: 57% v. 22% (P < 0.0001)</td></tr>
</table>

Authors: Davis et al. **Year: 2003**		
ADVERSE EVENTS: **Overall adverse effects reported:** • URTI • Injection-site reaction • Accidental injury • Dizziness • Flu Syndrome	**ETA** NR 28% 41% 17% 8% 5%	**Placebo** NR 16% 13% 6% 3% 10%
Significant differences in adverse events:	Injection-site reactions, URTIs, and accidental injury were the only reported adverse events achieving a statistically significant difference between the ETA and placebo groups. Patients receiving ETA experienced a statistically greater number of these adverse events.	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	Yes	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 11% **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** 14% 5.1%	**Placebo** 9% 0.7%
QUALITY RATING:	**Good**	

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: McLeod C et al.**[72] **Year:** 2007 **Country:** Multinational
FUNDING:	The HTA Programme on behalf of NICE
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 1611
AIMS OF REVIEW:	To assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (AS)
STUDIES INCLUDED IN META-ANALYSIS	9 placebo-controlled RCTs (2 of adalimumab, 5 of etanercept and 2 of infliximab)
TIME PERIOD COVERED:	Up to November, 2005
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs comparing an anti-TNFα agent (adalimumab, etanercept or infliximab) with placebo
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults diagnosed with active AS

Authors: McLeod C et al. **Year:** 2007 **Country:** Multinational	
CHARACTERISTICS OF INTERVENTIONS:	ADA (40 mg every 2 wks), ETA (25 mg twice/wk), or INF (5 mg/kg) vs. placebo
MAIN RESULTS:	Adalimumab vs. placebo ASAS 20 at 12 weeks RR (95% CI): 2.43 (1.76, 3.35); *P* < 0.00001 ASAS 70 at 12 weeks RR (95% CI): 5.47 (2.43, 12.31); *P* <0.00001 Etanercept vs. placebo ASAS 20 at 12 weeks RR (95% CI): 2.13 (1.73, 2.63); *P* < 0.00001 ASAS 20 at 24 weeks RR (95% CI): 2.53 (1.80, 3.57); *P* < 0.00001 ASAS 70 at 12 weeks RR (95% CI): 3.38 (2.10, 5.45) BASDAI score reduction at 12 weeks WMD (95% CI): -1.67 (-2.10, -1.24) BASDAI score reduction at 24 weeks WMD (95% CI): -2.00 (-2.61, -1.39) BASDAI % reduction at 12 weeks WMD (95% CI): -1797 (-23.37, -12.58) Infliximab vs. placebo ASAS 20 at 12 weeks RR (95% CI): 4.11 (2.62, 6.44); *P* < 0.00001 ASAS 20 at 24 weeks RR (95% CI): 3.18 (1.99, 5.08); *P* < 0.00001 Anti-TNF as a class vs. placebo ASAS 20 at 12 weeks RR (95% CI): 2.52 (2.14, 2.98); *P* < 0.00001 ASAS 20 at 24 weeks RR (95% CI): 2.80 (2.11, 3.71); *P* < 0.00001 ASAS 70 at 12 weeks RR (95% CI): 3.94 (2.61, 5.95); *P* < 0.00001 BASDAI at 12 weeks WMD (95% CI): -1.89 (-2.23, -1.55)
ADVERSE EVENTS:	NA
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes—the following electronic databases were searched: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness (DARE), EMBASE, Health Technology Assessment (HTA) database, ISI Web of Science, MEDLINE and NHS Economic Evaluation database; reference lists of included studies and company submissions were also searched.
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: van der Heijde et al.**[73] **Year: 2005** **Country:** Multinational	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab in patients with AS.	
DESIGN:	**Study design:** RCT **Setting:** 33 sites **Sample size:** 279	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg (wks 0,2,6,12,18) 24 weeks 201	**Placebo** N/A 24 weeks 78
INCLUSION CRITERIA:	AS according to the modified NY criteria for at least 3 months; BASDAI score of ≥4 (range 0-10), and with a spinal pain assessment score of ≥4 on a VAS (range 0-10 cm); normal chest radiograph within 3 months prior to randomization and either a negative purified protein derivative (PPD) skin test result for latent TB (in the US and Canada) or adequate screening with documented negative results for latent TB using local guidelines for high-risk or immunocompromised patients (in Europe).	
EXCLUSION CRITERIA:	Total ankylosis of the spine; other inflammatory rheumatic disease; fibromyalgia; a serious infection within 2 months; TB (active or latent) or recent contact with a person with active TB; opportunistic infection within 6 months of screening, hepatitis, HIV, a transplanted organ, malignancy, multiple sclerosis, or CHF; sulfasalazine or MTX within 2 weeks prior to screening, systemic corticosteroids within 1 month prior to screening, anti-TNF therapy other than INF within 3 months prior to screening, INF at any time prior to screening, DMARDs other than sulfasalazine or MTX within 6 months prior to screening, or cytotoxic drugs within 12 months prior to screening.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of NSAIDs, acetaminophen (paracetamol), or tramadol	

<table>
<tr><td colspan="3">Authors: van der Heijde et al.
Year: 2005</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes, but there were small differences in the sex ratio.
Disease severity: Moderate-severe (mean disease duration 10.5years)</td></tr>
<tr><td><u>Placebo</u>
Mean age (years): 41
Sex (% female): 12.8
Ethnicity (% Caucasian): 97.4
Other germane population qualities:
• DMARD use (%) NR
• MTX use (%) 0
• Corticosteroids use (%) NR
• BASDAI score (mean) 6.5
• BASFI score (mean) 6.0</td><td><u>INF</u>
40
21.9
98

NR
0
NR
6.6
5.7</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: ASAS20
Secondary Outcome Measures: ASAS40 and ASAS partial remission; BASFI; CRP level; BASDAI, BASMI; range-of-motion assessments; SF-36
Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• At week 24 significantly greater number of INF patients achieved ASAS20, ASAS40, partial remission, 50% improvement on the BASDAI and improvements greater than 2 on the BASFI than placebo patients. (All $P < 0.001$)
ASAS40: INF 47.0% vs. Placebo 12.0% Partial remission: INF 22.4% vs. Placebo 1.3%
BASDAI: INF 51.0% vs. Placebo 10.7% BASFI: INF 47.5% vs. Placebo 13.3%

Intermediate Outcome Measures:
ASAS20: INF 61.2% vs. Placebo 19.2% ($P < 0.001$)</td></tr>
</table>

Authors: van der Heijde et al. **Year: 2005**		
ADVERSE EVENTS:	**Placebo**	**INF**
Overall adverse effects reported %:	72.0	82.0
• Any infections	36.0	42.6
• Serious adverse event	2.7	3.5
• Infusion reaction	9.3	10.9
• Serious infection	0	1.0
• Pharyngitis	2.7	10.4
• Rhinitis	2.7	7.4
• Pruritus	6.7	4.0
• Nausea	10.7	3.5
• Arthritis	5.3	3.0
• Rash	5.3	2.5
Significant differences in adverse events:	NR	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall loss to follow-up:** 5 **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**Placebo**	**INF**
Loss to follow-up:	3	2
Withdrawals due to adverse events:	1	2
QUALITY RATING:	**Fair**	

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Antoni et al.**[74] and **Kavanaugh et al**.[75] **Year: 2005 and 2006** **Study name: IMPACT** (Infliximab Multinational Psoriatic Controlled Trial) **Country:** Multinational			
FUNDING:	NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network "Inflammatory Rheumatic Diseases" of the German Federal Ministry of Education and Science			
RESEARCH OBJECTIVE:	To evaluate the efficacy and tolerability of infliximab therapy for the articular and dermatologic manifestations of active psoriatic arthritis (PsA).			
DESIGN:	**Study design:** RCT **Setting:** 9 sites in clinics **Sample size:** 104			
	Weeks 0-16		**Weeks 16-50**	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 16 weeks 52	**INF** 5 mg/kg at weeks 0,2,6,14 16 weeks 52	**Placebo/INF** 5 mg/kg every 8 weeks 34 weeks 50	**INF/INF** 5 mg/kg every 8 weeks 34 weeks 49
INCLUSION CRITERIA:	Previous failure of treatment with ≥ 1 DMARDs; active peripheral polyarticular arthritis, defined as the presence of ≥ 5 swollen and tender joints (based on joint counts of 66 and 68, respectively) in conjunction with at least 1 of the following criteria: ESR ≥28 mm/hour, CRP level ≥ 15 mg/liter, and/or morning stiffness lasting 45 minutes or longer; negative results of serum tests for RF and negative results for active or latent TB by purified protein derivative skin test and chest radiography.			
EXCLUSION CRITERIA:	Any investigational drug within 3 months, positive tests for RF or latent TB; previous treatment with monoclonal antibody or fusion protein.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; dosage of 15 mg/week or more, with folic acid supplementation; leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, penicillamine, or azathioprine stable for 4 weeks; oral corticosteroids (dosage of 10 mg prednisone equivalent/day or less); NSAIDs stable for at least 2 weeks.			

Authors: Antoni et al. **Year: 2005**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Generally, with the exception of CRP **Disease severity:** Severe (mean disease duration 11.4 years)	
	Placebo	**INF**
Mean age (years):	45.2	45.7
Sex (% female):	42.3	42.3
Ethnicity:	NR	NR
Other germane population qualities:		
• Disease duration- years	11	11.7
• ACR 20 components		
# swollen joints	14.7	14.6
# tender joints	20.4	23.7
• CRP mg/liter- mean(median)	31.1(14.0)	21.7(9.9)
• DAS	5.4	5.5
• PASI	4.2	5.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 and modified van der Heijde-Sharp score for radiographic progression **Secondary Outcome Measures:** PASI score; ACR50; ACR70; DAS; HAQ; ratings of enthesitis and dactylitis; the Psoriatic Response Criteria score. **Timing of assessments:** 2,6,10,14,16, one year	
RESULTS:	**Health Outcome Measures:** • The proportion of INF patients that achieved a clinically significant response was significantly greater than the proportion of placebo patients at week 16 (All P < 0.001) **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 • **Treatment benefits were sustained through week 50** **Intermediate Outcome Measures:** • The proportion of INF patients that achieved an ACR20 response was significantly greater than the proportion of placebo patients at week 16 Placebo 5/52 (9.6%) vs. INF 34/52 (65.4%) P < 0.001 • Mean (median) changes from baseline to week 50 in the total modified vdH-S score were –1.95 (–0.50) for PBO/IFX and –1.52 (–0.50) for IFX/IFX patients (p = NS).	

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005 and 2006**			
ADVERSE EVENTS (%):	**Placebo (-week 16)**	**INF 5 mg (-week 16)**	**INF/INF 5 mg (week 16-50)**
Overall adverse effects reported:	65	73	84
• Treatment related events	47	56	69
• Infusion-associated			
All events	10	8	8
Treatment-related events	8	4	8
• Severe			
All events	4	6	12
Treatment-related events	2	4	6
• Serious			
All events	2	2	16
Treatment-related events	0	2	6
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 5% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**INF**	
Loss to follow-up:	2	3	
Withdrawals due to adverse events:	1	2	
QUALITY RATING:	**Fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Antoni et al.[76] and Kavanaugh et al.[77]** **Year: 2005** **Country:** Multinational	
FUNDING:	Centocor Inc and Schering-Plough	
RESEARCH OBJECTIVE:	The evaluation of infliximab with regards to efficacy, health related quality of life and physical function in patients with PsA. Patients with inadequate response at week 16 entered early escape.	
DESIGN:	**Study design:** RCT **Setting:** Clinical- 36 sites **Sample size:** 200	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 100	**INF** 5 mg/kg at weeks 0,2,6,14,22 24 weeks 100
INCLUSION CRITERIA:	Adults with active PsA (five or more swollen joints and five or more tender joints and either C reactive protein (CRP) levels of at least 15 mg/l and/or morning stiffness lasting 45 minutes or longer); diagnosed at least 6 months before the first infusion of study drug; an inadequate response to current or previous DMARDs or NSAIDs; patients had to have active plaque psoriasis with at least one qualifying target lesion at least 2 cm in diameter; negative test for RF in their serum.	
EXCLUSION CRITERIA:	Latent or active TB (that is, they had to have clear chest *x* ray findings and a negative purified protein derivative skin test); had chronic or clinically significant infection, malignancy, or CHF; or if they had used TNFα inhibitors previously.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of MTX, oral corticosteroids, NSAIDs	

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, except for sex **Disease severity:** Active plaque psoriasis and PsA (mean disease duration 8 years)	
	Placebo	**INF**
Mean age (years):	46.5	47.1
Sex (% female):	49	29
Ethnicity: (% white)	94	95
Other germane population qualities:		
• Polyarticular arthritis	47	53
• DIP joints of hand/feet	23	26
• Asymmetric peripheral arthritis	22	18
• NSAID use (%)	73	71
• MTX use (%)	45	47
• Corticosteroids use (%)	10	15
• SF-36 score (Physical/Mental)	31/47	33/45.5
• HAQ score	1.1	1.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20; HAQ; SF-36 **Secondary Outcome Measures:** ACR50/70; PsARC; PASI; dactylitis and enthesopathy **Timing of assessments:** Weeks 0,2,6,14,22,24	
RESULTS:	**Health Outcome Measures (Placebo vs. INF):** • ACR 50 (%) at week 14 3 vs. 36 ($P < 0.001$) and week 24 4 vs. 41 ($P < 0.001$) • ACR70(%) at week 14 1 vs. 15 ($P < 0.001$) and week 24 2 vs. 27 ($P < 0.001$) • Achieving PsARC (%) at week 14 27 vs. 77 ($P < 0.001$) and week 24 32 vs. 70 ($P < 0.001$) • HAQ (%) improvement at week 14 -18.4 vs. 48.6 ($P < 0.001$) and week 24 -19.4 vs. 46 ($P < 0.001$) • SF-36 (change from baseline) Physical week 14 1.1 vs. 9.1 ($P < 0.001$) and week 24 1.3 vs. 7.7 ($P < 0.001$) Mental week 14-1.2 vs. 3.8 ($P = 0.001$) and week 24 0.4 vs. 3.9 ($P = 0.047$) **Intermediate Outcome Measures (Placebo vs. INF):** • ACR20 at Week 14 11% vs. 58% ($P < 0.001$) and Week 24 16% vs. 54% ($P < 0.001$)	

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005**		
ADVERSE EVENTS (%):	**Placebo n=97**	**INF n=150 (includes escape)**
Overall adverse effects reported:	67	67
• URTI	14	10
• Headache	5	6
• Increased ALT	1	6
• Pharyngitis	4	5
• Sinusitis	4	5
• Dizziness	5	4
• AES leading to withdrawal	1	4
• Serious AEs	6	9
• Infusion reactions	6	7
Significant differences in adverse events:	None except for increased ALT (P = NR)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall loss to follow-up:** 7% **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**Placebo**	**INF**
Loss to follow-up:	8%	7%
Withdrawals due to adverse events:	1%	4%
QUALITY RATING:	**Fair**	

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors, article #: Genovese**[78] **Year: 2007** **Country:** US		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	safety and efficacy of adalimumab for the treatment of active psoriatic arthritis (PsA) in patients with an inadequate response to disease modifying antirheumatic drugs (DMARD)		
DESIGN:	**Study design:** placebo controlled, double-blind, randomized, multicenter study **Setting:** 16 sites in Canada and the United States **Sample size:** 100		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Adalimumab** adalimumab 40 mg (eow) 12 weeks 51	**placebo** 12 weeks 49	
INCLUSION CRITERIA:	at least 18 years of age, ≥ 3 swollen joints and ≥ 3 tender or painful joints, and either an active cutaneous lesion of chronic plaque psoriasis or a documented history of chronic plaque psoriasis diagnosed by the investigator or a dermatologist.		
EXCLUSION CRITERIA:	previous anti-TNF therapy; intravenous infusions or intraarticular injections of corticosteroids within 4 weeks of baseline; topical psoriasis therapies (e.g., keratolytics, coal tar, anthralin) within 2 weeks of baseline, ultravioletA(UVA) phototherapy, including psoralen and UVA, or use of a tanning booth within 2 weeks of the baseline visit; or oral retinoids within 4 weeks of the baseline visit, alefacept or siplizumab within 12 weeks, or any other biologic or investigational therapy within 6 weeks of the baseline visit, currently using or likely to need antiretroviral therapy. persistent or severe infections or a history of active tuberculosis, active nonpsoriatic skin disease, significant history of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease; neurologic symptoms suggestive of central nervous systemic demyelinating disease; and a history of malignancy other than carcinoma in situ of the cervix or adequately treated nonmetastatic squamous or basal cell skin carcinoma.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (<prednisone 10 mg/day), stable during the 4 weeks preceding the baseline visit. MTX (maximum allowable MTX dosage was 30 mg/week).or other DMARD stable during the 4 weeks preceding the baseline visit, with a minimum of 3 months of therapy **exception**: cyclosporine and tacrolimus (oral or topical)		

Authors: Genovese[78] **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe		
	Placebo	**Adalimumab**	
Mean age (years):	47.7	50.4	
Sex (% female):	49	43,1	
Ethnicity: Caucasian	93.9	98.0	
Other germane population qualities:			
• Symmetric polyarthritis	83.7	82.4	
• DIP joints of hand/feet	2	2	
• Asymmetric peripheral arthritis	14.3	9.8	
• DMARD use(%)	67.3	64.7	
• NSAID use (%)	85.7	72.6	
• MTX use (%)	46.9	47.1	
• Corticosteroids use (%)	18.4	7.8	
• HAQ DI score (0–3)	1,0	0,9	
• Duration of psoriasis, yrs	13.8	18.0	
• Duration of psoriatic arthritis, yrs	7.2	7,5	
• SF-36 Physical Component Summary score (0–100)	32.7	34.9	
• Patient global assessment of disease activity (0–100 mm VAS)	46.3	42.9	
• Physician global assessment of disease activity (0–100 mm VAS)	57.1	52,5	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** • ACR20 response rate at Week 12 • patient's assessment of pain during the previous week, • patient's global assessment of disease activity during the previous 24 hours,		

	• physician's global assessment of disease activity (current PsAactivity) **Secondary Outcome Measures:** • ACR50 and ACR70 response rates • PsARC • HAQ-DI) score • Short Form-36 Health Survey (SF-36) • Physical and Mental Component Summary (PCS and MCS) scores • FACIT-F • Target lesion assessment, • physician's global assessment for psoriasis • Dermatology Life Quality Index (DLQI) **Timing of assessments:** baseline and weeks 2, 4, 8, 12, 14, 18, and 24 for safety and efficacy assessments
RESULTS:	**Health Outcome Measures: ADA vs. placebo** at Week 12 • ACR50 (25% vs 2%; p = 0.001) • ACR70 (14% vs 0%; p = 0.013) • PsARC response 51% vs 24% (p = 0.007) • HAQ DI change –0.3 vs -0.1 (p = 0.010) • SF-36 PCS change 5.7 vs 2.8; (p = 0.082) • SF-36 MCS change 1.1 vs –0.6; (p = 0.242) • DLQI change –3.4 vs –1.7 (p = 0.171) **Intermediate Outcome Measures:** • ACR20 39% vs 16%(p = 0.012)

Authors: Genovese[78] **Year:2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious adverse events • URTI • Any infectious AE • Any serious infectious AE • Headache • Psoriatic arthropathy aggravated • Psoriasis aggravated • Diarrhea	**Placebo** 79.6 4.1 8.2 32.7 2.0 6.1 14.3 16.3 6.1	**ADA** 52.9 2.0 13.7 17.6 0 0 2.0 3.9 2.0	
Significant differences in adverse events:	adalimumab (52.9%) vs placebo (79.6%) ($p \leq 0.01$ attributed to study drug: adalimumab 7.5% vs placebo 28.6%		
ANALYSIS:	**ITT:** yes **Post randomization exclusions:** Yes-2 placebo pts did not receive drug administration		
ADEQUATE RANDOMIZATION:	**yes**		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 5,8% **Attrition differential high:** yes		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Placebo** 5 (9,8%) 1(1,9%)	**ADA** 1 (1,9%) 1 (1,9%)	**drug 3**
QUALITY RATING:	**fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Mease et al.**[79] **Year: 2000** **Country:** US	
FUNDING:	Immunex	
RESEARCH OBJECTIVE:	To study the efficacy and safety of etanercept in patients with psoriatic arthritis and psoriasis	
DESIGN:	**Study design:** RCT **Setting:** Single center in Seattle **Sample size:** 60	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25mg 2x weekly 12 weeks 30	**Placebo** N/A 12 weeks 30
INCLUSION CRITERIA:	Adults between 18 and 70 years who had active PsA (≥ 3 swollen, tender, or painful joints) at the time of enrollment; inadequate response to NSAIDs and were thought candidates for immunomodulatory therapy; hepatic transasminase concentrations no greater than 2x the upper limit of normal, hemoglobin 85 g/L or higher, platelet count 125000 per mL or more and serum creatinine 152-4 mmol/L or below	
EXCLUSION CRITERIA:	Evidence of skin conditions other than psoriasis	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX was allowed if <=25 mg/wk and stable for 4 weeks before study started; corticosteriods were allowed if the dose was less than or equal to 10 mg/day of prednisone, stable for at least 2 weeks before the first dose of study drug, and maintained at a constant dose throughout the study	

Authors: Mease et al. **Year: 2000**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR (mean disease duration 10 years)	
	ETA	**Placebo**
Median age (years):	46	43.5
Sex (% female):	40	47
Ethnicity (% white):	83	90
Other germane population qualities:		
• TJC	22.5	19
• SJC	14	14.7
• DMARD # previous usage	1.5	2
• MTX use (%)	47	47
• Corticosteroids use (%)	20	40
• DAS score	N/A	N/A
• HAQ score	1.3	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PsARC; PASI **Secondary Outcome Measures:** ACR20/50/70; CRP; tender and SJC; HAQ ESR **Timing of assessments:** Baseline, 4, 8, and 12 weeks	
RESULTS:	**Health Outcome Measures:** • The ETA group had statistically better outcomes on all clinical endpoints than the placebo group. 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 **Intermediate Outcome Measures:** • ACR20 was achieved by 73% ETA treated patients compared with 13% placebo treated patients (*P* < 0.0001) • CRP ETA 4 (3,11) vs. Placebo 14 (4,23) P<0.001	

Authors: Mease et al. **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • URI • Pharynigitis • Rhinitis • Sinusitis • Influenza syndrome • Injection site bruise • ISR • Fatigue	**ETA** NR 17(57%) 5 (17%) 5 (17%) 3 (10%) 0 6 (20%) 6 (20%) 4 (13%)	**Placebo** NR 17(57%) 3 (10%) 4 (13%) 2 (7%) 6 (20%) 5 (17%) 1 (3%) 0	
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 6.6% (4) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** 0 0	**Placebo** 4 0	**Placebo**—3 for lack of efficacy and 1 lost to follow-up
QUALITY RATING:	**Fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Mease et al.**[80] **Year: 2004** **Country:** US		
FUNDING:	Immunex		
RESEARCH OBJECTIVE:	To evaluate the safety, efficacy, and effect on radiographic progression of etanercept in patients with psoriatic arthritis		
DESIGN:	**Study design:** RCT **Setting:** 17 sites **Sample size:** 205		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 104	**ETA** 25 mg/2x weekly (subcutaneous) 24 weeks 101	
INCLUSION CRITERIA:	18-70 years and had active psoriatic arthritis (PsA) with at least 3 swollen and 3 tender joints at screening and a previous inadequate response to NSAID; had at lease one of the PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or AS-like arthritis; stable plaque psoriasis with a qualifying lesion		
EXCLUSION CRITERIA:	Oral retinoids, topical vitamin A or D analog preparations, and anthralin		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX therapy (stable 2 month at <=25 mg/week); corticosteriods (stable 4 weeks continued at <=10 mg/day of prednisone)		

Authors: Mease et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR (mean disease duration 9.1 years)		
	Placebo	**ETA**	
Mean age (years):			
Sex (% female):	47.3	47.6	
Ethnicity: (% white)	55	43	
Other germane population qualities:	91	90	
• Polyarticular arthritis			
• DIP joints of hand/feet	83	86	
• Asymmetric peripheral arthritis	50	51	
• NSAID use (%)	38	41	
• MTX use (%)	83	88	
• Corticosteroids use (%)	41	42	
• DAS score	15	19	
• HAQ score	N/A	N/A	
	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 **Secondary Outcome Measures:** ACR 50; ACR70: HAQ; SF-36; PsARC; PASI **Timing of assessments:** screening, baseline, weeks 4, 12, 24, and every 12 weeks thereafter		
RESULTS:	**Health Outcome Measures:** • 59% of ETA patients met ACR20 criteria compared with 15% placebo patients ($P < 0.0001$) • 23% of ETA patients eligible for psoriasis evaluation achieved at least 75% improvement in the psoriasis area and severity index, compared with 3% of placebo patients ($P = 0.001$) • Radiographic disease progression was inhibited in the ETA group at 12 months; the mean annualized rate of change over one year of treatment in the 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 ($P < 0.0001$)		

Authors: Mease et al. **Year: 2004**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • ISR • URTI • Injection site ecchymosis • Accidental injury • Headache • Sinusitis • UTI • Rash	**Placebo** NR 9 23 11 5 5 8 6 7	**ETA** NR 36 21 12 8 8 6 6 5	
Significant differences in adverse events:	Yes- ISR ($P < 0.001$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 40 (19.5%) **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** 31% 1%	**ETA** 8% 1%	
QUALITY RATING:	**Fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Mease et al.**[81] **Year: 2005** **Country:** Multi-national		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	Evaluation of efficacy and safety of adalimumab in patients with moderately to severely active PsA.		
DESIGN:	**Study design:** RCT **Setting:** Clinical- 50 sites **Sample size:** 313		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 162	**ADA** 40 mg every other week 24 weeks 151	
INCLUSION CRITERIA:	At least 18 years old; moderately to severely active PsA (defined as having at least 3 swollen joints and 3 tender or painful joints); either active psoriatic skin lesions or a documented history of psoriasis; a history of an inadequate response or intolerance to NSAID therapy for PsA.		
EXCLUSION CRITERIA:	Treatment within 4 weeks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids; topical treatments for psoriasis within 2 weeks of baseline, other than medicated shampoos or low-potency topical steroids; concurrent treatment with MTX at dosages >30 mg/week and/or corticosteroids in a prednisone-equivalent dosage of >10 mg/day; and anti-TNF therapy at any time; a history of neurologic symptoms suggestive of central nervous system demyelinating disease; history of active TB or listeriosis; presence of a severe infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of study entry.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX use was allowed during the study only if it had been taken for at least 3 months previously, with the dosage stable for at least 4 weeks prior to the baseline visit; after 12 weeks, patients who failed to have at least a 20% decrease in both swollen and TJCs on 2 consecutive visits could receive rescue therapy with corticosteroids or DMARDs.		

Authors: Mease et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe (mean disease duration 9.5 years)		
	Placebo	**ADA**	
Mean age (years):	49.2	48.6	
Sex (% female):	45.1	43.7	
Ethnicity (% white):	93.8	97.4	
Other germane population qualities:			
• Polyarticular arthritis (%)	69.8	64.2	
• DIP joints of hand/feet	NR	NR	
• Asymmetric peripheral arthritis (%)	24.7	24.5	
• NSAID use (%)	NR	NR	
• MTX use (%)	50	51	
• Corticosteroids use (%)	NR	NR	
• HAQ-DI score	1	1	
• Modified total Sharp score	19.1	22.7	
• PASI	8.3	7.4	
• Mean disease duration (years)	9.2	9.8	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 at week 12; change in modified total Sharp score at week 24 **Secondary Outcome Measures:** ACR20 response rate at week 24; ACR50 and 70 at weeks 12 and 24; PsARC; HAQ DI; SF-36 (physical and mental component summaries, PCS and MCS); PASI **Timing of assessments:** Baseline, 12 and 24 weeks		
RESULTS:	**Health Outcome Measures (ADA vs. placebo at 24 weeks):** • ACR50 39% vs. 6% ($P < 0.001$) • ACR70 23% vs. 1% ($P < 0.001$) • PASI75 59% vs. 1% ($P < 0.001$) (n=69 per group) • PsARC response rate 60% vs. 23% ($P <$ NR) • HAQ DI change -0.4 vs. -0.1 ($P < 0.001$) • SF-36 PCS change 9.3 vs. 1.4 ($P < 0.001$) • SF-36 MCS change 1.8 vs. 0.6 ($P = 0.288$) **Intermediate Outcome Measures:** • ACR20 57% vs. 15% ($P < 0.001$)		

Authors: Mease et al. **Year: 2005**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Serious adverse events • URTI • Nasopharyngitis • ISR • Headache • Hypertension • Psoriatic arthropathy aggravated • Arthralgia • Psoriasis aggravated • Diarrhea	**Placebo** NR 4.3 14.8 9.3 8.6 3.1 6.8 5.6 6.2 5.6	**ADA** NR 3.3 12.6 9.9 6.6 6.0 5.3 3.3 2.0 2.0 2.0	
Significant differences in adverse events:	None reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes-2 ADA patients prior to drug administration		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7.6% **Loss to follow-up differential high: No**		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events (includes AEs and abnormal lab values):**	**Placebo** 13 (8%) 5 (3.1%)	**ADA** 11 (7.3%) 5(3.3%)	
QUALITY RATING:	**Fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Mease et al.**[82] **Year: 2006** **Country:** Multinational		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of alefacept in combination with methotrxate for the treatment of PsA.		
DESIGN:	**Study design:** RCT- phase 2 **Setting:** Multi-center (27 sites) **Sample size:** 185		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ALE + MTX** 15 mg/weekly 12 wks trmt/12 wks follow-up 123	**Placebo + MTX** N/A 12 wks trmt/12 wks follow-up 62	
INCLUSION CRITERIA:	18-70 years; persistently active PsA (defined as 3 swollen joints and 3 tender joints) despite treatment with MTX for 3 months immediately prior to enrollment; MTX (10-25 mg/week) was required to be stable for 4 weeks prior to enrollment; patients were required to have CD4+ T cell counts at or above the lower limit of normal.		
EXCLUSION CRITERIA:	Treatment with INF, ADA, or systemic retinoids within 3 months; ERA or cyclosporine within 2 months; phototherapy or other DMARDs within 4 weeks; history of malignancy; unstable erythrodermic, pustular, or guttate psoriasis; serious local or systemic infection within the previous 3 months; HIV; active TB.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; stable doses of corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs		

<table>
<tr><td colspan="4">Authors: Mease et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No; more NSAID use in ALE group, and more prednisone in placebo group.</td></tr>
<tr><td></td><td><u>ALE + MTX</u></td><td><u>Placebo + MTX</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>45.6</td><td>45.5</td><td></td></tr>
<tr><td>Sex (% female):</td><td>50</td><td>63</td><td></td></tr>
<tr><td>Ethnicity:</td><td>98% white</td><td>98% white</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• NSAID use (%) diclofenac</td><td>41</td><td>24</td><td></td></tr>
<tr><td>• MTX use (mean dose/week)</td><td>13.7</td><td>14.6</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>8</td><td>15</td><td></td></tr>
<tr><td>• HAQ score</td><td>1.0</td><td>1.1</td><td></td></tr>
<tr><td>• PASI</td><td>10.2</td><td>9.6</td><td></td></tr>
<tr><td>• BSA $\geq$ 3 % (%)</td><td>47</td><td>47</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR20 response at 24 wks

Secondary Outcome Measures: ACR50 and 70; PASI50 and 75; PGA of clear or almost clear at week 14 and at any time. The pharmacodynamic end point was the change from baseline in CD4+ T cell counts

Timing of assessments: Screening and at baseline weeks 7, 14, 18, and 24.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures at 24 weeks:
• ACR20 response was achieved by a significantly greater proportion of patients receiving ALE + MTX (54%) vs. placebo + MTX (23%) ($P < 0.001$)
• ACR50 ALE + MTX (17%) vs. placebo + MTX (10%) and ACR70 ALE + MTX (7%) vs. placebo + MTX (2%) (P = NS for either)
• PASI50 response ALE + MTX (45%) vs. placebo + MTX (31%) (P = NS)
• PASSI75 ALE + MTX (28%) vs. placebo + MTX (24%) (P = NS)
• PGA clear or almost clear ALE + MTX (31%) vs. placebo + MTX (24%) (P = NS)</td></tr>
</table>

Authors: Mease et al. **Year: 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Increased ALT level • Back pain • Nasopharyngitis • URTI • Nausea	**ALE + MTX** NR 6 6 5 4 3	**Placebo + MTX** NR 2 3 11 8 6	
Significant differences in adverse events:	NR but infection rates appear to be higher in placebo + MTX group (i.e., URTI and nasopharyngitis)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	Yes, but method NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 3% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ALE + MTX** 4 (3%) 2 (2%)	**Placebo + MTX** 1 (2%) 0	
QUALITY RATING:	**Fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors:** Saad[83] **Year:** 2008 **Country:UK**
ARTICLE ID #:	[83]
FUNDING:	None
DESIGN:	**Study design:** SR, MetaAnalysis **Number of patients:** 982
AIMS OF REVIEW:	efficacy and safety of tumor necrosis factor-α (TNF-α) inhibitors in the management of psoriatic arthritis (PsA), use of adalimumab, etanercept, or infliximab (used at licensed therapeutic dosages)
STUDIES INCLUDED IN META-ANALYSIS	Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005 IMPACT 2, Antoni, Kavanaugh 2005 IMPACT
TIME PERIOD COVERED:	till May 2007
CHARACTERISTICS OF INCLUDED STUDIES:	double-blind RCT that compared the use of adalimumab, etanercept, or infliximab (used at licensed therapeutic dosages) against placebo or other active treatments and reported on efficacy and/or safety outcomes.
CHARACTERISTICS OF INCLUDED POPULATIONS:	PsA with at least 3 swollen joints and 3 tender or painful joints

Authors: Saad[83] **Year:** 2008 **Country:** UK	
CHARACTERISTICS OF INTERVENTIONS:	Adalimumab 40 mg SC every other wk Etanercept 25 mg SC twice/week Infliximab 5 mg/kg at Weeks 0 2, 6, 14 then every 8 weeks
MAIN RESULTS:	**Adalimumab, etanercept, and infliximab vs. placebo at 12–16 weeks (**Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005, Antoni, Kavanaugh 2005) • ACR20 pooled RR 4.35 (95% CI 3.24, 5.84) ACR50 pooled RR 10.37 (95% CI 6.36, 16.93) ACR70 pooled RR 16.51 (95% CI 6.74, 40.40) • PsARC pooled RR 2.60 (95%CI 2.22, 3.04) • PASI 50 pooled RR 5.50 (95% CI 2.53, 11.92) PASI 75 pooled RR 16.30 (95% CI 7.33, 36.28) PASI 90 pooled RR 34.64 (95% CI 6.95, 172.57) **Adalimumab vs placebo at 12 wks (**Mease 2005, Genovese 2007) • HAQ DI mean percentage change 26.67 (95% CI 20.13, 33.20) **infliximab vs. placebo at 14–16 weeks** (Antoni 2005, Antoni, Kavanaugh 2005) • HAQ DI mean percentage change 56.06 (95% CI 42.07,70.05) **Adalimumab vs placebo at 12 wks (**Gladman 2007 and Mease 2005, Genovese 2007) • SF-36 PCS WMD 5.54 (95% CI 0.64, 10.43) • SF-36 MCS WMD 0.88 (95% CI –0.99, 2.75) **Adalimumab vs placebo at 24 wks (**Gladman 2007 and Mease 2005, Genovese 2007) • SF-36 PCS WMD 7.90 (95% CI 5.63,10.17) SF-36 MCS WMD 1.20 (95% CI –1.06, 3.46) **infliximab vs. placebo at 14 weeks** (Antoni, Kavanaugh 2005) • SF-36 PCS WMD 8.00 (95% CI 5.27, 10.73), SF-36 MCS WMD 5.00 (95% CI 2.16, 7.84) **In direct comparisons** RR (95% CI) Efficacy ACR 20 Adalimumab vs etanercept 0.63 (0.22, 1.81) Adalimumab vs infliximab 0.60 (0.30, 1.20) Etanercept vs infliximab 0.96 (0.33, 2.76) PsARC Adalimumab vs etanercept 1.35 (0.67, 2.73) Adalimumab vs infliximab 0.77 (0.53, 1.13) Etanercept vs infliximab 0.57 (0.28, 1.17) Safety Serious AE Adalimumab vs etanercept 0.61 (0.12, 3.03) Adalimumab vs infliximab 0.52 (0.14, 2.01) Etanercept vs infliximab 0.64 (0.14, 2.96)
ADVERSE EVENTS:	Withdrawal for any reason • Adalimumab vs placebo RR0.83 (0.39, 1.74) Gladman 2007 and Mease 2005, Genovese 2007

	• Etanercept vs placebo RR 0.24 (0.12, 0.49) Mease 2000, 2001, 2004 • Infliximab RR1.50 (0.26, 8.61)Antoni 2005 • Pooled RR 0.48 (0.20, 1.18) Withdrawal due to AE • Pooled RR 2.14 (0.73, 6.27) Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2004; Antoni 2005, Antoni, Kavanaugh 2005 Serious AE • Pooled RR 0.98 (0.55, 1.77) Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005, Antoni, Kavanaugh 2005 Upper respiratory tract infections • Pooled 0.91 (0.65, 1.28)Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005, Antoni, Kavanaugh 2005 Injection site reactions • Etanercept vs placebo RR 4.27 (2.25, 8.13)*RR Mease 2000, 2001, 2004 • Adalimumab vs placebo) RR 1.44 (0.65, 3.17)Gladman 2007 and Mease 2005, Genovese 2007 • Pooled RR 2.48 (1.16, 5.29)Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004;
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Good

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Behm et al.**[84] **Year: 2008** **Country:** USA
FUNDING:	One author has been a consultant for Centocor and Abbott and is a PI for ongoing trials for Centocor, Abbott, Elan, and Otsuka.
DESIGN:	**Study design:** SR & MA **Number of patients:** INF = 952, ADA = 1130, CER = 668
AIMS OF REVIEW:	To conduct a systematic review of the evidence for the effectiveness of TNF-α blocking agents in the maintenance of remission in patients with Crohn's disease.
STUDIES INCLUDED IN META-ANALYSIS:	Two ADA studies (Colombel 2007, Sandborn, 2007); Feagan 2006; Hanauer 2002; Rutgeerts 1999; Sandborn 2001; Sandborn 2004; Sandborn 2007; Sands 2004; Schreiber 2007
TIME PERIOD COVERED:	1966 to July 2007
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized controlled trials involving patients with Crohn's disease who had a clinical response or clinical remission with a TNF-α blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-α blocking agent.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients greater than 17 years of age with refractory or steroid-dependent Crohn's disease as defined by conventional clinical, radiographic and endoscopic criteria. Patients were categorized as having active Crohn's disease (defined as Crohn's disease activity index [CDAI] > 150) with a response to induction therapy with an anti TNF-α agent in the presence or absence of concomitant steroid or immunosuppressive therapy, and patients with Crohn's disease (either active or in remission) that were unable to wean corticosteroids in the presence or absence of immunosuppressives.

Authors: Behm et al. **Year: 2008**	
CHARACTERISTICS OF INTERVENTIONS:	INF: 10 mg/kg every 8 weeks or 5 mg/kg every 4-8 weeks; ADA: 40-80 mg every one-two weeks
MAIN RESULTS:	**INF vs. placebo (Rutgeerts 1999, Hanauer 2002, Sands 2004)** Maintenance of remission (RR 2.50; 95% CI 1.64 to 3.80; P < 0.0001) Clinical response (RR 2.19; 95% CI 1.27 to 3.75; P = 0.005) corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.81; P = 0.01) complete healing of perianal and enterocutaneous fistulas (RR 1.87; 95%CI 1.15 to 3.04; P = 0.01) **ADA vs. placebo (Colombel 2007, Sandborn 2007)** maintenance of clinical remission (RR 1.82; 95% CI 1.06 to 3.13 **CER vs. placebo (Schreiber 2007)** maintenance of clinical remission (RR 1.68; 95% CI 1.30 to 2.16; P < 0.0001) clinical response (RR 1.74; 95% CI 1.41 to 2.13; P < 0.00001)
ADVERSE EVENTS:	Serious infection rate for TNF-α therapy 2.8-4%, did not differ significantly from placebo
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Fair**

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Colombel et al.[85] [86] and Feagan et al.[87] and Loftus et al.[88]** **Year: 2007, 2008, 2009** **Country:** Multinational		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	Efficacy and safety of ADA, administered subcutaneously, in the maintenance of response and remission in patients with moderate to severe Crohn's disease (CD),		
DESIGN:	**Study design:** RCT **Setting:** Multinational **Sample size:** 854 enrolled and had active run-in, 778 remaining at week 4 then randomized to three groups. The patients were stratified into "responders" and "non-responders" at week 4 (decrease in CDAI ≥70). All end-points except fistula and safety are reported for the "responders" population.		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 56 weeks 261 (170 responders, 91 non)	**ADA** 40mg/every second week 56 weeks 260 (172 responders, 88 non)	**ADA** 40mg/week 56 weeks 257 (157 responders, 100 non)
INCLUSION CRITERIA:	Men and women 18–75 years of age with known CD of at least 4 months' duration was moderately to severely active, as defined by a baseline CDAI score of 220–450 points.		
EXCLUSION CRITERIA:	ulcerative colitis, symptomatic obstructive disease, bowel resection within the past 6 months, an ostomy, extensive small bowel resection or short bowel syndrome; total parenteral nutrition; cancer, *Listeria*, human immunodeficiency virus, central nervous system demyelinating disease, or untreated tuberculosis; investigational chemical agents within 30 days or investigational biologic therapy within 3 months; antibiotic treatment for non-CD–related infections within 3 weeks; pregnant or breast-feeding; significant drug or alcohol abuse within the past year; poorly controlled medical conditions; treatment with ADA or participated in an ADA clinical study; enema therapy within 2 weeks; cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks; positive *Clostridium difficile* stool assay; clinically significant deviations in prespecified laboratory parameters.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent therapies for CD, including stable dosages (at least 4 weeks) of azathioprine, 6-mercaptopurine, MTX, 5-aminosalicylates, sulfasalazine, oral mesalamine, and CD-related antibiotics, were permitted, as were stable dosages (at least 2 weeks) of prednisone (≥30 mg/day or equivalent) or budesonide (≥9 mg/day) (patients could not be on both prednisone and budesonide). Patients who had received INF or any TNF antagonist other than ADA more than 12 weeks before could be enrolled provided that they did not exhibit initial nonresponse to the agent		

Authors: Colombel et al., Feagan et al., Loftus et al. **Year: 2007, 2008, 2009**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No (ADA 40mg/2nd week less severe- 6.5% fewer with fistulae) **Disease severity:** moderate to severe		
	Placebo	**ADA 40mg/2ND week**	**ADA 40mg/week**
Mean age (years):	36.9	36.8	37.8
Sex (% female):	62.1	62.7%	61.1%
Ethnicity:	94.3% white 3.1% black	94.2% white 2.7% black	89.9% white 4.7% black
Other germane population qualities:			
• Previous surgery for CD (%)	NR	NR	NR
• Patients with fistulae (%)	18.0%	11.5%	15.6%
• Mean baseline CDAI (after 4 week active lead-in)	209	195	209
• Mercaptopurine/Azathioprine use (%)	NR	NR	NR
• Corticosteroids use (%)	41.0%	38.1%	41.6%
• HAQ score	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** The percentage who achieved clinical remission (CDAI score <150) at weeks 26 and 56. NB: trial included 4 week open-label induction, "responders" (defined as a decrease in CDAI scores ≥70 points at week 4 compared with baseline) were randomized into the three groups as above. HQL: Zung Self-Rating Depression Scale, FACIT-F, IBDQ, SF-36, VAS (abdominal pain) 12-month risk of hospitalization and rate of surgery. **Secondary Outcome Measures:** (1) percentage of patients with a clinical response (decrease in CDAI score from baseline by ≥70 points and by ≥100 points) at weeks 26 and 56; (2) changes from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total scores at weeks 26 and 56; (3) percentage of patients in clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use; (4) percentage of patients in clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use for ≥90 days; (5) percentage of patients with fistula remission (closure of all fistulas that were draining at screening and baseline visits);		

	(6) previous/concomitant use of immunosuppressants (with vs. without), and previous use of TNF antagonists (experienced vs. naive); and (7) median time in clinical remission among randomized responders achieving remission. Post-hoc analyses were conducted to evaluate the sustainability of response and the response in certain subgroups: (1) percentage of patients with fistula closure at 26 weeks who continued to have fistula closure at 56 weeks and (2) clinical remission rates stratified by baseline C-reactive protein (CRP) concentration (<1 vs. ≥1 mg/dL). **Timing of assessments:** weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 40, 48, 56, and 60 (4-week follow-up period).
RESULTS:	**Health Outcome Measures:** • clinical remission (CDAI<150) week 26: ADA 40mg/2ND week 40%, ADA 40 mg/wk 47%, and placebo 17% p<0.001 • clinical remission (CDAI <150) week 56: ADA 40mg/2ND week 36%, ADA 40 mg/wk 41%, and placebo 12% $p < 0.001$ **Intermediate Outcome Measures:** • Decrease From Baseline in CDAI Score ≥100 week 56: ADA 40mg/2ND week 41.3%, ADA 40mg/wk 47.8%, placebo 16.5% • Decrease From Baseline in CDAI Score ≥70 week 56: ADA 40mg/2ND week 43.0%, ADA 40mg/wk 49.0%, placebo 17.6% • corticosteroid-free remission at week 56: ADA 40mg/2ND week 29%, ADA 40mg/wk 23%, placebo 6% • Complete fistula closure week 56: combined ADA groups 33% vs. placebo 33% $P = .016$ • IBDQ at week 56: ADA 40mg/2ND week 177 vs. ADA 40mg/wk 171 vs. placebo " >7 points below 170" (mean value not given) • SF-36 PCS week 56: ADA 40mg/2ND week 77% vs. placebo 61% had achieved an MCID improvement of 5 points or more($P < 0.01$) • SF-36 MCS week 56: ADA 40mg/2ND week 67% vs. placebo 54% had achieved an MCID improvement of 5 points or more($P < 0.05$) • 12-month risk of all-cause hospitalization: ADA 40mg/2ND week 13.5% vs. ADA 40mg/wk 11.7% vs. placebo 25.2% ($P < 0.01$). • Major surgery rate: ADA 40mg/2ND week 0.4% vs. ADA 40mg/wk 0.8% vs. placebo 3.8% • Subgroup analysis of patients with fistula (ADA = 70 placebo = 47) mean number of draining fistula per day during RCT, ADA 0.88 vs. placebo 1.34, $P = 0.043$.

Authors: Colombel et al., Feagan et al., Loftus et al. **Year: 2007, 2008, 2009**			
ADVERSE EVENTS:	**Placebo**	**ADA 40mg/2ND week**	**ADA 40mg/week**
Overall adverse effects reported:	84.7%	88.8%	85.6%
• AEs leading to discontinuation	13.4	6.9	4.7
• infections	36.8	46.2	44.4
• arthralgia	8.8	10.4	13.2
• headache	5.7	9.6	11.7
• injection site reaction	0.4	4.2	5.8
• urinary tract infection	1.5	4.2	5.8
Significant differences in adverse events:	Yes: discontinuation, arthalgia, headache, injection site reaction, urinary tract infection		
ANALYSIS:	**ITT:** modified ITT **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 41% (of original population) 35% of randomized population **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**ADA 40mg/2ND week**	**ADA 40mg/week**
Attrition overall:	44%	36%	25%
Attrition due to adverse events:	13.4%	6.9%	4.7%
QUALITY RATING:	**Fair**		

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Ghosh et al.**[89] **Year: 2003** **Country:** Multinational			
FUNDING:	Elan Pharmaceuticals and Biogen			
RESEARCH OBJECTIVE:	To determine the efficacy of Natalizumab for Active Crohn's Disease			
DESIGN:	**Study design:** RCT **Setting:** Multicenter (35) **Sample size:** 248			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo & placebo** 2 infusions 4 weeks apart 12 weeks 63	**NAT 3mg/kg & placebo** 2 infusions 4 weeks apart 12 weeks 68	**NAT 3mg/kg & NAT 3mg/kg** 2 infusions 4 weeks apart 12 weeks 66	**NAT 6mg/kg & NAT 6mg/kg** 2 infusions 4 weeks apart 12 weeks 51
INCLUSION CRITERIA:	Male and female patients at least 18 years of age who had clinical evidence of moderate-to-severe Crohn's disease, CDAI score between 220 and 450.			
EXCLUSION CRITERIA:	Patients who had received MTX, cyclosporine, or any investigational agents within three months before randomization were excluded; patients who were receiving azathioprine or mercaptopurine were required to have been taking a stable dose for at least four months before randomization. Other criteria for exclusion included prior treatment with any antibody agent, current use of oral prednisolone at a dose of more than 25 mg per day or another corticosteroid at an equivalent dose, current use of an elemental diet or parenteral nutrition, infectious or neoplastic diseases of the bowel, bowel surgery within three months before randomization, the presence of an ostomy, the presence of symptoms due mainly to fibrotic strictures, and a clinical impression that the patient was likely to require abdominal surgery soon.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	See above (prednisolone<25mg/day)			

Authors: Ghosh et al. **Year: 2003**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** moderate to severe			
	Placebo &placebo	**NAT 3mg/kg & placebo**	**NAT 3mg/kg & NAT 3mg/kg**	**NAT 6mg/kg & NAT 6mg/kg**
Mean age (years):	34	36	36	35
Sex (% female):	52	60	55	51
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Previous surgery for CD (%)	NR	NR	NR	NR
• Patients with fistulae (%)	10	16	12	25
• Mean baseline CDAI	300	288	300	298
• Mercaptopurine /Azathioprine use (%)	35	38	26	18
• Corticosteroids use (%)	49	46	56	63
• HAQ score	NR	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** clinical remission: CDAI < 150 at 6 weeks; clinical response: a decrease of least 70 points from baseline. **Secondary Outcome Measures:** serum level of CRP; HR-QOL (IBDQ) **Timing of assessments:** Week 2, 4, 6, 8, 12			
RESULTS:	**Health Outcome Measures:** • Week 12 remission: placebo 27% vs. 1 infusion of NAT 3mg/kg 28% vs. 2 infusions of NAT 3mg/kg 42% vs. 2 infusions of NAT 6mg/kg 39% ($P = 0.042$ for 2 infusions of 3mg/kg vs. placebo only) • Week 12 response: placebo 43% vs. 1 infusion of NAT 3mg/kg 50% vs. 2 infusions of NAT 3mg/kg 61% vs. 2 infusions of NAT 6mg/kg 65% ($P = 0.033$ for 2 infusions of 3mg/kg vs. placebo and $P = 0.018$ for 2 infusions of 6mg/kg) • IBDQ week 12 scores: placebo 145 vs. 1 infusion of NAT 3mg/kg 149 vs. 2 infusions of NAT 3mg/kg 161 vs. 2 infusions of NAT 6mg/kg 155 ($P = 0.021$ for 2 infusions of 3mg/kg vs. placebo and $P = 0.014$ for 2 infusions of 6mg/kg) • Patients used rescue medication during study: placebo 17% vs. 1 infusion of NAT 3mg/kg 21% vs. 2 infusions of NAT 3 mg/kg 15% vs. 2 infusions of Nat 6 mg/kg 12% (P = NS, data NR)			

Authors: Ghosh et al. **Year: 2003**				
ADVERSE EVENTS:	**Placebo & placebo**	**NAT 3mg/kg & placebo**	**NAT 3mg/kg & NAT 3mg/kg**	**NAT 6mg/kg & NAT 6mg/kg**
Overall adverse effects reported(%):	81	77	88	78
• Infections (%)	13	11	12	8
• abdominal pain (%)	17	12	15	18
• influenza syndrome (%)	8	14	11	20
• pain (%)	8	6	6	18
• infusion reaction (%)	0	0	2	2
• serious adverse events (%)	11	11	9	12
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	Yes			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall attrition:** 11% **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Placebo & placebo**	**NAT 3mg/kg & placebo**	**NAT 3mg/kg & NAT 3mg/kg**	**NAT 6mg/kg & NAT 6mg/kg**
Attrition overall:	15.9%	8.8%	9.1%	11.8%
Attrition due to adverse events :	3%	1%	3%	6%
QUALITY RATING:	**Good**			

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Hanauer et al.,[90] Lichtenstein et al.,[91] Feagan et al.,[92] Geboes et al.,[93] and Rutgeerts et al.[94]** **Year: 2002, 2003, 2003, 2005, 2006** **Country:** Multinational		
FUNDING:	Centocor, Malvern PA		
RESEARCH OBJECTIVE:	To assess the benefit of maintenance infliximab therapy in patients with active Crohn's disease who respond to a single infusion of infliximab, the impact of remission on patients' employment, quality of life, and hospitalization to validate clinical remission and health related quality of life and effect of infliximab on endoscopic and histologic disease activity and expression of inflammatory markers		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (55 sites) **Sample size:** 573 (48 mucosal biopsy substudy)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF dose 1** 5 mg/kg at weeks 2,6 & every 8 weeks thereafter 54 weeks 192 (18)	**INF dose 2** 5 mg/kg injections at weeks 2, 6, then 10 mg/kg every 8 weeks 54 weeks 193 (15)	**Placebo** N/A (responded to one initial dose of INF) 54 weeks 188 (15)
INCLUSION CRITERIA:	Crohn's disease of at least 3 months duration; CDAI score between 220 and 400		
EXCLUSION CRITERIA:	Previous treatment with INF or another agent targeted at TNF; pregnancy		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	5-aminosalicylates or antibiotics; corticosteroids; azathioprine or 6-mercatopurine; MTX		

Authors: Hanauer et al. **Year: 2002**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR; characterized week 2 responders and non-responders **Disease severity:** Moderate to severe
	All patients
Median age (years):	35
Sex (% female):	58
Ethnicity (White):	96%
Other germane population qualities:	
• Previous surgery for CD (%)	51%
• Median baseline CDAI	297
• Median baseline IBDQ	127
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Time to loss of response (CDAI score ≥ 175) up to and including week 54 among week 2 responders; proportion of week 2 responders in remission at week 30 (CDAI score < 150); Employment status; PCS and MCS of SF-36; IBDQ **Secondary Outcome Measures:** Employment status; hospitalizations, surgeries, and work loss; PCS and MCS of SF-36; IBDQ, Corticosteroid discontinuation; endoscopic healing **Timing of assessments:** Weeks 0,2,6,10,14,22,30,38,46,54; SF-36 taken at wk 10, 30, and 54

Authors: Hanauer et al. **Year: 2002**	
RESULTS:	**Health Outcome Measures: At 54 weeks** • Among patients unemployed at baseline, significantly more patients who achieved remission were employed (31%) than patients who did not achieve remission (16%) ($P < 0.05$) • Hospitalization rate, # of surgeries, and work loss were lower for responding patients ($P < 0.05$) • Patients in remission had significantly better MCS and PCS scores. ($P < 0.0001$) • Total IBDQ score was more significantly improved in the INF 5mg/kg group ($P < 0.05$) and the INF 10mg/kg group ($P < 0.001$) than the placebo group. • Significantly more patients discontinued corticosteroids in Active vs. Placebo OR: 4.2 (CI 1.5-11.5) **Intermediate Outcome Measures:** • Patients on active treatment were more likely to be in clinical remission at 30 weeks than patients taking placebo; OR: 2.7 (CI 1.6-4.6) • Patients on active treatment had a significantly longer time to loss of response than placebo patients; median 46 weeks for INF compared to 19 weeks for placebo ($P = 0.0002$) • Higher proportion of 2 week responders in combined scheduled maintenance group had complete mucosal healing at week 54 compared with episodic group (50% vs. 7%, $P=0.007$) • Significantly greater improvement in CDEIS occurred with scheduled maintenance compared with episodic treatment at week 54 ($P = 0.026$) • No strong relationship found between clinical remission and complete mucosal healing

Authors: Hanauer et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Intestinal Stenosis • Infusion reactions • Serum sickness like reactions	**INF 5mg/kg** 72 (37%) 3 (2%) 44 (23%) 5 (3%)	**INF 10mg/kg** 58 (30%) 5 (3%) 36 (19%) 6 (3%)	**Placebo** 78 (41%) 6 (3%) 17 (9%) 3 (2%)
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 124 (22%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF dose 1** 49 (26%) 29 (15%)	**INF dose 2** 37 (19%) 16 (8%)	**Placebo** 38 (20%) 5 (3%)
QUALITY RATING:	**Fair**		

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Lemann et al.**[95] **Year: 2006** **Country:** France	
FUNDING:	Schering Plough	
RESEARCH OBJECTIVE:	To evaluate the usefulness of short-term INF combined with azathioprine (AZA) or 6-mercaptopurine (6-MP) in steroid-dependent Crohn's disease patients.	
DESIGN:	**Study design:** RCT (stratified into AZA/6-MP failure or naïve) **Setting:** Multicenter (France) **Sample size:** 115	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 52 weeks 58	**INF** 5mg/kg 52 weeks 57
INCLUSION CRITERIA:	≥18 years old, luminal steroid-dependent CD (based on established clinical, endoscopic, radiologic, and histologic criteria). Steroid dependency was defined as follows: (1) prednisone had to be given for at least 6 months at a dosage 10 mg/day or more, with no interruption for more than 2 months within the past 6 months; (2) at least 2 clinical luminal relapses when tapering of steroids had been attempted, leading to an increase in the dose to more than 10 mg/day; and (3) the last attempt for steroid tapering had to be within the past 6 months. At baseline, patients had to be treated with prednisone 10 mg/day or more. Regarding AZA/6-MP status at baseline, 2 types of patients could be included: those in the naive stratum who did not receive AZA/6-MP in the past 2 years, and those in the failure stratum who still had clinically active disease (CDAI > 150) despite receiving AZA/6-MP for more than 6 months at a stable and appropriate dose (2–3 mg/kg/day for AZA and 1–1.5 mg/kg/day for 6-MP).	
EXCLUSION CRITERIA:	(1) contraindication to AZA/6-MP or to INF according to labeling recommendations; (2) treatment with an immunosuppressive drug other than AZA/6-MP in the past 6 months; (3) previous use of INF or other anti–tumor necrosis factor drugs including thalidomide; (4) concomitant treatment with aminosalicylates, budesonide, topical steroids, or artificial nutrition; or (5) presence of at least 1 of the following conditions: symptomatic stricture, intra-abdominal abscess or infection, severe sepsis within the past 3 months, tuberculosis, history of B or C hepatitis, human immunodeficiency virus infection, liver failure, pregnancy, breast-feeding, or participation in pharmaceutical research within the past 3 months.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	AZA, steroids, 6-MP (all patients)	

Authors: Lemann et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: mild – moderate - severe

	Failure/Placebo	Failure/INF	Naïve/Placebo	Naïve/INF
Mean age (years):	29	26	26	27
Sex (% female):	69	69	43	39
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Mean baseline CDAI	181	240	112	146
• Mercaptopurine/Azathioprine use (%)	All	All	None	None
• Corticosteroids use (%)	All	All	All	All
• disease duration	7	5	4	3

OUTCOME ASSESSMENT:

Primary Outcome Measures:
Rate of success, defined as a clinical remission (CDAI <150) off steroids at week 24.
Secondary Outcome Measures:
Success rate at week 12, rate of steroid resistance, cumulative dose of prednisone at week 24, steroids side effect score at weeks 6, 12, and 24, endoscopic improvement between inclusion and week 24, and adverse events.
Timing of assessments:
Week 0, 2, 6, 12, 24. Follow-up to week 24-52 all treatments could be given as necessary; patients who had a relapse or received additional infusions of INF were classified as treatment failures

RESULTS:

Health Outcome Measures (all results week 24 unless otherwise reported):

- the percentage of success (CDAI <150 and off steroids) was significantly higher in the INF group than in the placebo group (57% vs. 29%; OR, 3.3; 95% CI, 1.5–7.4; *P* = .003);
- in the naïve stratum the percentage of success was significantly higher in the INF group than in the placebo group (63% vs. 32%; OR, 3.7; 95% CI, 1.1–11.3; *P* = .02);
- In the failure stratum, the success rate also was higher in the INF group than in the placebo group at week 24 (50% vs. 26%; OR, 2.9; 95% CI, .9 –9.3; *P* = .08)
- Steroid resistance INF 5% vs. placebo 23%; OR, 5.1; 95% CI, 1.3–19.2; *P* = .01).
- The median cumulative dose (interquartile range) of prednisone was lower in the INF group at 1110 mg/24 wk (630 –1720 mg/24 wk) vs. 1870 mg/24 wk (1110 – 2710 mg/24 wk) (*P* = .002).
- no difference in side-effect steroid score

Authors: Lemann et al. **Year: 2006**		
ADVERSE EVENTS (WK 24): **Overall adverse effects reported:** • infections % • arhralgia, myalgia • nausea or vomiting • pancreatitis	**Placebo** 50% 28 22 5 3	**INF** 52% 32 14 18 0
Significant differences in adverse events:	No	
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Yes	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	Yes	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall attrition:** 7.8% **Attrition differential high:** No	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Placebo** 10.3% NR	**INF** 5.2% NR
QUALITY RATING:	**Fair**	

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: MacDonald and McDonald**[96] **Year: 2007** **Countries:** Multinational
FUNDING:	Funding for the IBD/FBD Review Group (October 1, 2005 -September 30, 2010) was provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch; the Canadian Agency for Drugs and Technologies in Health (CADTH); and the CIHR Institutes of Health Services and Policy Research; Musculoskeletal Health and Arthritis; Gender and Health; Human Development, Child and Youth Health; Nutrition, Metabolism and Diabetes; and Infection and Immunity. Miss Ila Stewart provided support for the IBD/FBD Review Group through the Olive Stewart Fund.
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 1692
AIMS OF REVIEW:	To determine the efficacy and safety of natalizumab for induction of remission in Crohn's disease.
STUDIES INCLUDED IN META-ANALYSIS:	4 studies: Ghosh 2003, Gordon 2001, Sandborn 2005, Targan 2006
TIME PERIOD COVERED:	1966 to September 2006
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs comparing natalizumab to a placebo or control therapy for the induction of remission in Crohn's disease
CHARACTERISTICS OF INCLUDED POPULATIONS:	Participants included patients > 18 years of age with Crohn's disease defined by conventional clinical, radiological and endoscopic criteria, which is categorized as being active (CDAI >150)

Authors: MacDonald and McDonald **Year: 2007**	
CHARACTERISTICS OF INTERVENTIONS:	Interventions involving natalizumab (300 mg or 3 to 4 mg/kg) vs. placebo or a control therapy
MAIN RESULTS:	*Failure to induce remission at twelve weeks:* The RR of failure to induce remission with natalizumab was statistically significant (RR=0.87, 95% CI 0.78 to 0.98). The absolute risk reduction or risk difference was calculated to be -0.09 (95% CI -0.17 to -0.01). The number of patients that need to be treated with three infusions of natalizumab (4 mg/kg) versus placebo to induce remission in one patient at twelve weeks was 12. The subgroup analyses demonstrated statistically significant differences in remission at twelve weeks favoring three infusions of natalizumab (4mg/kg) over placebo for patients with an elevated C-reactive protein at baseline (RR=0.81, 95% CI 0.71 to 0.92; NNT=8), for patients using immunosuppressants (RR=0.79, 95% CI 0.65 to 0.96; NNT=7) and for patients previously treated with anti-TNF therapy (RR=0.85, 95% CI 0.73 to 0.98; NNT=9). *Failure to induce clinical response at twelve weeks:* The RR of failure to induce clinical response with natalizumab was statistically significant (RR=0.79, 95% CI 0.67 to 0.95). The absolute risk reduction or risk difference was calculated to be -0.10 (95%CI -0.18 to -0.02). The number of patients that need to be treated with three infusions of natalizumab (4 mg/kg) versus placebo to induce clinical response in one patient at twelve weeks was 10. Subgroup analyses demonstrated statistically significant differences in clinical response at twelve weeks favouring three infusions of natalizumab (4 mg/kg) over placebo for patients with an elevated C-reactive protein at baseline (RR=0.71, 95% CI 0.58 to 0.86; NNT=7), for patients using immunosuppressants (RR=0.68, 95% CI 0.51 to 0.91; NNT=6) and for patients previously treated with anti-TNF therapy (RR=0.67, 95% CI 0.53 to 0.83; NNT=5). **Three infusions of natalizumab (300 mg) versus placebo** *Failure to induce clinical response at both weeks 8 and 12:* The RR of failure to induce clinical response with natalizumab at both weeks 8 and 12 was statistically significant (RR=0.77, 95% CI 0.67 to 0.89). The absolute risk reduction or risk difference was calculated to be -0.15 (95% CI -0.24 to -0.07). The number of patients that need to be treated with three infusions of natalizumab (300 mg) versus placebo to induce clinical response in one patient at both eight and twelve weeks was 7. A statistically higher proportion of natalizumab treated patients compared to placebo had a clinical response at all assessments (weeks 4, 8 and 12; $P < 0.001$).

	Failure to induce remission at both weeks 8 and 12: The RR of failure to induce clinical remission with natalizumab at both weeks 8 and 12 was statistically significant (RR=0.88, 95% CI 0.80 to 0.96). The absolute risk reduction or risk difference was calculated to be -0.10 (95% CI -0.17 to -0.03). The number of patients that need to be treated with three infusions of natalizumab (300 mg) versus placebo to induce clinical remission in one patient at both eight and twelve weeks was 10. A statistically higher proportion of natalizumab treated patients compared to placebo were in clinical remission at all assessments (weeks 4, 8 and 12; $P < 0.009$).
ADVERSE EVENTS:	Very little reported. "Two patients with multiple sclerosis treated with natalizumab in combination with interferon beta-1a and one patient with Crohn's disease treated with natalizumab in combination with azathioprine developed progressive multifocal leukoencephalopathy (PML) resulting in two patient deaths. A retrospective investigation was conducted to assess the risk of PML in natalizumab treated patients and no new cases were identified."
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Fair

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Sands et al.,**[97-99] **Lichtenstein et al.**[100] **Year: 2004, 2005, 2006** **Country:** Multinational		
FUNDING:	Centocor and NIH		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab in maintaining closure of draining fistulas among patients who had a response to a three dose induction regimen of infliximab		
DESIGN:	**Study design:** RCT **Setting:** 45 sites **Sample size:** 282		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 54 weeks 144	**INF** 5mg/kg of body weight 54 weeks 138	
INCLUSION CRITERIA:	Men and women, 18 or older, with Crohn's disease with single or multiple draining fistulas, including perianal and enterocutaneous fistulas, for at least 3 months; women with rectovaginal fistulas were included if they had at least one other enterocutaneous draining fistula.		
EXCLUSION CRITERIA:	Patients with rectovaginal fistulas but no enterocutaneous fistula; patients that had a stricture or abscess for which surgery might be indicated; previous treatment with INF		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, MTX, and antibiotics were permitted		

<table>
<tr><td colspan="4">Authors: Sands et al.
Year: 2004 and 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>36</td><td>37</td><td></td></tr>
<tr><td>Sex (% female):</td><td>52</td><td>45</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Previous surgery for CD (%)</td><td>55</td><td>57</td><td></td></tr>
<tr><td>• CDAI (%) ≥150</td><td>59</td><td>59</td><td></td></tr>
<tr><td>• CDAI (%) ≥220</td><td>32</td><td>34</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Time to loss of response defined by change in the number of draining fistulas
Secondary Outcome Measures: Crohn’s disease activity index (CDAI); Inflammatory bowel disease questionnaire (IBDQ), hospitalizations, hospitalization days, number of surgeries; new abscess
Timing of assessments: weeks 0, 2, 6, 10, 14, 22, 30, 38, 46,54</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Time to loss was significantly longer for patients with received INF maintenance therapy than for those who received placebo maintenance (more than 40 weeks vs. 14 weeks, $P < 0.001$).
• 62% of patients in placebo group had a loss of response vs. 42% in INF group ($P < 0.001$)
• At week 54, 19% of patients in placebo group had a complete absence of draining fistulas, as compared with 36% of INF patients ($P = 0.009$).
• Compared to placebo, INF patients had fewer hospitalizations (11 vs. 31; $P < 0.05$), fewer mean hospitalization days (0.5 vs. 2.5 days/100; $P < 0.05$), and fewer surgeries (65 vs. 126; $P < 0.05$)
Intermediate Outcome Measures:
• Median decrease in CDAI at week 54 was 15 for placebo and 40 for INF ($P = 0.04$)
• Median increase for IBDQ at week 54 was 5 for placebo and 10 for INF ($P = 0.03$)
2nd Year Safety Analysis:
• 15% (95%CI: 9-21%)of patients in INF maintenance group had at least one newly developed fistula-related abscess compared with 19% (95%CI: 12-25%) in placebo group ($P = 0.526$)
• Proportion of patients with a new fistula-related abscess was similar regardless of whether or not patients crossed over to a 5 mg/kg higher INF dose
• Number of fistula-related abscesses diagnosed over time did not differ between groups</td></tr>
</table>

Authors: Sands et al. **Year:2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • New fistula related abscesses • Infusion reactions • Developed antinuclear antibodies	**Placebo** 132 (92%) 48 (33%) 25 (17%) 24 (17%) 24 (18%)	**INF** 123 (89%) 22 (16%) 17 (12%) 22 (16%) 56 (46%)	
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Method NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Unable to assess; assume no loss to follow-up		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** NR 12 (8%)	**INF** NR 5 (4%)	
QUALITY RATING:	**Good**		

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Schreiber et al.[101] and Rutgeerts et al.[102]** **Year: 2005 and 2008** **Country:** Multinational			
FUNDING:	Celltech (now UCB)			
RESEARCH OBJECTIVE:	To investigate the safety and efficacy of certolizumab in Crohn's disease			
DESIGN:	**Study design:** RCT **Setting:** Multicenter (58) **Sample size:** 292 (291 ITT)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 20 weeks 73	**Certolizumab100** 100 mg wks 0,4,8 20 weeks 74	**Certolizumab200** 200 mg wks 0,4,8 20 weeks 72	**Certolizumab400** 400 mg wks 0,4,8 20 weeks 72
INCLUSION CRITERIA:	At least 18 years old with a clinical diagnosis of Crohn's disease as confirmed by radiologic, endoscopic, or histologic evidence following established diagnostic criteria; moderate to severe disease, defined by a CDAI score of 220–450 points over a 7-day screening period.			
EXCLUSION CRITERIA:	Suspected or diagnosed abscess at screening, a bowel perforation or evidence of noninflammatory obstruction during the 6 months before, extensive bowel resection, a functional colostomy or ileostomy, a positive stool culture for enteric pathogens, or a known history of tuberculosis; treatment for Crohn's disease with sodium cromoglycate, mycophenolate, or cyclosporine within 4 weeks, or receipt of other anti-TNF therapy with a biologic agent within 12 weeks; treated previously with any anti-TNF agent and either had experienced an infusion reaction that was suspected or confirmed to be associated with an immune response, or had showed a lack of clinical response to the first dose; participated in another clinical trial with certolizumab; involved in any other clinical drug trial within the 4 weeks			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Permitted if the patient was on a stable dose that could be continued throughout the 12-week duration			

<table>
<tr><td colspan="5">Authors: Schreiber et al. and Rutgeerts et al.
Year: 2005 and 2008</td></tr>
<tr><td rowspan="6">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: moderate-to-severe</td></tr>
<tr><td><u>Placebo</u></td><td><u>Certolizumab100</u></td><td><u>Certolizumab200</u></td><td><u>Certolizumab400</u></td></tr>
<tr><td>Mean age (years):</td><td>35.8</td><td>33.5</td><td>40.1</td><td>35.9</td></tr>
<tr><td>Sex (% female):</td><td>67.1</td><td>52.7</td><td>69.4</td><td>55.6</td></tr>
<tr><td>Ethnicity (% white):</td><td>96.6</td><td>96.6</td><td>96.6</td><td>96.6</td></tr>
<tr><td>Other germane population qualities:
• Disease duration (yrs)
• IBDQ</td><td>
7.95
122.9</td><td>
7.73
132.2</td><td>
8.84
122.9</td><td>
8.43
126.5</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: CDAI response (≥ 100 point decrease) or remission (CDAI score ≤ 150) at week 12

Secondary Outcome Measures: Remission (CDAI score ≤ 150), HRQOL at 12 weeks using IBDQ

Timing of assessments: Weeks 0,2,4,6,8,10,12</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• Week 12 response or remission: placebo 35.6% CER100 36.5% CER200 36.1% CER400 26.4%
• Week 12 remission placebo 23.3% CER100 27.0% CER200 19.4% CER400 44.4%
• Week 12 remission on IBDQ (>170) placebo 23.36%, CER100 38.4%, CER200 23.6%, CER400 38.9%: CER400 vs. placebo $P < 0.05$</td></tr>
</table>

Authors: Schreiber et al. and Rutgeerts et al. **Year: 2005 and 2008**				
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious AE • ISR	**Placebo** 69.9 8.2 2.7	**Certolizumab100** 77.0 9.5 6.8	**Certolizumab200** 76.4 13.9 5.6	**Certolizumab400** 65.8 8.2 2.7
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	Yes			
BLINDING OF OUTCOME ASSESSORS:	Yes but method NR			
ATTRITION (*overall*):	**Overall attrition:** 29% (85 withdrawals) **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Placebo**	**Certolizumab100**	**Certolizumab200**	**Certolizumab400**
Attrition overall:	27%	32%	26%	29%
Attrition due to adverse events:	11%	12%	10%	10%
QUALITY RATING:	**Fair**			

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Targan et al**[103] **Year: 2007** **Country:** Multinational **Trial name:** ENCORE	
FUNDING:	Elan Pharmaceuticals, Inc and Biogen Idec	
RESEARCH OBJECTIVE:	Evaluate the efficacy of natalizumab induction therapy in patients with Crohn's Disease	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (114 sites) **Sample size:** 509	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 250	**Natalizumab** 300 mg 12 weeks 259
INCLUSION CRITERIA:	Moderately to severe CD (based on clinical evaluation and CDAI scores ≥220 to ≤450) and objective evidence of inflammation as confirmed by elevated CRP concentrations (>2.87 mg/L (ULN)) as assessed by the study central laboratory at the screening visit. Required to have at least a 6-month history of CD, and radiologic or endoscopic studies were required within the previous 36 months or following prior surgical resection to confirm the diagnosis.	
EXCLUSION CRITERIA:	Short-bowel syndrome, an ostomy, a total colectomy, a stricture with obstructive symptoms, draining fistulas, an abdominal abscess, had received anti–tumor necrosis factor therapy within the previous 12 weeks, or had ever previously been treated with natalizumab	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	stable doses of 5-aminosalicylates, prednisone or an equivalent corticosteroid (≤20 mg/day), budesonide (≤6 mg/day), azathioprine, 6-mercaptopurine, MTX, and antibiotics	

Authors: Targan et al. **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** moderate – severe	
	Placebo	**Natalizumab**
Mean age (years):	37.7	38.1
Sex (% female):	59	59
Ethnicity (%):		
Black	2	1
White	94	95
Asian	<1	<1
Hispanic	<1	<1
Other	2	3
Other germane population qualities:		
• HAQ score	38	42
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Induction of response (≥70-point decrease from baseline in the CDAI score) at Week 8 sustained through Week 12 Proportion of patients with sustained remission (CDAI < 150) and response to remission over time **Secondary Outcome Measures:** IBDQ **Timing of assessments:** -2, 0, 4, 8, and 12 weeks	
RESULTS:	**Health Outcome Measures:** Response at Week 8 sustained through Week 12 NAT vs. placebo (48% vs. 32%, $P < 0.001$) Sustained remission: 26% vs. 16%, $P = 0.002$ Response at week 4: 51% vs. 37%, $P < 0.001$ Responses remained significantly higher at subsequent assessments ($P < .001$) in NAT patients NAT-treated patients had significantly higher remission rates at Weeks 4, 8, and 12 ($P < .009$)	

Authors: Targan et al. **Year: 2007**		
ADVERSE EVENTS: **Overall adverse effects reported:** • infections •	**Placebo** 75 (30%)	**Natalizumab** 90 (35%)
Significant differences in adverse events:	No	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (1)	
ADEQUATE RANDOMIZATION:	**NR**	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall attrition:** 16% **Attrition differential high:** No	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Placebo** 17% 13%	**Natalizumab** 15% 23 9%
QUALITY RATING:	**Fair**	

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Targan et al.**[104] **and Lichtenstein et al.**[105] **Year: 1997 and 2002** **Country:** North America and Europe			
FUNDING:	Centocor and an Orphan drug grant from the FDA			
RESEARCH OBJECTIVE:	To assess the efficacy of infliximab in Crohn's disease; patients not responding at 4 weeks were given open label infliximab at 10mg/kg			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (18 sites) **Sample size:** 108			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** Single infusion at 5 mg/kg 12 weeks 27	**INF** Single infusion at 10 mg/kg 12 weeks 28	**INF** Single infusion at 20 mg/kg 12 weeks 28	**Placebo** N/A 12 weeks 25
INCLUSION CRITERIA:	Crohn's disease for six months, with scores on the CDAI between 220 and 400			
EXCLUSION CRITERIA:	Cyclosporine, MTX, or experimental agents within three months before screening; symptomatic stenosis or ileal strictures; proctocolectomy or total colectomy; stoma; history of allergy to murine proteins; prior treatment with murine, chimeric, or humanized monoclonal antibodies; treatment with parenteral corticosteroids or corticotropin within four weeks before screening.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Mesalamine for 8 or more weeks; mercaptopurine or azathioprine for 6 or more months; coticosteroids			

<table>
<tr><td colspan="5">Authors: Targan et al. and Lichtenstein et al.
Year: 1997 and 2002</td></tr>
<tr><td rowspan="6">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: Moderate - severe</td></tr>
<tr><td><u>INF 5</u></td><td><u>INF10</u></td><td><u>INF20</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>37.0</td><td>39.3</td><td>36.0</td><td>38.5</td></tr>
<tr><td>Sex (% female):</td><td>48</td><td>54</td><td>54</td><td>40</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:
• Previous surgery for CD (%)
• Mean baseline CDAI</td><td>
44
312</td><td>
50
318</td><td>
50
307</td><td>
52
288</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: CDAI response of reduction of 70 or more points at 4 weeks

Secondary Outcome Measures: IBDQ and CRP(mg/liter)

Timing of assessments: 2, 4, and 12 weeks; patients not responding at 4 weeks were given an open-label dose of INF 10mg/kg</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• At 4 weeks, the end of the blinded portion, the CDAI response was significantly better in the active treatment groups (INF 5mg/kg 81% (P < 0.001 vs. placebo); INF 10mg/kg 50% (P = 0.003 vs. placebo); INF 20mg/kg 64% (P < 0.001 vs. placebo); placebo 17%
• IBDQ score increase was significantly better for active treatment (INF 5mg/kg 46 (P < 0.001 vs. placebo); INF 10mg/kg 30 (P = 0.02 vs. placebo); INF 20 (P = 0.03 vs. placebo); placebo 5
Intermediate Health Outcome Measure:
• CRP decreased significantly compared to placebo (P < 0.01)
• At 4 weeks, 48 non-responders were given a10mg/kg dose; 57% of persons initially on placebo responded and 34% of persons with 2nd INF dose responded</td></tr>
</table>

Authors: Targan et al. and Lichtenstein et al. **Year: 1997 and 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Headache • Nausea • URTI • Fatigue	**<u>One dose (n = 102)</u>** 76 (75%) 19 (19% 11 (11%) 8 (8%) 6 (6%)	**<u>Two doses (n = 29)</u>** 23 (79%) 3 (10%) 5 (17%) 4 (14%) 3 (10%)	**<u>Placebo (n = 25)</u>** 15 (60%) 5 (20%) 2 (8%) 3 (12%) 1 (4%)
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**<u>One dose</u>** NR NR	**<u>Two doses</u>** NR 2 (7%)	**<u>Placebo</u>** 0 NR
QUALITY RATING:	**Fair**		

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Brimhall et al.**[106] **Year: 2008** **Country:**
FUNDING:	None
DESIGN:	**Study design:** Systematic review **Number of patients:** 7931
AIMS OF REVIEW:	To evaluate and compare the efficacy and safety of biological agents in the treatment of plaque psoriasis
STUDIES INCLUDED IN META-ANALYSIS	**ALE (three trials)** n=1289 **EFA (five trials)** n=3130 **ETA (four trials)** n=2017 **INF (four trials)** n=1495
TIME PERIOD COVERED:	MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. were searched from inception to June 2005; an updating search was conducted in July 2006 to capture reports from the interim period
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized, controlled, double-blind, monotherapy trials
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with psoriasis

Authors: Brimhall et al.
Year: 2008

CHARACTERISTICS OF INTERVENTIONS:

ALE vs. placebo
EFA vs. placebo
ETA vs. placebo
INF vs. placebo

MAIN RESULTS:

NNT (95% CI)	PASI 50	PASI 75	PASI 90
ALE	4(3.07–4.48)	8 (5.05–12.20)	N/A
EFA	3(3.26–4.48)	4(3.36–5.24)	N/A
ETA	N/A	3(2.07–2.49)	5(4.29–5.88)
INF	N/A	2(1.24–1.38)	2(1.67–2.31)

ADVERSE EVENTS:

	NNH (95%CI)
ALE	15(7.63–142.86)
EFA	9(7.30–13.88)
ETA	46(–48–14)
INF	9(5.99–19.61)

COMPREHENSIVE LITERATURE SEARCH STRATEGY:

Yes

STANDARD METHOD OF APPRAISAL OF STUDIES:

Yes

QUALITY RATING:

Fair

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Gordon[107] and Shikiar[108]** **Year: 2006** **Country:** US and Canada		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	Efficacy and safety of ADA in patients with moderate to severe plaque psoriasis. After 12 week all patients were switched to active arms.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 147		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 52	**ADA EOW** 80 mg at week 0 and 40 mg EOW 12 weeks 45	**ADA Weekly** 80 mg at week 0 and 40 mg weekly 12 weeks 50
INCLUSION CRITERIA:	Men and women age 18 years and older with plaque psoriasis of at least 1-year duration and involving 5% or more of their body surface area.		
EXCLUSION CRITERIA:	History of neurologic symptoms suggestive of central nervous system demyelinating disease, or with a history of cancer or lymphoproliferative disease (other than successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low to mid dose topical corticosteroids		

<table>
<tr><td colspan="4">Authors: Gordon and Shikiar
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline:</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>ADA EOW</u></td><td><u>ADA Weekly</u></td></tr>
<tr><td>Mean age (years):</td><td>43</td><td>46</td><td>44</td></tr>
<tr><td>Sex (% female):</td><td>35</td><td>29</td><td>34</td></tr>
<tr><td>Ethnicity (% Caucasian):</td><td>92</td><td>89</td><td>90</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean PASI</td><td>16.0</td><td>16.7</td><td>14.5</td></tr>
<tr><td>• Mean body surface area involvement</td><td>28</td><td>29</td><td>25</td></tr>
<tr><td>• Mean duration of psoriasis -yrs</td><td>19</td><td>21</td><td>18</td></tr>
<tr><td>• Received prior systemic therapy (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75% and DLQI at 12 weeks
Secondary Outcome Measures: PASI 75 at 24 weeks and PGA, SF-36 Health Survey, and Euro QoL-5D (EQ-5D)
Timing of assessments: weeks 0, 1, 2, and 4, and then every 4 or 8 weeks thereafter.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• PASI 75% at 12 weeks Placebo 4% ADA EOW 53% ADA WK 80%
• PASI 100% at 12 weeks Placebo 0% ADA EOW 11% ADA WK 26%
• DLQI change at 12 weeks Placebo 1.3% (3.3, 0.7) ADA EOW 10.8 (13.1, 8.5) ADA WK 11.5 (13.6, 9.4) ADA(both) vs. placebo $P < 0.001$
• EQ-5D Index score change at 12 weeks Placebo 0.1 (0.07, 0.1) ADA EOW 0.21 (0.11, 0.31) ADA WK 0.19 (0.09, 0.28) ADA(both) vs. placebo $P < 0.001$
• EQ-5D VAS change at 12 weeks Placebo 0.5 (5.7, 6.8) ADA EOW 17.9 (10.5, 25.2) ADA WK 10.7 (4.1, 17.4) ADA EOW vs. placebo $P < 0.001$ and ADA WK vs. placebo $P = 0.013$
• SF-36 PCS change at 12 weeks Placebo 0.5 (2.4, 3.5) ADA EOW 3.6 (0.2, 7.0) ADA WK 5.5 (2.4, 8.6) ADA EOW vs. placebo $P = 0.118$ and ADA WK vs. placebo $P = 0.010$
• SF-36 MCS change at 12 weeks Placebo o.1 (3.5, 3.3) ADA EOW 7.8 (3.9, 11.8) ADA WK 5.2 (1.6, 8.9) ADA EOW vs. placebo $P < 0.001$ and ADA WK vs. placebo $P = 0.017$</td></tr>
</table>

Authors: Gordon and Shikiar **Year: 2006**			
ADVERSE EVENTS:	**Placebo**	**ADA EOW**	**ADA Weekly**
Overall adverse effects reported:	67.3%	62.2%	78.0%
• infections	0	0	8.0%
• Dyspepsia	0	0	8.0%
• Nausea	5.8%	6.7%	2.0%
• Injection site pain	5.8%	6.7%	12.0%
Significant differences in adverse events:	None reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 7 (5%) **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**ADA EOW**	**ADA Weekly**
Attrition overall:	3.8%	4.4%	6.0%
Attrition due to adverse events:	1.9%	4.4%	6.0%
QUALITY RATING:	**Fair**		

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors, article #: Menter [109] and Revicki [110, 111]** **Year: 2008 and 2007** **Country:** United States and Canada		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	Clinical efficacy and safety of adalimumab for moderate to severe psoriasis and investigate continuous versus interrupted therapy		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1212		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 16 weeks 398	**Adalimumab** 80 mg at wk 0 then 40 mg eow 16 weeks 814	**drug 3**
INCLUSION CRITERIA:	18 years or older, clinical diagnosis of psoriasis for at least 6 months, stable plaque psoriasis for at least 2 months before screening, moderate to severe plaque psoriasis defined as 10% or more of body surface area affected, a PASI score of 12 or greater, and PGA of at least moderate severity at the baseline.		
EXCLUSION CRITERIA:	history of neurologic symptoms suggestive of central nervous system demyelinating disease or with a history of cancer or lymphoproliferative disease (other than successfully treated nonmelanoma skin cancer or localized carcinoma in situ of the cervix)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low- to mid-potency topical corticosteroids applied to the palms, soles, face, and intertriginous areas		

Authors: Menter
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes

	Placebo	Adalimumab	drug 3
Mean age (years):	45.4	44.1	
Sex (% female):	35.4	32.9	
Ethnicity (% Caucasian):	90.2	91.2	
Other germane population qualities:			
• Mean PASI	18.8	19.0	
• Mean body surface area involvement	25.6	25.8	
• Mean duration of psoriasis	18.4 yrs	18.1 yrs	
• Received prior systemic therapy non/biologic (%)	22.1/13.3	23.1/11.9	

OUTCOME ASSESSMENT:

Primary Outcome Measures: PASI 75 at 16 weeks, % of patients losing an adequate response after week 33 to week 52 and DLQI
Secondary Outcome Measures: PGA, SF-36
Timing of assessments: Baseline and weeks 4,8,12,16,24,33,36,40,44,48,and 52

RESULTS:

Health Outcome Measures:

- PASI 75 at 16 weeks Placebo 7% vs. ADA 71% P < 0.001
- PASI 90 and 100 at 16 weeks Placebo 2% and 1% vs. ADA 45% and 20% P < 0.001
- PGA, clear or minimal at week 12, Placebo 4% vs. ADA 60% P < 0.001
- From weeks 33 to 52, patients rerandomized to placebo (28%; 68 of 240) compared with patients rerandomized to adalimumab (5%; 12 of 250) P < 0.001.

Measure	Placebo change from baseline at 16 weeks	ADA change from baseline at 16 weeks	
DLQI	1.9 (2.6, 1.3)	8.4 (8.8, 7.9)	P < 0.001
SF 36 PCS	0.4 (0.5, 1.2)	3.7 (3.1, 4.3)	P < 0.001
SF 36 MCS	0.3 (0.7, 1.4)	3.8 (3.1, 4.5)	P < 0.001
Patients global assessment	0.4 (0.5, 0.3)	1.7 (1.8, 1.6)	P < 0.001

Authors: Menter and Revicki **Year: 2008 and 2007**			
ADVERSE EVENTS %:	**Placebo**	**Adalimumab**	**drug 3**
Overall adverse effects reported:	55.5	62.2	
• Serious AE	1.8	1.8	
• Serious infection	1.0	0.6	
• Infection	22.4	28.9 P = 0.019	
• Malignincies (not NMSC)	0.3	0.2	
• NMSC	0.3	0.5	
• URTI	3.5	7.2 P = 0.01	
• Nasopharyngitis	6.5	5.3	
• Headache	3.8	4.9	
Significant differences in adverse events:	In infections and URTI – see above		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 74/1212 or 6.1% **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**Adalimumab**	**drug 3**
Attrition overall:	10.8%	3.8%	
Attrition due to adverse events:	1%	1%	
QUALITY RATING:	**Good**		

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors, article #: Paller et al.**[112] **Year: 2008** **Country:** US and Canada		
FUNDING:	Immunex, a wholly owned subsidiary of Amgen, and by Wyeth Pharmaceuticals.		
RESEARCH OBJECTIVE:	Efficacy and safety of etanercept in children and adolescents with moderate-to-severe plaque psoriasis		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 211		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 0.8 mg per kg 12 weeks 106	**Placebo** NA 12 weeks 105	
INCLUSION CRITERIA:	4 to 17 years; stable, moderate-to-severe plaque psoriasis at screening, defined as a psoriasis area-and-severity index (PASI) score of at least 12), a static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the BSA; a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.		
EXCLUSION CRITERIA:	pregnancy or lactation (sexually active patients were required to use contraception); guttate, erythrodermic, or pustular psoriasis; other skin conditions that would interfere with study evaluations; previous treatment with anti-TNF agents; major concurrent medical conditions; treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B, systemic psoriasis medications, oral or parenteral corticosteroids, topical corticosteroids, topical vitamin A or D analogue preparations, anthralin, or calcineurin inhibitor within a 14-day washout period before the study; and treatment with biologic agents within a 30-day washout period		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low-to-moderate-potency topical steroids on the scalp, axillae, or groin.		

<table>
<tr><td colspan="4">Authors: Paller
Year: 2008</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline:</td></tr>
<tr><td></td><td><u>Etanercept</u></td><td><u>Placebo</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>14</td><td>13</td><td></td></tr>
<tr><td>Sex (% female):</td><td>48</td><td>50</td><td></td></tr>
<tr><td>Ethnicity(% white):</td><td>78</td><td>71</td><td></td></tr>
<tr><td>Other germane population qualities:
• Mean PASI
• Mean body surface area involvement
• Mean duration of psoriasis
• Received prior systemic therapy or phototherapy (%)</td><td>
16.7
21.0

6.8 yrs
55</td><td>
16.4
20.0

5.8 yrs
59</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75 at week 12

Secondary Outcome Measures: PASI 50 and 90, physicians global assessment of clear or almost clear, Children’s Dermatology Life Quality Index

Timing of assessments: Baseline weeks 2,4,6,8,12 16 and every 4 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures at 12 weeks:
• PASI 75 etanercept 57% vs. placebo 11% $p < 0.001$
• PASI 50 etanercept 75% vs. placebo 23% $p < 0.001$
• PASI 90 etanercept 27% vs. placebo 7% $p < 0.001$
• Physicians global assessment of clear or almost clear etanercept 53% vs. placebo 13% $p < 0.001$
• CDLQI mean improvementetanercept 52% vs. placebo 18%</td></tr>
</table>

Authors: Paller et al. **Year: 2008**			
ADVERSE EVENTS: event rate per 100 pt/yrs	**Etanercept**	**Placebo**	
Overall adverse effects reported:	554.5	765.4	
• URTI	54.6	69.1	
• Headache	32.8	95.7	
• Nasophyrantgitis	31.5	53.2	
• Influenza	14.0	15.9	
• Streprococcal pharygitis	13.3	5.3	
• Cough	12.1	10.6	
• Pharyngolaryneal pain	12.1	31.9	
• Vomiting	12.1	10.6	
• Nasal congestion	10.3	15.9	
• Skin papilloma	9.7	0	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 3 **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Etanercept**	**Placebo**	**drug 3**
Attrition overall:	2%	1%	
Attrition due to adverse events:	0	1%	
QUALITY RATING:	**Fair**		

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Reich et al.**[113, 114], [115] **Year: 2005 and 2006 and 2007** **Country:** NR	
FUNDING:	Centocor and Schering-Plough	
RESEARCH OBJECTIVE:	To present the results of a phase III study, addressing the long-term safety, efficacy and productivity of infliximab for the treatment of skin and nail lesions in patients with psoriasis	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 378	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo / INF** 0, 2, and 6, through week 22. At weeks 24, 26, and 30, the placebo group crossed-over to infliximab 5 mg/kg induction and maintenance therapy through week 46. 77	**INF** 5 mg/kg (0, 2, and 6, and every 8 weeks week 46 301
INCLUSION CRITERIA:	Patients diagnosed with moderate to severe plaque psoriasis for ≥ 6 months; candidates for phototherapy or systemic therapy; PASI of ≥ 12 and ≥ 10% of their total body surface area affected by psoriasis.	
EXCLUSION CRITERIA:	History or risk of serious infection, lymphoproliferative disease, or active TB; previous treatment with INF or any other TNFα-antagonist was not allowed.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	2.5% hydrocortisone, or equivalent, applied topically to face, groin, or both, after week 10.	

Authors: Reich et al. **Year: 2005 and 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-to-severe	
	Placebo	**INF**
Mean age (years):	43.8	42.6
Sex (% female):	21	31
Ethnicity:	NR	NR
Other germane population qualities:		
• Psoriasis duration (yrs)	17.3	19.1
• Body surface area (%)	18	19
• PASI	22.8	22.9
• Patients with nail psoriasis (%)	86	81
• History of MTX use (%)	46	42
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 (≥ 75% improvement in baseline PASI) at week 10 and Quality of life DLQI and SF-36, 10-cm productivity visual analog scale (VAS), role-physical and role-emotional domain scores of the Short Form 36-Item questionnaire (SF-36). **Secondary Outcome Measures:** PASI 75 at week 24; PGA of cleared or minimal at week 10, 24, and 50; PASI 50; PASI 90; NAPSI at weeks 10, 24, and 50. **Timing of assessments:** NR	
RESULTS:	**Health Outcome Measures:** • At week 24, PASI 75 achieved by 82% (INF) vs. 4% (placebo) ($P < 0.0001$) • The % improvement in the NAPSI was significantly greater in INF-treated patients than placebo at weeks 10 and 24. Improvement from baseline • At week 24, DLQI INF 10.0 vs. placebo 0.2 ($P < 0.001$) • At week 24, SF-36 PCS INF 4.9 vs. placebo -1.4 ($P < 0.001$) • At week 24, SF-MCS INF 5.3 vs. placebo -0.5 ($P < 0.001$) • At week 24, Productivity VAS, INF – 0.2 ± 3.2 vs. placebo 2.5 ± 3.5 ($P < 0.001$) • At week 24, PGA response INF 74 vs. placebo 3%, ($P < 0.0001$) **Intermediate Outcome Measures:** • 6% and 2% of patients in INF group had asymptomatic increases in alanine aminotransferase and aspartate aminotransferase, respectively. • Fewer antibody-positive patients achieved PASI 75.	

Authors: Reich et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported (%)**	**Placebo/INF**	**INF**	
• URTI	16	15	
• Headache	12	14	
• Pain	5	6	
• Psoriasis	13	3	
• Severe adverse event	3	6	
• Infections	40	42	
• Neoplasms	0	1	
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION %(*overall*):	**Overall loss to follow-up:** 10.4% (24 weeks) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo/INF**	**INF**	
Loss to follow-up:	10.4	10.3	
Withdrawals due to adverse events:	7%	9%	
QUALITY RATING:	**Good**		

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Reich**[116] **Year:** 2008 **Country:** Multinational
ARTICLE ID #:	**#3619**
FUNDING:	Schering Plough INC
DESIGN:	**Study design:** Systematic Review and Meta-analysis **Number of patients: 7027**
AIMS OF REVIEW:	To conduct a meta-analysis to assess the effects of available biological agents on the severity of psoriasis, as well as to provide data on the effects of these agents on HRQoL.
STUDIES INCLUDED IN META-ANALYSIS	Lebwohl 2003, Krueger 2002, Ellis, Papp 2005, Leonardi 2005, Gordon 2003, Tyring 2006, Gottlieb 2003, Menter 2006, Chaudhari 2001, Ellis and Krueger, Dubertret 2006
TIME PERIOD COVERED:	1966 to December 2006
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs of at least 10 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with moderate to severe psoriasis

Authors: Reich
Year: 2008
Country: Multinational

CHARACTERISTICS OF INTERVENTIONS:	Infliximab, etanercept, efalizumab and alefacept
MAIN RESULTS:	RR (95% CI) Alefacept versus placebo PASI 50 2.57 (2.03, 3.25) PASI 75 3.37 (2.18, 5.23) PASI 90 – NR Mean difference DLQI 1.65 (1.23-2.07) Efalizumab versus placebo PASI 50 3.92 (3.28, 4.69) PASI 75 7.47 (5.2, 10.73) PASI 908.39 (2.63, 26.79) Mean difference DLQI 3.54 (2.07-5.02) Etanercept 25 BIW versus placebo PASI 50 5.41 (4.10, 7.14) PASI 75 10.68 (6.14, 18.57) PASI 90 18.35 (5.18, 65.01) Mean difference DLQI 5.66 (3.27-8.04) Etanercept 50 BIW versus placebo PASI 50 5.85 (4.77, 7.17) PASI 75 11.92 (8.17, 17.39) PASI 90 23.32 (10.38, 52.37) Mean difference DLQI 6.07 (3.99-8.16) Infliximab versus placebo PASI 50 7.35 (4.65, 11.61) PASI 75 25.48 (14.04, 46.23) PASI 90 53.94 (17.65, 164.89) Mean difference DLQI 8.52 (4.95-12.08)

Response = PASI 50

	Probability of response			Relative Risk		
Treatment	**Mean**	**2.5 CI**	**97.5 CI**	**Mean**	**2.5 CI**	**97.5 CI**
Etanercept-25mg	0.6258	0.5552	0.6958	4.34	3.74	5.19
Etanercept-50mg	0.7525	0.6986	0.8048	5.29	4.58	6.12
Efalizumab-1mg/kg	0.556	0.498	0.6107	3.91	3.36	4.50
Alefacept	0.4044	0.3373	0.4713	2.84	2.28	3.44
Infliximab-5mg/kg	0.9406	0.9172	0.9604	6.62	5.65	7.69
Response = PASI 75						
Etanercept-25mg	0.3592	0.2928	0.4317	9.06	7.03	11.53
Etanercept-50mg	0.5001	0.4348	0.5691	12.36	10.22	15.55
Efalizumab-1mg/kg	0.2939	0.2452	0.3435	7.41	5.96	9.09
Alefacept	0.1777	0.1343	0.2243	4.48	3.21	5.89
Infliximab-5mg/kg	0.8102	0.7592	0.8567	20.49	16.28	25.37
Response = PASI 90						
Etanercept-25mgBIW	0.1289	0.09218	0.1732	22.58	15.58	31.87
Etanercept-50mgBIW	0.2202	0.1729	0.2754	38.62	28.21	52.51

	Efalizumab-1mg/kg	0.09438	0.07069	0.1213	16.50	12.08	21.93
	Alefacept	0.04503	0.02979	0.06393	7.88	4.92	11.50
	Infliximab-5mg/kg	0.5427	0.4721	0.6164	95.74	67.74	131.30
ADVERSE EVENTS:	Not analyzed						
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes						
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR						
QUALITY RATING:	**Fair**						

Evidence Table 6. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors, article #: Saurat [117], Revicki[118]** **Year: 2007** **Country:** Multinational		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	Compare a biologic agent ADA with MTX, a traditional systemic agent, to define clearly the role of biologics in psoriasis		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 271		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 16 weeks 53	**Methotrexate** 7.5 to 25 mg weekly 16 weeks 110	**Adalimumab** 80 mg load then 40 mg eow 16 weeks 108
INCLUSION CRITERIA:	≥18 years of age with moderate to severe psoriasis, plaque psoriasis for at least 1 year and stable plaque psoriasis for at least 2 months, candidates for systemic therapy or phototherapy and to have had active psoriasis despite treatment with topical agents, naive to both TNF-antagonist therapy and methotrexate.		
EXCLUSION CRITERIA:	History of clinically significant haematological, renal or liver disease⁄abnormal laboratory values; with a history of demyelinating disease, cancer, or other lymphoproliferative disease (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and⁄or localized carcinoma in situ of the cervix); or who were immunocompromised.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Shampoos free of corticosteroids; bland emollients; and low-potency topical corticosteroids for the palms, soles, face, inframammary areas and groin only, not used within 24 h of a study visit		

<table>
<tr><td colspan="4">Authors: Saurat and Revicki
Year: 2007</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>Methotrexate</u></td><td><u>Adalimumab</u></td></tr>
<tr><td>Mean age (years):</td><td>40.7</td><td>41.6</td><td>42.9</td></tr>
<tr><td>Sex (% female):</td><td>34</td><td>33.6</td><td>33.2</td></tr>
<tr><td>Ethnicity (% Caucasian):</td><td>92.5</td><td>95.5</td><td>95.4</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean PASI</td><td>19.2</td><td>19.4</td><td>20.2</td></tr>
<tr><td>• Mean body surface area involvement</td><td>28.4</td><td>32.4</td><td>33.6</td></tr>
<tr><td>• Mean duration of psoriasis</td><td>18.8</td><td>18.9</td><td>17.9</td></tr>
<tr><td>• Received prior systemic therapy and/or phototherapy (%)</td><td>90.4</td><td>87.2</td><td>82.2</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75 at week 16 and DLQI

Secondary Outcome Measures: PASI 50, 90 and 100, and PGA and EuroQOL5D

Timing of assessments: baseline and at weeks 1, 2, 4, 8, 12 and 16.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures at 16 weeks:
PASI 75 ADA 79.6% vs. 35.5% MTX vs. Placebo 18.9% (vs. ADA RD 60.5% 95% CI 44.5 to 76.6 P < 0.001
PASI 100 ADA 16.7% vs. MTX 7.3% vs. placebo 1.9 P = .004
DLQI change from baseline (95% CI) ADA 9.1 (-10.4 to -7.8) vs. MTX-5.7 (-6.8 to -4.5) vs. placebo -3.4 (-5.2 to -1.6) ADA vs. placebo P < 0.001
EQ 5D Index Score change from baseline (95% CI) ADA 0.2 (0.2 to 0.3) vs. MTX 0.1 (0.1 to 0.2) vs. placebo 0.1 (0.0 to 0.2)
EQ-5D VAS change from baseline (95% CI) ADA 21.4 (16.6 to 26.3) vs. MTX 11.5 (6.5 to 16.5) vs5.7 (-1.4 to 12.8)
PGA ADA -1.6 vs. placebo -0.5 P < 0.001</td></tr>
</table>

Authors: Saurat and Revicki **Year: 2007**			
ADVERSE EVENTS %:	**Placebo**	**Methotrexate**	**Adalimumab**
Overall adverse effects reported:	79.2	81.8	73.8
• Serious AEs	1.9	0.9	1.9
• Infections (non-serious)	43.4	41.8	47.7
• Serious infections	0	0	0
• Nasopharyngitis	20.8	23.6	28.0
• Headache	9.4	10.9	13.1
• Pruritus	11.3	1.8	3.7
• Rhinitis	7.5	3.6	2.8
• Nausea	7.5	7.3	3.7
• Rhinorrhea	5.7	0	2.8
• Viral Infection	1.9	5.5	0
• Arthralgia	1.9	4.5	5.6
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 15 (5.5%) **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**Methotrexate**	**Adalimumab**
Attrition overall:	9.4%	5.5%	3.7%
Attrition due to adverse events:	<1%	5.5%	1%
QUALITY RATING:	**Good**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.**[119] **Year: 2005** **Country:** Sweden		
FUNDING:	Swedish Cancer Society; the insurance company AFA; Wyeth Ayerst, Schering-Plough, Abbott Immunology, and Bristol Myer Squibb; Swedish National Board of Health and Welfare		
RESEARCH OBJECTIVE:	To depict the cancer pattern of contemporary patients with RA and to understand the risk of solid cancer after TNF treatment by obtaining cancer data from cohorts treated in routine care rather than trials.		
DESIGN:	**Study design:** retrospective cohort **Setting:** small outpatient clinics and larger population based centers **Sample size:** 60,930		
INTERVENTION:	N/A **Inpatient RA cohort**	N/A **Early Arthritis RA cohort**	N/A **TNF antagonist cohort**
Dose:	N/A	N/A	N/A
Duration:	N/A	N/A	N/A
Sample size:	53,067	3,703	4,160
INCLUSION CRITERIA:	Inpatient Register RA cohort: inpatients above 16 years of age ever discharged with an RA diagnosis between January 1990 & December 31 2003. Early Arthritis RA cohort: patients with RA diagnosed from 1999 through 2003. TNF antagonist cohort: patients with RA treated with ETA, INF, or ADA.		
EXCLUSION CRITERIA:	Inpatient Register RA cohort: Patients who were also discharged with systemic lupus erythematosus, AS, or PsA; observed and expected cancers during the 1st year of follow up.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Askling et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: NR</td></tr>
<tr><td></td><td><u>Inpatient RA cohort</u></td><td><u>Early Arthritis RA cohort</u></td><td><u>TNF antagonist cohort</u></td></tr>
<tr><td>Mean age (years):</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>% age 45-74 years:</td><td>56.3</td><td>65.4</td><td>71.8</td></tr>
<tr><td>Sex (% female):</td><td>71.4</td><td>69.9</td><td>74.8</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• DAS28 score (mean)</td><td>NR</td><td>3.5</td><td>5.5</td></tr>
<tr><td>• HAQ score (mean)</td><td>NR</td><td>0.6</td><td>1.4</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: observed cancers
Secondary Outcome Measures: NR
Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
<u>Inpatient RA cohort</u>
• 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.
<u>Early Arthritis cohort</u>
• Overall, 138 solid cancers (SIR = 1.1, 95% CI 0.9 to 1.3), with a non-increased risk in women (SIR = 0.87, 95% CI 0.67 to 1.11, n=64) and an increased risk among men (SIR = 1.42, 95% CI 1.12 to 1.79, n=74)
<u>TNF antagonist cohort</u>
• 67 solid cancers observed (SIR = 0.9, 95% CI 0.7 to 1.2)
• RR of solid cancer was non-significantly reduced among women (SIR = 0.87, 95% CI 0.63 to 1.16, n = 45) but 1.06 (95% CI 0.67 to 1.61, n = 22) among men.</td></tr>
</table>

Authors: Askling et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Inpatient RA cohort** NR	**Early Arthritis RA cohort** NR	**TNF antagonist cohort** NR
QUALITY RATING:	**N/A**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.**[120] **Year: 2005** **Country:** Sweden		
FUNDING:	Swedish National Board of Health and Welfare		
RESEARCH OBJECTIVE:	To assess expected rates and relative risks of haematopoietic malignancies, especially those associated with TNF antagonists, in large population based cohorts of patients with RA.		
DESIGN:	**Study design:** Observational - cohort **Setting:** Inpatient **Sample size:** 60930		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Inpatient register** N/A various	**Early Arthritis** N/A	**TNF antagonist** ETA, INF or ADA various
INCLUSION CRITERIA:	Patients with RA in Sweden		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Askling et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NA **Disease severity:** Mild-moderate-severe		
	Inpatient register	**Early Arthritis**	**TNF antagonist**
Mean age (years):	NR	NR	NR
Sex (% female):	71.3%	70%	75%
Ethnicity:	NR	NR	NR
Other germane population qualities:	N/A	3.5	5.5
• DAS score	N/A	0.6	1.4
• HAQ score			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** risk of malignant lymphomas, and maybe also of leukemia and multiple myeloma		
RESULTS:	# SIR (95% CI)	**Inpatient register**	**Early Arthritis**	**TNF antagonist**
	All haematopoietic malignancies	481 1.7 (1.5 to 1.8)	15 1.6 (0.9 to 2.6)	11 2.1 (1.1 to 3.8)
	Malignant lymphoma(CLL also)	319 1.9 (1.7 to 2.1)	11 2.0 (1.0 to 3.5)	9 2.9 (1.3 to 5.5)
	After adjustment for sex, age, and disease duration, the lymphoma risk after exposure to TNF antagonists was no higher than in the other RA cohorts.(data not shown)			

Authors: Askling et al. **Year: 2005**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.**[121] **Year: 2007** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	The degree to which treatment with tumor necrosis factor (TNF) antagonists may be associated with increased risks for serious infections		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Swedish registers **Sample size:** 44 946		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**All anti-TNF** various NR 4167	**Anti-TNF 1998-2003** various NR 2692	**Controls from RA inpatient** various NR 10 295
INCLUSION CRITERIA:	The ARTIS, 4167 rheumatoid arthritis (RA) patients starting TNF antagonist treatment 1999 and 2003 were identified. Secondly, in the Swedish Inpatient Register, all individuals hospitalized for any reason and who also carried a diagnosis of RA, between 1964 and 2003 (n = 44 946 of whom 2692 also occurred in ARTIS), were identified. Thirdly, in the Swedish Inpatient Register, all hospitalizations listing an infection between 1999 and 2003 were identified		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

<table>
<tr><td colspan="3">Authors: Askling et al.
Year: 2007</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline:
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Mean disease duration
• DAS score
• HAQ score</td><td><u>All anti-TNF 1998–2003</u>
75%
NR

12.1 yrs
5.63
1.43</td><td><u>Anti-TNF 1998–2003, also in Inpatient Register RA cohort</u>
78%
NR

15.0 yrs
5.74
1.57</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: infection</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
Within the cohort of 44 496 RA patients, the risk ratio (RR (95% CI)) for infection associated with TNF antagonists –
1st year 1.43 (95% CI 1.18 to 1.73)
2nd year 1.15 (95% CI 0.88 to 1.51)
3rd year 0.82 (95% CI 0.62 to 1.08)

Age, duration of RA, HAQ, DMARD use other than MTX, and pre-treatment co-morbidity all predicted infection risk</td></tr>
</table>

Authors: Askling et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	see results
Significant differences in adverse events:	Yes
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Good**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Bongartz et al.**[122] **Year:** 2006 **Country:** Multinational
FUNDING:	Mayo Foundation; Abbott & Centocor
DESIGN:	**Study design:** systematic literature review with meta-analysis **Number of patients:** 5,005 patients randomized (9 trials)
AIMS OF REVIEW:	To assess extent to which anti-TNF antibody therapy may increase risk of serious infection and malignancies in patients with RA; to derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy.
STUDIES INCLUDED IN META-ANALYSIS	Keystone (2004), St Clair (2004), Furst (2003), Lipsky (2000), van de Putte (2003), Weinblatt (2003), Maini (1998), van de Putte (2004), and Westhovens (2004)
TIME PERIOD COVERED:	N/A
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized controlled trials of INF & ADA in which patients had ACR-diagnosed RA and were randomized to anti-TNF vs. placebo (or anti-TNF antibody + traditional DMARD vs. placebo + traditional DMARD). Both the patient and observer were masked. Trial had to be at least 12 weeks in duration (all trials were 3 to 12 months).
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with an ACR diagnosis of RA who were randomized to receive Anti-TNF or placebo

Authors: Bongartz et al. **Year: 2006**			
CHARACTERISTICS OF INTERVENTIONS:	Anti-TNF (INF or ETA), doses varied		
MAIN RESULTS:	• In patients with RA, anti-TNF treatment leads to increased risk of serious infection and a dose-dependent increased risk of malignancies. • Malignancies reported in 24 / 3493 (0.8%) patients who received ≥ 1 dose of anti-TNF vs. 2 / 1512 (0.2%) patients on control. • Pooled OR for malignancies in anti-TNF group vs. placebo group = 3.3 (95% CI, 1.2 – 9.1); NNH was 154 (95% CI 91 – 500) within a treatment period of 3 to 12 months • Serious infections reported in 126 anti-TNF- treated patients vs. 26 control group patients (OR, 2.0; 95% CI, 1.3 – 3.1); NNH was 59 (95% CI 39 – 125) within a treatment period of 3 to 12 months		
ADVERSE EVENTS (%): • Malignancy[1] • Serious infections[2] [1] OR = 3.29 (1.19 – 9.08) [2] OR = 2.01 (1.31 – 3.09)	**Anti-TNF** 23 / 3192 126 / 3493	**Control** 3 / 1428 26 / 1512	
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes: EMBASE, MEDLINE, Cochrane Library, and electronic abstracts of the annual scientific meetings both the EULAR and the American College of Rheumatology – through December 2005		
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes		
QUALITY RATING:	**Good**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Brassard**[123] **Year: 2006** **Country:** USA	
FUNDING:	Sanofi -Aventis	
RESEARCH OBJECTIVE:	To quantify the rate of *Mycobacterium tuberculosis* disease (TB) among a cohort of patients with rheumatoid arthritis (RA) and to assess whether the independent use of DMARDs is associated with the risk of developing TB.	
DESIGN:	**Study design:** Nested cohort **Setting:** Pharmaceutical database **Sample size:** 112,300- 386 cases of TB	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Case** varied 363 days 386	**Control** varied 364 days 38600
INCLUSION CRITERIA:	Age 18 or more years; diagnosis of RA during inpatient or outpatient visit; dispensed one or more anti-RA drug from 09/1998 to 12/2003	
EXCLUSION CRITERIA:	Prior history of TB	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

<table>
<tr><td colspan="4">Authors: Brassard
Year: 2006</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>Case</u></td><td><u>Control</u></td><td><u>P =</u></td></tr>
<tr><td></td><td>Mean age (years):</td><td>54</td><td>56</td><td>0.01</td></tr>
<tr><td></td><td>Sex (% female):</td><td>77.2</td><td>73.7</td><td>0.12</td></tr>
<tr><td></td><td>Ethnicity:</td><td>NR</td><td>NR</td><td>N/A</td></tr>
<tr><td></td><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td></td><td>• Biological DMARDs</td><td>17.4</td><td>11.8</td><td>0.008</td></tr>
<tr><td></td><td>• Infliximab</td><td>4.9</td><td>2.8</td><td>0.01</td></tr>
<tr><td></td><td>• Etanercept</td><td>8.3</td><td>6.1</td><td>0.07</td></tr>
<tr><td></td><td>• Anakinra</td><td>4.9</td><td>3.6</td><td>0.17</td></tr>
<tr><td></td><td>• DMARD use</td><td>50.8</td><td>44.1</td><td>0.008</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: TB

Timing of assessments: time of diagnosis</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Overall rate of 2.19 (95% CI, 1.97–2.41) cases per 1000 person-years of follow-up.
Exposed to TNF blocking agents the rate was 2.57 (95% CI, 1.89–3.26) cases per 1000 person-years.

Biological DMARDs RR (95% CI) 1.5 (1.1-1.9)
INF RR (95% CI) 1.6 (1.0–2.6)
ETA RR (95% CI) 1.2 (0.9–1.8)
AKA RR (95% CI) 1.3 (0.8–2.1)</td></tr>
</table>

Authors: Brassard **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	**No but they are not suppose to be.**		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A		
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Burmester**[124] **Year: 2007** **Country:** Multinational
FUNDING:	Abbott
RESEARCH OBJECTIVE:	Safety and efficacy of ADA in patients with RA
DESIGN:	**Study design:** Uncontrolled, open-label trial **Setting:** Multicenter **Sample size:** 6610
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 40 mg eow 12 weeks to 5 years 6610
INCLUSION CRITERIA:	Men and women >18 years of age with active, adult-onset RA; a disease duration of >3 months, a DAS28 of >3.2, and treatment failure with at least one traditional DMARD.
EXCLUSION CRITERIA:	Current pregnancy or breast feeding; any persistent or severe infection within 30 days of baseline; previous treatment with other TNF antagonists up to 2 months before enrolment; treatment with alkylating agents, total lymphoid irradiation, intravenous immunoglobulin or any investigational biologic agent; a history of active arthritis other than RA; any uncontrolled medical condition; a history or signs of demyelinating disease; active tuberculosis (TB) or histoplasmosis; malignancy (except for completely treated squamous or basal cell carcinoma).
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	DMARDs (defined as MTX, leflunomide (LEF), sulfasalazine (SSZ), chloroquine or hydroxychloroquine (antimalarials, AM), azathioprine (AZA), and parenteral or oral gold) or any combination of DMARDs, glucocorticoids (prednisone equivalent (10 mg/day), and NSAIDs

Authors: Burmester **Year: 2007**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	ADA
Mean age (years):	54
Sex (% female):	81
Ethnicity:	NR
Other germane population qualities:	
• Tender joint count	14
• Swollen joint count	10
• Mean disease duration	11
• DMARD use (%)	74
• MTX use (%)	53
• Corticosteroids use (%)	71
• DAS score	6.0
• HAQ score	1.64
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 at week 12 and safety **Secondary Outcome Measures:** EULAR **Timing of assessments:** weeks 2, 6, 12, and every 8 weeks thereafter
RESULTS:	**Health Outcome Measures:** • Week 12, 69% of patients achieved an ACR20 response, 83% a moderate, and 33% a good EULAR response • AEs 72.4% of patients (4783/6610), RA-related events (9.7% (641/6610)), headache (4.8% (317/6610)) and nasopharyngitis (4.4% (293/6610)), and 9% were considered severe. Serious AEs (SAEs) occurred in 13% (882/6610) of patients (equivalent to 28.4 SAEs/100 PYs) three most commonly reported SAEs were RA-related events (2.0% (135/6610)), pyrexia (0.4% (25/6610)) and osteoarthritis (0.3% (20/66100). • Standardized mortality ratio 1.07 (95% CI 0.75 to 1.49), with 35 deaths observed compared with 32.6 deaths expected in the general population. • 10.3% discontinued because of adverse events. • 3% of patients had serious infections

Authors: Burmester **Year: 2007**			
ADVERSE EVENTS per 100 pys:	**All**	**No DMARDs**	**Concomitant DMARDs**
All serious AEs:	28.4	40.0	24.6
• Blood and lymphatic system disorders	0.5	1.2	0.3
• Heart failure	0.4	0.8	0.3
• Infections and infestations	5.5	6.6	5.1
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall attrition:** 7% **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**ADA** 7% at 12 weeks 4.3% at 12 weeks, 10.3% at 5 years		
QUALITY RATING:	**N/A**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Chakravarty et al.**[125] **Year: 2005** **Country:** US		
FUNDING:	Bristol-Myers-Squibb		
RESEARCH OBJECTIVE:	To determine the rates of reported non-melanoma skin cancer (NMSC) in a large cohort of patients with RA in comparison to patients with osteoarthritis (OA) and to determine risk factors of the development of NMSC in patients with RA		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Multi-center **Sample size:** 15,789 (RA); 3,639 (OA)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	N/A		
INCLUSION CRITERIA:	Participants in the National Data Bank for Rheumatic Diseases (NDB); recruited from the 908 US rheumatologists; patients who returned at least 2 questionnaires between January 1999 and January 2003.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Chakravarty et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: NR</td></tr>
<tr><td></td><td><u>Patients with RA</u></td><td><u>Patients with OA</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>62</td><td>67</td><td></td></tr>
<tr><td>Sex (% female):</td><td>77</td><td>83</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>91</td><td>94</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• HAQ-DI score</td><td>1.09</td><td>1.07</td><td></td></tr>
<tr><td>• Skin cancer before NDB (%)</td><td>3.8</td><td>5.8</td><td></td></tr>
<tr><td>• History of smoking (%)</td><td>56</td><td>46</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Self-report of diagnosis of skin cancer; morbidity; mortality; comorbid conditions.
Timing of assessments: Semi-annual questionnaires</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• A total of 738 patients with RA reported new cases of NMSC during followup within the NDB; crude incidence rate = 18.1 / 1000 patient-years (95% CI, 16.8 – 19.4 / 1000 person-years).
• After excluding prevalent cases of NMSC, incidence rate was 15.2 / 1000 person-years (95% CI, 14.1 – 16.5).
• Based on multivariate Cox proportional hazard analysis restricted to patients with RA:
  • Use of prednisolone was associated with an increased hazard ratio (HR) (HR = 1.28, 95% CI: NR; P = 0.014) for development of NMSC.
  • No association found with use of leflunomide or MTX alone.
  • Use of any anti-TNF (ETA, INF, & ADA) alone showed a slightly increased risk
  • An approximately 2-fold HR for development of NMSC was found among patients with RA using both MTX and any TNF inhibitor (HR 1.97, P = 0.001)</td></tr>
</table>

Authors: Chakravarty et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** •	NR		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	NR		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** After initial assessment, ~ 8% of patients decline to participate each year. **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR		
QUALITY RATING:	N/A		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Chung et al.**[126] **Year: 2003** **Country:** US		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To assess the effectiveness and safety of infliximab in patients with CHF		
DESIGN:	**Study design:** RCT **Study name: ATTACH (Anti-TNF Therapy Against Congestive Heart Failure) Trial** **Setting:** University clinics (32 centers) **Sample size:** 150		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 28 weeks 49	**INF** 5 mg/kg 28 weeks 50	**INF** 10 mg/kg 28 weeks 51
INCLUSION CRITERIA:	Men and women at least 18 years old with stable New York Heart Association (NYHA) class III or IV heart failure associated with a radionuclide left ventricular ejection fraction ≤35% within 14 days before randomization		
EXCLUSION CRITERIA:	Hemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease; had experienced an acute myocardial infarction or coronary revascularization procedure within 2 months; or were likely to undergo coronary revascularization or heart transplant during the anticipated duration of the study; resuscitation from sudden death or a therapeutic discharge of an implanted implantable cardioverter defibrillator within 3 months or had received within 2 weeks or were likely to receive within the following 28 weeks any of the following: A class IC or III antiarrhythmic other than amiodarone; a calcium channel blocker other than amlodipine for hypertension or angina; a positive inotrope other than digoxin; or a NSAID other than aspirin; experienced a serious infection within 2 months; had latent TB or had had TB within 3 years; had a documented HIV infection; or had any other opportunistic infection within 6 months; treatment within 3 months of INF or other therapeutic agents that could interfere with the actions of TNFα (eg, ETA, pentoxifylline, thalidomide, or D2E7)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vasodilators or nitrates		

Authors: Chung et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Placebo	**INF5**	**INF10**
Mean age (years):	60 ± 12	62 ± 15	62 ± 13
Sex (% female):	24	14	16
Ethnicity (% white):	88	88	84
Current or prior angina (%):	29	18	24
Myocardial infarction (%):	63	50	67
Diabetes mellitus (%):	41	28	37
NYHA Class III/IV (%):	96/4	96/4	92/8
LVEF (%):	0.25 ± 0.07	0.23 ± 0.07	0.24 ± 0.06
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Change in clinical status, assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using pre-specified criteria **Timing of assessments:** 1,2,6,10,14,20,28 weeks		
RESULTS:	**Health Outcome Measures:** • 10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% CI 1.01 to 7.97; nominal P = 0.043 using log-rank test) • Patients in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than patients in the placebo or 5 mg/kg INF groups		

Authors: Chung et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported (# of patients with 1 or more) n (%):** • Dizziness • Dyspnea • Hypotension • Angina • Serious AEs • Serious infections	**Placebo** 40 (83.3) 2 (4.2) 6 (12.5) 0 (0.0) 1 (2.1) (29.2) (2.1)	**INF5** 47 (92.2) 16 (31.4) 10 (19.6) 3 (5.9) 3 (5.9) (23.5) (5.9)	**INF10** 42 (84.0) 10 (20.0) 12 (24.0) 4 (8.0) 4 (8.0) (44.0) (8.0)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** 6 in all, NR separately	**Overall loss to follow-up:** NR **Loss to follow-up differential high**: NR **Placebo** 1	**INF5** 2	**INF10** 5
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Curtis**[127] **Year: 2007** **Country:** USA		
FUNDING:	Funded by FDA CBER Award #223-02-1420 Task Order #1, the Maryland chapter of the Arthritis Foundation, grant HS10389 from AHRQ, K24 AR052361-01 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and T32 AR47512-03 from the NIH.		
RESEARCH OBJECTIVE:	Investigate a possible association between TNF-antagonist use and incident heart failure,		
DESIGN:	**Study design:** Cohort study **Setting:** US claims data **Sample size:** 4018		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Exposed** ETA or INF Various 1707	**Unexposed** N/A Various 2311	
INCLUSION CRITERIA:	At least two ICD9-CM diagnosis codes for RA (714.X) or CD (555.X) during the study period and also required that each individual had received an infusion or filled a prescription for a TNF- antagonist (i.e. ETA or INF) or filled at least three prescriptions for one of several selected immunosuppressive drugs.		
EXCLUSION CRITERIA:	HIV, organ transplantation or malignancy in the 6 months prior to the index date		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

<table>
<tr><td colspan="6">Authors: Curtis
Year: 2007</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="5">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>RA_INF</u></td><td><u>RA_ETA</u></td><td><u>Unexposed</u></td><td><u>CD_INF</u></td><td><u>Unexposed</u></td></tr>
<tr><td>N</td><td>330</td><td>808</td><td>983</td><td>569</td><td>1328</td></tr>
<tr><td>Mean age (years):</td><td>40</td><td>38</td><td>39</td><td>33</td><td>32</td></tr>
<tr><td>Sex (% female):</td><td>70</td><td>75</td><td>75</td><td>57</td><td>55</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:
• Cases HF</td><td>4</td><td>1</td><td>1</td><td>1</td><td>2</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="5">Primary Outcome Measures: Heart failure</td></tr>
<tr><td>RESULTS:</td><td colspan="5">Health Outcome Measures:
• RA treated with TNF-antagonist RR 4.3 (ns) compared with RA treated with conventional therapy
• CD treated with TNF-antagonist RR 1.2 (ns) compared with CD treated with conventional therapy

“In a cohort of more than 4000 RA and Crohn’s patients younger than 50 yrs, the cumulative incidence of presumed heart failure was low (4 and 1 case per 1000 patients, respectively).”</td></tr>
</table>

Authors: Curtis **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Curtis et al.**[128] **Year: 2007** **Country:** US		
FUNDING:	Maryland Chapter of the Arthritis Foundation, the Agency for Healthcare Research and Quality (grant HS-10389), and the NIH (grant K24-AR-052361-01 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and grant AR-47512-03).		
RESEARCH OBJECTIVE:	To evaluate the risk of serious bacterial infections associated with tumor necrosis factor		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Health care organization dataset **Sample size:** 5326		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**TNF antagonist** various various 2393	**MTX** various various 2933	
INCLUSION CRITERIA:	between May 1998 and December 2003 RA patients >18 years old who took only MTX or anti-TNF		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	other nonbiologic DMARDs		

Authors: Curtis et al. **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe		
	TNF antagonist	**MTX**	
Mean age (years):	50	55	
Sex (% female):	73	73	
Ethnicity:	NR	NR	
Other germane population qualities:			
• INF	33	0	
• ETA	50	0	
• ADA	3	0	
• >1 antiTNF	12	0	
• MTX use (%)	70	100	
•			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Infection **Timing of assessments:** various		
RESULTS:	**Health Outcome Measures:** • No. (%) of patients with any infection anti TNF 65 (2.7%) vs. MTX only 58 (2.0%) • Hazard ratio of infection TNF-antagonists was 1.9 (95% confidence interval [95% CI] 1.3–2.8) compared with patients who received MTX only.		

Authors: Curtis **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**TNF antagonist** see results	**MTX**	**drug 3**
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:**		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**TNF antagonist** N/A	**MTX**	**drug 3**
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Dixon et al.**[129] **Year: 2007** **Country:** UK		
FUNDING:	The British Society for Rheumatology is indirectly funded by Schering-Plough, Whety Laboratories, Abbot Laboratories, and Amgen		
RESEARCH OBJECTIVE:	To test the hypothesis that the anti-inflammatory effect of anti–tumor necrosis-α (anti-TNFα) therapy might lead to a reduction in the incidence of myocardial infarction (MI) in RA patients		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Data from BSRBR, a national prospective observational study **Sample size:** 10,829 (74 patients switched from comparison cohort and were included in analysis for both so actual number of patients=10,755); anti-TNF subgroup analysis: 7515		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNFα nonresponders** N/A N/A 1638	**Anti-TNFα responders** N/A N/A 5877	
INCLUSION CRITERIA:	Registered with BSRBR; diagnosed with RA; followed up for ≥ 6 months by July 31, 2006; Anti-TNFα cohort: treated with an anti-TNF drug, registered with BSRBR within 6 months of starting biologic therapy		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Lipid-lowering drugs, NSAIDS		

Authors: Dixon et al. **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Anti-TNFα nonresponders	**Anti-TNFα responders**	
Mean age (years):	57	56	
Sex (% female):	79	76	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	NR	NR	
• Swollen joint count	NR	NR	
• Median disease duration	11	7	
• DMARD use (%)	NR	100	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	45.3	42.9	
• DAS score	6.4	6.6	
• HAQ score	2.2	2.0	
• Prior MI (%)	2.9	2.6	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** MI rates **Timing of assessments:** N/A		
RESULTS:		**Nonresponders**	**Responders**
	Person-years	1815	9886
	No. of reported MIs	17	35
	Rate of MIs per 1000 person-yrs (95% CI)	9.4 (5.5-15.0)	3.5 (2.5-4.9)
	Incidence rate ratio	Referent	0.38 (0.21-0.67)
	Incidence rate ratio, adjusted for age and sex	Referent	0.38 (0.22-0.68)
	Incidence rate ratio, multivariate analysis	Referent	0.36 (0.19-0.69)
	Incidence rate ratio by sex, multivariate analysis		
	Male	Referent	0.31 (0.12-0.81)
	Female	Referent	0.46 (0.20-1.06)

Authors: Dixon et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	See above
Significant differences in adverse events:	see results
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**N/A**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Favalli**[130] **Year: 2008** **Country:** Italy			
FUNDING:	NR- but all of the authors have received consultancy fees or Congress invitations from Schering-Plough, Wyeth, and Abbott			
RESEARCH OBJECTIVE:	To estimate the incidence of serious infections in the patients treated with anti-TNFα agents for rheumatoid arthritis recorded in the Lombardy Rheumatology Network (LORHEN) registry.			
DESIGN:	**Study design:** Cohort registry **Setting:** Population based registry **Sample size:** 1064			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**All** Various Various 1064	**INF** Various Various 519	**ADA** Various Various 303	**ETA** Various Various 242
INCLUSION CRITERIA:	RA patients receiving at least one dose of Anti-TNF			
EXCLUSION CRITERIA:	Lost to follow up in less than 6 months			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes			

Authors: Favalli **Year: 2008**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe			
	All	**INF**	**ADA**	**ETA**
Mean age (years):	55.84	55.72	56.07	55.81
Sex (% female):	83.2	81.5	85.1	84.3
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Mean disease duration	9.44 yrs	9.28 yrs	9.56 yrs	9.63 yrs
• MTX use (%)	84.5	96.1	74.6	71.9
• Corticosteroids use (%)	84.2	88.4	76.9	84.3
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Infections-serious			
RESULTS:	**Health Outcome Measures:** • Incidence rate of infections was 35.9 per 1000 patients years			
		All	**INF**	**ADA**	**ETA**
	Any serious infection - n (%) Incidence rate (IR): number of events per 1000 patient-yrs (95% CI).	73 (6.9%) 35.90 (27.66–44.13)	42 (8.1%) 38.91 (27.14–50.67)	20 (6.6%) 38.17 (21.44–54.90)	11 (4.5%) 25.58 (10.46–40.69)

Authors: Favalli **Year: 2008**				
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**<u>All</u>** see results	**<u>INF</u>**	**<u>ADA</u>**	**<u>ETA</u>**
Significant differences in adverse events:	Factors that increased rate of serious infection – age at the time of starting biological drug treatment (*P* = 0.002), the baseline erythrocyte sedimentation rate ([ESR] *P* = 0.012), and the concomitant use of corticosteroids (*P* = 0.025).			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A			
ARE GROUPS COMPARABLE AT BASELINE:	Yes			
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes			
STATISTICAL ANALYIS ADEQUATE:	Yes			
ATTRITION (*overall*):	**Overall attrition:** **Attrition differential high:**			
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A			
QUALITY RATING:	**Fair**			

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Feltelius et al.**[131] **Year: 2005** **Country:** Sweden		
FUNDING:	Wyeth Research		
RESEARCH OBJECTIVE:	To describe a nationwide system for postmarketing follow up of new antirheumatic drugs; to analyze safety & effectiveness in an etanercept-treated cohort.		
DESIGN:	**Study design:** Observational (retrospective cohort) **Setting:** Swedish Society of Rheumatology database **Sample size:** 1,073		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg twice weekly ≥ 2 years 1,073		
INCLUSION CRITERIA:	Active RA; previous treatment with > 1 DMARD in addition to MTX.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Feltelius et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: Severe (high disease activity)</td></tr>
<tr><td></td><td><u>ETA</u></td><td></td><td></td></tr>
<tr><td>Mean age (years):</td><td>52</td><td></td><td></td></tr>
<tr><td>Sex (% female):</td><td>76.6</td><td></td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• DMARD use (%)</td><td>56.3</td><td></td><td></td></tr>
<tr><td>• MTX use (%)</td><td>40.1</td><td></td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>95.2</td><td></td><td></td></tr>
<tr><td>• DAS score</td><td>5.9</td><td></td><td></td></tr>
<tr><td>• HAQ score</td><td>1.62</td><td></td><td></td></tr>
<tr><td>• Mean CRP</td><td>45</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Disease activity (measured by CRP, ESR, HAQ, tender / SJC, patient & physician global assessment)
.
Secondary Outcome Measures: DAS28; EULAR; ACR20

Timing of assessments: Examinations at 0, 3, 6, 12, 18, & 24 months after inclusion.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• In 294 patients (27%), at least 1 adverse drug reaction was reported (421 reports; mean 1.5 report per patient; median 1; rand 1 to 6).
• 80 adverse drug reactions were serious and 331 were non-serious. The incidence of serious adverse events remained constant over time.</td></tr>
</table>

Authors: Feltelius et al. **Year: 2004**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Skin • Infection resistance mechanism • Respiratory system • General • Neurological • Gastrointestinal • Cardiovascular • Hematological • Musculoskeletal • Neoplasms	**ETA (n=540)** NR 24.8 16.7 13.7 13.0 5.4 5.2 4.8 3.2 2.2 2.0		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** N/A 59		
QUALITY RATING:	**N/A**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Fleischmann et al.**[132] [133]**and Schiff et al.**[134] **and Tesser et al.**[135] **Year**: **2003, 2004, 2006** **Country:** Multinational	
FUNDING:	Amgen Inc., Thousand Oaks, CA	
RESEARCH OBJECTIVE:	To evaluate the safety of AKA in a large population of patients with RA, typical of those seen in clinical practice. Additionally to determine the safety in a sub-population of patients with comorbid conditions; and to examine concomitant medication's effect on adverse events.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (169 sites) **Sample size:** 1414 (1399 enrolled)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/d 6 months (up to three years) 1116 (1346)	**Placebo** N/A 6 months 283
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria for at least 3 months; active disease defined by a minimum of 3 swollen joints and 3 tender joints or 45 minutes of morning stiffness; stable doses of NSAIDs and corticosteroids for one month; and stable doses of DMARDs for 2 months.	
EXCLUSION CRITERIA:	Pregnant or lactating; uncontrolled medical condition (e.g., diabetes with HgbA1c > 8%); malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix; Felty's syndrome; leukopenia; neutropenia; thrombocytopenia; abnormal liver function test result; hepatitis B or C positive; HIV positive.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS, corticosteroids, and DMARDs (except TNF inhibitors) either alone or in combination	

Authors: Fleischmann et al. and Schiff et al. and Tesser et al. **Year: 2003, 2004, 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild to severe	
	AKA	**Placebo**
Mean age (years):	54.6	55.7
Sex (% female):	74.7	74.6
Ethnicity (%):		
• White	87.8	90.1
• Black	6.1	5.3
• Hispanic	4.4	3.5
• Other	1.7	1.1
Other germane population qualities:		
• TJC	22.6	22.6
• SJC	18.8	18.3
• DMARD use (excluding MTX) (%)	47.7	47.7
• MTX use (%)	51.9	59.4
• Corticosteroids use (%)	57.0	60.8
• DAS score	NR	NR
• HAQ score	NR	NR
Comorbidities (Schiff 2004), %:		
• Asthma	9.8	8.1
• COPD	12.9	11.0
• Pneumonia	9.1	6.7
• DM	7.4	7.4
• CAD	5.7	5.7
• CHF	3.2	3.2

Authors: Fleischmann et al. and Schiff et al. and Tesser et al. **Year: 2003, 2004, 2006**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (measured by adverse events, serious adverse events, infections, study discontinuation, and death; WHO adverse reaction term dictionary) **Secondary Outcome Measures:** NR **Timing of assessments:** Day 1, week 1, and months 1,3, and 6.
RESULTS:	**Health Outcome Measures:** • After 6 months, the rate of spontaneous adverse events was not different between AKA and placebo, except for ISRs, which occurred much more frequently among AKA-treated patients than placebo-treated patients (72.6% v. 32.9%) *P*-value NR • 13.4% of patients in the AKA group withdrew due to adverse event compared to 9.2% in the placebo group, but the difference was not significant ($P = 0.057$); overall discontinuation rates were similar (21.6% vs. 18.7%) • Serious infections occurred more frequently in AKA than in placebo patients (2.1% v. 0.4%), but was not statistically significantly different but may be clinically significant. ($P = 0.068$) • In patients with comorbid conditions, there were no differences between the AKA group and the placebo group in incidence of serious adverse events or overall infectious events. • In patients with comorbid conditions, the rate of serious infectious events was increased relative to placebo (2.5% vs. 0.0%; P = NR). • There is a trend towards increased risk of serious infectious events with AKA in patients with pulmonary comorbidities versus placebo (3.4% v. 1.6%), but it failed to reach statistical significance. • Neutralizing anti-ANA antibodies detected in 0.8% of AKA patients NR for patients receiving placebo. • Adverse event profiles were similar between groups taking concomitant antihypertensive, antidiabetic and statin drugs. • From 0 to 3 years the overall cumulative rate exposure adjusted rate anakinra versus placebo (3 events per 100 pt yrs) • All AEs 689.8 vs. 1029.4 • SAEs 27.1 vs. 22.3 • Serious infections 5.4 vs. 1.6

	• Deaths 0.7 vs. 0.8 • ISRs 122.26 vs. 135.6 • RA progression 67.8 vs. 122.37 • URTI 26.09 vs. 58.7 • Headache 19.05 vs. 32.25 • Arthralgia 13.77 vs. 19.02 • Sinusitis 12.8 vs. 18.19 • Nausea 12.45 vs. 19.02 • Diarrhoea 11.26 vs. 16.54 Standardised incidence ratio for cancer observed versus expected (SEER) • All sites 17 vs. 20.58 SIR 0.83 95% CI 0.48 to 1.32 • Oral cavity and pharynx 1 vs. 0.44 SIR 2.26 95% CI 0.06 to 13.00 • Digestive system 2 vs. 3.49 SIR 0.57 95% CI 0.07 to 2.07 • Respiratory system 1 vs. 3.19 SIR 0.31 95% CI 0.01 to 1.75 • Malignant melanoma 4 vs. 0.73 SIR 5.48 95% CI 1.49 to 14.00 • Breast 3 vs. 4.70 SIR 0.64 95% CI 0.13 to1.86 • Female genital system 1 vs. 1.85 SIR 0.54 95% CI 0.01 to 3.02 • Urinary system 2 vs. 1.23 SIR 1.63 95% CI 0.20 to 5.89 • Lymphoma 3 vs. 0.81 SIR 3.71 95% CI 0.77 to 11.00 • Other 0 vs. 4.13 SIR 0.00 95% CI 0.00 to 0.89

Authors: Fleischmann et al. and Schiff et al. and Tesser et al. **Year: 2003, 2004, 2006**		
ADVERSE EVENTS:	**AKA**	**Placebo**
Overall adverse effects reported:	1,027 (92.0%)	261 (92.2%)
• Deaths	4 (0.4%)	1 (0.4%)
• Serious adverse events	86 (7.7%)	22 (7.8%)
• Severe adverse events	15.5%	13.1%
• ISRs	72.6%	32.9%
• Infectious episode	41.2%	43.5%
• Serious infection	2.1%	0.4%
• URTI	13.3	18.4
• Sinusitis	6.7	6.0
• Influenza-like	5.8	6.4
• UTI	4.6	5.3
• Bronchitis	3.4	4.6
• Infection (resistance mechanism body system)	2.9	3.2
Significant differences in adverse events:	• No significant differences reported. (No *P*-value was reported for ISRs.)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (15/1414)	
ADEQUATE RANDOMIZATION:	NR	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 394 (21%) **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**AKA**	**Placebo**
Loss to follow-up:	21.6%	18.7%
Withdrawals due to adverse events:	13.4%	9.2%
QUALITY RATING:	**Fair**	

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Friesen et al.**[136] **Year: 2004** **Country:** USA		
FUNDING:	NR		
RESEARCH OBJECTIVE:	Safety of INF treatment in pediatric patients with cd or uc		
DESIGN:	**Study design:** Retrospective data analysis **Setting:** Clinic **Sample size:** 111		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** various mean follow-up 19.9 months 111		
INCLUSION CRITERIA:	All INF infusions administered to patients with inflammatory bowel disease (IBD) at the Children's Mercy Hospital between July 1, 1998, and April 14, 2003.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant immunomodulating medication used included 6-mercaptopurine or azathioprine, also prednisone , budesonide, methotrexate		

<table>
<tr><td colspan="4">Authors: Friesen et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>INF</u></td><td></td><td></td></tr>
<tr><td>Mean age (years):</td><td>13.4</td><td></td><td></td></tr>
<tr><td>Sex (% female):</td><td>50</td><td></td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Ulcerative colitis</td><td>21%</td><td></td><td></td></tr>
<tr><td>• Crohns disease</td><td>79%</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Infusion reactions

Timing of assessments: various</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Reactions were seen in 8.1% of patients and in 1.5% of total infusions. Reactions occurred in 8% of CD patients and 9% of UC patients
• Unusual infections were seen in 3.6%</td></tr>
</table>

Authors: Friesen **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	See results
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	N/A
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	N/A
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	N/A

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Geborek et al.**[137] **Year: 2005** **Country:** Sweden		
FUNDING:	Österlund and Kock Foundations, King Gustav V 80 year fund, and Reumatikerförbundet		
RESEARCH OBJECTIVE:	To determine whether TNF blockers increase tumour risk in patients with RA by comparing an Anti-TNF cohort to a non-TNF cohort (other).		
DESIGN:	**Study design:** retrospective cohort study **Setting:** Rheumatology practices **Sample size:** 1557 (5551 patient years)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNF** INF or ETA 1.7 yrs 757	**Control** N/A N/A 800	
INCLUSION CRITERIA:	Patients with RA treated with ETA or INF		
EXCLUSION CRITERIA:	Tumor diagnosis prior to study		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Geborek et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>Anti-TNF</u></td><td><u>Other</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>56</td><td>64</td><td></td></tr>
<tr><td>Sex (% female):</td><td>76</td><td>73</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean disease duration</td><td>12</td><td>11</td><td></td></tr>
<tr><td>• Previous DMARD use (#)</td><td>3</td><td>1</td><td></td></tr>
<tr><td>• HAQ quartile > 3</td><td>61</td><td>41</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Cancer diagnoses in 4 categories, lymphomas, blood (leukemia + myeloma), smoking related (upper gastrointestinal tract + airway + urinary tract), and other malignancies (breast + genital + other gastrointestinal + abdominal cavity + skin + musculoskeletal).

Timing of assessments: Start of anti-TNF treatment or 1 July 1997 for the comparison cohort, until death or 31 December 2002.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures: Anti-TNF vs. Control
• All tumors: SIR 1.1 (95% CI 0.6 to 1.8) vs. 1.4 (95% CI 1.1 to 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 to 1.42) vs. 1.39 (95% CI 1.08 to 1.76)
• The hazard ratio indicates a higher risk of lymphoma for anti-TNF drugs than for controls (RR: 4.9; 95% CI 0.9 – 26.2)</td></tr>
</table>

Authors: Geborek et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions: N/A**		
ARE GROUPS COMPARABLE AT BASELINE:	**No**		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**N/A**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Gomez-Reino et al.**[138] **Year: 2003** **Country:** Spain	
FUNDING:	Agencia Española del Medicamento (Ministerio de Sanidad y Consumo); Spanish Society of Rheumatology	
RESEARCH OBJECTIVE:	To determine the long-term safety of infliximab and etanercept, in rheumatic diseases based on a national active-surveillance (BIOBADESAR: Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia) system following the commercialization of the drugs.	
DESIGN:	**Study design:** Database review **Setting:** 71 centers **Sample size:** 1540	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF and/or ETA** Various Mean 1.1 years 1540 (1578 treatments)	
INCLUSION CRITERIA:	Patients with rheumatic disease being treated with biologic response modifier.	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes	

Authors: Gomez-Reino et al. **Year: 2003**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe	
	INF and/or ETA	
Mean age (years):	51	
Sex (% female):	72%	
Ethnicity:	NR	
# of patients with:		
• RA	1265	
• PsA	89	
• AS	76	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events, primarily TB	
RESULTS:	**Health Outcome Measures:** • Background TB incidence in Spain in the year 2000 was 21 cases per 100,000 inhabitants • 1,893 cases of TB per 100,000 patients in the year 2000 and 1,113 cases per 100,000 patients in the year 2001 in patients treated with TNF • RR of patients treated with TNF compared general population 90.1 (95% CI 58.8-146.0) in the year 2000 and 53.0 (95% CI 34.5-89.0) in the year 2001. • Estimated annual incidence of TB among RA patients not exposed to TNF inhibitors was 95 cases per 100,000 • RR in RA patients who did not receive TNF of TB (adjusted for age and sex) was 4.13 (95% CI 2.59-6.83) relative to the background rate. • RR of TB in INF-treated RA patients versus RA patients not exposed to this therapy was 19.9 (95% CI 16.2-24.8) in the year 2000 and 11.7 (95% CI 9.5-14.6) in the year 2001.	

Authors: Gomez-Reino et al. **Year: 2003**		
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**INF and/or ETA** NR 118 (8%)	
Significant differences in adverse events:	N/A	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A	
ARE GROUPS COMPARABLE AT BASELINE:	NR	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes	
STATISTICAL ANALYSISADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF and/or ETA** 228 discontinued therapy (14%) 118 (8%)	
QUALITY RATING:	**N/A**	

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Harrison**[139] **Year: 2008** **Country:** United Kingdom		
FUNDING:	NR		
RESEARCH OBJECTIVE:	Incidence rate of psoriasis r in patients with RA treated with anti-TNFa therapy compared to those treated with traditional DMARDs		
DESIGN:	**Study design:** Cohort **Setting:** General practice **Sample size:** 12706		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Control** N/A N/A 2880	**Anti-TNF** Various N/A 9826	
INCLUSION CRITERIA:	First 4000 patients with RA starting each anti-TNFa therapy were required by The National Institute for Health and Clinical Excellence (NICE) to be registered with the BSRBR and followed up for information on drug use, disease activity and adverse events		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Harrison **Year: 2008**						
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe					
	Control		**Anti-TNF**		**drug 3**	
Mean age (years):	60		56.2			
Sex (% female):	72		76			
Ethnicity:	NR		NR			
Other germane population qualities:						
• Mean disease duration	7 yrs		11			
• DAS score	5.0		6.6			
• HAQ score	1.6		2.1			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Incidence of psoriasis in RA patients					
RESULTS:		**Control (DMARD)**	**Anti TNF**	**ETA**	**INF**	**ADA**
	# psoriasis	0	25	6	6	13
	rate psoriasis/ 1000 people years	0 (0.71)	1.04 (0.67-1.54)	0.59 (0.22-1.28)	0.88 (0.32 - 1.93)	1.84 (0.98-3.15)

Authors: Harrison **Year: 2008**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	see results
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** No **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	No but adjustments are made
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lebwohl et al**.[140] **Year: 2005** **Country:** US
FUNDING:	Amgen Inc., Thousand Oaks, CA and its subsidiaries. Most of the authors were employees of Amgen during the conduct of the study.
RESEARCH OBJECTIVE:	To determine the incidence of cutaneous squamous cell carcinoma (SCC) in patients with RA receiving etanercept for up to 5 years.
DESIGN:	**Study design:** Retrospective observational study with historical controls **Setting:** Clinical trial participants receiving ETA from private and institutional practices **Sample size:** 1442 (4257 patient-years)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** NR Mean 3.7 years 1442 (4257 pt-yrs)
INCLUSION CRITERIA:	Participant in one of various studies* of ETA in patients with RA; patients had active RA; and, received 10 to 50 mg ETA subcutaneously twice weekly for the majority of the time they received the study drug. Specific inclusion criteria varied by the included study. *783 from study with suboptimal response to at least 1 DMARD (8 studies); 557 patients diagnosed with RA within past 3 years, but had never received MTX; 102 patients were in a pharmacokinetic study of phase 3 study evaluating 2 different dosages of ETA in adult patients with RA.
EXCLUSION CRITERIA:	None.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Varied by individual study.

<table>
<tr><td colspan="4">Authors: Lebwohl et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR (probably at least moderate disease)</td></tr>
<tr><td></td><td><u>ETA</u></td><td></td><td></td></tr>
<tr><td>Mean age (years):</td><td>49.9</td><td></td><td></td></tr>
<tr><td>Sex (% female):</td><td>76.5</td><td></td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>87.4</td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Duration of disease, mean yrs</td><td>7.1</td><td></td><td></td></tr>
<tr><td>• Prior # DMARDs used</td><td>2.1</td><td></td><td></td></tr>
<tr><td>• Duration ETA exposure</td><td></td><td></td><td></td></tr>
<tr><td>o Mean</td><td>3.7</td><td></td><td></td></tr>
<tr><td>o Maximum</td><td>5.7</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
Incidence of SCC for patients receiving ETA for up to 5 years</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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
o From Arizona general population-based incidence study: 13.1 cases
o From Minnesota general population-based incidence study: 5.9 cases
• Number of cases of SCC per patient-year of exposure to ETA
o In the clinical trial population: 0.9/1000 patient-years
o From post-marketing surveillance data: .01/1000 patient-years

• Summary Statement: The incidence of SCC among patients taking ETA is likely no different from that of the general population.</td></tr>
</table>

Authors: Lebwohl et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**N/A**		
Significant differences in adverse events:	N/A		
ANALYSIS:	**N/A**		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lichtenstein et al.**[141] **Year: 2006** **Country:** Multinational		
FUNDING:	NR; at least one author affiliated with Centocor (makers of INF)		
RESEARCH OBJECTIVE:	To examine safety of CD therapies, including infliximab		
DESIGN:	**Study design:** Observational (prospective registry) **Setting:** Multicenter **Sample size:** 6,290 patients (212 centers)		
INTERVENTION: N/A **Dose:** **Duration:** **Sample size:**	**INF** NR Mean 1.9 years 3,179	**Other treatments** NR Mean 1.9 years 3,111	
INCLUSION CRITERIA:	Diagnosis of CD; no participation in any clinical trials; Age ≥ 18 (although not a criterion when enrollment began).		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Lichtenstein et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes, but trends towards INF group being sicker
Disease severity: Mild-to-moderate</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>Other</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>40.3</td><td>44.7</td><td></td></tr>
<tr><td>Sex (% female):</td><td>57.9</td><td>57.1</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>88.8</td><td>89.3</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Surgical admissions (No.)</td><td>17.5</td><td>13.8</td><td></td></tr>
<tr><td>• Medical admissions (No.)</td><td>14.4</td><td>9.1</td><td></td></tr>
<tr><td>• Disease severity mild-to-moderate (%)</td><td>50.1</td><td>47.9</td><td></td></tr>
<tr><td>• Prednisone use (%)</td><td>27.4</td><td>16.1</td><td></td></tr>
<tr><td>• Immunomodulator use (%)</td><td>49.4</td><td>32.2</td><td></td></tr>
<tr><td>• Narcotic analgesics use (%)</td><td>9.8</td><td>5.4</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Rate of death; rate of serious infection

Secondary Outcome Measures: NR

Timing of assessments: Enrollment, then semiannually</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Mortality rates = 0.53 per 100 patient-years in INF group vs. 0.43 per 100 patient-years in other treatments group (RR 1.24; [95% CI, 0.729 – 2.102]; P = 0.43).
• In adjusted model, only age (OR, 1.07; P < 0.001), duration of CD (OR 1.03; P = 0.006), and use of prednisone (OR 2.10; P = 0.016) were independent predictors of death.
• Use of INF was not a significant predictor of mortality.
• Although significant in unadjusted model, INFs effect on risk for serious infection in adjusted model was not significant (OR, 0.99; P = 0.97).
• In adjusted model race (OR, 0.54 for white vs. non-white, P = 0.030), CD duration (OR, 1.02; P = 0.011), moderate-to-severe CD (OR 2.11 vs. remission; P = 0.02), and use of prednisone (OR 2.21; P < 0.001), and use of narcotic analgesia (OR, 2.38; P < 0.001) were independent predictors of serious infection.</td></tr>
</table>

Authors: Lichtenstein et al. **Year: 2006**			
ADVERSE EVENTS (%): **Overall adverse events reported:** • Death, N • Serious infection, N	**Total cohort** NR 55 106		
Significant differences in adverse events:	See Health Outcomes		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Listing et al.**[142] **Year: 2005** **Country:** Germany			
FUNDING:	Joint grant from Essex, Wyeth, Amgen, and Abbott			
RESEARCH OBJECTIVE:	To estimate the incidence rates of serious and non-serious infections in patients with RA who start treatment with a biologic agent, and to compare these rates with those in patients with RA who receive conventional treatment.			
DESIGN:	**Study design:** Prospective cohort study **Setting:** Population-based **Sample size:** 1,529			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 512	**INF** 346	**AKA** 70	**DMARDs (control)** 601
INCLUSION CRITERIA:	Age 18-75, enrolled up to 9/1/2003;Cases: patients who met the ACR criteria for RA diagnosis and had new treatment with ETA, INF, or AKA; Controls: patients started on DMARD therapy after failure of ≥ 1 other DMARD, or with additional DMARD added to existing DMARD.			
EXCLUSION CRITERIA:	NR			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR			

Authors: Listing et al.
Year: 2005

POPULATION CHARACTERISTICS:

Groups similar at baseline: No
Disease severity: NR

	ETA	INF	AKA	DMARDs (control)
Mean age (years):	53.7	53.6	54.3	56.5
Sex (% female):	78.1	70.8	77.1	82.7
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• TJC	13.3	12.7	12.6	10.0
• SJC	10.5	10.8	10.2	7.7
• Median disease duration (yrs)	9	8	13	6
• DMARD use (%)	51.6	89.6	71.4	0
• MTX use (%)	33	64.5	61.4	20.1
• Glucocorticoids, any dose (%)	87.4	85.2	87.0	77.2
• DAS28 score	6.1	6.0	6.1	5.4

OUTCOME ASSESSMENT:

Primary Outcome Measures: Adverse events; DAS28; ESR; CRP; morning stiffness; and numerical rating scale for pain, general health, or fatigue.
Secondary Outcome Measures:
Timing of assessments: Baseline, 3,6, & 12 months

RESULTS:

Health Outcome Measures:
- See adverse events table

Authors: Listing et al. **Year: 2005**			
ADVERSE EVENTS per 100 patient-years:	**ETA**	**INF**	**Control**
Overall adverse effects reported:	22.6	28.3	6.8
• Total serious adverse events	6.4	6.2	2.3
• Respiratory tract infections*	7.0	11.4	1.8
• Flu-like illness+	2.7	4.0	0.7
• Skin infections^	6.0	7.7	2.6
• Bone & joint infection	1.03	0.61	0.18
• Urogenital tract infection$	2.69	1.54	0.70
• Sepsis/urosepsis	0.62	0	0.35
Significant differences in adverse events:	Total # of adverse events per 100 patient-years was 22.6 (95% CI 18.7-27.2) for ETA patients, 28.3 (95% CI 23.1-34.7) for INF patients, 6.8 (95% CI 5.0-9.4) for controls ($P < 0.0001$). Higher risk of infections for AKA, ETA, INF compared with DMARDS. Also a significant difference in serious adverse events ($P = 0.0016$); $^{*}P < 0.0001$; $^{+}P = 0.0038$; $^{\wedge}P = 0.0017$; $^{\$}P = 0.036$		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 11.1% **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Listing**[143] **Year: 2008** **Country:** Germany		
FUNDING:	Unconditional, joint grants from Essex and Wyeth since 2001, from Essex, Wyeth, and Amgen since January 2003, and from Essex, Wyeth, Amgen, and Abbott since September 2003.		
RESEARCH OBJECTIVE:	The hazard risk of developing or worsening heart failure in rheumatoid arthritis (RA) patients treated with tumor necrosis factor inhibitors.		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** German biologics register **Sample size:**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNF** NR 5 years 2757	**Control** NR 5 years 1491	**drug 3**
INCLUSION CRITERIA:	Treated with ADA, ETA, INF, or conventional DMARDs		
EXCLUSION CRITERIA:	Treated with AKA		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Listing **Year: 2008**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe		
	Anti-TNF	**Control**	**drug 3**
Mean age (years):	53.7	56.1	
Sex (% female):	78.1	78.9	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	NR	NR	
• Swollen joint count	9.3	6.8	
• Mean disease duration	9 yrs	6yrs	
• # DMARD use	3.6	1.9	
• MTX use (%)	NR	NR	
• Corticosteroids use	2302	1132	
• DAS score	5.8	5.1	
• HAQ score	NR	NR	
• Comorbidity – Heart failure/CHD/CVD/DM/ Chronic lung disease	2.7/5.4/37.3/8.2/7.3	1.5/7.0/38.2/8.6/6.4	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** all adverse events reported as heart failure, acute heart failure, congestive heart failure, or ventricular failure between May 1, 2001 and December 1, 2006 **Timing of assessments:** Baseline and at 3-, 6-, 12-, 18-, 24-, 30-, 36-, 48-, and 60-month follow-up		
RESULTS:	**Health Outcome Measures:** • Risk related to treatment with anti-TNF adjusted HR 1.66 [95% confidence interval 0.67–4.1], *P* = 0.28). • Adjusted HR for heart failure Anti-TNF vs. conventionals 1.85 95% CI 0.88-3.90 *P* = 0.11 • Adjusted HR for heart failure de novo Anti-TNF vs. conventionals 2.19 95% CI 0.90-5.33 *P* = 0.083 • Adjusted HR for heart failure in 98 patients prevalent heart failure Anti-TNF vs. conventionals 1.18 95% CI 0.30-4.733.90 *P* = 0.81		

Authors: Listing **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** •	**Anti-TNF** see results	**Control**	**drug 3**
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** Annual 5.1% **Attrition differential high:** NR		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**All** at 48 months 15.5% 2.4% died		
QUALITY RATING:	**Good**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lovell et al.**[60-62] **Year: 2000, 2003, and 2006** **Country:** US		
FUNDING:	Immunex Corporation, Children's Hospital Foundation of Cincinnati, NIH		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of etanercept in children with PJRA		
DESIGN:	**Study design:** RCT and open label extension **Setting:** Academic medical centers (children's hospitals) **Sample size:** 51 and 58		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 4 months 26	**ETA** 0.4 mg/kg body weight/2x weekly 4 months 25	**Extension** 0.4 mg/kg body weight/2x weekly up to 2 years/4 years 58/34
INCLUSION CRITERIA:	Ages 4-17 with active PJRA; active disease despite treatments with NSAIDs and MTX at doses of at least 10 mg/sq meter of body surface area per week; normal or nearly normal platelet, white cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal function tests		
EXCLUSION CRITERIA:	Pregnant and lactating patients were excluded along with patients with major concurrent medical conditions		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, low doses of corticosteroids (≤.2 mg of prednisone /kg/day with a max of 10 mg/day) or bother were permitted		

<table>
<tr><td colspan="5">Authors: Lovell et al.
Year: 2000, 2003, 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease characteristic: Polyarticular (mean disease duration 5.8 years)</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>ETA</u></td><td><u>Extension 2 years</u></td><td><u>Extension 4 years</u></td></tr>
<tr><td>Mean age (years):</td><td>12.2</td><td>8.9</td><td>10</td><td>10.6</td></tr>
<tr><td>Sex (% female):</td><td>58</td><td>76</td><td>67</td><td>81</td></tr>
<tr><td>Ethnicity: white (%)</td><td>88</td><td>56</td><td>74</td><td>84</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• Disease duration mean (years)</td><td>6.4</td><td>5.3</td><td>5.9</td><td>5.9</td></tr>
<tr><td>• TJC</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• SJC</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• DMARD use (%)</td><td>73</td><td>64</td><td>74</td><td>100</td></tr>
<tr><td>• MTX use (%)</td><td>69</td><td>64</td><td>72</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>50</td><td>24</td><td>38</td><td>41</td></tr>
<tr><td>• DAS score</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• HAQ score</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: Number of patients with disease flare (disease flare is based on worsening of 30% of more in 3 or 6 response variables and a minimum of 2 active joints)
Secondary Outcome Measures: Articular severity score, duration of morning stiffness, degree of pain, and CRP
Timing of assessments: day 1, day 15, and at the end of each month</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• Significantly more in placebo group (81%) than patients in ETA group (28%) had disease flare (P = 0.003)
• Rates of flare were constant and significantly lower in ETA group (P < 0.001) after adjustment for baseline effects
• At study endpoint , 72% of ETA group and 23% of placebo group met definition of 50% improvement (P = NR)
• Over 4 years the rate of serious adverse events 0.13 per patient year; the rate of serious infections 0.04 per patient-year.</td></tr>
</table>

Authors: Lovell et al. **Year: 2000; 2003; 2006**				
ADVERSE EVENTS:	**Open label**	**Double-blind portion**	**Extension 2 years**	**Extension 4 years**
Overall adverse effects reported:	NR	NR	NR	NR
▪ **Serious adverse events requiring hospitalization**	3%	NR	16% NR	NR NR
• ISR	39%	4%	NR	NR
• URTI	35%	NR	NR	NR
• Headache	20%	NR	NR	NR
• Abdominal pain	16%	NR	NR	NR
• Vomiting	14%	NR	NR	NR
• Rash	10%	NR	NR	NR
• Varicella-Zoster virus	NR	NR	5% requiring hospitalization	NR
Significant differences in adverse events:	Unable to determine- NR			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes			
ATTRITION (*treatment specific*):	**Open label**	**ETA**	**Placebo**	**Extension 2 years**	**Extension 4 years**
Loss to follow-up:	5	6 (24%)	19 (63%)	10 (17%)	24 (42%)
Withdrawals due to adverse events:	1	6- Disease flare	18-Disease flare	2-Adverse events 7-lack of efficacy	4-Adverse events 6-lack of efficacy
QUALITY RATING:	**Fair**				

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Maini et al**.[144, 145] **Year: 2004** **Country:** Multinational				
FUNDING:	Centocor				
RESEARCH OBJECTIVE:	Efficacy and safety of repeated administration of infliximab plus methotrexate over a 2-year period in patients with RA who previously experienced an incomplete response to methotrexate.				
DESIGN:	**Study design:** Open label extension of ATTRACT (Maini 1999) **Setting:** 34 sites **Sample size: 259 (428)**				
INTERVENTION: **Dose:** **Duration (RCT+ follow-up):** **Sample size (follow-up through 2 years):**	**Placebo + MTX** N/A+15 mg/wk 2 years 88(51)	**Infli3/8 + MTX** 3 mg/kg every 8 wks+15mg/wk 2 years 86(63)	**Infli3/4 + MTX** 3 mg/kg every 4 wks+15mg/wk 2 years 86(75)	**Infli10/8 + MTX** 10 mg/kg every 8 wks+15mg/wk 2 years 87(72)	**Infli10/4 + MTX** 3 mg/kg every 4 wks+15mg/wk 2 years 81(70)

Authors: Maini et al. **Year: 1999 and 2004**	
INCLUSION CRITERIA:	RA according to the 1987 ACR criteria and had evidence of active disease despite treatment with MTX; oral or parenteral MTX for at least 3 months with no break in treatment of more than 2 weeks during this period, the MTX dose must have been stable at 12·5 mg/week or more, for at least 4 weeks before screening and the patient must have been on a stable dose of folic acid for the same period; haemoglobin 5·3 mmol/L or more; white blood cells 3·5X10/L or more; neutrophils 1·5X10/L; platelets 100X10/L or more; serum aminotransferase and alkaline phosphatase concentration 2 times or less the upper limit of normal; and serum creatinine 150 μmol/L or less.
EXCLUSION CRITERIA:	Little or no ability for self-care; condition with signs and symptoms that might confound the diagnosis (eg, connective tissue disease or Lyme disease); used a DMARD other than MTX or received intraarticular, intramuscular, or intravenous corticosteroids in the 4 weeks before screening; any other agent to reduce TNF or had any previous use of cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents; or a history of known allergies to murine proteins; infected joint prosthesis during the previous 5 years; serious infections, such as hepatitis, pneumonia, pyelonephritis in the previous 3 months; any chronic infectious disease such as renal infection, chest infection with bronchiectasis or sinusitis; active TB requiring treatment within the previous 3 years; opportunistic infections such as herpes zoster within the previous 2 months; any evidence of active cytomegalovirus; active *Pneumocystis carinii*; or drug-resistant atypical mycobacterial infection; current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease; a history of lymphoproliferative disease including lymphoma or signs suggestive of disease, such as lymphadenopathy of unusual size or location (ie, lymph nodes in the posterior triangle of the neck, infraclavicular epitrochlear, or periaortic areas); splenomegaly; any known malignant disease except basal cell carcinoma currently or in the past 5 years.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (10 mg/kg or less prednisone equivalent) or NSAIDs must have been on a stable dose for at least 4 weeks before screening

Authors: Maini et al.
Year: 1999 and 2004

POPULATION CHARACTERISTICS: ***From 1999, not presented in Maini 2004 for treatment groups.***

Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe

	Placebo + MTX	Infli3/8 + MTX	Infli3/4 + MTX	Infli10/8 + MTX	Infli10/4 + MTX
Median age (years):	51	56	51	55	52
Sex (% female):	80	81	77	77	59
Ethnicity (% white):	89	93	88	91	76
Other germane population qualities:					
• TJC	N/A	N/A	N/A	N/A	N/A
• SJC	N/A	N/A	N/A	N/A	N/A
• DMARD use (%)	0	0	0	0	0
• MTX use (%)	100	100	100	100	100
• Corticosteroids use (%)	64	63	53	57	65
• NSAID use (%)	72	79	76	77	68
• DAS score	N/A	N/A	N/A	N/A	N/A
• HAQ score	N/A	N/A	N/A	N/A	N/A

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR 20/50/70, SHS

Secondary Outcome Measures: HAQ, SF-36

Timing of assessments: 102 weeks and 52 weeks for SHS

RESULTS:

Health Outcome Measures:
- INF treated patients maintained their improvements in ACR50, HAQ, and SF-36 throughout week 102

Intermediate Outcome Measures:
- Radiographic disease progression at week 102 was significantly lower in the INF group than in the placebo group ($P < 0.001$)
- SHS

Authors: Maini et al. **Year: 1999 and 2004**					
ADVERSE EVENTS: at 30 weeks **Overall adverse effects reported:** **More than 80% in all**	**Placebo** NR	**INF 3/8 + MTX** NR	**INF 3/4 + MTX** NR	**INF 10/8 + MTX** NR	**INF 10/4 + MTX** NR
• URTI	14 (16%)	29 (33%)	17 (20%)	21 (24%)	18 (23%)
• Headache	9 (10%)	22 (25%)	17 (20%)	21 (24%)	16 (20%)
• Sinusitis	4 (5%)	10 (11%)	6 (7%)	12 (14%)	14 (18%)
• Rash	4 (5%)	5 (6%)	7 (8%)	14 (16%)	12 (15%)
• Coughing	3 (3%)	8 (9%)	6 (7%)	11 (13%)	11 (14%)
• Back pain	2 (2%)	7 (8%)	7 (8%)	6 (7%)	7 (9%)
• Abdominal pain	7 (8%)	4 (4%)	8 (9%)	7 (8%)	8 (10%)
• Pain	4 (5%)	4 (4%)	3 (3%)	7 (8%)	6 (8%)
• UTI	3 (3%)	3 (3%)	2 (2%)	6 (7%)	9 (11%)
• Fever	4 (5%)	4 (4%)	7 (8%)	3 (3%)	7 (9%)
• Any infection	34 (40%)	47 (53%)	40 (47%)	56 (64%)	58 (73%)
• Infection requiring antimicrobials	18 (21%)	20 (23%)	24 (28%)	32 (37%)	30 (38%)
• Serious infections	5 (6%)	1 (1%)	5 (6%)	5 (6%)	3 (4%)
• Serious adverse events	14 (16%)	8 (9%)	11 (13%)	8 (9%)	10 (13%)
ADVERSE EVENTS: at 2 years					
• No. (%) of patients with serious AEs	28 (33)	29 (33)	20 (23)	25 (29)	26 (32)
• No. (%) of patients with serious infections	11 (13)	10 (11)	11 (13)	11 (13)	8 (10)
• No. (%) of patients with serious infusion reactions	0	0	1 (1)	0	0
• No. (%) of patient deaths	4 (5)	3 (3)	2 (2)	1 (1)	1 (1)
• No. (%) of patients with malignancies	1 (1)	1 (1)	0	3 (3)	5 (6)
Significant differences in adverse events:	Serious adverse events were reported by similar proportions of patients who received MTX only and INF plus MTX.				

Authors: Maini et al. **Year: 1999 and 2004**					
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No				
ADEQUATE RANDOMIZATION:	NR				
ADEQUATE ALLOCATION CONCEALMENT:	Yes				
BLINDING OF OUTCOME ASSESSORS:	NR				
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*):	**Placebo + MTX**	**INF 3/8 + MTX**	**INF 3/4 + MTX**	**INF 10/8 + MTX**	**INF 10/4 + MTX**
Loss to follow-up:	42%	27%	13%	28%	30%
Withdrawals due to adverse events:	NR	NR	NR	NR	NR
QUALITY RATING:	**Fair**				

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Nuki et al**.[146] **Year: 2002** **Country:** Multinational (Europe)		
FUNDING:	Amgen, INC		
RESEARCH OBJECTIVE:	Long-term safety and maintenance in the treatment of RA with anakinra. Safety was evaluated for all 472 patients, long term efficacy for 309 that continued into extension.		
DESIGN:	**Study design:** RCT 24 weeks, then double-blind parallel extension of 52 weeks for a total of 76 weeks **Setting:** Multicenter **Sample size:** 472 in 24 week study (309 in 52 week extension)		
INTERVENTION: Extension phase **Dose:** **Duration:** **Sample size:**	**AKA** 30 mg 52 weeks 111	**AKA** 75 mg 52 weeks 103	**AKA** 150 mg 52 weeks 95
INCLUSION CRITERIA:	Patients that had completed the initial 24 week study		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Nuki et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline: Yes** **Disease severity:** Mild-moderate-severe		
	Placebo to AKA (76)	**AKA to AKA (233)**	
Mean age (years):	53.1	52.7	
Sex (% female):	69.7	76.8	
Ethnicity:	NR	NR	
Other germane population qualities:			
• TJC	32.7	33.7	
• SJC	24.5	26.4	
• Mean disease duration	3.7	4.1	
• DMARD use (%)	73.7	71.7	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	40.8	47.6	
• DAS score	N/A	N/A	
• HAQ score	1.5	1.5	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20; radiographs; safety **Timing of assessments:** 24th week of extension for efficacy and 52nd week for safety analysis		
RESULTS:	**Health Outcome Measures:** • Overall AKA was well tolerated at all dose levels up to 76 weeks **Intermediate Outcome Measures:** • ACR 20 Placebo to AKA All doses Week 24 - 26 (34%) Week 48 - 39 (51%) ($P = 0.007$) AKA to AKA All doses Week 24 - 84 (36.1%) Week 48 - 97 (41.6%) ($P = 0.118$)		

Authors: Nuki et al. **Year: 2002**	**Extension phase – Weeks 24 to 76**		**Placebo phase – Weeks 0 to 24**	
ADVERSE EVENTS:	**Placebo to AKA (76)**	**AKA to AKA (233)**	**Placebo**	**AKA**
Overall adverse effects reported:	NR	NR	NR	NR
• Leukopenia	1 (1.3%)	4 (1.7%)	0	1 (0.3%)
• Infection	1 (1.3%)	4 (1.3%)	1 (0.8%)	4 (1.1%)
• Malignancy	1 (1.3%)	1 (0.4%)	0	2 (0.6%)
• Arthritis flare	4 (5.2%)	14 (6.0%)	17 (14%)	31 (8.8%)
• Granulocytopenia			0	17 (4.8%)
• Eosinophilia			0	17 (4.8%0
Significant differences in adverse events:	Hematologic changes under AKA therapy was the second most common reason for discontinuation in the extension phase (7.7%)			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	**Yes**			
ADEQUATE ALLOCATION CONCEALMENT:	N/A			
BLINDING OF OUTCOME ASSESSORS:	N/A			
ATTRITION (*overall*):	**Overall loss to follow-up:** 91 (29%) **Loss to follow-up differential high:** No			
ATTRITION (*treatment specific*):	**Placebo to AKA (76)**	**AKA to AKA (233)**		
Loss to follow-up:	21 (28%)	70(30%)		
Withdrawals due to adverse events:	14 (18%)	32 (14%)		
QUALITY RATING:	**N/A**			

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Salliot et al.**[147] **Year: 2009** **Country:** Multinational
FUNDING:	Two authors have received grants from pharmaceutical companies
DESIGN:	**Study design:** Systematic review & meta-analysis **Number of patients:** 6461 (745 RIT, 2945 ABA, 2771 AKA)
AIMS OF REVIEW:	To assess if RIT, ABA or AKA increases the risk of serious infections in patients with RA in published RCTs.
STUDIES INCLUDED IN META-ANALYSIS:	12 trials: ABA 5 trials (Moreland 2002, Kremer 2003 and 2005, Genovese 2005, Kremer 2006, Weinblatt 2006); AKA 4 trials (Bresnihan 1998, Cohen 2002, Cohen 2004, Schiff 2004); RIT 3 trials (Edwards 2004, Emery 2006, Cohen 2006)
TIME PERIOD COVERED:	Up to October, 2007
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized double-blind placebo controlled trials with a follow-up of 12-48 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult patients with RA according to ACR criteria with active disease despite DMARDs; 81% female with a mean age at inclusion of between 46 and 57 yrs

Authors: Salliot et al. **Year: 2009**	
CHARACTERISTICS OF INTERVENTIONS:	RIT (500mg or 1000mg), AKA (30-50 mg) or ABA (0.5 – 10 mg/kg) vs. placebo
MAIN RESULTS:	Number (%) of patients with at least 1 serious infection; OR (95% CI) RIT vs. placebo: 17 (2.3%) vs. 6 (1.5%); 1.45 (0.56-3.73) ABA vs. placebo: 49 (2.5%) vs. 18 (1.8%); 1.35 (0.78-2.32) AKA vs. placebo: 30 (1.4%) vs. 4 (0.5%); 2.75 (0.90-8.35) Risk of serious infections stratified by high-and low-dose: OR (95% CI) High dose RIT (1000 mg) vs. placebo: 1.68 (0.64-4.35) High dose ABA (10 mg/kg) vs. placebo: 1.35 (0.70-2.29) High dose AKA (≥ 100 mg) vs. placebo: 3.40 (1.11-10.46) Low dose RIT (500 mg) vs. placebo: 0.24 (0.01-4.33) Low dose ABA (≤ 2 mg/kg) vs. placebo: 0.84 (0.13-5.30) Low dose AKA (< 100 mg) vs. placebo: 0.51 (0.03-8.27) Analyses of subgroups according to age (< or > to median 52.7 yrs), concomitant intake of steroids (median 65% of patients) and RF positivity (median positivity 78% of patients) confirmed these results (data NR)
ADVERSE EVENTS:	See main results
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	A systematic review of the literature using PUBMED, EMBASE, Cochrane library and abstracts databases (American College of Rheumatology and European League Against Rheumatism annual meetings) was performed up to October 2007. This search was completed with data from the FDA, the European Agency for the Evaluation of Medicinal Products, and manufacturers.
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Schiff et al.,[134] Tesser et al.,[135] and Fleischmann et al.,[132]** **Year: 2003 and 2004** **Country:** Multinational	
FUNDING:	Amgen Inc., Thousand Oaks, CA	
RESEARCH OBJECTIVE:	To evaluate the safety of anakinra in a large population of patients with RA, typical of those seen in clinical practice. Additionally to determine the safety in a sub-population of patients with comorbid conditions; and to examine concomitant medication's effect on adverse events.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (169 sites) **Sample size:** 1414 (1399 enrolled)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/d 6 months 1116	**Placebo** N/A 6 months 283
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria for at least 3 months; active disease defined by a minimum of 3 swollen joints and 3 tender joints or 45 minutes of morning stiffness; stable doses of NSAIDs and corticosteroids for one month; and stable doses of DMARDs for 2 months.	
EXCLUSION CRITERIA:	Pregnant or lactating; uncontrolled medical condition (e.g., diabetes with HgbA1c > 8%); malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix; Felty's syndrome; leukopenia; neutropenia; thrombocytopenia; abnormal liver function test result; hepatitis B or C positive; HIV positive.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS, corticosteroids, and DMARDs (except TNF inhibitors) either alone or in combination	

Authors: Schiff et al., Tesser et al., and Fleischman et al. **Year: 2003 and 2004**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild to severe	
	AKA	**Placebo**
Mean age (years):	54.6	55.7
Sex (% female):	74.7	74.6
Ethnicity (%):		
• White	87.8	90.1
• Black	6.1	5.3
• Hispanic	4.4	3.5
• Other	1.7	1.1
Other germane population qualities:		
• TJC	22.6	22.6
• SJC	18.8	18.3
• DMARD use (excluding MTX) (%)	47.7	47.7
• MTX use (%)	51.9	59.4
• Corticosteroids use (%)	57.0	60.8
• DAS score	NR	NR
• HAQ score	NR	NR
Comorbidities (Schiff 2004), %:		
• Asthma	9.8	8.1
• COPD	12.9	11.0
• Pneumonia	9.1	6.7
• DM	7.4	7.4
• CAD	5.7	5.7
• CHF	3.2	3.2

Authors: Schiff et al., Tesser et al., and Fleischman et al. **Year: 2003 and 2004**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (measured by adverse events, serious adverse events, infections, study discontinuation, and death; WHO adverse reaction term dictionary) **Secondary Outcome Measures:** NR **Timing of assessments:** Day 1, week 1, and months 1,3, and 6.
RESULTS:	**Health Outcome Measures:** • After 6 months, the rate of spontaneous adverse events was not different between AKA and placebo, except for ISRs, which occurred much more frequently among AKA-treated patients than placebo-treated patients (72.6% v. 32.9%) *P*-value NR • 13.4% of patients in the AKA group withdrew due to adverse event compared to 9.2% in the placebo group, but the difference was not significant ($P = 0.057$); overall discontinuation rates were similar (21.6% vs. 18.7%) • Serious infections occurred more frequently in AKA than in placebo patients (2.1% v. 0.4%), but was not statistically significantly different but may be clinically significant. ($P = 0.068$) • In patients with comorbid conditions, there were no differences between the AKA group and the placebo group in incidence of serious adverse events or overall infectious events. • In patients with comorbid conditions, the rate of serious infectious events was increased relative to placebo (2.5% vs. 0.0%; P = NR). • There is a trend towards increased risk of serious infectious events with AKA in patients with pulmonary comorbidities versus placebo (3.4% v. 1.6%), but it failed to reach statistical significance. • Neutralizing anti-ANA antibodies detected in 0.8% of AKA patients NR for patients receiving placebo. • Adverse event profiles were similar between groups taking concomitant antihypertensive, antidiabetic and statin drugs.

Authors: Schiff et al., Tesser et al., and Fleischman et al. **Year: 2003 and 2004**		
ADVERSE EVENTS:	**AKA**	**Placebo**
Overall adverse effects reported:	1,027 (92.0%)	261 (92.2%)
• Deaths	4 (0.4%)	1 (0.4%)
• Serious adverse events	86 (7.7%)	22 (7.8%)
• Severe adverse events	15.5%	13.1%
• ISRs	72.6%	32.9%
• Infectious episode	41.2%	43.5%
• Serious infection	2.1%	0.4%
• URTI	13.3	18.4
• Sinusitis	6.7	6.0
• Influenza-like	5.8	6.4
• UTI	4.6	5.3
• Bronchitis	3.4	4.6
• Infection (resistance mechanism body system)	2.9	3.2
Significant differences in adverse events:	• No significant differences reported. (No P-value was reported for ISRs.)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (15/1414)	
ADEQUATE RANDOMIZATION:	NR	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 394 (21%) **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**AKA**	**Placebo**
Loss to follow-up:	21.6%	18.7%
Withdrawals due to adverse events:	13.4%	9.2%
QUALITY RATING:	**Fair**	

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Schiff et al.**[148] **Year: 2006** **Country:** Multinational		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	To assess the safety of adalimumab in global clinical trials and postmarketing surveillance among patients with RA		
DESIGN:	**Study design:** Retrospective data analysis of clinical trials; postmarketing surveillance **Setting:** Multi-clinical **Sample size:** 10,050 (12, 506 patient years)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** Various Various 10050		
INCLUSION CRITERIA:	Patients from randomized controlled trials, open label extensions, and two phase IIIb open label trials were and post-marketing spontaneous reports of adverse events in the United States		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Schiff et al.
Year: 2006</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• TJC
• SJC
• Mean disease duration
• DMARD use (%)
• MTX use (%)
• Corticosteroids use (%)
• DAS score
• HAQ score</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td>NR</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Serious adverse events including TB, and malignacies</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Rates per 100 patient years-
TB 0.27
Histoplasmosis 0.03
Demyelinating diseases 0.08
Lymphoma 0.12
SLE/lupus-like syndrome 0.10
CHF 0.28
• Incidence of Adverse events do not increase over time
• Long-term ADA treatment was generally safe</td></tr>
</table>

Authors: Schiff et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	NR		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	**N/A**		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	N/A		
STATISTICAL ANALYIS ADEQUATE:	N/A		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**N/A**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors, article #: Schneeweiss**[149] **Year: 2007** **Country:** USA				
FUNDING:	Engalitcheff Arthritis Outcomes Initiatives, Baltimore, Maryland				
RESEARCH OBJECTIVE:	To assess the association between the initiation of anti–tumor necrosis factor (anti-TNF) therapy and the risk of serious bacterial infections in routine care.				
DESIGN:	**Study design:** Retrospective – cohort study **Setting:** Pennsylvania Medicare beneficiaries **Sample size:** 15,597				
INTERVENTION:	**MTX**	**TNF antagonists**	**Cytotoxic DMARDs**	**Nontoxic DMARDs**	**Glucocorticoids**
Dose:	NR	NR	NR	NR	NR
Duration:	.58 yrs	1.29 yrs	0.64 yrs	0.73 yrs	0.20 yrs
Sample size:	1900	469	654	1957	10617
INCLUSION CRITERIA:	Medicare beneficiaries ages 65 years and older with RA who initiated use of a DMARD, including anti-TNF_ and glucocorticoids, between 1995 and 2003, patients had to demonstrate use of the health care system by filling at least 1 prescription for any drug and having at least 1 physician service in each of 2 consecutive 6-month periods in addition to being enrolled in the PACE program. Patients were identified as having RA if, at 3 physician visits, they had a diagnosis of RA				
EXCLUSION CRITERIA:	Any cancer (except nonmelanoma skin cancer) or human immunodeficiency virus/acquired immunodeficiency syndrome				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes – 84% of patients starting anti-TNF took at least one other DMARD.				

Authors: Schneeweiss
Year: 2007

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe

	MTX	TNF antagonists	Cytotoxic DMARDs	Nontoxic DMARDs	Glucocorticoids
# treatments	1900	469	654	1957	10617
Follow-up (yrs)	0.58	1.29	0.64	0.73	0.20
Mean age (years):	76	75	76	76	79
Sex (% female):	88	91	91	89	88
Ethnicity: % white/black/other	92/7/1	92/7/1	92/7/1	92/7/1	93/6/1
Other germane population qualities:					
•					

OUTCOME ASSESSMENT:

Primary Outcome Measures:
Hospitalization for serious bacterial infection

Secondary Outcome Measures: Hospitalization due to opportunistic infection

Timing of assessments: N/A

RESULTS:

Health Outcome Measures:
- **See AEs**

Intermediate Outcome Measures:
- **See AEs**

Authors: Schneeweiss **Year: 2007**					
ADVERSE EVENTS: event rate per 100 pt/yrs **Overall adverse effects reported:**	**MTX**	**TNF antagonists**	**Cytotoxic DMARDs**	**Nontoxic DMARDs**	**Glucocorticoids**
• Pneumonia	1.47 (0.75–2.18)	2.33(1.12-3.54)	1.43 (0.29-2.57)	0.91 (0.42-1.40)	3.16 (2.41-3.91)
• Septicemia or bacteremia	2.20(1.33-3.07)	2.16 (1.00-3.32)	3.66 (1.84-5.48)	2.31 (1.53-3.09)	6.34 (5.3-7.38)
• Osteomyelitis	0.27 (0.07-0.48)	0.49 (000-1.05)	0.48 (000-1.14)	0.63 (0.22-1.04)	0.80 (0.42-1.18)
• Any bacterial infection	3.77 (2.64-4.9)	4.89 (3.15-6.62)	5.36 (3.18-7.54)	3.75 (2.70-4.74)	9.39 (8.14-10.6)
Significant differences in adverse events:	Glucocorticoid users' incidence of serious bacterial infections was significantly higher than average incidence in this population (RR 2.1; 1.5 – 3.1); the risk of septicemia or bacteremia was particularly pronounced (RR 2.5) no increased rate of serious bacterial infections for those who initiated anti-TNF therapy (RR 1.0) or any other DMARDs compared with MTX				
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A				
ARE GROUPS COMPARABLE AT BASELINE:	No – there were differences in amount of followup, Anti –TNF 1.29 yr, glucocorticoids 0.2 yrs.				
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes				
STATISTICAL ANALYIS ADEQUATE:	Yes				
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A				
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A				
QUALITY RATING:	**Good**				

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Setoguchi**[150] **Year: 2008** **Country:** US			
FUNDING:	NR			
RESEARCH OBJECTIVE:	Whether TNF α antagonists pose an increased risk of HF in older patients with RA.			
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Medicare and drug benefit programs in 2 states (health care utilization databases) **Sample size:** 6595			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**TNFA with heart failure** 225	**MTX with heart failure** 808	**TNFA without heart failure** 777	**MTX without heart failure** 3783
INCLUSION CRITERIA:	Subjects aged ≥65, at least one recorded diagnosis of RA and filled at least one prescription of any TNFA ETA, INF, and ADA or MTX after the first RA diagnosis, at least one clinical service during each of 4 consecutive 6-month periods before the use of disease-modifying antirheumatic drugs (DMARDs)			
EXCLUSION CRITERIA:	Patients who had a diagnosis of HF in an outpatient file but no HF noted in a hospital discharge summary (n = 339)			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroids, DMARDs, nonsteroidal anti-inflammatory drug			

Authors: Setoguchi
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: ?
Disease severity: NR

	TNFA with heart failure	MTX with heart failure	TNFA without heart failure	MTX without heart failure
Mean age (years):	73	77	72	74
Sex (% female):	89	84	90	89
Ethnicity: White	88	92	89	91
Other germane population qualities:				
• Tender joint count				
• Swollen joint count				
• mean follow-up	1,6	1,7	1,8	2,5
• DMARD use (%)	24	4	24	5
• Noncytotoxic DMARDs (%)	35	22	32	26
• Corticosteroids use (%)	67	56	59	48
• DAS score				
• HAQ score				

OUTCOME ASSESSMENT:

Primary Outcome Measures: Effects of TNFAs compared to MTX on HF and/or death
Secondary Outcome Measures: deaths
Risk of death among patients with previous HF
Timing of assessments: study endpoints :the last use of TNFA or MTX, death, end of the study period, occurrence of HF

RESULTS:

Health Outcome Measures:
Incidence rates of HF hospitalization: in TNFA users : without history of HF crude rate ratio 1.43, with previous HF 1.39
Risk of TNFAs on HF hospitalization of combined group of patients with and without previous HF: HR 1.70, 95% CI 1.07-2.69)

Risk of death among patients with previous HF: adjusted hazard ratio 4.19 of death compared with MTX users (95% CI 1.48-11.89)
Intermediate Outcome Measures:

Authors: Setoguchi **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • HF admission Incidence Rate	TNFA with previous HF 108 with no HF 19 2 groups combined 35	MTX with previous HF 76 with no HF 14 2 groups combined 21	
Significant differences in adverse events:	70% increase in the risk of HF hospitalization among users of TNFA compared with users of MTX, regardless of history of previous HF		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	NR		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Attrition overall:** **Attrition due to adverse events:**	**Overall attrition:** N/A **Attrition differential high:** N/A		
	drug 1 N/A	**drug 2** N/A	**drug 3**
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Setoguchi et al.**[151] **Year: 2006** **Country:** US and Canada		
FUNDING:	Engalitchheff Arthritis Outcomes Initiative, Arthritis Foundation, and by a research grant from Novartis.		
RESEARCH OBJECTIVE:	To estimate the association between treatment with biologic disease-modifying antirheumatic drugs (DMARDs) and development of cancer in patients with RA.		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Population based **Sample size:** 8458		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologic DMARD** Various various 1152	**MTX** Various various 7306	
INCLUSION CRITERIA:	≥ 65 years in the US and Canada who had at least 1 claim with a diagnosis of RA and who were dispensed at least 1 prescription of any DMARD or corticosteroid after the first RA diagnosis during the study period		
EXCLUSION CRITERIA:	a diagnosis of any cancer (except non-melanoma skin cancer) or human immunodeficiency virus infection		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Setoguchi et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe		
	Biologic DMARD	**MTX**	**drug 3**
Mean age (years):	71.4	73.4	
Sex (% female):	73.1	73.1	
Ethnicity:	NR	NR	
Other germane population qualities:			
• ETA	743 [64%],	NA	
• INF	381 [33%],	NA	
• AKA	28 [2%]	NA	
• MTX use (%)	39%	100%	
• Corticosteroids use (%)			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** diagnosis of cancer **Timing of assessments:** when occurred		
RESULTS:	**Health Outcome Measures:** No increase in haematologic (HR: 1.37, 95% CI 0.71-2.65) or solid tumors (HR 0.91, 95% CI 0.65-1.26) with anti-TNF drugs compared with MTX		

Authors: Setoguchi et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**Biologic DMARD** see results	**MTX**	**drug 3**
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:**		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Biologic DMARD**	**MTX**	**drug 3**
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Simon et al.**[152] **Year: 2008** **Country:** Multinational (Europe & North America)
FUNDING:	Bristol-Myers Squibb
DESIGN:	**Study design:** Pooled data with meta-analysis **Number of patients:** 4134 in ABA trials, 41529 in DMARD cohorts
AIMS OF REVIEW:	To provide context for the malignancy experience in the RA ABA clinical development program (CDP) by performing comparisons with similar RA patients and the general population.
STUDIES INCLUDED IN META-ANALYSIS	7 ABA trials compared with 5 RA DMARD cohorts and with the general population (from the SEER cancer registry)
TIME PERIOD COVERED:	Up to 2007
CHARACTERISTICS OF INCLUDED STUDIES:	5 ABA trials were randomized, double-blind, placebo-controlled trials; all were 6-12 months in duration
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults with RA; most patients were 45-74 yrs of age

Authors: Simon et al. **Year: 2008**	
CHARACTERISTICS OF INTERVENTIONS:	Trials: ABA vs. placebo RA cohorts: non-biologic DMARDs only
MAIN RESULTS:	Summary SIR comparing the rate of total malignancies (excluding NMSC) in the ABA CDP with the pooled IR from the RA cohorts was 0.68 (95% CI: 0.37–1.26), indicating that the overall risk of cancer was not significantly increased in ABA treated patients compared to RA patients treated with DMARDs. For the comparison of the ABA clinical trial malignancy experience with the general population, the calculated SIR comparing cancer IRs in RA patients treated with ABA with IRs in the general population (SEER cancer registry) was 0.82 (95% CI: 0.61-1.08) for total malignancy excluding NMSC.
ADVERSE EVENTS:	See main results
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Solomon et al.**[153] **Year: 2006** **Country:** US		
FUNDING:	Engalitcheff Arthritis Outcomes Initiative; other relevant grant support was provided by the Arthritis Foundation, the NIH (grants K23-AR-48616, K24-02123, and P60-AR-47782), and research grants from Merck, Pfizer, and Savient.		
RESEARCH OBJECTIVE:	To investigate the effects of various immunosuppressive medications on the risk of cardiovascular events among a group of older patients with RA.		
DESIGN:	**Study design:** Nested case-control **Setting:** **Sample size:** 946 cases (266 on biologics monotherapy or biologics + MTX)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics monotherapy** NR N/A 149	**Biologics + MTX** NR N/A 117	
INCLUSION CRITERIA:	The source cohort was derived from Medicare beneficiaries receiving a drug benefit from the state of Pennsylvania. These individuals were required to have been diagnosed as having RA on at least 2 visits and to have filled a prescription for an immunosuppressive agent. Cases were defined as those patients who were hospitalized for a cardiovascular event such as myocardial infarction or stroke.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, coxib, clopidogrels, beta-blockers, statins		

Authors: Solomon et al. **Year: 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** NR	
	Cases	
Mean age (years):	81	
Sex (% female):	89	
Ethnicity (% white):	93	
Other germane population qualities:		
• Tender joint count	NR	
• Swollen joint count	NR	
• Mean disease duration	NR	
• DMARD use (%)	NR	
• MTX use (%)	NR	
• Corticosteroids use (%)	NR	
• DAS score	NR	
• HAQ score	NR	
• Prior MI	99	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** cardiovascular events **Timing of assessments:** N/A	
RESULTS:	**Health Outcome Measures:** • **Adjusted risk for cardiovascular events**	
	Biologics monotherapy	**Biologics + MTX**
Total No.	149	117
No (%) of cases	12 (8.1)	8 (6.8)
Composite primary outcome	1.0 (0.5, 1.9)	0.8 (0.3, 2.0)
MI (OR compared with MTX)	1.7 (0.5, 5.7)	1.8 (0.5, 6.8)
Stroke (OR compared with MTX)	1.5 (0.6, 4.1)	1.3 (0.4, 4.0)

Authors: Solomon et al. **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	N/A
Significant differences in adverse events:	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	**Cannot determine**
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Strangfeld et al.**[154] **Year: 2009** **Country:** Germany				
FUNDING:	RABBIT has been supported by an unconditional joint grant from Essex pharma (since 2001), Wyeth pharma (since 2001), Amgen (since January 2003), Abbott (since September 2003), Hoffmann-La Roche (since January 2007), and Bristol- Myers Squibb (since July 2007).				
RESEARCH OBJECTIVE:	To investigate whether TNFα inhibitors together as a class, or separately as either monoclonal anti– TNFα antibodies (ADA, INF) or a fusion protein (ETA), are related to higher rates of herpes zoster in patients with rheumatoid arthritis.				
DESIGN:	**Study design:** retrospective cohort **Setting:** Data from the German biologics register RABBIT, a prospective cohort **Sample size:** 5040				
INTERVENTION:	**ETA**	**INF**	**ADA**	**Total TNFα inhibitors**	**Controls**
Dose: **Duration:** **Sample size:**	N/A N/A 1252	N/A N/A 591	N/A N/A 1423	N/A N/A 3266	N/A N/A 1774
INCLUSION CRITERIA:	From May 1, 2001, to December 31, 2006, all patients with rheumatoid arthritis starting new treatment with either INF, ETA, ADA, or AKA and patients who were changing their DMARD treatment after at least 1 DMARD failure (control group) were asked by their rheumatologist to participate in the register. Once enrolled, data collection from the patients would continue until the end of 2011.				
EXCLUSION CRITERIA:					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:					

Authors: Strangfeld et al. **Year: 2009**						
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe					
	ETA **N = 1252**	**INF** **N = 591**	**ADA** **N = 1423**	**Total** **N = 3266**	**Controls** **N = 1774**	***P* Value**
Age, mean (SD), y	53.8 (12.5)	52.9 (12.7)	54.2 (12.0)	53.8 (12.3)	56.2 (11.4)	.001
Women, No. (%)	975 (77.8)	433 (73.3)	1141 (80.2)	2549 (78.0)	1394 (78.6)	.66
Rheumatoid factor–positive, No. (%)	1008 (80.5)	469 (79.4)	1143 (80.4)	2620 (80.3)	1271 (71.7)	.001
FFbH score, mean (SD) b	56.0 (22.9)	55.3 (21.6)	58.6 (23.4)	57.0 (22.9)	66.6 (21.5)	.001
Disease duration, median (IQR), y	9 (4-16)	8.5 (4-14)	10 (5-17)	9 (5-16)	6 (3 -12)	.001
DAS28, mean (SD)	5.8 (1.3)	5.9 (1.2)	5.7 (1.3)	5.8 (1.3)	5.0 (1.3)	.001
CRP, median (IQR), mg/L	16 (5-37)	17 (7-41)	13 (5-30)	17 (8-38)	8 (3-22)	.001
Previous DMARD therapies, No. (%)	3.6 (1.4)	3.7 (1.5)	3.5 (1.4)	3.5 (1.4)	1.8 (1.1)	.001
Glucocorticoids, No. (%)	1073 (86.1)	498 (84.4)	1154 (81.6)	2725 (83.8)	1354 (76.5)	.001
Prednisolone 10 mg/d, No. (%)	440 (35.1)	217 (36.7)	416 (29.2)	1073 (32.9)	343 (19.3)	.001
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hazard ratio (HR) of herpes zoster episodes following anti– TNFα treatment. **Secondary Outcome Measures:** **Timing of assessments:**					
RESULTS:	**Health Outcome Measures:** • Incidence rates for episodes of herpes zoster during anti–TNFα treatment and DMARD treatment were 9.8 (95% CI, 7.5-12.6) per 1000 patient-years and 5.1 (95% CI, 3.2-7.8) per 1000 patient-years. • For the monoclonal antibodies and ETA, the rates were 11.1 (95% CI, 7.9-15.1) per 1000 patient-years and 8.1 (95% CI, 5.0-12.4) per 1000 patient-years, respectively.					

	• In subgroup analysis, no significantly increased risk of herpes zoster for patients treated with ETA were found, whereas patients treated with either INF or ADA had a significantly increased risk (HR, 1.82 [95% CI, 1.05-3.15]) (Table 3), although this risk was lower than the study's predefined HR threshold of 2.5 for clinical significance. • Univariate Cox regression analysis showed risk of herpes zoster with DMARDs: (HR, 1 [Reference]; Anti–TNFα agents: (HR, 1.84 [95% CI, 1.13-3.00], ETA: (HR, 1.55 [95% CI, 0.85-2.82]; ADA/INF: (HR, 2.05 (95% CI, 1.22-3.45)

Authors: Strangfeld et al. **Year: 2009**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**See above**
Significant differences in adverse events:	NA
ANALYSIS:	**ITT:** NA **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**NA**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Suissa**[155] **Year: 2006** **Country:** Canada		
FUNDING:	Sanofi-Aventis, the Canadian Institutes of Health Research, the Fonds de la recherché en sante´ du Que´bec, and Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To assess the risk of acute myocardial infarction (AMI) associated with the use of disease-modifying antirheumatic drugs (DMARDs) and other medications commonly used in rheumatoid arthritis (RA).		
DESIGN:	**Study design:** nested case-control **Setting:** Canada **Sample size:** 6138 (from a cohort of 107,908)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**drug 1**	**drug 2**	**drug 3**
INCLUSION CRITERIA:	≥18 years old, diagnosis of RA (ICD-9 code 714) between January 1999 and December 2003. Cohort entry was the date of the first prescription for an anti-RA medication after January 1, 1999		
EXCLUSION CRITERIA:	AMI, old AMI		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	No restrictions		

<table>
<tr><td colspan="3">Authors: Suissa
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: No
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>AMI</u></td><td><u>controls</u></td></tr>
<tr><td>Mean age (years):</td><td>65 (12)</td><td>65 (12)</td></tr>
<tr><td>Sex (% female):</td><td>55</td><td>55</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Tender joint count</td><td>NR</td><td>NR</td></tr>
<tr><td>• Swollen joint count</td><td>NR</td><td>NR</td></tr>
<tr><td>• Mean disease duration</td><td>NR</td><td>NR</td></tr>
<tr><td>• DMARD use (%)</td><td>37</td><td>39</td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>NR</td><td>NR</td></tr>
<tr><td>• DAS score</td><td>NR</td><td>NR</td></tr>
<tr><td>• HAQ score</td><td>NR</td><td>NR</td></tr>
<tr><td>• Ischaemic heart disease</td><td>19</td><td>8</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures:
the rate ratio (RR) of AMI for each of the anti-RA medication classes, including biologic agents (with or without other DMARDs but not leflunomide)

Secondary Outcome Measures: N/A

Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• The adjusted RR of an AMI for the current use of biologic agents (RR 1.30, 95% CI 0.92–1.83)
• adjusted RR ETA 0.63 (95% CI 0.34–1.17) & INF 1.58 (95% CI 0.82–3.05)

Intermediate Outcome Measures:</td></tr>
</table>

Authors: Suissa **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Suissa**[156] **Year: 2004** **Country:** USA/Canada		
FUNDING:	Aventis		
RESEARCH OBJECTIVE:	Risk of hepatic events associated with the use of leflunomide and other DMARDs in patients with Rheumatoid Arthritis		
DESIGN:	**Study design:** retrospective nested case-control **Setting:** inpatient or outpatient encounter between January 1, 1998, and December 31, 2001 (Protocare longitudinal health benefit claims database, PharMetrics Integrated Outcomes Database) **Sample size:** 1402		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** NR NR NR	**INF** NR NR NR	**drug 3**
INCLUSION CRITERIA:	use of leflunomide, methotrexate, gold compounds, anti–tumor necrosis factor α agents, antimalarials, minocycline, chelating agents, sulfasalazine, or cytotoxics, 18 years or older		
EXCLUSION CRITERIA:	less than 3 months of eligibility in the health insurance plan before cohort entry with the outcome of interest during the 3-month period before cohort entry		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:			

Authors: Suissa **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** N/A		
	PharMetrics	Protocare	
	33,009	8876	
Mean age (years):	49	59	
Sex (% female):	75	76	
Ethnicity:			
Other germane population qualities:			
• DMARD use (%)	100	99.5	
• MTX use (%)	45	57	
• Leflunomide(%)	14	6	
• Biologic DMARD	4	0.5	
• Other DMARD	37	36	
• Leflunomide use at any time during follow-up (%)	16	14	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hepatic events, subacute liver necrosis (ICD 9 code 570), cirrhosis without use of alcohol (ICD 9 code 571.5), hepatic coma (ICD 9 code 572.2), and toxic, noninfectious hepatitis (ICD 9 code 573.3)		
RESULTS:	**Health Outcome Measures:** • 25 cases of serious hepatic events, for an overall rate of 4.9 per 10,000 per year. • 411 nonserious hepatic events, for a rate of 80.0 per 10,000 per year **serious hepatic events** • biologic DMARDs (RR = 5.5; 95% CI: 1.2 to 24.6) **nonserious hepatic events** • biologic DMARDs (RR = 1.5; 95% CI: 1.0 to 2.3)		

Authors: Suissa **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	see results
Significant differences in adverse events:	Fivefold increase in the risk of serious hepatic events associated with the use of biologic DMARDs significant for nonserious hepatic events not requiring hospitalization.
ANALYSIS:	**ITT:** **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	Subjects from the Protocare cohort were about 10 years older than those from the PharMetrics cohort
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**N/A**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Takeuchi**[157] **Year: 2008** **Country:** Japan
FUNDING:	Tanabe Seiyaku Co., Ltd
RESEARCH OBJECTIVE:	Safety of INF in patients with RA
DESIGN:	**Study design:** Observational – postmarketing surveillance study **Setting:** Multicenter **Sample size:** 5000
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 3 mg/kg at weeks 0,2,6 and then every 8 weeks 6 months 5000
INCLUSION CRITERIA:	All patients treated with INF between July /2003 and Dec 2004 with active disease despite treatment with MTX of greater than 6 mg /week for at least 3 months
EXCLUSION CRITERIA:	N/A – but in order for institutions to prescribe INF they had to agree to participate fully in this study.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Takeuchi **Year: 2008**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	INF
Mean age (years):	55.1 years
Sex (% female):	79
Ethnicity:	NR – assume Asian 100%
Other germane population qualities:	3.1
• Hepatic disorder	2.5
• Cardiac disorder	9.4
• Diabetes Mellitus	4.7
• Respiratory disease	1.2
• Haematological disease	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events and adverse drug reactions were compared to a clinical trial that was conducted in Japan
RESULTS:	**Health Outcome Measures:** **See adverse events and risk factors for bacterial pneumonia** OR 95% CI Comorbid Respiratory disease Yes vs. none 3.90 (2.35–6.47) $P < 0.001$ Male vs. female 1.94 (1.29–2.93) $P = 0.001$ 40s and under vs. 50s 0.25 (0.10–0.66) 50s 1.00 (reference) , $P < 0.001$ 60s vs. 50s 1.90 (1.18–3.07) 70s and over vs. 50s 2.57 (1.48–4.45)

Authors: Takeuchi **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious ADRs • ADRs Per 100 pt/yrs • infections • Serious infections	**PMS n = 5000** 28% 6.2 59.38 (59.07 to 59.69) 18.35 (18.18 to 18.52) 8.56 (8.44-8.68)	**Japanese clinical trial n = 141** 67.4 10.6 72.16 (70.1 to 73.61) 39.50 (38.4 to 40.57) 8.36 (7.87-8.85)	**drug 3**
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A		
QUALITY RATING:	N/A		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Weinblatt**[158] **Year: 2006** **Country:** USA and Canada			
FUNDING:	Bristol-Myers Squibb			
RESEARCH OBJECTIVE:	To assess the safety of ABA in patients with RA who have been receiving treatment with DMARDs and/or biologics for 3 months or more			
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1441			
INTERVENTION:	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Dose:	10 mg/kg days 1, 15, and 29, then every 4 weeks a total of 14 doses.	N/A	10 mg/kg days 1, 15, and 29, then every 4 weeks a total of 14 doses.	N/A
Duration:	1 year	1 year	1 year	1 year
Sample size:	856	418	103	64
INCLUSION CRITERIA:	Men and women ≥ 18 years of age; 1987 ACR criteria for the diagnosis of RA and the 1991 ACR criteria for RA functional classes I, II, III, or IV; active disease despite receiving background DMARDs and/or biologic therapy, warranting additional therapy at the discretion of the investigator; the average score for the patient's global assessment of disease activity, as assessed by VAS measurements at screening and randomization (day 1), was required to be >20 mm; at least 1 biologic and/or nonbiologic DMARD approved for RA for at least 3 months, and at a stable dose for at least 28 days prior to day 1; stable medical conditions such as CHF, asthma, COPD, and diabetes mellitus			
EXCLUSION CRITERIA:	Unstable or uncontrolled renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, or neurologic diseases, or any autoimmune disorder other than RA as the main diagnosis; active or chronic recurrent bacterial infections unless treated and resolved, active herpes zoster infection within the previous 2 months, hepatitis B or hepatitis C virus infection, and active or latent TB; pregnant or nursing.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Approved biologic and nonbiologic DMARDs, MTX, hydroxychloroquine, leflunomide, gold, azathioprine, AKA, ETA, INF, and ADA; stable, low-dose oral corticosteroids (10 mg/day or less) and/or stable doses of NSAIDs, including aspirin			

Authors: Weinblatt **Year: 2006**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe			
	Nonbiologic background therapy		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Mean age (years):	52.2	52.0	54.6	52.8
Sex (% female):	83.1	83.7	75.7	75.0
Ethnicity (%white):	83.9	83.3	97.1	92.2
Other germane population qualities:				
• Pain, 100-mm VAS	61.1	61.3	62.2	61.5
• HAQ - DI	1.5	1.5	1.5	1.6
• Mean disease duration – years	9.5	9.5	11.3	11.3
• MTX	80.7	80.4	56.3	56.3
• Corticosteroids	71.6	73.7	74.8	79.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety- adverse events and infusion reactions **Secondary Outcome Measures:** HAQ-DI; Patient's global assessment of disease activity, and physician's global assessment of disease activity **Timing of assessments:** days 1, 85, 169, and 253.			
RESULTS:	**Health Outcome Measures: ABA vs. placebo** HAQ-DI; -0.46 versus -0.25; $P < 0.001$ Patient's assessment of pain -26.3 vs. -16.4 $P < 0.001$ Patient's global assessment of disease activity -27.2 vs. -17.4 $P < 0.001$ Physician's global assessment of disease activity -33.5 vs. -23.6 $P < 0.001$ **Patients w/COPD** overall AEs ABA 97.3% (n = 37) and placebo 88.2% (n = 17). AEs involving the respiratory system ABA 43.2% versus placebo 23.5% SAEs ABA 27% versus placebo 5.9% **Patients with DM** overall AEs ABA 93.8% (n = 65) and placebo 90.3% (n = 31) Infections ABA 50.8% vs. placebo 58.1% SAEs ABA 21.5% vs. placebo 12.9%.			

Authors: Weinblatt **Year: 2006**				
ADVERSE EVENTS:	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Overall adverse effects reported:	89.7	86.1	95.1	89.1
• SAEs	11.7	12.2	22.3	12.5
• Neoplasms	3.2	3.8	6.8	1.6
• Infections	54.9	53.6	65.0	57.8
• Serious infections	2.6	2.4	5.8	1.6
• Death	0.6	1.0	0	0
Significant differences in adverse events:	Yes - ABA in combination with biologic background therapies was associated with an increase in the rate of serious adverse events			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 5			
ADEQUATE RANDOMIZATION:	NR			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall attrition:** 210 (14.6%) **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Attrition overall:	12.8%	18%	12.8%	18%
Attrition due to adverse events:	5%	4.3%	8.7%	3.1%
QUALITY RATING:	**Fair**			

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Westhovens et al.**[58] **Year: 2006** **Country:** Multinational		
FUNDING:	Centocor Research and Development, Inc		
RESEARCH OBJECTIVE:	To assess the risk of serious infections following 22 weeks of infliximab therapy		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1084		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo + MTX** N/A 22 weeks 363	**INF 3 + MTX** 3 mg/kg wks 0,2,6,14 22 weeks 360	**INF 10 + MTX** 10 mg/kg wks 0,2,6,14 2 weeks 361
INCLUSION CRITERIA:	Diagnosis of RA according to the ACR: had active disease despite receiving MTX; patients may or may not have been treated with other concomitant DMARDs.		
EXCLUSION CRITERIA:	opportunistic infections; serious infections during the 2 months prior to screening; known HIV, active, latent or history of TB with inadequate documentation of treatment; an inability to receive prophylaxis with isoniazid; history of lymphoproliferative disease or malignancy; CHF.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Chloroquine, azathioprine, penicillamine, oral or intramuscular gold, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, oral corticosteroids, or NSAIDs		

<table>
<tr><td colspan="4">Authors: Westhovens et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes - except for median disease duration but not statistically significant (P = 0.083)
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Placebo + MTX</u></td><td><u>INF 3 + MTX</u></td><td><u>INF 10 + MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>52.0</td><td>53.0</td><td>52.0</td></tr>
<tr><td>Sex (% female):</td><td>83.2</td><td>80.0</td><td>77.8</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:
• TJC</td><td></td><td></td><td></td></tr>
<tr><td>• SJC</td><td>22</td><td>22</td><td>22</td></tr>
<tr><td>• Median disease duration</td><td>15</td><td>15</td><td>15</td></tr>
<tr><td>• DMARD use (%)</td><td>8.4</td><td>7.8</td><td>6.3</td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• DAS score</td><td>59.2</td><td>59.2</td><td>59.0</td></tr>
<tr><td>• HAQ score</td><td></td><td></td><td></td></tr>
<tr><td>• Concomitant conditions predisposing to infection, no. (%)</td><td>1.5

29 (8.0)</td><td>1.5

29 (8.1)</td><td>1.5

20 (5.5)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Rate of serious infections

Secondary Outcome Measures: ACR 20/50/70; DAS28

Timing of assessments: Weeks 0, 2, 6, 14, 22</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Week 22
• ACR20 INF3 58% INF10 61% MTX 26%
• ACR50 INF3 32.1% INF10 35.4% MTX 9.7%
• ACR70 INF3 14.0% INF10 16.1% MTX 4.7%
• DAS28 response (mean) INF3 3.5 INF10 3.3 MTX 4.4
• All INF 3 or INF 10 vs. MTX had a statistical significance of P < 0.001</td></tr>
</table>

Authors: Westhovens **Year: 2006**			
ADVERSE EVENTS (%):	**Placebo + MTX**	**INF 3 + MTX**	**INF 10 + MTX**
Overall adverse effects reported:	66.2	69.7	72.3
• Serious infections	1.7	1.7	5.0
• Pneumonia	0	0.8	1.1
• Serious AEs	7.5	7.8	7.5
• Rash	1.7	4.7	4.4
Significant differences in adverse events:	Rate of serious infections was significantly higher in the 10mg/kg group compared to placebo: RR: 3.1 95% CI 1.2 – 7.9 No significant differences in serious infections in the 3 mg/kg group: RR 1.0 95% CI 0.3 – 3.1		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 18 from efficacy analysis		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7.6 % **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo + MTX**	**INF 3 + MTX**	**INF 10 + MTX**
Loss to follow-up:	6.3	7.2	8.9
Withdrawals due to adverse events:	2.2	5.0	5.5
QUALITY RATING:	**Good**		

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe**[159] **Year: 2007** **Country:** USA
FUNDING:	Grant support from Abbott, Amgen, Wyeth-Australia, Merck, and Pfizer.
RESEARCH OBJECTIVE:	To ascertain the relationship between anti–tumor necrosis factor (anti-TNF) therapy, MTX (MTX), and the risk of lymphoma in patients with rheumatoid arthritis
DESIGN:	**Study design:** Retrospective cohort **Setting:** Rheumatology practices **Sample size:** 19591
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Participants** Various on-going 19591
INCLUSION CRITERIA:	Patients in the study were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of the outcomes of RA, who completed semiannual questionnaires in the period from 1998 through 2005. Patients were recruited on an ongoing basis from the practices of US rheumatologists
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A

Authors: Wolfe **Year: 2007**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe
	Participants
Mean age (years):	59
Sex (% female):	77.2
Ethnicity:	NR
Other germane population qualities:	
• Mean disease duration	14.1 yrs
• Biologic agent use	55.3%
• INF use	40.3%
• ETA use	7.6%
• ADA use	68.0%
• MTX use	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Odds and rate of lymphoma
RESULTS:	**Health Outcome Measures:** Overall- lymphoma IR 105.9 (95% CI 86.6–129.5) per 100,000 person-years of exposure vs. SEER IR 1.8 (95% CI 1.5–2.2). OR anti-TNF therapy vs. not anti-TNF therapy was 1.0 (95% CI 0.6–1.8 [*P* _ 0.875]). OR for lymphoma anti-TNF plus MTX vs. MTX treatment alone was 1.1 (95% CI 0.6–2.0 [*P* = 0.710]).

Authors: Wolfe **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	see results
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	N/A
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N//A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Good**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[160] **Year: 2004** **Country:** Multinational	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To determine the baseline rate of TB in RA prior to the introduction of infliximab and to determine the rate of TB among those currently receiving inf.	
DESIGN:	**Study design:** Observational- prospective cohort study **Setting:** Multicenter **Sample size:** 17,242	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Pre-INF Various N/A 10,782	INF Various 2.5 years 6,640
INCLUSION CRITERIA:	RA and use of inf	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

<table>
<tr><td colspan="3">Authors: Wolfe et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes with slight exceptions in age and sex
Disease severity: N/A</td></tr>
<tr><td></td><td>Pre-INF</td><td>INF</td></tr>
<tr><td>Mean age (years):</td><td>59.8</td><td>61.4</td></tr>
<tr><td>Sex (% female):</td><td>76.9</td><td>73.5</td></tr>
<tr><td>Ethnicity (% white):</td><td>NR</td><td>NR</td></tr>
<tr><td></td><td>90.9</td><td>94.4</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Corticosteroid use (%)</td><td>54.6</td><td>50.4</td></tr>
<tr><td>• MTX use (%)</td><td>47.9</td><td>74.6</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: TB
Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
▪ In the pre-inf group, 1 case of TB developed during 16,173 patient-years of follow-up, yielding a rate of 6.2 cases (95% CI 1.6-34.4) per 100,000 patient years.
▪ In the inf group, the TB incidence rate among patients was 61.9 cases per 100,000 patient years.
▪ None of the TB patients had undergone a TB skin test and no cases of TB occurred in the 44-59% that had received the test.</td></tr>
</table>

Authors: Wolfe et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	Pre-INF or INF N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	INF N/A N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe**[161] **Year: 2007** **Country:** US
FUNDING:	
RESEARCH OBJECTIVE:	**Biologic Treatment of Rheumatoid Arthritis and the Risk of Malignancy**
DESIGN:	**Study design:** Observational study **Setting:** Registry, members of the US National Data Bank for Rheumatic Diseases (NDB) from the practices of US rheumatologists **Sample size:** 13,001 (6,282 received biologics)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics** various 3 years 6282
INCLUSION CRITERIA:	1 cancer-free phase before study participation and at least 2 observations
EXCLUSION CRITERIA:	For each specific cancer, patients with that preexisting cancer were excluded from the specific analysis of that cancer
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Prednisone , MTX , Leflunomide , Sulfasalazine , HCQ

Authors: Wolfe **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** NR		
Mean age (years):	58.5+/-13.1		
Sex (% female):	78		
Ethnicity: White, not Hispanic origin	92.5		
Other germane population qualities:			
• Mean disease duration	16.7 +/- 12.7		
• MTX use (%)	56.9		
• Corticosteroids use (%)	45.6		
• Leflunomide	18.7		
• Sulfasalazine	9.4		
• HCQ	25.2		
• INF	19.9		
• ETA	7.6		
• ADA	0.4		
• AKA	0.3		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** 1) rate of malignancy in RA 2) all biologic therapies considered as a group Duration of fu 3.0 years		
RESULTS:	**Health Outcome Measures:** 1) no increase in the overall rate of cancer in participating RA patients compared with SEER (Surveillance, Epidemiology, and End Results) data (SIR 1.0, 95% CI 1.0–1.1) lymphoma SIR 1.7, 95% CI 1.3–2.2 melanoma SIR 1.7, 95% CI 1.3–2.3 lung cancer SIR 1.2 95% CI 1.0–1.4 breast cancer SIR 0.8, 95% CI 0.6–0.9 colon cancer SIR 0.5, 95% CI 0.4–0.6 2) risk of nonmelanotic skin cancer (OR 1.5 [95% CI 1.2–1.8]) and possibly of melanoma (OR 2.3 [95% CI 0.9–5.4], $P = 0.070$) OR for all cancers overall 1.0 (95% CI 0.8–1.2) **Melanoma**: INF (OR 2.6 [95% CI 1.0–6.7], $P = 0.056$), ETA (OR 2.4 [95% CI 1.0–5.8], $P = 0.054$) **non-melanotic skin cancer**: INF (OR 1.7 [95% CI 1.3–2.2], $P < 0.001$), ETA (OR 1.2 [95% CI 1.0–1.5], $P = 0.081$)		

Authors: Wolfe **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**see results**
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**NA**
QUALITY RATING:	**Good**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[162] **Year: 2004** **Country:** U.S.		
FUNDING:	Centocor, Inc.		
RESEARCH OBJECTIVE:	To determine the frequency of heart failure in patients with RA, and to determine its predictors, particularly the use of anti-TNF therapy.		
DESIGN:	**Study design:** retrospective cohort study **Setting:** Multicenter (National Data Bank for Rheumatic Diseases) **Sample size:** 13,171		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Multiple		
INCLUSION CRITERIA:	Participation in the National Data Bank for Rheumatic Diseases study of the outcomes of arthritis; patient at participating rheumatology clinic;		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Wolfe et al.
Year: 2004

POPULATION CHARACTERISTICS:

Groups similar at baseline: N/A
Disease severity: NR

	Total population	Anti-TNF	INF	ETA	No anti-TNF
Mean age (years):	61	60	61.5	56.7	61.5
Sex (% female):	77	78	77	80	76
Ethnicity: % white	94	95	96	92	92
Other germane population qualities:					
• Mean disease duration	14.9	14.2	13.8	15.2	15.5
• DMARD or anti-TNF use (%)	86	NR	NR	NR	NR
• MTX use (%)	56	67	76	44	47
• Prednisone use (%)	39	47	49	39	33
• DAS score	3.6	3.7	3.7	3.6	3.5
• HAQ score	1.1	1.2	1.2	1.1	1.0

OUTCOME ASSESSMENT:

Primary Outcome Measures: NR
Secondary Outcome Measures: NR
Timing of assessments: Every 6 months for a total of 2 years.

RESULTS:

Health Outcome Measures:

- There were 461 cases of heart failure in the 13,171 patients 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, patients 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, the adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in the remaining patients ($P = 0.03$).
- Frequency of heart failure was 5.2% in men and 3.0% in women.
- In examining incident cases of heart failure in patients under age 50, no increase was found (0/1569 patients using anti-TNF vs. 3/1401 most using anti-TNF therapy).

Authors: Wolfe et al. **Year: 2004**				
ADVERSE EVENTS: **Overall adverse effects reported:**	**All Anti-TNF**	**INF**	**ETA**	**No Anti-TNF**
• All Heart Failure: adjusted rate	2.8	2.6	2.9	3.4 to 3.9
• Incident Heart Failure: adjusted rate	0.2	0.2	0.3	0.2 to 0.3
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A			
ARE GROUPS COMPARABLE AT BASELINE:	Yes			
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes			
STATISTICAL ANALYIS ADEQUATE:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR			
QUALITY RATING:	**Fair**			

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[163] **Year: 2006** **Country:** US
FUNDING:	Bristol-Meyers-Squibb
RESEARCH OBJECTIVE:	To evaluate the treatment of RA and the risk of hospitalization for pneumonia
DESIGN:	**Study design:** Prospective cohort study **Setting:** Rheumatology clinics **Sample size:** 16,788
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Various RA treatments** NR NR NR
INCLUSION CRITERIA:	Participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes including 5,317 enrolled as part of an INF safety registry and 1,852 as part of a leflunomide safety registry.
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Wolfe et al. **Year: 2006**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	Cohort
Mean age (years):	62.0
Sex (% female):	77.2
Ethnicity:	89.7% white, 4.8% black, 3.0% Hispanic, 1.0 Asian/Pacific Islander, 1.1% American Indian or Alaskan native, 0.5% Other
Other germane population qualities:	
• Mean disease duration	16.3 years
• DMARD use (lifetime #)	3.3
• MTX use (%)	54.5
• Prednisone use (%)	38.1
• HAQ score	1.1
• MTX (%)	54.5
• Hydroxychloroquine (%)	17.7
• Leflunomide (%)	14.4
• Sulfasalazine (%)	5.7
• INF (%)	36.9
• ETA (%)	12.8
• ADA (%)	4.3
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hospitalization for pneumonia and the variables that effect this
RESULTS:	**Health Outcome Measures:** Effect of treatment variables on the risk of pneumonia (adjusted for demographic variables-age, sex, smoking, education, and enrollment) • Prednisone HR 1.7 [95% CI 1.5-2.1]) • Leflunomide HR 1.3 [95% CI 1.0-1.5], *P* = 0.036), • Sulfasalazine 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).

Authors: Wolfe et al. **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	N/A
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:**
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 7. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Zink et al.**[164] **Year: 2005** **Country:** Germany		
FUNDING:	Essex Pharma, Wyeth Pharma, Amgen, and Abbott		
RESEARCH OBJECTIVE:	To compare drug continuation rates in patients with RA who start on a biological agent or on a DMARD after previous DMARD failure.		
DESIGN:	**Study design:** retrospective cohort study **Setting:** Clinical **Sample size:** 1523		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics** Varied 1 year 924	**DMARDs** Varied 1 year 599	
INCLUSION CRITERIA:	18 - 75 years old; meeting ACR criteria for RA; "cases" if a new treatment with INF, ETA, or AKA; "controls" if a conventional DMARD treatment was begun after failure of at least one previous therapy		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Zink et al.
Year: 2005

POPULATION CHARACTERISTICS:

Groups similar at baseline: No
Disease severity: Mild-moderate-severe

	ETA n=511	INF n=343	AKA n=70	Total Control Group n=599	Leflunomide n=120	Leflunomide+ MTX n=141
Mean age (years):	53.7	53.6	54.3	56.5	58.0	57.4
Sex (% female):	77.9	71.1	77.1	82.8	85.8	78.0
Ethnicity:	NR	NR	NR	NR	NR	NR
Other germane population qualities:						
• TJC	13.3	12.6	12.6	10.0	10.6	10.9
• SJC	10.4	10.7	10.2	7.7	7.4	8.5
• Mean disease duration	9.0	8.5	13.0	6.0	9.0	7.0
• Previous DMARD use (#)	3.9	3.7	4.2	2.1	2.4	2.2
• MTX use (%)	91.2	92.1	78.6	68.7	94.2	90.7
• Corticosteroids use (%)	NR	NR	NR	NR	NR	NR
• DAS score	6.1	6.0	6.1	5.4	5.5	5.6

OUTCOME ASSESSMENT:

Primary Outcome Measures: Treatment continuation at one year

Secondary Outcome Measures: Treatment continuation at 6 months

Timing of assessments: At each visit and every 6 months

RESULTS:

Health Outcome Measures:

- Treatment continuation at one year- ETA 68.6% (95% CI 62-75)) INF 65.4% (95% CI 58-73) AKA 59% (95% CI 41-77). AKA vs. ETA $P = 0.004$; $P = 0.03$ AKA vs. INF $P = 0.03$
- After 12 months, treatment discontinuation because of adverse events: INF: 18.7%; ETA: 12.6%; AKA: 16.3%

<table>
<tr><td colspan="4">Authors: Zink et al.
Year: 2005</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
• infections
• Y</td><td colspan="3">NR</td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">NR</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ARE GROUPS COMPARABLE AT BASELINE:</td><td colspan="3">Yes</td></tr>
<tr><td>ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:</td><td colspan="3">Yes</td></tr>
<tr><td>STATISTICAL ANALYIS ADEQUATE:</td><td colspan="3">Yes</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td><u>ETA</u>
31.4
12.6</td><td><u>INF</u>
34.6
18.7</td><td><u>AKA</u>
41
16.3</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Chung et al**.[126] **Year: 2003** **Country:** US		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To assess the effectiveness and safety of infliximab in patients with CHF		
DESIGN:	**Study design:** RCT **Study name: ATTACH (Anti-TNF Therapy Against Congestive Heart Failure)-Trial** **Setting:** University clinics (32 centers) **Sample size:** 150		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 28 weeks 49	**INF** 5 mg/kg 28 weeks 50	**INF** 10 mg/kg 28 weeks 51
INCLUSION CRITERIA:	Men and women at least 18 years old with stable New York Heart Association (NYHA) class III or IV heart failure associated with a radionuclide left ventricular ejection fraction ≤ 35% within 14 days before randomization		
EXCLUSION CRITERIA:	Hemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease; had experienced an acute myocardial infarction or coronary revascularization procedure within 2 months; or were likely to undergo coronary revascularization or heart transplant during the anticipated duration of the study; resuscitation from sudden death or a therapeutic discharge of an implanted implantable cardioverter defibrillator within 3 months or had received within 2 weeks or were likely to receive within the following 28 weeks any of the following: A class IC or III antiarrhythmic other than amiodarone; a calcium channel blocker other than amlodipine for hypertension or angina; a positive inotrope other than digoxin; or a NSAID other than aspirin; experienced a serious infection within 2 months; had latent TB or had had TB within 3 years; had a documented HIV infection; or had any other opportunistic infection within 6 months; treatment within 3 months of INF or other therapeutic agents that could interfere with the actions of TNFα (eg, ETA, pentoxifylline, thalidomide, or D2E7)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vasodilators or nitrates		

Authors: Chung et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Placebo	**INF5**	**INF10**
Mean age (years):	60 ± 12	62 ± 15	62 ± 13
Sex (% female):	24	14	16
Ethnicity (% white):	88	88	84
Current or prior angina (%):	29	18	24
Myocardial infarction (%):	63	50	67
Diabetes mellitus (%):	41	28	37
NYHA Class III/IV (%):	96/4	96/4	92/8
LVEF (%):	0.25 ± 0.07	0.23 ± 0.07	0.24 ± 0.06
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Change in clinical status, assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using pre-specified criteria **Timing of assessments:** 1,2,6,10,14,20,28 weeks		
RESULTS:	**Health Outcome Measures:** • 10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% CI 1.01 to 7.97; nominal $P = 0.043$ using log-rank test) • Patients in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than patients in the placebo or 5 mg/kg INF groups		

Authors: Chung et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported (# of patients with 1 or more) n (%):** • Dizziness • Dyspnea • Hypotension • Angina • Serious AEs • Serious infections	**Placebo** 40 (83.3) 2 (4.2) 6 (12.5) 0 (0.0) 1 (2.1) (29.2) (2.1)	**INF5** 47 (92.2) 16 (31.4) 10 (19.6) 3 (5.9) 3 (5.9) (23.5) (5.9)	**INF10** 42 (84.0) 10 (20.0) 12 (24.0) 4 (8.0) 4 (8.0) (44.0) (8.0)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** 6 in all, NR seperately	**Overall loss to follow-up:** NR **Loss to follow-up differential high**: NR **Placebo** 1	**INF5** 2	**INF10** 5
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Dixon et al.**[129] **Year: 2007** **Country:** UK		
FUNDING:	The British Society for Rheumatology is indirectly funded by Schering-Plough, Whety Laboratories, Abbot Laboratories, and Amgen		
RESEARCH OBJECTIVE:	To test the hypothesis that the anti-inflammatory effect of anti–tumor necrosis-α (anti-TNFα) therapy might lead to a reduction in the incidence of myocardial infarction (MI) in RA patients		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Data from BSRBR, a national prospective observational study **Sample size:** 10,829 (74 patients switched from comparison cohort and were included in analysis for both so actual number of patients=10,755); anti-TNF subgroup analysis: 7515		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNFα nonresponders** N/A N/A 1638	**Anti-TNFα responders** N/A N/A 5877	
INCLUSION CRITERIA:	Registered with BSRBR; diagnosed with RA; followed up for ≥ 6 months by July 31, 2006; Anti-TNFα cohort: treated with an anti-TNF drug, registered with BSRBR within 6 months of starting biologic therapy		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Lipid-lowering drugs, NSAIDS		

Authors: Dixon et al. **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Anti-TNFα nonresponders	**Anti-TNFα responders**	
Mean age (years):	57	56	
Sex (% female):	79	76	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	NR	NR	
• Swollen joint count	NR	NR	
• Median disease duration	11	7	
• DMARD use (%)	NR	100	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	45.3	42.9	
• DAS score	6.4	6.6	
• HAQ score	2.2	2.0	
• Prior MI (%)	2.9	2.6	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** MI rates **Timing of assessments:** N/A		
RESULTS:		**Nonresponders**	**Responders**
	Person-years	1815	9886
	No. of reported MIs	17	35
	Rate of MIs per 1000 person-yrs (95% CI)	9.4 (5.5-15.0)	3.5 (2.5-4.9)
	Incidence rate ratio	Referent	0.38 (0.21-0.67)
	Incidence rate ratio, adjusted for age and sex	Referent	0.38 (0.22-0.68)
	Incidence rate ratio, multivariate analysis	Referent	0.36 (0.19-0.69)
	Incidence rate ratio by sex, multivariate analysis		
	Male	Referent	0.31 (0.12-0.81)
	Female	Referent	0.46 (0.20-1.06)

Authors: Dixon et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	See above
Significant differences in adverse events:	see results
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Good**

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Fleischmann et al.**[165] **Year: 2005** **Country:** US
FUNDING:	Immunex Corporation
RESEARCH OBJECTIVE:	Long term safety of etanercept in elderly patients being treated for RA, AS, PsA
DESIGN:	**Study design:** Retrospective analysis **Setting:** 22 trials **Sample size:** 4322 (3893 unique subjects)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**All** NR Various 4322 (3893 unique subjects)
INCLUSION CRITERIA:	Participants of 18 RA, 2 PsA, 2 AS trials.
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

Authors: Fleischmann et al.
Year: 2005

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe

	RA		PsA		AS	
	Less than 65 years	**65 years and more**	**Less than 65 years**	**65 years and more**	**Less than 65 years**	**65 years and more**
Sample size:	2772	579	251	14	273	4
Median age (years):	47	70	46	70	42	65
Sex (% female):	77	73	46	71.4	24.5	0
Ethnicity (%white):	78.6	89.5	89.2	100	92.7	100
Other germane population qualities:	NR	NR	NR	NR	NR	NR

OUTCOME ASSESSMENT:

Primary Outcome Measures: Safety including all adverse events, serious adverse events, infectious events, medically important infections and deaths

Secondary Outcome Measures: Additional conditions of interest were also examined, demyelinating diseases, TB, lymphomas, and cardiovascular diseases.

Timing of assessments: N/A

RESULTS:

Health Outcome Measures:

- The incidence of all adverse events, serious adverse events, infectious events, medically important infections and malignancies were not significantly elevated in elderly subjects when compared with subjects less than 65 years of age
- Demyelinating diseases were seen only in subjects under the age of 65.

Authors: Fleischmann et al. **Year: 2005**				
	Age less than 65 years		**Age 65 years or more**	
ADVERSE EVENTS (%):	**Control (n= 1020)**	**ETA (n=2652)**	**Control (n= 170)**	**ETA (n=480)**
Overall adverse effects reported:	63.4	77.1	74.1	83.3
• Serious adverse event	4	14.3	17.6	29
• Infectious event	39.8	55.4	51.2	48.8
• Medically important event	1.3	4	7.1	10.4
Significant differences in adverse events:	Once the data is normalized with the control group data (patients from same studies that received placebo or MTX) there were no differences in adverse events or serious adverse events.			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions: NR**			
ADEQUATE RANDOMIZATION:	**N/A**			
ADEQUATE ALLOCATION CONCEALMENT:	N/A			
BLINDING OF OUTCOME ASSESSORS:	No			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
	Age less than 65 years		**Age 65 years or more**	
ATTRITION (*treatment specific*):	**Control (n= 1020)**	**ETA (n=2652)**	**Control (n= 1020)**	**ETA (n=2652)**
Loss to follow-up:	NR	NR	NR	NR
Withdrawals due to adverse events (%):	3.5	5.4	12.4	12.5
QUALITY RATING:	**Fair**			

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Fleischmann et al.,**[132] **Schiff et al.,**[134] **Tesser et al.**[135] **Year: 2003 and 2004** **Country:** Multinational	
FUNDING:	Amgen Inc., Thousand Oaks, CA	
RESEARCH OBJECTIVE:	To evaluate the safety of anakinra in a large population of patients with RA, typical of those seen in clinical practice. Additionally to determine the safety in a sub-population of patients with comorbid conditions; and to examine concomitant medication's effect on adverse events.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (169 sites) **Sample size:** 1414 (1399 enrolled)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/d 6 months 1116	**Placebo** N/A 6 months 283
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria for at least 3 months; active disease defined by a minimum of 3 swollen joints and 3 tender joints or 45 minutes of morning stiffness; stable doses of NSAIDs and corticosteroids for one month; and stable doses of DMARDs for 2 months.	
EXCLUSION CRITERIA:	Pregnant or lactating; uncontrolled medical condition (e.g., diabetes with HgbA1c > 8%); malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix; Felty's syndrome; leukopenia; neutropenia; thrombocytopenia; abnormal liver function test result; hepatitis B or C positive; HIV positive.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS, corticosteroids, and DMARDs (except TNF inhibitors) either alone or in combination	

Authors: Fleischmann et al. and Schiff et al. **Year: 2003 and 2004**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild to severe	
	AKA	**Placebo**
Mean age (years):	54.6	55.7
Sex (% female):	74.7	74.6
Ethnicity (%):		
• White	87.8	90.1
• Black	6.1	5.3
• Hispanic	4.4	3.5
• Other	1.7	1.1
Other germane population qualities:		
• TJC	22.6	22.6
• SJC	18.8	18.3
• DMARD use (excluding MTX) (%)	47.7	47.7
• MTX use (%)	51.9	59.4
• Corticosteroids use (%)	57.0	60.8
• DAS score	NR	NR
• HAQ score	NR	NR
Comorbidities (Schiff 2004), %:		
• Asthma	9.8	8.1
• COPD	12.9	11.0
• Pneumonia	9.1	6.7
• DM	7.4	7.4
• CAD	5.7	5.7
• CHF	3.2	3.2

Authors: Fleischmann et al. and Schiff et al. Year: 2003 and 2004	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (measured by adverse events, serious adverse events, infections, study discontinuation, and death; WHO adverse reaction term dictionary) **Secondary Outcome Measures:** NR **Timing of assessments:** Day 1, week 1, and months 1,3, and 6.
RESULTS:	**Health Outcome Measures:** • After 6 months, the rate of spontaneous adverse events was not different between AKA and placebo, except for ISRs, which occurred much more frequently among AKA-treated patients than placebo-treated patients (72.6% v. 32.9%) P-value NR • 13.4% of patients in the AKA group withdrew due to adverse event compared to 9.2% in the placebo group, but the difference was not significant ($P = 0.057$); overall discontinuation rates were similar (21.6% vs. 18.7%) • Serious infections occurred more frequently in AKA than in placebo patients (2.1% v. 0.4%), but was not statistically significantly different but may be clinically significant. ($P = 0.068$) • In patients with comorbid conditions, there were no differences between the AKA group and the placebo group in incidence of serious adverse events or overall infectious events. • In patients with comorbid conditions, the rate of serious infectious events was increased relative to placebo (2.5% vs. 0.0%; P = NR). • There is a trend towards increased risk of serious infectious events with AKA in patients with pulmonary comorbidities versus placebo (3.4% v. 1.6%), but it failed to reach statistical significance. • Neutralizing anti-ANA antibodies detected in 0.8% of AKA patients NR for patients receiving placebo. • Adverse event profiles were similar between groups taking concomitant antihypertensive, antidiabetic and statin drugs.

Authors: Fleischmann et al. and Schiff et al. and Tesser et al. **Year: 2003 and 2004**		
ADVERSE EVENTS:	**AKA**	**Placebo**
Overall adverse effects reported:	1,027 (92.0%)	261 (92.2%)
• Deaths	4 (0.4%)	1 (0.4%)
• Serious adverse events	86 (7.7%)	22 (7.8%)
• Severe adverse events	15.5%	13.1%
• ISRs	72.6%	32.9%
• Infectious episode	41.2%	43.5%
• Serious infection	2.1%	0.4%
• URTI	13.3	18.4
• Sinusitis	6.7	6.0
• Influenza-like	5.8	6.4
• UTI	4.6	5.3
• Bronchitis	3.4	4.6
• Infection (resistance mechanism body system)	2.9	3.2
Significant differences in adverse events:	• No significant differences reported. (No P-value was reported for ISRs.)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (15/1414)	
ADEQUATE RANDOMIZATION:	NR	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 394 (21%) **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**AKA**	**Placebo**
Loss to follow-up:	21.6%	18.7%
Withdrawals due to adverse events:	13.4%	9.2%
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Genevay**[166] **Year: 2007** **Country:** Switzerland		
FUNDING:	University and grants		
RESEARCH OBJECTIVE:	To evaluate the tolerance to and effectiveness of anti–tumor necrosis factor (anti-TNF) agents in elderly patients (>65 years old) with RA (ERA) in comparison with younger patients (YRA)		
DESIGN:	**Study design:** Observational cohort **Setting:** Multicenter **Sample size:** 1571		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**YRA** various median 3 years 1227	**ERA** various median 3 years 344	
INCLUSION CRITERIA:	All patients have been diagnosed as having RA according to the clinical judgment of their rheumatologist.		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Genevay **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** Mild-moderate-severe		
	YRA	**ERA**	
Median age (years):	51	71	
Sex (% female):	75	78.5	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Mean disease duration	11.5	14.3	
• DMARD use (%)			
• MTX use (%)	42	35.2	
• Corticosteroids use (%)	48.8	59.9	
• DAS score	4.2	4.5	
• HAQ score	1.23	1.4	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** DAS28 **Secondary Outcome Measures:** EULAR and HAQ **Timing of assessments:** Annually and when changes were made in treatment		
RESULTS:	**Health Outcome Measures:** • Mean change in DAS28 scores at 2 years (–0.65 versus –0.58) P = NS • Mean change in HAQ score ERA (– 0.02) than in YRA (– 0.1) $P < 0.001$ • EULAR good responders criteria at 1 year ERA 7.2% versus YRA 11.2%; $P < 0.05$ • EULAR poor responders ERA 60.2% versus YRA 51.5%; $P < 0.01$.		

Authors: Genevay **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**NR**		
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:**		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 128 (8%) **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**drug 1** 8% NR	**drug 2** 8% NR	**drug 3**
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Genovese et al.**[23] **Year: 2004** **Country:** US		
FUNDING:	Amgen, Inc., Thousand Oaks, CA		
RESEARCH OBJECTIVE:	To determine the potential for additive or synergistic effects of combination therapy with the selective anti-TNF-α agent etanercept and the anti-IL1 agent anakinra.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 242		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg *twice* per week 24 weeks 80	**½ ETA + AKA** 25 mg *once* per week; 100 mg/day 24 weeks 81	**ETA + AKA** 25 mg *twice* per week; 100 mg/day 24 weeks 81
INCLUSION CRITERIA:	Age 18 or greater; greater than 6-month history of RA diagnosed by ACR criteria; 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, received MTX for at least 16 weeks, with a stable dose in the range of 10-25 mg/week for at least 8 weeks.		
EXCLUSION CRITERIA:	Any DMARD other than MTX within the past 4 weeks; treatment with AKA or any protein-based TNF-alpha inhibitor; received any intraarticular or systemic corticosteroid injections within past 4 weeks; or, had a recent history of significant infection or other important concurrent illness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with stable doses of MTX and other stable medications, such as corticosteroids.		

<table>
<tr><td colspan="4">Authors: Genovese, et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes, but there is a slight overall trend to more severe disease in full ETA + AKA group.
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>½ ETA + AKA</u></td><td><u>ETA + AKA</u></td></tr>
<tr><td>Mean age (years):</td><td>54.4</td><td>53.8</td><td>55.7</td></tr>
<tr><td>Sex (% female):</td><td>82.5</td><td>71.6</td><td>77.8</td></tr>
<tr><td>Ethnicity (% white race):</td><td>86.3</td><td>77.8</td><td>75.3</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>31.0</td><td>31.0</td><td>35.9</td></tr>
<tr><td>• SJC</td><td>21.4</td><td>19.8</td><td>23.4</td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>48.8</td><td>54.3</td><td>44.4</td></tr>
<tr><td>• HAQ score</td><td>1.5</td><td>1.5</td><td>1.6</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR50 at week 24.
Secondary Outcome Measures: ACR20 and ACR70 at week 24; sustained ACR20 response (“response for at least 4 monthly measurements, not necessarily consecutive, with 1 occurring at month 6”); good or moderate EULAR response at week 24; improvement in the ACR core criteria components; duration of morning stiffness; the DAS; and the SF-36; plasma AKA and ETA concentrations and anti-AKA and anti-ETA antibody concentrations.
Timing of assessments: Baseline and weeks 2, 4, 8, 12, 16, 20, and 24; plasma concentrations at weeks 4, 12, and 24; antibody concentrations at weeks 12 and 24.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures (<u>ETA</u> v. <u>½ ETA + AKA</u> v. <u>ETA + AKA</u>), measure (95% CI):
• At week 24 there were no significant differences in outcomes between the treatment groups
ACR50 at week 24: 41% v. 39% v. 31% (P = 0.914, by 1-tailed t-test)
o OR (ETA + AKA v. ETA alone) 0.64 (90% CI: 0.37 to 1.09)
o Sensitivity analysis yielded similar results.
• ACR20 at week 24:
o 68% v. 51% v. 62% Only significant difference is between ETA alone and the ½ ETA + AKA group (P = 0.037).
• ACR70 at week 24: 21% v. 24% v. 14% (P-value NR)
• Sustained ACR20 response: between 43% and 54% of subjects in each group (specifics NR).
• EULAR response at week 24: 79% v. 66% v. 73% (P-value NR)
• Mean % reduction in DAS: 39% v. 41% v. 40% (P-value NR)</td></tr>
</table>

Authors: Genovese et al. **Year: 2004**			
ADVERSE EVENTS:	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Overall adverse effects reported, %:	90.0	95.1	93.8
• Infections	40.0	37.0	46.9
• URTI	20.0	11.1	13.6
• ISR	40.0	67.9	70.4
• Any serious adverse event	2.5	4.9	14.8
• Serious infection	0.0	3.7	7.4
Significant differences in adverse events:	Patients receiving ETA (any dosage) + AKA experienced more ISRs and serious adverse events than patients receiving ETA alone. *P*-values NR.		
ANALYSIS:	**ITT:** YES **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	**YES**		
ADEQUATE ALLOCATION CONCEALMENT:	Unknown		
BLINDING OF OUTCOME ASSESSORS:	YES		
ATTRITION (*overall*):	**Overall loss to follow-up:** 15.7% **Loss to follow-up differential high:** 15% between ETA alone and ½ ETA + AKA		
ATTRITION (*treatment specific*):	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Loss to follow-up:	7%	22%	20%
Withdrawals due to adverse events:	0%	8.6%	7.4%
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Gottlieb et al.**[167] **Year: 2005** **Country:**		
FUNDING:	Biogen Idec, Inc.		
RESEARCH OBJECTIVE:	To assess safety & efficacy of alefacept in elderly, obese, and diabetic patients with moderate to severe chronic plaque psoriasis by integrating data from 9 phase 2 & 3 clinical studies and their extensions.		
DESIGN:	**Study design:** Pooled analysis of RCTs **Setting:** Multicenter **Sample size:** 1,473		
INTERVENTION: N/A	**ALE in phase 2 studies**	**ALE in phase 3 studies**	**Placebo**
Dose:	0.025, 0.075, or 0.15mg/kg, or 7.5 mg IV	10 or 15mg IM, or 7.5 mg IV	N/A
Duration:	12 weeks	12 weeks	NR
Sample size:	NR	NR	NR
INCLUSION CRITERIA:	Participation in any of 9 multicenter, randomized, clinical studies; at least 16 years old; chronic plaque psoriasis for ≥ 12 months, involving ≥ 10% body surface area; CD4+ lymphocyte count above 400 cells/uL; no serious local or systemic infection within last 3 months.		
EXCLUSION CRITERIA:	History of malignancy, other than basal cell carcinomas or ≤ 3 cutaneous squamous cell carcinomas; use of phototherapy, systemic retinoids / steroids / fumarates, immunosuppressants, and high-potency corticosteroids within last 4 weeks.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Moderate-potency topical corticosteroids, vitamin D analogs, keratolytics, and coal tar on scalp, palms, groin, and soles only, and not within 2 weeks of study drug administration.		

<table>
<tr><td colspan="4">Authors: Gottlieb et al.
Year: 2005</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
•</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR</td></tr>
<tr><td>NR</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75 (75% reduction from baseline); Physician Global Assessment (PGA)

Timing of assessments: Adverse events collected during monthly interim visits.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• ALE was associated with substantial clinical improvement in the elderly, obese, & diabetic.
• ALE- treated patients had numerically higher degree of clinical improvement vs. placebo.
• 24%-33% of ALE-treated patients achieved PASI 75 at any time during 1st course, with 17%-26% achieving a PGA of “clear” or “almost clear.”
• Among those who received 3 courses of ALE, 41-58% achieved a PASI 75, and 33-37% achieved a PGA or “clear” or “almost clear.”</td></tr>
</table>

Authors: Gottlieb et al. **Year: 2005**			
ADVERSE EVENTS in 1st course:	**Elderly (n=99)**	**Obese (n=652)**	**Diabetic (n=122)**
Overall adverse effects reported:	NR	NR	NR
• Accidental injury	15.2%	16.7%	18.9%
• Headache	14.1%	16.6%	13.9%
• Pharyngitis	13.1%	16.4%	12.3%
• Rhinitis	12.1%	12.3%	12.3%
• Infection	11.1%	12.1%	NR
• Any malignancy	6.1%	1.2%	1.6%
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Kristensen**[168] **Year: 2008** **Country:** Sweden		
FUNDING:	Grants from Osterlund and Kock Foundations, King Gustav V 80 year fund, and Reumatikerforbundet.		
RESEARCH OBJECTIVE:	To identify factors predicting response to first TNF blocking treatment course in patients with established RA with a special focus on gender differences		
DESIGN:	**Study design:** Observational **Setting:** Multicenter- primary **Sample size:** 1565		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Males** Various 3 months 353	**Females** Various 3 months 1212	
INCLUSION CRITERIA:	A diagnosis of RA according to clinical judgment of the treating physician		
EXCLUSION CRITERIA:	Patients with <3 month of follow-up or having received previous courses of biologic therapy		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs and MTX		

Authors: Kristensen
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe

	Males	**Females**
Mean age (years):	58	55
Sex (% female):	0	100
Ethnicity:	NR	NR
Other germane population qualities:		
• Tender joint count	7.7	9.4
• Swollen joint count	9.9	9.7
• Mean disease duration	11 yrs	12 yrs
• DMARD use (%)	15	13
• MTX use (%)	66	61
• Corticosteroids use (%)	NR	NR
• DAS score	5.36	5.62
• HAQ score	1.12	1.42
• ADA	12%	16%
• ETA	34%	40%
• INF	54%	44%

OUTCOME ASSESSMENT:

Primary Outcome Measures: EULAR and ACR
Timing of assessments: Baseline, 3 months and 6 months

RESULTS:

Health Outcome Measures:

	Males		Females		Level of significance
	3 months n=353 (%)	6 months n = 308 (%)	3 months n = 1212 (%)	6 months n = 1020 (%)	
EULAR Good	21	22	19	21	NS
EULAR remission (DAS28<2.6)	18	18	16	17	NS
ACR50	22	24	25	24	NS
ACR70	8	9	8	8	NS

Authors: Kristensen **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	NR		
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 59 (3.7%) **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Takeuchi**[157] **Year: 2008** **Country:** Japan
FUNDING:	Tanabe Seiyaku Co., Ltd
RESEARCH OBJECTIVE:	Safety of INF in patients with RA
DESIGN:	**Study design:** Observational – postmarketing surveillance study **Setting:** Multicenter **Sample size:** 5000
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 3 mg/kg at weeks 0,2,6 and then every 8 weeks 6 months 5000
INCLUSION CRITERIA:	All patients treated with INF between July /2003 and Dec 2004 with active disease despite treatment with MTX of greater than 6 mg /week for at least 3 months
EXCLUSION CRITERIA:	N/A – but in order for institutions to prescribe INF they had to agree to participate fully in this study.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Takeuchi **Year: 2008**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	INF
Mean age (years):	55.1 years
Sex (% female):	79
Ethnicity:	NR – assume Asian 100%
Other germane population qualities:	3.1
• Hepatic disorder	2.5
• Cardiac disorder	9.4
• Diabetes Mellitus	4.7
• Respiratory disease	1.2
• Haematological disease	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events and adverse drug reactions were compared to a clinical trial that was conducted in Japan
RESULTS:	**Health Outcome Measures:** **See adverse events and risk factors for bacterial pneumonia** OR 95% CI Comorbid Respiratory disease Yes vs. none 3.90 (2.35–6.47) $P < 0.001$ Male vs. female 1.94 (1.29–2.93) $P = 0.001$ 40s and under vs. 50s 0.25 (0.10–0.66) 50s 1.00 (reference) , $P < 0.001$ 60s vs. 50s 1.90 (1.18–3.07) 70s and over vs. 50s 2.57 (1.48–4.45)

Authors: Takeuchi **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious ADRs • ADRs Per 100 pt/yrs • infections • Serious infections	**PMS n = 5000** 28% 6.2 59.38 (59.07 to 59.69) 18.35 (18.18 to 18.52) 8.56 (8.44-8.68)	**Japanese clinical trial n = 141** 67.4 10.6 72.16 (70.1 to 73.61) 39.50 (38.4 to 40.57) 8.36 (7.87-8.85)	**drug 3**
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A		
QUALITY RATING:	N/A		

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Weaver et al.**[54] **Year: 2006** **Country:** US				
FUNDING:	Immunex Corporation				
RESEARCH OBJECTIVE:	To evaluate the effectiveness of select biologics, methotrexate, and DMARDs in the management of adult RA in routine clinical practice.				
DESIGN:	**Study design:** Prospective observational **Setting:** 509 rheumatology practices **Sample size:** 5397 (includes 762 patients whose treatment strategies were not of interest to this review)				
INTERVENTION: **Dose (median wkly at baseline):** **Duration:** **Sample size:**	**MTX** 10 mg 12 months 941	**ETA** 50 mg 12 months 1251	**INF** 3.8 mg/kg every 8 wks 12 months 120	**ETA+MTX** 50 mg+15 mg 12 months 1783	**INF+MTX** 3.8mg/kg every 8 wks+15mg 12 months 540
INCLUSION CRITERIA:	Patients requiring a change in their existing RA treatment: ≥ 18 years; met ACR criteria for RA.				
EXCLUSION CRITERIA:	Active infection; pregnancy; concurrent enrollment in a clinical trial				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes				

Authors: Weaver et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: No
Disease severity: Mild-moderate-severe

	MTX	ETA	INF	ETA+MTX	INF+MTX
Mean age (years):	56.8	53.2	60.2	52.6	58.5
Sex (% female):	75	75	71	79	77
Ethnicity:	77	81	78	81	81
Other germane population qualities:					
• TJC	13.0	13.4	10.6	13.3	13.9
• SJC	11.3	11.1	14.8	11.5	12.0
• Mean disease duration	3.5	9.2	10.6	7.7	9.5
• DMARD naive (%)	75	65	15	4	4
• Corticosteroids use (%)	NR	NR	NR	NR	NR
• DAS score	N/A	N/A	N/A	N/A	N/A
• HAQ score	1.3	1.4	1.5	1.3	1.4

OUTCOME ASSESSMENT:

Primary Outcome Measures: Modified ACR 20 (doesn't include ESR or CRP)
Secondary Outcome Measures: HAQ, patient global and pain assessments, physician global assessment and 28-count swollen and tender joints
Timing of assessments: 12 months (± 1 month)

RESULTS:

Health Outcome Measures:

- Unadjusted mACR20 ETA+MTX 43% ETA 41% INF+MTX 35% INF 26% MTX 37%
- After adjusting for baseline covariates, ETA + MTX vs MTX OR 1.29, 95% CI 1.09-1.52; $P < 0.01$
- ETA vs. MTX OR 1.23, 95% CI 1.02-1.47; $P < 0.05$
- Significant differences were not observed between patients receiving MTX vs. INF + MTX (OR 0.96 CI 0.76-1.21 $P = 0.72$) or INF monotherapy (OR 0.66 95% CI 0.43-1.02 $P = 0.06$)
- Percent improvement on HAQ (vs MTX) MTX 7% (N/A) ETA 17% ($P < 0.001$) INF 1% (P =NS) ETA+MTX 17% ($P < 0.0001$) INF+MTX 3% (P = NS)

Authors: Weaver et al. **Year: 2006**					
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**MTX** NR	**ETA**	**INF**	**ETA+MTX**	**INF+MTX**
Significant differences in adverse events:	NR				
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A				
ARE GROUPS COMPARABLE AT BASELINE:	No				
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes				
STATISTICAL ANALYIS ADEQUATE:	Yes				
ATTRITION (*overall*):	**Overall loss to follow-up:** No **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*):	**MTX**	**ETA**	**INF**	**ETA+MTX**	**INF+MTX**
Loss to follow-up:	23%	31%	33%	39%	29%
Withdrawals due to adverse events:	4%	6%	11%	8%	9%
QUALITY RATING:	**Fair**				

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Weinblatt**[158] **Year: 2006** **Country:** USA and Canada			
FUNDING:	Bristol-Myers Squibb			
RESEARCH OBJECTIVE:	To assess the safety of ABA in patients with RA who have been receiving treatment with DMARDs and/or biologics for 3 months or more			
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1441			
INTERVENTION:	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Dose:	10 mg/kg days 1, 15, and 29, then every 4 weeks a total of 14 doses.	N/A	10 mg/kg days 1, 15, and 29, then every 4 weeks a total of 14 doses.	N/A
Duration:	1 year	1 year	1 year	1 year
Sample size:	856	418	103	64
INCLUSION CRITERIA:	Men and women at least 18 years of age who met the 1987 ACR; criteria for the diagnosis of RA and the 1991 ACR criteria for RA functional classes I, II, III, or IV; active disease despite receiving background DMARDs and/or biologic therapy, warranting additional therapy at the discretion of the investigator; the average score for the patient's global assessment of disease activity, as assessed by VAS measurements at screening and randomization (day 1), was required to be >20 mm; at least 1 biologic and/or nonbiologic DMARD approved for RA for at least 3 months, and at a stable dose for at least 28 days prior to day 1; stable medical conditions such as congestive heart failure (CHF), asthma, COPD, and diabetes mellitus			
EXCLUSION CRITERIA:	Unstable or uncontrolled renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, or neurologic diseases, or any autoimmune disorder other than RA as the main diagnosis; active or chronic recurrent bacterial infections unless treated and resolved, active herpes zoster infection within the previous 2 months, hepatitis B or hepatitis C virus infection, and active or latent tuberculosis; pregnant or nursing.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Approved biologic and nonbiologic DMARDs, MTX, hydroxychloroquine, leflunomide, gold, azathioprine, AKA, ETA, INF, and ADA; stable, low-dose oral corticosteroids (10 mg/day or less) and/or stable doses of NSAIDs, including aspirin			

Authors: Weinblatt **Year: 2006**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe			
	Nonbiologic background therapy		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Mean age (years):	52.2	52.0	54.6	52.8
Sex (% female):	83.1	83.7	75.7	75.0
Ethnicity (%white):	83.9	83.3	97.1	92.2
Other germane population qualities:				
• Pain, 100-mm VAS	61.1	61.3	62.2	61.5
• HAQ - DI	1.5	1.5	1.5	1.6
• Mean disease duration – years	9.5	9.5	11.3	11.3
• MTX	80.7	80.4	56.3	56.3
• Corticosteroids	71.6	73.7	74.8	79.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety- adverse events and infusion reactions **Secondary Outcome Measures:** HAQ-DI; Patient's global assessment of disease activity, and physician's global assessment of disease activity **Timing of assessments:** days 1, 85, 169, and 253.			
RESULTS:	**Health Outcome Measures: ABA vs. placebo** HAQ-DI; -0.46 versus -0.25; $P < 0.001$ Patient's assessment of pain -26.3 vs. -16.4 $P < 0.001$ Patient's global assessment of disease activity -27.2 vs. -17.4 $P < 0.001$ Physician's global assessment of disease activity -33.5 vs. -23.6 $P < 0.001$ **Patients w/COPD** overall AEs ABA 97.3% (n = 37) and placebo 88.2% (n = 17). AEs involving the respiratory system ABA 43.2% versus placebo 23.5% SAEs ABA 27% versus placebo 5.9% **Patients with DM** overall AEs ABA 93.8% (n = 65) and placebo 90.3% (n = 31) Infections ABA 50.8% vs. placebo 58.1% SAEs ABA 21.5% vs. placebo 12.9%.			

Authors: Weinblatt **Year: 2006**				
ADVERSE EVENTS:	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Overall adverse effects reported:	89.7	86.1	95.1	89.1
• SAEs	11.7	12.2	22.3	12.5
• Neoplasms	3.2	3.8	6.8	1.6
• Infections	54.9	53.6	65.0	57.8
• Serious infections	2.6	2.4	5.8	1.6
• Death	0.6	1.0	0	0
Significant differences in adverse events:	Yes - ABA in combination with biologic background therapies was associated with an increase in the rate of serious adverse events			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 5			
ADEQUATE RANDOMIZATION:	NR			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall attrition:** 210 (14.6%) **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Attrition overall:	12.8%	18%	12.8%	18%
Attrition due to adverse events:	5%	4.3%	8.7%	3.1%
QUALITY RATING:	**Fair**			

Evidence Table 8. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Weisman**[169] **Year: 2007** **Country:** United States		
FUNDING:	Immunex Corporation and by Wyeth Pharmaceuticals.		
RESEARCH OBJECTIVE:	To evaluate the safety of ETA in patients with rheumatoid arthritis (RA) and concomitant comorbidities		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 535		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 16 weeks 269	**ETA** 25 mg twice weekly 16 weeks 266	
INCLUSION CRITERIA:	At least 18 yrs of age, met the ACR criteria for RA [3], and had at least one qualifying comorbidity: diabetes mellitus (only patients taking insulin and/or oral hypoglycaemic agents), chronic pulmonary disease (asthma or chronic obstructive pulmonary disease), or pneumonia or recurrent infections (bronchitis, sinusitis, or urinary tract infection) in the preceding year.		
EXCLUSION CRITERIA:	Recent myocardial infarction, uncontrolled hypertension or severe pulmonary disease requiring continual oxygen therapy was excluded. A protocol amendment later excluded patients with angina pectoris.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroids, NSAIDs, DMARDs (except azathioprine, cyclosporine and cyclophosphamide) and pain medications at the discretion of their physicians.		

Authors: Weisman
Year: 2007

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe

	Placebo	ETA
Mean age (years):	59.3	60.6
Sex (% female):	78.1	60.6
Ethnicity:	77% white, 13% Hispanic, 6.3% Black	81% white, 12% Hispanic, 6% Black
Other germane population qualities:		
• Mean disease duration	9.4 years	10.1 years
• Diabetes-insulin	16.4%	17.7%
• Diabetes-oral only	33.1%	32.0%
• Chronic pulmonary disease	40.1%	44%
• Coronary artery disease	78.4%	83.5%
• Myocardial Infarction	73.6%	80.1%
• Hypertension	56.1%	63.5%

OUTCOME ASSESSMENT:

Primary Outcome Measures: incidence of medically important infections (MIIs; defined as those resulting in hospitalization or treatment with intravenous antibiotics).

Timing of assessments: baseline, weeks 8 and 16, and 30 days post–therapy

RESULTS:

Health Outcome Measures:

	Medically important infections		Serious Adverse Events	
% of patients	Placebo	ETA	Placebo	ETA
All patients	3.7	3.0	5.9	8.6
w/ diabetes	3.8	2.3	6.8	9.1
w/o diabetes	3.7	3.7	5.1	8.2
w/ chronic pulmonary disease	5.6	4.3	6.5	10.3
w/o chronic pulmonary disease	2.5	2.0	5.6	7.4

Six patients died on study [one placebo (cardiac arrest); five ETA (cardiac arrest, cardiomyopathy, coronary artery disease, respiratory failure and subarachnoid hemorrhage)].

Authors: Weisman **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	see results		
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:**		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 21% **Attrition differential high:** almost – 14%		
ATTRITION (*treatment specific*):	**Placebo**	**ETA**	
Attrition overall:	27.9%	13.9%	
Attrition due to adverse events:	6.7%	4.9%	
QUALITY RATING:	**Fair**		

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