# Drug Class Review

# Targeted Immune Modulators

**Final Update 2 Report**

**November 2009**

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**The medical literature relating to the topic is scanned periodically (see http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report based on the information contained in the scan. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.**

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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<br>JIA |
| Adalimumab | Humira® | Abbott | Subcutaneous | 10-20 days | 1-14 days | TNF inhibitor | RA<br>JIA<br>PsA<br>AS<br>Crohn's disease<br>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<br>Crohn's Disease |
| Efalizumab[a] | Raptiva® | Genentech | Subcutaneous | 6.2 days | 14 days | CD11a inhibitor | Plaque Psoriasis |
| Etanercept | Enbrel® | Amgen<br>Wyeth<br>Immunex | Subcutaneous | 4.3 days | 1-28 days | TNF inhibitor | RA<br>JIA<br>PsA<br>AS<br>Plaque psoriasis |
| Infliximab | Remicade® | Centocor | Intravenous | 9.8 days | 2-14 days | TNF inhibitor | RA<br>Crohn's disease<br>PsA<br>AS<br>Ulcerative colitis<br>Plaque psoriasis |
| Natalizumab | Tysabri® | Biogen-Idec | Intravenous | 7-15 days | 2-4 weeks | Anti-IgG4 | Crohn's disease |
| Rituximab | Rituxan® | Genentech<br>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<br>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<br>≥ 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<br>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<br>*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:<br>o Quality of Life<br>o Functional capacity<br>o Pain<br>o Reduction in the number of swollen or tender joints<br>o Response<br>o Remission<br>o Reduction of affected body surface area<br>o Hospitalizations<br>o Mortality<br>o Steroid withdrawal<br><br>• If no studies with health outcomes were available, we included intermediate outcomes:<br>o Radiological outcomes | • Outpatient study population<br><br>• Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM to another<br>o Good or fair quality<br>o ≥ 3 months study duration<br>o N ≥ 30<br><br>• When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials<br>o Good or fair quality<br>o ≥ 3 months study duration<br>o N ≥ 100<br><br>• Head-to-head observational studies were reviewed for quality of life, functional capacity, hospitalizations and mortality - outcome measures rarely assessed in controlled trials<br>o Good or fair quality<br>o ≥ 3 months study duration<br>o N ≥ 100 |
| **Safety/ Tolerability** | • Overall adverse events<br>• Withdrawals because of adverse events<br>• Serious adverse events<br>• Specific adverse events, including:<br>o Serious infectious diseases<br>o Lymphoma<br>o CHF<br>o Autoimmunity | • Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM drug to another<br>o Good or fair quality<br>o ≥ 3 months study duration<br>o N ≥ 30<br><br>• When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials<br>o Good or fair quality<br>o ≥ 3 months study duration<br>o N ≥ 100<br><br>• Observational studies<br>o Good or fair quality<br>o ≥ 6 months study duration<br>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]

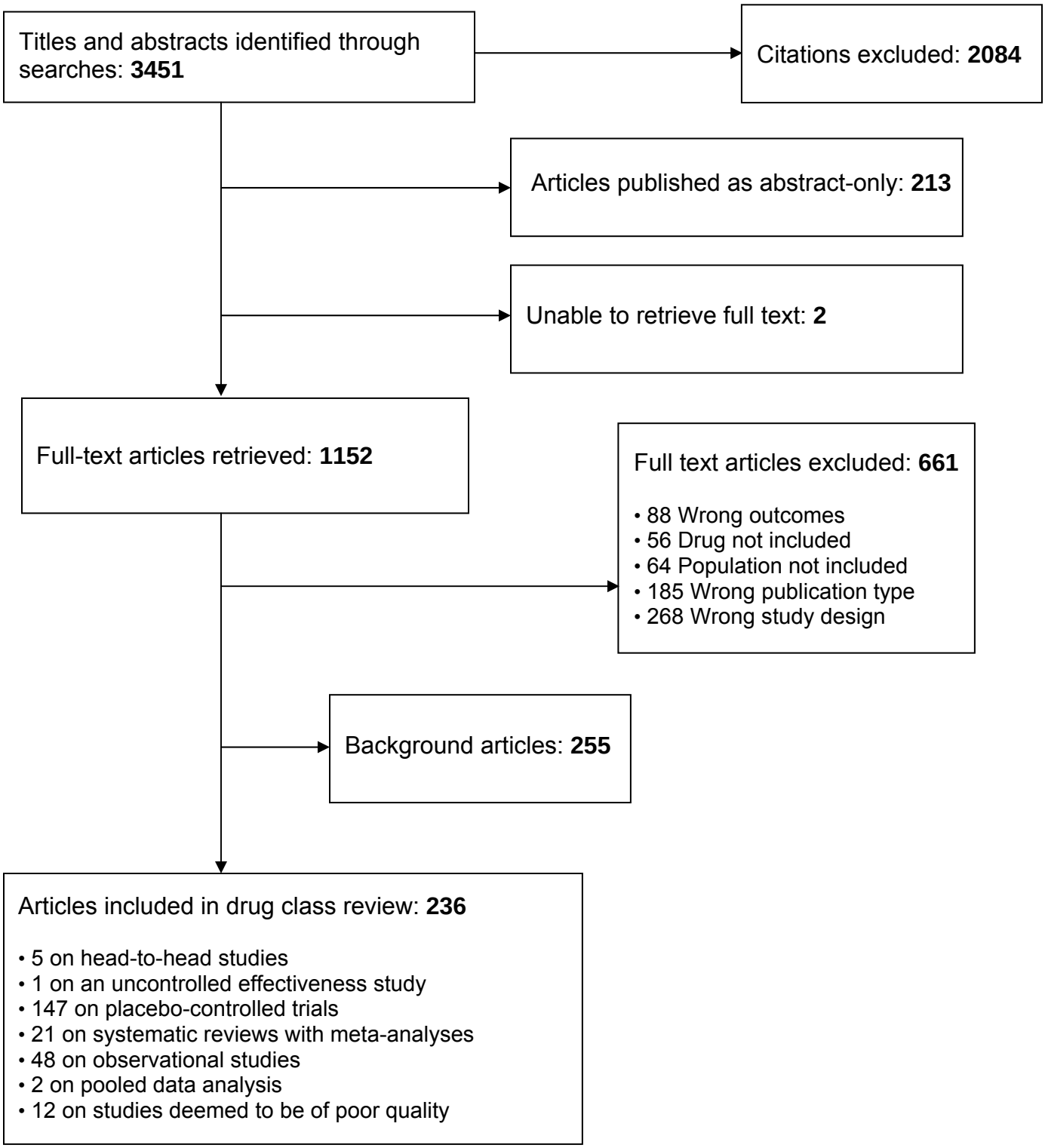
## RESULTS

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<br><br>ACR 50 response at 1 year:<br>45% vs. 36% | No dose increases for infliximab allowed | Moderate |
| Outcome: Radiographic progression | | | | | | | |
| No evidence | | | | | | | |
| ***Adalimumab compared with Etanercept*** | | | | | | | |
| Outcome: Health outcomes | | | | | | | |
| Direct:<br>1 / 356<br><br>Indirect: 4 /~ 2500 | Prospective cohort study<br><br>Meta-analyses and indirect comparisons of placebo-controlled trials | Good | Consistency between direct and indirect estimates | Mixed | Similar effects for ADA and ETA<br><br>EULAR response:<br>78% vs. 80% | none | Low |
| Outcome: Radiographic progression | | | | | | | |
| No evidence | | | | | | | |
| ***Adalimumab compared with Infliximab*** | | | | | | | |
| Outcome: Health outcomes | | | | | | | |
| Direct: 1 / 418<br><br>Indirect: 4 / ~ 2500 | Prospective cohort study<br><br>Meta-analyses and indirect comparisons of placebo-controlled trials | Good | Inconsistent results between direct and indirect evidence | Mixed | Direct:<br>EULAR response:<br>78% vs. 61%<br><br>Indirect:<br>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<br>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<br>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<br>Indirect: 5 / ~ 2500 | 1 open-label RCT<br>1 non-randomized controlled trial<br>4 prospective cohort studies | Good | Yes | Yes | ACR 20 response 74% vs. 60%<br>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**

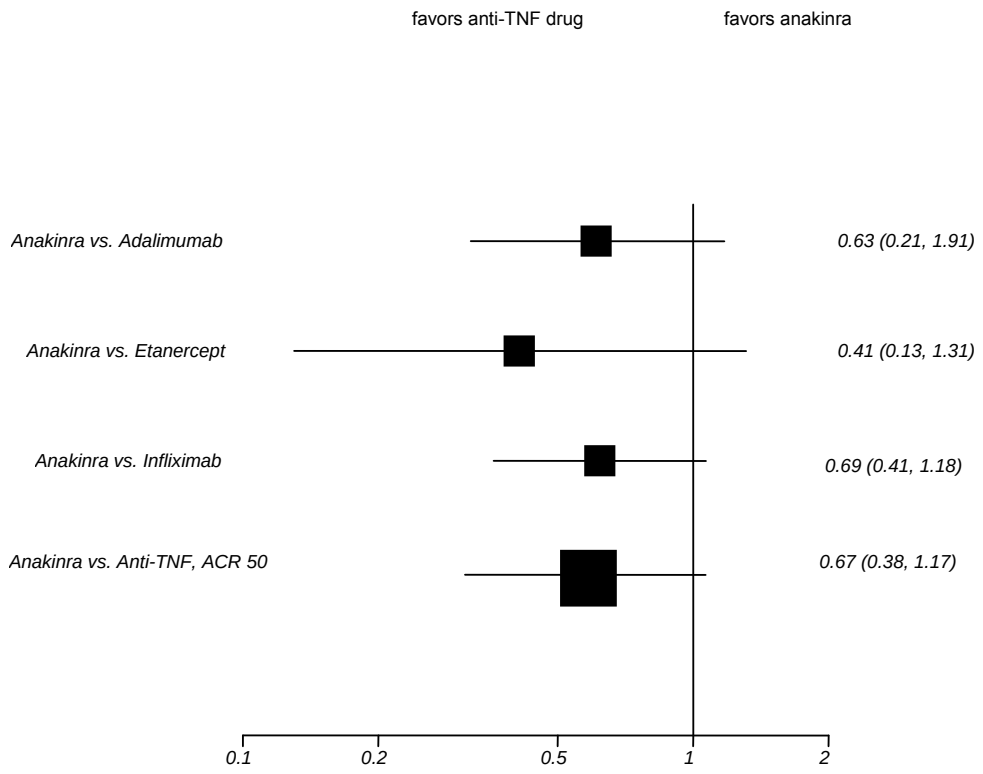


**Table 8. Adjusted indirect comparisons of targeted immune modulators for the treatment of rheumatoid arthritis**

| 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]<br><br>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]<br><br>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 psorasis (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)<br><br>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<br>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.

# REFERENCES


1. Choy, E.H. and G.S. Panayi, *Cytokine pathways and joint inflammation in rheumatoid arthritis.* N Engl J Med, 2001. 344(12): p. 907-16.
2. Greiner, A., et al., *Association of Anti-Cyclic Citrullinated Peptide Antibodies, Anti-Citrullin Antibodies, and IgM and IgA Rheumatoid Factors with Serological Parameters of Disease Activity in Rheumatoid Arthritis.* Ann N Y Acad Sci, 2005. 1050: p. 295-303.
3. Saag, K., et al., *American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.* Arthritis Care & Research, 2008. 59(6): p. 762-784.
4. Arnett, F.C., et al., *The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.* Arthritis Rheum, 1988. 31(3): p. 315-24.
5. Weiss, J.E. and N.T. Ilowite, *Juvenile idiopathic arthritis.* Pediatr Clin North Am, 2005. 52(2): p. 413-42, vi.
6. Reveille, J.D. and F.C. Arnett, *Spondyloarthritis: update on pathogenesis and management.* Am J Med, 2005. 118(6): p. 592-603.
7. Williamson, L., et al., *Extended report: nail disease in psoriatic arthritis--clinically important, potentially treatable and often overlooked.* Rheumatology (Oxford), 2004. 43(6): p. 790-4.
8. Anandarajah, A.P. and C.T. Ritchlin, *Pathogenesis of psoriatic arthritis.* Curr Opin Rheumatol, 2004. 16(4): p. 338-43.
9. Gladman, D.D., *Traditional and newer therapeutic options for psoriatic arthritis: an evidence-based review.* Drugs, 2005. 65(9): p. 1223-38.
10. Kavanaugh, A.F. and C.T. Ritchlin, *Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines.* J Rheumatol, 2006. 33(7): p. 1417-21.
11. Kornbluth, A. and D.B. Sachar, *Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee.* Am J Gastroenterol, 2004. 99(7): p. 1371-85.
12. Krueger, G.G., et al., *Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis?* J Am Acad Dermatol, 2000. 43(2 Pt 1): p. 281-5.
13. Gottlieb, A.B., *Psoriasis. Immunopathology and immunomodulation.* Dermatol Clin, 2001. 19(4): p. 649-57, viii.
14. Krueger, J.G., et al., *Role of growth factors, cytokines, and their receptors in the pathogenesis of psoriasis.* J Invest Dermatol, 1990. 94(6 Suppl): p. 135S-140S.
15. Lebwohl, M., *A clinician's paradigm in the treatment of psoriasis.* J Am Acad Dermatol, 2005. 53(1 Suppl 1): p. S59-69.
16. Gartlehner, G., et al., *A simple and valid tool distinguished efficacy from effectiveness studies.* J Clin Epidemiol, 2006. 59(10): p. 1040-8.
17. Welsing, P.M., G.F. Borm, and P. van Riel, *Minimal clinically important difference in radiological progression of joint damage. A definition based on patient perspective.* J Rheumatol, 2006. 33(3): p. 501-7.

18. Redelmeier, D.A. and K. Lorig, *Assessing the clinical importance of symptomatic improvements. An illustration in rheumatology.* Arch Intern Med, 1993. 153(11): p. 1337-42.
19. Wells, G.A., et al., *Minimum important difference between patients with rheumatoid arthritis: the patient's perspective.* J Rheumatol, 1993. 20(3): p. 557-60.
20. Bruynesteyn, K., et al., *Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference.* Arthritis Rheum, 2002. 46(4): p. 913-20.
21. Norris, S.L. and D. Atkins, *Challenges in using nonrandomized studies in systematic reviews of treatment interventions.* Ann Intern Med, 2005. 142(12 Pt 2): p. 1112-9.
22. Balk, E.M., J. Lau, and P.A. Bonis, *Reading and critically appraising systematic reviews and meta-analyses: a short primer with a focus on hepatology.* J Hepatol, 2005. 43(4): p. 729-36.
23. Harris, R.P., et al., *Current methods of the US Preventive Services Task Force: a review of the process.* Am J Prev Med, 2001. 20(3 Suppl): p. 21-35.
24. Anonymous, *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition).* 2001.
25. Egger, M., G.D. Smith, and D.G. Altman, *Systematic Reviews in Health Care (2nd edition).* 2001.
26. Bucher, H.C., et al., *The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials.* J Clin Epidemiol, 1997. 50(6): p. 683-91.
27. Song, F., et al., *Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses.* Bmj, 2003. 326(7387): p. 472.
28. Sauriol, L., et al., *Meta-analysis comparing newer antipsychotic drugs for the treatment of schizophrenia: evaluating the indirect approach.* Clin Ther, 2001. 23(6): p. 942-56.
29. Atkins, D., et al., *Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group.* BMC Health Serv Res, 2004. 4(1): p. 38.
30. Guyatt, G., et al., *Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force.* Chest, 2006. 129(1): p. 174-81.
31. Schiff, M., et al., *Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate.* Ann Rheum Dis, 2008. 67(8): p. 1096-103.
32. Geborek, P., et al., *Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden.* Ann Rheum Dis, 2002. 61(9): p. 793-8.
33. De Filippis, L., et al., *Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis.* Panminerva Med, 2006. 48(2): p. 129-35.

34. Weaver, A.L., et al., *Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry.* Curr Med Res Opin, 2006. 22(1): p. 185-98.
35. Kristensen, L.E., T. Saxne, and P. Geborek, *The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden.* Arthritis Rheum, 2006. 54(2): p. 600-6.
36. Kievit, W., et al., *The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data.* Ann Rheum Dis, 2008. 67(9): p. 1229-34.
37. Genovese, M.C., et al., *Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate.* Arthritis Rheum, 2004. 50(5): p. 1412-9.
38. Weinblatt, M., et al., *Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial.* Ann Rheum Dis, 2007. 66(2): p. 228-34.
39. Felson, D.T., et al., *The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials.* Arthritis Rheum, 1993. 36(6): p. 729-40.
40. Hyrich, K.L., et al., *Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register.* Arthritis Rheum, 2006. 54(6): p. 1786-1794.
41. Finckh, A., et al., *The effectiveness of anti-tumor necrosis factor therapy in preventing progressive radiographic joint damage in rheumatoid arthritis: a population-based study.* Arthritis Rheum, 2006. 54(1): p. 54-9.
42. St. Clair, E.W., et al., *Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial.* Arthritis Rheum, 2004. 50(11): p. 3432-43.
43. Nixon, R., N. Bansback, and A. Brennan, *The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons.* Rheumatology, 2007. 46(7): p. 1140-47.
44. Lee, Y.H., et al., *Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis.* Rheumatology International, 2008. 28(6): p. 553-559.
45. Wailoo, A., et al., *Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program. AHRQ Technology Assessment Program.* 2006.
46. Hochberg, M.C., et al., *Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis.* Ann Rheum Dis, 2003. 62 Suppl 2: p. ii13-6.
47. Clark, W., et al., *The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.* Health Technol Assess, 2004. 8(18): p. iii-iv, ix-x, 1-105.

48. Kremer, J.M., et al., *Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig.* N Engl J Med, 2003. 349(20): p. 1907-15.
49. Emery, P., et al., *Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life.* J Rheumatol, 2006. 33(4): p. 681-9.
50. Kremer, J.M., et al., *Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial.* Arthritis Rheum, 2005. 52(8): p. 2263-71.
51. Kremer, J.M., et al., *Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial.* Ann Intern Med, 2006. 144(12): p. 865-76.
52. Russell, A.S., et al., *Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment.* Ann Rheum Dis, 2007. 66(2): p. 189-94.
53. Moreland, L.W., et al., *Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion.* Arthritis Rheum, 2002. 46(6): p. 1470-9.
54. Genovese, M.C., et al., *Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition.* N Engl J Med, 2005. 353(11): p. 1114-23.
55. Westhovens, R., et al., *Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial.* Rheumatology (Oxford), 2006. 45(10): p. 1238-46.
56. Chen, Y.F., et al., *A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.* Health Technology Assessment, 2006. 10(42): p. 1-248.
57. Alonso-Ruiz, A., et al., *Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety.* BMC Musculoskelet Disord, 2008. 9: p. 52.
58. Navarro Sarabia, F., et al., *Adalimumab for treating rheumatoid arthritis (Brief record).* Journal of Rheumatology, 2006(6): p. 1075; 1081-1075; 1081.
59. Weinblatt, M.E., 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): p. 35-45.
60. Weinblatt, M.E., et al., *Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study.* Ann Rheum Dis, 2006. 65(6): p. 753-9.
61. Breedveld, F.C., 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): p. 26-37.
62. Furst, D.E., 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): p. 2563-71.

63. Keystone, E.C., 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): p. 1400-11.
64. van de Putte, L.B., 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): p. 1168-77.
65. van de Putte, L.B., 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): p. 508-16.
66. Kim, H.Y., et al., *A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate.* APLAR Journal of Rheumatology, 2007. 10(1): p. 9-16.
67. Miyasaka, N., *Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: The CHANGE study.* Modern Rheumatology, 2008. 18(3): p. 252-262.
68. Jiang, Y., 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): p. 1001-9.
69. Mertens, M. and J.A. Singh, *Anakinra for rheumatoid arthritis.* Cochrane Database Syst Rev, 2009(1): p. CD005121.
70. Cohen, S.B., 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): p. 1062-8.
71. Bresnihan, B., et al., *Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist.* Arthritis Rheum, 1998. 41(12): p. 2196-204.
72. Cohen, S., 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): p. 614-24.
73. Cohen, S.B., J.M. Woolley, and W. Chan, *Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis.* J Rheumatol, 2003. 30(2): p. 225-31.
74. Keystone, E., et al., *Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.* Arthritis Rheum, 2008. 58(11): p. 3319-29.
75. Blumenauer, B., et al., *Etanercept for the treatment of rheumatoid arthritis.* Cochrane Database Syst Rev, 2003(4): p. CD004525.
76. Jobanputra, P., et al., *The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.* Health Technol Assess, 2002. 6(21): p. 1-110.

77. Suarez-Almazor, M., et al., *Infliximab and etanercept in rheumatoid arthritis: systematic review of long-term clinical effectiveness, safety, and cost-effectiveness.* Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2007. Technology Report No 85.
78. Moreland, L.W., et al., *Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial.* Ann Intern Med, 1999. 130(6): p. 478-86.
79. Mathias, S.D., et al., *Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo.* Clin Ther, 2000. 22(1): p. 128-39.
80. Klareskog, L., 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): p. 675-81.
81. van der Heijde, D., 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): p. 328-34.
82. van der Heijde, D., 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): p. 1063-74.
83. Bathon, J.M., et al., *A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.* N Engl J Med, 2000. 343(22): p. 1586-93.
84. Genovese, M.C., et al., *Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.* Arthritis Rheum, 2002. 46(6): p. 1443-50.
85. Kosinski, M., et al., *Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response.* Am J Manag Care, 2002. 8(3): p. 231-40.
86. Genovese, M.C., et al., *Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis.* J Rheumatol, 2005. 32(7): p. 1232-42.
87. Van Der Heijde, D., 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): p. 3928-3939.
88. Lan, J.L., et al., *A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study.* J Formos Med Assoc, 2004. 103(8): p. 618-23.
89. Moreland, L.W., 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): p. 141-7.
90. Weinblatt, M.E., 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): p. 253-9.
91. Smolen, J.S., 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): p. 1020-30.

92. Breedveld, F.C., et al., *Infliximab in active early rheumatoid arthritis.* Ann Rheum Dis, 2004. 63(2): p. 149-55.
93. Blumenauer, B., et al., *Infliximab for the treatment of rheumatoid arthritis.* The Cochrane Database of Systematic Reviews, 2002(3).
94. Westhovens, R., 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): p. 1075-86.
95. Smolen, J.S., et al., *Infliximab treatment maintains employability in patients with early rheumatoid arthritis.* Arthritis Rheum, 2006. 54(3): p. 716-22.
96. Smolen, J.S., et al., *Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial.* Arthritis Rheum, 2006. 54(3): p. 702-10.
97. Abe, T., et al., *A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis.* J Rheumatol, 2006. 33(1): p. 37-44.
98. Maini, R.N., 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): p. 1552-63.
99. Maini, R., 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): p. 1932-9.
100. Kavanaugh, A., et al., *Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy.* J Rheumatol, 2000. 27(4): p. 841-50.
101. Lipsky, P.E., 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): p. 1594-602.
102. Maini, R.N., 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): p. 1051-65.
103. Zhang, F.C., et al., *Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China.* APLAR Journal of Rheumatology, 2006. 9(2): p. 127-130.
104. Edwards, J.C., et al., *Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis.* N Engl J Med, 2004. 350(25): p. 2572-81.
105. Strand, V., et al., *Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years.* Rheumatology (Oxford), 2006. 45(12): p. 1505-13.
106. Emery, P., et al., *The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial.* Arthritis Rheum, 2006. 54(5): p. 1390-400.
107. Mease, P.J., et al., *Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial.* J Rheumatol, 2008. 35(1): p. 20-30.

108. Keystone, E., et al., *Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies.* Ann Rheum Dis, 2009. 68(2): p. 216-21.
109. Keystone, E., et al., *Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy.* Arthritis Rheum, 2008. 59(6): p. 785-93.
110. Cohen, S.B., et al., *Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks.* Arthritis and Rheumatism, 2006. 54(9): p. 2793-2806.
111. Weinblatt, M., et al., *Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study.* Arthritis Rheum, 2006. 54(9): p. 2807-16.
112. Smolen, J., et al., *Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial.* Ann Rheum Dis, 2009. 68(6): p. 797-804.
113. Fleischmann, R., et al., *Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study.* Ann Rheum Dis, 2009. 68(6): p. 805-11.
114. Ruperto, N., et al., *Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial.* Lancet, 2008. 372(9636): p. 383-91.
115. Lovell, D.J., et al., *Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.* N Engl J Med, 2008. 359(8): p. 810-20.
116. Lovell, D.J., et al., *Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group.* N Engl J Med, 2000. 342(11): p. 763-9.
117. Ruperto, N., et al., *A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis.* Arthritis Rheum, 2007. 56(9): p. 3096-106.
118. Horneff, G., et al., *The German etanercept registry for treatment of juvenile idiopathic arthritis.* Ann Rheum Dis, 2004. 63(12): p. 1638-44.
119. van der Heijde, D., et al., *Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial.* Arthritis Rheum, 2006. 54(7): p. 2136-46.
120. Davis, J.C., Jr., et al., *Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study.* Arthritis Rheum, 2007. 57(6): p. 1050-7.
121. Revicki, D.A., et al., *Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: Results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS).* Journal of Rheumatology, 2008. 35(7): p. 1346-1353.
122. van der Heijde, D., et al., *Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis.* Ann Rheum Dis, 2006. 65(12): p. 1572-7.

123. Braun, J., et al., *Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly.* Rheumatology (Oxford), 2007. 46(6): p. 999-1004.
124. McLeod, C., et al., *Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.* Health Technol Assess, 2007. 11(28): p. 1-158, iii-iv.
125. van der Linden, S., H.A. Valkenburg, and A. Cats, *Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria.* Arthritis Rheum, 1984. 27(4): p. 361-8.
126. Calin, A., et al., *Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis.* Ann Rheum Dis, 2004. 63(12): p. 1594-600.
127. Gorman, J.D., K.E. Sack, and J.C.J. Davis, *Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha.* N Engl J Med, 2002. 346(18): p. 1349-56.
128. Davis, J.C.J., et al., *Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial.* Arthritis Rheum, 2003. 48(11): p. 3230-6.
129. van der Heijde, D., et al., *Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT).* Arthritis Rheum, 2005. 52(2): p. 582-91.
130. Braun, J., et al., *Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial.* Lancet, 2002. 359(9313): p. 1187-93.
131. Anderson, J.J., et al., *Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis.* Arthritis Rheum, 2001. 44(8): p. 1876-86.
132. Saad, A.A., et al., *Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials.* J Rheumatol, 2008. 35(5): p. 883-90.
133. Mease, P.J., et al., *Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis.* Arthritis Rheum, 2005. 52(10): p. 3279-3289.
134. Mease, P.J., D.D. Gladman, and E.C. Keystone, *Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: Results of a randomized, double-blind, placebo-controlled study.* Arthritis Rheum, 2006. 54(5): p. 1638-45.
135. Mease, P.J., et al., *Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.* Lancet, 2000. 356(9227): p. 385-90.
136. Mease, P.J., et al., *Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression.* Arthritis Rheum, 2004. 50(7): p. 2264-72.
137. Antoni, C.E., et al., *Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT).* Arthritis Rheum, 2005. 52(4): p. 1227-36.
138. Antoni, C., et al., *Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial.* Ann Rheum Dis, 2005. 64(8): p. 1150-7.
139. Kavanaugh, A., et al., *Infliximab improves health-related quality of life and physical function in patients with psoriatic arthritis.* Ann Rheum Dis, 2006. 65(4): p. 471-77.
140. Kavanaugh, A., et al., *The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year.* Ann Rheum Dis, 2006. 65(8): p. 1038-43.

141. Genovese, M.C., et al., *Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.* J Rheumatol, 2007. 34(5): p. 1040-50.
142. Van Der Heijde, D., et al., *Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2.* Arthritis and Rheumatism, 2007. 56(8): p. 2698-2707.
143. Kavanaugh, A., et al., *Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis.* Journal of Rheumatology, 2006. 33(11): p. 2254-2259.
144. Kavanaugh, A., et al., *Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial.* Ann Rheum Dis, 2007. 66(4): p. 498-505.
145. Colombel, J.F., et al., *Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial.* Gastroenterology, 2007. 132(1): p. 52-65.
146. Feagan, B.G., et al., *Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study.* Gastroenterology, 2008. 135(5): p. 1493-9.
147. Loftus, E.V., et al., *Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial.* Am J Gastroenterol, 2008. 103(12): p. 3132-41.
148. Colombel, J.F., et al., *Adalimumab for the treatment of fistulas in patients with Crohn's disease.* Gut, 2009.
149. Sandborn, W.J., et al., *Certolizumab pegol for the treatment of Crohn's disease.* N Engl J Med, 2007. 357(3): p. 228-38.
150. Schreiber, S., et al., *Maintenance therapy with certolizumab pegol for Crohn's disease.* N Engl J Med, 2007. 357(3): p. 239-50.
151. Schreiber, S., et al., *A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease.* Gastroenterology, 2005. 129(3): p. 807-18.
152. Rutgeerts, P., et al., *Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNFalpha, improves health-related quality of life in patients with moderate to severe Crohn's disease.* Int J Colorectal Dis, 2008. 23(3): p. 289-96.
153. Behm, B.W. and S.J. Bickston, *Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease.* Cochrane Database Syst Rev, 2008(1): p. CD006893.
154. Hanauer, S.B., et al., *Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.* Lancet, 2002. 359(9317): p. 1541-9.
155. Sands, B.E., et al., *Infliximab maintenance therapy for fistulizing Crohn's disease.* N Engl J Med, 2004. 350(9): p. 876-85.
156. Targan, S.R., et al., *A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group.* N Engl J Med, 1997. 337(15): p. 1029-35.
157. Lemann, M., et al., *Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial.* Gastroenterology, 2006. 130(4): p. 1054-61.

158. Geboes, K., et al., *Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease.* Curr Med Res Opin, 2005. 21(11): p. 1741-54.
159. Lichtenstein, G.R., et al., *Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries.* Am J Gastroenterol, 2004. 99(1): p. 91-6.
160. Feagan, B.G., et al., *The effects of infliximab maintenance therapy on health-related quality of life.* Am J Gastroenterol, 2003. 98(10): p. 2232-8.
161. Rutgeerts, P., et al., *Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease.* Gastrointest Endosc, 2006. 63(3): p. 433-42; quiz 464.
162. Sands, B.E., et al., *Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study.* Clin Gastroenterol Hepatol, 2004. 2(10): p. 912-20.
163. Lichtenstein, G.R., et al., *Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease.* Gastroenterology, 2005. 128(4): p. 862-9.
164. Sands, B.E., et al., *Maintenance infliximab does not result in increased abscess development in fistulizing Crohn's disease: results from the ACCENT II study.* Aliment Pharmacol Ther, 2006. 23(8): p. 1127-36.
165. Lichtenstein, G.R., et al., *Infliximab improves quality of life in patients with Crohn's disease.* Inflamm Bowel Dis, 2002. 8(4): p. 237-43.
166. MacDonald, J.K. and J.W. McDonald, *Natalizumab for induction of remission in Crohn's disease.* Cochrane Database Syst Rev, 2007(1): p. CD006097.
167. Sandborn, W.J., et al., *Natalizumab induction and maintenance therapy for Crohn's disease.* N Engl J Med, 2005. 353(18): p. 1912-25.
168. Ghosh, S., et al., *Natalizumab for active Crohn's disease.* N Engl J Med, 2003. 348(1): p. 24-32.
169. Targan, S.R., et al., *Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial.* Gastroenterology, 2007. 132(5): p. 1672-83.
170. Hyams, J., et al., *Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children.* Gastroenterology, 2007. 132(3): p. 863-73; quiz 1165-6.
171. Rutgeerts, P., et al., *Infliximab for induction and maintenance therapy for ulcerative colitis.* N Engl J Med, 2005. 353(23): p. 2462-76.
172. Feagan, B.G., et al., *The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients.* Am J Gastroenterol, 2007. 102(4): p. 794-802.
173. Gisbert, J.P., Y. Gonzalez-Lama, and J. Mate, *Systematic review: Infliximab therapy in ulcerative colitis.* Aliment Pharmacol Ther, 2007. 25(1): p. 19-37.
174. Gordon, K.B., et al., *Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study.* J Am Acad Dermatol, 2006. 55(4): p. 598-606.
175. Saurat, J.H., et al., *Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION).* Br J Dermatol, 2008. 158(3): p. 558-66.

176. Menter, A., et al., *Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial.* J Am Acad Dermatol, 2008. 58(1): p. 106-15.
177. Ellis, C.N. and G.G. Krueger, *Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes.* N Engl J Med, 2001. 345(4): p. 248-55.
178. Lebwohl, M., et al., *An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis.* Arch Dermatol, 2003. 139(6): p. 719-27.
179. Krueger, G.G., et al., *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): p. 821-33.
180. Gottlieb, A.B., et al., *A randomized trial of etanercept as monotherapy for psoriasis.* Arch Dermatol, 2003. 139(12): p. 1627-32; discussion 1632.
181. Papp, K.A., 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): p. 1304-12.
182. Leonardi, C.L., et al., *Etanercept as monotherapy in patients with psoriasis.* N Engl J Med, 2003. 349(21): p. 2014-22.
183. Tyring, S., et al., *Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial.* Lancet, 2006. 367(9504): p. 29-35.
184. Reich, K., et al., *Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial.* Lancet, 2005. 366(9494): p. 1367-74.
185. Reich, K., et al., *Comparative effects of biological therapies on the severity of skin symptoms and health-related quality of life in patients with plaque-type psoriasis: a meta-analysis.* Curr Med Res Opin, 2008. 24(5): p. 1237-54.
186. Brimhall, A.K., et al., *Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials.* Br J Dermatol, 2008. 159(2): p. 274-85.
187. Paller, A.S., et al., *Etanercept treatment for children and adolescents with plaque psoriasis.* N Engl J Med, 2008. 358(3): p. 241-51.
188. Feldman, S.R., et al., *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): p. 887-9.
189. Krueger, G.G., et al., *Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial.* Br J Dermatol, 2005. 153(6): p. 1192-9.
190. Reich, K., et al., *Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial.* Br J Dermatol, 2006. 154(6): p. 1161-8.
191. Shikiar, R., et al., *Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial.* J Dermatolog Treat, 2007. 18(1): p. 25-31.
192. Revicki, D., et al., *Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in*

*patients with moderate to severe plaque psoriasis.* Br J Dermatol, 2008. 158(3): p. 549-57.
193. Revicki, D.A., et al., *Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis.* J Dermatolog Treat, 2007. 18(6): p. 341-50.
194. Revicki, D.A., et al., *Adalimumab improves health-related quality of life in patients with moderate to severe plaque psoriasis compared with the United States general population norms: results from a randomized, controlled Phase III study.* Health Qual Life Outcomes, 2008. 6: p. 75.
195. Reich, K., et al., *Infliximab treatment improves productivity among patients with moderate-to-severe psoriasis.* European Journal of Dermatology, 2007. 17(5): p. 381-386.
196. Burmester, G.R., et al., *Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial.* Ann Rheum Dis, 2007. 66(6): p. 732-9.
197. Colombel, J.F., et al., *The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients.* Gastroenterology, 2004. 126(1): p. 19-31.
198. Fleischmann, R.M., et al., *Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial.* Arthritis Rheum, 2003. 48(4): p. 927-34.
199. Tesser, J., et al., *Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis.* J Rheumatol, 2004. 31(4): p. 649-54.
200. Schiff, M.H., et al., *The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions.* Arthritis Rheum, 2004. 50(6): p. 1752-60.
201. Schaible, T.F., *Long term safety of infliximab.* Can J Gastroenterol, 2000. 14 Suppl C: p. 29C-32C.
202. Ljung, T., et al., *Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County.* Gut, 2004. 53(6): p. 849-53.
203. Takeuchi, T., et al., *Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis.* Ann Rheum Dis, 2008. 67(2): p. 189-94.
204. Braun, J., et al., *Persistent clinical response to the anti-TNF-{alpha} antibody infliximab in patients with ankylosing spondylitis over 3 years.* Rheumatology (Oxford), 2005. 44(5): p. 670-6.
205. Schiff, M.H., et al., *Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis.* Ann Rheum Dis, 2006. 65(7): p. 889-94.
206. Langer, H.E. and B. Missler-Karger, *Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol.* Int J Clin Pharmacol Res, 2003. 23(4): p. 119-28.
207. Nuki, G., et al., *Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial.* Arthritis Rheum, 2002. 46(11): p. 2838-46.

208. Fleischmann, R.M., et al., *Safety of extended treatment with anakinra in patients with rheumatoid arthritis.* Ann Rheum Dis, 2006. 65(8): p. 1006-12.
209. Lovell, D.J., et al., *Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial.* Arthritis Rheum, 2003. 48(1): p. 218-26.
210. Zink, A., et al., *Treatment continuation in patients receiving biological agents or conventional DMARD therapy.* Ann Rheum Dis, 2005. 64(9): p. 1274-9.
211. *Rituxan® (rituximab) FDA label information. Available at:http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/103705s5256lbl.pdf.* 2008.
212. *Kineret® (anakinra) FDA label information. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/103950s5039lbl.pdf.* 2004.
213. *Humira® (adalimumab) FDA label information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125057s114lbl.pdf.* 2008.
214. *Enbrel® (etanercept) FDA label information. Available at http://www.fda.gov/cder/foi/label/2006/103795s5286lbl.pdf.* 2006.
215. *Amevive® (alefacept) FDA label information. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125036s100lbl.pdf.* 2009.
216. Feltelius, N., et al., *Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept.* Ann Rheum Dis, 2005. 64(2): p. 246-52.
217. Yousry, T.A., et al., *Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy.* N Engl J Med, 2006. 354(9): p. 924-33.
218. Favalli, E.G., et al., *Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients.* Autoimmunity Reviews, 2009. 8(3): p. 266-73.
219. Salliot, C., M. Dougados, and L. Gossec, *Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials.* Ann Rheum Dis, 2009. 68(1): p. 25-32.
220. Bongartz, T., et al., *Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies: Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials.* JAMA, 2006. 295(19): p. 2275-2285.
221. Baeten, D., 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): p. 829-34.
222. Askling, J., et al., *Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden.* Arthritis Rheum, 2005. 52(7): p. 1986-92.
223. Listing, J., et al., *Infections in patients with rheumatoid arthritis treated with biologic agents.* Arthritis Rheum, 2005. 52(11): p. 3403-12.
224. Askling, J., et al., *Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists.* Annals of the Rheumatic Diseases, 2007. 66(10): p. 1339-1344.
225. Schneeweiss, S., et al., *Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis.* Arthritis Rheum, 2007. 56(6): p. 1754-64.

226. Curtis, J.R., et al., *Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists.* Arthritis Rheum, 2007. 56(4): p. 1125-33.
227. Keane, J., et al., *Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent.* N Engl J Med, 2001. 345(15): p. 1098-104.
228. Bergstrom, L., et al., *Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists.* Arthritis Rheum, 2004. 50(6): p. 1959-66.
229. Mertz, L.E. and J.E. Blair, *Coccidioidomycosis in rheumatology patients: incidence and potential risk factors.* Ann N Y Acad Sci, 2007. 1111: p. 343-57.
230. Strangfeld, A., et al., *Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents.* Jama, 2009. 301(7): p. 737-44.
231. Lee, J.H., et al., *Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept.* Arthritis Rheum, 2002. 46(10): p. 2565-70.
232. Slifman, N.R., et al., *Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents.* Arthritis Rheum, 2003. 48(2): p. 319-24.
233. Ruderman, E.M. and J. Markenson, *Granulomatous infections and tumor necrosis factor antagonists therapy: update through June 2002.* Arthritis Rheum, 2003. 48(9): p. S241.
234. Brassard, P., A. Kezouh, and S. Suissa, *Antirheumatic drugs and the risk of tuberculosis.* Clin Infect Dis, 2006. 43(6): p. 717-22.
235. Gomez-Reino, J.J., et al., *Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report.* Arthritis Rheum, 2003. 48(8): p. 2122-7.
236. Wolfe, F., et al., *Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy.* Arthritis Rheum, 2004. 50(2): p. 372-9.
237. Baecklund, E., et al., *Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study.* Bmj, 1998. 317(7152): p. 180-1.
238. Geborek, P., et al., *Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas.* Ann Rheum Dis, 2005. 64(5): p. 699-703.
239. Bongartz, T., et al., *Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials.* Ann Rheum Dis, 2009. 68(7): p. 1177-1183.
240. Wolfe, F. and K. Michaud, *The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation.* Arthritis Rheum, 2007. 56(5): p. 1433-9.
241. Wolfe, F. and K. Michaud, *Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study.* Arthritis and Rheumatism, 2007. 56(9): p. 2886-2895.
242. Askling, J., et al., *Haematopoietic malignancies in rheumatoid arthritis: Lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists.* Annals of the Rheumatic Diseases, 2005. 64(10): p. 1414-1420.
243. Setoguchi, S., et al., *Tumor necrosis factor (alpha) antagonist use and cancer in patients with rheumatoid arthritis.* Arthritis and Rheumatism, 2006. 54(9): p. 2757-2764.

244. Askling, J., et al., *Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists.* Ann Rheum Dis, 2005. 64(10): p. 1421-6.
245. Simon, T.A., et al., *Malignancies in the rheumatoid arthritis abatacept clinical development program: An epidemiological assessment.* Ann Rheum Dis, 2008.
246. Chakravarty, E.F., K. Michaud, and F. Wolfe, *Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors.* J Rheumatol, 2005. 32(11): p. 2130-5.
247. Lebwohl, M., et al., *No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years.* Arch Dermatol, 2005. 141(7): p. 861-4.
248. Wolfe, F. and K. Michaud, *Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy.* Am J Med, 2004. 116(5): p. 305-11.
249. Dixon, W.G., et al., *Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register.* Arthritis Rheum, 2007. 56(9): p. 2905-12.
250. Setoguchi, S., et al., *Tumor necrosis factor-(alpha) antagonist use and heart failure in elderly patients with rheumatoid arthritis.* American Heart Journal, 2008. 156(2): p. 336-341.
251. Kwon, H.J., et al., *Case reports of heart failure after therapy with a tumor necrosis factor antagonist.* Ann Intern Med, 2003. 138(10): p. 807-11.
252. Coletta, A.P., et al., *Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH.* Eur J Heart Fail, 2002. 4(4): p. 559-61.
253. Chung, E.S., et al., *Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial.* Circulation, 2003. 107(25): p. 3133-40.
254. Suissa, S., S. Bernatsky, and M. Hudson, *Antirheumatic drug use and the risk of acute myocardial infarction.* Arthritis Care and Research, 2006. 55(4): p. 531-536.
255. Solomon, D.H., et al., *Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis.* Arthritis and Rheumatism, 2006. 54(12): p. 3790-3798.
256. Curtis, J.R., et al., *Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists.* Rheumatology (Oxford), 2007. 46(11): p. 1688-93.
257. Listing, J., et al., *Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis?* Arthritis Rheum, 2008. 58(3): p. 667-77.
258. Shakoor, N., et al., *Drug-induced systemic lupus erythematosus associated with etanercept therapy.* Lancet, 2002. 359(9306): p. 579-80.
259. De Bandt, M., et al., *Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey.* Arthritis Res Ther, 2005. 7(3): p. R545-51.
260. Vermeire, S., et al., *Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study.* Gastroenterology, 2003. 125(1): p. 32-9.

261. Harrison, M.J., et al., *Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register.* Annals of the Rheumatic Diseases, 2009. 68(2): p. 209-15.
262. Mohan, N., et al., *Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides.* Arthritis Rheum, 2001. 44(12): p. 2862-9.
263. *Remicade® (infliximab) FDA label information. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103772s5234lbl.pdf.* 2009.
264. Suissa, S., et al., *Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis.* American Journal of Medicine, 2004. 117(2): p. 87-92.
265. Braun, J., et al., *Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis.* Ann Rheum Dis, 2005. 64(2): p. 229-34.
266. Braun, J., et al., *Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial.* Arthritis Rheum, 2003. 48(8): p. 2224-33.
267. Listing, J., et al., *Impact of anti-tumour necrosis factor alpha treatment on admissions to hospital and days of sick leave in patients with ankylosing spondylitis.* Ann Rheum Dis, 2004. 63(12): p. 1670-2.
268. Lichtenstein, G.R., et al., *Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry.* Clin Gastroenterol Hepatol, 2006. 4(5): p. 621-30.
269. Wolfe, F., L. Caplan, and K. Michaud, *Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy.* Arthritis Rheum, 2006. 54(2): p. 628-34.
270. Lovell, D.J., et al., *Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis.* Arthritis Rheum, 2006. 54(6): p. 1987-1994.
271. Quartier, P., et al., *Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type.* Arthritis Rheum, 2003. 48(4): p. 1093-101.
272. Friesen, C.A., et al., *Safety of infliximab treatment in pediatric patients with inflammatory bowel disease.* J Pediatr Gastroenterol Nutr, 2004. 39(3): p. 265-9.
273. Fleischmann, R., et al., *Long-term safety of etanercept in elderly subjects with rheumatic diseases.* Ann Rheum Dis, 2006. 65(3): p. 379-84.
274. Genevay, S., et al., *Tolerance and effectiveness of anti-tumor necrosis factor (alpha) therapies in elderly patients with rheumatoid arthritis: A population-based cohort study.* Arthritis Care and Research, 2007. 57(4): p. 679-685.
275. Gottlieb, A.B., W.H. Boehncke, and M. Darif, *Safety and efficacy of alefacept in elderly patients and other special populations.* J Drugs Dermatol, 2005. 4(6): p. 718-24.
276. Weisman, M.H., et al., *A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases.* Rheumatology (Oxford), 2007. 46(7): p. 1122-5.
277. Kristensen, L.E., et al., *Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register.* Rheumatology (Oxford), 2008. 47(4): p. 495-9.

278. Katz, J.A., et al., *Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis.* Am J Gastroenterol, 2004. 99(12): p. 2385-92.
279. Keystone, E. and B. Haraoui, *Adalimumab therapy in rheumatoid arthritis.* Rheum Dis Clin North Am, 2004. 30(2): p. 349-64, vii.
280. Keystone, E.C., et al., *Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study.* Ann Rheum Dis, 2009. 68(6): p. 789-96.
281. Kay, J., et al., *Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study.* Arthritis Rheum, 2008. 58(4): p. 964-75.
282. Zhou, H., et al., *Pharmacokinetics and safety of golimumab, a fully human anti-TNF-(alpha) monoclonal antibody, in subjects with rheumatoid arthritis.* Journal of Clinical Pharmacology, 2007. 47(3): p. 383-396.
283. Kavanaugh, A., et al., *Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study.* Arthritis Rheum, 2009. 60(4): p. 976-86.
284. Inman, R.D., et al., *Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial.* Arthritis Rheum, 2008. 58(11): p. 3402-12.
285. Bathon, J.M., et al., *Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis.* J Rheumatol, 2006. 33(2): p. 234-43.
286. Bejarano, V., et al., *Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis.* Arthritis Rheum, 2008. 59(10): p. 1467-74.
287. Carmona, L., et al., *All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists.* Ann Rheum Dis, 2007. 66(7): p. 880-5.
288. Fleischmann, R.M., et al., *Response to etanercept (Enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trial results.* J Rheumatol, 2003. 30(4): p. 691-6.
289. Gerloni, V., et al., *Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study.* Arthritis Rheum, 2005. 52(2): p. 548-53.
290. Menter, A., et al., *Adverse drug events in infliximab-treated patients compared with the general and psoriasis populations.* J Drugs Dermatol, 2008. 7(12): p. 1137-46.
291. Moreland, L.W., et al., *Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience.* J Rheumatol, 2006. 33(5): p. 854-61.
292. Seong, S.S., et al., *Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers.* J Rheumatol, 2007. 34(4): p. 706-11.
293. Venkateshan, S.P., et al., *Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis.* Pharmacology, 2009. 83(1): p. 1-9.

294. Wolfe, F., L. Caplan, and K. Michaud, *Rheumatoid arthritis treatment and the risk of severe interstitial lung disease.* Scandinavian Journal of Rheumatology, 2007. 36(3): p. 172-178.

# 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:

Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews.* CRD Report Number 4. 2nd ed. University of York, UK; 2001.

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

# 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) $P = 0.15$

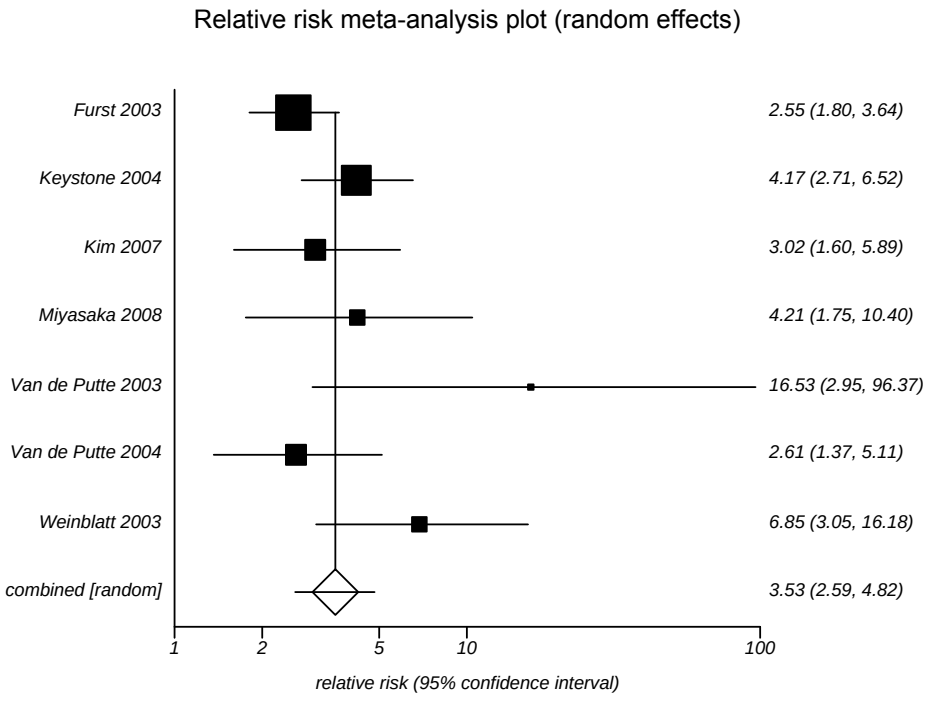
Moment-based estimate of between studies variance = 0.058945

$I^2$ (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

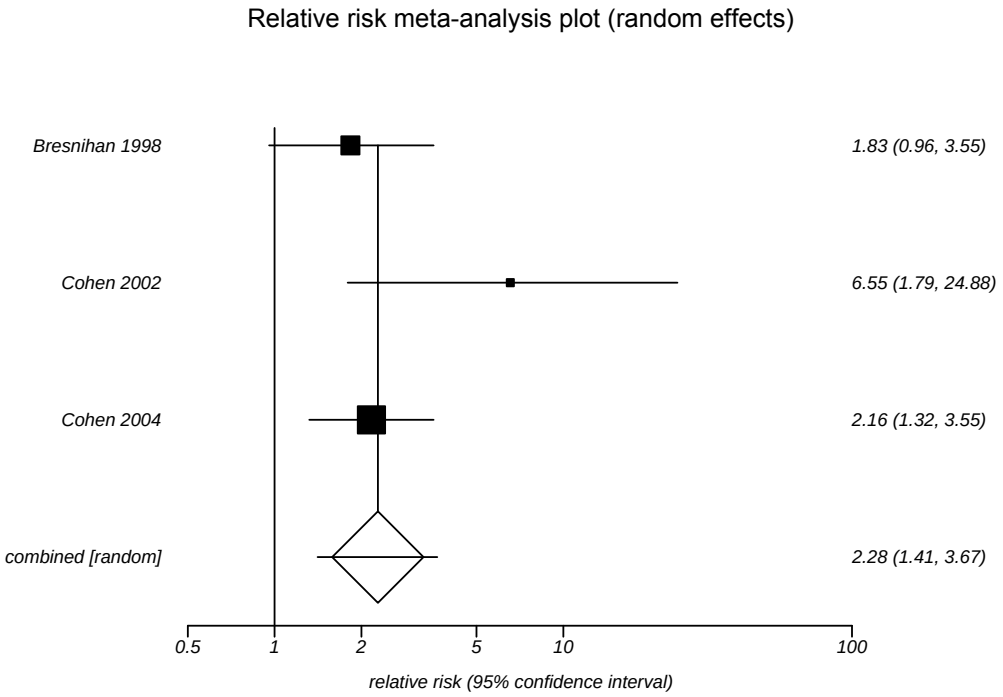
| Stratum | Relative risk | 95% CI (Koopman) | | M-H weight | |
|---|---|---|---|---|---|
| 1 | 1.825431 | 0.958312 | 3.546318 | 6.572238 | Bresnihan 1998 |
| 2 | 6.548673 | 1.790818 | 24.879122 | 1.208556 | Cohen 2002 |
| 3 | 2.1586 | 1.318936 | 3.55346 | 9.98004 | Cohen 2004 |

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

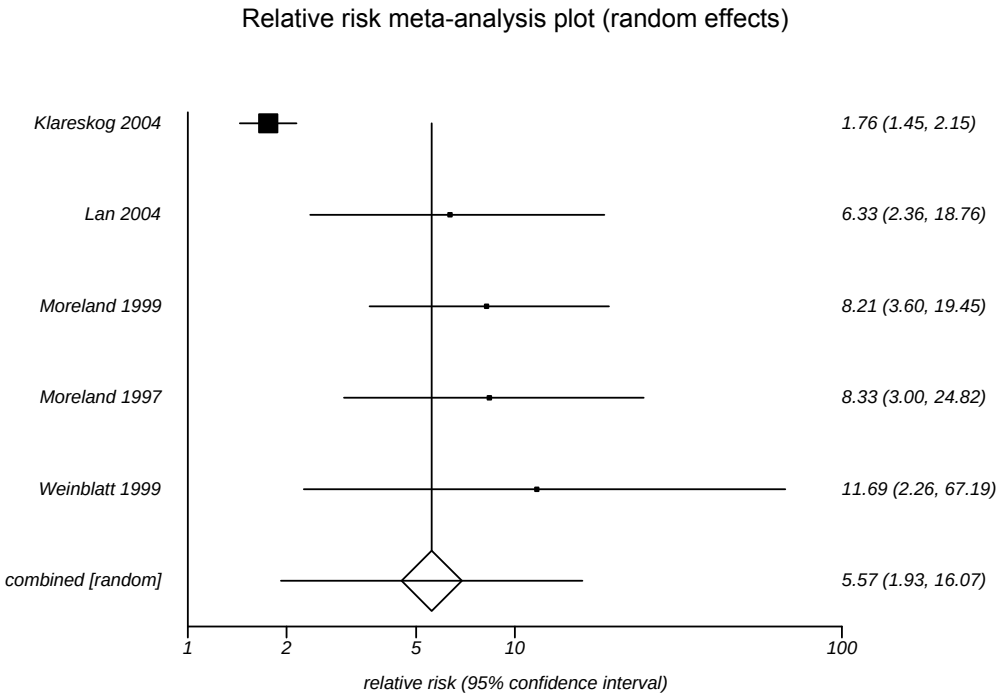
| Stratum | Relative risk | 95% CI (Koopman) | | M-H weight | |
|---|---|---|---|---|---|
| 1 | 1.757365 | 1.446 | 2.153791 | 41.267974 | Klareskog 2004 |
| 2 | 6.333333 | 2.362599 | 18.757771 | 1.5 | Lan 2004 |
| 3 | 8.205128 | 3.598388 | 19.451313 | 2.468354 | Moreland 1999 |
| 4 | 8.333333 | 2.998444 | 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.

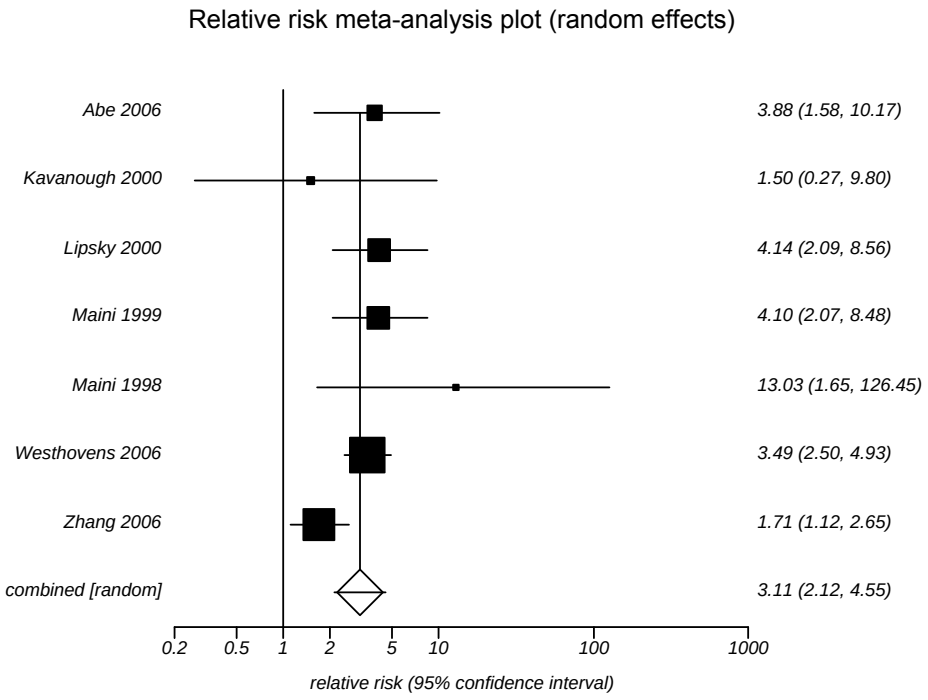
| Stratum | Relative risk | 95% CI (Koopman) | | % Weights (fixed, random) | | |
|---|---|---|---|---|---|---|
| 1 | 3.8775 | 1.576166 | 10.168522 | 5.685599 | 10.727026 | Abe 2006 |
| 2 | 1.5 | 0.269401 | 9.804675 | 1.392972 | 3.095502 | Kavanough 2000 |
| 3 | 4.141176 | 2.085196 | 8.555213 | 11.618948 | 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

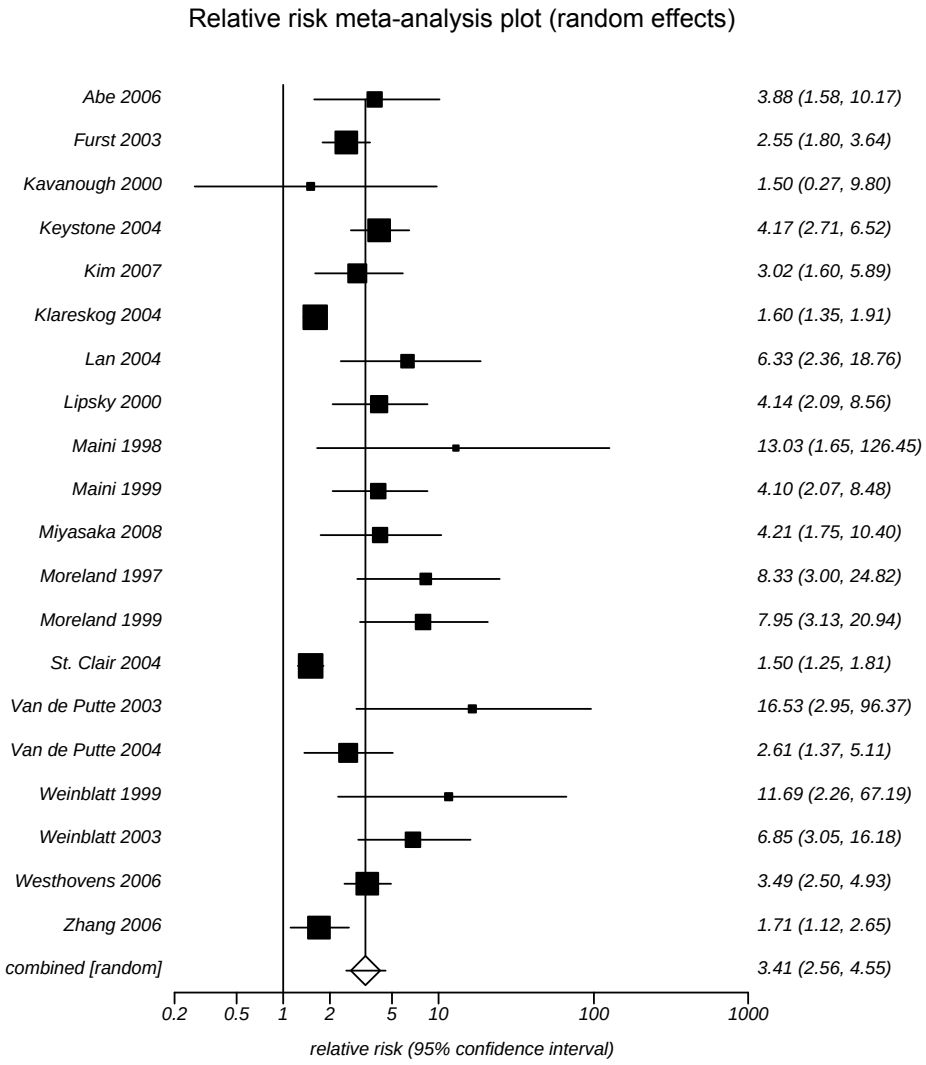
| Stratum | Relative risk | 95% CI (Koopman) | | % Weights (fixed, random) | | |
|---|---|---|---|---|---|---|
| 1 | 3.8775 | 1.576166 | 10.168522 | 1.275414 | 4.290628 | Abe 2006 |
| 2 | 2.552833 | 1.80314 | 3.63624 | 8.436866 | 7.579343 | Furst 2003 |
| 3 | 1.5 | 0.269401 | 9.804675 | 0.312477 | 1.564542 | 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**<br>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.<br><br>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**<br>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.<br><br>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**<br>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.<br><br>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**<br>Patients treated with REMICADE are at increased risk for developing serious infections that may lead to hospitalization or death.<br>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.<br>Reported infections include:<br>• 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.<br>• 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.<br>• Bacterial, viral and other infections due to opportunistic pathogens.<br>The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.<br>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.<br>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**<br>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.<br>• 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**
109. Chan JJ, Gebauer K. Treatment of severe recalcitrant plaque psoriasis with single-dose intravenous tumour necrosis factor-alpha antibody (infliximab). Australas J Dermatol 2003;44(2):116-20. **WRONG DESIGN**
110. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001;357(9271):1842-7. **WRONG DESIGN**
111. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003;98(6):1315-24. **WRONG DESIGN**
112. Chevillotte-Maillard H, Ornetti P, Mistrih R, Sidot C, Dupuis J, Dellas JA, et al. Survival and safety of treatment with infliximab in the elderly population. Rheumatology (Oxford) 2005;44(5):695-6. **WRONG PUBLICATION TYPE**
113. Chey WY. Infliximab for patients with refractory ulcerative colitis. Inflamm Bowel Dis 2001;7 Suppl 1:S30-3. **WRONG DESIGN**
114. Choy EH, Isenberg DA, Garrood T, Farrow S, Ioannou Y, Bird H, et al. Therapeutic benefit of blocking interleukin6 activity with an antiinterleukin6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, doubleblind, placebocontrolled, doseescalation trial. Arthritis & Rheumatism 2002;46(12):3143-50. **DRUG NOT INDLUCED**
115. Christidis DS, Liberopoulos EN, Tsiara SN, Drosos AA, Elisaf MS. Legionella pneumophila infection possibly related to treatment with infliximab. Infectious Diseases in Clinical Practice 2004;12(5):301-303. **WRONG POPULATION**
116. Coates LC, Cawkwell LS, Ng NW, Bennett AN, Bryer DJ, Fraser AD, et al. Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis. Rheumatology (Oxford) 2008;47(6):897-900. **WRONG DESIGN**
117. Coates LC, McGonagle DG, Bennett AN, Emery P, Marzo-Ortega H. Uveitis and tumour necrosis factor blockade in ankylosing spondylitis. Annals of the Rheumatic Diseases 2008;67(5):729-730. **WRONG PUBLICATION TYPE**
118. Cobo-Ibanez T, del Carmen Ordonez M, Munoz-Fernandez S, Madero-Prado R, Martin-Mola E. Do TNF-blockers reduce or induce uveitis? Rheumatology (Oxford) 2008;47(5):731-2. **WRONG PUBLICATION TYPE**
119. Cohen G, Courvoisier N, Cohen JD, Zaltni S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clin Exp Rheumatol 2005;23(6):795-800. **WRONG DESIGN**

120. Cohen JD. Successful treatment of psoriatic arthritis with rituximab. Ann Rheum Dis 2008;67(11):1647-8. **WRONG PUBLICATION TYPE**
121. Cohen RD. Efficacy and safety of repeated infliximab infusions for Crohn's disease: 1-year clinical experience. Inflamm Bowel Dis 2001;7 Suppl 1:S17-22. **WRONG DESIGN**
122. Cohen RD, Tsang JF, Hanauer SB. Infliximab in Crohn's disease: first anniversary clinical experience. Am J Gastroenterol 2000;95(12):3469-77. **WRONG DESIGN**
123. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007;27(4):369-73. **WRONG DESIGN**
124. Cole JC, Li T, Lin P, MacLean R, Wallenstein GV. Treatment impact on estimated medical expenditure and job loss likelihood in rheumatoid arthritis: re-examining quality of life outcomes from a randomized placebo-controlled clinical trial with abatacept. Rheumatology (Oxford) 2008;47(7):1044-50. **WRONG OUTCOME**
125. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: A literature review and potential mechanisms of action. Arthritis Care and Research 2008;59(7):996-1001. **WRONG DESIGN**
126. Colombel JF, Loftus EV, Jr., Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126(1):19-31. **WRONG DESIGN**
127. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis 2006;65(10):1357-62. **DRUG NOT INDLUCED**
128. Cornillie F, Shealy D, D'Haens G, Geboes K, Van Assche G, Ceuppens J, et al. Infliximab induces potent anti-inflammatory and local immunomodulatory activity but no systemic immune suppression in patients with Crohn's disease. Aliment Pharmacol Ther 2001;15(4):463-73. **WRONG DESIGN**
129. Corona R, Bigby M. What are the risks of serious infections and malignancies for patients treated with anti-tumor necrosis factor antibodies? Archives of Dermatology 2007;143(3):405-406. **WRONG PUBLICATION TYPE**
130. Corrao S, Pistone G, Arnone S, Calvo L, Scaglione R, Licata G. Safety of etanercept therapy in rheumatoid patients undergoing surgery: Preliminary report. Clinical Rheumatology 2007;26(9):1513-1515. **WRONG POPULATION**
131. Corrao S, Pistone G, Arnone S, Calvo L, Scaglione R, Licata G. Surgery during etanercept therapy in patients with rheumatoid arthritis: Is it time to follow patient preferences? Internal and Emergency Medicine 2008;3(1):73-75. **WRONG PUBLICATION TYPE**
132. Costanzo A, Mazzotta A, Papoutsaki M, Nistico S, Chimenti S. Safety and efficacy study on etanercept in patients with plaque psoriasis. Br J Dermatol 2005;152(1):187-9. **WRONG PUBLICATION TYPE**
133. Costanzo A, Peris K, Talamonti M, Di Cesare A, Fargnoli MC, Botti E, et al. Long-term treatment of plaque psoriasis with efalizumab: an Italian experience. Br J Dermatol 2007;156 Suppl 2:17-23. **WRONG DESIGN**
134. Cottone M, Mocciaro F, Scimeca D. Adalimumab induction for Crohn's disease. Gastroenterology 2006;130(6):1929. **WRONG PUBLICATION TYPE**
135. Covelli M, Scioscia C, Iannone F, Lapadula G. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after

discontinuation of infliximab. Clin Exp Rheumatol 2005;23(2):145-51. **WRONG DESIGN**

136. Criswell LA, Lum RF, Turner KN, Woehl B, Zhu Y, Wang J, et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis and Rheumatism 2004;50(9):2750-2756. **DRUG NOT INDLUCED**
137. Cross R. Another anti-TNF therapy for patients with Crohn's disease. Inflamm Bowel Dis 2008;14(3):425-7. **WRONG PUBLICATION TYPE**
138. Curtis JR, Martin C, Saag KG, Patkar NM, Kramer J, Shatin D, et al. Confirmation of administrative claims-identified opportunistic infections and other serious potential adverse events associated with tumor necrosis factor (alpha) antagonists and disease-modifying antirheumatic drugs. Arthritis Care and Research 2007;57(2):343-346. **WRONG DESIGN**
139. Curtis JR, Xi J, Patkar N, Xie A, Saag KG, Martin C. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis and Rheumatism 2007;56(12):4226-4227. **WRONG PUBLICATION TYPE**
140. Cush J, Kavanaugh A. FDA Meeting March 2003: Update on the Safety of New Drugs for Rheumatoid Arthritis. Part I: The Risk of Lymphoma with Rheumatoid Arthritis (RA) and TNF Inhibitors. Hotline. 2003. **WRONG PUBLICATION TYPE**
141. Cush JJ. Early rheumatoid arthritis - Is there a window of opportunity? Journal of Rheumatology 2007;34:1-7. **WRONG PUBLICATION TYPE**
142. Cvetkovic RS, Keating G. Anakinra. BioDrugs (New Zealand) 2002;16:303-11. **WRONG PUBLICATION TYPE**
143. Danese S, Mocciaro F, Guidi L, Scribano ML, Comberlato M, Annese V, et al. Successful induction of clinical response and remission with certolizumab pegol in Crohn's disease patients refractory or intolerant to infliximab: a real-life multicenter experience of compassionate use. Inflamm Bowel Dis 2008;14(8):1168-70. **WRONG PUBLICATION TYPE**
144. Davies A, Cifaldi MA, Segurado OG, Weisman MH. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. Journal of Rheumatology 2009;36(1):16-25. **WRONG OUTCOME**
145. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum 2005;53(4):494-501. **WRONG DESIGN**
146. Davis JC, Jr., van der Heijde DM, Braun J, Dougados M, Clegg DO, Kivitz AJ, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. Ann Rheum Dis 2008;67(3):346-52. **WRONG DESIGN**
147. Davis JC, van der Heijde DM, Braun J, Dougados M, Cush J, Clegg D, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis 2005;64(11):1557-62. **WRONG DESIGN**
148. Davis JC, Jr., Van der Heijde DM, Dougados M, Braun J, Cush JJ, Clegg DO, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. J Rheumatol 2005;32(9):1751-4. **WRONG OUTCOME**

149. Davis JJ, Webb A, Lund S, Sack K. Results from an open-label extension study of etanercept in ankylosing spondylitis. Arthritis Rheum 2004;51(2):302-4. **WRONG PUBLICATION TYPE**
150. Davis SA, Johnson RR, Pendleton JW. Demyelinating disease associated with use of etanercept in patients with seronegative spondyloarthropathies. Journal of Rheumatology 2008;35(7):1469-1471. **WRONG PUBLICATION TYPE**
151. De Bandt M, Sibilia J, Le Loet X, Prouzeau S, Fautrel B, Marcelli C, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 2005;7(3):R545-51. **WRONG DESIGN**
152. De Bandt M, Vittecoq O, Descamps V, Le Loet X, Meyer O. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol 2003;22(1):56-61. **WRONG PUBLICATION TYPE**
153. De Benedetti F, Martini A. Targeting the interleukin-6 receptor: A new treatment for systemic juvenile idiopathic arthritis? Arthritis and Rheumatism 2005;52(3):687-693. **WRONG PUBLICATION TYPE**
154. Delaunay C, Farrenq V, Marini-Portugal A, Cohen JD, Chevalier X, Claudepierre P. Infliximab to etanercept switch in patients with spondyloarthropathies and psoriatic arthritis: preliminary data. J Rheumatol 2005;32(11):2183-5. **WRONG DESIGN**
155. den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol 2002;29(11):2288-98. **WRONG DESIGN**
156. den Broeder AA, Creemers MC, Fransen J, de Jong E, de Rooij DJ, Wymenga A, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol 2007;34(4):689-95. **WRONG DESIGN**
157. den Broeder AA, de Jong E, Franssen MJ, Jeurissen ME, Flendrie M, van den Hoogen FH. Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. Ann Rheum Dis 2006;65(6):760-2. **WRONG DESIGN**
158. Deng A, Harvey V, Sina B, Strobel D, Badros A, Junkins-Hopkins JM, et al. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol 2006;142(2):198-202. **WRONG DESIGN**
159. Derot G, Marini-Portugal A, Maitre B, Claudepierre P. Marked regression of pulmonary rheumatoid nodules under etanercept therapy. J. Rheumatol. 2009;36(2):437-439. **WRONG DESIGN**
160. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008;371(9613):660-7. **DRUG NOT INDLUCED**
161. D'Haens G, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999;116(5):1029-34. **WRONG DESIGN**

162. Dhillon S, Lyseng-Williamson KA, Scott LJ. Etanercept - A review of its use in the management of rheumatoid arthritis. Drugs (New Zealand) 2007;67:1211-41. **WRONG PUBLICATION TYPE**
163. Dixon WG, Symmons DPM, Lunt M, Watson KD, Hyrich KL, Silman AJ, et al. Serious infection following anti-tumor necrosis factor (alpha) therapy in patients with rheumatoid arthritis: Lessons from interpreting data from observational studies. Arthritis and Rheumatism 2007;56(9):2896-2904. **WRONG OUTCOME**
164. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54(8):2368-2376. **DRUG NOT INDLUCED**
165. Do HHJ, Mohamed A, Klistorner A, Grigg J. Ophthalmic manifestations of demyelination secondary to etanercept. Clinical and Experimental Ophthalmology 2008;36(4):392-394. **WRONG PUBLICATION TYPE**
166. Doggrell SA. Efalizumab for psoriasis? Expert Opin Investig Drugs 2004;13(5):551-4. **WRONG PUBLICATION TYPE**
167. Doraiswamy VA. Nocardia infection with adalimumab in rheumatoid arthritis. Journal of Rheumatology 2008;35(3):542-543. **WRONG PUBLICATION TYPE**
168. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis and Rheumatism 2002;46(9):2294-2300. **DRUG NOT INDLUCED**
169. Dore RK, Mathews S, Schechtman J, Surbeck W, Mandel D, Patel A, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clinical and Experimental Rheumatology 2007;25(1):40-46. **WRONG DESIGN**
170. Dougados M, Combe B, Beveridge T, Bourdeix I, Lallemand A, Amor B, et al. IX 207887 in rheumatoid arthritis. A doubleblind placebocontrolled study. Arthritis & Rheumatism 1992;35(9):999-1006. **DRUG NOT INDLUCED**
171. Dougados M, Luo MP, Maksymowych WP, Chmiel JJ, Chen N, Wong RL, et al. Evaluation of the patient acceptable symptom state as an outcome measure in patients with ankylosing spondylitis: data from a randomized controlled trial. Arthritis Rheum 2008;59(4):553-60. **WRONG OUTCOME**
172. Dougados M, Schmidely N, Le Bars M, Lafosse C, Schiff M, Smolen JS, et al. Evaluation of different methods used to assess disease activity in rheumatoid arthritis: analyses of abatacept clinical trial data. Ann Rheum Dis 2009;68(4):484-9. **WRONG OUTCOME**
173. Drevlow BE, Lovis R, Haag MA, Sinacore JM, Jacobs C, Blosche C, et al. Recombinant human interleukin1 receptor type I in the treatment of patients with active rheumatoid arthritis. Arthritis & Rheumatism 1996;39(2):257-65. **DRUG NOT INDLUCED**
174. Dubertret L, Sterry W, Bos JD, Chimenti S, Shumack S, Larsen CG, et al. CLinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. Br J Dermatol 2006;155(1):170-81. **DRUG NOT INDLUCED**
175. Duftner C, Dejaco C, Larcher H, Schirmer M, Herold M. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic. Rheumatology International 2008;29(1):69-73. **WRONG DESIGN**

176. Dunlop H. Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis. Cmaj 2004;171(8):992-3. **WRONG DESIGN**
177. Durez P, Malghem J, Nzeusseu Toukap A, Depresseux G, Lauwerys BR, Westhovens R, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis Rheum 2007;56(12):3919-27. **DRUG NOT INDLUCED**
178. Durez P, Nzeusseu Toukap A, Lauwerys BR, Manicourt DH, Verschueren P, Westhovens R, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Ann Rheum Dis 2004;63(9):1069-74. **DRUG NOT INDLUCED**
179. Durez P, Van den Bosch F, Corluy L, Veys EM, De Clerck L, Peretz A, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. Rheumatology (Oxford) 2005;44(4):465-8. **WRONG DESIGN**
180. Dziadzio M, Keat A, Higgens C. Are anti-TNF(alpha) therapies too good? An audit of patients' compliance. Journal of Clinical Rheumatology 2007;13(5):296-297. **WRONG POPULATION**
181. Egnatios G, Warthan MM, Pariser R, Hood AF. Pustular psoriasis following treatment of rheumatoid arthritis with TNF-alpha inhibitors. J Drugs Dermatol 2008;7(10):975-977. **WRONG DESIGN**
182. Elkayam O, Caspi D. Infliximab induced lupus in patients with rheumatoid arthritis. Clin Exp Rheumatol 2004;22(4):502-3. **WRONG PUBLICATION TYPE**
183. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344(8930):1105-10. **WRONG DESIGN**
184. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H, et al. Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet 1994;344(8930):1125-7. **WRONG DESIGN**
185. Elliott RA. Poor adherence to medication in adults with rheumatoid arthritis - Reasons and solutions. Disease Management and Health Outcomes (New Zealand) 2008;16:13-29. **WRONG PUBLICATION TYPE**
186. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372(9636):375-82. **DRUG NOT INDLUCED**
187. Emery P, Seto Y. Role of biologics in early arthritis. Clin Exp Rheumatol 2003;21(5 Suppl 31):S191-4. **WRONG PUBLICATION TYPE**
188. Fairhurst DA, Ashcroft DM, Griffiths CE. Optimal management of severe plaque form of psoriasis. American Journal of Clinical Dermatology (New Zealand) 2005;6:283-94. **WRONG PUBLICATION TYPE**
189. Farah M, Al Rashidi A, Owen DA, Yoshida EM, Reid GD. Granulomatous hepatitis associated with etanercept therapy. Journal of Rheumatology 2008;35:349-51. **WRONG POPULATION**

190. Farahani P, Levine M, Gaebel K, Thabane L. Clinical data gap between phase III clinical trials (pre-marketing) and phase IV (post-marketing) studies: Evaluation of etanercept in rheumatoid arthritis. Canadian Journal of Clinical Pharmacology 2005;12(3):e254-e263. **WRONG DESIGN**
191. Farahani P, Levine M, Gaebel K, Wang EC, Khalidi N. Community-based evaluation of etanercept in patients with rheumatoid arthritis. J Rheumatol 2006;33(4):665-70. **WRONG DESIGN**
192. Farrell RJ, Shah SA, Lodhavia PJ, Alsahli M, Falchuk KR, Michetti P, et al. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. Am J Gastroenterol 2000;95(12):3490-7. **WRONG DESIGN**
193. Favero M, Schiavon F, Riato L, Carraro V, Punzi L. Rheumatoid arthritis is the major risk factor for septic arthritis in rheumatological settings. Autoimmunity Reviews 2008;8(1):59-61. **WRONG POPULATION**
194. Feagan BG, Sandborn WJ, Hass S, Niecko T, White J. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. Am J Gastroenterol 2007;102(12):2737-46. **WRONG POPULATION**
195. Feagan BG, Sandborn WJ, Lichtenstein G, Radford-Smith G, Patel J, Innes A. CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006;23(5):617-28. **DRUG NOT INDLUCED**
196. Feldman SR, Gordon KB, Bala M, Evans R, Li S, Dooley LT, et al. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. Br J Dermatol 2005;152(5):954-60. **WRONG DESIGN**
197. Feldman SR, Gottlieb AB, Bala M, Wu Y, Eisenberg D, Guzzo C, et al. Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. British Journal of Dermatology 2008;159(3):704-710. **WRONG DESIGN**
198. Fernandez-Nebro A, Irigoyen MV, Urena I, Belmonte-Lopez MA, Coret V, Jimenez-Nunez FG, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol 2007;34(12):2334-42. **WRONG DESIGN**
199. Ferraccioli GF, Assaloni R, Perin A. Drug-induced systemic lupus erythematosus and TNF-alpha blockers. Lancet 2002;360(9333):645; author reply 646. **WRONG PUBLICATION TYPE**
200. Ferrandiz C, Carrascosa JM. Managing moderate-to-severe psoriasis with efalizumab: experience at a single Spanish institute. British Journal of Dermatology (England) 2007;156:24-29. **WRONG DESIGN**
201. Figueiredo IT, Morel J, Sany J, Combe B. Maintenance and tolerability of infliximab in a cohort of 152 patients with rheumatoid arthritis. Clin Exp Rheumatol 2008;26(1):18-23. **WRONG DESIGN**
202. Finckh A, Ciurea A, Brulhart L, Kyburz D, Moller B, Dehler S, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56(5):1417-23. **WRONG DESIGN**

203. Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Annals of the Rheumatic Diseases 2006;65(6):746-752. **WRONG OUTCOME**
204. Fleischmann R. Safety and efficacy of etanercept in the elderly. Aging Health 2006;2(2):189-197. **WRONG PUBLICATION TYPE**
205. Fleischmann R, Iqbal I. Risk: benefit profile of etanercept in elderly patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis. Drugs & Aging 2007;24(3):239-254. **WRONG PUBLICATION TYPE**
206. Flendrie M, Creemers MC, Welsing PM, den Broeder AA, van Riel PL. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 2003;62 Suppl 2:ii30-3. **WRONG DESIGN**
207. Flendrie M, Creemers MC, Welsing PM, van Riel PL. The influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in patients with rheumatoid arthritis; a longitudinal observational study. Rheumatology (Oxford, England) 2005;44(4):472-478. **DRUG NOT INDLUCED**
208. Flendrie M, Vissers WH, Creemers MC, de Jong EM, van de Kerkhof PC, van Riel PL. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005;7(3):R666-76. **WRONG DESIGN**
209. Fraenkel L, Bogardus ST, Concato J, Felson DT, Wittink DR. Patient preferences for treatment of rheumatoid arthritis. Annals of the Rheumatic Diseases 2004;63(11):1372-1378. **WRONG OUTCOME**
210. Frampton JE, Scott LJ. Rituximab - In rheumatoid arthritis. BioDrugs (New Zealand) 2007;21:333. **WRONG PUBLICATION TYPE**
211. Frampton JE, Wagstaff AJ. Alefacept. American Journal of Clinical Dermatology (New Zealand) 2003;4:277-86. **WRONG PUBLICATION TYPE**
212. Frankel EH, Strober BE, Crowley JJ, Fivenson DP, Woolley JM, Yu EB, et al. Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. Cutis 2007;79(4):322-6. **WRONG DESIGN**
213. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis 2006;65(10):1373-8. **WRONG OUTCOME**
214. Friesen CA, Calabro C, Christenson K, Carpenter E, Welchert E, Daniel JF, et al. Safety of infliximab treatment in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2004;39(3):265-9. **WRONG DESIGN**
215. Fuerst M, Mohl H, Baumgartel K, Ruther W. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatology International 2006;26(12):1138-1142. **WRONG OUTCOME**
216. Furst DE. The Risk of Infections with Biologic Therapies for Rheumatoid Arthritis. Semin Arthritis Rheum 2008. **WRONG PUBLICATION TYPE**
217. Furst DE, Weisman M, Paulus HE, Bulpitt K, Weinblatt M, Polisson R, et al. Intravenous human recombinant tumor necrosis factor receptor p55-Fc IgG1 fusion protein, Ro 45-2081 (lenercept): Results of a dose-finding study in rheumatoid arthritis. Journal of Rheumatology 2003;30(10):2123-2126. **DRUG NOT INDLUCED**

218. Gadadhar H, Hawkins S, Huffstutter JE, Panda M. Cutaneous mucormycosis complicating methotrexate, prednisone, and infliximab therapy. J Clin Rheumatol 2007;13(6):361-2. **WRONG PUBLICATION TYPE**
219. Gade JN. Clinical update on alefacept: Consideration for use in patients with psoriasis. Journal of Managed Care Pharmacy (USA) 2004;10:S33-S37. **WRONG PUBLICATION TYPE**
220. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. American Journal of Health-System Pharmacy (USA) 2006;63:2451-65. **WRONG PUBLICATION TYPE**
221. Gamarra RM, McGraw SD, Drelichman VS, Maas LC. Serum sickness-like reactions in patients receiving intravenous infliximab. Journal of Emergency Medicine 2006;30(1):41-44. **WRONG POPULATION**
222. Garces M, Lozada CJ. Pharmacologic management of rheumatoid arthritis. Journal of Clinical Outcomes Management 2004;11(9):585-592. **WRONG PUBLICATION TYPE**
223. Garcia Vidal C, Rodriguez Fernandez S, Martinez Lacasa J, Salavert M, Vidal R, Rodriguez Carballeira M, et al. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. Clin Infect Dis 2005;40(5):756-9. **WRONG PUBLICATION TYPE**
224. Gardiner PV, Bell AL, Taggart AJ, Wright G, Kee F, Smyth A, et al. A potential pitfall in the use of the Disease Activity Score (DAS28) as the main response criterion in treatment guidelines for patients with rheumatoid arthritis. Annals of the Rheumatic Diseases 2005;64(3):506-507. **WRONG POPULATION**
225. Gaspersic N, Sersa I, Jevtic V, Tomsic M, Praprotnik S. Monitoring ankylosing spondylitis therapy by dynamic contrast-enhanced and diffusion-weighted magnetic resonance imaging. Skeletal Radiol 2008;37(2):123-31. **WRONG POPULATION**
226. Gavalas E, Kountouras J, Stergiopoulos C, Zavos C, Gisakis D, Nikolaidis N, et al. Efficacy and safety of infliximab in steroid-dependent ulcerative colitis patients. Hepato-gastroenterology 2007(76):1074; 9-1074; 9. **WRONG POPULATION**
227. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. Ann Rheum Dis 2008;67(8):1084-9. **WRONG DESIGN**
228. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008;67(4):547-54. **WRONG DESIGN**
229. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis 2008;67(8):1145-52. **WRONG DESIGN**
230. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Care and Research 2006;55(2):333-337. **WRONG POPULATION**

231. Gisbert JP, Panes J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol 2009;104(3):760-7. **WRONG PUBLICATION TYPE**
232. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. J Eur Acad Dermatol Venereol 2008;22(3):341-4. **WRONG DESIGN**
233. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol 2008;158(6):1345-9. **DRUG NOT INDLUCED**
234. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum 2007;56(2):476-88. **WRONG DESIGN**
235. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, Kerstens PJ, Grillet BA, de Jager MH, et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis 2007;66(9):1227-32. **WRONG OUTCOME**
236. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-90. **DRUG NOT INDLUCED**
237. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum 2008;58(2 Suppl):S126-35. **DRUG NOT INDLUCED**
238. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJSM, Hazes JMW, et al. Comparison of treatment strategies in early rheumatoid arthritis: A randomized trial. Annals of Internal Medicine 2007;146(6):406-415. **DRUG NOT INDLUCED**
239. Goldman JA, Xia HA, White B, Paulus H. Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept. Ann Rheum Dis 2006;65(12):1649-52. **WRONG OUTCOME**
240. Goldsmith DR, Wagstaff AJ. Etanercept - a review of its use in the management of plaque psoriasis and psoriatic arthritis. American Journal of Clinical Dermatology (New Zealand) 2005;6:121-36. **WRONG PUBLICATION TYPE**
241. Gomez-Gallego M, Meca-Lallana J, Fernandez-Barreiro A. Multiple sclerosis onset during etanercept treatment. Eur Neurol 2008;59(1-2):91-3. **WRONG PUBLICATION TYPE**
242. Gomez-Reino JJ, Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis research & therapy. 2006;8(1):R29. **WRONG DESIGN**
243. Gomez-Reino JJ, Carmona L, Descalzo MA. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Care and Research 2007;57(5):756-761. **WRONG DESIGN**
244. Gonzalez-Chavez JR, Berlingeri-Ramos AC, Sanchez Casiano MA. Puerto Rico psoriasis study group: efficacy and safety of etanercept. J Drugs Dermatol 2005;4(6):735-9. **WRONG DESIGN**

245. Gonzalez-Juanatey C, Llorca J, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Effect of anti-tumor necrosis factor (alpha) therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. Arthritis Care and Research 2006;55(1):150-153. **WRONG POPULATION**
246. Gordon FH, Lai CW, Hamilton MI, Allison MC, Srivastava ED, Fouweather MG, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology 2001;121(2):268-74. **WRONG DESIGN**
247. Gordon KB, Blum R, Papp K, Matheson R, Bolduc C, Hamilton T, et al. Efficacy and safety of adalimumab treatment in patients with moderate to severe psoriasis: a double-blind, randomized clinical trial. Psoriasis Forum 2007;13(1):4-11. **WRONG DESIGN**
248. Gordon KB, Gottlieb AB, Leonardi CL, Elewski BE, Wang A, Jahreis A, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. J Dermatolog Treat 2006;17(1):9-17. **WRONG DESIGN**
249. Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. Jama 2003;290(23):3073-80. **DRUG NOT INDLUCED**
250. Gornet JM, Couve S, Hassani Z, Delchier JC, Marteau P, Cosnes J, et al. Infliximab for refractory ulcerative colitis or indeterminate colitis: an open-label multicentre study. Aliment Pharmacol Ther 2003;18(2):175-81. **WRONG DESIGN**
251. Gottlieb A, Krueger JG, Bright R, Ling M, Lebwohl M, Kang S, et al. Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. J Am Acad Dermatol 2000;42(3):428-35. **WRONG DESIGN**
252. Gottlieb AB, Casale TB, Frankel E, Goffe B, Lowe N, Ochs HD, et al. CD4+ T-cell-directed antibody responses are maintained in patients with psoriasis receiving alefacept: results of a randomized study. J Am Acad Dermatol 2003;49(5):816-25. **WRONG OUTCOME**
253. Gottlieb AB, Chamian F, Masud S, Cardinale I, Abello MV, Lowes MA, et al. TNF inhibition rapidly down-regulates multiple proinflammatory pathways in psoriasis plaques. J Immunol 2005;175(4):2721-9. **WRONG DESIGN**
254. Gottlieb AB, Chaudhari U, Mulcahy LD, Li S, Dooley LT, Baker DG. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. J Am Acad Dermatol 2003;48(6):829-35. **WRONG DESIGN**
255. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004;51(4):534-42. **WRONG DESIGN**
256. Gottlieb AB, Gordon KB, Lebwohl MG, Caro I, Walicke PA, Li N, et al. Extended efalizumab therapy sustains efficacy without increasing toxicity in patients with moderate to severe chronic plaque psoriasis. J Drugs Dermatol 2004;3(6):614-24. **WRONG DESIGN**
257. Gottlieb AB, Hamilton T, Caro I, Kwon P, Compton PG, Leonardi CL. Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: updated results from an ongoing trial. J Am Acad Dermatol 2006;54(4 Suppl 1):S154-63. **WRONG DESIGN**

258. Gottlieb AB, Kircik L, Eisen D, Jackson JM, Boh EE, Strober BE, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. J Dermatolog Treat 2006;17(6):343-52. **WRONG DESIGN**
259. Gottlieb AB, Krueger JG, Wittkowski K, Dedrick R, Walicke PA, Garovoy M. Psoriasis as a model for T-cell-mediated disease: immunobiologic and clinical effects of treatment with multiple doses of efalizumab, an anti-CD11a antibody. Arch Dermatol 2002;138(5):591-600. **WRONG DESIGN**
260. Gottlieb AB, Leonardi CL, Goffe BS, Ortonne JP, van der Kerkhof PC, Zitnik R, et al. Etanercept monotherapy in patients with psoriasis: a summary of safety, based on an integrated multistudy database. J Am Acad Dermatol 2006;54(3 Suppl 2):S92-100. **WRONG DESIGN**
261. Green C. Using TNFalpha technology to treat rheumatoid arthritis. Hospital Pharmacist (Great Britain) 2004;11(Jul/Aug):286-91. **WRONG PUBLICATION TYPE**
262. Greenberg JD, Kishimoto M, Strand V, Cohen SB, Olenginski TP, Harrington T, et al. Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. Am J Med 2008;121(6):532-8. **WRONG DESIGN**
263. Greenwood MC, Rathi J, Hakim AJ, Scott DL, Doyle DV. Regression to the mean using the disease activity score in eligibility and response criteria for prescribing TNF-(alpha) inhibitors in adults with rheumatoid arthritis. Rheumatology 2007;46(7):1165-1167. **WRONG POPULATION**
264. Grijalva CG, Chung CP, Arbogast PG, Stein CM, F ME, Jr., Griffin MR. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45(10 Supl 2):S66-76. **WRONG OUTCOME**
265. Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: a review. Semin Arthritis Rheum 2008;37(4):251-5. **WRONG PUBLICATION TYPE**
266. Guel U, Goenuel M, Kilic A, Erdem R, Guenduez H, et al. Treatment of psoriatic arthritis with etanercept, methotrexate, and cyclosporin A. Clinical Therapeutics (USA) 2006;28:251-54. **WRONG POPULATION**
267. Guignard S, Gossec L, Bandinelli F, Dougados M. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. Clinical and Experimental Rheumatology 2008;26(3 SUPPL. 49):S23-S29. **WRONG DESIGN**
268. Guis S, Balandraud N, Bouvenot J, Auger I, Toussirot E, Wendling D, et al. Influence of -308 A/G polymorphism in the tumor necrosis factor (alpha) gene on etanercept treatment in rheumatoid arthritis. Arthritis Care and Research 2007;57(8):1426-1430. **WRONG OUTCOME**
269. Hadi A, Hickling P, Brown M, Al-Nahhas A. Scintigraphic evidence of effect of infliximab on disease activity in ankylosing spondylitis. Rheumatology (Oxford) 2002;41(1):114-6. **WRONG PUBLICATION TYPE**
270. Haibel H, Rudwaleit M, Brandt HC, Grozdanovic Z, Listing J, Kupper H, et al. Adalimumab reduces spinal symptoms in active ankylosing spondylitis: Clinical and

magnetic resonance imaging results of a fifty-two-week open-label trial. Arthritis and Rheumatism 2006;54(2):678-681. **WRONG DESIGN**

271. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: Results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis and Rheumatism 2008;58(7):1981-1991. **WRONG POPULATION**
272. Haibel H, Song IH, Rudwaleit M, Listing J, Hildemann S, Sieper J. Multicenter open-label study with infliximab in active ankylosing spondylitis over 28 weeks in daily practice. Clin Exp Rheumatol 2008;26(2):247-52. **WRONG DESIGN**
273. Halpern MT, Cifaldi MA, Kvien TK. Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group. Ann Rheum Dis 2008. **WRONG DESIGN**
274. Hamilton CD. Tuberculosis in the cytokine era: what rheumatologists need to know. Arthritis Rheum 2003;48(8):2085-91. **WRONG DESIGN**
275. Han C, Smolen J, Kavanaugh A, St Clair EW, Baker D, Bala M. Comparison of employability outcomes among patients with early or long-standing rheumatoid arthritis. Arthritis Rheum 2008;59(4):510-4. **WRONG OUTCOME**
276. Han C, Smolen JS, Kavanaugh A, van der Heijde D, Braun J, Westhovens R, et al. The impact of infliximab treatment on quality of life in patients with inflammatory rheumatic diseases. Arthritis Res Ther 2007;9(5):R103. **WRONG OUTCOME**
277. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130(2):323-33; quiz 591. **WRONG DESIGN**
278. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004;2(7):542-53. **WRONG OUTCOME**
279. Hanta I, Ozbek S, Kuleci S, Kocabas A. The evaluation of latent tuberculosis in rheumatologic diseases for anti-TNF therapy: Experience with 192 patients. Clinical Rheumatology 2008;27(9):1083-1086. **WRONG DESIGN**
280. Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med 2007;357(18):1874-6. **WRONG PUBLICATION TYPE**
281. Hassett AL, Li T, Buyske S, Savage SV, Gignac MA. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin 2008;24(5):1443-53. **WRONG OUTCOME**
282. Heiberg MS, Nordvag BY, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. Arthritis Rheum 2005;52(8):2506-12. **WRONG OUTCOME**
283. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol 2006;33(7):1439-41. **DRUG NOT INDLUCED**
284. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol 2004;31(10):2055-61. **WRONG DESIGN**

285. Herrlinger KR, Witthoeft T, Raedler A, Bokemeyer B, Krummenerl T, Schulzke JD, et al. Randomized, double blind controlled trial of subcutaneous recombinant human interleukin-11 versus prednisolone in active Crohn's disease. Am J Gastroenterol 2006;101(4):793-7. **DRUG NOT INDLUCED**
286. Hetland ML, Lindegaard HM, Hansen A, Podenphant J, Unkerskov J, Ringsdal VS, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Annals of the Rheumatic Diseases 2008;67(7):1023-1026. **WRONG OUTCOME**
287. Hetland ML, Unkerskov J, Ravn T, Friis M, Tarp U, Andersen LS, et al. Routine database registration of biological therapy increases the reporting of adverse events twentyfold in clinical practice. First results from the Danish Database (DANBIO). Scandinavian Journal of Rheumatology 2005;34(1):40-44. **WRONG DESIGN**
288. Hilzenrat N, Lamoureux E, Cohen A, Baron M. Hepatic overlap syndrome improved with infliximab. Gastroenterology and Hepatology 2006;2(2):88-89. **WRONG POPULATION**
289. Hofer M. Spondylarthropathies in children - Are they different from those in adults? Best Practice and Research in Clinical Rheumatology 2006;20(2):315-328. **WRONG PUBLICATION TYPE**
290. Horneff G, Burgos-Vargas R. TNF-(alpha) antagonists for the treatment of juvenile-onset spondyloarthritides. Clinical and Experimental Rheumatology 2002;20(6 SUPPL. 28):S-137-S-142. **WRONG PUBLICATION TYPE**
291. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann. Rheum. Dis. 2009;68(4):519-525. **WRONG DESIGN**
292. Horng MS. Early rheumatoid arthritis: Is there a best treatment? Journal of Clinical Outcomes Management 2007;14(5):233-234. **WRONG PUBLICATION TYPE**
293. Huang F, Wang L, Zhang J, Deng X, Guo J, Zhang Y. Risk of tuberculosis in a Chinese registry of rheumatoid arthritis and ankylosing spondylitis for tumour necrosis factor-(alpha) antagonists. APLAR Journal of Rheumatology 2006;9(2):170-174. **WRONG DESIGN**
294. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007;132(3):863-73; quiz 1165-6. **WRONG DESIGN**
295. Ilowite NT. Update on biologics in juvenile idiopathic arthritis. Current Opinion in Rheumatology 2008;20(5):613-618. **WRONG PUBLICATION TYPE**
296. Inanc N, Direskeneli H. Serious infections under treatment with TNF-(alpha) antagonists compared to traditional DMARDs in patients with rheumatoid arthritis. Rheumatology International 2006;27(1):67-71. **WRONG DESIGN**
297. Inoue H, Shiraki K, Okano H, Deguchi M, Yamanaka T, Sakai T, et al. Acute pancreatitis in patients with ulcerative colitis. Dig Dis Sci 2005;50(6):1064-7. **WRONG PUBLICATION TYPE**
298. Irvine EJ. Natalizumab increased clinical remission and clinical response in moderate-to-severe Crohn disease. ACP Journal Club 2003;139(2):44-44. **WRONG PUBLICATION TYPE**

299. Jacob SE, Sergay A, Kerdel FA. Etanercept and psoriasis, from clinical studies to real life. Int J Dermatol 2005;44(8):688-91. **WRONG DESIGN**
300. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005;32(7):1213-8. **WRONG DESIGN**
301. Joossens S, Daperno M, Shums Z, Van Steen K, Goeken JA, Trapani C, et al. Interassay and interobserver variability in the detection of anti-neutrophil cytoplasmic antibodies in patients with ulcerative colitis. Clin Chem 2004;50(8):1422-5. **WRONG PUBLICATION TYPE**
302. Kahn KL, MacLean CH, Wong AL, Rubenstein LZ, Liu H, Fitzpatrick DM, et al. Assessment of American College of Rheumatology quality criteria for rheumatoid arthritis in a pre-quality criteria patient cohort. Arthritis Care and Research 2007;57(5):707-715. **WRONG DESIGN**
303. Kapetanovic MC, Larsson L, Truedsson L, Sturfelt G, Saxne T, Geborek P. Predictors of infusion reactions during infliximab treatment in patients with arthritis. Arthritis research & therapy 2006;8(4):R131. **WRONG DESIGN**
304. Karie S, Gandjbakhch F, Janus N, Launay-Vacher V, Rozenberg S, Mai Ba CU, et al. Kidney disease in RA patients: Prevalence and implication on RA-related drugs management: The MATRIX study. Rheumatology 2008;47(3):350-354. **WRONG DESIGN**
305. Kass J. Ethical perspectives in neurology. CONTINUUM Lifelong Learning in Neurology 2008;14(1):205-210. **WRONG DESIGN**
306. Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. Dig Dis Sci 2007;52(6):1481-4. **WRONG DESIGN**
307. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58(4):964-75. **WRONG OUTCOME**
308. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345(15):1098-104. **WRONG DESIGN**
309. Keating GM, Jarvis B. Management of rheumatoid arthritis - Defining the role of etanercept. Disease Management and Health Outcomes (New Zealand) 2002;10:17-39. **WRONG PUBLICATION TYPE**
310. Keystone E, Fleischmann R, Emery P, Furst DE, Van Vollenhoven R, Bathon J, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: An open-label extension analysis. Arthritis and Rheumatism 2007;56(12):3896-3908. **WRONG DESIGN**
311. Keystone E, Freundlich B, Schiff M, Li J, Hooper M. Patients with Moderate Rheumatoid Arthritis (RA) Achieve Better Disease Activity States with Etanercept Treatment Than Patients with Severe RA. Journal of Rheumatology 2009;36(3):522-531. **WRONG OUTCOME**
312. Keystone EC, Haraoui B, Bykerk VP. Role of adalimumab in the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 2003;21(5 Suppl 31):S198-9. **WRONG PUBLICATION TYPE**

313. Keystone EC, Schiff MH, Kremer JM, Kafka S, Lovy M, DeVries T, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2004;50(2):353-63. **WRONG DESIGN**
314. Khanna M, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. J Dermatolog Treat 2003;14(4):229-32. **WRONG POPULATION**
315. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. Uk cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Current Medical Research and Opinion 2008;24(9):2639-2650. **WRONG OUTCOME**
316. Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two year period. Ann Rheum Dis 2002;61(2):171-3. **WRONG DESIGN**
317. Kimball AB, Jackson JM, Sobell JM, Boh EE, Grekin S, Pharmd EB, et al. Reductions in healthcare resource utilization in psoriatic arthritis patients receiving etanercept therapy: results from the educate trial. J Drugs Dermatol 2007;6(3):299-306. **WRONG DESIGN**
318. Kimball AB, Kawamura T, Tejura K, Boss C, Hancox AR, Vogel JC, et al. Clinical and immunologic assessment of patients with psoriasis in a randomized, double-blind, placebo-controlled trial using recombinant human interleukin 10. Arch Dermatol 2002;138(10):1341-6. **DRUG NOT INDLUCED**
319. Kimel M, Cifaldi M, Chen N, Revicki D. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35(2):206-15. **WRONG OUTCOME**
320. Kimura Y, Pinho P, Walco G, Higgins G, Hummell D, Szer I, et al. Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis. J Rheumatol 2005;32(5):935-42. **WRONG DESIGN**
321. Klareskog L, Gaubitz M, Rodriguez-Valverde V, Malaise M, Dougados M, Wajdula J. A long-term, open-label trial of the safety and efficacy of etanercept (Enbrel) in patients with rheumatoid arthritis not treated with other disease-modifying antirheumatic drugs. Ann Rheum Dis 2006;65(12):1578-84. **WRONG DESIGN**
322. Kling A, Mjorndal T, Rantapaa-Dahlqvist S. Sepsis as a possible adverse drug reaction in patients with rheumatoid arthritis treated with TNF(alpha) antagonists. Journal of Clinical Rheumatology 2004;10(3):119-122. **WRONG DESIGN**
323. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: A review and analysis of 127 cases. J Dermatolog Treat 2008:1-8. **WRONG DESIGN**
324. Kobelt G, Andlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology (Oxford) 2004;43(9):1158-66. **WRONG OUTCOME**
325. Kobelt G, Sobocki P, Mulero J, Gratacos J, Pocovi A, Collantes-Estevez E. The burden of ankylosing spondylitis in Spain. Value in Health 2008;11(3):408-415. **WRONG DESIGN**
326. Kohn A, Prantera C, Pera A, Cosintino R, Sostegni R, Daperno M. Infliximab in the treatment of severe ulcerative colitis: a follow-up study. Eur Rev Med Pharmacol Sci 2004;8(5):235-7. **WRONG DESIGN**

327. Konttinen L, Honkanen V, Uotila T, Pollanen J, Waahtera M, Romu M, et al. Biological treatment in rheumatic diseases: Results from a longitudinal surveillance: Adverse events. Rheumatology International 2006;26(10):916-922. **WRONG POPULATION**
328. Konttinen L, Tuompo R, Uusitalo T, Luosujarvi R, Laiho K, Lahteenmaki J, et al. Anti-TNF therapy in the treatment of ankylosing spondylitis: the Finnish experience. Clinical Rheumatology 2007;26(10):1693-1700. **WRONG DESIGN**
329. Korzenik JR. Infliximab for fistulas: a hole in one? Inflamm Bowel Dis 2000;6(1):62-3. **WRONG PUBLICATION TYPE**
330. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum 2008;58(4):953-63. **WRONG DESIGN**
331. Kremer JM, Weinblatt ME, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Jackson CG, et al. Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. Arthritis Rheum 2003;48(6):1493-9. **WRONG DESIGN**
332. Krishnan R, Cella D, Leonardi C, Papp K, Gottlieb AB, Dunn M, et al. Effects of etanercept therapy on fatigue and symptoms of depression in subjects treated for moderate to severe plaque psoriasis for up to 96 weeks. Br J Dermatol 2007;157(6):1275-7. **WRONG PUBLICATION TYPE**
333. Krishnan S, Banquet A, Newman L, Katta U, Dozor AJ, et al. Lung lesions in children with Crohn's disease presenting as nonresolving pneumonias and response to infliximab therapy. Pediatrics (USA) 2006;117:1440-43. **WRONG DESIGN**
334. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis 2008;67(3):364-9. **WRONG OUTCOME**
335. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8(6):R174. **WRONG OUTCOME**
336. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford) 2003;42(5):617-21. **WRONG DESIGN**
337. Krueger G, Callis K. Potential of tumor necrosis factor inhibitors in psoriasis and psoriatic arthritis. Archives of Dermatology (USA) 2004;140:218. **WRONG OUTCOME**
338. Krueger GG, Elewski B, Papp K, Wang A, Zitnik R, Jahreis A. Patients with psoriasis respond to continuous open-label etanercept treatment after initial incomplete response in a randomized, placebo-controlled trial. J Am Acad Dermatol 2006;54(3 Suppl 2):S112-9. **WRONG DESIGN**
339. Krueger GG, Gottlieb AB, Sterry W, Korman N, Van De Kerkhof P. A multicenter, open-label study of repeat courses of intramuscular alefacept in combination with other psoriasis therapies in patients with chronic plaque psoriasis. J Dermatolog Treat 2008;19(3):146-55. **WRONG DESIGN**
340. Kruithof E, Van den Bosch F, Baeten D, Herssens A, De Keyser F, Mielants H, et al. Repeated infusions of infliximab, a chimeric anti-TNFalpha monoclonal antibody, in

patients with active spondyloarthropathy: one year follow up. Ann Rheum Dis 2002;61(3):207-12. **WRONG POPULATION**
341. Kuehn BM. Severe fungal infections linked to drugs. JAMA - Journal of the American Medical Association 2008;300(14):1639. **WRONG PUBLICATION TYPE**
342. Kumar A. Experience with anti-tumor necrosis factor-(alpha) therapy in India. APLAR Journal of Rheumatology 2006;9(2):136-141. **WRONG OUTCOME**
343. Kump LI, Castaneda RAC, Androudi SN, Reed GF, Foster CS. Visual Outcomes in Children with Juvenile Idiopathic Arthritis-Associated Uveitis. Ophthalmology 2006;113(10):1874-1877. **WRONG POPULATION**
344. Kupecz D, Berardinelli C. Using anakinra for adult rheumatoid arthritis. In: Nurse Practitioner (USA); 2002. p. 62.
345. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003;138(10):807-11. **WRONG DESIGN**
346. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 2003;62(3):245-7. **WRONG POPULATION**
347. Lambert RG, Salonen D, Rahman P, Inman RD, Wong RL, Einstein SG, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2007;56(12):4005-14. **WRONG OUTCOME**
348. Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD. Ulcerative Colitis: Diagnosis and Treatment. American family physician 2007;76(9):1323-1330. **WRONG PUBLICATION TYPE**
349. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res 2003;23(4):119-28. **WRONG DESIGN**
350. Langley RGB, Carey WP, Rafal ES, Tyring SK, Caro I, Wang X, et al. Incidence of infection during efalizumab therapy for psoriasis: analysis of the clinical trial experience. Clinical Therapeutics 2005;27(9):1317-1328. **WRONG DESIGN**
351. Lanzarotto F, Carpani M, Chaudhary R, Ghosh S. Novel treatment options for inflammatory bowel disease: targeting alpha4 integrin. Drugs 2006;66(9):1179-1189. **WRONG PUBLICATION TYPE**
352. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006;3:CD005112. **WRONG DESIGN**
353. Le Loet X, Nordstrom D, Rodriguez M, Rubbert A, Sarzi-Puttini P, Wouters JMGW, et al. Effect of anakinra on functional status in patients with active rheumatoid arthritis receiving concomitant therapy with traditional disease modifying antirheumatic drugs: Evidence from the OMEGA trial. Journal of Rheumatology 2008;35(8):1538-1544. **WRONG DESIGN**
354. Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N Engl J Med 2003;349(21):2004-13. **DRUG NOT INDLUCED**

355. Lee HH, Song IH, Friedrich M, Gauliard A, Detert J, Rowert J, et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. Br J Dermatol 2007;156(3):486-91. **WRONG POPULATION**
356. Lee JH, Slifman NR, Gershon SK, Edwards ET, Schwieterman WD, Siegel JN, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 2002;46(10):2565-70. **WRONG DESIGN**
357. Lee W, Reveille JD, Davis Jr JC, Learch TJ, Ward MM, Weisman MH. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. Annals of the Rheumatic Diseases 2007;66(5):633-638. **WRONG DESIGN**
358. Leon A, Nguyen A, Letsinger J, Koo J. An attempt to formulate an evidence-based strategy in the management of moderate-to-severe psoriasis: a review of the efficacy and safety of biologics and prebiologic options. Expert Opin Pharmacother 2007;8(5):617-32. **WRONG PUBLICATION TYPE**
359. Leonardi C, Menter A, Hamilton T, Caro I, Xing B, Gottlieb AB. Efalizumab: results of a 3-year continuous dosing study for the long-term control of psoriasis. Br J Dermatol 2008;158(5):1107-16. **WRONG DESIGN**
360. Leonardi CL, Papp KA, Gordon KB, Menter A, Feldman SR, Caro I, et al. Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. J Am Acad Dermatol 2005;52(3 Pt 1):425-33. **DRUG NOT INDLUCED**
361. Leonardi CL, Toth D, Cather JC, Langley RG, Werther W, Compton P, et al. A review of malignancies observed during efalizumab (Raptiva) clinical trials for plaque psoriasis. Dermatology 2006;213(3):204-14. **DRUG NOT INDLUCED**
362. Lepore L, Kiren V. Autologous bone marrow transplantation versus alternative drugs in pediatric rheumatic diseases. Haematologica 2000;85(11 SUPPL.):89-92. **WRONG PUBLICATION TYPE**
363. Lepore L, Marchetti F, Facchini S, Leone V, Ventura A. Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis. Clin Exp Rheumatol 2003;21(2):276-7. **WRONG PUBLICATION TYPE**
364. Lequerre T, Vittecoq O, Klemmer N, Goeb V, Pouplin S, Menard JF, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol 2006;33(7):1307-14. **WRONG DESIGN**
365. Levalampi T, Korpela M, Vuolteenaho K, Moilanen E. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: Adverse events and other reasons leading to discontinuation of the treatment. Rheumatology International 2008;28(3):261-269. **WRONG POPULATION**
366. Levalampi T, Korpela M, Vuolteenaho K, Moilanen E. Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: Adverse events and other reasons for discontinuation of treatment. Scandinavian Journal of Rheumatology 2008;37(1):6-12. **WRONG DESIGN**
367. Lewis JD. Anti-TNF antibodies for Crohn's disease--in pursuit of the perfect clinical trial. N Engl J Med 2007;357(3):296-8. **WRONG PUBLICATION TYPE**
368. Li T, Gignac M, Wells G, Shen S, Westhovens R. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept

in Inadequate responders to Methotrexate (AIM) trial. Clin Ther 2008;30(4):734-48. **WRONG OUTCOME**

369. Lichtenstein GR. Infliximab: lifetime use for maintenance is appropriate in Crohn's Disease. PRO: maintenance therapy is superior to episodic therapy. Am J Gastroenterol 2005;100(7):1433-5. **WRONG PUBLICATION TYPE**
370. Lichtenstein GR, Olson A, Travers S, Diamond RH, Chen DM, Pritchard ML, et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol 2006;101(5):1030-8. **WRONG OUTCOME**
371. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum 2007;56(10):3248-52. **WRONG DESIGN**
372. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: Health status, disease process, and damage. Annals of the Rheumatic Diseases 2002;61(12):1055-1059. **WRONG DESIGN**
373. Liozon E, Ouattara B, Loustaud-Ratti V, Vidal E. Severe polymyositis and flare in autoimmunity following treatment with adalimumab in a patient with overlapping features of polyarthritis and scleroderma. Scand J Rheumatol 2007;36(6):484-6. **WRONG PUBLICATION TYPE**
374. Listing J, Strangfeld A, Rau R, Kekow J, Gromnica-Ihle E, Klopsch T, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther 2006;8(3):R66. **DRUG NOT INDLUCED**
375. Ljung T, Karlen P, Schmidt D, Hellstrom PM, Lapidus A, Janczewska I, et al. Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County. Gut 2004;53(6):849-53. **WRONG DESIGN**
376. Loftus EV. Infliximab: lifetime use for maintenance is appropriate in Crohn's Disease. CON: "lifetime use" is an awfully long time. Am J Gastroenterol 2005;100(7):1435-8. **WRONG PUBLICATION TYPE**
377. Lorenz HM, Grunke M, Hieronymus T, Antoni C, Nusslein H, Schaible TF, et al. In vivo blockade of tumor necrosis factoralpha in patients with rheumatoid arthritis: longterm effects after repeated infusion of chimeric monoclonal antibody cA2. Journal of Rheumatology 2000;27(2):304-10. **WRONG OUTCOME**
378. Lorenzi AR, Clarke AM, Wooldridge T, Waldmann H, Hale G, Symmons D, et al. Morbidity and mortality in rheumatoid arthritis patients with prolonged therapy-induced lymphopenia: Twelve-year outcomes. Arthritis and Rheumatism 2008;58(2):370-375. **WRONG DESIGN**
379. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58(5):1496-504. **WRONG DESIGN**
380. Lowe NJ, Gonzalez J, Bagel J, Caro I, Ellis CN, Menter A. Repeat courses of intravenous alefacept in patients with chronic plaque psoriasis provide consistent safety and efficacy. Int J Dermatol 2003;42(3):224-30. **WRONG DESIGN**
381. Luc M, Gossec L, Ruyssen-Witrand A, Salliot C, Duclos M, Guignard S, et al. C-reactive protein predicts tumor necrosis factor-(alpha) blocker retention rate in axial ankylosing spondylitis. Journal of Rheumatology 2007;34(10):2078-2081. **WRONG OUTCOME**

382. Lyseng-Williamson KA, Plosker GL. Etanercept - A pharmacoeconomic review of its use in rheumatoid arthritis. PharmacoEconomics (New Zealand) 2004;22:1071. **WRONG DESIGN**
383. Mahadevan U, Kane S, Sandborn WJ, Cohen RD, Hanson K, Terdiman JP, et al. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. Aliment Pharmacol Ther 2005;21(6):733-8. **WRONG POPULATION**
384. Maillard H, Ornetti P, Grimault L, Ramon JF, Ducamp SM, Saidani T, et al. Severe pyogenic infections in patients taking infliximab: a regional cohort study. Joint Bone Spine 2005;72(4):330-4. **WRONG DESIGN**
385. Maksymowych WP, Mallon C, Richardson R, Conner-Spady B, Jauregui E, Chung C, et al. Development and validation of a simple tape-based measurement tool for recording cervical rotation in patients with ankylosing spondylitis: Comparison with a goniometer-based approach. Journal of Rheumatology 2006;33(11):2242-2248. **WRONG OUTCOME**
386. Maksymowych WP, Poole AR, Hiebert L, Webb A, Ionescu M, Lobanok T, et al. Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis. J Rheumatol 2005;32(10):1911-7. **WRONG OUTCOME**
387. Malipeddi AS, Rajendran R, Kallarackal G. Disseminated tuberculosis after anti-TNF(alpha) treatment. Lancet 2007;369(9556):162. **WRONG POPULATION**
388. Mangge H, Gindl S, Kenzian H, Schauenstein K. Atopic Dermatitis as a Side Effect of Anti-Tumor Necrosis Factor-(alpha) Therapy. Journal of Rheumatology 2003;30(11):2506-2507. **WRONG POPULATION**
389. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109(13):1594-602. **WRONG POPULATION**
390. Maradit-Kremers H, Nicola PJ, Crowson CS, O'Fallon WM, Gabriel SE. Patient, disease, and therapy-related factors that influence discontinuation of disease-modifying antirheumatic drugs: A population-based incidence cohort of patients with rheumatoid arthritis. Journal of Rheumatology 2006;33(2):248-255. **WRONG DESIGN**
391. Markowitz J, Hyams J, Mack D, Leleiko N, Evans J, Kugathasan S, et al. Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol 2006;4(9):1124-9. **DRUG NOT INDLUCED**
392. Marotte H, Charrin JE, Miossec P. Infliximab-induced aseptic meningitis. Lancet 2001;358(9295):1784. **WRONG PUBLICATION TYPE**
393. Martin M, Kosinski M, Bjorner JB, E WJ, Jr., Maclean R, Li T. Item response theory methods can improve the measurement of physical function by combining the modified health assessment questionnaire and the SF-36 physical function scale. Qual Life Res 2007;16(4):647-60. **WRONG OUTCOME**
394. Martini A. Etanercept improves active polyarticular juvenile rheumatoid arthritis. Clin Exp Rheumatol 2001;19(2):122-4. **WRONG PUBLICATION TYPE**
395. Marzo-Ortega H, McGonagle D, Jarrett S, Haugeberg G, Hensor E, O'Connor P, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 2005;64(11):1568-75. **WRONG DESIGN**

396. Mastroianni A, Minutilli E, Mussi A, Bordignon V, Trento E, D'Agosto G, et al. Cytokine profiles during infliximab monotherapy in psoriatic arthritis. Br J Dermatol 2005;153(3):531-6. **WRONG DESIGN**
397. Matteson E, Cush J. Reports of leflunomide hepatotoxicity in patients with rheumatoid arthritis. Hotline. 2001. **WRONG PUBLICATION TYPE**
398. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology (Oxford) 2002;41(1):116-7. **WRONG PUBLICATION TYPE**
399. McGinnis JK, Murray KF. Infliximab for ulcerative colitis in children and adolescents. J Clin Gastroenterol 2008;42(8):875-9. **WRONG POPULATION**
400. McGonagle D, Tan AL, Madden J, Taylor L, Emery P. Rituximab use in everyday clinical practice as a first-line biologic therapy for the treatment of DMARD-resistant rheumatoid arthritis. Rheumatology 2008;47(6):865-867. **WRONG DESIGN**
401. Mease PJ. Cytokine blockers in psoriatic arthritis. Ann Rheum Dis 2001;60 Suppl 3:iii37-40. **WRONG PUBLICATION TYPE**
402. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. J Rheumatol 2006;33(4):712-21. **WRONG DESIGN**
403. Mease PJ, Ritchlin CT, Martin RW, Gottlieb AB, Baumgartner SW, Burge DJ, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol 2004;31(7):1356-61. **WRONG OUTCOME**
404. Menter A, Cather JC, Baker D, Farber HF, Lebwohl M, Darif M. The efficacy of multiple courses of alefacept in patients with moderate to severe chronic plaque psoriasis. Journal of the American Academy of Dermatology 2006(1):61; 3-61; 3. **WRONG DESIGN**
405. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007;56(1). **WRONG DESIGN**
406. Menter A, Gordon K, Carey W, Hamilton T, Glazer S, Caro I, et al. Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. Arch Dermatol 2005;141(1):31-8. **DRUG NOT INDLUCED**
407. Menter A, Leonardi CL, Sterry W, Bos JD, Papp KA. Long-term management of plaque psoriasis with continuous efalizumab therapy. Journal of the American Academy of Dermatology (USA) 2006;54:S182-S188. **WRONG PUBLICATION TYPE**
408. Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci 2007;1111:343-57. **WRONG DESIGN**
409. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol 2006;33(12):2412-5. **WRONG OUTCOME**
410. Mikula CA. Anti-TNFalpha: new therapy for Crohn's disease. Gastroenterology Nursing 1999;22(6):245-248. **WRONG PUBLICATION TYPE**
411. Mikuls TR, Kazi S, Cipher D, Hooker R, Kerr GS, Richards JS, et al. The association of race and ethnicity with disease expression in male US veterans with rheumatoid arthritis. Journal of Rheumatology 2007;34(7):1480-1484. **WRONG DESIGN**
412. Militello G, Xia A, Stevens SR, Van Voorhees AS. Etanercept for the treatment of psoriasis in the elderly. J Am Acad Dermatol 2006;55(3):517-9. **WRONG DESIGN**

413. Mittendorf T, Dietz B, Sterz R, Cifaldi MA, Kupper H, Von Der Shulenburg JM. Personal and economic burden of late-stage rheumatoid arthritis among patients treated with adalimumab: An evaluation from a patient's perspective. Rheumatology 2008;47(2):188-193. **WRONG DESIGN**
414. Mittendorf T, Dietz B, Sterz R, Kupper H, Cifaldi MA, Von Der Schulenburg JM. Improvement and longterm maintenance of quality of life during treatment with adalimumab in severe rheumatoid arthritis. Journal of Rheumatology 2007;34(12):2343-2350. **WRONG DESIGN**
415. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001;44(12):2862-9. **WRONG DESIGN**
416. Mohan N, Edwards ET, Cupps TR, Slifman N, Lee JH, Siegel JN, et al. Leukocytoclastic vasculitis associated with tumor necrosis factor-(alpha) blocking agents. Journal of Rheumatology 2004;31(10):1955-1958. **WRONG DESIGN**
417. Montecucco C. Remission, a therapeutic goal in inflammatory arthropathies? Clinical data from adalimumab studies. Drugs 2006;66(14):1783-1795. **WRONG PUBLICATION TYPE**
418. Mor IJ, Vogel JD, Moreira Ada L, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. Dis Colon Rectum 2008;51(8):1202-7; discussion 1207-10. **WRONG POPULATION**
419. Moreland L, Gugliotti R, King K, Chase W, Weisman M, Greco T, et al. Results of a phaseI/II randomized, masked, placebocontrolled trial of recombinant human interleukin11 (rhIL11) in the treatment of subjects with active rheumatoid arthritis. Arthritis Research 2001;3(4):247-52. **DRUG NOT INDLUCED**
420. Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Longterm safety and efficacy of etanercept in patients with rheumatoid arthritis. Journal of Rheumatology 2001;28(6):1238-44. **WRONG OUTCOME**
421. Moreland LW, Margolies G, Heck LW, Jr., Saway A, Blosch C, Hanna R, et al. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 1996;23(11):1849-55. **WRONG DESIGN**
422. Moreland LW, McCabe DP, Caldwell JR, Sack M, Weisman M, Henry G, et al. Phase I/II trial of recombinant methionyl human tumor necrosis factor binding protein PEGylated dimer in patients with active refractory rheumatoid arthritis. J Rheumatol 2000;27(3):601-9. **DRUG NOT INDLUCED**
423. Moreland LW, Pratt PW, Bucy RP, Jackson BS, Feldman JW, Koopman WJ. Treatment of refractory rheumatoid arthritis with a chimeric anti-CD4 monoclonal antibody. Long-term followup of CD4+ T cell counts. Arthritis Rheum 1994;37(6):834-8. **DRUG NOT INDLUCED**
424. Moreland LW, Pratt PW, Mayes MD, Postlethwaite A, Weisman MH, Schnitzer T, et al. Double-blind, placebo-controlled multicenter trial using chimeric monoclonal anti-CD4 antibody, cM-T412, in rheumatoid arthritis patients receiving concomitant methotrexate. Arthritis Rheum 1995;38(11):1581-8. **DRUG NOT INDLUCED**
425. Mori M, Takei S, Imagawa T, Imanaka H, Maeno N, Kurosawa R, et al. Pharmacokinetics, efficacy, and safety of short-term (12 weeks) etanercept for methotrexate-refractory

polyarticular juvenile idiopathic arthritis in Japan. Modern Rheumatology 2005;15(6):397-404. **WRONG DESIGN**
426. Morrow T. Natalizumab: FDA is concerned -- should managed care be, too? Formulary 2006;41(4):184. **WRONG PUBLICATION TYPE**
427. Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46(4):894-8. **WRONG PUBLICATION TYPE**
428. Murray KM, Dahl SL. Recombinant human tumor necrosis factor receptor (p75) Fc fusion protein (TNFR:Fc) in rheumatoid arthritis. Ann Pharmacother 1997;31(11):1335-8. **WRONG DESIGN**
429. Myers A, Clark J, Foster H. Tuberculosis and treatment with infliximab. N Engl J Med 2002;346(8):623-6. **WRONG PUBLICATION TYPE**
430. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: A nested, case-control study. Arthritis Care and Research 2008;59(8):1090-1096. **WRONG DESIGN**
431. Napierkowski J, Wong RK. Natalizumab: a new hope for Crohn's disease? Am J Gastroenterol 2003;98(5):1197-9. **WRONG PUBLICATION TYPE**
432. Narayanan K, Anand KP. Long-term follow up of infliximab therapy in inflammatory arthritis. Indian Journal of Rheumatology 2007;2(1):8-10. **WRONG DESIGN**
433. Navarra SV, Raso AA, Lichauco JJ, Tan PP. Clinical experience with infliximab among Filipino patients with rheumatic diseases. APLAR Journal of Rheumatology 2006;9(2):150-156. **WRONG DESIGN**
434. Nielsen S, Ruperto N, Gerloni V, Simonini G, Cortis E, Lepore L, et al. Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. Clinical and Experimental Rheumatology 2008;26(4):688-692. **WRONG DESIGN**
435. Nikas SN, Temekonidis TI, Zikou AK, Argyropoulou MI, Efremidis S, Drosos AA. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: A pilot study. Annals of the Rheumatic Diseases 2004;63(1):102-103. **WRONG PUBLICATION TYPE**
436. Nikas SN, Voulgari PV, Alamanos Y, Papadopoulos CG, Venetsanopoulou AI, Georgiadis AN, et al. Efficacy and safety of switching from infliximab to adalimumab: A comparative controlled study. Annals of the Rheumatic Diseases 2006;65(2):257-260. **WRONG DESIGN**
437. Nishida K, Okada Y, Nawata M, Saito K, Tanaka Y. Induction of hyperadiponectinemia following long-term treatment of patients with rheumatoid arthritis with infliximab (IFX), an anti-TNF-alpha antibody. Endocrine Journal 2008;55(1):213-216. **WRONG DESIGN**
438. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized antiinterleukin6 receptor antibody: a multicenter, doubleblind, placebocontrolled trial. Arthritis & Rheumatism 2004;50(6):1761-9. **DRUG NOT INDLUCED**
439. Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid-refractory ulcerative colitis: a randomized pilot study. Eur J Gastroenterol Hepatol 2004;16(11):1167-71. **WRONG DESIGN**

440. Odegard S, Finset A, Mowinckel P, Kvien TK, Uhlig T. Pain and psychological health status over a 10-year period in patients with recent onset rheumatoid arthritis. Annals of the Rheumatic Diseases 2007;66(9):1195-1201. **WRONG DESIGN**
441. Ohlsson V, Baildam E, Foster H, Jandial S, Pain C, Strike H, et al. Anakinra treatment for systemic onset juvenile idiopathic arthritis (SOJIA). Rheumatology (Oxford) 2008;47(4):555-6. **WRONG PUBLICATION TYPE**
442. Oka H, Nishioka K, Togo M, Ochi T. The efficacy of infliximab for patients with rheumatoid arthritis in Japan: Results of 5000 cases by post-marketing surveillance data. APLAR Journal of Rheumatology 2006;9(2):142-145. **WRONG DESIGN**
443. Olsen NJ, Brooks RH, Cush JJ, Lipsky PE, St Clair EW, Matteson EL, et al. A double-blind, placebo-controlled study of anti-CD5 immunoconjugate in patients with rheumatoid arthritis. The Xoma RA Investigator Group. Arthritis Rheum 1996;39(7):1102-8. **WRONG DESIGN**
444. Ornetti P, Chevillotte H, Zerrak A, Maillefert JF. Anti-tumour necrosis factor-alpha therapy for rheumatoid and other inflammatory arthropathies: update on safety in older patients. Drugs Aging 2006;23(11):855-60. **WRONG PUBLICATION TYPE**
445. Ortonne JP, Lebwohl M, Em Griffiths C. Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis. Eur J Dermatol 2003;13(2):117-23. **WRONG OUTCOME**
446. Ortonne JP, Shear N, Shumack S, Henninger E. Impact of efalizumab on patient-reported outcomes in high-need psoriasis patients: results of the international, randomized, placebo-controlled Phase III Clinical Experience Acquired with Raptiva (CLEAR) trial. BMC Dermatol 2005;5:13. **DRUG NOT INDLUCED**
447. Ostor AJK, Crisp AJ, Somerville MF, Scott DGI. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. British Medical Journal 2004;329(7477):1266. **WRONG DESIGN**
448. Paget SA. Efficacy of anakinra in bone: Comparison to other biologics. Advances in Therapy (USA) 2002;19:27-39. **WRONG DESIGN**
449. Pallotta P, Cianchini G, Ruffelli M, Puddu P. Infliximab-induced lupus-like reaction in a patient with psoriatic arthritis. Rheumatology 2006;45:116-17. **WRONG PUBLICATION TYPE**
450. Palylyk-Colwell E, McGahan L. Rituximab for rheumatoid arthritis. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH) 2006. **WRONG PUBLICATION TYPE**
451. Panayi GS. B cell-directed therapy in rheumatoid arthritis clinical experience. Journal of Rheumatology 2005;32:19-24. **WRONG OUTCOME**
452. Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? Clinical and Experimental Rheumatology 2005;23(6):861-866. **WRONG DESIGN**
453. Papp K, Bissonnette R, Krueger JG, Carey W, Gratton D, Gulliver WP, et al. The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. J Am Acad Dermatol 2001;45(5):665-74. **WRONG DESIGN**
454. Papp KA, Bressinck R, Fretzin S, Goffe B, Kempers S, Gordon KB, et al. Safety of efalizumab in adults with chronic moderate to severe plaque psoriasis: a phase IIIb,

randomized, controlled trial. Int J Dermatol 2006;45(5):605-14. **DRUG NOT INDLUCED**
455. Papp KA, Camisa C, Stone SP, Caro I, Wang X, Compton P, et al. Safety of efalizumab in patients with moderate to severe chronic plaque psoriasis: review of clinical data. part II. J Cutan Med Surg 2005;9(6):313-23. **DRUG NOT INDLUCED**
456. Papp KA, Caro I, Leung HM, Garovoy M, Mease PJ. Efalizumab for the treatment of psoriatic arthritis. J Cutan Med Surg 2007;11(2):57-66. **DRUG NOT INDLUCED**
457. Pavelka K, Gatterova J, Tegzova D, Jarosova K, Tomasova Studynkova J, Svobodnik A, et al. Radiographic progression of rheumatoid arthritis in patients from the Czech National Registry receiving infliximab treatment. Clinical and Experimental Rheumatology 2007;25(4):540-545. **WRONG DESIGN**
458. Pearce DJ, Feldman SR. Update on infliximab: An intravenous biologic therapy for psoriasis. Expert Review of Dermatology 2007;2(6):707-713. **WRONG PUBLICATION TYPE**
459. Peddle L, Butt C, Snelgrove T, Rahman P. Interleukin (IL) 1alpha, IL1beta, IL receptor antagonist, and IL10 polymorphisms in psoriatic arthritis. Ann Rheum Dis 2005;64(7):1093-4. **WRONG PUBLICATION TYPE**
460. Persley KM. Infliximab infusion reactions: desensitizing ourselves to the danger. Inflamm Bowel Dis 2004;10(1):62-3. **WRONG DESIGN**
461. Peyrin-Biroulet L, Laclotte C, Bigard MA. Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. Aliment Pharmacol Ther 2007;25(6):675-80. **WRONG POPULATION**
462. Phillips K, Husni ME, Karlson EW, Coblyn JS. Experience with etanercept in an academic medical center: Are infection rates increased? Arthritis Care and Research 2002;47(1):17-21. **WRONG DESIGN**
463. Pincus T, Chung C, Segurado OG, Amara I, Koch GG. An index of patient reported outcomes (PRO-Index) discriminates effectively between active and control treatment in 4 clinical trials of adalimumab in rheumatoid arthritis. Journal of Rheumatology 2006;33:2146-52. **WRONG OUTCOME**
464. Pincus T, Ferraccioli G, Sokka T, Larsen A, Rau R, Kushner I, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology (Oxford) 2002;41(12):1346-56. **WRONG OUTCOME**
465. Posten W, Swan J. Recurrence of alopecia areata in a patient receiving etanercept injections. Arch Dermatol 2005;141(6):759-60. **WRONG DESIGN**
466. Poupardin C, Lemann M, Gendre JP, Sabate JM, Marteau P, Chaussade S, et al. Efficacy of infliximab in Crohn's disease. Results of a retrospective multicenter study with a 15-month follow-up. Gastroenterol Clin Biol 2006;30(2):247-52. **WRONG OUTCOME**
467. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340(18):1398-405. **WRONG DESIGN**
468. Prince FH, Twilt M, Ten Cate R, Van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in JIA: the Dutch national register. Ann Rheum Dis 2008. **WRONG DESIGN**

469. Probert CS, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott ID, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut 2003;52(7):998-1002. **WRONG DESIGN**
470. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52(1):27-35. **WRONG DESIGN**
471. Rahimi R, Nikfar S, Abdollahi M. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohn's disease? A systematic meta-analysis of controlled clinical trials. Biomed Pharmacother 2007;61(1):75-80. **WRONG DESIGN**
472. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis technique confirms the effectiveness of anti-TNF-alpha in the management of active ulcerative colitis when administered in combination with corticosteroids. Med Sci Monit 2007;13(7):PI13-8. **WRONG DESIGN**
473. Ramos-Casals M, Brito-Zeron P, Munoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: Analysis of 233 cases. Medicine 2007;86(4):242-251. **WRONG DESIGN**
474. Rankin EC, Choy EH, Kassimos D, Kingsley GH, Sopwith AM, Isenberg DA, et al. The therapeutic effects of an engineered human anti-tumour necrosis factor alpha antibody (CDP571) in rheumatoid arthritis. Br J Rheumatol 1995;34(4):334-42. **DRUG NOT INDLUCED**
475. Rau R, Sander O, Wassenberg S. Erosion healing in rheumatoid arthritis after anakinra treatment. Annals of the Rheumatic Diseases 2003;62(7):671-673. **WRONG OUTCOME**
476. Rau R, Simianer S, van Riel PL, van de Putte LB, Kruger K, Schattenkirchner M, et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol 2004;33(3):145-53. **WRONG DESIGN**
477. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. Ann Rheum Dis 2008;67(6):855-9. **DRUG NOT INDLUCED**
478. Reddy P. Infliximab (Remicade). Conn Med 1999;63(7):413-6. **WRONG DESIGN**
479. Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136(2):441-50 e1; quiz 716. **WRONG DESIGN**
480. Reinisch W, Sandborn WJ, Bala M, Yan S, Feagan BG, Rutgeerts P, et al. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. Inflamm Bowel Dis 2007;13(9):1135-40. **WRONG OUTCOME**
481. Revicki DA, Willian MK, Menter A, Saurat JH, Harnam N, Kaul M. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. Dermatology 2008;216(3):260-70. **WRONG DESIGN**

482. Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. Am J Gastroenterol 2001;96(3):722-9. **WRONG DESIGN**
483. Ricart E, Sandborn WJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. Gastroenterology 1999;117(5):1247-48. **WRONG PUBLICATION TYPE**
484. Rich P, Griffiths CEM, Reich K, Nestle FO, Scher RK, Li S, et al. Baseline nail disease in patients with moderate to severe psoriasis and response to treatment with infliximab during 1 year. Journal of the American Academy of Dermatology 2008;58(2):224-231. **WRONG OUTCOME**
485. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Experiment Ophthalmol 2005;33(5):461-8. **WRONG DESIGN**
486. Ritchlin C. Efficacy and safety of infliximab for the treatment of psoriatic arthritis. Nat Clin Pract Rheumatol 2006;2(6):300-1. **WRONG PUBLICATION TYPE**
487. Robinson DM, Keating GM. Infliximab - In ankylosing spondylitis. Drugs (New Zealand) 2005;65:1283-91. **WRONG PUBLICATION TYPE**
488. Romero-Mate A, Garcia-Donoso C, Cordoba-Guijarro S. Efficacy and safety of etanercept in psoriasis/psoriatic arthritis - An updated review. American Journal of Clinical Dermatology (New Zealand) 2007;8:143-55. **WRONG PUBLICATION TYPE**
489. Roos JC, Ostor AJ. Orbital cellulitis in a patient receiving infliximab for Ankylosing spondylitis. Am J Ophthalmol 2006;141(4):767-9. **WRONG DESIGN**
490. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology (Oxford) 2006;45(10):1294-7. **WRONG POPULATION**
491. Roux CH, Brocq O, Leccia N, Giacchero D, Breuil V, Albert C, et al. New-onset psoriatic palmoplantaris pustulosis following infliximab therapy: A class effect? Journal of Rheumatology 2007;34(2):434-437. **WRONG POPULATION**
492. Rozenbaum M, Boulman N, Slobodin G, Ayubkhanov E, Rosner I. Polyarthritis flare complicating rheumatoid arthritis infliximab therapy: A paradoxic adverse reaction. Journal of Clinical Rheumatology 2006;12(6):269-271. **WRONG DESIGN**
493. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis 2004;63(6):665-70. **WRONG DESIGN**
494. Russell GH, Katz AJ. Infliximab is effective in acute but not chronic childhood ulcerative colitis. J Pediatr Gastroenterol Nutr 2004;39(2):166-70. **WRONG POPULATION**
495. Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999;117(4):761-9. **WRONG DESIGN**
496. Rybar I, Rozborilova E, Zanova E, Micekova D, Solovic I, Rovensky J. The effectiveness for prevention of tuberculosis in patients with inflammatory rheumatic diseases treated with TNF inhibitors. Bratislavske lekarske listy 2008;109(4):164-167. **WRONG DESIGN**
497. Saeed SA, Crandall WV. Managing Crohn disease in children and adolescents - Focus on tumor necrosis factor antagonists. Pediatric Drugs (New Zealand) 2008;10:31-38. **WRONG PUBLICATION TYPE**

498. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology 2007;46(2):327-334. **WRONG DESIGN**
499. Sample C, Bailey RJ, Todoruk D, Sadowski D, Gramlich L, Milan M, et al. Clinical experience with infliximab for Crohn's disease: the first 100 patients in Edmonton, Alberta. Can J Gastroenterol 2002;16(3):165-70. **WRONG DESIGN**
500. Sandborn WJ, Feagan BG, Hanauer SB, Present DH, Sutherland LR, Kamm MA, et al. An engineered human antibody to TNF (CDP571) for active Crohn's disease: a randomized double-blind placebo-controlled trial. Gastroenterology 2001;120(6):1330-8. **DRUG NOT INDLUCED**
501. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56(9):1232-9. **WRONG DESIGN**
502. Sandborn WJ, Pardi DS. Clinical management of pouchitis. Gastroenterology 2004;127(6):1809-14. **WRONG PUBLICATION TYPE**
503. Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis 2007;13(1):2-11. **WRONG DESIGN**
504. Sands BE, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. Inflamm Bowel Dis 2001;7(2):83-8. **WRONG DESIGN**
505. Sands BE, Winston BD, Salzberg B, Safdi M, Barish C, Wruble L, et al. Randomized, controlled trial of recombinant human interleukin-11 in patients with active Crohn's disease. Aliment Pharmacol Ther 2002;16(3):399-406. **DRUG NOT INDLUCED**
506. Sanmarti R, Gomez-Centeno A, Ercilla G, Larrosa M, Vinas O, Vazquez I, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: A two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clinical Rheumatology 2007;26(7):1111-1118. **DRUG NOT INDLUCED**
507. Saraceno R, Schipani C, Mazzotta A, Esposito M, Di Renzo L, De Lorenzo A, et al. Effect of anti-tumor necrosis factor-alpha therapies on body mass index in patients with psoriasis. Pharmacological Research 2008;57(4):290-5. **WRONG OUTCOME**
508. Schaible TF. Long term safety of infliximab. Can J Gastroenterol 2000;14 Suppl C:29C-32C. **WRONG DESIGN**
509. Schaible TF. Infliximab therapy in patients with rheumatoid arthritis and Crohn's disease... adapted from a presentation by Thomas F. Schaible, PhD., at the NHIA Tenth Annual Conference, Las Vegas, Nevada, February 20-23, 2001. Infusion 2001;7(6):2p. **WRONG PUBLICATION TYPE**
510. Schiff MH. Durability and rapidity of response to anakinra in patients with rheumatoid arthritis. Drugs (New Zealand) 2004;64:2493-2501. **WRONG PUBLICATION TYPE**
511. Schiff MH, Whelton A. Renal toxicity associated with disease-modifying antirheumatic drugs used for the treatment of rheumatoid arthritis. Seminars in Arthritis and Rheumatism 2000;30(3):196-208. **WRONG PUBLICATION TYPE**

512. Schiff MH, Yu EB, Weinblatt ME, Moreland LW, Genovese MC, White B, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients: Patient-reported outcomes from multiple controlled and open-label extension studies. Drugs and Aging 2006;23(2):167-178. **WRONG DESIGN**
513. Schlesselman LS. Certolizumab pegol. Formulary 2008;43(1):22-28. **WRONG PUBLICATION TYPE**
514. Schmajuk G, Schneeweiss S, Katz JN, Weinblatt ME, Setoguchi S, Avorn J, et al. Treatment of older adult patients diagnosed with rheumatoid arthritis: Improved but not optimal. Arthritis Care and Research 2007;57(6):928-934. **WRONG OUTCOME**
515. Schreiber S, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S, et al. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. Gastroenterology 2000;119(6):1461-72. **DRUG NOT INDLUCED**
516. Schwetz BA. From the Food and Drug Administration. Jama 2002;287(9):1103. **WRONG PUBLICATION TYPE**
517. Scott DL. Pursuit of optimal outcomes in rheumatoid arthritis. PharmacoEconomics (New Zealand) 2004;22:13. **WRONG PUBLICATION TYPE**
518. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. The New England journal of medicine. 2006;355(7):704-712. **WRONG PUBLICATION TYPE**
519. Seiderer J, Goke B, Ochsenkuhn T. Safety aspects of infliximab in inflammatory bowel disease patients. A retrospective cohort study in 100 patients of a German University Hospital. Digestion 2004;70(1):3-9. **WRONG POPULATION**
520. Settergren M, Tornvall P. Does TNF-alpha blockade cause plaque rupture? Atherosclerosis 2004;173(1):149. **WRONG PUBLICATION TYPE**
521. Sfikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. Arthritis Rheum 2005;52(8):2513-8. **WRONG PUBLICATION TYPE**
522. Sfriso P, Ravaioli F. Adalimumab in juvenile rheumatoid arthritis. N Engl J Med 2008;359(23):2495; author reply 2496-7. **WRONG PUBLICATION TYPE**
523. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet 2002;359(9306):579-80. **WRONG PUBLICATION TYPE**
524. Shatin D, Rawson NSB, Curtis JR, Braun MM, Martin CK, Moreland LW, et al. Documented tuberculin skin testing among infliximab users following a multi-modal risk communication interventions. Pharmacoepidemiology and Drug Safety 2006;15(1):11-18. **WRONG DESIGN**
525. Shenker N, Haigh R, Clarke A. Worse patient VAS occurs at weeks 7 and 8 after infliximab infusions. Annals of the Rheumatic Diseases 2005;64(3):502-503. **WRONG PUBLICATION TYPE**
526. Shergy WJ, Isern RA, Cooley DA, Harshbarger JL, Huffstutter JE, Hughes GM, et al. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. J Rheumatol 2002;29(4):667-77. **WRONG DESIGN**
527. Shields CJ, Winter DC, Becker JM, Prushik SG, Stucchi AF, Reinshagen M, et al. Infliximab for ulcerative colitis... Rutgeerts P, Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med

2005;353:2462-76. New England Journal of Medicine 2006;354(13):1424-1426. **WRONG PUBLICATION TYPE**

528. Shin ISJ, Baer AN, Kwon HJ, Papadopoulos EJ, Siegel JN. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor (alpha) antagonist therapy. Arthritis and Rheumatism 2006;54(5):1429-1434. **WRONG POPULATION**
529. Shin JI, Kim MJ, Lee JS. Graves' disease, rheumatoid arthritis, and anti-tumor necrosis factor-alpha therapy. J. Rheumatol. 2009;36(2):449-450; author reply 450. **WRONG PUBLICATION TYPE**
530. Sichletidis L, Settas L, Spyratos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis 2006;10(10):1127-32. **WRONG DESIGN**
531. Siddha SK, Burden AD. Recognition and treatment of psoriasis in children. Paediatrics and Child Health 2007;17(10):390-394. **WRONG PUBLICATION TYPE**
532. Sidiropoulos P, Bertsias G, Kritikos HD, Kouroumali H, Voudouris K, Boumpas DT. Infliximab treatment for rheumatoid arthritis, with dose titration based on the Disease Activity Score: Dose adjustments are common but not always sufficient to assure sustained benefit. Annals of the Rheumatic Diseases 2004;63(2):144-148. **WRONG DESIGN**
533. Sidiropoulos P, Kritikos HD, Siakka P, Mamoulaki M, Kouroumali H, Voudouris K, et al. Low dose of infliximab is inadequate in most patients with spondylarthropathies. Clin Exp Rheumatol 2005;23(4):513-6. **WRONG DESIGN**
534. Sieper J, Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. Rheumatology (Oxford) 2005;44(12):1525-30. **WRONG DESIGN**
535. Simon D. Management of growth retardation in juvenile idiopathic arthritis. Hormone research 2007;68 Suppl 5(-):122-125. **DRUG NOT INDLUCED**
536. Sinha A, Patient C. Rheumatoid arthritis in pregnancy: Successful outcome with anti-TNF agent (Etanercept). Journal of Obstetrics and Gynaecology 2006;26(7):689-691. **WRONG POPULATION**
537. Slifman NR, Gershon SK, Lee JH, Edwards ET, Braun MM. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum 2003;48(2):319-24. **WRONG DESIGN**
538. Smith GR, Tymms KE, Falk M. Etanercept treatment of renal amyloidosis complicating rheumatoid arthritis. Internal Medicine Journal 2004;34(9-10):570-572. **WRONG POPULATION**
539. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Care and Research 2007;57(8):1431-1438. **DRUG NOT INDLUCED**
540. Smolen JS. What is the place of recently approved T cell-targeted and B cell-targeted therapies in the treatment of rheumatoid arthritis? Lessons from global clinical trials. Journal of Rheumatology 2007;34(Suppl 79):15-20. **WRONG PUBLICATION TYPE**
541. Sokka T, Kautiainen H, Hakkinen A, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. Journal of Rheumatology 2004;31(6):1073-1082. **DRUG NOT INDLUCED**

542. Sorbera LA, Rabasseda X, Castaner RM. Adalimumab. Antiarthritic treatment of IBD. Drugs of the Future 2001;26(7):639-646. **WRONG PUBLICATION TYPE**
543. Sorrentino D, Terrosu G, Avellini C, Maiero S. Infliximab with low-dose methotrexate for prevention of postsurgical recurrence of ileocolonic Crohn disease. Arch Intern Med 2007;167(16):1804-7. **WRONG POPULATION**
544. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46(6):1451-9. **WRONG OUTCOME**
545. Stack WA, Mann SD, Roy AJ, Heath P, Sopwith M, Freeman J, et al. Randomised controlled trial of CDP571 antibody to tumour necrosis factor-alpha in Crohn's disease. Lancet 1997;349(9051):521-4. **DRUG NOT INDLUCED**
546. Starmans-Kool MJ, Peeters HR, Houben HH. Pustular skin lesions in patients treated with infliximab: report of two cases. Rheumatol Int 2005;25(7):550-2. **WRONG DESIGN**
547. Sterry W, Stingl G, Langley RG, Zacharie H, Lahfa M, Giannetti A, et al. Clinical Experience Acquired with Raptiva (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from extended treatment in an international, Phase III, placebo-controlled trial. J Dtsch Dermatol Ges 2006;4(11):947-56. **WRONG DESIGN**
548. Stokes DG, Kremer JM. Potential of tumor necrosis factor neutralization strategies in rheumatologic disorders other than rheumatoid arthritis. Seminars in Arthritis and Rheumatism 2003;33(1):1-18. **WRONG POPULATION**
549. Strand V, Cohen S, Crawford B, Smolen JS, Scott DL. Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. Rheumatology (Oxford) 2004;43(5):640-7. **WRONG OUTCOME**
550. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: Evidence from randomized controlled trials. American Journal of Managed Care (USA) 2008;14:239-53. **WRONG PUBLICATION TYPE**
551. Su C, Salzberg BA, Lewis JD, Deren JJ, Kornbluth A, Katzka DA, et al. Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis. Am J Gastroenterol 2002;97(10):2577-84. **WRONG DESIGN**
552. Suissa S, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2008;21(1):234-8. **WRONG OUTCOME**
553. Sun YN, Lu JF, Joshi A, Compton P, Kwon P, Bruno RA. Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. J Clin Pharmacol 2005;45(4):468-76. **WRONG DESIGN**
554. Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL. The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis. Health Technol Assess 2005;9(34):iii-iv, ix-x, 1-78. **WRONG OUTCOME**
555. Taddio A, Marchetti F. Adalimumab in juvenile rheumatoid arthritis. N. Engl. J. Med. 2008;359(23):2495-2496; author reply 2496-2497. **WRONG PUBLICATION TYPE**
556. Takeuchi T, Yamanaka H, Inoue E, Nagasawa H, Nawata M, Ikari K, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a

rheumatoid arthritis management group in Japan: One-year outcome of joint destruction (RECONFIRM-2J). Modern Rheumatology 2008;18(5):447-454. **WRONG DESIGN**

557. Tam JW, Lee GJ, Song JC. Focus on... Efalizumab: a new biologic therapy for the control of chronic plaque psoriasis. Formulary 2004;39(1):20. **WRONG PUBLICATION TYPE**
558. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol 2008;18(2):146-52. **WRONG DESIGN**
559. Tang B, Rahman M, Waters HC, Callegari P. Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. Clin Ther 2008;30(7):1375-84. **WRONG OUTCOME**
560. Tauber T, Daniel D, Barash J, Turetz J, Morad Y. Optic neuritis associated with etanercept therapy in two patients with extended oligoarticular juvenile idiopathic arthritis. Rheumatology (Oxford) 2005;44(3):405. **WRONG PUBLICATION TYPE**
561. Tauber T, Turetz J, Barash J, Avni I, Morad Y. Optic neuritis associated with etanercept therapy for juvenile arthritis. J Aapos 2006;10(1):26-9. **WRONG DESIGN**
562. Taylor KD, Plevy SE, Yang H, Landers CJ, Barry MJ, Rotter JI, et al. ANCA pattern and LTA haplotype relationship to clinical responses to anti-TNF antibody treatment in Crohn's disease. Gastroenterology 2001;120(6):1347-55. **WRONG OUTCOME**
563. Temekonidis TI, Alamanos Y, Nikas SN, Bougias DV, Georgiadis AN, Voulgari PV, et al. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. Ann Rheum Dis 2003;62(12):1218-20. **WRONG DESIGN**
564. ten Cate R, van Suijlekom-Smit LWA, Brinkman DMC, Bekkering WP, Jansen-van Wijngaarden CJA, Vossen JM. Etanercept in four children with therapy-resistant systemic juvenile idiopathic arthritis [1]. Rheumatology 2002;41(2):228-229. **WRONG PUBLICATION TYPE**
565. Thayu M, Leonard MB, Hyams JS, Crandall WV, Kugathasan S, Otley AR, et al. Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. Clin Gastroenterol Hepatol 2008;6(12):1378-84. **WRONG DESIGN**
566. Thornton J, Beresford MW, Clayton P. Improving the evidence base for treatment of juvenile idiopathic arthritis: The challenge and opportunity facing the MCRN/ARC Paediatric Rheumatology Clinical Studies Group. Rheumatology 2008;47(5):563-566. **WRONG PUBLICATION TYPE**
567. Ting G, Schneeweiss S, Katz JN, Weinblatt ME, Cabral D, Scranton RE, et al. Performance of a rheumatoid arthritis records-based index of severity. Journal of Rheumatology 2005;32(9):1679-1687. **WRONG OUTCOME**
568. Titelbaum DS, Degenhardt A, Kinkel RP. Anti-tumor necrosis factor alpha-associated multiple sclerosis. AJNR Am J Neuroradiol 2005;26(6):1548-50. **WRONG DESIGN**
569. Tom WL, Miller MD, Hurley MY, Suneja T, Obadiah JM, et al. Efalizumab-induced autoimmune pancytopenia. British Journal of Dermatology (England) 2006;155:1045. **WRONG POPULATION**
570. Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-

TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford) 2004;43(6):712-8. **WRONG DESIGN**

571. Treitl M, Korner M, Becker-Gaab C, Tryzna M, Rieger J, Pfeifer KJ, et al. Magnetic resonance imaging assessment of spinal inflammation in patients treated for ankylosing spondylitis. Journal of Rheumatology 2008;35(1):126-136. **WRONG POPULATION**
572. Trethewey P. The role of tumor necrosis factor inhibitors in patients with RA: when rheumatoid arthritis symptoms don't respond to DMARDs or when these agents cause intolerable adverse effects, TNF inhibitors can slow disease activity and improve quality of life. JAAPA: Journal of the American Academy of Physician Assistants 2002;15(9):23. **WRONG PUBLICATION TYPE**
573. True DG, Penmetcha M, Peckham SJ. Disseminated cryptococcal infection in rheumatoid arthritis treated with methotrexate and infliximab. J Rheumatol 2002;29(7):1561-3. **WRONG POPULATION**
574. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc 2008;83(2):181-94. **WRONG DESIGN**
575. Tubach F, Ravaud P, Salmon-Ceron D, Petitpain N, Brocq O, Grados F, et al. Emergence of Legionella pneumophila pneumonia in patients receiving tumor necrosis factor-alpha antagonists. Clin Infect Dis 2006;43(10):e95-100. **WRONG DESIGN**
576. Turkiewicz AM, Moreland LW. Psoriatic Arthritis - Current concepts on pathogenesis-oriented therapeutic options. Arthritis and Rheumatism (USA) 2007;56:1051-1066. **WRONG PUBLICATION TYPE**
577. Tweezer-Zaks N, Shiloach E, Spivak A, Rapoport M, Novis B, Langevitz P. Listeria monocytogenes sepsis in patients treated with anti-tumor necrosis factor-alpha. Israel Medical Association Journal 2003;5(11):829-830. **WRONG DESIGN**
578. Twilt M, Schulten AJM, Verschure F, Wisse L, Prahl-Andersen B, Van Suijlekom-Smit LWA. Long-term followup of temporomandibular joint involvement in juvenile idiopathic arthritis. Arthritis Care and Research 2008;59(4):546-552. **WRONG PUBLICATION TYPE**
579. Tynjala P, Lahdenne P, Vahasalo P, Kautiainen H, Honkanen V. Impact of anti-TNF treatment on growth in severe juvenile idiopathic arthritis. Ann Rheum Dis 2006;65(8):1044-9. **WRONG DESIGN**
580. Tynjala P, Vahasalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. Ann. Rheum. Dis. 2009;68(4):552-557. **WRONG DESIGN**
581. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol 2007;143(6):719-26. **WRONG DESIGN**
582. Unit of Health Economics Technology Assessment. Rituximab in patients with rheumatoid arthritis:systematic review and economic evaluation (Brief record). Budapest: Unit of Health Economics and Technology Assessment in Health Care (HUNHTA) 2006. **WRONG PUBLICATION TYPE**
583. Utset TO, Auger JA, Peace D, Zivin RA, Xu D, Jolliffe L, et al. Modified anti-CD3 therapy in psoriatic arthritis: a phase I/II clinical trial. J Rheumatol 2002;29(9):1907-13. **WRONG DESIGN**

584. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. New England Journal of Medicine 2005;353(4):362-368. **WRONG POPULATION**
585. van de Kerkhof P, Griffiths CE, Christophers E, Lebwohl M, Krueger GG. Alefacept in the treatment of psoriasis in patients for whom conventional therapies are inadequate. Dermatology 2005;211(3):256-63. **WRONG DESIGN**
586. Van den Bosch F, Kruithof E, Baeten D, De Keyser F, Mielants H, Veys EM. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis 2000;59(6):428-33. **WRONG DESIGN**
587. Van den Bosch F, Kruithof E, Baeten D, Herssens A, de Keyser F, Mielants H, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. Arthritis Rheum 2002;46(3):755-65. **WRONG POPULATION**
588. Van Den Brande JM, Braat H, Van Den Brink GR, Versteeg HH, Van Deventer SJ, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology 2003;124:1774-85. **WRONG OUTCOME**
589. van der Heijde D, Burmester G, Melo-Gomes J, Codreanu C, Mola EM, Pedersen R, et al. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. Ann Rheum Dis 2008;67(2):182-8. **WRONG DESIGN**
590. van der Heijde D, Han C, DeVlam K, Burmester G, van den Bosch F, Williamson P, et al. Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: results from a randomized, placebo-controlled trial. Arthritis Rheum 2006;55(4):569-74. **WRONG OUTCOME**
591. Van Der Heijde D, Landewe R, Baraliakos X, Houben H, Van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis and Rheumatism 2008;58(10):3063-3070. **WRONG DESIGN**
592. van der Heijde D, Landewe R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58(5):1324-31. **WRONG DESIGN**
593. van der Heijde D, Landewe R, Klareskog L, Rodriguez-Valverde V, Settas L, Pedersen R, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum 2005;52(1):49-60. **WRONG OUTCOME**
594. van der Heijde D, Pangan AL, Schiff MH, Braun J, Borofsky M, Torre J, et al. Adalimumab effectively reduces the signs and symptoms of active ankylosing spondylitis in patients with total spinal ankylosis. Ann Rheum Dis 2008;67(9):1218-21. **WRONG POPULATION**
595. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Ewals JA, Han KH, Hazes JM, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis & Rheumatism 2009;61(1):4-12. **DRUG NOT INDLUCED**

596. Van Eijk Y, Boonen A, Schulpen G, Schrijnemaekers V, Fiolet H, Van Linden SD. Safety and patient satisfaction of infliximab administration in an extramural setting supervised by a rheumatology specialist nurse. Annals of the Rheumatic Diseases 2006;65(2):276. **WRONG DESIGN**
597. Van Pelt JP, De Jong EM, Seijger MM, Van Hooijdonk CA, De Bakker ES, Van Vlijmen IM, et al. Investigation on a novel and specific leukotriene B4 receptor antagonist in the treatment of stable plaque psoriasis. Br J Dermatol 1998;139(3):396-402. **DRUG NOT INDLUCED**
598. van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Ann Rheum Dis 2006. **WRONG DESIGN**
599. Van Riel PLCM, Freundlich B, MacPeek D, Pedersen R, Foehl JR, Singh A. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Annals of the Rheumatic Diseases 2008;67(8):1104-1110. **DRUG NOT INDLUCED**
600. Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. Annals of the Rheumatic Diseases 2003;62(12):1241-1242. **WRONG PUBLICATION TYPE**
601. Vazquez I, Graell E, Gratacos J, Canete JD, Vinas O, Ercilla MG, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clinical and Experimental Rheumatology 2007;25(2):231-238. **DRUG NOT INDLUCED**
602. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology (Oxford, England) 2008;47(4):535-541. **WRONG OUTCOME**
603. Verbsky JW, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. J Rheumatol 2004;31(10):2071-5. **WRONG DESIGN**
604. Veres G, Baldassano RN, Mamula P. Infliximab therapy in children and adolescents with inflammatory bowel disease. Drugs 2007;67(12):1703-1723. **WRONG PUBLICATION TYPE**
605. Vergel YB, Hawkins NS, Claxton K, Asseburg C, Sculpher MJ, et al. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology 2007;46:1729. **WRONG OUTCOME**
606. Vermeire S, Louis E, Carbonez A, Van Assche G, Noman M, Belaiche J, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. Am J Gastroenterol 2002;97(9):2357-63. **WRONG DESIGN**
607. Vermeire S, Noman M, Van Assche G, Baert F, Van Steen K, Esters N, et al. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. Gastroenterology 2003;125(1):32-9. **WRONG DESIGN**

608. Verstappen SMM, Jacobs JWG, Huisman AM, Van Rijthoven AWAM, Sokka T, Bijlsma JWJ. Functional Health Assessment Questionnaire (HAQ) and psychological HAQ are associated with and predicted by different factors in rheumatoid arthritis. Journal of Rheumatology 2007;34(9):1837-1840. **WRONG DESIGN**
609. Viguier M, Richette P, Aubin F, Beylot-Barry M, Lahfa M, Bedane C, et al. Onset of psoriatic arthritis in patients treated with efalizumab for moderate to severe psoriasis. Arthritis Rheum 2008;58(6):1796-802. **WRONG POPULATION**
610. Viscido A, Habib FI, Kohn A, Papi C, Marcheggiano A, Pimpo MT, et al. Infliximab in refractory pouchitis complicated by fistulae following ileo-anal pouch for ulcerative colitis. Aliment Pharmacol Ther 2003;17(10):1263-71. **WRONG DESIGN**
611. Viscido A, Kohn A, Papi C, Caprilli R. Management of refractory fistulizing pouchitis with infliximab. Eur Rev Med Pharmacol Sci 2004;8(5):239-46. **WRONG DESIGN**
612. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. Journal of Rheumatology 2007;34(5):952-957. **WRONG OUTCOME**
613. Visvanathan S, van der Heijde D, Deodhar A, Wagner C, Baker DG, Han J, et al. Effects of infliximab on markers of inflammation and bone turnover and associations with bone mineral density in patients with ankylosing spondylitis. Annals of the rheumatic diseases 2009(2):175-82. **WRONG OUTCOME**
614. Visvanathan S, Wagner C, Marini JC, Baker D, Gathany T, Han J, et al. Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. Annals of the Rheumatic Diseases 2008(4):511; 7-511; 7. **WRONG OUTCOME**
615. Visvanathan S, Wagner C, Smolen J, St. Clair EW, Hegedus R, Baker D, et al. IgG and IgM anticardiolipin antibodies following treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Arthritis and Rheumatism 2006;54(9):2840-2844. **WRONG OUTCOME**
616. Voigtlander C, Luftl M, Schuler G, Hertl M. Infliximab (anti-tumor necrosis factor alpha antibody): a novel, highly effective treatment of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease). Arch Dermatol 2001;137(12):1571-4. **WRONG DESIGN**
617. Vojvodich PF, Hansen JB, Andersson U, Savendahl L, Hagelberg S. Etanercept treatment improves longitudinal growth in prepubertal children with juvenile idiopathic arthritis. Journal of Rheumatology 2007;34(12):2481-2485. **WRONG POPULATION**
618. Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI, Drosos AA. Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med 2005;118(5):515-20. **WRONG DESIGN**
619. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. Annals of the Rheumatic Diseases 2008;67(4):567-570. **WRONG DESIGN**
620. Vultaggio A, Matucci A, Parronchi P, Rossi O, Palandri F, Romagnani S, et al. Safety and tolerability of infliximab therapy: Suggestions and criticisms based on wide clinical experience. International Journal of Immunopathology and Pharmacology 2008;21(2):367-374. **WRONG POPULATION**

621. Wagner-Weiner L. Pediatric rheumatology for the adult rheumatologist. Journal of Clinical Rheumatology 2008;14(2):109-119. **WRONG PUBLICATION TYPE**
622. Wallace CA. Current management of juvenile idiopathic arthritis. Best Practice and Research in Clinical Rheumatology 2006;20(2):279-300. **WRONG PUBLICATION TYPE**
623. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. Clin Infect Dis 2004;39(8):1254-5. **WRONG PUBLICATION TYPE**
624. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38(9):1261-5. **WRONG DESIGN**
625. Walsh CAE, Minnock P, Slattery C, Kennedy N, Pang F, Veale DJ, et al. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. Rheumatology 2007;46(7):1148-1152. **WRONG DESIGN**
626. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. Inflamm Bowel Dis 2007;13(4):424-30. **WRONG OUTCOME**
627. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 2004;31(10):1912-7. **WRONG DESIGN**
628. Watt I, Cobby M. Treatment of rheumatoid arthritis patients with interleukin-1 receptor antagonist: radiologic assessment. Semin Arthritis Rheum 2001;30(5 Suppl 2):21-5. **WRONG OUTCOME**
629. Weber RW. Adverse reactions to biological modifiers. Current Opinion in Allergy and Clinical Immunology 2004;4(4):277-283. **WRONG POPULATION**
630. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther 2003;25(6):1700-21. **WRONG DESIGN**
631. Weiss JE, Ilowite NT. Juvenile Idiopathic Arthritis. Rheumatic Disease Clinics of North America 2007;33(3):441-470. **WRONG PUBLICATION TYPE**
632. Wellington K, Perry CM. Efalizumab. American Journal of Clinical Dermatology (New Zealand) 2005;6:113-15. **WRONG PUBLICATION TYPE**
633. Wells G, Li T, Maxwell L, Maclean R, Tugwell P. Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis 2008;67(2):260-5. **WRONG OUTCOME**
634. Wells GA, Boers M, Li T, Tugwell PS. Investigating the validity of the minimal disease activity state for patients with rheumatoid arthritis treated with abatacept. J Rheumatol 2009;36(2):260-5. **WRONG OUTCOME**
635. Wendling D, Auge B, Streit G, Toussirot E, Mathieu S. Lack of short-term efficacy of rituximab upon symptoms of ankylosing spondylitis treated for an associated vasculitis. Joint Bone Spine 2008;75(4):510-511. **WRONG POPULATION**

636. Wendling D, Balblanc JC, Briancon D, Brousse A, Lohse A, Deprez P, et al. Onset or exacerbation of cutaneous psoriasis during TNFalpha antagonist therapy. Joint Bone Spine 2008;75(3):315-8. **WRONG POPULATION**
637. Wendling D, Balblanc JC, Brousse A, Lohse A, Lehuede G, Garbuio P, et al. Surgery in patients receiving anti-tumour necrosis factor alpha treatment in rheumatoid arthritis: an observational study on 50 surgical procedures. Ann Rheum Dis 2005;64(9):1378-9. **WRONG DESIGN**
638. Wendling D, Racadot E, Wijdenes J, Sibilia J, Flipo RM, Cantagrel A, et al. A randomized, double blind, placebo controlled multicenter trial of murine anti-CD4 monoclonal antibody therapy in rheumatoid arthritis. J Rheumatol 1998;25(8):1457-61. **DRUG NOT INDLUCED**
639. Wenzl HH, Reinisch W, Jahnel J, Stockenhuber F, Tilg H, Kirchgatterer A, et al. Austrian infliximab experience in Crohn's disease: a nationwide cooperative study with long-term follow-up. Eur J Gastroenterol Hepatol 2004;16(8):767-73. **WRONG DESIGN**
640. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009. **WRONG DESIGN**
641. Wick MC, Ernestam S, Lindblad S, Bratt J, Klareskog L, Van Vollenhoven RF. Adalimumab (Humira(registered trademark)) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade(registered trademark)) or etanercept (Enbrel(registered trademark)): Results from the STURE registry at Karolinska University Hospital. Scandinavian Journal of Rheumatology 2005;34(5):353-358. **WRONG POPULATION**
642. Winter TA, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. Aliment Pharmacol Ther 2004;20(11-12):1337-46. **WRONG DESIGN**
643. Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. Clin Infect Dis 2008;46(11):1738-40. **WRONG DESIGN**
644. Wislowska M, Jakubicz D. Preliminary evaluation in rheumatoid arthritis activity in patients treated with TNF-(alpha) blocker plus methotrexate versus methotrexate or leflunomide alone. Rheumatology International 2007;27(7):641-647. **WRONG DESIGN**
645. Wolfe F, Michaud K, Simon T. Can severity be predicted by treatment variables in rheumatoid arthritis administrative data bases? Journal of Rheumatology 2006;33(10):1952-1956. **WRONG OUTCOME**
646. Wolfe F, Rasker JJ, Boers M, Wells GA, Michaud K. Minimal disease activity, remission, and the long-term outcomes of rheumatoid arthritis. Arthritis Care and Research 2007;57(6):935-942. **WRONG DESIGN**
647. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. American Journal of Clinical Dermatology 2008;9(1):1-14. **WRONG PUBLICATION TYPE**

648. Woo JH, Lee HJ, Sung ILH, Kim TH. Changes of clinical response and bone biochemical markers in patients with ankylosing spondylitis taking etanercept. Journal of Rheumatology 2007;34(8):1753-1759. **WRONG POPULATION**
649. Woo P. Anakinra treatment for systemic juvenile idiopathic arthritis and adult onset Still disease. Annals of the Rheumatic Diseases 2008;67(3):281-282. **WRONG PUBLICATION TYPE**
650. Wright T, Cron RQ. Pediatric rheumatology for the adult rheumatologist II: Uveitis in juvenile idiopathic arthritis. Journal of Clinical Rheumatology 2007;13(4):205-210. **WRONG PUBLICATION TYPE**
651. Wu EQ, Yu AP, Tang J, Atanasov PD, Chao J, Mulani P. Effect of sustained remission and clinical response on the risk of hospitalization in patients with Crohn's disease. Managed Care Interface 2008;21(3):20-23. **WRONG PUBLICATION TYPE**
652. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Modern Rheumatology 2007;17(4):283-289. **WRONG DESIGN**
653. Yazdani-Biuki B, Wohlfahrt K, Mulabecirovic A, Mueller T, Hermann J, Graninger WB, et al. Long term treatment of psoriatic arthritis with infliximab. Ann Rheum Dis 2004;63(11):1531-2; author reply 1532. **WRONG PUBLICATION TYPE**
654. Yazici Y, Erkan D, Lockshin MD. Etanercept in the treatment of severe, resistant psoriatic arthritis: continued efficacy and changing patterns of use after two years. Clin Exp Rheumatol 2002;20(1):115. **WRONG POPULATION**
655. Yazici Y, Erkan D, Paget SA. Monitoring by rheumatologists for methotrexate-, etanercept-, infliximab-, and anakinra-associated adverse events. Arthritis and Rheumatism (USA) 2003;48:2769-2772. **WRONG OUTCOME**
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**
657. Yoshizaki K, Nishimoto N, Mihara M, Kishimoto T. Therapy of rheumatoid arthritis by blocking IL-6 signal transduction with a humanized anti-IL-6 receptor antibody. Springer Semin Immunopathol 1998;20(1-2):247-59. **WRONG PUBLICATION TYPE**
658. Yount S, Sorensen MV, Cella D, Sengupta N, Grober J, Chartash EK. Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis. Clin Exp Rheumatol 2007;25(6):838-46. **WRONG OUTCOME**
659. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354(9):924-33. **WRONG POPULATION**
660. Zhou H, Buckwalter M, Boni J, Mayer P, Raible D, Wajdula J, et al. Population-based pharmacokinetics of the soluble TNFr etanercept: a clinical study in 43 patients with ankylosing spondylitis compared with post hoc data from patients with rheumatoid arthritis. Int J Clin Pharmacol Ther 2004;42(5):267-76. **WRONG OUTCOME**
661. Zhou H, Parks V, Patat A, Le Coz F, Simcoe D, Korth-Bradley J. Absence of a clinically relevant interaction between etanercept and digoxin. J Clin Pharmacol 2004;44(11):1244-51. **WRONG POPULATION**

# 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.