Drug Class Review

Targeted Immune Modulators

Final Update 3 Report

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The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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The literature on this topic is scanned periodically

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

STRUCTURED ABSTRACT

Purpose

We systematically compared the efficacy, effectiveness, and safety (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

Data Sources

To identify published studies, we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2009 (January) to 2011 (October). We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data, requested dossiers of information from pharmaceutical manufacturers, and retrieved relevant citations from reference lists of included studies.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to our standard review methods.

Results and Conclusion

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.

For rheumatoid arthritis, low-and moderate-strength evidence indicated that some targeted immune modulators are more efficacious than others. These results were based on three head-to-head trials, several large observational studies, and indirect comparisons of placebo-controlled trials. The evidence is currently insufficient to reliably determine the comparative effectiveness for other indications and in subgroups.

Low-strength evidence indicated that serious infections are less common with abatacept than the other drugs and that the rate of adverse events is greater with infliximab than adalimumab or etanercept. Likewise, more patients receiving infliximab withdrew due to adverse events than abatacept, adalimumab, etanercept, and golimumab. Infusion or allergic reactions contributed to the difference in risk.

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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 12 additional agents since that time for treating various rheumatic conditions, inflammatory bowel diseases, and plaque psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), efalizumab (2003), abatacept (2005), rituximab (2006), natalizumab (2008), certolizumab pegol (2008), golimumab (2009), ustekinumab (2009), and tocilizumab (2010). Table 1 summarizes currently approved biologics in the United States, including trade name, manufacturer, route of administration, approved (labeled) uses, and dosage.

Table 1. Included interventions

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Abatacept	Orencia® Bristol Myers Squibb	CTLA 4-Ig	Rheumatoid arthritis	Intravenous infusion dosed according to body weight (<60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter. Following single intravenous loading dose according to body weight specified above, the first 125 mg subcutaneous injection within 1 day, followed by 125 mg once weekly. Patients unable to receive an infusion may initiate weekly subcutaneous injections without an intravenous loading dose. Patients transitioning from intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of next scheduled intravenous dose.
			Juvenile rheumatoid arthritis[a] (6 years and older)	See Canadian product label
			Juvenile idiopathic arthritis (6 years and older)	10 mg/kg for patients <75 kg; adults schedule for patients >75kg (maximum dose 1000 mg) on weeks 0, 2, and 4 and then every 4 weeks thereafter.
Adalimumab	Humira® Abbott	TNF Inhibitor	Rheumatoid arthritis	40 mg every other week as subcutaneous injection; may increase to 40 mg weekly for adalimumab monotherapy.
			Psoriatic arthritis, ankylosing spondylitis	40 mg every other week as subcutaneous injection.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Juvenile idiopathic arthritis[b] (4 years of age and older)	15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week. ≥ 30 kg (66 lbs): 40 mg every other week.
			Crohn's disease	Initial subcutaneous dose (Day 1) 160 mg (four 40 mg injections in 1 day or two 40 mg injections daily 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	Amevive® Astellas	CD2 antagonist	Plaque psoriasis	15 mg given once weekly as an intramuscular 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	Kineret® Biovitrum/ Amgen	IL-1 receptor antagonist	Rheumatoid arthritis	100 mg daily as subcutaneous injection; dose should be decreased to 100 mg every other day in renal insufficiency.
Certolizumab pegol	Cimzia® UCB, Inc	TNF Inhibitor	Rheumatoid arthritis	400 mg subcutaneous injection 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[b]	400 mg subcutaneous injection initially and at weeks 2 and 4. If response occurs 400 mg subcutaneously every 4 weeks.
Etanercept	Enbrel® Amgen Pfizer Immunex	TNF Inhibitor	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	50 mg once weekly as subcutaneous injection.
			Juvenile idiopathic arthritis (2-17 years)[c]	0.8 mg/kg weekly (maximum 50 mg weekly), given as 1 or 2 subcutaneous injections.
			Plaque psoriasis	50 mg given twice weekly as a subcutaneous injection for 3 months, followed by 50 mg weekly.
Golimumab	Simponi® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	50 mg subcutaneous injection once a month in combination with methotrexate.[d]
			Psoriatic arthritis, ankylosing spondylitis	50 mg subcutaneous injection once a month with or without methotrexate or other DMARDs.[e]
Infliximab	Remicade® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	*Adult:* 3 mg/kg intravenous induction at 0, 2, and 6 weeks with methotrexate followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treating as often as every 4 weeks.
			Crohn's disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to 10 mg/kg. *Pediatric* [f,g]: 5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Psoriatic arthritis	5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter, with or without methotrexate.
			Ankylosing spondylitis	5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 6 weeks thereafter.
			Active ulcerative colitis	5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. *Pediatric*[f]: 5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by maintenace regimen of 5 mg/kg every 8 weeks.
			Plaque psoriasis	5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.
Natalizumab	Tysabri® Biogen-Idec	Anti-alpha-4 integrin subunit	Crohn's disease[b]	300 mg intravenous infusion every 4 weeks.
Rituximab	Rituxan® Genentech Hoffman-La Roche[h]	Anti-CD 20a	Rheumatoid arthritis	Two 1000 mg intravenous infusion on days 1 and 15 in combination with methotrexate. Subsequent courses administered every 24 weeks or based on clinical evaluation but not sooner than every 16 weeks.
Tocilizumab	Actemra® Genentech	IL-6 receptor monoclonal antibody	Rheumatoid arthritis	Start dose 4 mg/kg, increase up to 8 mg/kg given every 4 weeks with or without DMARD. Increase to 8 mg/kg based on clinical response. Dose exceeding 800 mg/ infusion not recommended.
			Systemic juvenile idiopathic arthritis[b] (2 years and older)	Body weight <30 kg: 12 mg/kg intravenous infusion every 2 weeks. Body weight ≥30 kg: 8 mg/kg every 2 weeks.
Ustekinumab	Stelara® Janssen Biotech	IL-12 and IL-23 monoclonal antibody	Plaque psoriasis	Body weight ≤100 kg (220 lbs), recommended dose 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks by subcutaneous injection Body weight >100 kg (220 pounds), recommended dose 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Abbreviations: AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.
[a] Approved only in Canada
[b] Not approved in Canada
[c] In Canada, pediatric: 4-17 years
[d] Not approved in combination with methotrexate in Canada
[e] Not approved in combination with methotrexate/other DMARDs in Canada
[f] In United States., pediatric: 6-17 years
[g] In Canada, pediatric: ≥9 years
[h] Manufacturer in Canada
Note: Table 1 provides manufacturer and approved indications in the United States and Canada and dosage and administration information in the United States relative to indications covered in this report. Readers should refer to the Health Canada product monograph of individual drug products for dosing information for Canada.

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, golimumab,

and infliximab all bind to both the circulating and transmembrane forms of tumor necrosis factor alpha, inhibiting its biological activity. They do not neutralize lymphotoxin alpha. Adalimumab is a fully human monoclonal antibody that blocks tumor necrosis factor alpha's 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. Golimumab is a human monoclonal antibody that binds to tumor necrosis factor alpha. Infliximab is a chimeric (mouse/human) antitumor necrosis factor alpha antibody. 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.

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 and alefacept exert their immune regulation by interfering with T lymphocyte activation and efalizumab blocks lymphocyte activation and migration. 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 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 immunoglobulin G4 antibody that binds to the alpha 4 subunit of alpha 4β1 and alpha4β7 integrins expressed on the surface of all leukocytes except neutrophils. It inhibits adhesion of leukocytes to receptors. 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.

Tocilizumab is a recombinant humanized monoclonal antibody against the interleukin-6 receptor. Interleukin-6 is a pro inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes, and fibroblasts and has been shown to play a role in immune response, such as those involved in autoimmune diseases.

Finally, ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit used by both the interleukin-12 and interleukin-23 cytokines. Interleukin-12 and

interleukin-23 are naturally occurring cytokines that are involved in inflammatory and immune responses.

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. While these drugs may be used in other conditions, such as systemic lupus erythematosus or vasculitis, the participating organizations of the Drug Effectiveness Review Project have elected to focus on these indications as the key uses at this time. 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 80% of patients with rheumatoid arthritis but is frequently negative in early disease. A more specific marker, anticyclic citrullinated peptide antibody, may be a useful marker in patients with early disease.[2] Table 2 presents the recently adapted classification criteria for rheumatoid arthritis modified by the American College of Rheumatology and the European League Against Rheumatism in 2010.[3] The previous criteria (American College of Rheumatology criteria from 1987[4]) were developed for use in clinical trials, and were thought to be relatively insensitive in early disease.

Treatment is aimed at controlling pain and inflammation and ultimately, achieving tight control of the disease to slow or arrest 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.[5] 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.[6] Lifelong therapy is usually necessary.

Table 2. American College of Rheumatology - European League Against Rheumatism classification criteria for rheumatoid arthritis[a] (revised 2010)

A.	**Joint involvement**	**Score**
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints	5
B.	**Serology**	
	Negative RF *and* negative ACPA	0
	Low-positive RF *or* low-positive ACPA	2
	High-positive RF *or* high-positive ACPA	3
C.	**Acute-phase reactants**	
	Normal CRP *and* normal ESR	0
	Abnormal CRP *or* abnormal ESR	1
D.	**Duration of symptoms**	
	<6 weeks	0
	≥6 weeks	1

Abbreviations: ACPA, anti citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

[a] A score of ≥6/10 is needed for classification of a patient as having definite rheumatoid arthritis.[3]

Target population for this test:

1. Patients who have at least 1 joint with definite clinical synovitis (swelling)
2. Patients with the synovitis not better explained by another disease.

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 three established subtypes: pauciarticular (less than five joints involved), polyarticular (five or more joints involved), and systemic (arthritis with fever and a rash).[7]

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. Nonsteroidal anti-inflammatory drugs are first line therapy and are usually fairly well tolerated in children.[8] 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.[9] 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 nonsteroidal anti-inflammatory drugs were the standard of care for the treatment of ankylosing spondylitis, as they are effective in treating pain and stiffness.[10] 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. Because tumor necrosis factor has been implicated in the pathophysiology of ankylosing spondylitis, biologic agents targeting tumor necrosis factor are now recommended as part of the standard treatment approach.[10,11]

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 concurrent plaque psoriasis.[12] Dactylitis, swelling of a whole digit, is a characteristic clinical finding. Enthesitis, spondylitis, sacroiliitis, and inflammatory eye disease (uveitis) may occur. Diagnostic criteria are presented in Table 3.

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.[13] The first line of treatment is nonsteroidal anti-inflammatory drugs, although in most cases disease-modifying antirheumatic drugs are necessary. Neither of these approaches is likely to prevent or slow joint damage. If disease continues to be active despite the use of nonsteroidal anti-inflammatory drugs, methotrexate, other oral disease-modifying antirheumatic drugs or

biologics should be employed.[14,15] Therapy in persons with psoriatic arthritis should take into account concomitant psoriasis of the skin.

Table 3. CASPAR classification criteria for psoriatic arthritis (2006)[16]

	Presence of inflammatory articular disease (joint, spine, or entheseal)	
PLUS three points from the following		
1	Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.	2 points
	OR a personal history of psoriasis	1 point
	OR a family history of psoriasis	1 point
2	Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination	1 point
3	A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range	1 point
4	Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist	1 point
5	Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	1 point

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 gastrointestinal 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, maintaining remission, and preventing complications.[17] 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 or are sometimes used in a "top-down" approach before other therapies. In general, all available medical therapies are

implemented before surgical therapy is considered, except in cases of catastrophic complications such as acute colonic obstruction, massive hemorrhage, or bowel perforation.[17]

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory bowel disease that is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain, and is 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.[18]

Treatment is aimed at reducing and maintaining remission of symptoms and inflammation and prevention complications.[19] Distal disease, limited to the region below the descending colon, may be reached by topical treatments. 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 and is recommended by the American College of Gastroenterologists for patients who are steroid refractory or who are steroid dependent despite adequate therapy with thiopurines.[18] Indications for surgery include excessive bleeding, perforation, carcinoma, and toxic colitis.

Plaque Psoriasis

Plaque psoriasis is a chronically recurring, debilitating inflammatory disease that affects the skin, scalp, and joints. It is characterized by erythrosquamous scaling lesions and ranges in severity from mild to severe. Patients with moderate to severe disease experienced significant deterioration of quality of life.[20] The exact pathogenesis of plaque psoriasis is still unknown, however pathophysiological evidence suggests that an overproduction of proinflammatory cytokines plays an important role.[21,22] In particular, tumor necrosis factor levels and interleukin-12 and interleukin-23 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. Mild psoriasis is defined as affecting less than 5% of the body surface area; moderate psoriasis affects 5% to 10%; and severe psoriasis is defined as more than 10% of the body surface area affected.[20,23]

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.[24] Conventional therapy includes topical treatments (e.g., emollients, topical corticosteroids, vitamin D_3 analogues, tazarotene, coal tar, and dithranol), phototherapy (e.g., broadband ultraviolet B light, narrow band ultraviolet B light, and psoralen plus ultraviolet A light), and systemic therapy (e.g., methotrexate, cyclosporine, retinoids, and fumarates).[23] In addition, biologic agents such as adalimumab, alefacept, efalizumab, etanercept, infliximab, and ustekinumab 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 pain, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as radiological progression). 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 to be treated with an intervention for one 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 policymakers 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, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab 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 harms associated with the use of these drugs?

3. Do the included drugs differ in effectiveness or harms in the following subgroups:
    - Different genders or different racial, age, or socioeconomic groups?
    - Patients with comorbidities?
    - Patients taking other commonly prescribed drugs?
    - Patients with early aggressive compared with persistent rheumatoid arthritis?

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 Research Triangle Institute-International-University of North Carolina Evidence-based Practice Center.[25] Studies conducted in community-based settings that use less stringent eligibility criteria (i.e., broad range of

population characteristics and disease severity), have long follow-up periods (i.e., greater than one year), and assess health outcomes are characterized as *effectiveness* studies. Studies conducted in more highly selected populations over shorter periods of time are characterized as *efficacy* studies. We summarize the results of efficacy and effectiveness studies separately as the results of effectiveness studies are more generalizable than results from highly selected populations (i.e., efficacy studies). However, effectiveness studies may have lower internal validity because of a higher risk of bias.

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

Table 4. Outcome measures and study eligibility criteria

Outcome	Outcome measures	Study eligibility criteria
Efficacy / Effectiveness	• Health outcomes: o Quality of Life o Functional capacity o Pain o Reduction in the number of swollen or tender joints o Response o Remission o Reduction of affected body surface area o Hospitalizations o Mortality o Steroid withdrawal • If no studies with health outcomes were available, we included intermediate outcomes: o Radiological outcomes	• Outpatient study population • Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM to another o Good or fair quality o ≥12 weeks study duration • When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials o Good or fair quality o ≥12 weeks study duration • Head-to-head observational studies were reviewed for quality of life, functional capacity, hospitalizations and mortality - outcome measures rarely assessed in controlled trials o Good or fair quality o ≥ 12 weeks study duration o N ≥ 100
Safety/ Tolerability	• Overall adverse events • Withdrawals because of adverse events • Serious adverse events • Specific adverse events, including: o Serious infectious diseases o Lymphoma o CHF o Autoimmunity	• Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM drug to another o Good or fair quality o ≥ 12 weeks study duration • When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials o Good or fair quality o ≥ 12 weeks study duration • Head-to-head observational studies were reviewed for harms o Good or fair quality o > 12 weeks study duration o N ≥ 100 • Observational studies o Good or fair quality o ≥ 6 months study duration o N ≥ 1000

Abbreviations: 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 is health outcomes (see Table 4). For head-to-head studies, however, we 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).[26] 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 was 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.[27,28]

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.[29] 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, for Update 3 we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2009 (January) to 2011 (October) using included drugs (abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab), indications (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis), and study designs as search terms (see Appendix B for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical

reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X4, Thomson Reuters).

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 12 weeks duration with an outpatient study population were eligible for inclusion.

In addition, we reviewed well-conducted, head-to-head observational studies with a follow-up of at least 12 weeks 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.[30] 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. 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.[31] For each section, we included results from the most recent and best-quality systematic review and meta-analysis and did not include data from older meta-analyses where these had been superseded in terms of included studies and analysis. 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, and 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, and 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 intent-to-treat results if available.

Validity Assessment

We assessed the internal validity (quality) of trials based on predefined criteria developed by the United States Preventive Services Task Force (ratings: good-fair-poor)[32] and the National Health Service Centre for Reviews and Dissemination.[33] 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, whether eligibility criteria were specified, use of intent-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,[34] independent of the reason and the use of intent-to-treat analysis. We adopted no formal cut-off point of loss to follow-up because some studies defined withdrawals due to acute worsening of the disease as an outcome measure.

Trials that had a fatal flaw in one 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 (meta-analyses of placebo-controlled trials or indirect comparisons). 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 used metaregressions as a statistical method for adjusted indirect comparisons. 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.[35,36] 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 50 response (numbers refer to percentage improvement [see Appendix D 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 index) and applied a random effects model. We used random effects metaregressions to determine the relative risk of achieving American College of Rheumatology 50 response between two drugs.

All statistical analyses were conducted using Stata, version 11.2 (StataCorp LP, College Station, Texas) or RevMan Version 5.1, (Review Manager, Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Peer Review

We requested and received peer review of the report from four content or methodology experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/peer-reviewers.cfm.

Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from six pharmaceutical companies.

Grading the Strength of the Evidence

We graded strength of evidence based on the methods guidance established for the Evidence-based Practice Center program of the Agency for Healthcare Research and Quality.[37] Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains: risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships).

As described in Owens, et al., evaluating risk of bias includes assessment of study design and aggregate quality of studies.[37] We judged good-quality studies to yield evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same

direction. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. We graded evidence as being precise when results had a low degree of uncertainty. A precise estimate is one that would allow a clinically useful conclusion; an imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions.[37]

As shown in Table 5, we used four grades to designate strength of evidence: high, moderate, low, and insufficient. Grades reflect the strength of the body of evidence to answer key questions on the comparative efficacy, effectiveness, and harms of targeted immune modulators. They do not refer to the general efficacy or effectiveness.

Table 5. Definitions of the grades of the overall strength of evidence

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

This approach does not incorporate other factors that might be relevant to assess reliably the comparative efficacy, effectiveness, and harms; such considerations can include funding sources and comparable dosing. For this review, we reported these additional factors and highlighted any problems that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

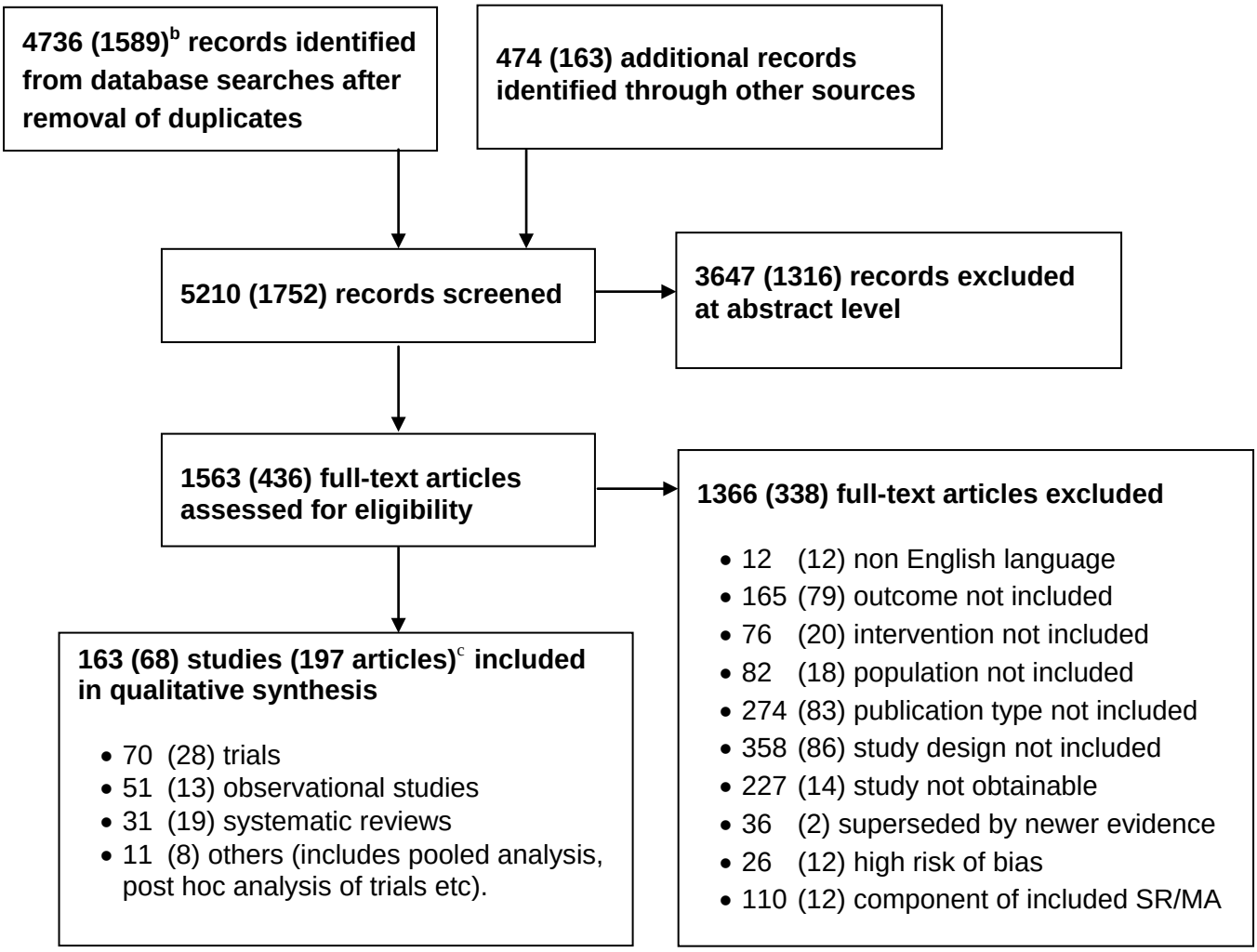
We dually evaluated the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain. We reconciled all disagreements in grades through consensus discussion.

RESULTS

Overview

For Update 3, literature searches identified 1589 citations. We received dossiers from five pharmaceutical manufacturers: Abbot, Amgen, Centocor Ortho Biotech, Genentech, and UCB Inc. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 436 citations. After re-applying the criteria for inclusion, we ultimately included 78 new publications, representing 68 unique studies. See Appendix G for a list of excluded studies and reasons for exclusion at this stage. Figure 1 shows the flow of study selection.

Figure 1. Results of literature search[a]



[a] DERP uses a modified PRISMA flow diagram.[38]
[b] Numbers in parentheses are results of the literature search new to Update 3
[c] The number of included studies differs from the number of included articles because 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, golimumab, infliximab, rituximab, and tocilizumab.

We included 16 trials, 21 systematic reviews and meta-analyses, and seven observational studies. Only one randomized controlled trial was a double-blinded head-to-head trial.[39] One study was characterized as an effectiveness trial.[40] 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 that we found on the comparative efficacy of targeted immune modulators was a fair randomized controlled trial that compared abatacept with infliximab in patients with inadequate response to methotrexate.[39] At 6 months, no differences in efficacy were apparent between patients treated with abatacept or infliximab. The strength of evidence is moderate. After 1 year, however, 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.

Other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis were limited to one small randomized controlled trial and multiple nonrandomized or observational studies rendering evidence of low strength. These studies indicated no differences in efficacy between adalimumab and etanercept but greater response rates for adalimumab and etanercept compared with infliximab.

Overall, seven studies indicated that etanercept is more efficacious than infliximab.[40-46] The only study with a randomized allocation of patients, however, was a fair, small (n=32) open-label trial.[41] Results indicated greater response rates in patients treated with etanercept than with infliximab (74.4% compared with 60% after 54 weeks; P=NR). Six head-to-head observational studies and one nonrandomized trial also reported similar findings of greater efficacy of etanercept than infliximab.[40,42-46] The strength of evidence was moderate.

Two prospective cohort studies based on Dutch[44] and a Danish[45] registries reported greater efficacy with adalimumab than infliximab. In the Danish (n=1452), 35% of patients treated with adalimumab achieved a LUNDEX-corrected American College of Rheumatology 50 response at 12 months, compared with 25% of patients on infliximab ($P< 0.001$). The strength of evidence was low.

Indirect comparisons of placebo-controlled randomized controlled trials suggest that etanercept is statistically significantly more efficacious than abatacept, anakinra, infliximab, and

tocilizumab (range of relative risks from 2.31 to 3.30). No statistically significant differences in efficacy could be detected among adalimumab, anakinra, infliximab, and tocilizumab. The strength of evidence was low, except for the comparison of etanercept with infliximab for which the strength of evidence was moderate.

Data were too heterogeneous to conduct indirect comparisons of certolizumab pegol, golimumab, and rituximab with other targeted immune modulators.

Good to fair evidence was found from meta-analyses and large randomized controlled trials that abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab are statistically significantly more efficacious than placebo for the treatment of rheumatoid arthritis. Treatment effects were large and consistent across studies.

Study populations and outcome measures

All patients suffered from active rheumatoid arthritis and most randomized controlled trials employed the American College of Rheumatology criteria[4,47] 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 nonsteroidal anti-inflammatory drugs or oral corticosteroids in addition to the study medication. The majority of trials enrolled patients who had failed at least one disease-modifying antirheumatic drug treatment or were on a stable dose of methotrexate with unsatisfactory response. Some studies enrolled populations that had also failed an antitumor necrosis factor drug. 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 D). 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 modulator treatment. Because these studies included unselected populations, findings were probably more applicable to the average rheumatoid arthritis patient than results from efficacy trials. Limitations with respect to risk of bias have to be kept in mind though.

Sponsorship

All trials were funded by the pharmaceutical industry. Meta-analyses and cohort studies usually had public or a mix of public and industry funding. Some meta-analyses reported no external funding.

Detailed assessment: Direct evidence on comparative effectiveness

Overall, we included eight head-to-head studies comparing one targeted immune modulator to another.[39-45,48] 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 6.

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.[39] This study enrolled 431 patients and randomized them to abatacept (10 mg/kg every 4 weeks + methotrexate), infliximab (3 mg/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 statistically significant differences in efficacy were obvious between treatments at 6 months (DAS 28: abatacept –2.53, infliximab –2.25; *P*=NR). At 1 year, however, significantly more patients on abatacept than on infliximab achieved American College of Rheumatology 20 response (American College of Rheumatology 20 response 72.4 compared with 55.8%; *P*=NR); American College of Rheumatology 50/70 responses were numerically greater for patients on abatacept than infliximab but differences did not reach statistical significance (American College of Rheumatology 50 response 45.5 compared with 36.4%; *P*=NR; American College of Rheumatology 70 response 26.3 compared with 20.6 %; *P*=NR). 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 a good[44] and a fair[45] observational study. Both studies were based on national registers of targeted immune modulators (the Danish DANBIO [Danish Biological] and the Dutch DREAM [Dutch Rheumatoid Arthritis Monitoring]) and were conducted prospectively in primary care based populations. Both studies enrolled patients who had failed at least one conventional disease-modifying antirheumatic drug and were started on a targeted immune modulator. The choice of the treatment and dosing was at the discretion of the treating rheumatologist. Overall, 356 patients were followed up for 12 months in the study based on the DREAM register,[44] and 969 patients in the study based on the DANBIO register.[45]

After 12 months of follow-up, treatment responses in both studies were similar for patients on adalimumab and etanercept. The primary outcome of the DREAM study was the DAS28 course over a 12 months follow-up, as analyzed on an intent-to-treat basis.[44] 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).[44] Results of the DANBIO study were not based on an intent-to-treat principle (patients who withdrew from treatment before 6 months were excluded). Results, however, also presented similar effectiveness between adalimumab and etanercept. The LUNDEX corrected ([fraction of starters still in the study after given months] x [fraction responding at given months]) American College of Rheumatology 50 response was 35% for adalimumab and 32% for etanercept after 12 months.[45] Discontinuation rates in both studies were similar in patients on

adalimumab and etanercept (e.g., 22% compared with 21% in the study based on the DREAM register; *P*=NR[44]).

Adalimumab compared with infliximab

The same prospective cohort studies based on the DREAM and the DANBIO registers described above also compared the effectiveness of adalimumab with infliximab.[44,45] In both studies, patients treated with adalimumab had statistically significantly better response rates after 12 months of follow-up than patients treated with infliximab. For example, in the DREAM study (N=418), patients on adalimumab had statistically significantly greater 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) than patients on infliximab.[44] Likewise, in the Danish DANBIO study (n=1452), 35% of patients treated with adalimumab achieved a LUNDEX-corrected American College of Rheumatology 50 response at 12 months, compared with 25% of patients on infliximab (*P*<0.001).[45]

During the 12 months follow-up, discontinuation rates in both studies were statistically significantly higher in patients on infliximab than on adalimumab (e.g., DREAM register: 31% compared with 22%; *P*<0.049).[44]

Etanercept compared with infliximab

The only study for this comparison with a randomized allocation of interventions was a fair, small (n=32) open-label randomized controlled trial that compared etanercept (25 mg twice weekly) with infliximab (3 mg/kg, weeks 0, 2, 6, and every 2 months).[41] 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 the Health Assessment Questionnaire (–32.30 compared with –21.60; *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 response rates. It has to be noted that in this study the dosage of infliximab (3mg/kg) was lower than the recommended regimen (5 mg/kg). Therefore, results have to be interpreted cautiously.

In addition we identified six observational studies[42-46,48] and one nonrandomized trial.[40] With respect to the comparative effectiveness of etanercept and infliximab, these studies reported similar findings as the head-to-head trial mentioned above.

For example, in the nonrandomized, 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 statistically 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.[40] Comparisons at other time points, generally favored etanercept over infliximab although most differences failed to achieve statistical significance, which is probably attributable to a lack of power.

Some of the six observational studies were based on data collected for registries in Denmark,[45] the Netherlands,[44] Sweden,[43] the United Kingdom,[48] and the United States.[42] 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 and sometimes statistically significantly greater response rates than infliximab after up to 3 years of follow-up.

The largest of these observational studies was a prospective cohort study based on the Rheumatoid Arthritis DMARD Intervention and Utilization Study program.[42] 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 good retrospective cohort study did not meet our eligibility criteria; nevertheless we presented findings because this study was the only one that compared radiographic progression between etanercept and infliximab.[49] 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 less 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 two targeted immune modulators.[50,51] 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.[50] 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 (25 mg twice weekly) compared with abatacept (2 mg/kg) monotherapy reached similar conclusions.[51] The combination was associated with increased serious adverse events but only limited additional clinical benefit.

Table 6. 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[39]	RCT	431	12 months	Abatacept vs. infliximab	DAS 28	ACR 20/50/70, HAQ, SF-36	Active RA for at least 1 year; had failed methotrexate treatment; mean disease duration: 7.9 years	Greater response rates with abatacept than with infliximab at study endpoint	Fair
Adalimumab compared with etanercept									
Hetland et al, 2010[45]	Prospective cohort study (DANBIO registry)	969	12 months	Adalimumab vs. etanercept	ACR 70	EULAR, DAS28	Population-based; active RA; started a biologic; mean disease duration: 8.5 years	Treatment response similar for adalimumab and etanercept	Fair
Kievit et al., 2008[44]	Prospective cohort study (DREAM registry)	556	12 months	Adalimumab vs. etanercept	DAS 28	SF-36	Population-based; active RA; started a biologic; mean disease duration: 6.5 years	DAS 28 and SF-36 physical component statistically similar between adalimumab and etanercept	Good
Adalimumab compared with infliximab									
Hetland et al, 2010[45]	Prospective cohort study (DANBIO registry)	1452	12 months	Adalimumab vs. infliximab	ACR 70	EULAR, DAS28	Population-based; active RA; started a biologic; mean disease duration: 8.5 years	Statistically significantly better response rates on ACR and EULAR for adalimumab than infliximab	Fair
Kievit et al., 2008[44]	Prospective cohort study (DREAM registry)	418	12 months	Adalimumab vs. infliximab	DAS 28	SF-36	Population-based; active RA; started a biologic; mean disease duration: 6.5 years	Improvements on DAS 28 and SF-36 physical component statistically significantly better for adalimumab than for infliximab	Good
Etanercept compared with infliximab									
De Filippis et al, 2006[41]	Open-label randomized controlled trial	32	12 months	Etanercept vs. Infliximab	ACR 20	ACR 50/70, HAQ	Active RA for at least 2 years; had failed methotrexate treatment; mean disease duration: NR	ACR response rates and HAQ higher for etanercept than for infliximab at 12 months	Fair
Fernandez-Nebro et al., 2007[46]	Prospective cohort study	139	6 months	Etanercept vs. infliximab	DAS 28, EULAR	HAQ	Active RA ; had failed DMARD treatment; mean disease duration: 9.7 years	DAS 28 was statistically significantly better for etanercept than infliximab	Fair
Geborek et al. 2002[40]	Non-randomized trial	301	12 months	Etanercept vs. infliximab	ACR 20/50	DAS28	Population-based; active RA; had failed at least 1 DMARD treatment; mean disease duration: 14.5 years	ACR 20 response rates statistically significantly greater for etanercept than for infliximab at 3 months and 6 months ; no differences at 12 months	Fair
Hetland et al, 2010[45]	Prospective cohort study (DANBIO register)	1333	12 months	Etanercept vs. infliximab	ACR 70	EULAR, DAS28	Population-based; active RA; started a biologic; mean disease duration: 8.5 years	Statistically significantly better response rates on ACR and EULAR for etanercept than infliximab	Fair
Hyrich et al, 2006[48]	Prospective cohort study (UK registry)	3694	6 months	Etanercept vs. infliximab	EULAR	DAS 28	Population-based; active RA; started a biologic; mean disease duration: 14.6 years	EULAR response rates numerically greater for etanercept than for infliximab at 6 months	Fair

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Kievit et al., 2008[44]	Prospective cohort study (DREAM registry)	440	12 months	Etanercept vs. infliximab	DAS 28	SF-36	Population-based; active RA; started a biologic; mean disease duration: 6.5 years	DAS 28 and SF-36 physical component statistically significantly better for etanercept than infliximab (*P*<0.001)	Good
Kristensen et al. 2006[43]	Prospective cohort study (Swedish registry)	949	3 years	Etanercept vs. infliximab	EULAR	ACR 20/50/70	Population-based; active RA; started a biologic; mean disease duration: 13.4 years	Moderate EULAR and ACR response rates numerically greater for etanercept than for infliximab at 3 years	Fair
Weaver et al. 2006[42]	Prospective cohort study (US registry)	3694	12 months	Etanercept vs. infliximab	ACR 20	HAQ	Primary-care based; active RA; patients who needed change in treatment regimen; mean disease duration: NR	ACR 20 response rates numerically greater for etanercept than for infliximab at 12 months	Fair
Combination strategies									
Genovese et al., 2004[50]	RCT	242	24 weeks	Etanercept + methotrexate vs. etanercept + anakinra + methotrexate	ACR 50	ACR 20/70, SF-36	> 6 months history of active RA; stable methotrexate regimen; mean disease duration: 10 years	No additional benefit from etanercept-anakinra combination therapy; Adverse events rates statistically significantly higher in combination than in etanercept group	Fair
Weinblatt et al., 2007[51]	RCT	121	6 months	Abatacept + etanercept vs. etanercept	ACR 20	ACR 50/70, HAQ	Chronic RA: on etanercept for at least 3 months; mean disease duration: 12.9 years	No additional benefit from abatacept-etanercept combination therapy; Adverse events rates statistically significantly higher in combination than in abatacept group	Fair

Abbreviations: ACR 20/50/70, American College of Rheumatology, numbers refer to percentage improvement; ASHI, arthritis-specific health index; DAS28, disease activity score28; DANBIO, Danish Biological; DMARD, disease-modifying antirheumatic drug; DREAM, Dutch Rheumatoid Arthritis Monitoring; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; 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 indirect comparisons based on metaregressions of placebo-controlled trials to compare the treatment effects of individual targeted immune modulators. We included data from published studies or from the US Food and Drug Administration Center for Drug Evaluation Research website. For all analyses we used only data derived from study arms at or near the recommended dosage. We limited analyses to comparisons of targeted immune modulators in combination with methotrexate compared with methotrexate monotherapy. We excluded treatment arms of targeted immune modulators without concomitant methotrexate.

Our population of interest for indirect comparisons was patients who had active arthritis despite treatment with a disease-modifying antirheumatic drug. We excluded studies from indirect comparisons that enrolled patients who were disease-modifying antirheumatic drug-naïve or who had failed a trial with an antitumor necrosis factor drug. We also excluded studies that switched patients from the placebo group to the active treatment if they had an unsatisfactory response at a specific point in time during the study.

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 eight tender joints at baseline would need to have fewer than six swollen and four tender joints at the trial endpoint. This would be accompanied by at least a 50% improvement in at least three of the following five 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 indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[52] 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 studies with duration of between 3 and 12 months. Sensitivity analyses based on different study durations did not substantially change the point estimates of the treatment effect.

Results of indirect comparisons are depicted in Figure 2. Findings suggested that no substantial differences in efficacy exist among abatacept, adalimumab, anakinra, and infliximab. Given the wide confidence intervals, however, clinically significant differences could not be excluded with certainty.

Findings of indirect comparisons also suggest that etanercept is statistically significantly more efficacious than abatacept, adalimumab, anakinra, and infliximab (Figure 2; range of relative risks, 2.31 to 3.30). For these analyses, we have excluded a landmark trial on etanercept, namely the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study.[53,54] We excluded the TEMPO study because it enrolled a mixed population of methotrexate-naive patients (about 57%) and patients who had been on prior methotrexate treatment. Patients who had either failed prior methotrexate treatment or experienced toxic effects were also excluded from this study. As a consequence of the large proportion of methotrexate-naïve patients, more than 40% of patients achieved an American College of Rheumatology 50 response in the methotrexate control group. This percentage was substantially higher than in other etanercept studies (American College of Rheumatology 50 response in the methotrexate monotherapy group ranges from 3% to 10%).

In a sensitivity analysis including the TEMPO trial, etanercept did not have a statistically significant advantage in American College of Rheumatology 50 response rates compared with other targeted immune modulators (Figure 3).

The evidence on certolizumab pegol, golimumab, and rituximab was insufficient or too heterogeneous to be included for indirect comparisons.

Using information from placebo-controlled trials, multiple research groups used various statistical models to produce indirect comparisons of treatment effects of targeted immune modulators.[55-63] Most of these studies included the TEMPO trial and concluded that antitumor necrosis factor drugs have similar efficacy. One study reported that antitumor necrosis factor drugs as a class have a greater probability of achieving American College of Rheumatology 50 response than abatacept (odds ratio, 1.52; 95% CI, 1.0 to 6.37).[59]

A good British health technology assessment determined the comparative efficacy and safety of targeted immune modulators in patients with rheumatoid arthritis who have failed an antitumor necrosis factor drug.[61]An indirect comparison rendered no differences in efficacy between abatacept and rituximab. Data were insufficient to conduct other indirect comparisons.

Credible or confidence intervals of most indirect comparisons, however, were wide leading to inconclusive results without statistical significance. Results of studies employing indirect comparisons, therefore, must be interpreted cautiously because clinically significant differences among targeted immune modulators cannot be ruled out with certainty. Table 7 summarizes studies that conducted indirect comparisons.

Figure 2. Adjusted indirect comparisons of targeted immune modulators for American College of Rheumatology 50 response

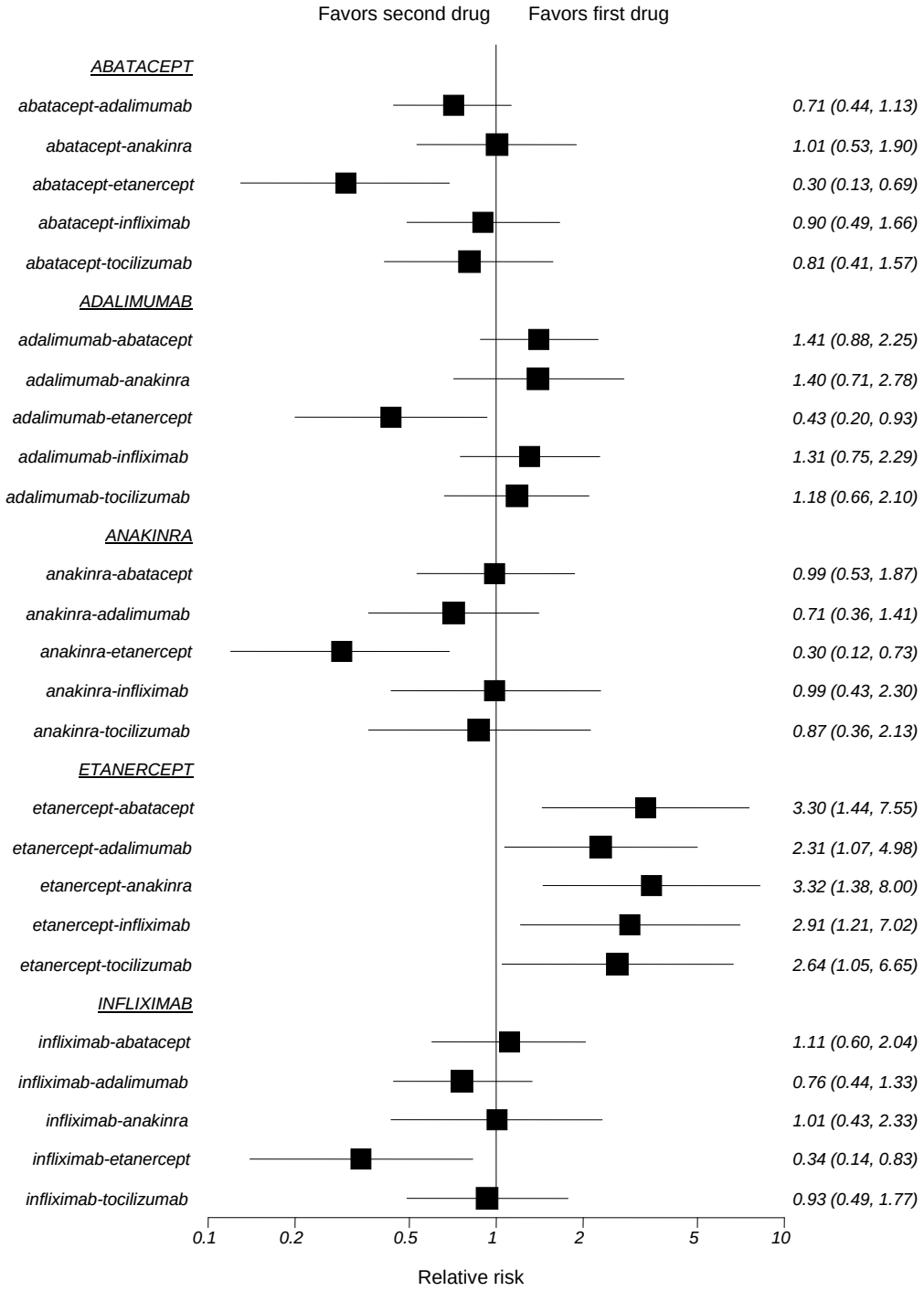


Figure 3. Adjusted indirect comparisons of etanercept including the TEMPO study for American College of Rheumatology 50 response

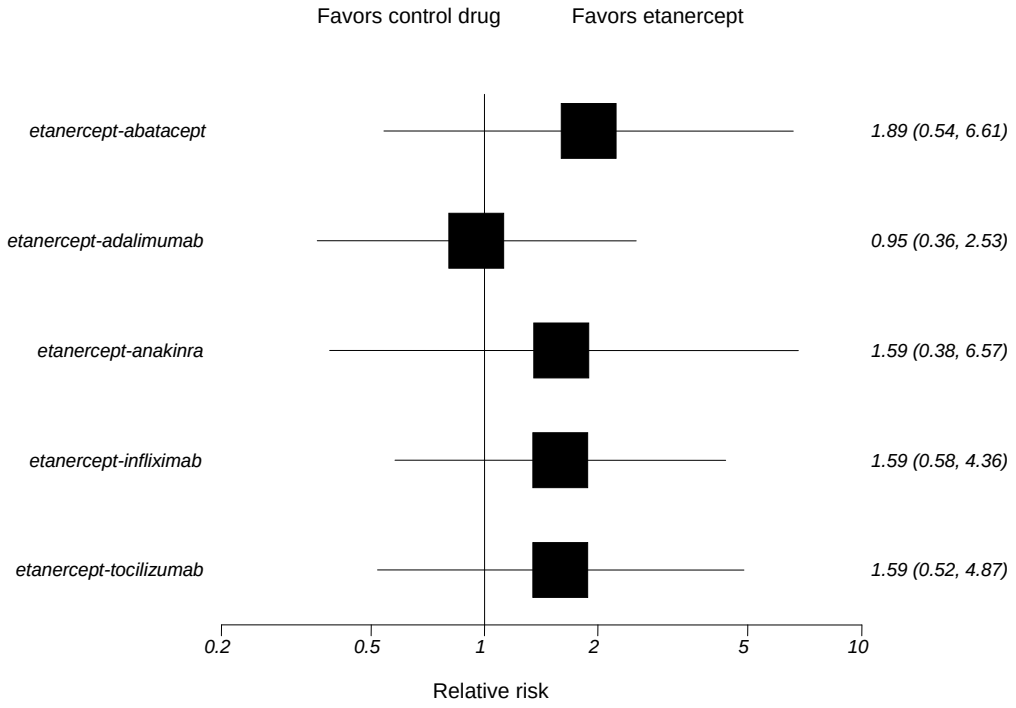


Table 7. Characteristics and results of studies conducting indirect comparisons

Author Year	Comparisons	Primary outcome	Conclusion	Rating
Devine, et al., 2011[60]	Certolizumab pegol, adalimumab, etanercept, golimumab, infliximab, rituximab, tocilizumab	ACR 50	Similar efficacy among targeted immune modulators	Fair
Launois, et al., 2011[58]	Certolizumab pegol, adalimumab, etanercept, golimumab, infliximab, tocilizumab	ACR 20/50/70	Numerically higher ACR 50 response rates for certolizumab pegol than for comparators	Fair
Lee, et al. 2008[56]	Adalimumab, etanercept, infliximab	ACR 20/50,70, withdrawal	Adalimumab and infliximab are more efficacious than etanercept	Fair
Malottki, et al., 2011[61]	Abatacept, adalimumab, etanercept, infliximab, rituximab	ACR 20/50,70, withdrawal	No differences in efficacy between abatacept and rituximab in patients who have failed prior anti-TNF treatment	Good
Nixon, et al., 2007[55]	Adalimumab, anakinra, etanercept, infliximab	ACR 20/50, HAQ	Anakinra is the least effective therapy. No differences among anti-TNF drug in efficacy	Fair
Salliot, et al., 2011[59]	Abatacept, certolizumab pegol, adalimumab, etanercept, golimumab, infliximab, rituximab, tocilizumab	ACR 50	Similar efficacy except anti-TNF drugs as a class have higher ACR 50 response rates than abatacept	Good
Schmitz, et al. 2011[63]	Certolizumab pegol, adalimumab, etanercept, golimumab, infliximab	ACR 20, ACR 50, HAQ	Etanercept superior to infliximab and golimumab; certolizumab pegol superior to infliximab and adalimumab	Fair
Singh, et al., 2010[57]	Certolizumab pegol, adalimumab, etanercept, golimumab, infliximab, rituximab	ACR 50	Similar efficacy, except anakinra was less efficacious than adalimumab and etanercept	Fair
Turkstra, et al., 2011[62]	Abatacept, adalimumab, anakinra, certolizumab pegol; etanercept, golimumab, infliximab, rituximab, tocilizumab	ACR 20/50/70	Certolizumab pegol and etanercept might be more efficacious than other drugs; anakinra is the least efficacious	Fair

Abbreviations: ACR, American College of Rheumatology 20/50/70; TNF, tumor necrosis factor.

Detailed assessment: Evidence on the general efficacy

Multiple placebo-controlled randomized controlled trials and meta-analyses provided evidence on the general efficacy of abatacept,[64-73] adalimumab,[74-86] anakinra,[87-92] certolizumab pegol,[93-98] etanercept,[48,53,54,76,99-109] golimumab,[110-113]infliximab,[76,114-127] rituximab,[128-135] and tocilizumab.[136-142] Most of these studies were conducted in patients who had failed synthetic disease-modifying antirheumatic drug treatment.

In the following section, 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 reported the pooled estimates but did not describe the results of individual component studies, except when outcome measures of interest were reported (e.g., quality of life, functional capacity) that were not quantitatively analyzed in a meta-analysis. Table 8 summarizes studies included for general efficacy.

Abatacept

A well-conducted systematic review and meta-analysis of seven randomized controlled trials including 2908 patients treated with abatacept or placebo reported statistically significantly higher American College of Rheumatology 50 response rates for patients on abatacept (relative risk, 2.21; 95% CI, 1.73 to 2.82) after 12 months of treatment.[64] The number needed to treat to achieve American College of Rheumatology 50 response was 5 (95% CI, 4 to 7). Patients treated with abatacept also showed statistically significant improvement in pain, physical function, and disease activity.

Adalimumab

Two well-conducted meta-analyses examined the efficacy of adalimumab in patients with rheumatoid arthritis.[75,76] Overall these studies included data on more than 2800 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 one additional responder on American College of Rheumatology 20/50/70 were 5, 5, and 7, respectively.[76] A placebo-controlled trial (n=47) conducted in Asian patients reported similar findings.[74]

Anakinra

We identified one recent high-quality meta-analyses on the general efficacy of anakinra.[88] The study included information on 2876 patients.[88] 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, and Patient Global Assessment). The numbers needed to treat to achieve one additional responder on American College of Rheumatology 20/50/70 were 8, 9, and 22, respectively. A placebo controlled trial (n=54) conducted in Asian patients reported similar findings.[143]

Certolizumab pegol

A good systematic review and meta-analysis of five randomized controlled trials including almost 2400 patients treated with certolizumab pegol or placebo reported statistically significantly higher American College of Rheumatology 50 response rates for patients on certolizumab pegol (relative risk, 2.6; 95% CI, 1.3 to 4.9) than placebo after a mean follow-up of 24 weeks.[93] The number needed to treat to achieve American College of Rheumatology 50 response was 4 (95% CI, 3 to 5). Patients treated with certolizumab pegol were also statistically significantly more likely to achieve remission (odds ratio, 3.88; 95% CI, 2.33 to 6.45) or improvement in quality of life.

Two studies, included in the systematic review above, also reported on work productivity and work days missed because of rheumatoid arthritis.[94,95] In the RAPID (Rheumatoid Arthritis Prevention of Structural Damage) 1 and RAPID 2 trials, patients on certolizumab pegol had statistically significantly greater work productivity and statistically significantly fewer work days missed due to rheumatoid arthritis than those on placebo.[144]

Etanercept

Two good meta-analyses examined the efficacy of etanercept in patients with rheumatoid arthritis.[75,145] Findings showed statistically significantly greater American College of Rheumatology 50 response rates after 6 months for patients treated with etanercept than placebo

(relative risk, 5.28; 95% CI, 3.12 to 8.92). The numbers needed to treat to achieve 1 additional responder on American College of Rheumatology 20/50 were 6 and 6, respectively.[76]

One trial compared etanercept to methotrexate over 52 weeks in patients with early active disease.[102] 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 statistically 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.[103]

Golimumab

A good systematic review and meta-analysis of four randomized controlled trials including more than 1700 patients treated with golimumab or placebo reported statistically significantly higher American College of Rheumatology 50 response rates for patients on golimumab (relative risk, 2.6; 95% CI, 1.3 to 4.9) than placebo after 14 to 24 weeks of treatment.[110] The number needed to treat to achieve American College of Rheumatology 50 response was 5 (95% CI, 2 to 20). Patients treated with golimumab were also statistically significantly more likely to achieve remission (relative risk, 5.12; 95% CI, 1.34 to 4.94) or improvement in physical function and disease activity.

Infliximab

Four well-conducted meta-analyses determined the general efficacy of infliximab in rheumatoid arthritis.[76,127,146,147] Pooled results of these studies reported statistically 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 with 5% for placebo. The number needed to treat to achieve one additional response was 4.

Rituximab

Four fair-quality studies assessed the general efficacy of rituximab for the treatment of patients with disease-modifying antirheumatic drug resistant rheumatoid arthritis.[128,130,132-135] All five trials reported statistically significantly better efficacy outcomes for rituximab- than for placebo treated patients. For example, 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%; $P<0.0001$).[132-134] 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%; $P<0.001$).

Tocilizumab

Two systematic reviews, one good[148] and one fair[149] quality, confirmed the general efficacy of tocilizumab for the treatment of patients with rheumatoid arthritis. The good systematic review included eight randomized controlled trials which were conducted in clinically heterogeneous populations.[148] Some of the included studies enrolled patients with active rheumatoid arthritis despite methotrexate treatment, others included patients who had also failed antitumor necrosis factor drug treatment. Patients received 8 mg/kg or 4 mg/kg of intravenous tocilizumab every 4

weeks, or placebo. Pooled estimates showed statistically significantly greater response (American College of Rheumatology 50 response: relative risk, 3.17, 95% CI, 2.72 to 3.67) and remission rates (DAS28: 8.74; 95% CI, 6.26 to 11.8) of patients treated with tocilizumab than placebo. The number needed to treat to achieve one additional responder on American College of Rheumatology 50 was 5.[148] Similarly, quality of life (Health Assessment Questionnaire) was also statistically significantly better in patients on tocilizumab).

Table 8. Studies included for general efficacy in rheumatoid arthritis

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ABATACEPT									
Maxwell et al., 2009[64]	MA	2908	12 months	Abatacept + methotrexate vs. placebo + methotrexate	ACR 50	Pain, HAQ, adverse events	Patients with active RA	Statistically significantly greater improvements on all outcome measures for abatacept	Good
ADALIMUMAB									
Alonso-Ruiz et al. 2008[76]	MA	2869	Varying	Adalimumab + methotrexate vs. placebo + methotrexate	ACR 20/50/70	Withdrawals	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates statistically significantly greater with adalimumab than with placebo	Good
Chen et al., 2009[74]	RCT	47	12 weeks	Adalimumab + methotrexate vs. placebo + methotrexate	Number of swollen joints	ACR 20/50/70,pain, HAQ	Active RA; had failed at least 1 DMARD treatment	Statistically significantly fewer swollen joints with adalimumab than with placebo	Fair
Wiens et al., 2010[75,86]	MA	2691	Up to 52 weeks	Adalimumab + methotrexate vs. placebo + methotrexate	ACR 20/50/70	Safety	Active RA; had failed at least 1 DMARD treatment; mean disease duration: NR	ACR 20/50/70 response rates statistically significantly greater with adalimumab than with placebo	Fair
ANAKINRA									
Bao et al., 2011[143]	RCT	54	24 weeks	Anakinra + methotrexate vs. placebo + methotrexate	ACR20	ACR50/70	Active RA; had failed methotrexate treatment; mean disease duration: NR	ACR 20/50/70 response rates statistically significantly greater with anakinra than with placebo;	Fair
Mertens et al. 2009[88]	MA	2876	6 mo	Anakinra + methotrexate vs. placebo + methotrexate	ACR 20/50/ 70	HAQ, withdrawals	Adults with RA	ACR 20/50/70 response rates statistically significantly greater with anakinra than with placebo;	Good

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
CERTOLIZUMAB PEGOL									
Ruiz Garcia et al., 2011[93]	MA	2394	Mean 24 weeks	Certolizumab pegol + methotrexate vs. placebo + methotrexate	ACR 50	ACR 20, DAS20, HAQ	Active RA; had failed at least 1 DMARD treatment	Response and remission rates statistically significantly greater with certolizumab pegol than with placebo	Good
ETANERCEPT									
Alonso-Ruiz et al. 2008[76]	MA	1637	Varying	Etanercept + methotrexate vs. placebo + methotrexate	ACR 20/50/70	Withdrawals	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates statistically significantly greater with etanercept than with placebo	Good
Bathon et al. 2000[102-104]	RCT	632	52 weeks	Etanercept vs. methotrexate	ACR 20/50/ 70	SF-36, HAQ, ACR-N, modified Sharp	early, active RA; mean disease duration: 1 year.	Up to 6 months statistically significantly higher ACR 50/70 response rates for etanercept than for methotrexate; no differences after. At 12 months no differences in ACR 20 but less joint erosion for etanercept; no statistically significant differences in SF-36, HAQ, and ASHI scores	Fair
Wiens et al., 2010[75,145]	MA	1612	Up to 52 weeks	Etanercept + methotrexate vs. placebo + methotrexate	ACR 20/50/70	Safety	Active RA; had failed at least 1 DMARD treatment; mean disease duration: NR	ACR 20/50 response rates statistically significantly greater with etanercept than with placebo	Fair

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
GOLIMUMAB									
Singh et al., 2010[110]	MA	1714	14-24 weeks	Golimumab + methotrexate vs. placebo + methotrexate	ACR 50	DAS 28, safety	Patients with active RA	ACR 50 response, remission, reduction in disease activity significantly better with golimumab	Good
INFLIXIMAB									
Alonso-Ruiz et al. 2008[76]	MA	2581	Varying	Infliximab + methotrexate vs. placebo + methotrexate	ACR 20/50/70	Withdrawals	Active RA; had failed at least 1 DMARD treatment	ACR 20/50/70 response rates statistically significantly greater with infliximab than with placebo	Good
Wiens et al., 2010[75,127]	MA	2100	Up to 52 weeks	Infliximab + methotrexate vs. placebo + methotrexate	ACR 20/50/70	Safety	Active RA; had failed at least 1 DMARD treatment; mean disease duration: NR	ACR 20/50/70 response rates statistically significantly greater with infliximab than with placebo	Fair
RITUXIMAB									
Cohen et al. 2006 (REFLEX)[132-134]	RCT	520	24 weeks	Rituximab + methotrexate vs. placebo + methotrexate	ACR 20	ACR 50/70, DAS 28, HAQ SF-36	Active RA; had failed antitumor necrosis factor therapy; mean disease duration: 11.9 years.	ACR 20/50/70 response rates and DAS-28 scores were statistically significantly greater with rituximab + methotrexate than with methotrexate	Fair

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Edwards et al. 2004[128,129]	RCT	161	24 weeks	Rituximab + methotrexate vs. rituximab + placebo vs. rituximab + cyclophosphamide vs. methotrexate + placebo	ACR 50	ACR 20/70, DAS28	Active RA; had failed at least 1 DMARD treatment; mean disease duration: 10.5 years.	ACR 20/50/70 response rates and DAS28scores were statistically significantly greater with rituximab + methotrexate than with methotrexate + placebo	Fair
Emery et al. 2006 (DANCER)[130]	RCT	465	24 weeks	Rituximab (500 mg) + methotrexate vs. rituximab (1000 mg) + methotrexate vs. methotrexate + 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 years.	ACR 20/50/70 response rates and DAS28 scores were statistically significantly greater with rituximab + methotrexate than with methotrexate + placebo	Fair
Emery, et al., 2010 (SERENE)[135]	RCT	511	24 weeks	Rituximab (500 mg) + methotrexate vs. rituximab (1000 mg) + methotrexate vs. methotrexate + placebo	ACR 20	ACR 50/70, DAS28, HAQ-DI	Active RA; had failed at least 1 DMARD; mean disease duration: 7.1 years.	ACR 20/50/70 response rates and DAS28 scores were statistically significantly greater with rituximab + methotrexate than with methotrexate + placebo	Fair

Author Year	Study design	Number	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
TOCILIZUMAB									
An et al., 2010[149]	MA	2,691	Up to 24 weeks	Tocilizumab (4 mg/kg or 8 mg/kg) + methotrexate vs. placebo	ACR 20/50/70	NR	Active RA despite DMARD treatment	ACR 20/50/70 response rates were statistically significantly greater with tocilizumab + methotrexate than with methotrexate + placebo	Fair
Singh et al., 2010[148]	MA	3334	Up to 24 weeks	Tocilizumab + methotrexate vs. placebo + methotrexate	ACR 50	DAS 28, HAQ	Active RA despite DMARD or anti-TNF treatment	Significantly greater response and remission rates with tocilizumab	Good

Abbreviations: ACR 20/50/70, American College of Rheumatology, numbers refer to percentage improvement; ACR-N, numeric index of the American College of Rheumatology response; ASHI, arthritis-specific health index; DAS28, disease activity score; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; MA, meta-analysis; RA, rheumatoid arthritis; RCT, randomized controlled trial; RF, rheumatoid factor; SF-36, Medical Outcomes Study Short Form 36 Health Survey.

Juvenile Idiopathic Arthritis

Currently abatacept, adalimumab, etanercept, and tocilizumab 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 9). Five randomized controlled trials provided fair evidence that abatacept,[150,151] adalimumab,[152] etanercept,[153] infliximab,[154] and tocilizumab[155] are more efficacious than placebo for the treatment of juvenile idiopathic arthritis. Except for the infliximab trial, however, the highly selected study populations were 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 9.

Study populations and outcome measures

Patients suffered from active polyarticular juvenile idiopathic arthritis and were between 2 and 19 years of age. They had active disease despite treatment with corticosteroids and methotrexate. Patients with concurrent medical conditions were excluded from trials. One trial on the efficacy and safety of tocilizumab included only patients suffering from systemic-onset juvenile idiopathic arthritis.[155] 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 continue 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 three of the six 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 withdrawal trial rated as fair enrolled 190 patients between 6-17 years with active juvenile idiopathic arthritis who had failed at least one disease-modifying antirheumatic drug or an antitumor necrosis factor drug (adalimumab, etanercept, or infliximab).[150] After 4 months of an open-label run-in phase with abatacept 10 mg/kg, 122 patients were randomized to continuing abatacept treatment or placebo for 6 months. Patients who did not respond or adhere to treatment (American College of Rheumatology Pediatric 30 criteria for improvement) or who had intolerable adverse events (45% of the original population) were excluded from the randomized trial phase. This 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 three of six core response variables, with at least 30% improvement in no more than one variable. After 6 months statistically 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). In addition, this trial assessed the participation in daily activities and the health-related quality of life with the Child Health Questionnaire.[151] The questionnaire includes physical, emotional, and social aspects of quality of life as well as pain and sleep assessments. Contrary to the efficacy analysis about disease flare, the intent-to-treat principle was not applied for this outcome. This trial showed a high overall attrition (34%) and a high differential attrition (18% for abatacept and 50% for placebo) in the 6-month maintenance phase. An observed-cases analysis of this trial showed a nonsignificant increase in physical and in psychosocial aspects of quality of life in the abatacept group compared with the placebo group. Furthermore, no statistically significant differences between the abatacept and the placebo group were observed in sleep quality and in pain reduction. Patients randomized to abatacept experienced a higher gain in school days than patients in the placebo group (P=0.033).

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.[152] 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 withdrawal study rated as fair randomized 51 patients to etanercept (0.4 mg/kg twice weekly) or placebo.[153] After 4 months, statistically 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 controlled trial was preceded by an active run-in phase. Only patients who adhered to 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.[156] In this study, which did not meet our eligibility criteria for the evaluation of efficacy, 61% had a 50% improvement of symptoms at 3 months and 72% at 6 months. Patients in this analysis, however, 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 nonsystemic 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 (3 mg/kg) + methotrexate and placebo + methotrexate.[154] This was the only study conducted in pediatric patients that did not use a withdrawal design. After 14 weeks more patients on infliximab achieved the American College of Rheumatology Pediatric Scale 30 criteria for improvement compared with those patients on placebo 64% compared with 39%). Improvement according to this scale was the primary outcome measure of this study. This difference, however, did not achieve statistical significance ($P=0.12$). Similarly, patients on infliximab had a greater number of responses according to the American College of Rheumatology Pediatric Scale 50/70 than patients on placebo, without statistical significance.

Tocilizumab

One fair randomized controlled trial investigated the efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis.[155]

After a 6 week open-label active lead-in phase, 43 responders to treatment (out of 56 enrolled Japanese patients) were randomized to tocilizumab (8 mg/kg every 2 weeks) or placebo.[155] Methotrexate, ciclosporin, and other disease-modifying antirheumatic drugs as well as immunosuppressive drugs were not allowed throughout the study. After 12 weeks, 80% of the patients in the tocilizumab group and 17% of the patients in the placebo ($P<0.0001$) group maintained an American College of Rheumatology Pediatric Scale 30 response and C-reactive protein concentrations of less than 15 mg/L. Patients who fell below these criteria were withdrawn for rescue medication.

Table 9. 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[150,151]	Withdrawal RCT	122	6 months	Abatacept vs. placebo	Disease flare	Safety Quality of life	Active juvenile idiopathic arthritis; had failed at least 1 DMARD or antitumor necrosis factor drug; mean disease duration: NR	Significantly fewer patients on abatacept than on placebo experienced disease flare; no sign. Increase in quality of life but sign. Gain in school days for patients on abatacept	Fair
ADALIMUMAB									
Lovell et al., 2008[152]	Withdrawal RCT	133	4 months	Adalimumab vs. placebo	Disease flare	ACR Pedi 30/50/70	Active juvenile idiopathic arthritis; had failed at least 1 DMARD; mean disease duration: 3.8 years	Significantly fewer patients on adalimumab than on placebo experienced disease flare	Fair
ETANERCEPT									
Lovell et al., 2000[153]	Withdrawal RCT	51	4 months	Etanercept 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 methotrexate treatment; mean disease duration: 5.8 years.	Significantly fewer patients on etanercept than on placebo experienced disease flare	Fair
INFLIXIMAB									
Ruperto et al. 2007[154]	RCT	122	3.5 months	Infliximab + methotrexate vs. placebo + methotrexate	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 years	Numerically greater response for patients on infliximab than on placebo; no statistical significance	Fair
TOCILIZUMAB									
Yokota et al. 2008[155]	Withdrawal RCT	43	12 weeks	Tocilizumab vs. placebo	Disease flare base on ACR Pedi 30	CRP	Systemic-onset juvenile idiopathic arthritis, Japanese patients;	Significantly fewer patients on tocilizumab than on placebo experienced disease flare	Fair

Abbreviations: ACR Pedi, American College of Rheumatology Pediatric criteria; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug.

Ankylosing Spondylitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ankylosing spondylitis: adalimumab, etanercept, golimumab, and infliximab. We did not find any head-to-head trials of biologics for ankylosing spondylitis. We located one systematic review and meta-analysis that presented pooled results from nine randomized, placebo-controlled trials of adalimumab, etanercept, and infliximab.[157] In addition we located four randomized placebo-controlled trials that were not included in the systematic review as they have been published more recently: two assessed etanercept,[158,159] one assessed golimumab,[160] and one assessed infliximab.[161] We did not detect any studies on abatacept, alefacept, anakinra, certolizumab pegol, natalizumab, rituximab, tocilizumab, or ustekinumab. Included studies are presented in Table 10. We did not include studies on early ankylosing spondylitis (nonradiological axial spondyloarthritis).

Summary of the findings

No direct evidence on the comparative effectiveness of targeted immune modulators for the treatment of ankylosing spondylitis exists (Table 10). The strength of the evidence is insufficient. Good-to-fair evidence exists for the general efficacy of adalimumab, etanercept, golimumab, and infliximab compared with placebo.

In this section, we present evidence from one systematic review[157] that included two trials of adalimumab,[162,163] five trials of etanercept,[164-168] and two trials of infliximab.[169,170] In addition, we located four newer randomized placebo-controlled trials: two assessed etanercept,[158,159] one assessed golimumab,[160] and one assessed infliximab.[161] Overall, adalimumab, etanercept, golimumab, and infliximab are statistically significantly more efficacious than placebo for the treatment of ankylosing spondylitis. Treatment effects are large and consistent across studies.

Study populations and outcome measures

All patients suffered from active ankylosing spondylitis and were diagnosed based on the modified New York criteria.[171] Disease duration and concomitant treatments varied across studies. Most patients used nonsteroidal anti-inflammatory drugs in addition to the study medication. Most trials allowed corticosteroids and disease-modifying antirheumatic drugs as concomitant treatments.[158-161,165-168,172-174] Patients in two of the infliximab trials were permitted to take only nonsteroidal anti-inflammatory drugs in addition to the study drug.[169,170] One study examined the efficacy of infliximab in patients with severe ankylosing spondylitis.[169] 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.[175] This scale combines measures of global disease activity with functional capacity, pain, and acute phase laboratory parameters (see Appendix D). In addition, the Bath Ankylosing Spondylitis Disease Activity Index was frequently assessed.

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 attempted to provide indirect evidence on the comparative effectiveness of adalimumab, etanercept, and infliximab for adults with ankylosing spondylitis.[157] The analysis used results from 1611 patients with ankylosing spondylitis comparing adalimumab, etanercept, or infliximab compared with placebo. We excluded the adjusted indirect comparisons portion of the meta-analysis because of poor quality: the heterogeneity amongst the component studies was too high to provide reliable results. The strength of the evidence is insufficient.

Detailed assessment: Evidence on the general efficacy

Due to the lack of head-to-head trials, we reviewed placebo-controlled trials. We included one systematic review[157] that provided a meta-analysis of pooled results from two trials of adalimumab,[162,163] five trials of etanercept,[164-168] and two trials of infliximab.[169,170] In addition, we located four newer randomized placebo-controlled trials: two assessed etanercept,[158,159] one assessed golimumab,[160] and one assessed infliximab.[161] Overall, adalimumab, etanercept, golimumab, and infliximab were statistically significantly more efficacious than placebo for the treatment of ankylosing spondylitis.

We summarized evidence on the general efficacy of targeted immune modulators for the treatment of ankylosing spondylitis in Table 10. This, however, does not provide evidence on the comparative efficacy and tolerability of targeted immune modulators.

Adalimumab

We identified one high-quality meta-analysis on the general efficacy of adalimumab.[157] The study included information on two trials of adult patients with moderate-to-severe ankylosing spondylitis. Pooled results for 397 patients demonstrated greater rates of improvement for adalimumab compared with placebo on Assessment in Ankylosing Spondylitis 20, Assessment in Ankylosing Spondylitis 50, and Assessment in Ankylosing Spondylitis 70 at 12 weeks and 24 weeks (all $P<0.001$). Both the Assessment in Ankylosing Spondylitis 20% improvement and 70% improvement criterion were achieved more frequently in adalimumab patients than placebo (Assessments in Ankylosing Spondylitis 20 relative risk, 2.43; 95% CI, 1.76 to 3.35; Assessments in Ankylosing Spondylitis 70 relative risk, 5.47; 95% CI, 2.43 to 12.31).

Etanercept

We identified one high quality meta-analysis on the general efficacy of etanercept.[157] The study included information on five trials of adult patients with ankylosing spondylitis.[164-168] Pooled results from the four trials of 12 weeks duration (total of 602 patients)[165-168] showed that etanercept was superior to placebo for Assessment in Ankylosing Spondylitis 20 (relative risk, 2.13; 95% CI, 1.73 to 2.63), Assessment in Ankylosing Spondylitis 50 (relative risk, 3.53; 95% CI, 2.50 to 4.98), and Assessment in Ankylosing Spondylitis 70 (relative risk, 3.38; 95% CI, 2.10 to 5.45). Results of a recent randomized controlled trial of 83 patients conducted in Europe are consistent with the meta-analysis.[159]

One additional fair-quality study not included in the meta-analysis was conducted in 40 patients with active ankylosing spondylitis who were classified as being “work unstable” using

the Ankylosing Spondylitis Work Instability Scale.[158] Patients were randomized to 25 mg etanercept twice weekly or placebo and the change in their work stability measure was determined. Secondary outcomes included the Bath Ankylosing Spondylitis Disease Activity Index and quality of life measures, work participation, and hours of work lost. Etanercept was not statistically significantly different to placebo for any of the outcomes measured.

Golimumab

We identified one fair-quality randomized controlled trial of 356 adult patients with active ankylosing spondylitis who received either golimumab 50 mg, golimumab 100 mg, or placebo every 4 weeks for 24 weeks.[160] The patients were eligible to cross over from placebo to the active therapy or from 50 mg golimumab to the higher dose after 14 weeks if they had not experienced adequate improvement, and we presented the data for the period before crossover (i.e., up to 14 weeks). Significantly more patients in the golimumab groups achieved an Assessment in Ankylosing Spondylitis 20 response than in the placebo group (data for two active arms were pooled: relative risk of Assessment in Ankylosing Spondylitis 20 response at 14 weeks was 2.74, 95% CI, 1.78 to 4.22). Likewise, statistically significantly more patients in the golimumab arms experienced a Bath Ankylosing Spondylitis Disease Activity Index 50% response (data for active arms are pooled, relative risk, 2.74; 95% CI, 1.60 to 4.69). Patients who received golimumab in this trial also experienced an improvement in quality of life compared with placebo (SF-36 physical and mental component summary scores, $P<0.05$).

Infliximab

We identified one high-quality meta-analysis on the general efficacy of infliximab[157] and one newer randomized controlled trial of low-dose infliximab.[161] The systematic review included information on two trials of adult patients with ankylosing spondylitis.[169,170] Pooled results from 348 patients showed a relative risk of Assessment in Ankylosing Spondylitis 20 response at 12 weeks of 4.11 (95% CI, 2.62 to 6.44). This result should be interpreted with caution due to high statistical heterogeneity (I^2=76%). The relative risk of Assessment in Ankylosing Spondylitis 20 response in the third randomized controlled trial of 76 patients with active ankylosing spondylitis was 1.81 (95% CI, 1.02 to 3.22).[161] Nonetheless, response rates for Assessment in Ankylosing Spondylitis 50 at 12 weeks[161] and Assessment in Ankylosing Spondylitis 20 at 24 weeks[170] were consistent with infliximab being superior to placebo.

Table 10. 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[157]	SR and MA	397	12 weeks	Adalimumab / placebo	ASAS 20% improvement at 12 weeks	ASAS 50/70, BASDAI	Adults with AS	Response rates on ASAS 20/50/70 were statistically significantly greater for adalimumab than for placebo	Good
ETANERCEPT									
McLeod et al., 2007[157]	SR and MA	602	12-24 weeks	Etanercept / placebo	ASAS 20% improvement at 12 weeks	ASAS 50/70, BASDAI	Adults with AS	Response rates on ASAS 20/50/70 were statistically significantly greater for adalimumab than for placebo	Good
Barkham et al., 2010[158]	RCT	40	12 weeks	Etanercept (25 mg twice weekly) + standard treatment vs. placebo + standard treatment	Change in work instability (AS-WIS)	BASDAI, ASQoL, BASFI, work participation	Adults with AS and work unstable	No statistically significant differences in work instability of QoL between etanercept and placebo	Fair
Dougados et al., 2011[159]	RCT	83	12 weeks	Etanercept 50 mg once weekly vs. placebo	VAS, BASDAI, BASFI, BASMI	Pulmonary function tests	Adults with AS	Improvement in BASDAI statistically significantly greater for etanercept than placebo	Fair
GOLIMUMB									
Inman et al., 2008[160]	RCT	356	14 weeks	Golimumab 50 mg every four weeks, golimumab 100 mg every two weeks vs. placebo	ASA20	ASAS40, ASAS5/6, BASDAI, BASFI, back pain, night pain, sleep disturbance, QoL	Adults with AS	Response rate on ASA20 and BASDI50% statistically significantly better in golimumab compared with placebo	Fair
INFLIXIMAB									
McLeod et al., 2007[157]	SR and MA	348	Various	Infliximab / placebo	ASAS 20% improvement at 12 weeks	ASAS 50/70, BASDAI	Adults with AS	Response rates on ASAS 20//50/70 were statistically significantly greater for infliximab than for placebo	Good

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Inman et al., 2010[161]	RCT	76	12 weeks	Infliximab 3 mg/kg (low dose) vs. placebo	ASA20	ASAS40, ASAS50, ASAS70, BASDAI, BASFI, BASMI, QoL	Adults with AS	Response rates on ASAS 20//50/70 were statistically significantly greater for infliximab than for placebo	Fair

Abbreviations: AS, ankylosing spondylitis; ASAS 20/50/70, Assessment in Ankylosing Spondylitis 20/50/70% improvement; AS-WIS: Ankylosing Spondylitis Work Instability Scale; BASDAI, Bath AS Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; MA, Meta-analysis; QoL, quality of life; 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, infliximab, and golimumab.

We included two systematic reviews and meta-analyses that analyzed the same six trials of adalimumab, etanercept, and infliximab. The reviews provided comparisons between the three biologics using two different statistical methods of indirect comparisons.[176,177] In addition, we included four placebo-controlled randomized controlled trials assessing the efficacy of abatacept,[178] alefacept,[179] golimumab,[180] and ustekinumab.[181,182] The studies ranged in duration from 12 to 22 weeks. Finally, we included one open-label registry study of adalimumab, etanercept, and infliximab for data on quality of life.[183] We did not find any studies on anakinra, certolizumab pegol, natalizumab, rituximab, or tocilizumab. Included studies are presented in Table 11.

Summary of findings

No direct evidence from head-to-head randomized controlled trials on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in adults or children exists.

Two systematic reviews and meta-analyses conducted indirect comparisons of adalimumab, etanercept, and infliximab for the treatment of psoriatic arthritis in adults.[176,177] Both analyses suggested that the three treatments are more efficacious than placebo but no statistically significant differences among adalimumab, etanercept, and infliximab could be detected. One prospective observational registry study of 595 patients with psoriatic arthritis showed that adalimumab, etanercept, and infliximab have similar positive effects on quality of life.[183] The strength of the evidence for the comparative effectiveness of adalimumab, etanercept, and infliximab was low.

In addition, evidence indicated that alefacept combined with methotrexate is more efficacious than methotrexate alone[179] and that abatacept, golimumab, and ustekinumab are more efficacious than placebo.[178,180,181]

At this time there are no studies, placebo or head-to-head, that evaluate the use of targeted immune modulators in children with psoriatic arthritis (Table 11).

Table 11. 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
ABATACEPT									
Mease et al. 2011[178]	RCT	170	6 months	Abatacept 3-30 mg/kg vs. placebo	ACR 20	HOQ, SF-36, PASI	Active PsA despite DMARD therapy and one target skin lesion	Abatacept had statistically significantly better response than placebo for doses 10-30 mg/kg	Fair
ADALIMUMAB									
Saad et al. 2008[176]	SR and MA	413	12-24 weeks	Adalimumab + methotrexate vs. placebo + methotrexate	ACR 20/50/70 PsARC	PASI 50/75/90 SF-36, HAQ-DI	Adults with PsA	Adalimumab had statistically significantly better outcomes than placebo	Good
Rodgers et al., 2011[177]	SR and MA	982	12 weeks	Adalimumab + methotrexate vs. placebo + methotrexate	PsARC	ACR20	Adults with PsA	Adalimumab had statistically significantly better outcomes than placebo	Good
ALEFACEPT									
Mease et al. 2006[179]	RCT	185	24 weeks (12 weeks treatment, 12 weeks observation)	Alefacept + methotrexate vs. placebo + methotrexate	ACR 20	ACR 50/70, PASI, PGA	Active PsA; failed at least 1 DMARD; mean disease duration: NR	Alefacept had statistically significantly better ACR 20 than placebo	Fair
ETANERCEPT									
Saad et al. 2008[176]	SR and MA	265	12-24 weeks	Etanercept + methotrexate vs. methotrexate + placebo	ACR 20/50/70 PsARC	PASI 50/75/90	Adults with PsA	Etanercept had statistically significantly better outcomes than placebo	Good

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Rodgers et al., 2011[177]	SR and MA	982	12 weeks	Etanercept + methotrexate vs. placebo + methotrexate	PsARC	ACR20	Adults with PsA	Etanercept had statistically significantly better outcomes than placebo	Good
GOLIMUMAB									
Kavanaugh et al., 2009[180]	RCT	405	16 weeks	Golimumab vs. placebo	ACR20	ACR50/70, PsARC, DAS28, SF-36	Adults with PsA	Golimumab had statistically significantly better outcomes than placebo	Fair
INFLIXIMAB									
Saad et al. 2008[176]	SR and MA	304	12-24 weeks	Infliximab + methotrexate vs. placebo + methotrexate	ACR 20/50/70 PsARC	PASI 50/75/90	Adults with PsA	Infliximab had statistically significantly better outcomes than placebo	Good
Rodgers et al., 2011[177]	SR and MA	982	12 weeks	Infliximab + methotrexate vs. placebo + methotrexate	PsARC	ACR20	Adults with PsA	Infliximab had statistically significantly better outcomes than placebo	Good
USTEKINUMAB									
Gottlieb et al., 2009.[181,182]	RCT	146	12 weeks	ustekinumab vs. placebo	ACR 20	PASI 75, DLQI	Adults with PsA	Significantly more ustekinumab patients achieved ACR20 and DLQI than placebo	Fair

Abbreviations: ACR, American College of Rheumatology; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; MA, meta-analysis; 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.

Study populations and outcome measures

All patients suffered from active psoriatic arthritis. All trials consisted of patients who had previously failed a disease-modifying antirheumatic drug.

All trials assessed response rates as defined by the American College of Rheumatology. In addition, most 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 D. In addition, the Psoriasis Area and Severity Index was used in some 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.

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. One fair-quality prospective observational registry study from the United Kingdom (the British Society for Rheumatology Biologics Register) followed 596 psoriatic arthritis patients for 6 months and showed that adalimumab, etanercept, and infliximab have similar positive effects on quality of life.[183] For example, the mean improvements in Short Form 36 Health Survey mental component scale were: adalimumab 49.2 (standard deviation, 11.4); etanercept 48.7 (standard deviation, 12.2); and infliximab 48.6 (standard deviation, 10.9). There were no statistically significant differences between the groups after adjusting for baseline variables such as sex, age, and severity of disease.

Detailed assessment: Indirect evidence on the comparative effectiveness

Two systematic reviews provided indirect evidence on the comparative effectiveness of adalimumab, etanercept, and infliximab for adults with moderate to severe plaque psoriatic arthritis.[176,177] The reviews employed different statistical techniques for the indirect comparisons; however the same six trials and 982 patients were included in both reviews. Both methods of indirect comparison, adjusted indirect comparisons as proposed by Bucher[176] and Bayesian mixed treatment comparison,[177] suggested that the three treatments are all more efficacious than placebo but that no statistically significant differences between adalimumab, etanercept, and infliximab exist. Using Bayesian analysis one group of reviewers calculated the probability of a psoriatic arthritis response criteria response for each comparator: 59% for adalimumab (95% CI, 44 to 71), 71% for etanercept (95% CI, 57 to 83), and 80% for infliximab (95% CI, 67 to 89). The second review came to a similar conclusion using an adjusted indirect comparison approach: the relative risk of an American College of Rheumatology 20 response for adalimumab compared with etanercept was 0.63 (95% CI, 0.22 to 1.81), for adalimumab compared with infliximab was 0.60 (95% CI, 0.30 to 1.20), and for etanercept compared with infliximab was 0.96 (95% CI, 0.33 to 2.76).

Table 12 summarizes the study conducting indirect comparisons.

Table 12. Characteristics and results of studies conducting direct and adjusted-indirect comparisons

Author, year	Comparisons	Primary outcome	Conclusion	Quality
Saad et al., 2010[183]	Adalimumab, etanercept, infliximab	QoL	Adalimumab, etanercept, and infliximab have similar positive effects on quality of life	Fair
Saad et al., 2008[176]	Adalimumab, etanercept, infliximab	ACR and PsARC	No statistically significant differences between adalimumab, infliximab, and etanercept	Good
Rodgers et al., 2011[177]	Adalimumab, etanercept, infliximab	PsARC	No statistically significant differences between adalimumab, infliximab, and etanercept for probability of achieving PsARC response	Good

Abbreviations: ACR, American College of Rheumatology; PsARC, psoriatic arthritis response criteria; TIM, targeted immune modulator; QoL, quality of life.

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.

Abatacept

We identified one fair-quality 6-month randomized controlled trial of abatacept compared with placebo in 170 patients with chronic psoriatic arthritis and one target skin lesion greater than 2 cm in diameter.[178] All patients had failed prior therapy with a disease-modifying antirheumatic drug or another targeted immune modulator. Three doses of abatacept were used: 3 mg/kg, 10 mg/kg, or 30 mg/kg for two doses, followed by 10 mg/kg. Significantly more patients in the 30-10 mg/kg group and the 30 mg/kg group achieved the primary endpoint, an American College of Rheumatology 20 response, compared with the placebo group. American College of Rheumatology 20 response rates were 42% for the 30-10 mg/kg group, 48% for the 10 mg/kg group, 33% for the 3 mg/kg group, and 19% for the placebo group, respectively. Compared with placebo the differences for 30-10 mg/kg (P=0.022) and 10 mg/kg (P=0.0006) groups were statistically significant, but not the difference between placebo and the 3 mg/kg group (P=0.121).

Adalimumab

We identified two high quality meta-analyses that demonstrate the general efficacy of adalimumab.[176,177] Altogether, the reviews included information on 413 adult patients with psoriatic arthritis from trials of adalimumab compared with placebo. Pooled results presented statistically significantly greater improvements of adalimumab than placebo-treated patients on all included outcome measures. Patients who received adalimumab were more likely to achieve the Psoriatic Arthritis Response Criteria (relative risk, 2.33; 95% CI, 1.80 to 3.01) compared with placebo. Similarly, the adalimumab treated patients were more likely to achieve an

American College of Rheumatology 20 response (relative risk, 3.42; 95% CI, 2.08 to 5.63), American College of Rheumatology 50 (relative risk, 8.71; 95% CI, 4.30 to 17.66), or American College of Rheumatology 70 (relative risk, 15.75; 95% CI, 4.44 to 55.82) than the placebo treated patients (all $P<0.05$).

Alefacept

One fair-quality phase II trial reported on the use of alefacept in psoriatic arthritis.[179] The study included 185 patients suffering from moderate to severe psoriatic arthritis who had an inadequate response to methotrexate therapy. Patients were randomized to 15 mg of alefacept weekly or placebo for 12 weeks. The alefacept group had statistically significantly greater response rates on American College of Rheumatology 20 than the placebo group (54% compared with 23%; $P<0.001$. There were no statistically significant differences in the other outcomes including the American College of Rheumatology 50/70, Psoriasis Area and Severity Index, and Physician Global Assessment, although 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 two high-quality meta-analyses on the general efficacy of etanercept.[176,177] Both reviews pooled results from the same two trials of 265 adult patients with psoriatic arthritis. 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. Similarly, the etanercept treated patients were much more likely to reach an American College of Rheumatology 50 or 70 (relative risk, 10.68; 95% CI, 4.40 to 25.89 and relative risk, 14.75; 95% CI, 1.97 to 110.51, respectively) than the placebo-treated patients (all $P<0.05$).

The original publications of the two etanercept trials provided additional data on quality of life.[184,185] In both trials patients received 25 mg of etanercept twice weekly or placebo for 12 to 24 weeks.[184,185] Improvement in quality of life, as measured by the Health Assessment Questionnaire, was statistically significantly better for etanercept than placebo in both studies. Mean improvements were 83% in etanercept- compared with 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 ($P<0.0001$).

Golimumab

We identified one fair multi-center trial of 405 patients randomized to 50mg or 100mg of golimumab at weeks 0, 4, 8, 12, 16, and 20 compared with placebo.[180] Patients who failed to respond the therapy were eligible for escape at week 16 so we considered the results in the placebo-controlled phase up until week 14. Significantly more patients in the golimumab groups achieved the primary outcome of an American College of Rheumatology 20 response at week 14 (golimumab 50 mg 51%, golimumab 100 mg 45%, placebo 9%, $P<0.001$). Likewise, the improvement in the physical component summary score for the SF-36 instrument (which measures quality of life) were significantly better in both golimumab groups compared with

placebo (mean ± SD: golimumab 50 mg 6.53 ± 8.88, golimumab 100 mg 7.85 ± 9.55, and placebo 0.63 ± 7.68, $P<0.001$).[180]

Infliximab

We identified two high-quality meta-analyses on the general efficacy of infliximab.[176,177] Both reviews pooled the results for two trials of infliximab compared with placebo, with 304 patients. 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 (relative risk, 5.71; 95% CI, 3.53 to 9.25); American College of Rheumatology 50 (relative risk, 14.73; 95% CI, 5.11 to 42.43); or American College of Rheumatology 70 (relative risk, 19.21; 95% CI, 3.77 to 97.87) than placebo treated patients (all $P<0.05$).

Separate publications of the original trials offered additional data on quality of life.[186-189] In both studies patients were randomized to 5 mg/kg of infliximab or placebo at weeks 0, 2, 6, 14, and 16 (total of 16 weeks),[186] or weeks 0, 2, 6, 14, and 22 (total of 22 weeks).[187] Improvement in quality of life (measured by the Health Assessment Questionnaire) was statistically significantly greater for infliximab patients compared with placebo patients.[186,187] Mean improvements were 49.8% in infliximab compared with –1.6% in placebo-treated patients in the smaller study ($P<0.001$). In the larger study, at 14 weeks the mean improvement was 48.6% in the infliximab group and an 18.4% loss in the placebo group ($P<0.001$).

Ustekinumab

We identified one multi-center trial of 146 patients with active psoriatic arthritis randomized to ustekinumab 63-90 mg per dose or placebo for 12 weeks.[181,182] Significantly more patients who received 12 weeks of ustekinumab achieved the primary outcome of an American College of Rheumatology 20 response than those who received placebo for the first 12 weeks of the trial (42% vs. 14% respectively, $P=0.0002$).[181] Likewise, 60% of patients in the ustekinumab group achieved a response on the Dermatology Life Quality Index compared with 25% of the placebo patients ($P<0.001$).[182]

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.

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 findings

Overall, the strength of evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease was insufficient (Table 13). 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 one recent, good-quality systematic review and meta-analysis of all four targeted immune modulators approved by the US Food and Drug Administration for Crohn's disease.[190] The review assessed two outcomes, failure of remission and relapse of disease activity, and analyzed the subgroup of patients with fistulizing disease separately. Overall, the review included 27 randomized controlled trials: eight on adalimumab,[191-196] seven on certolizumab pegol,[197-201] seven on infliximab,[202-208] and six on natalizumab.[209-213]

Pooled results regarding the general efficacy of targeted immune modulators for Crohn's disease showed consistent results. Infliximab demonstrated statistically significant greater efficacy than placebo for inducing remission and preventing relapse in all patients and in healing and maintaining remission in fistulizing Crohn's disease.[190] Natalizumab was superior to placebo in inducing remission and preventing relapse in patients with Crohn's disease.[190] Adalimumab demonstrated statistically significant greater efficacy than placebo for inducing remission. Both single trials on evaluating the efficacy of adalimumab for maintaining response demonstrated statistically significant greater efficacy than placebo. Certolizumab pegol was superior to placebo only in preventing relapse but there was a trend showing a greater efficacy than placebo in inducing remission.[190] Overall, Adalimumab and certolizumab pegol were not shown to be more efficacious compared with placebo for inducing remission and healing in fistulizing Crohn's disease.[190] In particular, the evidence from currently available trials on investigating the efficacy of targeted immune modulators in patients with fistulizing Crohn's disease was insufficient.

We did not find any evidence that met our eligibility criteria on the general efficacy of abatacept, alefacept, anakinra, etanercept, golimumab, rituximab, tocilizumab, or ustekinumab 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 targeted immune modulators with other agents (azathioprine, 6-mercaptopurine or methotrexate) leads to clinically and statistically greater improvements than monotherapy. We did not include studies of targeted immune modulators compared with active therapies for Crohn's disease.

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

Study populations and outcome measures

Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up. Generally, patients were allowed to remain on stable doses of corticosteroids in all trials. Some trials involved tapering of corticosteroids in the evaluation of maintenance. All patients suffered from active Crohn's disease for at least 3 months. Some patients also had abdominal or perianal fistulas, a serious complication of Crohn's disease characterized by abnormal connection between the gut and the skin with small bowel or colonic contents draining to the skin surface for at least 3 months. Most studies included patients with a Crohn's Disease Activity Index score between 220 and 400. However, some trials included patients with Crohn's Disease Activity Index 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 Crohn's Disease Activity Index to characterize disease severity. The Crohn's Disease Activity Index assesses eight 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 D) to yield a composite score between 0 and 600; scores below 150 indicate remission while scores above 450 indicate very severe illness. Response commonly was characterized by a Crohn's Disease Activity Index reduction greater than or equal to 70 points. Several studies utilized the Inflammatory Bowel Disease Questionnaire. This questionnaire identifies 32 individual items categorized within four major quality of life domains (primary bowel symptoms, systemic symptoms, social impairment, and altered emotional function). Some studies assessed surrogate parameters such as C-reactive protein concentrations as an objective 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.

To assess the severity of pediatric Crohn's disease activity the pediatric Crohn's disease activity index (PCDAI) is widely used. It is based on the assessment of five dimensions: subjective reporting of disease severity, presence of extraintestinal manifestations, physical examination findings, weight and height, and blood tests.[214]

Sponsorship

All of the randomized controlled trials received funding from the pharmaceutical industry. The included meta-analysis was funded by the American College of Gastroenterology. 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 13 summarizes studies included for general efficacy.

Adalimumab

We included one systematic review and meta-analysis for adalimumab compared with placebo.[190] The review presented pooled results for two outcomes (failure to achieve remission and failure to prevent relapse) in all patients and in the subgroup of patients with fistulizing disease. Overall, up to eight trials provided evidence from up to 1462 patients. In addition, we presented results on further outcomes such as quality of life when this information was available from the original publications.

To assess the efficacy of adalimumab for preventing the failure to achieve remission in active Crohn's disease one review[190] included three randomized placebo-controlled trials with a total of 714 patients.[191-193] Remission rates at 4 weeks favored adalimumab: 75.8% of adalimumab patients (342 of 451) (40/20 mg to 160/80 mg at week 0 and 2) failed to achieve remission, compared with 90.9% of placebo patients (239 of 263) (relative risk, 0.85; 95% CI, 0.79 to 0.91; I^2=0%).[190]

To assess the efficacy of adalimumab in failing to prevent relapse, one review[190] pooled the results of the CHARM and CLASSIC II trials.[194,195] Briefly, the Crohn's Trial of the Fully Human Antibody for Remission Maintenance (CHARM) enrolled 884 patients with moderately to severely active Crohn's disease (CDAI ≥ 220 and ≤ 450) for an induction period of 4 weeks.[194,196,215,216] In this fair study, 499 responders (decrease in CDAI score ≥ 70) were randomized to placebo, adalimumab 40 mg every second week, or adalimumab 40 mg every week. The second fair trial on the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC) randomized 299 patients.[195] At week four, 55 patients in remission (CDAI score < 150) were randomly assigned to receive blinded subcutaneous maintenance treatment with adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo from weeks 4 to 56. The meta-analyses of 554 patients from these two trials showed no statistically significant difference between adalimumab and placebo in the efficacy of preventing relapse (CDAI score ≥150).[190] The relative risk of failing to prevent relapse was not statistically significant 0.54 (95% CI, 0.27 to 1.07).[190] This meta-analysis showed high heterogeneity (I^2=70%) which is probably attributable to the different populations of the included trials and should be considered in using these results. Adalimumab was more efficacious compared with placebo in both trials. The relative risk for adalimumab of failing to prevent relapse was 0.34 (95% CI, 0.16 to 0.75) in the CLASSIC II trial and 0.7 (95% CI, 0.63 to 0.77) in the CHARM trial. A subgroup analysis of 194 patients with fistulas from three randomized controlled trials with a duration of 4 to 26 weeks[191,192,196] showed that adalimumab is not superior to placebo for healing of fistulas: the relative risk of not achieving healing of fistulizing Crohn's disease was 0.94 (95% CI, 0.76 to 1.17).[190] This meta-analysis showed high heterogeneity (I^2=78%) which is probably attributable to the integration of all fistula types and different durations of follow-up. Considering solely the results of the CHARM trial with a follow-up time of 26 weeks the relative risk of not achieving healing of fistulizing Crohn's disease was 0.80 (95% CI, 0.66 to 0.97).[190]

Reports of the CHARM trial provided information on hospitalization and steroid-sparing effects for Crohn's disease.[215,217] 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).[215] At week 56, 29% of patients receiving adalimumab every other week and 23% of patients receiving adalimumab weekly compared with 6% of placebo-treated patients achieved corticosteroid-free remission (P<0.001 and P=0.008).[217]

Health reported quality of life (determined by Inflammatory Bowel Disease Questionnaire and Short Form 36 Health Survey) was better in adalimumab-treated patients.[216] 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.

Certolizumab pegol

We included one systematic review and meta-analysis for certolizumab pegol compared with placebo.[190] The review presented pooled results for two outcomes (failure to achieve remission and failure to prevent relapse) in all patients and in the subgroup of patients with fistulizing disease. Overall, up to seven trials provided evidence from up to 2074 patients. In addition, we presented results on further outcomes such as quality of life when this information was available from the original publications.

Based on two randomized placebo-controlled trials with a duration of 12 weeks[197,198] and two randomized controlled trials with a duration of 6 weeks[199,200] including 1481 patients, the reviewers calculated a relative risk of not achieving remission (CDAI score < 150) for certolizumab pegol-treated patients of 0.95 (95% CI, 0.9 to 1.01; I^2=0%). The treatment regimens differed between studies, ranging from 5 mg/kg to 20 mg/kg as a single acute dose intravenously in one trial at the beginning of the trial to 100 mg to 400 mg subcutaneously at weeks 0, 4 and 8 in another trial. The current recommended dose of certolizumab pegol for Crohn's disease is 400mg subcutaneously at weeks 0, 2, and 4, followed by 400 mg every four weeks. There was no subgroup analysis investigating the effect of the duration of the trials and the usage of the recommended dose and application form.[190]

To assess the relative risk of failure in prevention relapse, one placebo-controlled trial was located. The PRECiSE 2 trial (The Pegylated antibody fRagment Evaluation in Crohn's dIsease Safety and Efficacy)[201] randomized 428 responders. By week 26, the relative risk of failure in preventing relapse in certolizumab pegol-treated patients compared with placebo was 0.73 (95% CI, 0.63 to 0.85).[190]

A subgroup analysis of 165 patients suffering from fistulizing Crohn's disease reported in two randomized controlled trials[199,201] showed no statistically significant difference between certolizumab pegol and placebo in failure to heal of fistulizing Crohn's disease. The calculated risk ratio of not healing fistulizing Crohn's disease was 0.97 (95% CI, 0.77 to 1.22).[190]

A post hoc analysis of 290 patients assessed health-related quality of life data.[218] The percentage of patients achieving remission on the Inflammatory Bowel Disease Questionnaire (defined as a score > 170 points) at week 12 was statistically significantly greater for certolizumab pegol 400 mg doses compared with placebo (38.9% compared with 23.3%, $P \leq 0.05$). The comparison of 100 mg and 200 mg doses of certolizumab pegol with placebo did not show any statistically significant difference. Further evidence on the improvement of health-related quality of life was provided in the PRECiSE 1 trial.[199] Forty-two percent of the certolizumab-treated patients compared with 33% of the placebo-treated patients (P=0.01) had a response on the Inflammatory Bowel Disease Questionnaire by week 26.

Infliximab

We included one systematic review and meta-analysis to assess the efficacy in inducing remission and maintaining response of infliximab compared with placebo in all patients and in the subgroup of patients with fistulizing disease.[190] Overall, up to seven trials provided evidence from up to 1062 patients. In addition, we presented results on further outcomes such as quality of life when this information was available from the original publications. To assess the relative risk of not achieving remission for infliximab (5 or 20 mg/kg) compared with placebo the meta-analysis[190] included three 10- to 12-week trials based on 560 patients.[202-204] The relative risk of not achieving remission was statistically significantly lower in infliximab-treated patients compared with placebo-treated patients (relative risk, 0.68; 95% CI, 0.52 to 0.9).[190]

To assess the efficacy of infliximab (5 to 10 mg/kg) compared with placebo in preventing relapse, one meta-analysis[190] pooled the results of two 30 to 44 week randomized controlled trials including 408 patients.[205,206] The relative risk of not preventing relapse was statistically significantly lower in infliximab compared with placebo (relative risk, 0.72; 95% CI, 0.63 to 0.83).[190]

A subgroup analysis of 94 patients suffering from fistulizing Crohn's disease reported in one randomized controlled trial[207] showed superiority of infliximab compared with placebo in healing of fistulizing Crohn's disease (relative risk, 0.62; 95% CI, 0.48 to 0.81).[190]

The systematic review[190] located one randomized controlled trial that assessed efficacy of infliximab compared with placebo in preventing relapse.[208] In this trial (ACCENT II),[208] 195 patients with Crohn's disease and one or more draining abdominal or perianal fistulas who responded to three open-label 5 mg/kg infusions of infliximab were randomized to maintenance treatment with 8-week infusions of infliximab 5 mg/kg or placebo. The reviewers calculated a relative risk of loss of response of 0.81 (95% CI, 0.68 to 0.96).[190] In addition, at six weeks, infliximab also was more efficacious than placebo in a subgroup of women with rectovaginal fistulas (fistula closure 61% and 45%, respectively).[219] No differences between active treatment and placebo were found in the number of fistula-related abscesses.[220]

Moreover, several articles included in the meta-analysis provided information on quality of life and further outcomes: Trials assessing efficacy of infliximab in inducing remission revealed that quality of life scores assessed by Inflammatory Bowel Disease Questionnaire and C-reactive protein concentrations were significantly better than placebo in patients treated with infliximab ($P<0.05$ and $P<0.01$, respectively).[221]

The ACCENT I trial, which assessed the efficacy of infliximab in maintaining response, showed that compared with placebo, infliximab-treated patients had better endoscopic healing, fewer hospitalizations, fewer surgeries, fewer hours lost from work, better quality of life scores, and corticosteroid-sparing effects ($P<0.05$ for all).[206,222-224] Additional analyses found scheduled maintenance treatment with infliximab to have better mucosal healing than episodic treatment ($P=0.007$).[225]

Further outcomes reported in articles on the ACCENT II trial, which assessed the efficacy of infliximab in maintaining response in the subgroup of patients with fistulizing Crohn's disease, were that infliximab-treated patients had fewer hospitalizations (11 vs. 31; $P<0.05$), fewer mean hospitalization days (0.5 vs. 2.5 days/100; $P<0.05$), and fewer surgeries and procedures (65 vs. 126; $P<0.05$).[226]

Natalizumab

We included one systematic review and meta-analysis to assess the efficacy of natalizumab in inducing remission and maintaining response of infliximab compared with placebo in Crohn's disease patients.[190] Overall, up to six trials provided evidence from up to 2125 patients. In addition, we presented results on further outcomes such as quality of life when this information was available from the original publications.

To assess the efficacy of natalizumab (300 mg or 3 to 6 mg/kg) for inducing remission in active Crohn's disease one review[190] included five 2- to 12-week randomized placebo-controlled trials with a total of 1771 patients. The reviewers calculated a relative risk of natalizumab failing to induce remission in active luminal Crohn's disease of 0.88 (95% CI, 0.83 to 0.94).[190]

To assess the relative risk of failure of natalizumab in preventing relapse, one placebo-controlled trial was located.[211] After an induction period of 300 mg of natalizumab at week 0, 4,

and 8, 354 (48.9%) responders at week 12 (CDAI score of 0 to 220 and a decrease in CDAI score > 70 points) were randomized to an infusion of 300 mg of natalizumab every 4 weeks or placebo for 60 weeks. The reviewers calculated a relative risk of preventing relapse in quiescent luminal Crohn's disease of 0.71 (95% CI, 0.61 to 0.84).[190]

Two induction phase trials[210,213] and one maintenance trial included in the meta-analysis[227] investigated the treatment benefits of natalizumab compared with placebo on quality of life. One trial[210] randomly assigned 248 patients to one of four treatment arms: one or two infusions of 3 mg/kg natalizumab, two infusions of 6 mg/kg natalizumab, or placebo. At week 6, all three natalizumab groups had statistically 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 two-infusion natalizumab group was statistically significantly better than placebo ($P=0.021$). In the ENCORE trial,[213] 309 patients were randomized to natalizumab or placebo. Natalizumab showed statistically significantly greater improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire score improvement at week 12 (+26.7 compared with +15.2, $P<0.001$).

In the ENACT-2 maintenance trial natalizumab-treated patients showed a statistically significant increase in quality of life at week 60 compared with placebo-treated patients (measured by Inflammatory Bowel Disease Questionnaire): increase of 53.9 points compared with 35.5 points, respectively ($P<0.001$).[227]

Table 13. 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									
Ford et al. 2011[190]	MA	194 - 714	4 – 56 weeks	Adalimumab vs. placebo	Clinical remission (CDAI < 150) at week 4; Relapse (CDAI ≥ 150) at week 56; Closure or absence of fistulas		Moderate-to-severe active CD (CDAI ≥ 220 and ≤ 450)	Adalimumab superior to placebo for clinical remission and maintaining response; no difference between adalimumab and placebo for other outcomes	Good
Colombel et al., 2007[194] Feagan et al., 2008[215] Loftus et al., 2008[216] Colombel et al. 2009[196] Kamm et al., 2011 [217] Included in MA by Ford et al.,[190] CHARM	RCT	778	2 week active run-in plus 54 weeks	Induction Adalimumab 2 weeks then Adalimumab vs. placebo	Clinical remission (CDAI <150) at weeks 26 and 56; response		Moderate-to-severe active CD (CDAI ≥ 220 and ≤ 450)	Adalimumab superior for all outcomes, such as lower all-cause hospitalization, better quality of life, steroid-sparing effects	Fair
CERTOLIZUMAB PEGOL									
Ford et al. 2011[190]	MA	165 - 1,481	6-26 weeks; Responders at week 6, were followed to week 26;	Certolizumab vs. placebo	Clinical remission (CDAI < 150) at week 4; Relapse (CDAI ≥ 150) at week 56at week 26; Closure or absence of fistulas		Moderate-to-severe active CD (CDAI ≥ 220 and ≤ 450) over 3 month	Certolizumab superior to placebo for maintaining response, no difference between Certolizumab and placebo in other outcomes	Good

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Schreiber et al., 2005[198] and Rutgeerts et al., 2008[218] Included in MA by Ford et al.,[190]	RCT	292	20 weeks	Certolizumab pegol 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	Certolizumab pegol at all doses better than placebo for all outcomes	Fair
INFLIXIMAB									
Ford et al., 2011[190], Present et al., 1999[207]	MA	94 - 560	10-18 weeks; after induction period of 2 weeks, responders followed up to week 30-44	Infliximab vs. placebo	Clinical remission (CDAI < 150); Relapse (CDAI ≥ 150 or need for surgery, or escalation of medical therapy at 30-44 weeks; Absence of draining fistulas at two visits, 18 weeks	Off cortico-steroids	Moderate-to-severe active CD (CDAI ≥ 220 and ≤ 450); draining abdominal or perianal fistulas of at least three months' duration in CD adult patients	Infliximab superior to placebo in all three outcomes	Good
Sands et al., 2004[208,219,220,226] ACCENT II	RCT	282	54 weeks	Infliximab vs. placebo	Time to loss of response after randomization (week 14)	CDAI, IBDQ, hospital-izations, hospital-ization days, surgeries	> 3 month history of active CD with multiple draining fistulas and 14 week response (≥ 50% closure) to 3 open label doses of infliximab 5 mg/kg	Significantly longer time to loss of response, fewer draining fistulas, greater improvement in CDAI and IBDQ, fewer hospital-izations, and surgeries for Infliximab compared with placebo; no difference in fistula-related abscesses for maintenance	Fair

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Hanauer et al., 2002[206,222-225] Included in MA by Ford et al.,[190] ACCENT I	RCT	573	54 weeks	Infliximab vs. placebo	Proportion of week 2 responders in remission at week 30; time to loss of response	Employment status/work loss, IBDQ surgeries, SF-36, hospital-izations, corticosteroid discontinu-uation , endoscopic healing	> 3 month history of moderate to severe Crohn's disease and CDAI response at 2 weeks to single dose 5 mg/kg infliximab	Better quality of life, better endoscopic healing, fewer surgeries and hospitalizations, and less work loss in infliximab	Fair
Targan et al., 1997[202] and Lichtenstein et al., 2002[221] Included in MA by Ford et al.,[190]	RCT	108	12 weeks	Infliximab 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 infliximab compared with placebo	Fair
NATALIZUMAB									
Ford et al., 2011[190]	MA	354 - 1,771	2-12 weeks; responders at week 12 followed up to week 60	Natalizumab vs. placebo	Remission (CDAI < 150); Relapse (CDAI ≥ 150) or need for intervention		Moderate-to-severe active CD (CDAI ≥ 220 and ≤ 450)	Natalizumab superior to placebo in inducing remission and maintaining response	Good
Ghosh et al., 2003[210] Included in MA by Ford et al.,[190]	RCT	248	12 weeks	Natalizumab 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 Natalizumab groups vs. placebo; improvement statistically significant for 2 infusion Natalizumab group at week 12	Good

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Targan et al., 2007[213] Included in MA by Ford et al.,[190] ENCORE Trial	RCT	509	12 weeks	Natalizumab 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	Natalizumab statistically significantly greater in improvement for all outcomes	Fair

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MA, meta-analysis; RCT, randomized controlled trial; SF-36, Short Form 36 Health Survey.

Crohn's Disease in Children

The only drug which is currently approved by the US Food and Drug Administration for the treatment of Crohn's disease in children is infliximab.

No new studies meeting our eligibility criteria were identified during the updated search. No evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease in children exists. We identified one systematic review of the evidence base for the medical treatment of pediatric inflammatory bowel disease.[228] Due to the short time frame of the literature research the systematic review was rated poor. In addition, no placebo-controlled trials on children with Crohn's disease met our eligibility criteria.

We identified one 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 two different dosing regimens of infliximab.[229] We briefly described the REACH study because it is the only study we found that included children. In this study, 112 patients with a Pediatric Crohn's Disease Activity Index 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 in adults and children.

Summary of findings

No head-to-head evidence on the comparative effectiveness of targeted immune modulators for the treatment of ulcerative colitis exists (see Table 14). The strength of the evidence is insufficient.

We located one recent, good-quality systematic review and meta-analysis of targeted immune modulators for inducing remission in ulcerative colitis.[190] This review pooled the results of five randomized controlled trials of 5 mg/kg infliximab compared with placebo. Patients were allowed stable doses of corticosteroids in all trials. The reviewers calculated a relative risk of 0.72 (95% CI, 0.57 to 0.91) for a *failure* to achieve remission, i.e., infliximab is more efficacious than placebo.

Study populations and outcome measures

One systematic review and meta-analysis pooled the results of five randomized controlled trials (from four publications).[230-233] Trials measured clinical and endoscopic disease remission and quality of life. All patients suffered from active ulcerative colitis and had previously failed or were receiving 5-aminosalicylate and steroid treatments.

Sponsorship

All of the included trials in 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 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 located one recent, good-quality systematic review and meta-analysis of targeted immune modulators for inducing remission in ulcerative colitis.[190] This review pooled the results of five randomized controlled trials of 5 mg to 20 mg/kg infliximab compared with placebo.[230-233] Patients suffered from active ulcerative colitis, unresponsive to corticosteroid therapy. Patients were allowed concomitant stable doses of corticosteroids in all trials. The duration of the trials varied from 6 to 12 weeks. In total, data from 827 patients was pooled. The reviewers calculated a relative risk of 0.72 (95% CI, 0.57 to 0.91) for a failure to achieve remission, indicating that infliximab is more efficacious than placebo. One 6-week randomized controlled trial of infliximab compared with placebo did not meet our eligibility criteria as the duration of follow-up was too short however provided evidence of quality of life.[232] The authors found no statistical difference in quality of life between the 20 patients treated with placebo and the 23 patients treated with infliximab after 6 weeks of therapy. Table 14 provides a summary of the evidence for the general efficacy of infliximab for ulcerative colitis.

Ulcerative Colitis in Children

Infliximab is the only targeted immune modulator currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in children. We did not locate any randomized controlled trials of targeted immune modulators in the pediatric population of patients with ulcerative colitis.

Table 14. Summary of efficacy trials in adult patients with ulcerative colitis

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
INFLIXIMAB									
Ford et al. 2011[190]	SR and MA	827	6 to 12 weeks	Infliximab 5 mg/kg to 20 mg/kg vs. placebo	Inducing remission (clinical and endoscopic scores)	None	Adults with UC	Relative risk of failure to achieve remission 0.72 (0.57 to 0.91) favoring therapy with infliximab	Good

Abbreviations: MA, meta-analysis; SR; systematic review; UC, ulcerative colitis.

Plaque Psoriasis

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

Summary of findings

We located one fair-quality, randomized, head-to-head trial of etanercept compared with ustekinumab for the treatment of severe plaque psoriasis.[234] In the trial 903 patients were randomized to 50 mg etanercept twice weekly or two doses of ustekinumab (45 mg or 90 mg) in a 12-week period. Significantly more patients in both ustekinumab groups achieved the primary outcome of a PASI 75 response compared with etanercept. The strength of evidence for this comparison was low.

Fair to good evidence from multiple placebo-controlled randomized controlled trials demonstrated the general efficacy of adalimumab, alefacept, etanercept, infliximab, and ustekinumab for achieving a Psoriasis Area and Severity Index 75 response in adults with plaque psoriasis. Specifically, we located 17 placebo-controlled trials that assessed the efficacy of targeted immune modulators for the treatment of plaque psoriasis in adults: five on adalimumab,[235-239] three on alefacept,[240-242] five on etanercept,[243-247] one on infliximab,[248] and three on ustekinumab.[249-251] The studies on alefacept and etanercept were pooled in a meta-analysis.[252] We did not find any studies on other targeted immune modulators. In addition, one study assessed the efficacy of etanercept in children and adolescents.[253] Significantly more children in the etanercept group than in the placebo group experienced a response. Included studies are presented in Table 15.

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 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 some studies.

All studies assessed Psoriasis Area and Severity Index 50 or Psoriasis Area and Severity Index 75 as one of the primary outcome measures (see Appendix D). 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 were 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 placebo in an identical container to active treatment) to guarantee blinding; and 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

Etanercept compared with ustekinumab

We located one fair-quality, randomized, head-to-head trial that compared etanercept with ustekinumab in 903 patients with moderate-to-severe plaque psoriasis.[234] The doses of targeted immune modulator in the three arms were: 50 mg etanercept twice weekly, ustekinumab 45 mg at week 0 and week 4, or ustekinumab 90 mg at week 0 and week 4. The trial lasted 12 weeks and patients and study personnel administering the drugs were not blinded to treatment allocation. All other study personnel including assessors and data managers were blinded to treatment allocation. The results of this one trial indicated that ustekinumab is superior to etanercept for treating plaque psoriasis. Significantly more patients in both ustekinumab groups achieved the primary outcome of a Psoriasis Area and Severity Index 75 response compared with etanercept (etanercept 50 mg, 56.8%; ustekinumab 45 mg, 67.5%; ustekinumab 90 mg, 73.8%; $P<0.001$). Similarly, statistically significantly more patients in both ustekinumab groups demonstrated cleared or minimal disease with the Physician's Global Assessment (etanercept 50 mg, 49%; ustekinumab 45 mg, 65.1%; ustekinumab 90 mg, 70.6%; $P<0.001$).

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 small number 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 did not provide evidence on the comparative efficacy and tolerability of targeted immune modulators.

Adalimumab

Two good[236,237] and three fair[235,238,239] studies provided evidence on the general efficacy of adalimumab for the treatment of moderate to severe plaque psoriasis in adult patients. All five trials had a primary endpoint of PASI 75 or hfPGA between week 12 and 16 and included one arm where patients received an initial dose of 80 mg adalimumab subcutaneously followed by 40 mg adalimumab every other week. Furthermore, one trial included methotrexate as a comparison arm[236] and one trial also included a dose of adalimumab that is higher than the approved dose for plaque psoriasis (80 mg initial dose followed by 40 mg weekly).[235] One trial looked specifically at patients with psoriasis of the hands and/or feet.[239] 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 81% of patients in the adalimumab every other week arms achieved a Psoriasis Area and Severity Index 75 response compared with 4% to 19% of placebo-treated patients.

Specifically, in the largest good-quality trial 1212 patients were randomized to adalimumab every other week or placebo for 16 weeks.[237] Adalimumab was superior to placebo

at week 16 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 statistically significantly greater improvement in Physician Global Assessment, Dermatology Life Quality Index, and health-related quality of life measures. Results from the other good-quality trial and the fair-quality trials were similar.[235,236,238,239]

One trial randomized 72 patients with moderate-to-severe plaque psoriasis of the hands and/or feet to adalimumab or placebo.[239] The 49 patients who received an 80 mg loading dose of adalimumab followed by 40 mg every other week demonstrated statistically significantly greater improvement in the Physician Global Assessment of hands and/or feet, the Erythema, Scaling, Induration, Fissuring scale, and the Nail Psoriasis Severity Index (NAPSI) score, than those who received placebo at 16 weeks (Physician Global Assessment of hands and/or feet score of clear or almost clear in 31% of adalimumab patients vs. 4% of placebo patients, P=0.01; >75% improvement in Erythema, Scaling, Induration, Fissuring scale in 29% of adalimumab vs. 4% of placebo, P=0.03; mean percentage Nail Psoriasis Severity Index improvement 50% for adalimumab vs. 8% for placebo P=0.02).[239]

Alefacept

One fair-quality systematic review[252] included three randomized controlled trials[240-242] of alefacept compared with placebo for patients with plaque psoriasis in meta-analyses. Overall, the studies included data on 1001 patients treated with intravenous 0.075 mg/kg, intravenous 7.5 mg, or intramuscular 15 mg of alefacept or placebo for plaque psoriasis. Compared with placebo, statistically significantly more patients taking alefacept experienced a Psoriasis Area and Severity Index 75 response (relative risk, 3.70; 95% CI, 2.43 to 5.75; number needed to treat, 8; 95% CI, 5 to 12).[252]

Etanercept

One fair meta-analysis examined the efficacy of etanercept in 2017 patients with plaque psoriasis.[252] Results were pooled from four placebo-controlled trials comparing 25 mg once weekly, 25 mg twice weekly, and 50 mg twice weekly.[243-246,254,255] Compared with placebo, statistically significantly more patients taking etanercept experienced a Psoriasis Area and Severity Index 75 response (relative risk, 10.43; 95% CI, 7.20 to 15; number needed to treat, 3; 95% CI, 2 to 4).[252] One additional fair-quality trial published after the systematic review showed similar results for Psoriasis Area Severity Index 75 with a statistically significant effect for etanercept compared with placebo (P<0.0001).[247] This study also demonstrated improved quality of life using the Dermatology Life Quality Index scale in the etanercept group compared with placebo (P<0.0001).[256]

Infliximab

One good randomized controlled trial assessed the efficacy and safety of infliximab for 378 patients randomized to 24 weeks of infliximab (5 mg/kg) or placebo for treatment of plaque psoriasis.[248] At week 24, 82% of patients on infliximab and 4% of patients on placebo achieved a Psoriasis Area and Severity Index 75 response (P<0.0001). In addition, the infliximab group had statistically significantly greater improvements on Short Form 36 Health Survey, Dermatology Life Quality Index,[257] work productivity (assessed by visual analogue scale and Short Form 36 Health Survey),[258] nail psoriasis and severity index, and Physician Global Assessment.[248] Several other trials of infliximab for plaque psoriasis did not meet our formal eligibility criteria because they had a duration of 10 weeks.[259-261]

Ustekinumab

Three fair-quality 12-week randomized placebo-controlled trials assessed the efficacy and safety of ustekinumab in 2316 patients with plaque psoriasis.[249-251] Trials included patients with moderate-to-severe plaque psoriasis of at least 6 months duration affecting at least 10% of body surface area. Approximately 70 percent of included patients were male and the average Psoriasis Arthritis Severity Index score at baseline was 20. All three trials were sponsored by the maker of ustekinumab. Multiple different ustekinumab dosing regimens were compared with placebo in the trials: a single 45 mg dose, a 45 mg dose every 4 weeks, a single 90 mg dose, a 90 mg dose every 4 weeks, a 45 mg dose at week 0 and week 4, and a 90 mg dose at week 0 and week 4. The primary outcome in all three trials was a Psoriasis Arthritis Severity Index 75 response at 12 weeks. Ustekinumab is highly efficacious for plaque psoriasis compared with placebo and statistically significantly more patients taking ustekinumab achieved a Psoriasis Arthritis Severity Index 75 response (pooled relative risk, 20.68; 95% CI, 13.9 to 30.7, see appendix E). Similarly, the ustekinumab-treated patients in all three trials demonstrated a statistically significantly greater improvement in quality of life compared with placebo (using the Dermatology Life Quality Index scale).

Children

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

We found one fair-quality randomized controlled trial of etanercept in children.[253] 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 for at least 6 months were randomized to etanercept 0.8 mg/kg weekly 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.[262] 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 16 summarizes efficacy trials in children with plaque psoriasis.

Table 15. Summary of efficacy trials in patients with plaque psoriasis

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT compared with USTEKINUMB									
Griffiths et al., 2010[234]	RCT	903	12 weeks	Etanercept 50 mg twice weekly / ustekinumab 45 mg or 90 mg two doses in 12 weeks	PASI 75	PGA, PASI 90	Adult patients with plaque psoriasis (of at least 6 months duration and involving >10% body surface area)	Both ustekinumab doses superior to etanercept for PASI 75, PGA, and PASI90	Fair
ADALIMUMAB									
Gordon et al., 2006[235] Shikiar, 2007[263]	RCT	147	12 weeks	Adalimumab / 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 adalimumab compared with placebo	Fair
Saurat et al., 2008[236] Revicki, 2008[264]	RCT	271	16 weeks	Adalimumab / methotrexate / 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 adalimumab compared with both methotrexate and placebo. Significant improvement in HQL for adalimumab compared with placebo	Good
Menter et al., 2008[237] Revicki, 2007[265] Revicki, 2008[266]	RCT	1212	16 weeks	Adalimumab / 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 adalimumab compared with placebo	Good
Asahina et al., 2010[238]	RCT	169	16 weeks	Adalimumab vs. placebo	PASI 75	PASI 50 & 90, PGA, DLQI, SF-36	Adult patients with moderate to severe chronic plaque psoriasis	Significant improvement in PASI, DLQI, SF-36 in adalimumab compared with placebo	Fair

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Leonardi et al., 2011[239]	RCT	72	16 weeks	Adalimumab vs. placebo	hfPGA	ESIF, NAPSI, pain (VAS)	Adult patients with moderate to severe chronic plaque psoriasis of the hands and/or feet	Significant improvement in hfPGA, ESIF, pain in adalimumab compared with placebo	Fair
ALEFACEPT									
Brimhall et al 2008[252]	MA	1001	12 weeks	3 RCTs of alefacept/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									
Brimhall et al 2008[252]	MA	2017	12 - 24 weeks	4 RCTs of etanercept/placebo	PASI	None	Adult patients with plaque psoriasis without any systemic treatment	NNT for PASI 75 response 3 (95% CI, 2.07 to 2.49)	Fair
Reich, et al., 2009[256]van de Kerkhof, 2008[247]	RCT	142	12 weeks	Etanercept 50 mg weekly / placebo	PASI75	DLQI, EQ-5D	Adult patients with moderate to severe chronic plaque psoriasis	Significantly greater improvement on PASI 75, DLQI measures for infliximab than for placebo	Fair
INFLIXIMAB									
Reich et al., 2005[248] Reich et al., 2006[257] Reich et al., 2007[258]	RCT	378	24 weeks (double-blind placebo cross-over to infliximab at week 24, total duration 46 weeks)	infliximab / placebo	PASI	PGA, NAPSI, DLQI, SF-36, work productivity	Adult patients with plaque psoriasis without any systemic treatment	Significantly greater improvement on all outcome measures for infliximab than for placebo	Good

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
USTEKINUMAB									
Kreuger, et al. 2007[249]	RCT	320	12 weeks	ustekinumab / placebo	PASI 75	DLQI, PGA	Adult patients with moderate to severe chronic plaque psoriasis	Significantly greater improvement on PASI 75, DLQI measures for ustekinumab than for placebo	Fair
Leonardi, et al., 2008[250,267]	RCT	766	12 weeks	ustekinumab / placebo	PASI 75	DLQI, PGA	Adult patients with moderate to severe chronic plaque psoriasis	Significantly greater improvement on PASI 75, DLQI measures for ustekinumab than for placebo	Fair
Papp et al., 2008[251]	RCT	1230	12 weeks	ustekinumab / placebo	PASI 75	DLQI, PGA	Adult patients with moderate to severe chronic plaque psoriasis	Significantly greater improvement on PASI 75, DLQI measures for ustekinumab than for placebo	Good

Abbreviations: DLQI, Dermatology Life Quality Index; EFA, efalizumab; EFA, efalizumab; ESIF: Erythema, Scaling, Induration, Fissuring scale; EQ-5D, European Quality of Life – 5 Dimensions; hfPGA: Physician's Global Assessment of the hands and/or feet; HQL, health-related quality of life; 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 16. 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[253,262,268]	RCT	211	12 weeks	Etanercept / 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 etanercept compared with placebo	Fair

Abbreviations: CDQLI: Children's Dermatology Quality of Life Index; DLQI, Dermatology Life Quality Index; 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

Eighteen head-to-head studies (almost exclusively observational studies) provided direct evidence on the harms associated with targeted immune modulators.[39,40,43,45,234,269-281] Other evidence came from indirect comparisons of over 200 randomized controlled trials with placebo or disease-modifying antirheumatic drug controls (including two head-to-head randomized controlled trials).[39,234,282] We located evidence on serious infection, malignancy, cardiovascular harms, rates of serious harms, withdrawal due to harms, and specific adverse events such as injection site reactions.

Evidence on the comparative risk of serious infections with targeted immune modulators was low strength. Evidence from short-term trials (median 6 months), using indirect comparison meta-analyses, indicated serious infections are less common with abatacept than with certolizumab, infliximab, and tocilizumab while certolizumab appeared to have a higher risk than adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, or placebo.[282] Analyses of only the antitumor necrosis factor monoclonal antibodies (adalimumab, certolizumab, golimumab, and infliximab) indicated that as a group, they have an increased risk compared with control groups (odds ratio, 1.49; 95% CI, 1.17 to 1.90), while the other targeted immune modulators, including etanercept (which blocks tumor necrosis factor by blocking receptors), did not. Limited observational evidence indicated an increased risk with antitumor necrosis factor drugs etanercept, infliximab, and adalimumab (hazard ratio, 1.2; 95% CI, 1.1 to 1.5) compared with disease-modifying drugs and that among the targeted immune modulators the risk of hospitalization with infection was higher with infliximab than anakinra, adalimumab, and etanercept.[270,283] These studies found that and that the risk was highest in the first 6 months of treatment and among those with other risk factors for infection. The risk of tuberculosis appeared to be elevated with the use of targeted immune modulators as a group (odds ratio, 4.68; 95% CI, 1.18 to 18.60) based on trial data.[282] Comparisons between the drugs were more limited, with low strength evidence indicating increased risk of tuberculosis with adalimumab compared with etanercept (adjusted incidence rate ratio, 4.1; 95% CI, 1.4 to 12.4) and a nearly statistically significant increased risk with infliximab compared with etanercept (3.1; 95% CI, 1.0 to 9.5). The median time to diagnosis of tuberculosis (anywhere, including reactivation of tuberculosis) was 13.4 months from start of therapy. While there was a small increase in risk of herpes zoster with antitumor necrosis factor drugs as a group (pooled hazard ratio 1.42 (95% CI, 1.14 to 1.78), risk was not increased with etanercept. The strength of this evidence was low. The evidence on adalimumab and infliximab was insufficient to draw conclusions. The strength of evidence comparing the risk of serious infections with targeted immune modulators was low strength. Evidence on the risk of other specific serious infections was insufficient strength to make conclusions.

On the whole, a broad range of evidence did not indicate a clear increase in risk of malignancy in general with the use of targeted immune modulators. There was evidence suggesting that the risk of nonmelanoma skin cancer is increased with the use of the antitumor necrosis factor drugs adalimumab, infliximab, and etanercept (relative risk, 2.02; 95% CI, 1.11 to

3.95).[284] Observational evidence supported these findings, although the risk estimates were somewhat lower magnitude. The strength of evidence comparing the risk of malignancy with targeted immune modulators is low strength. Although the US Food and Drug Administration issued a warning about the potential increased risk of malignancy in children, evidence in children is insufficient for making conclusions.

While case reports have indicated potential risk of various other serious adverse events, strength of evidence on the comparative risk of heart failure, autoimmunity, demyelination, and serious hepatic events with targeted immune modulator drugs is insufficient at this time.

Comparative evidence on overall adverse events, discontinuation of drug due to adverse events, and other measures of short-term tolerability was low to moderate strength, depending on the specific outcome. The rates of overall adverse events occurring with targeted immune modulators did not differ statistically significantly between the drugs. In short-term trials, abatacept and anakinra had lower risk of a serious adverse event compared with other targeted immune modulators.[282] Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with abatacept, adalimumab, etanercept, and golimumab.[45,282] Infusion or allergic reactions contributed to the increased risk of discontinuation with infliximab (hazard ratio, 2.11; 95% CI, 1.23 to 3.62).[278]

Evidence on the comparative risk of adverse events associated with targeted immune modulators in children is very limited and was insufficient strength to make conclusions. The adverse event profiles appeared similar to those seen in adults, with small numbers of children experiencing serious adverse events including serious infections and injection site or infusion reactions.

Study Populations and Outcome Measures

The vast majority of patients included in studies assessing adverse events had rheumatoid arthritis. Few trials used objective scales such as the Utvalg for Kliniske Undersogelser Side Effect Scale or the adverse reaction terminology from the World Health Organization. Most trials combined patient-reported adverse events with a regular clinical examination by an investigator. The short duration of trials limited the validity of adverse events assessment with respect to rare but serious adverse events. See Table 19 for a description of the studies providing direct evidence for this section. In both trials and observational studies, determining whether assessment methods were unbiased and adequate was difficult. Many of the observational studies were based on patient registries; biased selection and inadequate statistical adjustment for confounding are concerns.

Sponsorship

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

Detailed Assessment

Appendix F summarizes black box warnings, precautions, and bold letter warnings issued by the US Food and Drug Administration for individual targeted immune modulators.

Serious infections

Because of the immunosuppressive nature of targeted immune modulators, the potential for increased risk of serious infections including tuberculosis, pneumonia, osteomyelitis, sepsis, or progressive multifocal leukoencephalopathy must be considered. Most infections were lower respiratory tract infections (34%) or skin and soft tissue infections (21%). Most long-term observational studies supported these findings.[283,285-292] The most common serious opportunistic infections were cases of tuberculosis. Other opportunistic infections have been reported: candida,[293] coccidiomycosis,[294,295] herpes zoster,[296] histoplasmosis,[297] listeriosis,[298] and pneumocystis carinii.[299] The incidence rate of infections with adalimumab, etanercept, and infliximab has been estimated at 35.9 per 1000 patient-years, based on a retrospective cohort study of 1064 rheumatoid arthritis patients.[269]

The most comprehensive and highest-quality systematic review of serious infections associated with targeted immune modulators was a Cochrane review of 209 trials and extension studies published up to January 2010.[282] The authors conducted a network meta-analysis (mixed-effects logistic regression using an arm-based random-effects model within an empirical Beyes framework and Poisson distribution) on the incidence of serious infections with all of the targeted immune modulators using data from published systematic reviews with meta-analyses, including data from 119 studies and 41 036 patients. No reviews of natalizumab or alefacept were available at the time so the two drugs were not included. Serious infections were included based on individual study definitions, typically deaths, hospitalizations, and use of intravenous antibiotics associated with infection. The overall quality of the bodies of evidence (using the GRADE rating system) was high for abatacept and certolizumab and moderate for all others except rituximab, which was rated low quality. Relative to control groups, only certolizumab was associated with a statistically significant increase in risk of serious infection (odds ratio, 3.51; 95% CI, 1.59 to 7.79). Abatacept (odds ratio, 0.57; 95% CI, 0.30 to 1.08) was the only drug with a point estimate on the side of a lower risk compared with control, while all other targeted immune modulators point estimates were on the side of increased odds. As a group, the targeted immune modulators did not result in increased odds of a serious infection compared with control groups (pooled odds ratio, 1.19; 95% CI, 0.94 to 1.26). In indirect comparisons (network analysis adjusted for dose), abatacept resulted in statistically significantly lower odds of a serious infection compared with certolizumab, infliximab, and tocilizumab while certolizumab was associated with greater odds than adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and placebo (Table 17).

Table 17. Statistically significant indirect comparisons: Serious Infection

Drug	Comparator drug	Odds ratio	95% confidence interval
Abatacept	Certolizumab	0.16	0.06 to 0.43
Abatacept	Infliximab	0.39	0.20 to 0.77
Abatacept	Tocilizumab	0.36	0.15 to 0.83
Adalimumab	Certolizumab	0.32	0.13 to 0.76
Anakinra	Certolizumab	0.31	0.10 to 0.95
Certolizumab	Etanercept	3.32	1.43 to 7.75
Certolizumab	Golimumab	2.73	1.04 to 7.13
Certolizumab	Infliximab	2.42	1.05 to 5.60
Certolizumab	Rituximab	3.61	1.53 to 8.48
Certolizumab	Placebo	3.51	1.59 to 7.79

Evidence not included in the network meta-analysis above comprised of 52-week results of a trial of golimumab in patients with rheumatoid arthritis whose 24-week results were included in the analysis,[113] a small placebo-controlled trial of rituximab,[300] and three meta-analyses of single drugs.[301-303] The studies were similar to those included in the meta-analysis, and their results did not conflict with the network analysis results. For example, at 52 weeks, patients taking 100 mg of golimumab had the highest rate of serious infections (3.8% to 10%) compared with the 50 mg dose groups (1.9%) or placebo group (0.8%).[113] A small fair-quality trial of patients with rheumatoid arthritis who had failed at least one course of antitumor necrosis factor drugs received one course of open-label rituximab and then were randomized to placebo or rituximab for a second course.[300] There was no difference between groups in the rate of serious infection at week 48 (2% in each group). A pooled analysis of only abatacept trials and extension studies made comparisons of rates of hospitalization due to infection and pneumonia between trial rates and estimates from epidemiological studies.[302] Neither analysis showed a statistically significant increase in risk with abatacept. A similar pooled analysis of rituximab data found the rate of serious infection to be 4.31 per 100 patient-years and did not find an increase in risk over five courses of treatment.[303]A pooled analysis of certolizumab studies in patients with Crohn's disease found that continued treatment following remission resulted in a rate of 7.8% serious infections compared with 6.0% in groups assigned to interrupted treatment (allowing a period of comparison of treatment or no treatment during remission).[301]

Direct evidence from observational studies of targeted immune modulators included a good-quality prospective cohort study of registry data on patients with rheumatoid arthritis in Britain.[270] A total of 15 396 patients were included in this analysis. As a group antitumor necrosis factor drugs (adalimumab, etanercept and infliximab) resulted in statistically significant increase in risk for serious infections compared with disease-modifying antirheumatic drugs (adjusted hazard ratio, 1.2; 95% CI, 1.1 to 1.5) and the risk was highest during the first 6 months of treatment (hazard ratio, 1.8; 95% CI, 1.3 to 2.6). Mortality within 30 days of serious infection, however, was statistically significantly lower with antitumor necrosis factor drugs (hazard ratio, 0.5; 95% CI, 0.3 to 0.8). There were no statistically significant differences in risk of serious infection found between drugs, no difference in hospital stay, and no difference in risk in older patients. A fair quality retrospective cohort study of administrative medical and pharmacy data on 6992 patients with rheumatoid arthritis identified hospitalizations with ICD-9 codes for infection and who were treated with a targeted immune modulator.[283] In contrast to the study above, across all patients, regardless of whether they were using a targeted immune modulator drug for the first time or were switching from another such drug, abatacept (adjusted hazard ratio, 0.68; 95% CI, 0.48 to 0.96), adalimumab (adjusted hazard ratio, 0.52; 95% CI, 0.39 to 0.71) and etanercept (adjusted hazard ratio 0.64; 95% CI, 0.49 to 0.84) had statistically significantly fewer hospitalizations with infection compared with infliximab. Rituximab was not found statistically significantly different. The study found also that the patients underlying risk for infection was a significant confounder.

Progressive multifocal leukoencephalopathy

In June 2009, the manufacturer of efalizumab voluntarily withdrew 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 one in 1000 patients treated with natalizumab for a mean of 17.9 months.[304] A descriptive report of 52 cases occurring in patients receiving rituximab revealed that the majority of patients were taking other immunosuppressive treatments concomitantly.[305] No evidence eligible for this review was available about the risk for progressive multifocal leukoencephalopathy for any of the other targeted immune modulators.

Tuberculosis

A good-quality Cochrane review of 209 studies (163 trials involving 50 010 patients and 46 extension studies involving 11 954 patients) found the risk of reactivation of tuberculosis to be statistically significantly elevated when trial data for the targeted immune modulators were combined (odds ratio, 4.68; 95% CI, 1.18 to 18.60), but data were inadequate for comparison among the drugs using a network meta-analysis.[282] A pooled analysis of abatacept trials and extensions studies included a larger number of extension studies than the Cochrane review (seven vs. two) and found an incidence of 0.04 per 100 patient-years, a rate that was considered similar to population norms.[302] This study was not based on a comprehensive search for literature, nor did it critically appraise the studies.

Of six observational studies,[271,288,306-309] the best comparative evidence was low strength and came from a study of a British registry of 10 649 patients with rheumatoid arthritis treated with etanercept, infliximab, or adalimumab.[271] A comparison group of 3232 patients treated with disease-modifying antirheumatic drugs was also included, but no case of tuberculosis occurred in this group. This analysis showed statistically significant increased risk of tuberculosis with adalimumab compared with etanercept (adjusted incidence rate ratio, 4.1; 95% CI, 1.4 to 12.4). The adjusted incidence rate ratio for infliximab was nearly statistically significant (3.1, 95% CI, 1.0 to 9.5). The median time to event was 13.4 months from start of therapy. Considering that the rates of tuberculosis infection in Britain are higher than in the United States, the absolute rates may be lower but it is unlikely that the relative rates across the drugs would differ.

Five other observational studies[288,306-310] specifically determined the risk of tuberculosis or granulomatous infections during treatment with antitumor necrosis factor therapy and found an increased risk. A study of patients from the National Data Bank for Rheumatic Diseases reported an incidence 52.5 cases per 100 000 patient-years.[310] Two other database analyses used the Spanish BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia)[309] and different Swedish databases[288] which included data on infliximab and etanercept. Both reports indicated a substantially increased risk for tuberculosis in patients treated with etanercept or infliximab compared with those taking standard disease-modifying antirheumatic drugs. The Swedish study reported a 4-fold increased risk of tuberculosis (relative risk, 4.0; 95% CI, 1.3 to 12) for patients on antitumor necrosis factor treatment compared with rheumatoid arthritis patients not exposed to etanercept or infliximab.[288] Based on postmarketing surveillance data in Japan, a study of etanercept reported a rate of 0.1%, however not all cases were proven to be incident cases.[306] A separate report from the same database reported a rate of 0.22 per 100 patient-years with tocilizumab.[307] Neither report was comparative.

The incidence of tuberculosis across these studies may have been differentially affected by the implementation over time of recommendations for screening prior to starting a targeted immune modulator drug.

Opportunistic infections

A fair-quality retrospective study of 202 patients from a French registry of patients with opportunistic infection and who were receiving antitumor necrosis factor drugs examined the risk of *nontuberculosis* opportunistic infections associated with specific drugs.[272] Using the general French population as the reference group, the annual adjusted incidence rate was highest with infliximab, 290.0 (95% CI, 0.0 to 835.8); lowest with etanercept, 7.1 (95% CI, 0.0 to 24.2); and 61.8 (95% CI, 0.0 to 162.5) with adalimumab (rates per 100 000 patient-years). Using a case-control design with 38 cases and 114 controls, multivariate analysis indicated an increased risk with infliximab ($P<0.0001$) or adalimumab ($P=0.02$) relative to etanercept, as well as exposure to corticosteroids ($P=0.002$).

Herpes zoster

Two cohort studies suggested that the risk of herpes zoster is not increased with etanercept, but differed on whether it is protective against the infection. The evidence from these studies was too diverse to draw conclusions about adalimumab and infliximab.[273,296] A fair-quality retrospective cohort study of data on 20 357 patients in the Veteran's Affairs healthcare system treated for rheumatoid arthritis was conducted using administrative data and involved 3565 patients taking an antitumor necrosis factor drug.[273] The other used data from a German registry of over 5000 patients with rheumatoid arthritis collected prospectively, with 3266 patients treated with an antitumor necrosis factor drug.[296] Both studies found a small increase in overall risk of herpes zoster with the combined group of drugs, but only one was statistically significant (hazard ratio, 1.38; 95% CI, 1.08 to 1.77)[296] while the other was not (hazard ratio, 1.63; 95% CI, 0.97 to 2.74);[273] pooling these together resulted in a statistically significant, but small, increase in risk: hazard ratio 1.42 (95% CI, 1.14 to 1.78). Evaluating the individual drugs, neither study indicated an increased risk with etanercept; the study using Veteran's Affairs data found the risk with etanercept to be statistically significantly reduced (hazard ratio, 0.62; 95% CI, 0.40 to 0.95)[273] while the study using registry data found a nonstatistically significant increased risk (hazard ratio, 1.36; 95% CI, 0.73 to 2.55). The results of analyses of the other two drugs differed. The study of Veteran's Affairs data had more events overall and was able to analyze the drugs individually, finding a nonstatistically significant increased risk with infliximab (hazard ratio, 1.32; 95% CI, 0.85 to 2.03), and a statistically significant decreased risk with adalimumab (hazard ratio, 0.53; 95% CI, 0.31 to 0.91).[273] The registry-based study combined data for these two drugs due to inadequate numbers of events and found a statistically significant increase in risk, although small (hazard ratio 1.82, 95% CI, 1.05 to 3.15).[296] This study, however, did an additional analysis of 1344 patients who contributed data to both the antitumor necrosis factor group and the "conventional DMARD" group. They conducted this subgroup analysis in order to account for potential selection bias that may have resulted in patients at higher baseline risk of herpes zoster being prescribed antitumor necrosis factor drugs. This subgroup did in fact have a significantly higher risk of herpes zoster than the other patients (hazard ratio, 2.4; 95% CI, 1.5 to 3.9). Adjusting for age and propensity score, adalimumab and infliximab (combined data) resulted in a greater increased risk compared with disease-modifying antirheumatic drugs (hazard ratio, 2.91; 95% CI, 1.35 to 6.30) than in the overall analysis, while etanercept did not (hazard ratio, 1.09; 95% CI, 0.39 to 3.06).

Lymphoma and other malignancies

Adults

The baseline risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, was generally increased in patients with rheumatoid arthritis.[311] The best estimate of risk for each targeted immune modulator came from two good-quality systematic reviews. A large, good-quality systematic review of 25 trials and extension studies, including 12 945 patients, found the risk of malignancy to be 1% to 5.7% with etanercept, 0.16% to 5.1% with infliximab, and 0.1% to 1.1% with adalimumab.[177] The risk of lymphoproliferative cancer was estimated to be 0% with abatacept, 0.2% with adalimumab, 0.1% with certolizumab, 0.4% with etanercept, 0% with golimumab, 0.1% with infliximab, and 0% with rituximab in 13 open-label extension studies including 11 954 patients with 325 904 person-months of observation.[282]

The evidence on the potential increased risk of malignancy with targeted immune modulators relative to each other or other treatments was conflicting and the strength of the evidence was low. A comprehensive systematic review found the pooled risk of lymphoproliferative malignancies for the targeted immune modulators to be odds ratio 0.53 (95% CI, 0.17 to 1.66).[282] Two individual patient data meta-analyses, one of etanercept in 3316 patients with rheumatoid arthritis only[312] and the other of almost 23 000 patients receiving adalimumab, infliximab, and etanercept for any indication, were unable to show statistically significant increases in risk of malignancy.[284] Based on trials conducted up to year 2006, the hazard ratio of malignancy with etanercept taken for at least 12 weeks compared with control was 1.84 (95% CI, 0.79 to 4.28). Focusing only on the antitumor necrosis factor drugs adalimumab, infliximab, and etanercept, Askling, et al. conducted an individual patient data meta-analysis based on 74 trials that were at least 4 weeks long and conducted up to year 2009.[284] These authors concluded that in addition to the short-term nature of the trials not being adequate to identify cancer risk, variation in baseline cancer risk and reporting details across the trials made it impossible to differentiate cancer risk among the drugs. Overall, 0.84% of those on antitumor necrosis factor drug compared with 0.64% of those in control groups developed cancer during the trial period, resulting in a relative risk of 0.99 (95% CI, 0.61 to 1.68) for any malignancy with the drugs as a group. Cochrane reviews of antitumor necrosis factor drugs approved in recent years (since 2008) assessing the risk of malignancy have not found increased incidence based on the limited short-term trial evidence: based on three trials of 1179 patients, the odds ratio with certolizumab was 1.26 (95% CI, 0.26 to 6.08)[93] and a review of golimumab reported no evidence on malignancies.[110] A good-quality systematic review of antitumor necrosis factor drugs that included these newer drugs also found a nonstatistically significant increase in risk of malignancy for the drugs as a group (1.48, 95% CI, 0.71 to 3.09) as well as individual estimates.[313]

Multiple large retrospective cohort studies also have not detected an increased risk of solid tumors in patients taking antitumor necrosis factor drugs (primarily adalimumab, etanercept and infliximab).[275,314-317] For example, a large retrospective Swedish cohort study, based on data of more than 60 000 rheumatoid arthritis patients, found similar standardized incidence ratios for solid cancers (standard incidence ratio, 0.8; 95% CI, 0.4 to 1.8)[316] and hematopoietic malignancies (relative risk, 1.1; 95% CI, 0.6 to 2.1)[318] between rheumatoid arthritis patients treated with antitumor necrosis factor medications and those on conventional therapy using both a contemporary and a historic control. Using this same cohort, a study of incidence of any cancer by duration of exposure to antitumor necrosis factor medications indicted no increased risk over time (less than 1 year, 1 to 2 years, and more than 2 years) with etanercept, infliximab, or

adalimumab.[274] Using data from a German registry of over 5000 patients with rheumatoid arthritis, a statistically significant difference in cancer recurrence was not found among those exposed to antitumor necrosis factor drugs or anakinra and those not exposed.[275] However, the numbers of patients with prior malignancy were small (N=122).

A good-quality meta-analysis of more than 5000 rheumatoid arthritis patients from adalimumab and infliximab placebo-controlled efficacy trials found an increased risk of any malignancy with the antitumor necrosis factor drugs relative to placebo.[319] 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. Two pooled analyses of adalimumab, one in 10 041 patients with rheumatoid arthritis and one in 3160 patients with Crohn's disease, reported no statistically significant increase compared with populations standards.[320,321]

Multiple large retrospective cohort studies have also not detected an increased risk of hematopoietic malignancies in patients taking antitumor necrosis factor drugs (primarily adalimumab, etanercept, and infliximab).[274,314,315,318,322] Limiting to the risk of lymphoma, two studies indicated an increased risk with tumor necrosis factor drugs. A fair-quality retrospective cohort study of 1557 Swedish patients found a substantially increased relative risk of lymphoma for patients treated with antitumor necrosis factor drugs compared with those on non antitumor necrosis factor medications (hazard ratio, 4.9; 95% CI, 0.9 to 26.2), although results did not reach statistical significance.[323] Similarly, a poor-quality study of 1064 Italian patients also found an increased risk of lymphoma with antitumor necrosis factor drugs compared with general population estimates.[324] This study was poor quality for reasons related to the way in which the outcomes were defined, measured, and ascertained.

While these studies did not clearly show or rule out an increased risk of any malignancy with antitumor necrosis factor drugs, the evidence on skin cancer was somewhat more consistent. An individual patient data meta-analysis based on 74 trials of antitumor necrosis factor drugs of at least 4 weeks duration (above) found that the risk of nonmelanoma skin cancers was statistically significantly increased (relative risk, 2.02; 95% CI, 1.11 to 3.95).[284] Three observational studies of patients with rheumatoid arthritis reported on skin cancer incidence with exposure to antitumor necrosis factor drugs.[314,325,326] Increased risk of nonmelanotic skin cancer was found in two studies;[314,325] the highest-quality study (N=13 001) found a statistically significantly increased risk of nonmelanotic skin cancer with infliximab (odds ratio, 1.7; 95% CI, 1.3 to 2.2), and a near statistically significant increased risk with etanercept (odds ratio, 1.2; 95% CI, 1.0 to1.5),[314] while the other study of unclear quality (N=15789) found a statistically significantly increased risk of antitumor necrosis factor drugs (etanercept, infliximab or adalimumab) compared with methotrexate (hazard ratio, 1.28; 95% CI, NR; *P*=0.014).[325] A small fair-quality study (N=1442) found no increased incidence of cutaneous squamous cell carcinoma with etanercept (crude rate: 2.8 cases per 1000 patients).[326]

Evidence on the risk of malignancies with targeted immune modulators that work thorough mechanisms other than antagonizing tumor necrosis factor was very limited. A Cochrane review of abatacept (not an antitumor necrosis factor drug) compared with placebo pooled data from four trials of 2444 patients and found the odds ratio for any malignancy at 12 months was 1.02 (95% CI, 0.59 to 1.75).[327] A pooled analysis of 2578 patients with rheumatoid arthritis who received at least one course of rituximab was also found similar to population standards.[303]

Children

In 2009 the US Food and Drug Administration issued a warning about an increased risk of cancer in children and adolescents who receive antitumor necrosis factor drugs (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm). The warning was 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 antitumor necrosis factor drugs. Based only on the data reported in the warning, 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 antitumor necrosis factor treatment. We found no further studies reporting on the risk of malignancy in children receiving antitumor necrosis factor drugs.

Cardiovascular events and congestive heart failure

The existing evidence on the risk of cardiovascular events and congestive heart failure with antitumor necrosis factor therapy was mixed and no direct evidence comparing the drugs was found.

A large, good-quality Cochrane review estimated the rate of congestive heart failure to be 0.1% with adalimumab, 0.3% with etanercept, 0.7% with golimumab, and 0% with infliximab.[282] 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) for patients treated with antitumor necrosis factor drugs compared with those not treated with antitumor necrosis factor drugs over a 2 year period.[328] In contrast, a retrospective cohort study based on Medicare data reported a statistically significantly higher risk for hospitalization due to congestive heart failure in rheumatoid arthritis patients treated with antitumor necrosis factor drugs compared with those on methotrexate (hazard ratio, 1.70; 95% CI, 1.07 to 2.69).[329] An analysis of data from the MedWatch system reported that half of the patients who developed new onset congestive heart failure under etanercept or infliximab treatment did not have any identifiable risk factors.[330] However, five retrospective cohort studies could not detect statistically significant differences supporting an increased or a decreased risk for cardiovascular events or congestive heart failure between antitumor necrosis factor treatment and conventional rheumatoid arthritis[331-335] or Crohn's disease treatment.[333]

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 antitumor necrosis factor drugs after 6 months compared with nonresponders (3.5 events per 1000 patient-years compared with 9.4 events per 1000 patient-years).[334] Using this same registry, the authors evaluated the risk of first venous thrombotic event in patients exposed to antitumor necrosis factor drugs and found no evidence of increased risk with the drugs as a group or between the drugs (etanercept, infliximab, and adalimumab).[271]

Pooled analysis of three placebo-controlled trials of ustekinumab in patients with psoriasis did not find an increased risk of myocardial infarction, stroke, or cardiovascular death compared with placebo over 12 to 20 weeks (risk difference 0.1%, 95% CI -0.3 to 0.4%).[336] These outcomes did not include nonfatal heart failure.

Other serious adverse events*: autoimmunity, demyelination and hepatic events*

Evidence from randomized controlled trials and observational studies was 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, suggested an association between infliximab and drug induced lupus and other autoimmune diseases.[285,287,337,338] Lupus-like syndromes have also been reported for adalimumab.[339] 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.[340] Development of antinuclear, antidouble-stranded DNA, or antihistone antibodies have also been reported in regulatory trials of other antitumor necrosis factor alpha drugs.[341,342] A retrospective cohort study indicated an increased risk of new onset psoriasis in rheumatoid arthritis patients treated with antitumor necrosis factor drugs.[343]

Similarly, reports from MedWatch indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[339,344] Similar cases have been seen in regulatory trials of adalimumab.[342] All neurologic events partially or completely resolved after discontinuation of treatment.

A retrospective cohort study based on more than 1400 patients treated with either etanercept or infliximab reported a substantially increased risk of serious hepatic events with targeted immune modulators (relative risk, 5.5; 95% CI, 1.2 to 24.6).[345] The wide confidence intervals, however, indicate the uncertainty of these results.

General tolerability and safety

Adults

The most comprehensive and highest-quality systematic reviews of harms associated with targeted immune modulators in adults was a Cochrane review of 209 studies published up to January 2010 (163 trials involving 50 010 patients and 46 extension studies involving 11 954 patients) that conducted a network meta-analysis on the major adverse events associated with all of the targeted immune modulators except natalizumab, alefacept, and efalizumab.[282] Two placebo-controlled trials (one of abatacept and one of adalimumab) published since this review were found but did not contribute important new information beyond what is included in the review.[178,239] Other studies not included in this review that did provide additional evidence are discussed below.

Total adverse events

The good-quality review and network analysis by Singh, et al. did not find any statistically significant differences in overall adverse event rates between the drugs.[282]A small head-to-head trial (N=100) of infliximab, etanercept, and adalimumab not included in this review found the rate of overall adverse events to be highest with infliximab (23%), followed by etanercept (17%) and lowest with adalimumab (statistical analysis not undertaken, presumably due to the small numbers of patients included).[276]

A nonrandomized trial using the adverse reaction terminology from the World Health Organization found no statistically significant differences in adverse events were reported between etanercept and infliximab.[40] 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.[105,122,125,339,346-348]

Withdrawal due to adverse events

Based on a network analysis of trials, Singh, et al., found that infliximab resulted in higher rates of withdrawal from study due to adverse events than the other targeted immune modulators. Compared to infliximab, the odds ratios were statistically significantly lower for abatacept (odds ratio, 0.53; 95% CI, 0.29 to 0.95), adalimumab (odds ratio, 0.50; 95% CI, 0.32 to 0.78), etanercept (odds ratio, 0.63; 95% CI, 0.41 to 0.95), and golimumab (odds ratio, 0.55; 95% CI, 0.30 to 0.99).[282] Comparisons of infliximab to anakinra, certolizumab, rituximab and tocilizumab were not statistically significant, nor were any other comparisons among the drugs.

Several observational studies have reported on discontinuation of targeted immune modulators.[45,277-281] Three reported only raw rates of discontinuation due to adverse events. A German retrospective, population-based cohort study reported rates of 16% for anakinra, 13% for etanercept, and 19% for infliximab after 12 months.[277] A very small (N=127) retrospective cohort study of a Finnish registry of patients with psoriatic arthritis reported rates of 50% with anakinra (one of two patients due to leukocytopenia and elevated alanine aminotransferase), 15% with infliximab, and 1.3% with etanercept after 24 months of treatment.[279] A retrospective cohort study of an Italian registry reported 20% with either infliximab or adalimumab and 12% with etanercept.[281] Two deaths in this study (with 6 months of follow-up) were thought to be related to study drug. One was due to heart failure while taking adalimumab and the other was due to postinfective cerebritis while taking etanercept. 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.[349]

The other three cohort studies were based on registries of patients with rheumatoid or psoriatic arthritis from Denmark, Switzerland, and Britain and reported adjusted risk of discontinuation due to an adverse event among infliximab, etanercept, and adalimumab.[45,278,280] These studies confirmed the findings of the trials reported above that infliximab has a higher risk of discontinuation due to adverse events compared with the other two drugs. For example in the Danish study (N=469 in analysis), the hazard ratios were 1.77 (95% CI, 1.34 to 2.34) compared with adalimumab and 2.65 (95% CI, 1.88 to 3.73) compared with etanercept.[45] Infusion or allergic reactions contributed to the increased risk of discontinuation were hazard ratio 2.11 (95% CI, 1.23 to 3.62).[278] The third study did not make direct comparisons, but did evaluate the risk of discontinuing drug due to adverse events over time, finding that the risk increased somewhat over time for adalimumab and etanercept, but much more for infliximab. At the third year of follow-up, the hazard ratio for still being on drug was 0.91 (95% CI, 0.84 to 0.95) for etanercept and 0.92 (95% CI, 0.75 to 0.98) for adalimumab compared with 0.72 (95% CI, 0.72 to 0.890) for infliximab.[280]

Serious adverse events (as a group)

The good-quality Cochrane review of 209 studies conducted a network analysis of the rate of serious adverse events associated with the targeted immune modulators.[282] Serious adverse events were included based on individual study definitions (e.g., events requiring medical intervention with or without the need for hospitalization). The overall quality of the bodies of evidence was rated high for abatacept and anakinra, and moderate for all others, using the GRADE system. Relative to control groups, no single targeted immune modulator resulted in

statistically significantly greater odds of a serious adverse event. Abatacept (odds ratio, 0.65; 95% CI, 0.42 to 1.01) and anakinra (odds ratio, 0.55; 95% CI, 0.29 to 1.06) had point estimates on the side of a lower odds compared with control, while all other targeted immune modulators had point estimates on the side of increased odds. In indirect comparisons (network analysis) these two drugs showed significantly lower odds of a serious adverse event compared with most other targeted immune modulators (Table 18).The authors of this review noted that the high dropout rate in some studies may influence the observable adverse event rates, and that there may be a differential effect depending on whether one group experienced a higher dropout rate than another.

Table 18. Statistically significant differences in serious adverse events

Drug	Comparator drug	Odds ratio (95% confidence interval)
Abatacept	certolizumab	0.45 (95% CI, 0.24 to 0.82)
Abatacept	etanercept	0.53 (95% CI, 0.32 to 0.88)
Abatacept	infliximab	0.50 (95% CI, 0.31 to 0.82)
Abatacept	rituximab	0.59 (95% CI, 0.36 to 0.98)
Abatacept	tocilizumab	0.52 (95% CI, 0.27 to 0.99)
Anakinra	Certolizumab	0.38 (95% CI, 0.18 to 0.82)
Anakinra	Etanercept	0.45 (95% CI, 0.22 to 0.91)
Anakinra	Infliximab	0.43 (95% CI, 0.21 to 0.86)
Anakinra	Tocilizumab	0.44 (95% CI, 0.20 to 0.99)

Injection site or infusion reactions

Injection site reactions (adalimumab, alefacept, anakinra, certolizumab pegol, and etanercept) and infusion reactions (abatacept, infliximab, natalizumab, and rituximab) were the most commonly and consistently reported adverse events. In clinical trials of infliximab, 17% of patients experienced infusion reactions. These were mostly nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. Ten percent of rheumatoid arthritis patients in a Japanese post marketing surveillance of 5000 patients reported infusion reaction with infliximab.[350] A similar post market surveillance study from Japan reported a rate of 3.5% with etanercept (based on over 7000 patients).[306] The rates of infusion reactions reported in abatacept and natalizumab studies were 9% and 11%, respectively. In efficacy trials of rituximab up to 32% of patients experienced infusion reactions during the first infusion.

A small proportion of infusion reactions resembled anaphylactic reactions or led to convulsions and were considered serious adverse events; approximately 0.5% of infusions of infliximab resulted in severe reactions.[285] Less than 2% of patients in clinical trials discontinued infliximab because of infusion reactions. However, as noted above, in an observational study based on a Swiss registry of patients with rheumatoid arthritis, infusion, or allergic reactions contributed to increased risk of discontinuation with infliximab compared with etanercept or adalimumab (hazard ratio, 2.11; 95% CI, 1.23 to 3.62).[278]

In contrast, injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity. 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 was consistent with numbers reported in the respective package inserts.[342,351,352] Relative to placebo certolizumab did not result in higher risk of injection site reactions at 400 mg (odds ratio, 0.69; 95% CI, 0.31 to 1.49), but was increased at the lower dose (200 mg; odds ratio, 4.59; 95% CI, 1.38 to 15.32).[93]

Combination strategies in adults

The combination of two antitumor necrosis factor drugs with a targeted immune modulator of a different mechanism of action 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).[50] 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, two 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%).[51,353] In a small fair-quality trial of rituximab added to either etanercept or adalimumab, the combination therapy resulted in 6% of patients with a serious adverse event compared with 0% in the control group, and 5.5% withdrew due to adverse events compared with 0%.[354] The difference in adverse events appeared to be related to differences in the rate of infusion reactions, although the 24-week duration of the study may not have been adequate to identify other differences.

Children

No evidence on the comparative safety of targeted immune modulators in children exists. In the following paragraphs we summarize the scarce evidence that exists on the safety of targeted immune modulators in pediatric populations. Overall, various methodological issues limited the quality and applicability of this body of evidence.

A major limitation was that the studies had small sample sizes and lacked power to detect rare but potentially serious adverse events. Furthermore, many of the studies used run-in periods, which seriously compromised the external validity of findings. During these run-in periods, with the active drug, only patients who responded, adhered to treatment, and had no intolerable adverse events were randomized to continuing active treatment or to placebo. Therefore, 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 focused on results from the open-label run-in phases that included a less selected population than the randomized phases.

Five randomized controlled trials provided information on the general tolerability and safety of targeted immune modulators in children; four were in children with juvenile idiopathic arthritis and one in children with plaque psoriasis. Drugs studied were abatacept,[150] adalimumab,[152] etanercept,[153,253] and infliximab.[154] Generally, adverse event 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,[152] 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.

Injection site reactions (39% of children) and upper respiratory tract infections were the most commonly reported adverse events with etanercept during the run-in phase of a trial in children with juvenile idiopathic arthritis.[153] Nine children (15%) had to be hospitalized because of serious adverse events during the 2-year extension phase.[153,355] Fifty percent of the children received etanercept up to 4 years and the rate of serious adverse events in these children was 0.04 per patient-year.[356] In the second trial of etanercept, in 211 children with plaque psoriasis, four serious adverse events occurred during the run-in phase treatment with etanercept including three serious infections.[253] Injection site reactions were reported to be mild and transient. In an uncontrolled trial of etanercept (n=60), 20% of children withdrew over a 12-month period because of adverse events including severe infections, pancytopenia, and cutaneous vasculitis.[357] 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 trials.[156] Overall, 3.4% of etanercept-treated children withdrew because of adverse events.

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 children treated with infliximab experienced acute infusion reactions.[154] A case series of children (N=11) with Crohn's disease or ulcerative colitis reported infusion reactions in 8.1% of children.[358] By comparison, only 4% of children on abatacept reported acute infusion reactions.[150]

A study of data from a registry of 202 children treated with infliximab as maintenance therapy for at least one year for Crohn's disease reported one case of conversion of purified protein derivative skin test with a chest x-ray negative for tuberculosis, one case of varicella infection requiring hospitalization, one malignancy ultimately determined to be Hodgkin's disease, and one death due to cardiac arrest (more than 6 months following discontinuation of infliximab).[359]

Table 19. Summary of studies with direct comparisons of adverse events in adults receiving targeted immune modulators

Author, year	Study design	N	Drug	Population	Results	Quality rating
Serious infections						
Salmon-Ceron, 2011[272]	Case Control RATIO Registry	38 cases 114 controls	Etanercept Adalimumab Infliximab	Mixed	Risk of opportunistic infections was greater with infliximab and adalimumab than etanercept	Fair
Dixon, 2010[271]	Prospective cohort study BSRBB Registry	10 712	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	Risk of tuberculosis was statistically significantly higher with infliximab and adalimumab than with etanercept.	Fair
Galloway, 2011[270]	Prospective cohort study BSRBB Registry	11 798	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	The risk of serious infection did not differ between the drugs, but was slightly increased for the group vs. DMARDs.	Good
McDonald, 2010[273]	Retrospective cohort study Veterans Affairs	3661	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	Relative to controls, etanercept and adalimumab have a lower risk of herpes zoster; risk with infliximab is similar to controls.	Fair
Favalli, 2009[269]	Retrospective cohort study	1064	Adalimumab Etanercept Infliximab	Rheumatic diseases	Treatment with adalimumab, etanercept, infliximab is associated with an increased risk of infections	Fair
Malignancy						
Askling, 2009[274]	Retrospective cohort study Multiple Swedish Registries	6366	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	Incidence of malignancy not increased overall, or by duration of exposure up to 3 years).	Good
Strangfeld, 2010 [275]	Retrospective cohort study RABBIT Registry	5120	Etanercept Adalimumab Infliximab Anakinra	Rheumatoid Arthritis	Cancer recurrence was not found to be increased in patients taking etanercept, adalimumab, or infliximab	Fair
Geborek, 2005[323]	Retrospective cohort study	1557	Etanercept Infliximab	Rheumatoid Arthritis	Higher risk of lymphoma for anti-TNF drugs	Fair
Overall risk of adverse events and discontinuation due to adverse events						
Hetland, 2010[45]	Prospective cohort study DANBIO Registry	2326	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	Infliximab has a higher risk of discontinuing drug due to adverse events than, adalimumab or etanercept	Good
Marchesoni, 2009[281]	Prospective cohort study LOHREN Registry	1064	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	Infliximab and adalimumab had a higher risk of discontinuing drug due to adverse events than etanercept	Fair

Author, year	Study design	N	Drug	Population	Results	Quality rating
Du Pan, 2009[278]	Prospective cohort study SCQM-RA Registry	2364	Etanercept Adalimumab Infliximab	Rheumatoid Arthritis	Risk of discontinuation due to adverse events higher with Infliximab than etanercept and adalimumab. Infusion or allergic reactions contributed to the increased rate.	Fair
Saad, 2009[280]	Prospective cohort study BSRBB Registry	566	Etanercept Adalimumab Infliximab	Psoriatic Arthritis	The risk of discontinuing drug due to adverse events increased more over time with infliximab than with adalimumab and etanercept,	Fair
Virkki, 2010[279]	Prospective cohort study ROB-FIN Registry	127	Etanercept Infliximab Anakinra Adalimumab	Psoriatic Arthritis	Rate of discontinuing drug due to adverse events was highest with anakinra, followed by infliximab and lowest with etanercept	Fair
Zink, 2005[277]	Retrospective cohort study	1523	Anakinra, Etanercept Infliximab	Rheumatoid Arthritis	Similar discontinuation rates because of adverse events among anakinra, etancercept and infliximab	Fair
Kristensen, 2006[43]	Retrospective cohort study	949	Etanercept Infliximab	Rheumatoid Arthritis	More patients discontinued infliximab than etanercept due to adverse events.	Fair
Griffiths, 2010[234]	RCT	903	Etanercept Ustekinumab	Psoriasis	Overall adverse events and withdrawals due to adverse events similar: Injection-site reactions more frequent with etanercept than ustekinumab	Fair
Atteno, 2010[276]	RCT	100	Etanercept Adalimumab Infliximab	Psoriatic Arthritis	Infliximab and etanercept resulted in higher rates of adverse events than adalimumab (23%, 17%, 6%; *P*<0.001)	Fair
Schiff, 2008[39]	RCT	431	Abatacept Infliximab	Rheumatoid Arthritis	Abatacept resulted in lower rates of serious AEs (9.6 vs. 18.2%), serious infections (1.9 vs. 8.5%) and discontinuations due to AEs (3.2 vs. 7.3%)	Fair

Abbreviations: AE, adverse event; DMARD, disease-modifying antirheumatic drug; RCT, randomized controlled trial; TNF, tumor necrosis factor.

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 between targeted immune modulators in effectiveness or adverse events among subgroups was 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 with another or compared with the general population. Subgroup analyses and indirect evidence from placebo-controlled trials provided evidence for some targeted immune modulator drugs in certain subpopulations.

Evidence on the effect of age was mixed. Indirect evidence from three studies[360-362] indicated 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, while two studies on rheumatoid arthritis patients found treatment response to be better in younger patients than older patients[42] and adverse events found to be significantly higher in patients 70 years and older.[350]

Limited evidence on the effect of race on differences in effectiveness or harms of targeted immune modulators exists. Similar to findings in predominantly white populations, indirect evidence from placebo-controlled trials showed that adalimumab and ustekinumab had better response rates compared with placebo in Asian patients with plaque psoriasis and rheumatoid arthritis.[74,238,366] Patients of non white ethnicity had a six-fold increased risk of tuberculosis compared with white patients treated with antitumor necrosis factor drugs in patients with rheumatoid arthritis.[271]

The evidence on differences between men and women is sparse: one study reported on efficacy and one study reported on adverse events. A pooled analysis of nine efficacy studies of alefacept did not detect any differences in efficacy and safety for obese or diabetic patients with plaque psoriasis.[362]

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[362,363] while three studies reported an increased risk of the occurrence of adverse events.[350,353,364]

All studies are shown in Table 20, 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 nine efficacy studies of alefacept did not show any differences in efficacy and safety in patients older than 65 years compared with younger patients during 12 weeks of treatment.[362]

This finding was supported by a pooled data analysis of 18 rheumatoid arthritis trials, two psoriatic arthritis trials, and two ankylosing spondylitis trials.[360] This analysis detected no statistically 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 antitumor necrosis factor treated patients older than and younger than 65 years.[361]

In contrast, a prospective cohort study[42] (N=3694) indicated that response to treatment in rheumatoid arthritis patients treated with etanercept and infliximab was better in those younger than 65 years.[42] A post marketing surveillance of 5000 rheumatoid arthritis patients reported a difference in adverse events in older patients.[350] Risk factor for bacterial pneumonia in infliximab-treated patients was statistically 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). In a prospective cohort study of antitumor necrosis factor drugs in patients with inflammatory bowel disease, analysis by age indicated that treatment with infliximab or adalimumab resulted in 11% with severe infections and 10% of deaths among those patients 65 years or older, compared with 2.6% and 1% respectively for patients under 65.[365] Similarly, another prospective cohort study of 4167 Swedish rheumatoid arthritis patients taking antitumor necrosis factor drugs (adalimumab, etanercept or infliximab) in the ARTIS register[290] showed a higher relative risk for hospitalization for any infection associated with antitumor necrosis factor drugs with age over 55 years (>64 years, relative risk, 2.12 [95% CI, 1.48 to 3.04]; 56 to 63 years, relative risk, 1.51 [95% CI, 1.05 to 2.19]; 46-55 years, relative risk, 1.30 [95% CI, 0.89 to 1.89]; <46 years, relative risk, 1.0]) (baseline reference). However, both the studies did not specify the results by specific antitumor necrosis factor drug used.

Racial groups

In general, trials were conducted predominantly in white populations. Similar to the findings in predominantly white populations, indirect evidence from two fair-quality, short-term (12 and 24 weeks) trials of Asian patients with plaque psoriasis concluded that adalimumab[238] and ustekinumab[366] were statistically significantly better than placebo based on the Psoriasis Area and Severity Index 75 as the primary measure for response. Additional outcome measures were the Dermatology Life Quality Index and Physician Global Assessments. In another fair-quality 12-week trial in Taiwanese patients with rheumatoid arthritis maintained on methotrexate and treated with adalimumab or placebo, no statistically significant difference was found on the American College of Rheumatology 20, 50, and 70 criteria. Significant differences were found in the number of swollen joints (*P*=0.011), patient global assessment of disease activity (*P*=0.040), pain visual analogue scale (*P*=0.015), and disability indices of the health assessment questionnaire (*P*=0.031), favoring adalimumab.[74]

In a good-quality cohort study, based on the British Society for Rheumatology Biologics Register of almost 14 000 patients, non white patients were found at statistically significantly greater risk of developing tuberculosis compared with white patients taking antitumor necrosis factor drugs.[271] Age, sex, and calendar year-adjusted incidence rate ratio for active tuberculosis in non white compared with white patients with rheumatoid arthritis was 6.5 (95% CI, 2.8 to 15.3). In contrast, tuberculosis was the cause of death in six white patients and zero non white patients. However, ethnicity data were missing for 15% of patients in the overall registry and for 18% of those diagnosed with tuberculosis.

Gender

We did not identify any study specifically designed to compare the effects of targeted immune modulators in females compared with males. On average, study populations comprised of more

females than males; this fact reflects population and disease demographics and does not provide insight into treatment differences.

The available evidence was of low methodological quality and findings were mixed. One prospective observational study of rheumatoid arthritis patients treated with antitumor necrosis factor drugs found no statistically significant differences in treatment response between men and women at 3 and 6 months of follow-up.[367] The Japanese post marketing surveillance study of infliximab (described above)[350] reported that men were statistically 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 suggested that effectiveness or adverse events differed between females and males.

Comorbidities

Overall, the evidence of the effect of certain comorbid conditions on the efficacy and safety of targeted immune modulators was mixed. Three studies reported on rheumatoid arthritis patients with comorbid respiratory disease.[350,353,364] One randomized controlled trial assigned rheumatoid arthritis patients with asthma or chronic obstructive pulmonary disease to 16 weeks of treatment with etanercept or placebo.[364] 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 statistically significantly elevated (1.58; 95% CI, 0.65 to 3.87). A post marketing surveillance of the safety of infliximab in rheumatoid arthritis patients reported a statistically 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).[350] A subgroup analyses from one randomized controlled trial found that more adverse events were reported in rheumatoid arthritis patients with chronic obstructive pulmonary disease taking abatacept compared with placebo.[353] 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, two in rheumatoid arthritis patients,[353,364] and one in plaque psoriasis.[362] One trial stratified randomization of 535 rheumatoid arthritis patients by diagnosis of diabetes (with or without another comorbidity).[364] Subjects were treated with etanercept (25 mg twice weekly) or placebo for 16 weeks 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 statistically significantly elevated (1.34; 95% CI, 0.59 to 3.08).

These findings were supported by a subgroup analysis of a randomized controlled trial of rheumatoid arthritis patients with diabetes treated with abatacept.[353] 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]).[353] Rates of serious adverse events were higher in the abatacept group (21.5% compared with placebo 12.9%).

Results from a pooled analysis of nine efficacy studies of alefacept for the treatment of plaque psoriasis indicated that alefacept has similar efficacy and safety in obese and diabetic patients compared with patients without these comorbidities.[362]

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, and central nervous system-related events).[363,368] Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

In a prospective cohort study of 4167 Swedish rheumatoid arthritis patients taking antitumor necrosis factor drugs (adalimumab, etanercept or infliximab),[290] the risk for hospitalization with any infection was significantly increased for patients with comorbid cardiovascular disease, adjusted relative risk 1.61 (1.24 to 2.07) or pre-existing infection, adjusted relative risk 1.63 (1.28 to 2.07). However, this study did not report results by specific antitumor necrosis factor drugs.

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 antitumor necrosis factor therapy is mixed. A large retrospective cohort study (N=13171) 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 antitumor necrosis factor therapy compared with those not treated with antitumor necrosis factor medications over a 2 year period.[328] 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 antitumor necrosis factor therapy after 6 months compared with nonresponders (3.5 events/1000 patient-years compared with 9.4 events/1000 patient-years).[334]

By contrast, indirect evidence indicates an increased risk of worsening heart failure and mortality during antitumor necrosis factor alpha therapy. One trial[369] 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.[369] This evidence on congestive heart failure is presented in greater detail in Key Question 2.

Other subgroups

We found a case series of 131 pregnant women exposed to infliximab; however, this study did not meet our eligibility criteria.[370] 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 with 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, and infliximab) may be associated with an increased risk of serious infections, an increased risk of neutropenia, and no additional benefit compared with monotherapy. This evidence came from a 24-week trial comparing concurrent treatment with anakinra and etanercept to etanercept monotherapy in patients with rheumatoid arthritis.[50] Patients treated with both anakinra and etanercept had a 7% rate of serious infections compared with 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 one or more concomitant medications (e.g., 5-aminosalicylates, antibiotics, antivirals, azathioprine, corticosteroids, folic acid, narcotics, nonsteroidal anti-inflammatory agents, 6-mercaptopurine and methotrexate) 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.[371] 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 with 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.[372] 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 20. Summary of studies assessing subgroups

Author, year	Study design	N	Duration	Drug	Population	Results	Quality Rating
Age							
Fleischmann et al. 2005[360]	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[361]	Retrospective cohort	1571	Median 3 years	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[362]	Pooled analysis of efficacy trials	NR	12 weeks	Alefacept	Patients with plaque psoriasis	No differences in efficacy and adverse events between patients older and younger than 65 years	Fair
Takeuchi et al. 2008[350]	Postmarketing surveillance	5000	6 months	Infliximab	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[42]	Prospective cohort study	3694	52 weeks	Etanercept Infliximab	Patients with RA	Patients younger than 65 years had better response	Fair
Race							
Asahina 2010[238]	RCT	169	24 weeks	Adalimumab	Patients with plaque psoriasis	Significantly higher response rates in Japanese patients treated with drug compared with placebo	Fair
Chen, 2009[74]	RCT	47	12	Adalimumab	Patients with RA	No significant difference in ACR 20 response rates in Taiwanese patients treated with drug compared with placebo	Fair
Tsai 2011[366]	RCT	121	36 weeks	Ustekinumab	Patients with plaque psoriasis	Significantly higher response rates with drug compared with placebo in Taiwanese and Korean patients	Fair
Dixon 2010[271]	Prospective cohort study BSRBR Registry	13739	7345 person-years DMARD, 34025 person-years anti-TNF	Adalimumab Etanercept Infliximab	Patients with RA	Incidence rate of tuberculosis statistically significantly higher in non white patients	Fair
Comorbidities							
Chung et al. 2003[369]	RCT	150	28 weeks	Infliximab	Patients with CHF	Infliximab-treated (10 mg) patients were more likely to die or have heart failure than placebo-treated patients	Fair

Author, year	Study design	N	Duration	Drug	Population	Results	Quality Rating
Gottlieb et al. 2005[362]	Pooled analysis of efficacy trials	NR	12 weeks	Alefacept	Patients with plaque psoriasis	No differences in efficacy and adverse events in diabetic and obese patients compared with the general study population	Fair
Dixon et al. 2007[334]	Retrospective cohort study	10840	16126 person years	Adalimumab etanercept, infliximab	Patients with RA	Significantly reduced risk of myocardial infarction in responders to anti-TNF treatment compared with non responders	Good
Schiff et al. 2004[363] and Fleischmann et al. 2003[368]	Subgroup analyses of RCT	1414	6 months	Anakinra	Patients with RA	Incidence rates of adverse events similar in patients with comorbidities	Fair
Takeuchi et al. 2008[350]	Postmarketing surveillance	5000	6 months	Infliximab	Patients with RA	Significantly higher risk factor for bacterial pneumonia in patients with comorbid respiratory disease	NA
Weinblatt et al. 2006[353]	Subgroup analyses of RCT	NR	52 weeks	Abatacept vs. placebo	Patients with RA	More SAEs in abatacept-treated patients with COPD or DM	Fair
Weisman et al. 2007[364]	RCT	535	16 weeks	Etanercept vs. placebo	Patients with RA and ≥ 1 comorbidity	Etanercept associated with small increases in incidence of SAEs in patients with diabetes and COPD	Fair
Wolfe et al. 2004[328]	Retrospective cohort study	13171	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[50]	RCT	242	24 weeks	Anakinra + etanercept	Patients with RA	Patients treated with both anakinra and etanercept had a 7% rate of serious infection, compared with no infections observed with Etanercept alone.	Fair
Tesser et al. 2004[371]	RCT	1399	6 months	Anakinra	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[367]	Prospective observational study	1565	3 months	Anti-TNF	Patients with RA	Gender did not influence treatment response	Fair
Takeuchi et al. 2008[350]	Postmarketing surveillance	5000	6 months	Infliximab	Patients with RA	Significantly higher risk factor for bacterial pneumonia in men vs. women	NA

Abbreviations: AS, ankylosing spondylitis; BSRBR, British Society for Rheumatology Biologics Register; CD, Crohn's disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; 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 5210 abstracts and the inclusion of 163 studies. The large majority of these studies were 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 21).

In summary, insufficient evidence exists for most comparisons about the efficacy, effectiveness, and safety of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab 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. Infliximab, natalizumab, rituximab, and tocilizumab require intravenous administration. Abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, and ustekinumab can be administered subcutaneously. Alefacept requires an intramuscular injection. Furthermore, administration intervals differ substantially: adalimumab requires an injection once every other week, anakinra has to be administered daily, etanercept once a week, certolizumab pegol every other week, tocilizumab every 4 weeks, golimumab monthly, and ustekinumab every 4 to 12 weeks.

Key Question 1. Comparative Effectiveness

Rheumatoid Arthritis

One fair-quality, double-blinded head-to head trial provided 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 one 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 had high applicability. None of these studies provided any evidence on radiographic outcomes.

Adjusted indirect comparisons suggested greater efficacy for etanercept than abatacept, adalimumab, anakinra, and infliximab for the treatment of rheumatoid arthritis. One landmark trial was excluded from our analyses because of heterogeneity of population.[53,54] If this trial is included in the indirect comparisons no statistical advantage for etanercept remains.

The general efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, infliximab, and rituximab for the treatment of rheumatoid arthritis was well established by multiple good to fair randomized controlled trials and meta-analyses. Effect sizes were 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, infliximab, and tocilizumab for the treatment of juvenile idiopathic arthritis is supported by one randomized controlled trial for each drug. Sample sizes of these studies, however, were small (overall data on only 471 patients) and active run-in periods limited the applicability of results. In efficacy trials statistically significantly fewer patients on targeted immune modulators (20% to 37%) experienced disease flares than children treated with placebo (53% to 83%).

Ankylosing Spondylitis

No head-to-head trials provided direct evidence on the comparative efficacy of targeted immune modulators for ankylosing spondylitis. The general efficacy of adalimumab, etanercept, golimumab, and infliximab for the treatment of moderate to severe ankylosing spondylitis was supported by several good to fair randomized controlled trials and one 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. Two systematic reviews conducted indirect comparisons and summarized the comparative efficacy quantitatively. The authors reported no statistically significant differences between adalimumab, etanercept, and infliximab. One prospective registry study showed no difference in quality of life between adalimumab, etanercept, and infliximab. The strength of the evidence for comparative effectiveness was low. The general efficacy of abatacept, adalimumab, alefacept, etanercept, golimumab, infliximab, and ustekinumab for the treatment of active psoriatic arthritis was supported by several good to fair randomized controlled trials. 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 provided direct evidence on the comparative efficacy of targeted immune modulators for Crohn's disease. The general efficacy of adalimumab, certolizumab pegol, infliximab, and natalizumab for the treatment of moderate to severe Crohn's disease was supported by several good to fair randomized controlled trials and meta-analyses including 6901 patients. 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 provided evidence on the comparative efficacy of biologics for ulcerative colitis. The general efficacy of infliximab for the treatment of active ulcerative colitis was supported by one meta-analysis that pooled the results of five randomized controlled trials. In the 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. The strength of the evidence is insufficient.

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

Plaque Psoriasis

One head-to-head trial provided evidence on the comparative effectiveness of etanercept compared with ustekinumab for the treatment of severe plaque psoriasis. Ustekinumab had greater efficacy than etanercept. This trial was small and had some methodological flaws and therefore the strength of evidence for this comparison is low. The general efficacy of adalimumab, alefacept, etanercept, infliximab, and ustekinumab for the treatment of moderate to severe plaque psoriasis was supported by multiple good to fair randomized controlled trials. In efficacy trials 50% to 81% of patients treated with targeted immune modulators achieved a Psoriasis Area and Severity Index 75 response, compared with 2% 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 overall grade of the evidence on comparative harms associated with targeted immune modulators was low in adults and insufficient in children. Eighteen head-to-head studies (almost exclusively observational studies) provided direct evidence on the harms associated with targeted immune modulators. Other evidence came from indirect comparisons of over 200 randomized controlled trials with placebo or disease-modifying antirheumatic drug controls. For newer targeted immune modulators such as alefacept, natalizumab, or rituximab long-term safety data were generally missing. The rates of overall adverse events occurring with targeted immune modulators did not differ statistically significantly between the drugs. In short-term trials, abatacept and adalimumab had lower risk of serious adverse events compared with other targeted immune modulators. Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with abatacept, adalimumab, etanercept, and golimumab. Infusion or allergic reactions contributed to the increased risk of discontinuation.

Indirect evidence from short-term trials indicated that serious infections are less common with abatacept than with certolizumab, infliximab, and tocilizumab while certolizumab appeared to have a higher risk than adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab,

or placebo. Subgroup analyses indicated that the antitumor necrosis alpha monoclonal antibodies as a group (adalimumab, certolizumab, golimumab, and infliximab) have an increased risk compared with control groups, while etanercept (a tumor necrosis factor receptor antagonist) did not. Limited, low strength, observational evidence also indicated an increased risk with antitumor necrosis factor drugs etanercept, infliximab, and adalimumab and that the risk is highest in the first 6 months of treatment. Evidence was mixed on whether infliximab has a higher risk than the other drugs. The risk of herpes zoster is not increased with use of etanercept; the risk with other drugs is not clear or unknown. The risk of tuberculosis appeared to be elevated with the use of targeted immune modulators as a group based on trial data. Low strength of evidence indicated increased risk with adalimumab compared with etanercept and an increased risk with infliximab, although this difference did not reach statistical significance. The median time to event was 13.4 months from start of therapy.

On the whole, a broad range of evidence does not indicate a clear increased risk of malignancy in general with the use of targeted immune modulators. There is evidence suggesting that the risk of nonmelanoma skin cancer is increased with the use of the antitumor necrosis factor drugs adalimumab, infliximab, and etanercept. Observational evidence supported these findings, although the risk estimates are somewhat lower magnitude. The strength of evidence evaluating the comparative risk of malignancy is low. Although the US Food and Drug Administration has issued a warning about the potential increased risk of malignancy in children, evidence in children was insufficient for making conclusions.

Evidence on the comparative risk of adverse events associated with targeted immune modulators in children was very limited and is insufficient to make conclusions. The adverse event profiles appeared similar to those seen in adults, with small numbers of children experiencing serious adverse events including serious infections and injection site or infusion reactions.

Key Question 3. Subgroups

The overall grade of the evidence on efficacy and tolerability in subgroups was insufficient, largely because we did not identify any study specifically designed to compare the effect of targeted immune modulators in one subgroup of patients with another. Subgroup analyses and indirect evidence from placebo-controlled trials provided evidence for some drugs.

Indirect evidence from two pooled analyses and a retrospective cohort indicated 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. Adverse event rates were not different in patients with ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis who were older or younger than 65 years, 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.

Similar to findings in predominantly white populations, indirect evidence from placebo-controlled trials showed that adalimumab and ustekinumab had better response rates compared with placebo in Asian patients with plaque psoriasis and rheumatoid arthritis. Patients of non white ethnicity had a six-fold increased risk of tuberculosis compared with white patients treated with antitumor necrosis factor drugs in patients with rheumatoid arthritis.

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

Strength of the Evidence

Overall the strength of evidence for answering the key questions about comparative effectiveness of targeted immune modulators for the included conditions is low. Very few head-to-head trials were available and where indirect analyses were performed or included in this review the results sometimes conflicted with available head-to-head data, further decreasing our confidence in this evidence. For the one comparison where head-to-head and indirect evidence agreed we rated the strength of the evidence as moderate. Conflicting results decreased our confidence to low, and for many comparisons we had neither direct nor indirect evidence and had to rely on placebo-controlled efficacy data and therefore rated the strength of evidence for the comparative effectiveness as insufficient.

The evidence on comparative harms with targeted immune modulators was insufficient for some outcomes and generally low strength for others. For example, evidence in adults on malignancy and serious infections (as a group) was low strength because it depended on evidence from observational studies and indirect comparisons of placebo-controlled trials. Evidence on the comparative risk of adverse events associated with targeted immune modulators in children was limited to the few available placebo-controlled trials and was insufficient to make conclusions.

Overall strength of evidence to determine the differences between targeted immune modulators in effectiveness or adverse events among subpopulations was insufficient. No head-to-head trials were available and therefore placebo controlled trials and cohort studies formed the basis of the majority of evidence in subgroups.

Applicability

The applicability of the results are limited by the scope of the Key Questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were often underrepresented

For example, randomized trials of patients with rheumatoid arthritis trials were conducted in highly selected populations. In contrast, several observational studies were primary care-based and enrolled unselected patients who were treated with targeted immune modulators for rheumatoid arthritis. Overall, the direction of effect was similar between RCTs and observational studies but there might be differences in the magnitude of effects. None of the head-to-head studies investigated radiographic progression, a measure that is frequently used by clinicians to assess the progression of the disease.

In other conditions most patients had moderate or severe disease and had usually failed initial therapy with other agents (disease-modifying antirheumatic drugs or corticosteroids). Some trials exclusively enrolled patients with severe disease, i.e., more than 10% body surface area in plaque psoriasis, or a Crohn’s disease activity index as high as 450. Trials of patients with

early ankylosing spondylitis (nonradiological axial spondyloarthritis) were not included in this review.

The evidence assessing harms associated with targeted immune modulators included primarily patients with rheumatoid arthritis, with the second most represented population being patients with psoriatic arthritis. The direct evidence (trials or observational studies) generally pooled results for the antitumor necrosis factor drugs adalimumab, etanercept, and infliximab most often compared with disease-modifying antirheumatic drugs and with minimal analyses comparing the drugs to each other. Analyses using indirect evidence from placebo-controlled trials were available for all drugs except alefacept and natalizumab. Outcomes in observational studies included serious infections, malignancies, and cardiovascular events. Few trials used objective scales to assess adverse events.

Evidence on subgroups is primarily focused on the difference in the efficacy and harms of patients 65 years and older compared with those younger than 65. For racial groups, the evidence is limited mostly to placebo controlled trials in Asian patients with plaque psoriasis and rheumatoid arthritis with adalimumab being the most commonly used drug. The evidence on comorbid conditions is found primarily in rheumatoid arthritis patients with comorbid respiratory disease or diabetes. The evidence most represents the antitumor necrosis factor drugs infliximab and etanercept.

Methodological Limitations

This review has several limitations that should be noted. We did not include studies published in languages other than English, and we did not systematically search for unpublished studies. Few direct head-to-head comparisons of the included drugs have been conducted, which limits our conclusions to indirect comparisons of placebo controlled trials for most outcomes. 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. Nevertheless, findings must be interpreted cautiously. This uncertainty lowers the strength of the evidence due to heterogeneity of trial populations, interventions, and outcome measures. Finally, the individual studies included in our review had methodological limitations, with most receiving only a fair rating for internal validity.

Relevant Trials in Progress

The following trials were published after our searches and will be considered for inclusion in any further updates:

Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: Current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. Mar 2012;71(3):319-326.

Gallego-Galisteo M, Villa-Rubio A, Alegre-del Rey E, et al. Ann Rheum Dis. Published Online First September 29, 2011; doi:10.1136/annrheumdis-2011-200228.

Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab Inhibits Structural Joint Damage in Rheumatoid Arthritis Patients With Inadequate Responses to Methotrexate Results From the Double-Blind Treatment Phase of a Randomized Placebo-Controlled Trial of Tocilizumab Safety and Prevention of Structural Joint Damage at One Year. Arthritis and rheumatism. Mar 2011;63(3):609-621. http://clinicaltrials.gov/ct2/show/NCT00106535

(ULTRA 1) Adalimumab for Induction of Clinical Remission in Moderately to Severely Active Ulcerative Colitis: Results of a Randomised Controlled Trial. Reinisch, et al. Gut published online January 5, 2011m doi: 10.1136/gut.2010.221127

Walter Reinisch, William J Sandborn, Daniel W Hommes, et al. Gut published online January 5, 2011. doi: 10.1136/gut.2010.221127.

Table 21. 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 2 observational studies similar effectiveness between adalimumab and etanercept
	Low	Based on 2 observational studies, greater effectiveness of adalimumab than infliximab
	Moderate	Based on 2 trials and 5 observational studies, greater effectiveness of etanercept than infliximab.
	Low	Based on indirect comparisons, greater effectiveness of etanercept than abatacept; etanercept than anakinra; and etanercept than tocilizumab.
	Low	Based on indirect comparisons, similar efficacy between abatacept and adalimumab; abatacept and anakinra; abatacept and tocilizumab; adalimumab and anakinra; adalimumab and tocilizumab; anakinra and infliximab; anakinra and tocilizumab; and infliximab and tocilizumab.
	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	Insufficient	No comparative evidence available.
1. Comparative effectiveness for psoriatic arthritis	Low	Based on indirect comparisons and a prospective registry study, 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	Low	Based on one randomized controlled trial, ustekinumab is more efficacious than etanercept
2. Comparative harms	Low	*Serious Infections (as a group)* Less common with abatacept based on indirect comparisons and one randomized controlled trial. Certolizumab pegol associated with greater odds

Key question	Strength of evidence	Conclusion
		than adalimumab, anakinra, etanercept, golimumab, infliximab, and rituximab. The antitumor necrosis factor drugs adalimumab, etanercept, and infliximab have higher risk than DMARDs based on observational studies. Tuberculosis: risk of higher with adalimumab than etanercept based on one observational study. Herpes Zoster: risk is not increased with etanercept based on 2 observational studies, but risk with other drugs is unclear or insufficient.
	Low	*Malignancy:* Based on three observational studies and indirect comparisons, risk of non melanoma skin cancer is greater with the antitumor necrosis factor drugs adalimumab, etanercept, and infliximab than non targeted immune modulator therapy, but no increased risk of any malignancy or differences between drugs found.
	Low	*Overall adverse events:* Based on one randomized controlled trial, adalimumab has lower rate than infliximab or etanercept. Based on seven observational studies, the rate is greater with infliximab than adalimumab or etanercept. Based on one randomized controlled trial, rates similar between etanercept and ustekinumab: Injection-site reactions more frequent with etanercept than ustekinumab. In short-term trials, abatacept and anakinra have lower risk of a serious adverse event than other targeted immune modulators.
	Low	*Discontinuations due to adverse events*: Based on seven observational studies and indirect comparisons, the rate is greater with infliximab than abatacept, anakinra, etanercept and golimumab. Infusion or allergic reactions contributed to the difference in risk.
	Insufficient	*Children*: No comparative evidence available.
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	No direct comparisons available. Based on indirect evidence, adalimumab and ustekinumab had better efficacy than placebo in Asian patients with plaque psoriasis and rheumatoid arthritis. Based on one observational study, non white patients had increased risk of tuberculosis than white patients treated with antitumor necrosis factor drugs in patients with rheumatoid arthritis.
3. Subgroups – comorbidities	Insufficient	The evidence is mixed and was insufficient to draw conclusions.

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 (> 12 months) data on safety.

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Appendix A. Glossary

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

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

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

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

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

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

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

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

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

Applicability: see *External Validity*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Generalizability: See *External Validity.*

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

Harms: See *Adverse Event*

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

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

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

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

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

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

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

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

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent 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 intent-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 strategy

PubMed 10.4.2011:

Search	Most Recent Queries	Result
#1	Search "Arthritis, Rheumatoid"[Mesh] OR ankylosing spondylitis OR ankylosing arthritis OR "Arthritis, Psoriatic"[Mesh] OR "Crohn Disease"[Mesh] OR "Colitis, Ulcerative"[Mesh] OR "Arthritis, Juvenile Rheumatoid"[Mesh] OR juvenile idiopathic arthritis OR "plaque psoriasis"[All Fields] OR ("Plaque"[All Fields] AND ("psoriasis"[MeSH] OR "psoriasis"[All Fields]))	147501
#2	Search #1 Limits: Humans, Publication Date from 2011/01/01 to 2011/11/01	2402
#3	Search "abatacept"[Substance Name] OR "abatacept"[All Fields] OR "Orencia"[All Fields] OR 332348-12-6[rn]	2073
#4	Search "adalimumab"[Substance Name] OR "adalimumab"[All Fields] OR "Humira"[All Fields] OR 331731-18-1[rn]	2299
#5	Search "alefacept"[Substance Name] OR "alefacept"[All Fields] OR "Amevive"[All Fields] OR 222535-22-0[rn]	373
#6	Search "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR "Anakinra"[All Fields] OR "Kineret"[All Fields] OR 143090-92-0[rn]	3571
#7	Search "CDP870"[Substance Name] OR "Certolizumab"[All Fields] OR "Cimzia"[All Fields] OR 428863-50-7[rn]	294
#8	Search "TNFR-Fc fusion protein"[Substance Name] OR "etanercept"[All Fields] OR "Enbrel"[All Fields] OR 185243-69-0[rn]	4197
#9	Search "infliximab"[Substance Name] OR "infliximab"[All Fields] OR "Remicade"[All Fields] OR 170277-31-3[rn]	6926
#10	Search "natalizumab"[Substance Name] OR "natalizumab"[All Fields] OR "Tysabri" [All Fields] OR 189261-10-7[rn]	772
#11	Search "rituximab"[Substance Name] OR "rituximab"[All Fields] OR "Rituxan"[All Fields] OR 174722-31-7[rn]	8369
#12	Search "tocilizumab"[Substance Name] OR "actemra"[All Fields] OR "RoActemra"[All Fields] OR 375823-41-9[rn]	253
#13	Search "monoclonal antibody CNTO 1275 "[Substance Name] OR "ustekinumab"[All Fields] OR "Stelara"[All Fields] OR 815610-63-0[rn]	170
#14	Search "golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]	139
#15	Search #2 AND (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	411
#16	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	5758499
#17	Search #15 AND #16	326

#18	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	457055
#19	Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]	50368
#20	Search "Comparative Study"[Publication Type]	1531593
#21	Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab])	43070
#22	Search Search "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 "Longitudinal Studies"[Mesh] OR "Evaluation Studies "[Publication Type] OR "Multicenter Study "[Publication Type] OR "Prospective Studies"[Mesh] OR "Validation Studies "[Publication Type] OR observational stud*	1595122
#23	Search #17 Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study	106
#24	Search #17 AND (#18 OR #19 OR #20 OR #21 OR #22)	157
#25	Search #23 OR #24 Sort by: Author	170

Cochrane 10.4.2011:

ID	Search	Hits
#1	"Arthritis, Rheumatoid"[Mesh] OR ankylosing spondylitis OR ankylosing arthritis OR "Arthritis, Psoriatic"[Mesh] OR "Crohn Disease"[Mesh] OR "Colitis, Ulcerative"[Mesh] OR "Arthritis, Juvenile Rheumatoid"[Mesh] OR juvenile idiopathic arthritis OR "plaque psoriasis"[All Fields] OR ("Plaque"[All Fields] AND ("psoriasis"[MeSH] OR "psoriasis"[All Fields]))	6649
#2	(#1), in 2011	71
#3	"abatacept"[Substance Name] OR "abatacept"[All Fields] OR "Orencia"[All Fields] OR 332348-12-6[rn]	67
#4	"adalimumab"[Substance Name] OR "adalimumab"[All Fields] OR "Humira"[All Fields] OR 331731-18-1[rn]	241
#5	"alefacept"[Substance Name] OR "alefacept"[All Fields] OR "Amevive"[All Fields] OR 222535-22-0[rn]	110
#6	"Interleukin 1 Receptor Antagonist Protein"[Mesh] OR "Anakinra"[All Fields] OR "Kineret"[All Fields] OR 143090-92-0[rn]	148
#7	"CDP870"[Substance Name] OR "Certolizumab"[All Fields] OR "Cimzia"[All Fields] OR 428863-50-7[rn]	43

#8	"TNFR-Fc fusion protein"[Substance Name] OR "etanercept"[All Fields] OR "Enbrel"[All Fields] OR 185243-69-0[rn]	474
#9	"infliximab"[Substance Name] OR "infliximab"[All Fields] OR "Remicade"[All Fields] OR 170277-31-3[rn]	581
#10	"natalizumab"[Substance] OR "natalizumab"[All Fields] OR "Tysabri"[All Fields]	87
#11	"rituximab"[Substance Name] OR "rituximab"[All Fields] OR "Rituxan"[All Fields] OR 174722-31-7[rn]	619
#12	"tocilizumab"[Substance Name] OR "actemra"[All Fields] OR "RoActemra"[All Fields] OR 375823-41-9[rn]	30
#13	"monoclonal antibody CNTO 1275 "[Substance Name] OR "ustekinumab"[All Fields] OR "Stelara"[All Fields] OR 815610-63-0[rn]	22
#14	"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]	33
#15	(#2 AND (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14))	22
#16	"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	352094
#17	(#15 AND #16)	21

IPA and CINAHL 10.4.2011:

#	Query	Limiters/Expanders	Last Run Via	Results
S4	S3	Limiters - Published Date from: 20110101-20111131; English Language; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	51
S3	S1 and S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	1368

S2	(MH "Arthritis, Rheumatoid+") OR (MH "Arthritis, Psoriatic") OR (MH "Arthritis, Juvenile Rheumatoid") OR (MH "Spondylitis, Ankylosing") OR (MH "Crohn Disease") OR (MH "Colitis, Ulcerative") OR "plaque psoriasis"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	12727
S1	"abatacept" OR "Orencia" OR "adalimumab" OR "Humira" OR "alefacept" OR "Amevive" OR "Interleukin 1 Receptor Antagonist Protein" OR "Anakinra" OR "Kineret" OR "CDP870" OR "Certolizumab" OR "Cimzia" OR "TNFR-Fc fusion protein" OR "etanercept" OR "Enbrel" OR "infliximab" OR "Remicade" OR "natalizumab" OR "Tysabri" OR "rituximab" OR "Rituxan" OR "tocilizumab" OR "actemra" OR "RoActemra" OR "monoclonal antibody CNTO 1275" OR "ustekinumab" OR "Stelara" OR “Golimumab” OR “Simponi”	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	6129

EMBASE 10.4.2011:

No.	Query	Results
#1	'rheumatoid arthritis'/exp OR 'juvenile rheumatoid arthritis'/exp OR 'ankylosing spondylitis'/exp OR 'psoriatic arthritis'/exp OR 'crohn disease'/exp OR 'ulcerative colitis'/exp OR 'psoriasis vulgaris'/exp	218,194
#2	'abatacept'/exp OR 'adalimumab'/exp OR 'alefacept'/exp OR 'recombinant interleukin 1 receptor blocking agent'/exp OR 'certolizumab pegol'/exp OR 'etanercept'/exp OR 'infliximab'/exp OR 'natalizumab'/exp OR 'rituximab'/exp OR 'tocilizumab'/exp OR 'ustekinumab'/exp OR 'golimumab'/exp	52,069
#3	#1 AND #2	19,912
#4	'systematic review'/exp OR 'randomized controlled trial'/exp OR 'clinical trial'/exp OR 'meta analysis'/exp OR 'case control study'/exp OR 'cohort analysis'/exp OR 'epidemiology'/exp OR 'cross-sectional study'/exp OR 'crossover procedure'/exp OR 'follow up'/exp OR 'longitudinal study'/exp OR 'validation study'/exp OR 'observational study'/exp OR 'comparative study'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp	3,648,876
#5	#3 AND #4	9,967

#6	#5 AND 'human'/de AND 2011:py	719
#7	'treatment outcome'/exp OR 'drug efficacy'/exp OR 'adverse drug reaction'/exp OR 'adverse outcome'/exp OR 'drug safety'/exp OR 'drug withdrawal'/exp OR 'treatment withdrawal'/exp OR 'harm reduction'/exp OR 'mortality'/exp OR 'morbidity'/exp OR 'toxicity'/exp	2,329,954
#8	#6 AND #7	487

PubMed 2.2.2011:

Search	Most Recent Queries	Result
#1	Search "Arthritis, Rheumatoid"[Mesh] OR ankylosing spondylitis OR ankylosing arthritis OR "Arthritis, Psoriatic"[Mesh] OR "Crohn Disease"[Mesh] OR "Colitis, Ulcerative"[Mesh] OR "Arthritis, Juvenile Rheumatoid"[Mesh] OR juvenile idiopathic arthritis OR "plaque psoriasis"[All Fields] OR ("Plaque"[All Fields] AND ("psoriasis"[MeSH] OR "psoriasis"[All Fields]))	142828
#2	Search "abatacept"[Substance Name] OR "abatacept"[All Fields] OR "Orencia"[All Fields] OR 332348-12-6[rn]	1980
#3	Search #1 AND #2	301
#4	Search "adalimumab"[Substance Name] OR "adalimumab"[All Fields] OR "Humira"[All Fields] OR 331731-18-1[rn]	1984
#5	Search #1 AND #4	1236
#6	Search "alefacept"[Substance Name] OR "alefacept"[All Fields] OR "Amevive"[All Fields] OR 222535-22-0[rn]	356
#7	Search #1 AND #6	129
#8	Search "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR "Anakinra"[All Fields] OR "Kineret"[All Fields] OR 143090-92-0[rn]	3419
#9	Search #1 AND #8	495
#10	Search "CDP870"[Substance Name] OR "Certolizumab"[All Fields] OR "Cimzia"[All Fields] OR 428863-50-7[rn]	244
#11	Search #1 AND #10	143
#12	Search "TNFR-Fc fusion protein"[Substance Name] OR "etanercept"[All Fields] OR "Enbrel"[All Fields] OR 185243-69-0[rn]	3859
#13	Search #1 AND #12	2178
#14	Search "infliximab"[Substance Name] OR "infliximab"[All Fields] OR "Remicade"[All Fields] OR 170277-31-3[rn]	6387
#15	Search #1 AND #14	3992
#16	Search "natalizumab"[Substance Name] OR "natalizumab"[All Fields] OR "Tysabri" [All Fields] OR 189261-10-7[rn]	669
#17	Search #1 AND #16	82
#18	Search "rituximab"[Substance Name] OR "rituximab"[All Fields] OR "Rituxan"[All Fields] OR 174722-31-7[rn]	7388
#19	Search #1 AND #18	499
#20	Search "tocilizumab"[Substance Name] OR "actemra"[All Fields] OR "RoActemra"[All Fields] OR 375823-41-9[rn]	191
#21	Search #1 AND #20	136
#22	Search "monoclonal antibody CNTO 1275 "[Substance Name] OR "ustekinumab"[All Fields] OR "Stelara"[All Fields] OR 815610-63-0[rn]	118
#23	Search #1 AND #22	42
#24	Search #3 OR #5 OR #7 OR #9 OR #11 OR #13 OR #15 OR #17 OR #19	6515
#25	Search ((#24) AND "2009/01/01"[Entrez Date] : "3000"[Entrez Date]) AND	1498

	"0"[Entrez Date] : "3000"[Entrez Date]	
#26	Search #21 OR #23 OR #25	1634
#27	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	5545591
#28	Search #26 AND #27	1232
#29	Search #28 Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study	291
#30	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	437720
#31	Search #28 AND #30	178
#32	Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]	45534
#33	Search #28 AND #32	30
#34	Search "Comparative Study"[Publication Type]	1499111
#35	Search #28 AND #34	87
#36	Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab])	38150
#37	Search #28 AND #36	35
#38	Search "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 "Longitudinal Studies"[Mesh] OR "Evaluation Studies "[Publication Type] OR "Multicenter Study "[Publication Type] OR "Prospective Studies"[Mesh] OR "Validation Studies "[Publication Type] OR observational stud*	1512287
#39	Search #28 AND #38	345
#40	Search #29 OR #31 OR #33 OR #35 OR #37 OR #39 Sort by: Author	549
#41	Search #40 Limits: Humans Sort by: Author	537

Cochrane 2.2.2011:

ID	Search	Hits
#1	"Arthritis, Rheumatoid"[Mesh] OR (ankylosing[All Fields] AND ("arthritis"[MeSH Terms] OR "arthritis"[All Fields])) OR "Arthritis, Psoriatic"[Mesh] OR "Crohn Disease"[Mesh] OR "Colitis, Ulcerative"[Mesh] OR "Arthritis, Juvenile Rheumatoid"[Mesh] OR ("arthr	6489
#2	"abatacept"[Substance] OR "abatacept"[All Fields] OR "Orencia"[All Fields] OR "adalimumab"[Substance] OR "adalimumab"[All Fields] OR "Humira"[All Fields] OR "alefacept"[Substance] OR "alefacept"[All Fields] OR "Amevive"[All Fields] OR "222535-22-0"[EC/RN	1930
#3	(#1 AND #2)	789
#4	(#3), from 2009 to 2011	190
#5	"tocilizumab"[Substance] OR "actemra"[All Fields] OR "RoActemra"[All Fields] OR "monoclonal antibody CNTO 1275 "[Substance] OR "ustekinumab"[All Fields] OR "Stelara"[All Fields]	43
#6	(#1 AND #5)	31
#7	(#4 OR #6)	217
#8	(#7)	214

EMBASE 2.2.2011:

embase
BIOMEDICAL ANSWERS

ID	Search	Results	Date of search
9	#8 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim) AND [humans]/lim AND ([embase]/lim OR [embase classic]/lim)	408	03 Feb 2011
8	#4 OR #6 AND 'human'/de	4692	03 Feb 2011
7	#4 OR #6	5899	03 Feb 2011
6	#1 AND #5	625	03 Feb 2011
5	'tocilizumab'/exp OR 'ustekinumab'/exp	848	03 Feb 2011
4	#1 AND #2 AND (2009:py OR 2010:py OR 2011:py)	5686	03 Feb 2011
3	#1 AND #2	16605	03 Feb 2011
2	'abatacept'/exp OR 'adalimumab'/exp OR 'alefacept'/exp OR 'recombinant interleukin 1 receptor blocking agent'/exp OR 'certolizumab pegol'/exp OR 'etanercept'/exp OR 'infliximab'/exp OR 'natalizumab'/exp OR 'rituximab'/exp	44052	03 Feb 2011
1	'rheumatoid arthritis'/exp OR 'ankylosing spondylitis'/exp OR 'psoriatic arthritis'/exp OR 'crohn disease'/exp OR 'ulcerative colitis'/exp OR 'juvenile rheumatoid arthritis'/exp OR 'psoriasis vulgaris'/exp	204679	03 Feb 2011

IPA and CINAHL 2.2.2011:

#	Query	Limiters/Expanders	Last Run Via	Results
S9	S5 OR S7	Limiters - Exclude MEDLINE records; Human; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	288
S8	S5 or S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	568
S7	S1 and S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	87
S6	"tocilizumab" OR "actemra" OR "RoActemra" OR "monoclonal antibody CNTO 1275" OR "ustekinumab" OR "Stelara"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	125
S5	S3 and S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	500
S4		Limiters - Published Date from: 20090101-20111231 Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	428894
S3	S1 and S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	2417
S2	"abatacept" OR "abatacept" OR "Orencia" OR "adalimumab" OR "adalimumab" OR "Humira" OR "alefacept" OR "alefacept" OR "Amevive" OR "Interleukin 1 Receptor Antagonist Protein" OR "Anakinra" OR "Kineret" OR "CDP870" OR "Certolizumab" OR "Cimzia" OR "TNFR-Fc fusion protein" OR "etanercept" OR "Enbrel" OR "infliximab" OR "infliximab" OR "Remicade" OR "natalizumab" OR "natalizumab" OR "Tysabri" OR "rituximab" OR "rituximab" OR "Rituxan"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	5487
S1	rheumatoid arthritis OR ankylosing arthritis OR ankylosing spondylitis OR psoriatic arthritis OR crohn's disease OR crohn disease OR ulcerative colitis OR plaque psoriasis OR juvenile rheumatoid arthritis OR juvenile idiopathic arthritis	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text;International Pharmaceutical Abstracts	14630

INAHTA 2.2.2011:

	Search	Matching records
#1	"abatacept" OR "Orencia" OR "adalimumab" OR "Humira" OR "alefacept" OR "Amevive" OR "Interleukin 1 Receptor Antagonist Protein" OR "Anakinra" OR "Kineret" OR "CDP870" OR "Certolizumab" OR "Cimzia" OR "TNFR-Fc fusion protein" OR "etanercept" OR "Enbrel" OR "infliximab" OR "Remicade" OR "natalizumab" OR "Tysabri" OR "rituximab" OR "Rituxan"	377
#2	#1 RESTRICT YR 2009 2011	83
#3	"tocilizumab" OR "actemra" OR "RoActemra" OR "monoclonal antibody CNTO 1275" OR "ustekinumab" OR "Stelara" OR “Golimumab” OR “Simponi”	10
#4	#2 OR #3	91

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 - Abatacept

1. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. *J Rheumatol.* Apr 2006;33(4):681-689.
2. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med.* Sep 15 2005;353(11):1114-1123.
3. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* Aug 2005;52(8):2263-2271.
4. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med.* Jun 20 2006;144(12):865-876.
5. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med.* Nov 13 2003;349(20):1907-1915.
6. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis.* Feb 2007;66(2):189-194.
7. Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Annals of the Rheumatic Diseases. 2009(11):1708-1714.
8. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. *Rheumatology (Oxford).* Oct 2006;45(10):1238-1246.

Rheumatoid Arthritis - Adalimumab

1. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* Jan 2006;54(1):26-37.
2. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol.* 2003;30(12):2563-2571.
3. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate

therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 2004;50(5):1400-1411.
4. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR Journal of Rheumatology.* 2007;10(1):9-16.
5. 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):252-262.
6. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis.* 2004;63(5):508-516.
7. van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis.* 2003;62(12):1168-1177.
8. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 2003;48(1):35-45.
9. 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.* Jun 2006;65(6):753-759.

Rheumatoid Arthritis - Anakinra

1. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum.* 1998;41(12):2196-2204.
2. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2002;46(3):614-624.
3. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. *Ann Rheum Dis.* 2004;63(9):1062-1068.
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):225-231.
5. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. *Arthritis Rheum.* 2000;43(5):1001-1009.

Rheumatoid Arthritis - Certolizumab pegol

1. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis.* Jun 2009;68(6):805-811.
2. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* Nov 2008;58(11):3319-3329.
3. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis.* Jun 2009;68(6):797-804.
4. Strand V, Mease P, Burmester GR, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res Ther.* 2009;11(6):R170.
5. Strand V, Smolen JS, van Vollenhoven RF, et al. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. *Ann Rheum Dis.* Vol 70. 2011/03/19 ed2011:996-1002.

Rheumatoid Arthritis - Etanercept

1. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol.* Jul 2005;32(7):1232-1242.
2. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet.* Feb 28 2004;363(9410):675-681.
3. 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):618-623.
4. 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):128-139.
5. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med.* Jul 17 1997;337(3):141-147.
6. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med.* Mar 16 1999;130(6):478-486.
7. Van Der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis and Rheumatism.* 2007;56(12):3928-3939.
8. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum.* Apr 2006;54(4):1063-1074.

9. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis.* Mar 2006;65(3):328-334.
10. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med.* Jan 28 1999;340(4):253-259.

Rheumatoid Arthritis - Golimumab

1. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum.* Apr 2008;58(4):964-975.
2. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis.* Jun 2010;69(6):1129-1135.
3. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet.* Jul 18 2009;374(9685):210-221.

Rheumatoid Arthritis - Infliximab

1. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol.* Jan 2006;33(1):37-44.
2. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis.* 2004;63(2):149-155.
3. 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):841-850.
4. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med.* Nov 30 2000;343(22):1594-1602.
5. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet.* 1999;354(9194):1932-1939.
6. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998;41(9):1552-1563.
7. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum.* 2004;50(4):1051-1065.
8. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical

improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum.* Apr 2005;52(4):1020-1030.
9. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. *Arthritis Rheum.* Mar 2006;54(3):716-722.
10. St. Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50(11):3432-3443.
11. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum.* Apr 2006;54(4):1075-1086.
12. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China. *APLAR Journal of Rheumatology.* 2006;9(2):127-130.

Rheumatoid Arthritis – Rituximab

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

Rheumatoid Arthritis – Tocilizumab

1. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis.* Nov 2008;67(11):1516-1523.
2. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* Oct 2008;58(10):2968-2980.
3. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis and Rheumatism.* 2006;54(9):2817-2829.
4. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis.* Sep 2007;66(9):1162-1167.
5. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol.* 2009;19(1):12-19.

6. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized antiinterleukin6 receptor antibody: a multicenter, doubleblind, placebocontrolled trial. *Arthritis & Rheumatism.* Jun 2004;50(6):1761-1769.
7. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* Jun 2004;50(6):1761-1769.
8. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet.* Mar 22 2008;371(9617):987-997.

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.* Jul 26 2001;345(4):248-255.
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):131-139.
3. 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.* Feb 2004;150(2):317-326.
4. Finlay AY, Salek MS, Haney J. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. *Dermatology.* 2003;206(4):307-315.
5. Gordon KB, Langley RG. Remittive effects of intramuscular alefacept in psoriasis. *J Drugs Dermatol.* Dec 2003;2(6):624-628.
6. 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.* Dec 2003;139(12):1563-1570.
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.* Jul 2003;17 Suppl 2:17-24.
8. Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. *Br J Dermatol.* Apr 2003;148(4):784-788.
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Appendix D. Instruments used to measure outcomes in trials involving targeted immune modulators

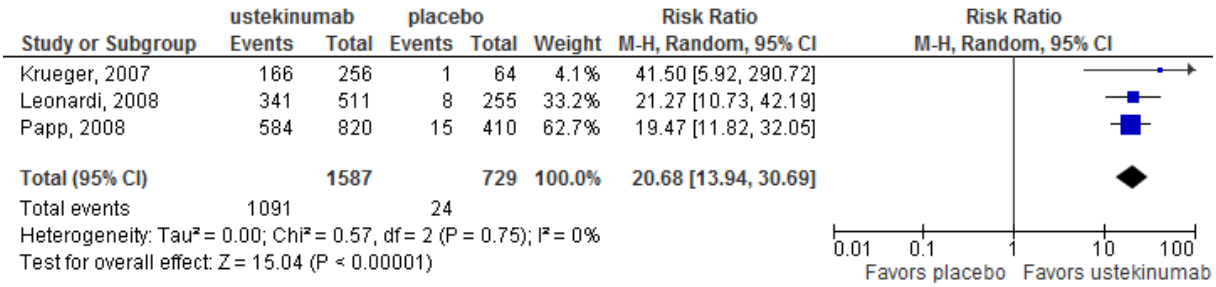
Abbreviation	Name	Condition(s) used in	General description	Range and direction
ACR 20/50/70	American College of Rheumatology, numbers refer to percentage improvement	RA, JIA, PsA	Improvement is defined by at least 20% improvement in TJC and in SJC, and at least 20% improvement in 3 of the 5 measures: 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 Lomotil 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 Index of Severity	CD	Segment score averaged over segments on which data were available, ulcerated stenosis in any segment, and nonulcerated stenosis in any segment.	0-44, lower is better

Abbreviation	Name	Condition(s) used in	General description	Range and direction
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/behavioral, role/social-physical, bodily pain (bodily pain), behavior, 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 color, pain, tiredness, swelling, bleeding, aching and burning.	0-100, lower is better
ESR	Erythrocyte 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	

Abbreviation	Name	Condition(s) used in	General description	Range and direction
			8 categories of functioning which represent a 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, European League Against Rheumatism; 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 E. Forest plot of meta-analysis



Appendix F. Boxed warnings of included drugs[1-8]

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Orencia® (abatacept)	None listed
Humira® (adalimumab) Remicade® (Infliximab)	Below is the boxed warning on Humira®. Similar boxed warnings are listed for Remicade®(Infliximab). WARNINGS: SERIOUS INFECTIONS AND MALIGNANCY SERIOUS INFECTIONS Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. HUMIRA should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: • Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use. • Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. • Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria. The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. MALIGNANCY Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants
Amevive® (alefacept)	None listed
Kineret® (anakinra)	None listed
Cimzia® (certolizumab pegol)	WARNINGS: SERIOUS INFECTIONS Patients treated with CIMZIA are at increased risk for developing serious infections

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. CIMZIA should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: • Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA use. • Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. • Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria. The risks and benefits of treatment with CIMZIA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. MALIGNANCY Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is not indicated for use in pediatric patients.
Enbrel® (etanercept) Simponi® (Golimumab)	Following is the boxed warning issued on Enbrel®. Similar boxed warnings have been issued on Simponi®(Golimumab). WARNINGS SERIOUS INFECTIONS AND MALIGNANCIES SERIOUS INFECTIONS Patients treated with Enbrel are at increased risk for developing serious infections that may lead to hospitalization or death .Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Enbrel should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: • Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Enbrel use and during therapy. Treatment for latent infection should be initiated prior to Enbrel use. • Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	systemic illness. • Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria. The risks and benefits of treatment with Enbrel should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Enbrel, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. MALIGNANCIES Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel.
Tysabri® (natalizumab)	WARNING: PROGRESSIV MUTIFOCAL LEUKOENCEPHAOPATHY TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking TYSABRI who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI as monotherapy. • Because of the risk of PML, TYSABRI is available only through a special restricted 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)	WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) 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) with Rituxan monotherapy. 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.
Actemra®	WARNING: RISK OF SERIOUS INFECTIONS

Trade names (active ingredients)	Boxed warnings, warnings and precautions
(Tocilizumab)	Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death ¡see Warnings and Precautions (5.1), Adverse Reactions (6.1)). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt ACTEMRA until the infection is controlled. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use. • Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy
Stelara® Ustekinumab	Not listed

Appendix F References

1. Abbott Laboratories. Humira Product Label. http://www.rxabbott.com/pdf/humira.pdf. Accessed November 8, 2011.
2. Amgen Inc. Enbrel Product Label. http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf. Accessed November 8, 2011.
3. Biogen Idec Inc. Tysabri Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125104s0658lbl.pdf. Accessed November 8, 2011.
4. Biogen Idec Inc and Genentech Inc. Rituxan Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103705s5344lbl.pdf. Accessed November 8, 2011.
5. Genentech Inc. Actemra Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125276s0022s0023lbl.pdf. Accessed November 8, 2011.
6. Janssen Biotech Inc. Simponi Product Label. http://www.simponi.com/sites/default/files/pdf/prescribing-information.pdf. Accessed November 8, 2011.
7. Janssen Biotech Inc. Remicade Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5301lbl.pdf. Accessed November 8, 2011.
8. UCB Inc. Cimzia Product Label. http://www.cimzia.com/pdf/Prescribing_Information.pdf. Accessed November 8, 2011.

Appendix G. Excluded studies

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

Exclusion codes: 1=non English language, 2=ineligible outcome, 3=ineligible intervention, 4=ineligible population, 5=ineligible publication type, 6=ineligible study design

Excluded trials	Exclusion code
Aalto K, Honkanen V, Lahdenne P. Iron status during anti-TNF therapy in children with juvenile idiopathic arthritis. Clinical Rheumatology. 2011;30(1):115-119.	2
Aletaha D, Funovits J, Breedveld FC, Sharp J, Segurado O, Smolen JS. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis and rheumatism. 2009(5):1242-1249. http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/230/CN-00700230/frame.html.	2
Aletaha D, Funovits J, Smolen JS. Physical disability in rheumatoid arthritis is associated with cartilage damage rather than bone destruction. Ann Rheum Dis. May 2011;70(5):733-739.	6
Anis A, Zhang W, Emery P, et al. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford). Oct 2009;48(10):1283-1289.	4
Atzeni F, Boccassini L, Antivalle M, Salaffi F, Sarzi-Puttini P. Etanercept plus ciclosporin versus etanercept plus methotrexate for maintaining clinical control over psoriatic arthritis: a randomised pilot study. Ann Rheum Dis. Apr 2011;70(4):712-714.	6
Baraliakos X, Listing J, Fritz C, et al. Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years-early clinical response predicts long-term outcome. Rheumatology. 2011;50(9):1690-1699.	6
Braun J, van der Heijde D, Doyle MK, et al. Improvement in hemoglobin levels in patients with ankylosing spondylitis treated with infliximab. Arthritis Rheum. Aug 15 2009;61(8):1032-1036.	2
Chen RL, Tao Y, Lin ZY, Huang CH, Huang WH. Efficacy and safety of adalimumab in patients with rheumatoid arthritis. Chinese Journal of New Drugs. 2011;20(2):152-155+166.	1
Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res (Hoboken). Jul 2010;62(7):965-969.	2
Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis. Vol 69. 2010/05/05 ed2010:1158-1161.	2
Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. Apr 15 2010;362(15):1383-1395.	4
Colombel JF, Sandborn WJ, Rutgeerts P, et al. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. Am J Gastroenterol. May 2009;104(5):1170-1179.	6
Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Annals of the Rheumatic Diseases. 2009(7):1146-1152.	6
Crandall W, Hyams J, Kugathasan S, et al. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. J Pediatr Gastroenterol Nutr. Vol 49. 2009/06/30 ed2009:183-190.	6
Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum. Mar 2010;62(3):674-682.	4
Emery P, Fleischmann R, van der Heijde D, et al. The Effects of Golimumab on Radiographic Progression in Rheumatoid Arthritis Results of Randomized Controlled Studies of Golimumab Before Methotrexate Therapy and Golimumab After Methotrexate Therapy. Arthritis and rheumatism. May 2011;63(5):1200-1210.	2

Excluded trials	Exclusion code
Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor (alpha) monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis and rheumatism. 2009;60(8):2272-2283.	4
Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol. Jul 2009;36(7):1429-1441.	2
Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pharmacol Ther. May 2010;48(5):297-308.	2
Feagan BG, Hanauer SB, Coteur G, Schreiber S. Evaluation of a daily practice composite score for the assessment of Crohn's disease: The treatment impact of certolizumab pegol. Alimentary Pharmacology and Therapeutics. 2011;33(10):1143-1151.	2
Genovese MC, Breedveld FC, Emery P, et al. Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients. Ann Rheum Dis. Dec 2009;68(12):1894-1897.	6
Gerlag DM, Hollis S, Layton M, et al. Preclinical and clinical investigation of a CCR5 antagonist, AZD5672, in patients with rheumatoid arthritis receiving methotrexate. Arthritis Rheum. Nov 2010;62(11):3154-3160.	3
Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int. Sep 2010;30(11):1437-1440.	6
Gibofsky A, Palmer WR, Keystone EC, et al. Rheumatoid arthritis disease-modifying antirheumatic drug intervention and utilization study: safety and etanercept utilization analyses from the RADIUS 1 and RADIUS 2 registries. J Rheumatol. Jan 2011;38(1):21-28.	6
Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther. 2010;12(3):R113.	2
Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Journal of Dermatology. 2011;165(3):652-660.	6
Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF, Griffin MR. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology. 2010;49(1):82.	3
Gustavsson A, Jarnerot G, Hertervig E, et al. Clinical trial: Colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study. Alimentary Pharmacology and Therapeutics. 2010;32(8):984-989.	6
Hashimoto J, Garnero P, van der Heijde D, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Modern rheumatology / the Japan Rheumatism Association. 2009(3):273-282.	6
Haugeberg G, Conaghan PG, Quinn M, Emery P. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Annals of the Rheumatic Diseases. 2009(12):1898-1901.	6
Hu C, Xu Z, Zhang Y, Rahman MU, Davis HM, Zhou H. Population approach for exposure-response modeling of golimumab in patients with rheumatoid arthritis. J Clin Pharmacol. May 2011;51(5):639-648.	2
Ilowite N, Porras O, Reiff A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clinical Rheumatology. 2009(2):129-137.	6
Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. Clinical	2

Excluded trials	Exclusion code
Rheumatology. 2009(4):413-419.	
Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. Expert Rev Clin Immunol. Mar 2010;6(2):189-195.	4
Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. Jan 2010;69(1):88-96.	4
Kallimanis PG, Xenos K, Markantonis SL, et al. Serum levels of transforming growth factor-(beta)1 in patients with mild psoriasis vulgaris and effect of treatment with biological drugs. Clinical and Experimental Dermatology. 2009;34(5):582-586.	4
Kameda H, Ueki Y, Saito K, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: A randomized trial. Modern Rheumatology. 2010;20(6):531-538.	6
Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. Ann Rheum Dis. Jan 2010;69(1):222-225.	6
Keystone EC, Curtis JR, Fleischmann RM, et al. Rapid Improvement in the Signs and Symptoms of Rheumatoid Arthritis Following Certolizumab Pegol Treatment Predicts Better Longterm Outcomes: Post-hoc Analysis of a Randomized Controlled Trial. Journal of Rheumatology. 2011;38(6):990-996.	2
Keystone EC, Kavanaugh A, Weinblatt ME, Patra K, Pangan AL. Clinical consequences of delayed addition of adalimumab to methotrexate therapy over 5 years in patients with rheumatoid arthritis. J Rheumatol. May 2011;38(5):855-862.	2
Klarenbeek NB, van der Kooij SM, Huizinga TJ, et al. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Annals of the Rheumatic Diseases. 2010(7):1342-1345.	6
Koffeman EC, Genovese M, Amox D, et al. Epitope-specific immunotherapy of rheumatoid arthritis: clinical responsiveness occurs with immune deviation and relies on the expression of a cluster of molecules associated with T cell tolerance in a double-blind, placebo-controlled, pilot phase II trial. Arthritis Rheum. Nov 2009;60(11):3207-3216.	2
Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor (alpha) antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis and rheumatism. 2010;62(4):917-928.	6
Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab Inhibits Structural Joint Damage in Rheumatoid Arthritis Patients With Inadequate Responses to Methotrexate Results From the Double-Blind Treatment Phase of a Randomized Placebo-Controlled Trial of Tocilizumab Safety and Prevention of Structural Joint Damage at One Year. Arthritis and rheumatism. Mar 2011;63(3):609-621.	2
Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. Jul 2009;60(7):1895-1905.	3
Landells I, Searles G, Bissonnette R, Shear NH, Vender R, Lui H. Efficacy outcomes in patients using alefacept in the AWARE study. J Cutan Med Surg. Dec 2009;13 Suppl 3:S122-130.	6
Lichtenstein GR, Thomsen OO, Schreiber S, et al. Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. Clin Gastroenterol Hepatol. Jul 2010;8(7):600-609.	6
Lie E, van der Heijde D, Uhlig T, et al. Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. Ann Rheum Dis. Jan 2011;70(1):157-163.	2
Lin Q, Gu JR, Li TW, et al. Value of the peripheral blood B-cells subsets in patients with ankylosing spondylitis. Chinese medical journal. 2009(15):1784-1789. http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/678/CN-00731678/frame.html.	2
Lisbona MP, Maymo J, Perich J, Almirall M, Carbonell J. Rapid reduction in tenosynovitis of	2

Excluded trials	Exclusion code
the wrist and fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. Ann Rheum Dis. Jun 2010;69(6):1117-1122.	
Loftus EV, Jr., Johnson SJ, Wang ST, Wu E, Mulani PM, Chao J. Risk-benefit analysis of adalimumab versus traditional non-biologic therapies for patients with Crohn's disease. Inflamm Bowel Dis. Jan 2011;17(1):127-140.	6
Luger TA, Barker J, Lambert J, et al. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol. Aug 2009;23(8):896-904.	7
Lukas C, Landewe R, Fatenejad S, Van Der Heijde D. Subtle changes in individual joints result in both positive and negative change scores in a patient: Results from a clinical trial in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009;68(11):1691-1695.	2
Lukas C, van der Heijde D, Fatenajad S, Landewe R. Repair of erosions occurs almost exclusively in damaged joints without swelling. Ann Rheum Dis. May 2010;69(5):851-855.	2
Maksymowych WP, Salonen D, Inman RD, Rahman P, Lambert RG. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. J Rheumatol. Aug 1 2010;37(8):1728-1734.	2
Massarotti EM. FAST4WARD: implications for the clinician. Int J Clin Pract. Jul 2009;63(7):986-988.	1
Mease PJ, Cohen S, Gaylis NB, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. J Rheumatol. Vol 37. 2010/03/03 ed2010:917-927.	6
Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Annals of the Rheumatic Diseases. 2009(5):702-709.	6
Otomo K, Koike T. [TNF inhibitors for treatment of rheumatoid arthritis]. Nippon Naika Gakkai Zasshi. Oct 10 2008;97(10):2405-2412.	1
Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. Aliment Pharmacol Ther. Jun 2010;31(12):1296-1309.	6
Pincus T, Furer V, Keystone E, Yazici Y, Bergman MJ, Luijtens K. RAPID3 (Routine Assessment of Patient Index Data 3) severity categories and response criteria: Similar results to DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) in the RAPID 1 (Rheumatoid Arthritis Prevention of Structural Damage) clinical trial of certolizumab pegol. Arthritis Care Res (Hoboken). Aug 2011;63(8):1142-1149.	2
Prince FHM, Twilt M, Ten Cate R, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: The Dutch national register. Annals of the Rheumatic Diseases. 2009;68(5):635-641.	6
Radovits BJ, Kievit W, Fransen J, et al. Influence of age on the outcome of antitumour necrosis factor alpha therapy in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009;68(9):1470-1473.	3
Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. Rheumatology. 2010;49(4):812.	2
Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. Jun 2011;60(6):780-787.	6
Rigby W, Ferraccioli G, Greenwald M, et al. Effect of rituximab on physical function and quality of life in patients with rheumatoid arthritis previously untreated with methotrexate. Arthritis Care Res (Hoboken). May 2011;63(5):711-720.	4
Ringold S, Bittner R, Neogi T, Wallace CA, Singer NG. Performance of rheumatoid arthritis disease activity measures and juvenile arthritis disease activity scores in polyarticular-course juvenile idiopathic arthritis: Analysis of their ability to classify the american college of rheumatology pediatric measures of response and the preliminary criteria for flare and inactive disease. Arthritis Care and Research. 2010;62(8):1095-1102.	2
Rubbert-Roth A, Tak PP, Zerbini C, et al. Efficacy and safety of various repeat treatment	6

Excluded trials	Exclusion code
dosing regimens of rituximab in patients with active rheumatoid arthritis: Results of a Phase III randomized study (MIRROR). Rheumatology. 2010;49(9):1683-1693.	
Rudwaleit M, Claudepierre P, Wordsworth P, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. J Rheumatol. Apr 2009;36(4):801-808.	6
Rudwaleit M, Gooch K, Michel B, et al. Adalimumab improves sleep and sleep quality in patients with active ankylosing spondylitis. Journal of Rheumatology. 2011;38(1):79-86.	6
Rudwaleit M, Olivieri I, Boki KA, et al. Adalimumab is effective and well tolerated in treating patients with ankylosing spondylitis who have advanced spinal fusion. Rheumatology (Oxford). May 2009;48(5):551-557.	6
Ruemmele FM, Lachaux A, Cézard JP, et al. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflammatory bowel diseases. 2009(3):388-394.	6
Sandborn WJ, Abreu MT, D'Haens G, et al. Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. Clin Gastroenterol Hepatol. Aug 2010;8(8):688-695 e682.	6
Sandborn WJ, Schreiber S, Hanauer SB, Colombel JF, Bloomfield R, Lichtenstein GR. Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECiSE 4 Study. Clin Gastroenterol Hepatol. Aug 2010;8(8):696-702 e691.	6
Scheinberg M, Guedes-Barbosa LS, Mangueira C, et al. Yellow fever revaccination during infliximab therapy. Arthritis care & research. 2010(6):896-898. http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/348/CN-00751348/frame.html.	2
Schreiber S, Colombel JF, Bloomfield R, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. Am J Gastroenterol. Jul 2010;105(7):1574-1582.	2
Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Annals of the Rheumatic Diseases. 2009(6):823-827. http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/893/CN-00704893/frame.html.	2
Smolen JS, van der Heijde DM, Aletaha D, et al. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Annals of the Rheumatic Diseases. 2009(10):1535-1540. http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/611/CN-00720611/frame.html.	2
Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford). Nov 2009;48(11):1429-1434.	6
Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Journal of Dermatology. 2011;165(3):661-668.	3
Stubenrauch K, Wessels U, Birnboeck H, Ramirez F, Jahreis A, Schleypen J. Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clinical Therapeutics. 2010;32(9):1597-1609.	2
Takahashi S, Takagi S, Shiga H, et al. Scheduled maintenance therapy with infliximab improves the prognosis of Crohn's disease: a single center prospective cohort study in Japan. Tohoku J Exp Med. 2010;220(3):207-215.	6
Toedter GP, Blank M, Lang Y, Chen D, Sandborn WJ, de Villiers WJ. Relationship of C-reactive protein with clinical response after therapy with ustekinumab in Crohn's disease. Am J Gastroenterol. Nov 2009;104(11):2768-2773.	6

Excluded trials	Exclusion code
Valentine JF, Fedorak RN, Feagan B, et al. Steroid-sparing properties of sargramostim in patients with corticosteroid-dependent Crohn's disease: A randomised, double-blind, placebo-controlled, phase 2 study. Gut. 2009;58(10):1354-1362.	3
Van den Bosch F, Manger B, Goupille P, et al. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. Ann Rheum Dis. Feb 2010;69(2):394-399.	6
Van Der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-Year results of PREMIER. Journal of Rheumatology. 2010;37(11):2237-2246.	6
van der Heijde D, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther. 2009;11(4):R127.	2
Van Der Heijde D, Schiff MH, Sieper J, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: Long-term results from the ATLAS trial. Annals of the Rheumatic Diseases. 2009;68(6):922-929.	6
van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009(7):1153-1158.	6
van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. Aug 8 2009;374(9688):459-466.	6
van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomized, placebo-controlled trial. Arthritis Rheum. Jul 2011;63(7):1782-1792.	3
Viola F, Civitelli F, Di Nardo G, et al. Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. Am J Gastroenterol. Oct 2009;104(10):2566-2571.	6
Wakabayashi H, Sudo A, Hasegawa M, Oka H, Uchida A, Nishioka K. Retrospective clinical study of the efficacy of lower-dose methotrexate and infliximab therapy in patients with rheumatoid arthritis. Clin Rheumatol. Jun 2010;29(6):671-675.	6
Zhang J, Zhang YM, Zhang JL, Deng XH, Huang F. Efficacy of etanercept in patients with ankylosing spondylitis: A double-blind, randomized, placebo controlled trial. Chinese Journal of New Drugs. 2009;18(19):1846-1849+1881.	1
Zhao FT, Zhao H, Wang YL. Efficacy of etanercept on ankylosing spondylitis. Journal of Shanghai Jiaotong University (Medical Science). 2009;29(12):1506-1508.	1
Zhao H, Zhao FT, Wang YL. Therapeutic effects of different doses of recombinant human tumor necrosis factor-receptor II: IgG Fc fusion protein on rheumatoid arthritis. Journal of Shanghai Jiaotong University (Medical Science). 2009;29(12):1509-1511.	1

Appendix H. Studies with poor internal validity

1. Bergman GJ, Hochberg MC, Boers M, Wintfeld N, Kielhorn A, Jansen JP. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum. Jun 2010;39(6):425-441.
2. Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. Jul 2007;66(7):880-885.
3. Dretzke J, Edlin R, Round J, et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess. Feb 2011;15(6):1-244.
4. Feagan BG, Reilly MC, Gerlier L, Brabant Y, Brown M, Schreiber S. Clinical trial: the effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the PRECiSE 2 study. Aliment Pharmacol Ther. Jun 2010;31(12):1276-1285.
5. Gerloni V, Pontikaki I, Gattinara M, 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. Feb 2005;52(2):548-553.
6. Huang ML, Ran ZH, Shen J, Li XB, Xu XT, Xiao SD. Efficacy and safety of adalimumab in Crohn's disease: meta-analysis of placebo-controlled trials. J Dig Dis. Jun 2011;12(3):165-172.
7. Langley RG, Strober BE, Gu Y, Rozzo SJ, Okun MM. Benefit-risk assessment of tumour necrosis factor antagonists in the treatment of psoriasis. Br J Dermatol. Jun 2010;162(6):1349-1358.
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Appendix I. Evidence profiles

Table 1. 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 Adalimumab							
Outcome: ACR 50 response							
Direct: 0 Indirect: 10 / ~ 3000	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for abatacept and adalimumab. ACR 50 response: RR 0.71 (0.44-1.13)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Abatacept compared with Anakinra							
Outcome: ACR 50 response							
Direct: 0 Indirect: 7 / ~ 1900	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for abatacept and anakinra. ACR 50 response: RR 1.01 (0.53-1.90)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Abatacept compared with Etanercept							
Outcome: ACR 50 response							
Direct: 0 Indirect: 8 / ~ 1700	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Lower efficacy for abatacept than etanercept. ACR 50 response: RR 0.30 (0.13-0.69)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Abatacept compared with Infliximab							
Outcome: ACR 50 response							
Direct: 1/ 431	RCT	Fair	Consistent results between direct and	Direct evidence	Direct: Similar efficacy for abatacept and infliximab at	No dose increases for infliximab allowed	

			indirect evidence		6 months. ACR 50 response: 45% vs. 36%		Moderate
Indirect: 10/~ 3000	Indirect comparisons of placebo-controlled trials	Good		Indirect evidence	Indirect: Similar efficacy for abatacept and infliximab. ACR 50 response: RR 0.90 (0.49-1.66)	none	
Outcome: Radiographic progression							
No evidence							
Abatacept compared with Tocilizumab							
Outcome: ACR 50 response							
Direct: 0 Indirect: 7 / ~ 4000	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for abatacept and tocilizumab. ACR 50 response: RR 0.81 (0.41-1.57)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Adalimumab compared with Anakinra							
Outcome: ACR 50 response							
Direct: 0 Indirect: 11 / ~ 3300	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for adalimumab and anakinra. ACR 50 response: RR 1.40 (0.71-2.78)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Adalimumab compared with Etanercept							
Outcome: ACR 50 response							
Direct: 2 / 1325 Indirect: 12 /~ 3100	Prospective cohort studies Indirect comparisons of placebo-controlled trials	Good	Inconsistent results between direct and indirect evidence.	Mixed	Direct: Similar efficacy for adalimumab and etanercept at 12 months. ACR 50: 35% vs. 32% Indirect: Lower efficacy for adalimumab than etanercept. ACR 50 response: RR 0.43 (0.20-0.93)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Adalimumab compared with Infliximab							
Outcome: ACR 50 response							
Direct: 2 /1870		Good	Inconsistent results	Mixed		none	Low

Indirect: 14 / ~ 4400	Prospective cohort studies Indirect comparisons of placebo-controlled trials		between direct and indirect evidence.		Direct: Greater efficacy for adalimumab than infliximab. ACR 50 response: 31 vs. 22% Indirect: Similar efficacy for adalimumab and infliximab. ACR 50 response: RR 1.31 (0.75-2.29)		
Outcome: Radiographic progression							
No evidence							Insufficient
Adalimumab compared with Tocilizumab							
Outcome: ACR 50 response							
Direct: 0 Indirect: 11 / ~ 5400	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for adalimumab and tocilizumab. ACR 50 response: RR 1.18 (0.66-2.10)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Anakinra compared with Etanercept							
Outcome: ACR 50 response							
Direct: 0 Indirect: 9 / ~ 2000	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Lower efficacy for anakinra than etanercept. ACR 50 response: RR 0.29 (0.12-0.69)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Anakinra compared with Infliximab							
Outcome: ACR 50 response							
Direct: 0 Indirect: 11 / ~ 3300	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for anakinra and infliximab. ACR 50 response: RR 0.99 (0.43-2.30)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient
Anakinra compared with Tocilizumab							
Outcome: ACR 50 response							
Direct: 0 Indirect: 8 / ~ 4300	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for anakinra and tocilizumab. ACR 50 response: RR 0.87 (0.36-2.13)	none	Low
Outcome: Radiographic progression							
No evidence							Insufficient

Etanercept compared with Infliximab								
Outcome: ACR 50 response								
Direct 6 / 8435 Indirect: 12 / ~ 3100	1 open-label RCT 1 nonrandomized controlled trial 4 prospective cohort studies	Good	Yes	Yes	Direct: ACR 20 response 74% vs. 60% Indirect: Greater efficacy for etanercept than infliximab in indirect comparisons. ACR 50 response: RR 2.91 (1.21-7.02)	none	Moderate	
Outcome: Radiographic progression								
Etanercept compared with Tocilizumab								
Outcome: ACR 50 response								
Direct: 0 Indirect: 9 / ~ 4100	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Greater efficacy for etanercept than adalimumab. ACR 50 response: RR 2.64 (1.05-6.65)	none	Low	
Outcome: Radiographic progression								
No evidence							Insufficient	
Infliximab compared with Tocilizumab								
Outcome: ACR 50 response								
Direct: 0 Indirect: 11 / ~ 5400	Indirect comparisons of placebo-controlled trials	Good	NA	Indirect evidence	Indirect: Similar efficacy for infliximab and tocilizumab. ACR 50 response: RR 0.93 (0.49-1.77)	none	Low	
Outcome: Radiographic progression								
No evidence							Insufficient	

Abbreviations: ACR: American College of Radiology; EULAR, European League Against Rheumatism; NA, not applicable; RCT, randomized controlled trial; RR, relative risk.

Table 2. 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							

Table 3. 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							

Table 4. 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 ≈ 982	MA with indirect comparison of placebo trials*	Fair	Yes	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 ≈ 982	MA with indirect comparison of placebo trials*	Fair	Yes	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 ≈ 982	MA with indirect comparison of placebo trials*	Fair	Yes	Indirect	ACR 20 RR (95% CI) 0.96 (0.33, 2.76) PsARC RR (95% CI) 0.57 (0.28, 1.17)	None	Insufficient
Adalimumab compared with etanercept compared with infliximab							

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall grade of the evidence
Outcome: Health outcomes							
Indirect: 1 N ≈ 982	MA with indirect comparison of placebo trials*	Good	Yes	Indirect	Probability of PsARC response: adalimumab 59% (44%-71%) etanercept 71% (57%-83%) infliximab 80% (67%-87%)	None	Insufficient
Outcome: Quality of life							
Direct: 1 N=596	Observational study	Fair	NA	Direct	Improvement in QoL similar for patients taking Adalimumab, etanercept, and infliximab	None	Insufficient

*Indirect comparisons performed using adjusted indirect method{Saad, 2008 #3649} or Bayesian methods{Rodgers, 2011 #6750} Probability of response (95% credibility interval) using Bayesian indirect methods)
ACR 20/50/70, American College of Rheumatology, numbers refer to percentage improvement; MA, meta-analysis; NA, not applicable; PsARC, Psoriatic Arthritis Response Criteria; QoL: Quality of Life: RR, relative risk.

Table 5. 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							

Table 6. 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 7. 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							

Table 8. 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 9. 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							

Table 10. 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
Etanercept compared with ustekinumab							
Outcome: Health outcomes (PASI 75)							
1 / 903	RCT	Fair	NA	Yes	RR 1.26 (95% CI 1.13 to 1.40) favoring ustekinumab	None	Insufficient
Outcome: Quality of life							
No evidence							
Outcome: Safety							
1 / 903	RCT	Fair	NA	Yes	Overall safety similar between etanercept and ustekinumab, fewer ISRs	None	Insufficient

DLQI, Dermatology Life Quality Index; ISR: injection site reactions; NA: not applicable; PASI: Psoriasis Area and Severity Index.

Table 11. 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							

Table 12. Evidence profile of comparisons of targeted immune modulators for adverse events in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall grade of the evidence
Outcome: Serious Infections						
5/26,847	Cohort	Moderate	Inconsistent	Direct	increased risk of tuberculosis with adalimumab compared with etanercept (adjusted incidence rate ratio 4.1, 95% CI 1.4 to 12.4) Increased risk of serious infections overall with antitumor necrosis factor drugs hazard ratio 1.2, 95% CI 1.1 to 1.5); no differences between drugs identified to date	Low
1/ 431	RCT	Fair	N/A	Direct evidence	Higher rates of serious infections with infliximab than abatacept (8.5% vs. 1.9%; *P*=NR)	Moderate
Malignancy						
3/13,043	Cohort	Moderate	Inconsistent	Direct	Increased risk of non melanoma skin cancer with antitumor necrosis factors drugs as a group (relative risk 2.02 (95% CI 1.11 to 3.95) ; no differences between drugs identified to date Majority of studies find no increased risk with targeted immune modulates grouped by mechanism of action; no differences between drugs identified to date	Low
Overall risk of adverse events and Discontinuation due to adverse events						
7/8949	Cohort	Moderate	Consistent	Direct	Majority of studies find higher rates of adverse events and discontinuation with infliximab when compared to adalimumab or etanercept.	Low
Etanercept vs. Ustekinumab						
1/903	RCT	Moderate	NA	Direct	Overall adverse events and withdrawals due to adverse events similar: Injection-site reactions more frequent with etanercept than ustekinumab	Moderate
Etanercept vs. Adalimumab versus Infliximab						
1/100	RCT	Moderate	NA	Direct	Infliximab and etanercept resulted in higher rates of adverse events than adalimumab (23%, 17%, 6%; p<0.001)	Moderate
Abatacept vs. Infliximab						
1/431	RCT	Moderate	NA	Direct	Abatacept resulted in lower rates of serious AEs (9.6 vs 18.2%) and discontinuations due to AEs (3.2 vs 7.3%)	Moderate

Table 13. 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 direct evidence							

Table 14. Evidence profile of comparisons of targeted immune modulators for efficacy and harms in subgroups

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 direct evidence							