Drug Class Review

Targeted Immune Modulators

Final Update 4 Report

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The literature on this topic is scanned periodically

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STRUCTURED ABSTRACT

Purpose

We systematically compared the efficacy, effectiveness, and harms (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, tofacitinib, 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 up to 2013 (November). We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data, requested dossiers of information from pharmaceutical manufacturers, and retrieved relevant citations from reference lists of included studies.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 standard streamlined Drug Effectiveness Review Project methods.

Results and Conclusion

For rheumatoid arthritis, we did not find any direct evidence for most comparisons among approved targeted immune modulators (48 out of 55 possible comparisons). Low strength evidence indicates similar efficacy between targeted immune modulators if direct head-to-head trials were available. Most of the comparisons, however, are based on single-study evidence and it is likely that future trials will change these estimates.

A single head-to-head randomized trial for psoriatic arthritis indicates equivalent efficacy between adalimumab, etanercept, and infliximab (insufficient strength of evidence) and for plaque psoriasis a single head-to-head randomized trial of etanercept and ustekinumab shows ustekinumab to be more efficacious (low strength of evidence).

For Crohn's disease, 1 trial suggested differences in discontinuation of treatment for loss of response or adverse events, but no difference in quality of life (insufficient strength of evidence).

The most comparative evidence on harms was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab. Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with adalimumab and etanercept (moderate strength of evidence) and more serious adverse events than abatacept (low strength of evidence). Injection site reactions were less frequent for patients receiving abatacept compared with adalimumab and infliximab (low strength of evidence).

Evidence that infliximab has a higher comparative risk for serious infections compared with abatacept, adalimumab, and etanercept was moderate strength. For tuberculosis specifically,

low strength evidence suggests a greater risk with adalimumab and infliximab compared with etanercept. For herpes zoster, low strength evidence suggests no differences.

The strength of evidence comparing the risk of malignancy with targeted immune modulators is low strength; however it suggests no differences exist. Direct evidence on the comparative risk of any adverse events associated with targeted immune modulators in children does not exist and therefore is insufficient strength to make conclusions.

One trial suggests no difference between adalimumab or tocilizumamb for the subgroups age, gender, duration of disease, and use of previous disease-modifying therapy (insufficient strength of evidence).

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INTRODUCTION

Targeted immune modulators (TIMs), 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 14 additional agents since that time for treating various chronic inflammatory and autoimmune disorders, including different types of arthritis, inflammatory bowel diseases, plaque psoriasis and multiple sclerosis: 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), and tofacitinib (2012). Table 1 summarizes currently available targeted immune modulators approved in the United States for the included indications, 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	CD80/86–CD28 T-cell co-stimulation modulator	Rheumatoid arthritis	Intravenous infusion should be administered in 30-minute 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 SC injection within 1 day, followed by 125 mg once weekly. Patients unable to receive an infusion may initiate weekly SC injections without an intravenous loading dose. Patients transitioning from intravenous therapy to SC administration should administer the first SC dose instead of next scheduled intravenous dose.
			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 SC injection; may increase to 40 mg weekly for adalimumab monotherapy.
			Psoriatic arthritis, ankylosing spondylitis	40 mg every other week as SC injection.
			Juvenile idiopathic arthritis (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.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Crohn's disease	Initial SC dose (Day 1) 160 mg (4 40 mg injections in 1 day or 2 40 mg injections daily for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). 2 weeks later (Day 29) begin a maintenance dose of 40 mg every other week.
			Ulcerative colitis	Initial SC dose (Day 1) 160 mg (4 40 mg injections in 1 day or 2 40 mg injections daily for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). 2 weeks later (Day 29) continue with a dose of 40 mg every other week. Only continue in patients who have shown evidence of clinical remission by 8 weeks (Day 57) of therapy.
			Plaque psoriasis	80 mg initial SC dose followed by 40 mg every other week starting 1 week after initial dose (beyond 1 year has not been evaluated in controlled clinical studies).
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 SC injection; dose should be decreased to 100 mg every other day in renal insufficiency (CLcr< 30 mL/min).
			Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	1-2 mg/kg initial SC dose (adjusted in 0.5 to 1.0 mg/kg to a maximum of 8 mg/kg daily), once or split into twice daily administrations.
Certolizumab pegol	Cimzia® UCB, Inc	TNF Inhibitor	Rheumatoid arthritis	400 mg (given as 2 SC injections of 200 mg each) 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'sdisease	400 mg (given as 2 SC injections of 200 mg each) initially and at weeks 2 and 4. If response occurs, follow with 400 mg SC every 4 weeks.
			Psoriatic Arthritis	400 mg (given as 2 SC injections of 200 mg each) initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
			Ankylosingspondylitis	400 mg (given as 2 SC injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Etanercept	Enbrel® Amgen Pfizer Immunex	TNF Inhibitor	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	50 mg once weekly as SC injection.
			Juvenile idiopathic arthritis (2-17 years)	0.8 mg/kg weekly (maximum 50 mg weekly), given as 1 or 2 SC injections.
			Plaque psoriasis	50 mg given twice weekly as a SC injection for 3 months, followed by 50 mg weekly.
Golimumab	Simponi® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	50 mg SC injection once a month in combination with methotrexate.[d]
			Rheumatoid arthritis	2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks
			Psoriatic arthritis, ankylosing spondylitis	50 mg SC injection once a month with or without methotrexate or other DMARDs.[e]
			Ulcerative colitis	200 mg initially administered by SC injection at week 0, followed by 100 mg at week 2 and then 100 mg every 4 weeks.
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*:5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter.
			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*: 5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by maintenance 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'sdisease	300 mg intravenous infusion every 4 weeks.
			Multiple sclerosis	300 mg intravenous infusion over one hour every four weeks.
Rituximab	Rituxan® Genentech	Anti-CD 20a	Rheumatoid arthritis	2 1000 mg intravenous infusion on days 1 and 15 in combination with

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
	Hoffman-La Roche[h]			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 inhibitor monoclonal antibody	Rheumatoid arthritis	Intravenous dosage (a 60-minute single intravenous drip infusion): 4 mg/kg every 4 weeks initially, followed by an increase to 8 mg/kg every 4 weeks based on clinical response, with or without DMARD. Reduction of dose from 8 mg/kg to 4 mg/kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia Dose exceeding 800 mg/ infusion are not recommended. SC dosage: Body weight <100 kg: 162 mg every other week, followed by an increase to every week based on clinical response, with or without DMARD; Body weight ≥ 100 kg: 162 mg every week.
			Polyarticular juvenile idiopathic arthritis (2 years and older)	Body weight <30 kg: 10 mg/kg as a 60-minute single intravenous infusion every 4 weeks. Body weight ≥30 kg: 8 mg/kg every 4 weeks.
			Systemic juvenile idiopathic arthritis (2 years and older)	Body weight <30 kg: 12 mg/kg as a 60-minute single intravenous infusion every 2 weeks. Body weight ≥30 kg: 8 mg/kg every 2 weeks.
Tofacitinib	Xeljanz®/ Pfizer	JAK inhibitor	Rheumatoid arthritis	5 mg twice daily in combination with methotrexate or other non-biologic DMARDs. Dose should be decreased to 5 mg once daily in moderate and severe renal impairment and moderate hepatic impairment. See Xeljanz® label for more information on dose modifications in lymphopenia, neutropenia and anemia.
Ustekinumab	Stelara® Janssen Biotech	IL-12/23 p40 inhibitor	Plaque psoriasis	Body weight ≤100 kg (220 lbs), 45 mg SC injection initially and 4 weeks later, followed by 45 mg every 12 weeks by SC injection Body weight >100 kg (220 pounds), 90 mg SC injection initially and 4 weeks later, followed by 90 mg every 12 weeks.
			Psoriatic arthritis	45 mg SC injection initially and 4 weeks later, followed by 45 mg every 12 weeks; in co-existent moderate-to-severe plaque psoriasis weighing >100 kg (220 lbs), 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Abbreviations: AS, ankylosing spondylitis; CLcr, creatinine clearance; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; IL, interleukin; JIA, juvenile idiopathic arthritis; JAK, Janus kinase; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis; TNF, tumor necrosis factor.

Targeted immune modulators work by selectively blocking mechanisms involved in the inflammatory and immune response. Tumor necrosis factor (TNF) 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 (TNF-α), inhibiting its biological activity. They do not neutralize lymphotoxin alpha. Adalimumab is a fully human monoclonal antibody that blocks TNF-α'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 TNF-α conjugated to an approximately 40kDa polyethylene glycol. Golimumab is a human monoclonal antibody that binds to tumor necrosis factor alpha. Infliximab is a chimeric (mouse/human) anti-TNF-α antibody. Etanercept is a soluble dimeric form of the p75 TNF-α receptor linked to the Fc portion of human immunoglobulin G1. It exerts its action by binding circulating TNF-α and lymphotoxin-α and preventing it from interacting with a cell surface receptor. To explore an oral treatment that reduces the production of TNF-α and other inflammatory mediators, type 4 phosphodiesterases (PDE4) inhibitors have been developed. PDE4 is a key enzyme in the degradation of cyclic adenosine monophosphate (cAMP), an intracellular second messenger that plays an important role in controlling a network of pro-inflammatory and anti-inflammatory mediators. Apremilast is an orally available PDE4 inhibitor that modulates production of a wide range of inflammatory mediators involved in psoriasis and psoriatic arthritis.

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).

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^{TM}Prescribing Program. Under the TOUCH^{TM}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.

Tofacitinib is the first TIM for the treatment of rheumatoid arthritis. It is the first selective Janus kinase (JAK) inhibitor approved by US Food and Drug Administration, which is indicated to be used as monotherapy or in combination with methotrexate or other non-biological disease-modifying antirheumatic drugs (DMARDs). Janus kinase are intracellular enzymes that mediate signaling by surface receptors for several important cytokines that have pivotal role in propagation of inflammation in rheumatoid arthritis.

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 efficacy, effectiveness, and harms 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. TNF-α 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, anticycliccitrullinated 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 (ACR) and the European League Against Rheumatism (EULAR) 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, anticitrullinated 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 3 established subtypes: pauciarticular (less than 5 joints involved), polyarticular (5 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. Nonsteroidalanti-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, sacroilitis, 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): ≥ 3 points from the following 5 categories:		
1	Evidence of current 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] The induction and maintenance of mucosal (and histologic) healing has been introduced as newer goal therapy. Mild disease may be controlled with 5-aminosalicylate drugs or antibiotics. If the disease is resistant to these interventions or is more severe, corticosteroids such as prednisone and budesonide 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.[18] 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, adalimumab and golimumab have been approved by the US Food and Drug Administration for treatment of moderate to severe active ulcerative colitis after the failure of conventional therapy.[19,20] 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.[21] The exact pathogenesis of plaque psoriasis is still unknown, however pathophysiological evidence suggests that an overproduction of proinflammatory cytokines plays an important role.[22,23] 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.[21,24]

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.[25] 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).[24] In addition, biologic agents such as adalimumab, alefacept, etanercept, infliximab, and ustekinumab have been approved by the US Food and Drug Administration for the treatment of moderate to severe plaque psoriasis.

Scope and Key Questions

The purpose of this review is to compare the effectiveness and harms of targeted immune modulators for patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. We compare abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, tofacitinib, and ustekinumab. In previous reports, we included placebo-controlled trials as part of the evidence base, along with head-to-head trials and systematic reviews. A new, streamlined approach was used for this update of the review which focuses on head-to-head randomized trials for efficacy and effectiveness and also includes head-to-head observational studies for harms.

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 RTI-UNC 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.[26] 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 1 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. For assessing efficacy, and effectiveness our review includes head-to-head randomized trials. In addition, for harms we also included large head-to-head 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 Employability, productivity o Clinical improvement o Disease remission o Pain o Reduction in the number of swollen or tender joints o Reduction in disease-related hospitalizations o Reduction in disease-specific mortality o Rebound / flare o Joint destruction 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 comparing one TIM drug to another ≥12 weeks study duration
Harms/ Tolerability	• Overall adverse events • Withdrawals due to adverse events • Serious adverse events • Specific adverse events, including: o Lymphoma o All malignancies o Serious infectious diseases o Herpes zoster o Opportunistic infections • Mortality	• Outpatient study population • Head-to-head randomized controlled clinical trials comparing one TIM drug to another • ≥ 12 weeks study duration • Head-to-head observational studies were reviewed for harms • > 12 weeks study duration • n ≥ 100

Abbreviations: 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 1). 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); however, we also include radiographic outcomes. Many clinicians view radiographic changes as important parameters of treatment success or failure.

METHODS

Literature Search

To identify articles relevant to each key question, for Update 4 we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2011 (October) to 2013 (November) using included drugs (abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, tofacitinib, 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 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® X5, 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 included only head-to-head evidence. Head-to-head trials and studies were defined as those comparing one targeted immune modulator with another. For efficacy and effectiveness outcomes, we only included head-to-head randomized controlled trials of at least 12 weeks duration with an outpatient study population. For the section on harms we also included large ($n \geq 100$), head-to-head observational studies with a follow-up of at least 12 weeks to augment findings from trials. Throughout this report we refer to randomized controlled trials as "trials" and all observational studies, including prospective and retrospective cohort studies, database analyses, etc., as "studies".

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. For head-to-head trials in rheumatoid arthritis we also included radiological changes. Harms outcomes included overall and specific adverse events (e.g., serious infections and malignancy), including withdrawals attributable to adverse events.

Data Abstraction

We 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 risk of bias (quality rating) of trials based on predefined criteria developed by the United States Preventive Services Task Force (ratings: good-fair-poor)[27] and the National Health Service Centre for Reviews and Dissemination.[28] External validity (generalizability) was assessed but did not influence quality ratings.

2 independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third, independent party. Elements of risk of bias assessment for randomized trials 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. For observational studies we also assessed the comparability of baseline characteristics, whether the included groups consisted of new users, and the method of statistical adjustment for baseline confounding.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study,[29] independent of the reason and the use of intention-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 1 or more categories were rated poor and given less weight in the summary of evidence in this 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. Furthermore, the ratings of good-fair-poor were specific to study type, meaning that a fair quality observational study is nonetheless at higher risk of bias than a fair-quality randomized trial.

Data Synthesis

Throughout this report we synthesized the literature qualitatively. We were not able to perform meta-analysis because data were too sparse; rarely was more than one trial available for each comparison.

Peer Review

We will request peer review of the report from a content/methodology expert. Their comments will be reviewed and, where possible, incorporated into the final report. All comments and the authors' proposed actions will be reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of this 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 will be posted to the Drug Effectiveness Review Project website for public comment.

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.[30] Strength of evidence is graded only for major comparisons and major outcomes. The strength of evidence for each outcome or comparison that we graded incorporates scores on 4 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., 2010, evaluating risk of bias includes assessment of study design and aggregate quality of studies.[30] 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.[30]

As shown in Table 5, we used 4 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.

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

High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before conclusion.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching 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 4, literature searches identified 1501 citations. In combination with previous searches, we have now identified 6704 relevant citations in total over the history of this report. For this update, we received dossiers from 5 pharmaceutical manufacturers: Abbvie, Amgen, Genentech, Janssen and UCB Inc.

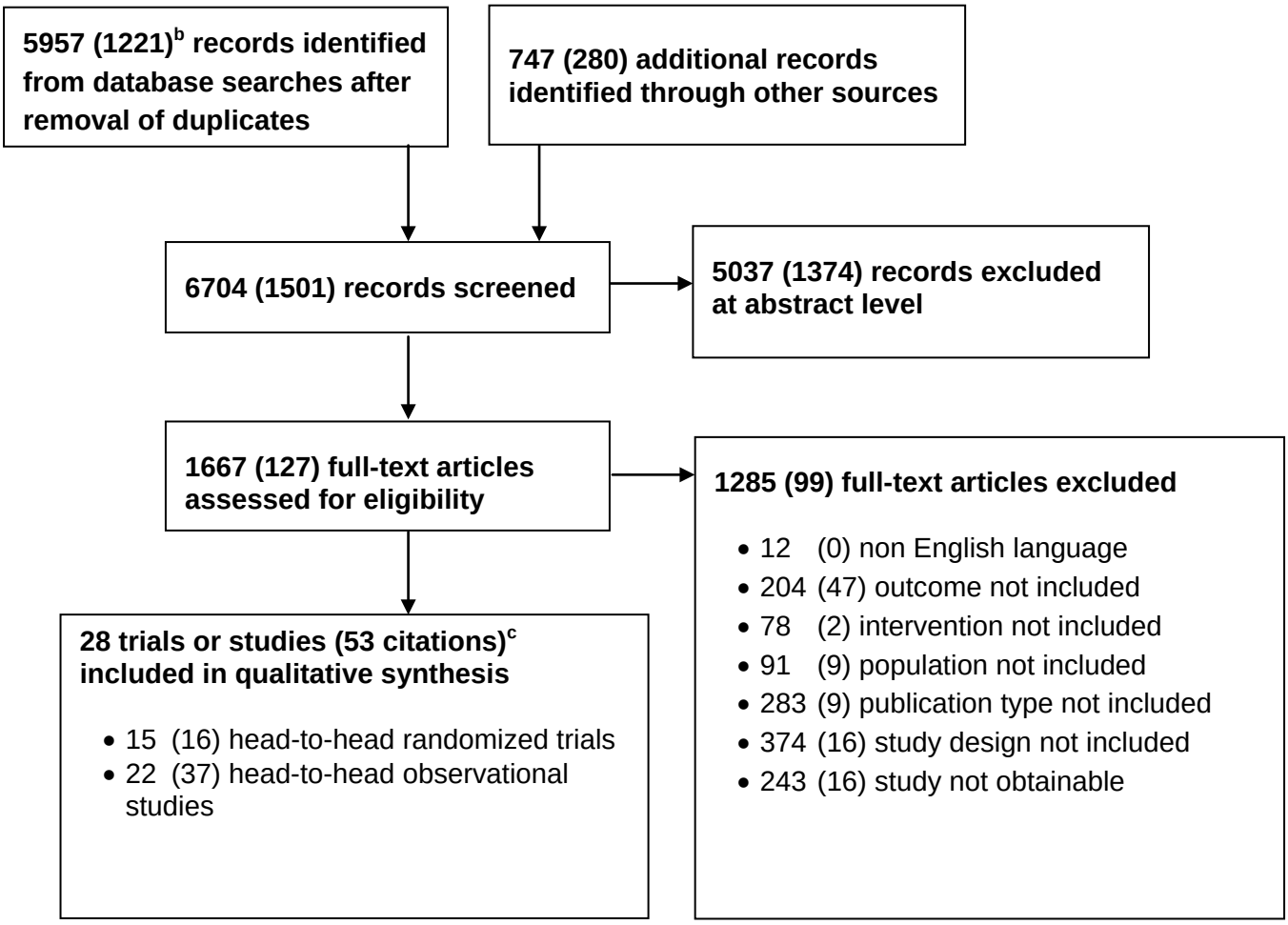
The previous version of this report included head-to-head trials randomized trials and observational studies as well as placebo-controlled trials and systematic reviews and network meta-analyses. For this update we removed the data from placebo-controlled trials and from systematic reviews with indirect comparisons and concentrated exclusively on direct head-to-head evidence.

Altogether we now have evidence from 15 head-to-head randomized trials and from 22 head-to-head observational studies. The number of included citations is larger because multiple publications report on data from the same trial or study. This is particularly the case for data from large national registries where analyses for different harms such as infections or malignancies are reported in separate publications. Overall, we included 16 citations for the 15 randomized trials and 37 citations from the 22 included observational studies. Of these, 8 publications of randomized trials and 20 publications from observational studies were new to this update.

We used a system of flagging references that were not formally eligible for this report but may be of interest to the stakeholders. In appendix F we list the systematic reviews and network meta-analyses that were detected in our searches but not eligible for this update. In appendix H we list the references of placebo-controlled trials of targeted immune modulators detected in our searches but not eligible for this update. This list includes drugs that were not formally included in this report (e.g., because their approval occurred after the search dates in November 2013). We did not locate any head-to-head trial or study of any targeted immune modulator not formally included in this update.

Figure 1 shows the flow of study selection for this update (in brackets) and for the entire history of this report.

Figure 1. Results of literature search[a]



[a] DERP uses a modified PRISMA flow diagram.[31]
[b] Numbers in parentheses are results of the literature search new to Update 4
[c] The number of included studies differs from the number of included citations 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, tocilizumab, and tofacitinib.
We included 10 trials[32-41] of which 3 were open-label randomized controlled trials.[32-34] All included trials were efficacy studies, conducted in narrowly defined populations and/or limited to less than 12 months of follow-up. We did not find any comparative effectiveness studies for rheumatoid arthritis.

Summary of findings

Of the 55 possible head-to-head comparisons for the approved drugs, we found direct head-to-head evidence from trials for 7 comparisons and 3 combination strategies. For most comparisons, the evidence is limited to a single, fair trial funded by the producer of one of the compared drugs.

Single trial evidence indicates that efficacy outcomes are similar between abatacept and adalimumab,[32] adalimumab and etanercept,[33] adalimumab and tofacitinib,[37]and etanercept and tocilizumab.[33] The evidence is mixed regarding differences in efficacy between adalimumab and tofacitinib.[37,38] The strength of evidence for these comparisons is low or insufficient.

For the comparison of abatacept with infliximab the only double-blinded head-to-head trial indicated no differences in efficacy between patients treated with abatacept or infliximab after 6 months.[36] The study did not allow for dose adjustments for infliximab, results after 1 year, therefore, are biased towards a greater efficacy of abatacept. For the comparison of adalimumab with tocilizumab, a fair double-blinded randomized controlled trial reported statistically significantly lower response rates for patients treated with adalimumab than tocilizumab.[35] Tocilizumab, however, was used at a higher starting dose than FDA approved. The dosing equivalence in this study, therefore, is questionable and findings have to be interpreted cautiously.

In contrast, a small open-label randomized controlled trial, indicated no differences in treatment effects between adalimumab and tocilizumab.[33] The strength of evidence is low.

A fair, small (n=32), open-label randomized controlled trial indicated greater response rates in patients treated with etanercept than with infliximab (74.4% compared with 60% after 54 weeks; *P*=NR).[34] The strength of evidence is insufficient.

Evidence based on 3 fair randomized controlled trials indicates that combination therapies etanercept and anakinra, etanercept and abatacept, and rituximab and anti-TNF drugs (adalimumab, etanercept) do not lead to additional benefits but cause significantly higher rates of adverse events.[39-41]

Study populations and outcome measures

All patients suffered from active rheumatoid arthritis and most trials employed the American College of Rheumatology criteria to classify the diagnosis of rheumatoid arthritis. [4,42] 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 1 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, DAS28 Activity Score28) combine measures of global disease activity with counts of tender and swollen joints and acute phase laboratory parameters (see Appendix C). In addition, most studies evaluated health outcomes such as quality of life, functional capacity (e.g., Short Form 36 Health Survey, Health Assessment Questionnaire Disability Index, arthritis-specific health index), or discontinuation rates due to disease worsening.

Sponsorship

All trials were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on comparative effectiveness

Overall, we included 10 head-to-head trials comparing one targeted immune modulator to another.[32-41] None of them was classified as an effectiveness study. Out of 55 possible comparisons based on 11 approved drugs, the available trials were limited to the following 7 comparisons: abatacept vs. adalimumab, abatacept vs. infliximab, adalimumab vs. etanercept, adalimumab vs. tocilizumab, adalimumab vs. tofacitinib, etanercept vs. infliximab, and etanercept vs. tocilizumab. We could not find any head-to-head trial evidence for anakinra, certolizumab pegol, golimumab, and rituximab. Included studies are summarized in Table 6.

Abatacept compared with adalimumab

The only evidence (AMPLE trial) for this comparison with a randomized allocation of interventions was a fair, open-label randomized controlled trial that compared abatacept (125 mg weekly) and adalimumab (40 mg every other week) in combination with methotrexate in a population of patients with active rheumatoid arthritis who were naïve to treatment with biologicals and had an inadequate response to methotrexate.[32] The study was designed to test the non-inferiority of abatacept compared with adalimumab and was funded by the producer of abatacept. The primary outcome measure was American College of Rheumatology 20 response at 12 months. At study endpoint response rates were similar between patients treated with abatacept and adalimumab (American College of Rheumatology 20: 64.8% vs. 63.4%). Other efficacy outcomes were also similar for patients on abatacept or adalimumab. At 1 year, patients in both groups had similar American College of Rheumatology 50 (46.2% vs. 46.0%) and American College of Rheumatology 70 (29.2 vs. 26.2%) responses. Likewise, patients treated with abatacept had similar improvements on Disease Activity Score28 (-2.30 vs. -2.27)

and the Health Assessment Questionnaire Disability Index (-0.60 vs. 0.59) compared with patients on adalimumab. Radiographic progression also showed no statistically significant differences between the 2 treatment groups. The strength of the evidence is low.

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.[36] 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 (Disease Activity Score28: 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. The strength of the evidence is low.

Adalimumab compared with etanercept

The only study with a randomized allocation for this comparison was a small, fair, open-label randomized controlled trial that compared adalimumab monotherapy (n=21; 40 mg every 2 weeks), etanercept monotherapy (n=21; 25 mg twice a week), and tocilizumab monotherapy (n=22; 8mg/kg every 4 weeks), to assess changes in arterial stiffness.[33] As secondary outcomes, this study also assessed changes on the Health Assessment Questionnaire Disability Index and the Disease Activity Score28-ESR (erythrocyte sedimentation rate) after 24 weeks of treatment. The statistical analysis was performed as a "completers analyses" only; however few patients dropped out of the study (2 persons in the adalimumab group and 1 person in the etanercept group). Consequently, results of the completers' analyses are probably similar to an intention-to-treat-analysis. After 24 weeks, patients in the adalimumab and the etanercept groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.69 vs. 0.68) and the Disease Activity Score28-ESR (-2.12 vs. -2.84). The strength of the evidence is insufficient.

Adalimumab compared with tocilizumab

Two fair trials, a double-blinded randomized controlled trial[35] and a small open-label randomized controlled trial[33] compared adalimumab monotherapy (40 mg every 2 weeks) with tocilizumab monotherapy (8 mg/kg every 4 weeks). The open-label trial assessed changes in arterial stiffness as the primary outcome. As secondary outcomes, this trial also determined changes on the Health Assessment Questionnaire Disability Index and the Disease Activity Score28-ESR after 24 weeks of treatment.

The double-blinded randomized controlled trial (ADACTA study) was funded by the producer of tocilizumab and enrolled 326 patients who were unable to tolerate methotrexate. The primary endpoint was the change in Disease Activity Score 28 score from baseline to week 24. Across both groups, 21% of patients withdrew from the assigned group to receive escape treatment or entirely drop-out of the study. After 24 weeks, patients treated with adalimumab had statistically significantly smaller improvements on the Disease Activity Score28 than patients treated with tocilizumab (-1.8 vs. -3.3; $P<0.0001$). Likewise, fewer patients treated with adalimumab achieved remission (Disease Activity Score28<2.6; 10.5% vs. 39.9%; $P<0.0001$), American College of Rheumatology 50 (27.8% vs. 47.2%; $P=0.0002$), or American College of Rheumatology 70 (17.9% vs. 32.5%; $P=0.0023$) response than patients on tocilizumab. Mean changes on the Health Assessment Questionnaire Disability Index (-0.5 vs. -0.7; $P=0.07$) and the SF-36 physical component score (7.6 vs. 9.2; $P=0.16$) were similar between adalimumab and tocilizumab groups. It has to be noted though that in this trial tocilizumab was used at a higher dosage than FDA approved. Because the dosing equivalence, therefore, is questionable, findings have to be interpreted cautiously.

Results of the small, open-label randomized controlled trial showed similar improvements between patients treated with adalimumab or tocilizumab.[33] After 24 weeks, patients in the adalimumab and the tocilizumab groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.69 vs. 0.68) and the Disease Activity Score28-ESR (-2.12 vs. -2.84). Statistical analysis was a completers analysis only, however, only few patients dropped out of the study (2 persons in the adalimumab group and 1 person in the tocilizumab group). The strength of the evidence is low.

Adalimumab compared with tofacitinib

Two fair double-blinded randomized controlled trials assessed the comparative benefits and harms of adalimumab and tofacitinib in patients with rheumatoid arthritis who had an inadequate response to methotrexate treatment.[37,38] Both trials were funded by the producer of tofacitinib, 1 of the 2 trials was a phase IIb dose-ranging study.[38]

The larger of the 2 randomized controlled trials (ORAL Standard) enrolled 717 patients with active rheumatoid arthritis who experienced an incomplete response to methotrexate treatment and randomized them to adalimumab (40 mg every other week), tofacitinib 5 mg (twice daily), tofacitinib 10 mg (twice daily), or placebo.[37] At 6 months patients treated with adalimumab or the 2 tofacitinib regimens had similar American College of Rheumatology 20 response rates (adalimumab: 47.2%: tofacitinib 5 mg: 51.5%; tofacitinib 10 mg: 52.6%). American College of Rheumatology 50/70 responses and Health Assessment Questionnaire Disability Index were also similar between the 3 treatment groups. The dose-ranging study reported substantially lower American College of Rheumatology 20 response rates after 12 weeks of treatment for patients treated with adalimumab (40 mg every other week) than those on tofacitinib 5 mg or 10 mg (35.9% vs. 59.2% vs. 70.5%: P = NR).[38] The strength of the evidence is low.

Etanercept compared with infliximab

The only included trial 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).[34] 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 mg-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 Disability Index (–32.30 compared with –21.60; *P*=NR). The trial 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 trial the dosage of infliximab (3 mg/kg) was fixed for 54 weeks at the lower end of the recommended regimen (3-10 mg/kg). Therefore, results have to be interpreted cautiously. The strength of the evidence is insufficient.

Etanercept compared with tocilizumab

The only trial with a randomized allocation for this comparison was a small, fair, open-label randomized controlled trial that compared etanercept monotherapy (n=21; 25 mg twice a week), tocilizumab monotherapy (n=22; 8 mg/kg every 4 weeks), and adalimumab monotherapy (n=21; 40 mg every 2 weeks) to assess changes in arterial stiffness.[33] As secondary outcomes, this trial also assessed changes on the Health Assessment Questionnaire Disability Index and the Disease Activity Score28-ESR after 24 weeks of treatment. Statistical analyses were completers' analyses only, however, only few patients dropped out of this trial (1 person each in the etanercept and tocilizumab group). Consequently, results of the completer's analyses are probably similar to an intention-to-treat-analysis. After 24 weeks, patients in the etanercept and the tocilizumab groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.68 vs. 0.70) and the Disease Activity Score28-ESR (-2.84 vs. -2.10). The strength of the evidence is insufficient.

Targeted immune modulators combination strategies

Three trials determined the potential for additive or synergistic effects of combination therapy of 2 targeted immune modulators.[39-41] The largest, 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.[39] 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.

The second trial, examining a combination of abatacept (2 mg/kg) and etanercept (25 mg twice weekly) compared with abatacept (2 mg/kg) monotherapy reached similar conclusions.[40] The combination was associated with increased serious adverse events but only limited additional clinical benefit.

The third trial, the TAME (Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Tolerability and Safety of Rituximab when given in Combination with Methotrexate and Etanercept or Methotrexate and Adalimumab) study , assessed the benefits and harms of adding rituximab (2 infusions of 500mg intravenously, 2 weeks apart) to the treatment regimen of 54 patients who had active rheumatoid arthritis despite treatment with adalimumab or etanercept and methotrexate.[41] Similar to results of the other 2 studies described above, combination therapy was associated with increased serious adverse events but only limited additional clinical benefit. The strength of the evidence is moderate.

Table 6. Summary of head-to-head trials in adult patients with rheumatoid arthritis

Authors, Year	Study design	Number of patients	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ABATACEPT compared with ADALIMUMAB									
Weinblatt et al., 2013 (AMPLE)[32]	Open-label RCT	646	12 months	Abatacept vs. Adalimumab	ACR 20	ACR 50/70, DAS28, HAQ	Active RA for less than 5 years; had failed Methotrexate treatment; mean disease duration: 1.8 years	Treatment response similar for Abatacept and Adalimumab	Fair
ABATACEPT compared with INFLIXIMAB									
Schiff et al., 2008[36]	RCT	431	12 months	Abatacept vs. Infliximab	DAS28	ACR 20/50/70, HAQ, SF-36	Active RA for at least 1 year; had failed Methotrexate treatment; mean disease duration: 7.9 years	Treatment response similar for Abatacept and Infliximab after 6 months. Greater response for Abatacept than Infliximab after 12 months (no dose adjustment allowed for infliximab)	Fair
ADALIMUMAB compared with ETANERCEPT									
Kume et al., 2011[33]	Open-label RCT	42	6 months	Adalimumab vs. Etanercept vs. Tocilizumab	Arterial stiffness	DAS28, HAQ	Active RA; mean disease duration: 10 months	Treatment response similar for Adalimumab and Etanercept	Fair
ADALIMUMAB compared with TOCILIZUMAB									
Gabay et al., 2013 (ADACTA)[35]	RCT	326	6 months	Adalimumab vs. Tocilizumab	DAS28	HAQ, EULAR, ACR 20/50/70, SF-36	Active RA in patients who did not tolerate Methotrexate; mean disease duration: 6.8 years	Treatment response lower for Adalimumab than Tocilizumab	Fair
Kume et al., 2011[33]	Open-label RCT	43	6 months	Adalimumab vs. Etanercept vs. Tocilizumab	Arterial stiffness	DAS28, HAQ	Active RA; mean disease duration: 10 months	Treatment response similar for Adalimumab and Tocilizumab	Fair
ADALIMUMAB compared with TOFACITINIB									
van Vollenhoven et al., 2012 (ORAL Standard) [37]	RCT	717	12 months	Adalimumab vs. Tofacitinib	ACR 20	ACR 50/70, DAS28, HAQ	Active RA with an inadequate response to Methotrexate treatment; mean disease duration:6.9 to 9.0 years	Treatment response similar for Adalimumab and Tofacitinib	Fair

Authors, Year	Study design	Number of patients	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Fleischmann et al., 2012[38]	RCT	384	3 months	Adalimumab vs. Tofacitinib	ACR 20	ACR 50/70, DAS28, HAQ, SF-36	Active RA with an inadequate response to Methotrexate treatment; mean disease duration:7.7to 10.8 years	ACR response rates lower for Adalimumab than Tofacitinib	Fair
ETANERCEPT compared with INFLIXIMAB									
De Filippis et al, 2006[34]	Open-label RCT	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
ETANERCEPT compared with TOCILIZUMAB									
Kume et al., 2011[33]	Open-label RCT	43	6 months	Adalimumab vs. Etanercept vs. Tocilizumab	Arterial stiffness	DAS28, HAQ	Active RA; mean disease duration: 10 months	Treatment response similar for Etanercept and Tocilizumab	Fair
Combination strategies									
Genovese et al., 2004[39]	RCT	242	6 months	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
Greenwald et al., 2011 (TAME study)[41]	RCT	51	6 months	Rituximab+Adalimumab or Etanercept+Methotrexate vs. Adalimumab or Etanercept+Methotrexate	Serious infections	Other serious adverse events, ACR 20/50/70, DAS28	Active RA despite treatment with Adalimumab or Etanercept+Methotrexate for at least 12 weeks; mean disease duration: 10.5 years	Limited additional benefit from combination therapy; Serious adverse events numerically higher in combination than in monotherapy group	Fair
Weinblatt et al., 2007[40]	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	Limited additional benefit from Abatacept-Etanercept combination therapy; Serious adverse event 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; DAS28, disease activity score28; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, 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

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

Ankylosing Spondylitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ankylosing spondylitis: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.

Summary of findings

We did not find any head-to-head trials of targeted immune modulators for ankylosing spondylitis.

Psoriatic Arthritis

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

We located 1 poor-quality randomized head-to-head trial of adalimumab, etanercept, and infliximab.[43] In this trial, 100 psoriatic arthritis patients were randomized and received 12 months of treatment. The main methodological problems with this trial were that the methods of randomization, allocation concealment, loss to follow up, and statistical analysis are poorly reported and the baseline characteristics of the three groups differ. Nonetheless, the American College of Rheumatology 20 response rates were similar: adalimumab 70%; etanercept 72%; and infliximab 75%. Overall, the strength of evidence for this comparison was insufficient.

We did not locate any head-to-head evidence on other targeted immune modulators for psoriatic arthritis. We did not find any comparative effectiveness studies for psoriatic arthritis.

Study populations and outcome measures

The 100 patients in the available head-to-head randomized trial were recruited from a university hospital clinic in Italy.[43] 60% of the patients were women. The patients had a mean age of 48.5 years (standard deviation 12.5 years) with disease of moderate severity. Patients who had previously used antitumor necrosis factor drugs were excluded, as were patients requiring more than 10 mg prednisone per day or with escalating non-steroidal medication doses.

The outcome assessed in this trial were not designated as “primary” or “secondary” but included: American College of Rheumatology 20 response, Psoriasis Area and Severity Index, Health Assessment Questionnaire, tender joint count, swollen joint count, and adverse events. There were some differences in baseline characteristics of the groups; the infliximab patients had

higher Health Assessment Questionnaire scores and lower number of swollen joints and the etanercept patients had more severe associated skin psoriasis.

Sponsorship

No details on the sponsorship of this trial are provided although the authors state they have no disclosures.

Detailed assessment: Direct evidence on comparative effectiveness

We included 1 head-to-head trial comparing adalimumab with etanercept and infliximab.[43] We could not find any head-to-head evidence for any of the other targeted immune modulators. The included trial is summarized in Table 7.

Adalimumab compared with etanercept and infliximab

The only included head-to-head trial was a poor, randomized head-to-head trial comparing adalimumab with etanercept and infliximab.[43] In this trial 100 patients with psoriatic arthritis seen in a university hospital in Italy were randomized to receive: 40 mg adalimumab every other week; 25 mg etanercept twice per week; or 5 mg/kg infliximab every 6 to 8 weeks. An induction regimen for infliximab was not described. Dose adjustment was permitted in this trial. Of the 1240 patients seen in the outpatient clinic during the 3-year recruitment period, 100 were determined to have active disease and were considered eligible for the trial. Patients who had previously trialed antitumor necrosis factor drugs were excluded, as were patients taking more than 10 mg prednisolone daily or requiring increasing amounts of non-steroidal drug therapy. The trial duration was 12 months.

The methodological quality of this trial is difficult to assess due to poor reporting. Neither the method of randomization nor the method of allocation concealment is described. The authors do not declare which outcomes are primary or secondary, nor do they conduct any statistical adjustment for the baseline differences in the groups (the infliximab group had less severe joint disease at baseline and the etanercept group had more severe skin disease). The authors do not report on loss to follow-up of patients or on their approach to missing data. The overall quality of this trial is therefore poor.

The efficacy results indicate that the three groups experiences similar improvements. The proportion of patients achieving an American College of Rheumatology 20 response at 12 months in the groups was: adalimumab 70%; etanercept 72%; infliximab 75%. The authors report on some differences in the other reported outcomes but they do not say whether adjustment for multiple testing was performed and they do not adjust for differences in baseline characteristics of the groups so these results are not reliable. The strength of evidence is insufficient.

Psoriatic Arthritis in Children

No targeted immune modulators are currently approved for the specific use of psoriatic arthritis in children. No evidence on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in children exists.

Table 7. Summary of head-to-head trials in adult patients with psoriatic arthritis

Authors, Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB compared with ETANERCEPT compared with INFLIXIMAB									
Atteno, et al. 2010[43]	RCT	100	12 months	Adalimumab vs. Etanercept vs. Infliximab	ACR 20	HAQ, PASI, TJC, SJC, adverse events	Adults with psoriatic arthritis with an inadequate response to DMARDs	Similar ACR 20 response rates: adalimumab 70%, etanercept 72%, infliximab 75%	Poor

Abbreviations: DMARDs: disease modifying anti-rheumatic drugs; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area and Severity Index; RCT, randomized controlled trial; TJC, tender joint count; SJC, swollen joint count.

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.

Overall, the strength of evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease was insufficient. We located 1 fair-quality, open-label, randomized, head-to-head trial of subcutaneous adalimumab compared with intravenous infliximab for the treatment of Crohn's disease.[44] In the trial 73 patients with a satisfactory response to infliximab therapy were randomized to continue infliximab (5 mg/kg intravenously every 6-8 weeks) for 56 weeks or to switch to adalimumab (80 mg subcutaneously at inclusion and 40 mg subcutaneously every other week for 54 weeks). Significantly more patients in the adalimumab group discontinued treatment for loss of response or adverse events compared with the infliximab group. Due an interim analysis revealing this difference, recruitment to the trial was stopped early before reaching the planned patient population. The strength of evidence for this comparison was insufficient.

We did not locate any head-to-head evidence on other targeted immune modulators for Crohn's disease. We did not find any comparative effectiveness studies for Crohn's disease.

Study populations and outcome measures

All 73 randomized adult patients in the study by Van Assche, et al., 2012, had luminal Crohn's disease treated with infliximab maintenance therapy with stable dosing intervals of at least 6 weeks for at least the last 6 months.[44] Further inclusion criteria were complete response with symptom control and a Crohn's Disease Activity Index (CDAI) of less than 200. The Crohn's Disease Activity Index assesses 8 related variables (e.g., number of liquid or soft stools per day, severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of abdominal mass, the use or nonuse of antidiarrheal drugs, the hematocrit, and body weight; see Appendix C) 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.

The majority of patients were receiving 8-weekly treatment with infliximab (83% adalimumab vs. 76% infliximab) and some patients were on concomitant immunosuppression (17% adalimumab vs. 5% infliximab, overall 11%). No previous adalimumab treatment was allowed. Patients with imminent need for surgery, previous infliximab doses of more than 5 mg/kg intravenously, draining abdominal enterocutaneous fistula, and patients with contraindications for further antitumor necrosis factor therapy were excluded from the trial. There were no statistically significant differences at baseline between the treatment groups, although patients randomized to the adalimumab group had been on infliximab treatment longer than patients in the infliximab group (32 months vs. 63 months, respectively P=0.07) and were receiving more concomitant immunosuppression (P=0.15).

The main outcome that was assessed for both groups was the proportion of patients who needed rescue therapy with steroids or anti-tumor necrosis factor dose escalation or had to terminate the allocated treatment early. Analysis was based on an intention-to-treat analysis. Secondary outcomes were an increase in Crohn's Disease Activity Index of more than 100 compared to baseline and quality of life measured with the Inflammatory Bowel Disease

Questionnaire (IBDQ). C-reactive protein (CRP) was used as a marker of disease activity and harms measures were also obtained.

Sponsorship

The authors stated that they worked independently on the study; nevertheless most authors declared competing interests due to financial grants from the pharmaceutical industry, including both companies (Abbott/AbbVie and Janssen Biotech, formerly Centocor) producing the investigated drugs.

Detailed assessment: Direct evidence on comparative effectiveness

We included 1 head-to-head switch trial comparing adalimumab with infliximab.[44] We could not find any head-to-head evidence for any of the other targeted immune modulators. The included trial is summarized in Table 8.

Adalimumab compared with infliximab

The only included head-to-head trial was a fair, open-label switch trial comparing adalimumab with infliximab.[44] The trial randomized 73 patients with ongoing infliximab maintenance therapy to continue their current infliximab regime (5 mg/kg intravenously every 6-8 weeks) for 56 weeks or to switch to adalimumab (80 mg subcutaneously at inclusion and 40 mg subcutaneously every other week for 54 weeks). Significantly more patients in the adalimumab group required dose escalation compared with the infliximab group: 47% vs. 16%, respectively; P=0.003. Likewise, significantly more patients in the adalimumab group terminated treatment early (6 patients for loss of efficacy and 4 patients due to adverse effects) compared with the infliximab group (1 patient due to adverse effects): 28% vs. 2%, respectively; P<0.01. An increase in Crohn's Disease Activity Index of 100 or more points was observed in 28% in patients treated with adalimumab compared to 19% in the infliximab group. Median Inflammatory Bowel Disease Questionnaire scores were similar between groups and throughout the study. The scores in the adalimumab group were 197 (interquartile range 181-212) at baseline and 193 (interquartile range 160-214) at week 54, whereas in the infliximab group they were 191 (interquartile range 172-203) at baseline and 188 (interquartile range 170-204) at week 54. The strength of evidence is insufficient.

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.

Summary of findings

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease in children exists.

Table 8. Summary of head-to-head trials in adult patients with Crohn's disease

Authors, Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB compared with INFLIXIMAB									
Van Assche et al., 2012[44]	RCT (switch)	73	12 months	Adalimumab vs. Infliximab	Patient preference of Adalimumab over Infliximab; Need of rescue therapy or treatment termination	CDAI >100 above baseline; Quality of life (IBDQ)	Adults with luminal CD (CDAI <200) treated with Infliximab for at least 6 months with complete response	Infliximab superior to adalimumab for treatment termination and dose escalation; no difference in IBDQ scores	Fair

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; RCT, randomized controlled trial.

Ulcerative Colitis

Adalimumab, golimumab and infliximab are currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in adults.

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

Summary of findings

No head-to-head evidence on the comparative effectiveness of targeted immune modulators for the treatment of ulcerative colitis exists for adults or children.

Plaque Psoriasis

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

Summary of findings

We located 1 fair-quality, randomized, head-to-head trial of etanercept compared with ustekinumab for the treatment of moderate-to-severe plaque psoriasis.[45] In the trial 903 patients were randomized to 50 mg etanercept twice weekly or 2 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 Psoriasis Area and Severity Index 75 response compared with etanercept. The strength of evidence for this comparison was low. We did not find any comparative effectiveness studies for plaque psoriasis.

Study populations and outcome measures

The included head-to-head trial enrolled patients who had a history of plaque psoriasis for more than 6 months, with more than 10% of body surface area involved. The minimum Psoriasis Area and Severity Index score to meet inclusion criteria was 12 and patients were candidates for systemic treatment. Patients were excluded if they had nonplaque disease, a recent infection, or malignancy. Prior therapy with biologic agents more than 3 months (or 5 half-lives) was not an exclusion criterion for this trial.

This trial assessed the Psoriasis Area and Severity Index 75 and Psoriasis Area and Severity Index 90 as one the primary outcome measures (see Appendix C). The Physician Global Assessment was also measured. The methodological quality of this trial was fair.

Sponsorship

The included trial was funded by the pharmaceutical company that produces ustekinumab.

Detailed assessment: Direct evidence on comparative effectiveness

Etanercept compared with ustekinumab

We located 1 fair-quality, randomized, head-to-head trial that compared etanercept with ustekinumab in 903 patients with moderate-to-severe plaque psoriasis.[45] The doses of targeted immune modulator in the 3 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 1 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). In this study patients over 90kg received the higher dose of ustekinumab (90mg) although the higher dose is recommended for patients who weigh more than 100kg. The strength of evidence is low.

Plaque Psoriasis in Children

No targeted immune modulators are currently approved for the treatment of plaque psoriasis in children.

Summary of findings

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of plaque psoriasis in children exists.

Table 9. Summary of head-to-head trials in patients with plaque psoriasis

Authors, Year	Study design	Number of patients	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT compared with USTEKINUMB									
Griffiths et al., 2010[45]	RCT	903	12 weeks	Etanercept 50 mg twice weekly / Ustekinumab 45 mg or 90 mg 2 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

Abbreviations: 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 harms associated with the use of targeted immune modulators?

Summary of Findings

Thirty-five head-to-head trials or studies provided direct evidence on the harms associated with targeted immune modulators: 13 randomized trials with 4292 included patients[32,35-41,43-47] and data from 37 publications of head-to-head observational studies (from 22 different national registries or databases) with data gathered from more than 100 000 individuals.[48-84]

- General tolerability
  - overall rate of any adverse event
  - withdrawal/discontinuation due to adverse events
  - rates of serious adverse events
  - injection or infusion reactions
  - mortality
- Infections as harms
  - serious infections
  - tuberculosis
  - opportunistic infections
  - herpes zoster
- Malignancy
  - overall malignancies
  - non-melanoma skin cancer
  - melanoma skin cancer
- Other harms
  - cardiovascular harms
  - interstitial lung disease; and
- Harms from combination strategies of more than one targeted immune modulator
- Harms in children

The most comparative evidence was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab (36 publications included only these 3 drugs). Table 13 and Table 14 provide a description of the randomized trials and observational studies providing direct evidence for this section. We did not locate any direct comparative evidence from trials or observational studies on the following targeted immune modulators: alefacept; certolizumab pegol; golimumab; or natalizumab.

The included trials were of 12 weeks to 12 months duration. The comparative rates of overall adverse events occurring with targeted immune modulators did not differ (or any differences did not reach statistical significance).[32,35,36,38,43-45,64] Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with adalimumab and etanercept (moderate strength of evidence),[44,56,58,59,67] and more serious adverse events than abatacept (low strength of evidence).[36] Injection site reactions were less frequent for patients receiving abatacept compared with both adalimumab and infliximab (both low strength of evidence) and greater for etanercept than ustekinumab (low strength of evidence).[32,36,45]

Evidence that infliximab has a higher comparative risk for serious infections compared with abatacept, adalimumab, and etanercept was moderate strength.[37,48,49,64,68,72,74,75,81,85] For tuberculosis specifically, low strength evidence suggests a greater risk with adalimumab and infliximab compared with etanercept.[50,62,63,69] For herpes zoster, low strength evidence suggests no differences.[52,76,78,84]

The strength of evidence comparing the risk of malignancy with targeted immune modulators is low strength; however it suggests no differences exist.[53,54,56,65,83] Evidence from 2 studies showed no difference between adalimumab, etanercept, and infliximab for risk of mortality (low strength of evidence).[66,70]

Comparative evidence for regimes where 2 targeted immune modulators were given in combination showed an increased risk of serious adverse events, withdrawal due to adverse events, and serious infections (high strength of evidence).[39,41,47,86]

No direct evidence exists on the comparative risk of harms for targeted immune modulators for children.

Study populations and outcome measures

The majority of publications of randomized trials and observational studies assessing adverse events included patients with rheumatoid arthritis. Most randomized trials used objective scales such as the Utvalg for Kliniske Undersogelser Side Effect Scale or the adverse reaction terminology from the World Health Organization and provided catalogued adverse event profiles in supplementary material available online or via the US Food and Drug Administration's website clinicaltrials.gov. The observational studies tended to rely on the International Classification of Disease (ICD) codes or hospital admissions, and linked these diagnoses with accounts of medication prescriptions from their databases. The definition of serious infection, for example, included the use of intravenous antibiotics, hospitalization, death, or disability following an infective diagnosis.

The short duration and small size of randomized trials limited the validity of adverse events assessment with respect to rare but serious adverse events. In contrast, observational studies included over 100 000 patients; however observational study results are vulnerable to selection bias (despite statistical adjustment for confounding) and therefore evidence gained from observational studies regarding the direct comparisons between the targeted immune modulators should be interpreted with caution and received a lower strength of evidence rating. Much of the evidence from large databases or registries was published separately for each adverse event although the data comes from the same pool of patients. Database data was available from Asian countries, European countries, and the United States. In Table 14 we provide a list of the included international registries and databases and the corresponding publications with a brief summary of the results.

Sponsorship

The majority of randomized trials included for this key question were funded by the pharmaceutical industry. Many of the observational studies were independently funded (national funders).

Detailed Assessment

In this section we will first address the general tolerability of the targeted immune modulators, relying on data from the included randomized trials. For other rare harms, such as infections and malignancy, we use the results of observational studies because their larger size allows for an adequate number of cases to make sensible head-to-head comparisons. Finally, we address other classes of harms such as cardiovascular risk and respiratory disease as well as provide a description of the risk of harms in using targeted immune modulators concomitantly. Appendix D summarizes black box warnings, precautions, and bold letter warnings issued by the US Food and Drug Administration for individual targeted immune modulators.

General tolerability

We located 9 head-to-head randomized trials with 3706 patients that provided evidence on general tolerability for multiple comparisons.[32,35-38,43-46] Table 10 lists the available comparisons from head-to-head randomized trials and presents the relative risk of general tolerability and harms (including overall risk of any adverse event, withdrawal due to adverse events, serious adverse events, and injection site or infusion reactions) based on data we extracted from publications or from the FDA website portal www.clinicaltrials.gov. Direct comparative evidence was available for 7 combinations of targeted immune modulators.

Overall frequency of any adverse event

We located 8 head-to-head randomized trials with 3581 patients that provided evidence on overall adverse events for multiple comparisons.[32,35-38,43-45] The included trials provide direct comparative evidence for 7 combinations of targeted immune modulators.

The majority of trials were conducted in patients with rheumatoid arthritis; only 1 trial was in patients with Crohn's disease,[44] and 1 in patients with plaque psoriasis.[45] The duration of trials varied from 12 weeks to 12 months and the rate of adverse events in the included trials varied from 15% to 87%,[32,43] but it was generally greater than 50%. The trials were all of fair quality. The most common adverse events that occurred in the included trials were: headache, urinary tract infection, respiratory infections, and muscle pain.

Table 10 presents the calculated relative risk for overall adverse events for each comparison. There was no statistically significant difference in the relative risk of overall adverse events between any of the targeted immune modulators included in the trials and the point estimates centered on 1, i.e., there was no difference between the drugs. For the majority of direct comparisons only 1 trial was available with data for analysis. The confidence intervals of the calculated relative risks for general harms often do not exclude a clinically important difference and therefore the strength of the evidence for overall adverse events is insufficient for all the specific comparisons we present here.

Table 10. Head-to-head comparisons of targeted immune modulators in randomized controlled trials for general tolerability

Authors, Year	Overall adverse events RR (95% CI)	Withdrawal due to adverse events RR (95% CI)	Serious adverse events RR (95% CI)	Injection site reactions / Infusion reactions RR (95% CI)	Quality rating
Abatacept vs. Adalimumab					
Weinblatt, et al., 2013[32]	1.02 (0.96 – 1.08)	0.57 (0.28 – 1.16)	1.10 (0.69 – 1.77)	0.41 (0.22 – 0.79)	Fair
Abatacept vs. Infliximab					
Schiff, et al., 2008[36]	0.97 (0.88 – 1.07)	0.44 (0.16 – 1.22)	0.45 (0.20 – 0.99)	0.28 (0.13 – 0.60)	Fair
Adalimumab vs. Etanercept					
Jobanputra, et al., 2012[46]	NR	0.83 (0.39 – 1.78)	0.86 (0.31 – 2.40)	0.47 (0.23 – 0.96)	Poor
Atteno, et al., 2010[43]	0.35 (0.08 – 1.63)	NR	NR	NR	Poor
Adalimumab vs. Infliximab					
Atteno, et al., 2010[43]	0.25 (0.06 – 1.12)	NR	NR	NR	Poor
Van Assche, et al., 2012[44]	1.14 (0.89 – 1.46)*	6.17 (0.78 – 48.71)*	9.95 (0.57 – 174.1)*	8.22 (1.08 – 62.46)*	Fair
Adalimumab vs. Tocilizumab					
Gabay, et al., 2013[35]	1.01 (0.91 – 1.11)	1.11 (0.46 – 2.66)	0.84 (0.45 – 1.58)	NR	Fair
Adalimumab vs. Tofacitinib					
Fleischmann, et al., 2012[38]	0.92 (0.64 – 1.33)	3.70 (0.43 – 31.96)	2.73 (0.11 – 65.43)	NR	Fair
van Vollenhoven, et al., 2012[37]	0.99 (0.82 – 1.19)	0.71 (0.32 – 1.57)	0.42 (0.15 – 1.16)	NR	Fair
Etanercept vs. Ustekinumab					
Griffiths, et al., 2010[45]	1.03 (0.94 – 1.13)	1.60 (0.61 – 4.23)	0.80 (0.24 – 2.64)	6.26 (4.00 – 9.81)	Fair

* This trial recruited patients with a response to infliximab and randomized them to continue infliximab or switch to adalimumab and therefore is a selected population of patients who have tolerated infliximab therapy for at least 6 months.[44]
Abbreviations: AEs: adverse events; NR: not reported; RR: relative risk
Data were extracted from publications of trials and from www.clinicaltrials.gov and the relative risks with confidence intervals calculated by the authors of this report.

Withdrawal / discontinuation due to adverse events

Eight randomized controlled trials with 3606 patients presented data on withdrawal due to adverse events[32,35-38,44-46] and we calculated the relative risk of withdrawal due to adverse events for 7 comparisons (Table 10). The majority of trials were of fair quality; one was poor. The duration of trials varied from 12 weeks to 12 months and the overall rate of withdrawal due to adverse events in the included trials was 4.9%.

There was no statistically significant difference in withdrawal due to adverse events for any comparison based on the results from the randomized trials. Because withdrawal from randomized controlled trials was a rare event, none of the trials were sufficiently large to detect an effect and the confidence intervals of the estimates are very wide. Observational studies are generally larger than trials and therefore more able to detect rare outcomes and also may more accurately reflect real-world conditions. We therefore report on additional data on discontinuation of therapy from publications of observational studies for this outcome. (In the terminology of observational studies, researchers referred to "discontinuation" rather than "withdrawal", hence we use both terms here.)

Nine observational studies with 12 219 included patients reported on the comparative risk of discontinuation of targeted immune modulators due to adverse events.[55-61,67,77] These studies mostly included patients taking the antitumor necrosis factor drugs adalimumab, etanercept, and infliximab. 1 study included data on tocilizumab.[67] Many of the studies were large and consisted of thousands of patient-years of follow-up data. Most conducted adjustment for baseline risk using Cox or propensity modeling.

Table 11 presents the results of the 5 included observational studies that conducted direct statistical comparisons of the targeted immune modulators adalimumab, etanercept, and infliximab in patients with rheumatoid arthritis and conducted appropriate statistical adjustment for baseline risk factors. Overall, infliximab was consistently associated with the highest risk of discontinuation due to adverse events. In several studies the adjusted hazard ratio for discontinuation due to adverse events was significantly higher for infliximab compared with etanercept (moderate strength of evidence).[56,58,59,67] Likewise, in 2 studies the adjusted hazard ratio for discontinuation due to adverse events favored adalimumab over infliximab (moderate strength of evidence).[56,57] The comparative evidence for adalimumab and etanercept was not as consistent; in 2 cases patients receiving etanercept discontinued significantly less often than patients receiving adalimumab,[57,59] and in another study the difference favored adalimumab; however this was not statistically significant (low strength of evidence).[58] The results of 1 additional observational study that compared 1755 patients with plaque psoriasis and analyzed the rate of discontinuing therapy were consistent with the aforementioned results in rheumatoid arthritis patients.[61] Compared with patients taking methotrexate (the baseline case), both adalimumab and etanercept were associated with a lower chance of discontinuation due to adverse events (adjusted odds ratio 0.48, 95% CI, 0.30 to 0.75; adjusted odds ratio 0.34, 95% CI, 0.23 to 0.49, respectively). In contrast infliximab had a higher odds ratio of discontinuation due to adverse events (odds ratio 1.3, 95% CI, 0.78 to 2.17) albeit not statistically significant. 9% of patients who discontinued infliximab cited "life-threatening side effects" as the reason in this study.

In the 1 study that compared etanercept and tocilizumab (not shown in Table 11) the adjusted hazard ratio favored etanercept (HR 1.98, 95% CI 1.04 to 3.76).[67] In the study including anakinra the difference between anakinra and etanercept and infliximab was not statistically significant (insufficient strength of evidence).[55]

Table 11. Head-to-head comparisons of antitumor necrosis factor biologics in observational studies - results for discontinuation due to adverse events (hazard ratios adjusted for baseline risk)

Authors, Year	Follow-up	Adalimumab versus Etanercept aHR (95%CI)	Adalimumab versus Infliximab aHR (95%CI)	Etanercept versus Infliximab aHR (95%CI)	Quality rating
Du Pan, et al., 2009[56]	3867 PY	-	0.67 (0.45 to 0.97) Favors adalimumab	0.79 (0.55 to 1.13) Favors etanercept	Fair
Saad, et al., 2009[58]	566 patients, 2.3 years	0.74 (0.21 to 2.66) Favors adalimumab	-	3.12 (1.41 to 6.89) Favors etanercept	Fair
Marchesoni, et al., 2009[59]	1064 patients, 23 months	2.09 (1.29 to 3.38) Favors etanercept	-	1.49 (0.93 to 2.40) Favors etanercept	Fair
Hetland, et al., 2010[57]	4796 PY	1.5 (1.04 to 2.16) Favors etanercept	1.77 (1.34 to 2.34) Favors adalimumab	-	Good
Sakai, et al., 2012[67]	1607 PY	-	-	1.69 (1.14 to 2.51) Favors etanercept	Fair

Abbreviations: aHR: adjusted hazard ratio; PY: patient-years
Data taken directly form publications, different models for adjustment were used.

Three studies reported only crude rates of discontinuation and did not perform any statistical adjustment for baseline risk; however the results were nonetheless consistent with other reports. In an Italian registry of plaque psoriasis patients the crude rate of discontinuation due to adverse events was significantly higher for infliximab compared with etanercept (8.8% vs. 2.8%, *P*=0.002).[77] A Swedish prospective observational study with 5 years of follow up for 949 rheumatoid arthritis patients showed a significantly higher rate of withdrawal due to adverse events for infliximab than for etanercept (*P*<0.001, unadjusted).[60] A German retrospective, population-based cohort study reported rates of 16% for anakinra, 13% for etanercept, and 19% for infliximab after 12 months (not significant).[55]

Serious adverse events

The majority of included trials presented data on serious adverse events or this data was available in supplementary reports of the trials. We calculated the relative risk of serious adverse events for 7 comparisons (Table 10). Overall, the number of serious adverse events was low (5.9% overall) resulting in wide confidence intervals. There was 1 statistically significant difference between targeted immune modulators gathered from the head-to-head randomized controlled trials; the relative risk of serious adverse events for abatacept compared with infliximab is 0.45 (95% CI, 0.20 to 0.99) favoring abatacept.[36] Importantly, the confidence interval for this estimate includes the possibility that there is no clinically relevant difference between abatacept and infliximab and patients receiving abatacept had a lower rate of serious adverse events than those receiving placebo (5.1% compared with 11.8%, respectively), which gives concern to the validity of the observations of serious adverse events in this study. Furthermore, for all of the other available comparisons, there were no statistically significant differences and therefore the strength of the evidence for the comparative incidence of serious adverse events is insufficient.

Injection site or infusion reactions

We located data on infusion or injection site reactions from 5 head-to-head trials containing 2178 patients (Table 10).[32,36,44-46] Overall, injection site and infusion reactions occurred in 11% of patients in the included head-to-head trials. Infusion reactions consisted of mostly nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. A small proportion of infusion reactions resembled anaphylactic reactions or lead to convulsions. In contrast, injection site reactions mainly included erythema, pruritus, rash, and pain of mild to moderate severity.

Calculation of the relative risk for an infusion or injection site reaction revealed a significant difference between the drugs in all 5 comparisons and the effect was so large that most of the calculated relative risks ruled out a clinically equivalent effect. In one trial abatacept has a lower risk of injection site reaction than adalimumab (relative risk 0.41, 95% CI, 0.22 to 0.79) [32] and in a second trial the intraveneous loading dose of abatacept had a lower risk of infusion reaction than infliximab (relative risk 0.28 95% CI, 0.13 to 0.60).[36] The strength of evidence for these 2 comparisons is low. In the other comparison involving infliximab, the risk of an injection site reaction was higher for adalimumab compared with the risk of infusion reaction for infliximab (relative risk 8.22 95% CI, 1.08 to 62.46).[44] This trial recruited patients with a response to infliximab and randomized them to continue infliximab or switch to adalimumab and therefore this a selected population of patients who have tolerated infliximab therapy for at least 6 months. The results regarding the higher number of adverse events in the adalimumab comparison group must be interpreted with extreme caution and the strength of

evidence is insufficient. Adalimumab was compared with etanercept in one pragmatic randomized trial.[46] The risk of injection site reactions was lower for adalimumab compared with etanercept (relative risk 0.47 95% CI, 0.23 to 0.96) but the strength of evidence is insufficient because the confidence interval includes a region where the 2 drugs are equivalent. Furthermore, this trial followed patients for up to 2 years and in that time over 50% of the originally randomized population ceased taking the 2 drugs. The final direct comparison of targeted immune modulators reported data on the number of injection site reactions in patients receiving etanercept compared with ustekinumab for plaque psoriasis.[45] The relative risk of injection site reaction was significantly greater for the etanercept group (relative risk 6.26 95% CI, 4.00 to 9.81); strength of evidence low.

Mortality

We located 2 publications of comparative data from observational studies on mortality.[66,70] In these studies, data from patients in the biologics registries was linked with mortality data from national death registries. The studies indicate that there is no difference between the antitumor necrosis factor drugs (low strength of evidence). Specifically, 1 publication reported data from 5212 patients (19 118 patient-years) from the Swedish ARTIS database (Anti-Rheumatic Therapy in Sweden biologics registry).[66] Overall, 179 patients died. There were no differences in adjusted hazard ratio of death for adalimumab or infliximab compared with etanercept (hazard ratio 1.3, 95% CI, 0.9 to 2.0; hazard ratio 1.1, 95% CI, 0.7 to 1.7 respectively). A second analysis of 29 367 patients with rheumatoid arthritis, inflammatory bowel disease, psoriatic disease, or ankylosing spondylitis conducted propensity matching to analyze 1754 deaths and determined there were no significant differences between the antitumor necrosis factor drugs: adalimumab compared with etanercept hazard ratio 0.95, 95% CI, 0.81 to 1.10; adalimumab compared with infliximab hazard ratio 1.06, 95% CI, 0.89 to 1.26.[70]

Serious infections

The number of overall serious infections was reported in 3 of the included randomized controlled trials providing direct comparative data for adalimumab and tofacitinib [37,38] and adalimumab and tocilizumab.[35] In all 3 trials (n=1428) very few serious infections occurred, with no events occurring in 3 out of 6 arms. This makes sensible comparison of the rates for the drugs using trial data impossible.

We identified 9 observational studies with 55 359 patients containing data on the comparative risk between targeted immune modulators for serious infections.[48,49,64,65,68,72,74,75,81] Definitions of serious infections were typically deaths, hospitalizations, and use of intravenous antibiotics associated with infections and the studies included mostly rheumatoid arthritis patients. For this outcome we located only comparative data on abatacept and the 3 antitumor necrosis factor drugs adalimumab, etanercept, and infliximab. Table 12 presents the results from studies that conducted direct comparisons of targeted immune modulators with adjustment for baseline confounding factors. We included studies where authors reported that they conducted comparisons and that these were "not statistically significant" but did not report on the adjusted hazard ratios because not reporting these non-significant results would constitute publication bias. Overall, infliximab was consistently associated with the highest risk of serious infections. Etanercept was associated with a lower risk of serious infections than adalimumab in 3 studies,[48] the comparison reached statistical significance after adjustment for baseline confounders in 2.[64,75] The strength of evidence is moderate. We located only 1 study which conducted a direct

comparison of abatacept, adalimumab, etanercept, or rituximab compared with infliximab for risk of hospitalized infections.[81] The adjusted hazard ratio was significantly lower for abatacept, adalimumab, and etanercept compared with infliximab.

Table 12. Head-to-head comparisons of antitumor necrosis factor biologics in observational studies - adjusted hazard ratios for serious infections

Authors, Year Follow-up	Abatacept vs. Infliximab aHR (95%CI)	Adalimumab vs. Etanercept aHR (95%CI)	Adalimumab vs. Infliximab aHR (95%CI)	Etanercept vs. Infliximab aHR (95%CI)	Rituximab vs. Infliximab aHR (95%CI)	Quality rating
Favalli, et al., 2009[48] 1064 patients 24 months	-	1.73 (0.77 to 3.87) Favors Etanercept	-	1.48 (0.70 to 3.14) Favors Etanercept	-	Fair
Curtis, et al., 2011[81] 6992 patients	0.68 (0.48 to 0.96) Favors Abatacept	-	0.52 (0.39 to 0.71) Favors Adalimumab	0.64 (0.49 to 0.84) Favors Etanercept	0.81 (0.55 to 1.20) Favors Rituximab	Fair
Galloway, et al., 2011[49] 11 798 patients 3.9 years	-	No statistically significant difference	No statistically significant difference	No statistically significant difference	-	Good
Grijalva, et al., 2011[72] 10 242 PY	-	-	1.23 (1.02 to 1.48) Favors Adalimumab	1.26 (1.07 to 1.47) Favors Etanercept	-	Fair
Atzeni, et al., 2012[75] 2769 patients	-	2.2 (1.1 to 4.4) Favors Etanercept	-	4.9 (2.7 to 8.9) Favors Etanercept	-	Fair
Curtis, et al., 2012[74] 11 657 PY	-	-	1.49 (1.05 to 2.10) Favors Adalimumab	1.52 (1.08 to 2.12) Favors Etanercept	-	Fair
Sakai, 2012[68] 1480 PY	-	-	-	No significant difference	-	Fair
Thyagarajan, 2012[65] 13296 PY	-	No statistically significant difference	No statistically significant difference	No statistically significant difference	-	Poor
van Dartel, 2013[64] 2356 patients 16-19 months	-	1.83 (1.49 to 2.26) Favors Etanercept	-	2.04 (1.62 to 2.58) Favors Etanercept	-	Fair

Abbreviations: aHR; adjusted hazard ratio; PY: patient-years
Data taken directly from publications, different models for adjustment were used

Tuberculosis

We located 4 studies containing follow-up on 19 701 patients that reported on the comparative risk of tuberculosis in patients taking the tumor necrosis factor alpha antagonists adalimumab, etanercept, or infliximab.[50,62,63,69] 2 studies contained patients with rheumatoid arthritis.[50,62] 1 study included 8418 patients with diverse indications receiving antitumor necrosis factor-alpha agents and insured by Kaiser Permanente Northern California.[63] The largest study provided data on 10712 rheumatoid arthritis patients in the BRSBR.[50] The smaller studies from Korea,[69] and China[62] are limited by their size. They included patients with ankylosing spondylitis[69] and rheumatoid arthritis.[62] The results of these 4 studies consistently showed that etanercept is associated with a lower risk of developing tuberculosis than adalimumab or infliximab although baseline risk of tuberculosis differed between settings. The strength of evidence is low.

Specifically, in the British registry study of 10 712 rheumatoid arthritis patients treated with etanercept, infliximab, or adalimumab 40 cases of tuberculosis occurred in 28 447 patient-years of follow-up (rate 95/100 000 patient-years (95% CI, 63 to 138). 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 comparative 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).[50] The adjusted incidence rate ratio for infliximab was almost statistically significantly greater than for etanercept (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.

An analysis of a mixed population of US patients receiving adalimumab, etanercept, or infliximab showed a similar picture, with overall rates of tuberculosis infections for the pooled group of antitumor necrosis factor drugs elevated compared with 2 control groups (the general population and other rheumatoid arthritis patients); crude incident rate per 100 000 patient-years 56 (95% CI, 24 to 111); 2.8 (95% CI, 2.6 to 3.9); and 8.7 (95% CI, 5.3 to 13.2) respectively.[63] In total 16 cases of tuberculosis occurred in the anti-tumor necrosis factor group and despite differences in the point estimates, due to the small number of cases confidence intervals were largely overlapping: adalimumab 91 (95% CI, 19 to 276; etanercept 17 (95% CI, 0 to 41); and infliximab 83 (95% CI, 10 to 156) per 100 000 patient-years. In addition, these rates are based on unadjusted crude incidences. This study also conducted an analysis of nontuberculosis mycobacterial (NTM) infections. Overall 18 cases of NTM infection occurred in 20 330 patient-years of observations. The patterns of comparison with control groups was similar to tuberculosis, and the rates between drugs also showed the lowest risk with etanercept but largely overlapping confidence intervals: adalimumab 122 (95% CI, 3 to 241); etanercept 35 (95% CI, 1 to 69); and infliximab 116 (95% CI, 30 to 203) per 100 000 patients-years.

Two small studies add limited data to the comparative evidence of risk of tuberculosis because so few cases of tuberculosis or nontuberculosis mycobacterial infections occurred. In a small study of 919 Korean patients with ankylosing spondylitis in a Korean University Hospital 3 cases of tuberculosis occurred in the 354 patients who were exposed to an anti-tumor necrosis factor drug.[69] This study is too small to draw any conclusions on comparative risk; however 2 cases occurred in patients receiving infliximab (a rate of 540 per 100 000 patient-years) and 1 case in a patient taking adalimumab (308 per 100 000 patient-years), compared with none in 1214 patient-years of follow up in the etanercept group. Similarly, in a study of 217 Chinese patients with rheumatoid arthritis 5 cases of tuberculosis or nontuberculosis mycobacterial

infections occurred and the crude rates for adalimumab and etanercept were similar (2.2% vs. 2.8% respectively).[62]

Opportunistic infections

A fair-quality retrospective study of 202 patients from a French registry of patients with opportunistic infection and who were receiving anti-tumor necrosis factor drugs examined the risk of nontuberculosis opportunistic infections associated with specific drugs.[51] 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 adalimumab (odds ratio 10.0 95% CI, 2.3 to 44.4) and infliximab (odds ratio 17.6 95% CI, 4.3 to 72.9) relative to etanercept. The strength of evidence is insufficient.

Herpes zoster

We did not locate any usable data on the incidence of herpes zoster in randomized controlled trials because the trials were too small to detect this rare adverse event; however 4 observational studies provide evidence on the comparative risk of varicella zoster virus (herpes zoster, chicken pox, or shingles) in over 45 000 rheumatoid arthritis patients receiving the anti-tumor necrosis factor drugs adalimumab, etanercept, and infliximab.[52,76,78,84] The primary aim of these studies was to compare the rates of herpes zoster in all rheumatoid arthritis patients and therefore the publications provided data on the comparison of anti-tumor necrosis factor drugs as a group compared with non-biologic disease-modifying antirheumatic drugs; however we restrict reporting here to the data comparing the targeted immune modulators directly. 3 studies performed statistical adjustment for baseline risk including age, sex, race, residence, disease duration, disease severity (DAS28), disability (HAQ score), baseline steroid exposure, smoking status, relevant co-morbidity (diabetes, chronic obstructive pulmonary disease, history of cancer) and year of entry into the study and these therefore provide more reliable data.[76,78,84] 1 study provided only crude rates.[52]

Overall, most of the comparisons produced non-significant hazard ratios and therefore we cannot conclude with any certainty that one targeted immune modulator has a higher risk of herpes zoster than the other targeted immune modulators. The strength of evidence is low. In 3 studies adalimumab had the lowest hazard ratio of herpes zoster,[52,76,78] and this difference was significant for the comparison with infliximab in 1 study.[78] For the comparison between infliximab and etanercept it is likely that there is no difference in risk although results were conflicting. Data from the 2 large studies (which conducted adjustment for baseline risk) showed an adjusted hazard ratio of 1.09 95% CI, 0.82 to 1.45 for etanercept compared with infliximab,[76] or largely overlapping confidence intervals.[78] An analysis of the German RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy) database showed that infliximab and adalimumab increased herpes zoster risk, while etanercept did not, however this was based on a subgroup analysis with few cases. A description of the specific results from the 4 included studies follows.

A large US study using the SABER database analyzed the increase in risk of herpes zoster following initiation of a new anti-tumor necrosis factor drug.[76] 271 herpes zoster cases were observed in 21 817 person-years of follow-up. Neither crude incident rates nor hazard ratios adjusted for propensity score quintiles and baseline corticosteroid use differed between the anti-tumor necrosis factor drugs (adjusted hazard ratio compared with infliximab for adalimumab

0.85 95% CI, 0.55 to 1.22 and for etanercept 1.09 95% CI, 0.82 to 1.45). A similar analysis of 11 881 patients taking anti-tumor necrosis factor agents from the BSRBR (The British Society for Rheumatology Biologics Registers) compared rates of skin infections, including herpes zoster specifically.[78] There were 275 cases of shingles in the anti-tumor necrosis factor cohort. No significant difference was apparent when comparing the rates of shingles for etanercept with adalimumab and infliximab combined; however the risk of shingles was significantly higher with infliximab when compared with adalimumab (hazard ratio 1.5; 95% CI, 1.1 to 2.0). The adjusted hazard ratios using propensity modeling for each agent compared with non-biological disease-modifying antirheumatic drugs were: adalimumab 1.5, 95% CI, 0.9 to 2.4; etanercept 1.7, 95% CI, 1.0 to 2.7; infliximab 2.2, 95% CI, 1.4 to 3.4. Finally, 1 study used data from the prospective German RABBIT (Rheumatoid Arthritis – observation of biologics therapy) registry of over 3266 patients with rheumatoid arthritis treated with an anti-tumor necrosis factor drug included 6112 patient-years of follow up.[84] Overall, 60 cases of herpes zoster in patients receiving anti-tumor necrosis factor agents were recorded. Evaluating the individual drugs, the risk of herpes zoster was not significantly increased with etanercept; (hazard ratio, 1.36; 95% CI, 0.73 to 2.55) but was increased for combined data for adalimumab and infliximab (hazard ratio 1.82, 95% CI, 1.05 to 3.15).

The German study included an additional analysis of 1344 patients (1736 patient years) who contributed data to both the anti-tumor necrosis factor group and the "conventional disease-modifying antirheumatic drugs" group.[84] They conducted this subgroup analysis in order to account for potential selection bias – despite propensity analysis - that may have resulted in patients at higher baseline risk of herpes zoster being prescribed anti-tumor necrosis factor drugs. In this subgroup only 31 cases of herpes zoster were recorded which may reduce the accuracy of the findings. Adjusting for age and propensity score, adalimumab and infliximab (combined data) resulted in a significantly greater risk of herpes zoster compared with disease-modifying antirheumatic drugs (hazard ratio, 2.91; 95% CI, 1.35 to 6.30) for this subgroup, while etanercept did not (hazard ratio, 1.09; 95% CI, 0.39 to 3.06).

Skin infections

In addition to detecting cases of herpes zoster, the analysis of 11 881 patients taking anti-tumor necrosis factor agents from the British Society for Rheumatology Biologics Registers compared rates of serious skin and soft tissue infections such as Staphylococcus aureus, Streptococcus, Pseudomonas, and others.[78] There were 309 cases of serious skin and soft tissue infection in the anti-tumor necrosis factor cohort. After adjustment for risk factors using a propensity model no significant difference was detected between the anti-tumor necrosis factor groups and a comparison group of 3673 patients taking non-biological disease-modifying antirheumatic drugs (hazard ratio 1.3, 95% CI, 0.8 to 2.2). Neither was there any significant difference between the drugs: adjusted hazard ratios adalimumab 1.1, 95% CI, 0.6 to 2.1; etanercept 0.5, 95% CI, 0.9 to 2.5; infliximab 1.5, 95% CI, 0.9 to 2.5. The strength of evidence is insufficient.

Septic arthritis

One report from the British Society for Rheumatology Biologics Registers of 11881 patients with rheumatoid arthritis taking the anti-tumor necrosis factor drugs adalimumab, etanercept, and infliximab compared the rates of septic arthritis between the drugs and with patients taking non-biologic disease-modifying antirheumatic drugs.[73] The risk of septic arthritis was significantly higher for patients taking anti-tumor necrosis factor agents compared with non-biologic disease-

modifying antirheumatic drugs (adjusted hazard ratio 2.3, 95% CI, 1.2 to 4.4); however it was similar for all of the 3 anti-tumor necrosis factor drugs compared with non-biologic disease-modifying antirheumatic drugs (adalimumab 1.9, 95% CI, 0.9 to 4.0; etanercept 2.5, 95% CI, 1.3 to 4.4; infliximab 2.4, 95% CI, 1.0 to 5.8). The strength of evidence is insufficient.

Malignancies

We located 5 reports from large observational database studies that analyzed the incidence of any malignancy (excluding melanoma or non-melanoma skin cancer) in patients with rheumatoid arthritis (n=27 886).[53,54,56,65,83] Overall, the studies included over 90 000 patient-years of data. Overall, there were no significant difference in the risk of malignancy between adalimumab, anakinra, etanercept, and infliximab. Furthermore, where adjusted hazard or odds rations were given, these are conflicting, favoring different targeted immune modulators in different studies. This body of evidence is limited because of the rare nature of the event malignancy and the strength of the evidence is low.

For example, a large retrospective Swedish cohort study, based on data of 25 695 patient-years of rheumatoid arthritis patients, found similar relative risk of any malignancy for etanercept (relative risk 0.78, 95% CI, 0.61 to 1.00), infliximab (relative risk 1.09, 95% CI, 0.91 to 1.30), and adalimumab (relative risk 1.32, 95% CI, 0.87 to 1.98).[53] In one analysis of 3867 patient-years of data from a Swiss registry of rheumatoid arthritis patients 15 cases of malignancy were the reason for discontinuation of adalimumab, etanercept, or infliximab.[56] The adjusted hazard ratio for discontinuation due to malignancy revealed no significant difference between the 3 anti-tumor necrosis factor drugs, although the confidence intervals were wide due to the small number of cases: adalimumab versus infliximab hazard ratio 0.20, 95% CI, 0.37 to 1.06; etanercept versus infliximab hazard ratio 0.54, 95% CI, 0.16 to 1.85. Similarly, an analysis of 7734 rheumatoid arthritis patients compared fatal malignancy incidence rates over the 3 anti-tumor necrosis factor drugs and did not find any significant differences (21 fatal malignancies occurred).[65]

In a large US database of rheumatoid arthritis 6282 patients were receiving biologic therapy and there were 231 cases of cancer detected.[83] The adjusted odds ratio for the incidence of any cancer for the individual targeted immune modulators was not elevated for any drug compared with patients not receiving biologic therapy: adalimumab odds ratio 0.7, 95% CI, 0.3 to 1.6; anakinra odds ratio 0.8, 95% CI, 0.3 to 1.8; etanercept odds ratio 1.0, 95% CI, 0.8 to 1.3; infliximab odds ratio 1.0, 95% CI, 0.8 to 1.3. Furthermore, the results for all malignancies with more than 20 incident cases were also reported and none of these reached statistical significance for biologics as a group or any single drug (cancers reported: bladder, breast, colon, leukemia, lung, lymphoma, non-Hodgkin's lymphoma, prostate).

Using data from the German RABBIT registry of 5120 patients with rheumatoid arthritis, 1 publication analyzed the adjusted hazard ratio of incidence of cancer for anti-tumor necrosis factor drugs as a class and for anakinra.[54] Neither group had a significantly higher risk of cancer compared with the groups of patients receiving conventional disease-modifying antirheumatic drugs: anti-tumor necrosis factor hazard ratio 0.70, 95% CI, 90.44 to 1.12; anakinra hazard ratio 1.39, 95% CI, 0.56 to 3.48.

Non-melanoma skin cancer

We located 3 publications reporting on large databases of 24 154 rheumatoid arthritis patients that calculated the risk of non-melanoma skin cancers (NMSC) or keratinocyte skin cancers

(such as basal and squamous cell carcinomas) for patients receiving the tumor necrosis alpha antagonists adalimumab, etanercept, or infliximab.[79,80,83] We did not locate any comparative evidence for the risk of malignancies for targeted immune modulators that work thorough mechanisms other than antagonizing tumor necrosis factor.

Overall, the studies contrasted as to whether an increased risk for non-melanoma skin cancers exists for rheumatoid arthritis patients taking anti-tumor necrosis factor drugs; however as the scope of this report is to analyze the comparative evidence on harms we will not go into detail on the overall results for targeted immune modulators and skin cancer here. In the 3 publications that we located the risk of non-melanoma skin cancer was not significantly different for etanercept compared with infliximab. Only 1 study included data on adalimumab and this suggested a higher risk of non-melanoma skin cancer compared with etanercept. Due to this inconsistency and imprecision the strength of the evidence is insufficient.

Specifically, in the analysis of the Veteran's Affairs healthcare system database the anti-tumor necrosis factor group contained 11 084 patient-years of data.[79] Non-melanoma skin cancer occurred at a rate of 18.9 per 1000 patient-years and patients receiving a tumor necrosis factor alpha antagonist had a higher risk of developing non-melanoma skin cancer compared with those on non-biologic disease-modifying antirheumatic drugs (hazard ratio 1.42; 95% CI, 1.24, 1.63). In a comparative analysis the authors determined that the risk of developing non-melanoma skin cancer was significantly higher for adalimumab compared with etanercept (0.036 versus 0.021/patient-year respectively, $P<0.0001$) but not for infliximab compared with etanercept (0.028 versus 0.021/patient-year respectively, $P=0.260$).

Similarly, in 2 other database analyses no difference was detected between rates of basal cell carcinoma or non-melanoma skin cancer in patients receiving etanercept or infliximab.[80,83] In the analysis of 11 881 patients from the British Society for Rheumatology Biologics Registers receiving an anti-tumor necrosis factor drug the overall risk of basal cell carcinoma was not elevated for patients taking anti-tumor necrosis factor drugs (adjusted hazard ratio 0.95, 95% CI, 0.53 to 1.71), and neither was any significant different between the rates for the individual agents observed: adalimumab hazard ratio 0.68 (95% CI, 0.33 to 1.38); etanercept hazard ratio 0.69 (95% CI, 0.37 to 1.29); and infliximab hazard ratio 1.15 (95% CI, 0.60 to 2.21).[80] 1 observational study of patients in the US National Databank for Rheumatic Diseases registry (n=13 001) found a statistically significantly increased risk of non-melanoma skin cancer for the pooled analysis of both drugs (odds ratio 1.5, 95% CI, 1.2–1.8).[83] This significance remained for the analysis of infliximab alone (odds ratio, 1.7; 95% CI, 1.3 to 2.2), but was no longer statistically significant for etanercept (odds ratio, 1.2; 95% CI, 1.0 to1.5) and no difference between the 2 drugs was found.

Melanoma skin cancer

We located 1 database study that reported on the comparative incidence of melanoma.[83] This analysis of 6282 patients from the US National Databank for Rheumatic Diseases registry who received targeted immune modulator therapy compared the rates of melanoma in patients receiving the TNF-α antagonists etanercept and infliximab. Overall, a non-significant increase in the rate of melanoma was observed (odds ratio 2.3, 95% CI, 0.9 to 5.4, P = 0.070). For the individual drugs, the odds ratios for melanoma were almost identical: infliximab odds ratio 2.6, 95% CI, 1.0 to 6.7, and etanercept odds ratio 2.4, 95% CI, 1.0 to 5.8. The Strength of evidence is insufficient.

Malignancies in children

In 2009 the US Food and Drug Administration issued a warning about an increased risk of cancer in children and adolescents who receive anti-tumor 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 anti-tumor 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 anti-tumor necrosis factor treatment. We found no further studies reporting directly on the head-to-head risk of malignancy in children receiving targeted immune modulator drugs.

Cardiovascular events and congestive heart failure

We located very little evidence on the comparative risk of cardiovascular adverse events. 1 publication of data from a large database study (n=13 171) based on the National Databank for Rheumatic Diseases did not detect any difference between the anti-tumor necrosis factor drugs for risk of incident heart failure.[82] Specifically, no significant differences between etanercept and infliximab in the risk of incident heart failure were detected over 2 years, although the numbers of cases were small. The strength of evidence is insufficient.

Other serious adverse events: interstitial lung disease

One publication of data from a mixed cohort of 4200 patients insured with Kaiser Permanente Northern California and receiving anti-tumor necrosis factor agents for rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, or inflammatory bowel disease performed an analysis of the incidence rates of interstitial lung disease.[71] Overall, anti-tumor necrosis factor treatment did not seem to be associated with an increased risk of interstitial lung disease (comparison with rheumatoid arthritis patients not exposed to anti-tumor necrosis factor drugs gave a hazard ratio of 1.03, 95% CI, 0.51 to 2.07). Likewise, the head-to-head comparisons of adalimumab, etanercept, and infliximab showed no significant differences between the drugs. The strength of evidence is insufficient.

Combination strategies in adults

We located 4 randomized controlled trials that randomized patients to a combination of targeted immune modulators (n=586).[39,41,47,86] The combination of 2 anti-tumor necrosis factor drugs with a targeted immune modulator of a different mechanism of action substantially increased the frequency of serious adverse events; strength of evidence is high.

For example, in a fair-quality randomized controlled trial of 244 patients with rheumatoid arthritis 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).[39] Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6% compared with 7.4%; *P*=NR). Similarly, 2 fair-quality studies examining a combination of abatacept (2 mg/kg) and etanercept (25 mg twice weekly) compared with etanercept monotherapy revealed that the combination was associated with a substantial increase in serious adverse events (16.5% compared with 2.8%).[40] The second randomized controlled trial studied the addition of abatacept to another targeted immune modulator (background

adalimumab, anakinra, etanercept, or infliximab) compared with a background targeted immune modulator and placebo in 167 rheumatoid arthritis patients. Again, both serious adverse events and serious infections were higher in the combination group (22.3% vs. 12.5%, and 5.8% vs. 1.6% respectively).[47] In a small fair-quality trial of rituximab added to either etanercept or adalimumab for rheumatoid arthritis, 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%.[41] 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 direct evidence on the comparative harms of targeted immune modulators in children exists. Previous versions of this review have summarized the scarce evidence that exists on the harms of targeted immune modulators in pediatric populations from placebo-controlled trials and from observational studies of single targeted immune modulators. Due to the restriction in the scope of this update and the focus on direct head-to-head evidence we are unable to draw any conclusions on the comparative incidence of harms from targeted immune modulators in children.

Table 13. Summary of randomized trials with direct comparisons of adverse events in adults receiving targeted immune modulators

Authors, Year	Study design Name	N	Duration	Comparison	Population	Results	Quality rating
Head-to-head RCTs							
Weinblatt, et al., 2013[32]	RCT AMPLE	646	12 months	Abatacept vs. Adalimumab	Rheumatoid Arthritis	Lower risk of injection site reactions for Adalimumab compared with abatacept (RR 0.41, 95% CI, 0.22 to 0.79) No other significant differences in harms	Fair
Schiff, et al., 2008[36,87]	RCT ATTEST	431	6 months	Abatacept vs. 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
Jobanputra, et al., 2012[46]	RCT RED-SEA	125	12 months	Adalimumab vs. Etanercept	Rheumatoid Arthritis	Relative risk of injection site reactions with Adalimumab than etanercept, RR 0.47 95% CI, 0.23 to 0.96. No other significant differences in harms	Poor
Atteno, et al., 2010[43]	RCT	100	12 months	Etanercept vs. Adalimumab vs. Infliximab	Psoriatic Arthritis	Infliximab and Etanercept resulted in higher rates of adverse events than Adalimumab (23%, 17%, 6%; *P*<0.001)	Poor
Van Assche, et al., 2012[44]	RCT SWITCH	73	12 months	Adalimumab vs. Infliximab	Crohn's Disease	No significant differences in harms	Fair
Gabay, et al., 2013[35]	RCT ADACTA	325	24 weeks	Adalimumab vs. Tocilizumab	Rheumatoid Arthritis	Risk of adverse events, serious adverse events, and withdrawal similar.	Fair
Van Vollenhoven, et al., 2012[37]	RCT Oral Standard	717	3 months	Adalimumab vs. Tofacitinib	Rheumatoid Arthritis	No significant differences in harms	Fair
Fleischmann, et al., 2012[38]	RCT	386	12 weeks	Adalimumab vs. Tofacitinib	Rheumatoid Arthritis	No significant differences in harms	Fair
Griffiths, et al., 2010[45]	RCT	903	12 weeks	Etanercept vs. Ustekinumab	Plaque Psoriasis	Overall adverse events and withdrawals due to adverse events similar: Injection-site reactions more frequent with Etanercept than Ustekinumab	Fair

Authors, Year	Study design Name	N	Duration	Comparison	Population	Results	Quality rating
Head-to-head RCTs of combination strategies							
Weinblatt, et al., 2007[40]	RCT	121	12 months	Abatacept & Etanercept vs Etanercept alone	Rheumatoid Arthritis	More serious adverse events in the combination group (16.5% vs. 2.8%)	Fair
Weinblatt, et al., 2007[47]	RCT	167	12 months	Abatacept & another TIM* vs. another TIM* alone	Rheumatoid Arthritis	More serious adverse events in the combination group (22.3% vs. 12.5%) and more serious infections (5.8% vs. 1.6%).	Fair
Greenwald, et al., 2011[41]	RCT TAME	54	24 weeks	Riuximab added to Adalimumab or Etanercept vs. Adalimumab or Etanercept alone	Rheumatoid Arthritis	Greater number of serious adverse events in the combination groups compared with Adalimumab or Etanercept alone (6% vs. 0%).	Fair
Genovese, et al., 2010[39]	RCT	244	6 months	Anakinra added to Etanercept vs. Etanercept alone	Rheumatoid Arthritis	Higher rate of serious adverse events in combination arm compared with Etanercept alone.	Fair

* Another TIM included Adalimumab, Anakinra, Etanercept, or Infliximab
Abbreviations: AE, adverse event; CI, confidence interval; DMARD: disease-modifying antirheumatic drug; RCT: randomized controlled trial; RR, relative risk; TIM, targeted immune modulator; TNF: tumor necrosis factor

Table 14. Summary of observational studies with direct comparisons of adverse events in adults receiving targeted immune modulators

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
ARTIS (Anti-Rheumatic Therapy in Sweden biologics registry) SWEDEN						
Simard, et al., 2012[66]	5 212	19 118 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	No difference in HR of death for 3 drugs	Fair
BSRBB (British Society for Rheumatology Biologics Register) UK						
Dixon, et al., 2010[50]	10 712	34 025 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Risk of tuberculosis : Adalimumab vs. Etanercept (IRR 4.1; 95% CI, 1.4 to 12.4) Infliximab vs. Etanercept (IRR 3.1, 95% CI, 1.0 to 9.5)	Fair
Galloway, et al., 2011[49]	11 798	Median follow-up 3.9 years	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	The risk of serious infection did not differ between the drugs, but was slightly increased for the group vs. DMARDS	Good
Saad, et al., 2009[58]	566	Mean follow-up 2.3 PY	Adalimumab Etanercept Infliximab	Psoriatic Arthritis	The risk of discontinuing drug due to adverse events increased more over time with Infliximab than with Adalimumab and Etanercept.	Fair
Galloway, et al., 2011[73]	11 881	NR	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	The risk of septic arthritis does not differ between drugs	Fair
Mercer, et al., 2012[80]	13 784	43 798 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	No difference between the drugs in risk of basal cell carcinoma.	Fair
Galloway, et al., 2013[78]	11 181	17 048 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	The risk of shingles was significantly higher with Infliximab when compared with Adalimumab (HR 1.5; 95% CI, 1.1 to 2.0). No differences for serious skin and soft tissue infections.	Fair
DANBIO (nationwide registry of biological therapies in Denmark) DENMARK						
Hetland, et al., 2010[57]	2 326	4796 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Infliximab has a higher risk of discontinuing drug due to adverse events than Adalimumab (HR 1.77, 95% CI, 1.34 – 2.34) and Etanercept (HR 2.65, 95% CI 1.88 – 3.73)	Good

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
DCERN (Dermatology Clinical Effectiveness Research Network) US						
Yeung, et al., 2013[61]	1 755	Median duration 6-20 months	Adalimumab Etanercept Infliximab	Plaque Psoriasis	More patients receiving Infliximab discontinued therapy compared with Adalimumab or Etanercept.	Fair
DREAM (Dutch RA monitoring registry) NETHERLANDS						
Van Dartel, et al., 2013[64]	2 356	4832 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Significantly lower risk of serious infection with Etanercept compared with Adalimumab (HR 1.83, 95% CI, 1.49 – 2.26) and Infliximab (HR 2.04, 95% CI 1.62 to 2.58)	Fair
GISEA (Italian registry) ITALY						
Atzeni, et al., 2012[75]	2 769	NR	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Hazard ratios for serious infections: Adalimumab vs. Etanercept HR 2.2, 95% CI, 1.1 to 4.4; Infliximab vs. Etanercept HR 4.9, 95% CI 2.7 to 8.9	Fair
Hanyang (Hanyang University Hospital Korea) KOREA						
Kim, et al., 2011[69]	354	1784 patient-yea PY rs	Adalimumab Etanercept Infliximab	Anyklosing Spondylitis	No difference in incidence of tuberculosis	Poor
Kaiser (Kaiser Permanente Northern Carolina) US						
Winthrop, et al., 2013[63]	8 418	20 330 PY	Adalimumab Etanercept Infliximab	Mixed	Similar incidence of tuberculosis for all 3 drugs	Poor
Herrinton, et al., 2013[71]	4 200	Mean follow-up 3.14 years	Adalimumab Etanercept Infliximab	Mixed	No difference in rates of interstitial lung disease	Fair
LOHREN, ITALY						
Marchesoni, et al., 2009[59]	1 064	23 months	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Discontinuation due to adverse events significantly higher for Adalimumab compared with Etanercept (HR 2.09, 95% CI, 1.29 to 3.38)	Fair
Favalli, et al., 2009[48]	1 064	24 months	Adalimumab Etanercept Infliximab	Rheumatic diseases	o difference in risk of serious infection between Adalimumab, Etanercept, and Infliximab	Fair
Medicare, US						
Curtis, et al., 2012[74]	11 657	10 240 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Hazard ratio for serious infection was significantly higher for Infliximab compared with Adalimumab (HR 1.49, 95% CI, 1.05 - 2.10) and for Infliximab compared with Etanercept (HR 1.52, 95% CI, 1.08 - 2.12)	Fair

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
Optuminsight (Life Sciences Research Database (formally Ingenix Normative Health Information DB)) US						
Thyagarajan, et al., 2012[65]	7 734	13 296 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Incidence rate of fatal infections and fatal malignancies similar between drugs	Poor
OSCAR (Outcome and Survival rate Concerning Anti-TNF Routine treatment) ITALY						
Esposito, et al., 2013[77]	650	Mean follow-up 28.9 months	Adalimumab Etanercept Infliximab	Plaque Psoriasis	Crude rate of discontinuation due to adverse events was significantly higher for infliximab compared with etanercept (8.8% vs. 2.8%, *P*=0.002)	Poor
RABBIT (rheumatoid arthritis – observation of biologic therapy register) GERMANY						
Strangfeld, et al., 2010[54]	5 120	NR	Etanercept Adalimumab Infliximab Anakinra	Rheumatoid Arthritis	Cancer recurrence was not found do be increased in patients taking etanercept, adalimumab, or infliximab	Fair
Zink, et al., 2005[55]	1 523	12 months	Anakinra Etanercept Infliximab	Rheumatoid Arthritis	Discontinuation due to AEs 16% for anakinra, 13% for etanercept, and 19% for infliximab after 12 months (difference not significant)	Fair
Strangfeld, et al., 2009[84]	3 266	6112 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	The risk of herpes zoster was not significantly increased with etanercept; the (HR 1.36; 95% CI, 0.73 - 2.55) but was increased for combined data for adalimumab and infliximab (HR 1.82, 95% CI, 1.05 - 3.15) compared with nbDMARDs.	Fair
RATIO (Research Axed on Tolerance of biotherapies) FRANCE						
Salmon-Ceron, et al., 2011[51]	38 cases 114 controls	3 years	Adalimumab Etanercept Infliximab	Mixed	Risk of opportunistic infections was greater with infliximab and adalimumab than etanercept	Fair
REAL (Rheumatoid Arthritis Patients for Long-term Safety) JAPAN						
Sakai, et al., 2012[68]	747	1480 PY	Etanercept Infliximab	Rheumatoid Arthritis	No significant difference in incidence of serious infections.	Fair
Sakai, et al., 2012[67]	1 022	1607 PY	Etanercept Infliximab Tocilizumab	Rheumatoid Arthritis	Hazard ratio of discontinuation due to adverse events significantly higher for both infliximab and tocilizumab compared with etanercept	Fair
SABER (including US Medicaid and Medicare, Tennessee, PAAD/PACE, KPNC) US						
Grijalva, et al., 2011[72]	10 242	NR	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Infliximab has a higher risk of serious infections compared with both adalimumab (HR 1.23, 95% CI, 1.02 - 1.48) and etanercept (HR 1.26, 95% CI, 1.07 - 1.47)	Fair

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
Herrinton, et al., 2012[70]	29 368	Median follow-up 1.79 years	Adalimumab Etanercept Infliximab	Mixed	No significant differences between drugs	Fair
Winthrop, et al., 2013[76]	33 324	28 392 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Adjusted HR compared with infliximab for herpes zoster for adalimumab 0.85 95% CI, 0.55 to 1.22 and for etanercept 1.09 95% CI, 0.82 to 1.45	Fair
SCQM-RA (Swiss Clinical Quality Management in Rheumatic Diseases) SWITZERLAND						
Du Pan, et al., 2009[56]	2 364	3867 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Risk of discontinuation due to adverse events higher with infliximab than adalimumab (HR 0.67, 95% CI 0.45 – 0.97) and similar for etanercept and infliximab (HR 0.79, 95% CI 0.55 – 1.13)	Fair
SSATG (South Swedish Arthritis Treatment Group register) SWEDEN						
Kristensen, et al., 2006[60]	949	60 months	Etanercept Infliximab	Rheumatoid Arthritis	Significantly more patients discontinued infliximab than etanercept due to adverse events (P<0.001)	Fair
Swedish (Swedish Inpatient Register, the Swedish Outpatient Register, and the Swedish Early RA Register) SWEDEN						
Askling, et al., 2009[53]	6 366	25 693 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	No significant difference in incidence of malignancy.	Good
TAIWAN						
Yang, et al., 2012[62]	271	Median 36 months	Adalimumab Etanercept	Rheumatoid Arthritis	No difference between adalimumab and etanercept for tuberculosis, other infections, malignancy, or mortality.	Poor
National Databank for Rheumatic Diseases, US						
Wolfe, et al., 2004[82]	13 171	2 years	Etanercept Infliximab	Rheumatoid Arthritis	No significant differences between etanercept and infliximab in the risk of incident heart failure	Poor
Wolfe, et al., 2007[83]	13 001	49 000 PY	Adalimumab Anakinra Etanercept Infliximab	Rheumatoid Arthritis	Similar risk of overall mortality, no significant differences for lymphoma, melanoma, or NMSC	Good
Veterans Affairs, Austin (Austin Automation Centre (AAC)) US						
McDonald, et al., 2010[52]	3 661	71 000 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Etanercept (HR 0.62, 95% CI, 0.40–0.95) and adalimumab (HR 0.53, 95% CI 0.31–0.91) were associated with lower risk of HZ and infliximab with a higher risk (HR 1.32, 95% CI, 0.85-2.03)	Fair

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
Amari, et al., 2011[79]	4 088	11 084 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Number of non-melanoma skin cancers significantly greater in adalimumab treated patients than etanercept (0.036/PY vs. 0.021/PY, P<0.0001), numerically greater in infliximab group (0.028/PY)	Fair

Abbreviations: AE, adverse event; DMARD, disease-modifying anti-rheumatic drug; HR, hazard ratio; IRR: incidence rate ratio; nbDMARD: non-biologic DMARD; NMSC: non-melanoma skin cancer; NR, not reported; OR: odds ratio; PY: patient-years; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Key Question 3. Subgroups

Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early vs. established disease?

Summary of Findings

The majority of the trials did not contain any information about the effectiveness and harms of targeted immune modulators in 1 subgroup of patients compared with another or compared with the general population. 1 head-to-head trial analyzed the effect of potential baseline predictors of achieving a 70% improvement of American College of Rheumatology-criteria in patients with rheumatoid arthritis with either adalimumab or tocilizumab after 24 weeks (Table 15).[35] No statistically significant or clinically meaningful difference could be determined between the following subgroups: age (50-65 vs. < 50 or > 65 years); gender; duration of rheumatoid arthritis (< 2 vs. ≥ 2 years); number of previous disease-modifying antirheumatic drugs (0-5). No absolute numbers of the individual subgroup-analyses were available, because the results were illustrated graphically. Overall, the strength of evidence to determine differences of the effectiveness and harms among subgroups in patients treated with targeted immune modulators is insufficient (Table 15).

Detailed Assessment

Age

One head-to-head trial with 326 rheumatoid arthritis patients assessed the effect of age as a predictor of achieving a 70% improvement of American College of Rheumatology-criteria with either adalimumab or tocilizumab after 24 weeks. [35] No statistically significant or clinically relevant difference could be determined between patients aged 50 to 65 years compared to patients younger than 50 or older than 65 years.

Based on findings of only 1 trial with no precise specification of absolute or relative numbers, no general conclusion can be drawn about differences of the effectiveness and harms of targeted immune modulators among different age-groups.

Racial groups

Five head-to-head randomized controlled trials provided information concerning ethnic origins of the study-population.[32,35,37-39] The percentage of the white population among 2242 patients in these trials with rheumatoid arthritis ranged from 70% to 90%. No subgroup-analysis was performed in any of the 5 randomized controlled trials to assess the comparative effectiveness and harms of targeted immune modulators for different racial groups and therefore the strength of evidence is insufficient.

Gender

In 1 head-to-head trial 80% of the included patients with rheumatoid arthritis were women.[35] The authors assessed the effect of gender as a predictor of achieving a 70% improvement of American College of Rheumatology-criteria with either adalimumab or tocilizumab after 24 weeks. No statistically significant difference could be detected between women and men. On average, the majority of the included head-to-head trials comprised 80% to 90% women.[32,33,35,37-

[39,88,89] This fact reflects population and disease demographics and does not provide insight into treatment differences. Overall, the evidence for gender-specific differences for the effectiveness and harms of targeted immune modulators is insufficient.

Comorbidities

We did not identify any head-to-head trial that analyzed the effects of targeted immune modulators in populations with comorbidities. The evidence of the effect of comorbid conditions on the efficacy and harms of targeted immune modulators is insufficient.

Other commonly prescribed medications

The majority of patients in the included head-to-head trial received 1 or more concomitant medications. No formal drug interaction studies have been performed with any targeted immune modulators. Overall, the evidence is insufficient that concomitant medications result in differences in the effectiveness or harms of targeted immune modulators.

Early versus established disease

One head-to-head randomized controlled trial[35] with 326 patients with rheumatoid arthritis analyzed if disease duration of less than 2 years compared to 2 years or greater or the number of previous disease-modifying antirheumatic drugs (0-5) has any impact on achieving a 70% improvement of American College of Rheumatology-criteria in patients with rheumatoid arthritis with either adalimumab or tocilizumab after 24 weeks. No statistically significant difference could be detected between any of the subgroups.

Table 15. Summary of studies assessing subgroups

Authors, Year	Study design	N	Duration	Drug	Population	Results	Quality Rating
Age							
Gabay et al. 2013[35]	RCT	326	24 weeks	Adalimumab vs. Tocilizumab	Rheumatoid Arthritis	No differences in efficacy between patients aged 50 to 65 years compared to patients younger than 50 or older than 65 years	Fair
Gender							
Gabay et al. 2013[35]	RCT	326	24 weeks	Adalimumab vs. Tocilizumab	Rheumatoid Arthritis	No differences in efficacy between women and men	Fair
Early vs. established disease							
Gabay et al. 2013[35]	RCT	326	24 weeks	Adalimumab vs. Tocilizumab	Rheumatoid Arthritis	No differences in patients with a duration of rheumatoid arthritis of < 2 years vs. ≥ 2 years; no differences in patients with various numbers of previous DMARDs (0-5).	Fair

Abbreviations: DMARD, disease-modifying antirheumatic drug; RCT, randomized controlled trial; vs, versus

SUMMARY

Our conclusions are based on the review of 6704 abstracts and the inclusion of a total of 53 publications (of 15 head-to-head randomized controlled trials and 22 head-to-head observational studies). Almost all of the included randomized trials were funded by the pharmaceutical industry and could be classified as efficacy trials with highly selected patients. We did not locate any trials that enrolled less selected, primary care based populations and that would be classified as providing evidence on effectiveness. Table 16 provides a summary of the evidence available for each key question.

In summary, no or insufficient evidence exists for most comparisons about the efficacy, effectiveness, and harms of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, tofacitinib, 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. Tofacitinib is the only orally administered drug. Infliximab, natalizumab, and rituximab require intravenous administration. Abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, tocilizumab, 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 2 to 4 weeks, tocilizumab every 4 weeks, golimumab monthly, and ustekinumab every 12 weeks.

Key Question 1. Comparative Effectiveness

Rheumatoid Arthritis

Single trial evidence indicates that efficacy outcomes are similar between abatacept and adalimumab, adalimumab and etanercept, adalimumab and tofacitinib, and etanercept and tocilizumab. The evidence is mixed regarding differences in efficacy between adalimumab and tofacitinib. The strength of evidence for these comparisons ranges between low and insufficient.

For the comparison of abatacept with infliximab the only double-blinded head-to-head trial indicated no differences in efficacy between patients treated with abatacept or infliximab after 6 months. The strength of evidence is low. After 1 year, however, abatacept was statistically significantly more efficacious on most outcome measures than infliximab. 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.

For the comparison of adalimumab with tocilizumab, a fair double-blinded randomized controlled trial reported statistically significantly lower response rates for patients treated with adalimumab than tocilizumab. In this study, however, tocilizumab was used at a higher starting dose than approved. Because of the questionable dosing equivalence, findings have to be interpreted cautiously. In contrast, a small open-label randomized controlled trial indicated no differences in treatment effects between adalimumab and tocilizumab. The strength of evidence is low.

A fair, small (n=32) open-label randomized controlled trial indicated greater response rates in patients treated with etanercept than with infliximab. The strength of evidence is insufficient.

Evidence based on 3 fair randomized controlled trials indicates that combination therapy with more than one targeted immune modulator does not lead to an additional benefit. The strength of evidence is moderate.

Juvenile Idiopathic Arthritis

No head-to-head trial comparing targeted immune modulators for the treatment juvenile idiopathic arthritis were detected.

Ankylosing Spondylitis

No head-to-head trials provided comparative evidence on the efficacy of targeted immune modulators for ankylosing spondylitis.

Psoriatic Arthritis

One head-to-head randomized trial provided evidence on the comparative efficacy of the targeted immune modulators adalimumab, etanercept, and infliximab for psoriatic arthritis. This trial had major methodological shortcomings and imbalance in the baseline disease severity of the groups; however it indicated that the three drugs have similar efficacy. The strength of evidence is insufficient.

No studies on the effectiveness or harms of targeted immune modulators for the treatment of psoriatic arthritis in children are available.

Crohn's Disease

One head-to-head switch trial provided evidence on the comparative efficacy of adalimumab compared with infliximab for the treatment of Crohn's disease. Switching from infliximab to adalimumab resulted in higher treatment discontinuation and termination rates than maintaining infliximab therapy. Patient recruitment in this trial was stopped early before reaching planned number of patients due to an interim analysis revealing this difference. The strength of evidence for this comparison is insufficient.

No head-to-head trials provided direct evidence on the comparative efficacy of targeted immune modulators for Crohn's disease in a pediatric population.

Ulcerative Colitis

No head-to-head trials provided evidence on the comparative efficacy of biologics for ulcerative colitis in adults or children.

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 minor methodological flaws and therefore the strength of evidence for this comparison is low.

Key Question 2. Comparative Harms

Thirteen trials and data from 37 publications of observational studies (representing 22 unique patient data sets from national registries or cohort studies) provided direct evidence on the harms associated with targeted immune modulators (50 citations in total). We almost exclusively located evidence regarding the 3 tumor necrosis factor-inhibiting drugs adalimumab, etanercept, and infliximab. For newer targeted immune modulators such as alefacept, certolizumab pegol, golimumab, natalizumab, harms data were completely missing.

The rates of overall adverse events occurring with targeted immune modulators did not differ statistically significantly between the drugs. In general, infliximab was associated with more serious adverse events, higher rates of withdrawal due to adverse events, and higher rates of serious infections. Abatacept and ustekinumab appeared to cause fewer injection site reactions and etanercept more, but this is based on low or insufficient strength evidence.

There are likely no differences in overall mortality, herpes zoster, malignancy in general and skin cancer specifically, and cardiovascular and respiratory harms (generally insufficient strength of evidence). Opportunistic infections, including tuberculosis, may be less common with etanercept than the other drugs (low or insufficient strength of evidence).

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. Likewise, we did not locate any head-to-head evidence on the comparative risk of other adverse events associated with targeted immune modulators in children.

Key Question 3. Subgroups

The overall grade of the evidence on efficacy and harms 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.

The majority of trials did not contain any information about the effectiveness and harms of targeted immune modulators in 1 subgroup of patients compared with another or compared with the general population. A 24 week head-to-head randomized controlled trial that compared tocilizumab with adalimumab in patients with rheumatoid arthritis showed no statistically significant difference for efficacy among subgroups of different age, between women and men, in patients with disease duration of < 2 compared to ≥ 2 years and a various number of previous disease-modifying antirheumatic drugs. None of the included trials provided information of differences among subgroups based on racial origin or subgroups with various comorbidities.

Overall, the strength of evidence to determine differences between targeted immune modulators in effectiveness or harms among subgroups was insufficient.

Strength of the Evidence

Overall the strength of evidence for answering the key questions about comparative efficacy, effectiveness and harms of targeted immune modulators for the included conditions is low. Very few head-to-head trials were available for assessing efficacy, or effectiveness, and where direct comparisons were performed the small size of trials meant that confidence intervals for rare outcomes were wide. For assessing harms, many publications now exist that report on data from large national registries of targeted immune modulators; however despite sophisticated statistical methods for adjusting for baseline risk, concerns about confounding (selection bias) and regarding the ability of registry studies to detect all relevant events (detection bias) persist, reducing the strength of the evidence. This is combined with a persistent inability to determine if no observed difference between the targeted immune modulators means there is no difference or means there is not yet enough data (reflected in confidence intervals that include both a clinically important difference and no effect). Therefore, the strength of evidence for harms was often low or insufficient. Direct head-to-head evidence on the comparative risk of adverse events associated with targeted immune modulators in children does not exist and the strength of evidence is therefore insufficient.

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. In the included trials, patients met narrowly defined inclusion criteria, had few comorbidities, and used few concomitant medications. For rheumatoid arthritis, most patients had moderate or severe disease and had usually failed initial therapy with other agents (disease-modifying antirheumatic drugs or corticosteroids). Minorities, older patients, and the most seriously ill patients were underrepresented. The majority of evidence for harms was on patients with rheumatoid arthritis, although this can probably be extrapolated to patients taking targeted immune modulators for other conditions.[90]

Only a few head-to-head trials reported limited data of the efficacy and harms of targeted immune modulators in subgroups. The majority of the head-to-head trials were performed in primarily white populations with rheumatoid arthritis, mean age of 40 years to 65 years, and a high percentage of women. The mean duration of rheumatoid arthritis in the study populations ranged from 9 months to 11 years. Based on the available evidence it is unclear if other racial groups or patients older than 65 years or sex-specific differences exist regarding the efficacy and harms of targeted immune modulators.

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, and we limited this streamlined report to direct head-to-head evidence only. Appendix H lists the placebo-controlled trials we detected in our latest searches for the included drugs and conditions which have been published since the last update of this report. We detected 90 potentially eligible publications. We do not know if some of these represent repeat publications of data from trials already

included in the previous report; however the large scope of updating the indirect evidence from placebo-controlled trials is evident. Unfortunately, the lack of head-to-head evidence available to us does limit the confidence of our estimates. Finally, the individual studies included in our review had methodological limitations, with most receiving only a fair rating for risk of bias.

For assessing harms, estimates from trials alone were restricted because of the short duration of the included trials. Furthermore, it is probable that categories such as “all adverse events” are too general and do not permit adequate granularity to compare the incidence of specific adverse events between the drugs, even when these may differ. In this sense we are restricted by the reporting of the trial data. In contrast, observational data from registries may be large enough to detect rare but important outcomes, as well as considered more pragmatic when analyzing harms; however it is prone to bias.

Table 16. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
1. Comparative efficacy for rheumatoid arthritis	Low	Based on 1 open-label randomized controlled trial, similar efficacy between abatacept and adalimumab.
	Low	Based on 1 randomized controlled trial, no difference in efficacy between abatacept and infliximab.
	Insufficient	Based on 1 small open-label randomized controlled trial similar efficacy between adalimumab and etanercept
	Low	Based on 1 randomized controlled trial with questionable dosing equivalence and a contradicting open-label trial lower efficacy of adalimumab than tocilizumab
	Low	Based on 1 randomized controlled trial and a contradicting dose ranging trial similar efficacy between adalimumab and tofacitinib.
	Insufficient	Based on 1 small open-label randomized controlled trial similar efficacy between etanercept and infliximab
	Insufficient	Based on 1 small open-label randomized controlled trial similar efficacy between etanercept and tocilizumab
	Moderate	Based on 3 RCTs combination strategies of etanercept with anakinra or abatacept, and rituximab with adalimumab or etanercept do not lead to additional benefits but cause more harms.
	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	Insufficient	Based on 1 head-to-head RCT, no difference in efficacy between adalimumab, etanercept and infliximab.
1. Comparative effectiveness for Crohn's disease	Insufficient	Based on 1 head-to-head RCT, switching from infliximab to adalimumab had higher treatment discontinuation and termination rates compared with maintaining infliximab.
1. Comparative effectiveness for ulcerative colitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for plaque psoriasis	Low	Based on 1 head-to-head RCT, ustekinumab is more efficacious than etanercept
2. Comparative harms	Insufficient	*Overall adverse events for all comparisons:* Based on 8 RCTs, likely no difference between TIMs
	Moderate	*Discontinuations due to adverse events*: Based on 8 RCTs and 9 observational studies, the rate is greater with infliximab than adalimumab and etanercept
	Low	*Serious adverse events:* Based on 1 RCT, more serious adverse events with infliximab than abatacept
	Low	*Injection-site reactions*: Based on 5 RCTs, lower risk for abtacept compared with adalimumab and infliximab and ustekinumab compared with etanercept
	Moderate	*Serious Infections:* Based on 9 observational studies, abatacept, adalimumab,

Key question	Strength of evidence	Conclusion
		and etanercept all cause less serious infections than infliximab
	Low	*Mortality* Based on 2 observational studies no difference between adalimumab, etanercept, and infliximab
	Low	*Tuberculosis* Based on 4 observational studies increased risk with adalimumab and infliximab compared with etanercept
	Insufficient	*Opportunistic infections* Based on 1 observational study no difference between adalimumab, etanercept, and infliximab
	Low	*Herpes zoster* Based on 4 observational studies no difference between adalimumab, etanercept, and infliximab
	Insufficient	*Skin infections* Based on 1 observational study no difference between adalimumab, etanercept, and infliximab
	Insufficient	*Septic arthritis* Based on 1 observational study no difference between adalimumab, etanercept, and infliximab
	Low	*Malignancy* Based on 5 observational studies no difference between adalimumab, anakinra, etanercept, and infliximab
	Insufficient	*Non-melanoma skin cancer and melanoma* Based on 3 observational studies no difference between adalimumab, etanercept, and infliximab
	Insufficient	*Cardiovascular harms* Based on 1 observational study no difference between etanercept and infliximab
	Insufficient	*Interstitual lung disease* Based on 1 observational study no difference between adalimumab, etanercept, and infliximab
	High	*Combination strategies* Increase in risk of serious adverse events, withdrawals, and serious infections with combination therapy
3. Subgroups – age	Insufficient	The evidence is insufficient to draw conclusions.
3. Subgroups – ethnicity	Insufficient	The evidence is insufficient to draw conclusions.
3. Subgroups – gender	Insufficient	The evidence is insufficient to draw conclusions.
3. Subgroups – disease duration	Insufficient	The evidence is insufficient to draw conclusions.

Abbreviations: RCT, randomized controlled trial

CONCLUSIONS

Overall, data from highly-selected and short-term randomized trials in patients with rheumatoid arthritis provides evidence on comparative efficacy and shows that the efficacy of the targeted immune modulator drugs is similar. For plaque psoriasis ustekinumab is more efficacious than etanercept. Most direct evidence on the comparative harms of targeted immune modulators exists for rheumatoid arthritis and for patients receiving adalimumab, etanercept, and infliximab. Overall, where differences between the agents were detected, infliximab is associated with a greater risk of serious adverse events, serious infections, and withdrawal due to adverse events.

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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.

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 (heart 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 of bias: 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.

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 26.11.2013

#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]))	160200
#2	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])) Filters: Humans	143289
#3	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])) Filters: Publication date from 2011/10/01; Humans	9791
#4	Search ("abatacept"[Substance Name] OR "abatacept"[All Fields] OR "Orencia"[All Fields] OR 332348-12-6[rn])	2388
#5	Search "adalimumab"[Substance Name] OR "adalimumab"[All Fields] OR "Humira"[All Fields] OR 331731-18-1[rn]	3466
#6	Search "alefacept"[Substance Name] OR "alefacept"[All Fields] OR "Amevive"[All Fields] OR 222535-22-0[rn]	423
#7	Search "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR "Anakinra"[All Fields] OR "Kineret"[All Fields] OR 143090-92-0[rn]	4095
#8	Search "CDP870"[Substance Name] OR "Certolizumab"[All Fields] OR "Cimzia"[All Fields] OR 428863-50-7[rn]	448
#9	Search "TNFR-Fc fusion protein"[Substance Name] OR "etanercept"[All Fields] OR "Enbrel"[All Fields] OR 185243-69-0[rn]	5276
#10	Search "infliximab"[Substance Name] OR "infliximab"[All Fields] OR "Remicade"[All Fields] OR 170277-31-3[rn]	8673
#11	Search "natalizumab"[Substance Name] OR "natalizumab"[All Fields] OR "Tysabri" [All Fields] OR 189261-10-7[rn]	1188
#12	Search "rituximab"[Substance Name] OR "rituximab"[All Fields] OR "Rituxan"[All Fields] OR 174722-31-7[rn]	11568
#13	Search "tocilizumab"[Substance Name] OR "actemra"[All Fields] OR "RoActemra"[All Fields] OR 375823-41-9[rn]	525
#14	Search "monoclonal antibody CNTO 1275 "[Substance Name] OR "ustekinumab"[All Fields] OR "Stelara"[All Fields] OR 815610-63-0[rn]	401
#15	Search "golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]	295
#18	Search "tofacitinib" [Supplementary Concept] OR "janus kinase inhibitor"[all fields] OR "Xeljanz"[all fields] OR 690550[m]	178

#19	Search (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #18)	32125
#20	Search (#3 AND #19)	1665
#21	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	6874137
#22	Search (#20 AND #21)	1311
#23	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]) Filters: Publication date from 2011/10/01; Humans	47523
#24	Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] Filters: Publication date from 2011/10/01; Humans	13864
#25	Search "Comparative Study"[Publication Type] Filters: Publication date from 2011/10/01; Humans	67825
#26	Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab]) Filters:Publication date from 2011/10/01; Humans	12952
#27	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* Filters: Publication date from 2011/10/01; Humans	215201
#37	Search (#20 AND #21) Filters: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial	409
#39	Search (#20 AND (#23 OR #24 OR #25 OR #26 OR #27))	749
#40	Search (#37 OR #39)	786

COCHRANE 26.11.2013

#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]))	7364
#2	Search abatecept 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 tysarbi or rituximab or rituxan or tocilizumab or actemra or roactemra or "monoclonal antibody CNTO 1275 " or ustekinumab or Stelara or golimumab or simponi or tofacitinib or xeljanz	2628
#3	Search #1 AND #2	1138
#4	Search "Treatment Outcome" or outcome or efficacy or effectiveness or adverse or safety or withdrawal* or harm or mortality or morbidity or function* or toxicity	393894
#5	Search #3 and #4	932

#6	Limit Reviews	45
#7	Limit 2011	10

IPA 26.11.2013

#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])) AND (abatecept 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 tysarbi or rituximab or rituxan or tocilizumab or actemra or roactemra or "monoclonal antibody CNTO 1275 " or ustekinumab or Stelara or golimumab or simponi or tofacitinib or xeljanz)	661
#2	Limit 2011, English, Articles about Human Studies	149

CINAHL 26.11.2013

#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])) AND (abatecept 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 tysarbi or rituximab or rituxan or tocilizumab or actemra or roactemra or "monoclonal antibody CNTO 1275 " or ustekinumab or Stelara or golimumab or simponi or tofacitinib or xeljanz)	1550
#2	Limit 2011, English, Exclude MEDLINE records	71

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#1	'rheumatoid arthritis'/exp OR 'rheumatoid arthritis' OR 'juvenile rheumatoid arthritis'/exp OR 'juvenile rheumatoid arthritis' OR 'ankylosing spondylitis'/exp OR 'ankylosing spondylitis' OR 'psoriatic arthritis'/exp OR 'psoriatic arthritis' OR 'crohn disease'/exp OR'crohn disease' OR 'ulcerative colitis'/exp OR 'ulcerative colitis' OR 'psoriasis vulgaris'/exp OR 'psoriasis vulgaris'	257316
#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 OR 'tofacitinib'/exp	75590
#3	'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	4024224
#4	'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	560573
#5	#1 AND #2 AND #3 AND #4	2341
#6	Limit Humans, No MEDLINE, 10/01/2011	555

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#1	abatecept 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 tysarbi or rituximab or rituxan or tocilizumab or actemra or roactemra or "monoclonal antibody CNTO 1275 " or ustekinumab or Stelara or golimumab or simponi or tofacitinib or xeljanz; LIMIT 10/01/2011	23

Appendix C. 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.

Abbreviation	Name	Condition(s) used in	General description	Range and direction
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
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	For DI, 0-3, lower is better

Abbreviation	Name	Condition(s) used in	General description	Range and direction
			death.	
HAQ-DI	Disability Index of the Health Assessment Questionnaire	all	Patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities.	0-60, higher is worse
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 D. Boxed warnings of included drugs

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 have 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

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Cimzia® (certolizumab pegol)	WARNINGS: SERIOUS INFECTIONS Patients treated with CIMZIA 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. 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.

Trade names (active ingredients)	Boxed warnings, warnings and precautions
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 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

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	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® (Tocilizumab)	WARNING: RISK OF SERIOUS INFECTIONS 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)	None listed
Xeljanz® (Tofacitinib)	WARNING: SERIOUS INFECTIONS AND MALIGNANCY Patients treated with Xeljanz 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 Xeljanz until the infection is controlled.

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Xeljanz use and during therapy. Treatment for latent infection should be initiated prior to Xeljanz use. • Invasive fungal infections, including cryptococcosis and pneumocystosis. 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 Xeljanz 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 Xeljanz, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy

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http://www.accessdata.fda.gov/Scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_Appr

ovalHistory#labelinfo
Accessed March, 20, 2014
13. PV PRISM CV. Xeljanz Product Label.
http://www.accessdata.fda.gov/Scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo
Accessed May, 21,2014

Appendix E. Excluded studies

The following full-text trials were considered for inclusion but failed to meet the criteria for the update of 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
Anink J, Otten MH, Gorter SL, Prince FH, van Suijlekom-Smit LW, et al. Treatment choices of paediatric rheumatologists for juvenile idiopathic arthritis: etanercept or adalimumab? Rheumatology (Oxford). 2013;52:1674	2
Arkema EV, van Vollenhoven RF, Askling J. Incidence of progressive multifocal leukoencephalopathy in patients with rheumatoid arthritis: a national population-based study. Annals of the Rheumatic Diseases. November 1, 2012 2012;71(11):1865-1867	2
Assa A, Hartman C, Weiss B, et al. Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. J Crohns Colitis. Jun 2013;7(5):369-376	2
Bengi G, Akpinar H. What is the importance of infliximab and cyclosporine in the treatment of corticosteroid-refractory severe ulcerative colitis? Turkish Journal of Gastroenterology. 2012;23(SUPPL.2):7-12	5
Bigby M. The use of anti-interleukin-12/23 agents and major adverse cardiovascular events. Archives of Dermatology. 2012;148(6):753-754	5
Bissonnette R, Poulin Y, Guenther L, Lynde CW, Bolduc C, Nigen S. Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study. J Eur Acad Dermatol Venereol. Dec 2011;25(12):1402-1408	2
Bonafede M, Fox KM, Watson C, Princic N, Gandra SR. Treatment patterns in the first year after initiating tumor necrosis factor blockers in real-world settings. Adv Ther. Aug 2012;29(8):664-674	2
Bonafede M, Johnson BH, Fox KM, Watson C, Gandra SR. Treatment patterns with etanercept and adalimumab for psoriatic diseases in a real-world setting. J Dermatolog Treat. Oct 2013;24(5):369-373	2
Brunasso AM, Puntoni M, Delfino C, Massone C. Different response rates between palmoplantar involvement and diffuse plaque psoriasis in patients treated with infliximab. Eur J Dermatol. Jan-Feb 2012;22(1):133-135	6
Busquets D, Aldeguer X. Clinical experience with adalimumab in anti-TNF-naive patients with ulcerative colitis. J Crohns Colitis. Jun 2013;7(5):e195	5
Cadth. Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness (Structured abstract). Health Technology Assessment Database. 2012(4). http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000695/frame.html	6
Canhao H, Rodrigues AM, Mourao AF, et al. Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. Rheumatology (Oxford). Nov 2012;51(11):2020-2026	2
Chastek B, Fox KM, Watson C, Gandra SR. Etanercept and adalimumab treatment patterns in psoriatic arthritis patients enrolled in a commercial health plan. Adv Ther. Aug 2012;29(8):691-697	2
Chu LH, Portugal C, Kawatkar AA, Stohl W, Nichol MB. Racial/ethnic differences in the use of biologic disease-modifying antirheumatic drugs among California Medicaid rheumatoid arthritis patients. Arthritis Care Res (Hoboken). Feb 2013;65(2):299-303	2
Condino G, Calabrese E, Zorzi F, et al. Anti-TNF-alpha treatments and obstructive symptoms in Crohn's disease: a prospective study. Dig Liver Dis. Mar 2013;45(3):258-262	6

Excluded trials	Exclusion code
Cullen G, Kroshinsky D, Cheifetz AS, Korzenik JR. Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: A new series and a review of 120 cases from the literature. Alimentary Pharmacology and Therapeutics. 2011;34(11-12):1318-1327	6
Da Silva JAP, Jacobs JWG, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Annals of the Rheumatic Diseases. March 1, 2006 2006;65(3):285-293	2
Deepak P, Sifuentes H, Sherid M, Stobaugh D, Sadozai Y, Ehrenpreis ED. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: results of the REFURBISH study. Am J Gastroenterol. Jan 2013;108(1):99-105	2
Dewedar AM, Shalaby MA, Al-Homaid S, Mahfouz AM, Shams OA, Fathy A. Lack of adverse effect of anti-tumor necrosis factor-alpha biologics in treatment of rheumatoid arthritis: 5 years follow-up. Int J Rheum Dis. Jun 2012;15(3):330-335	2
Dixon WG, Watson KD, Lunt M, et al. Influence of Anti-Tumor Necrosis Factor Therapy on Cancer Incidence in Patients With Rheumatoid Arthritis Who Have Had a Prior Malignancy: Results From the British Society for Rheumatology Biologics Register. Arthritis care & research. Jun 2010;62(6):755-763	2
Du Pan SM, Scherer A, Gabay C, Finckh A. Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients. Ann Rheum Dis. Jun 2012;71(6):997-999	4
Duru N, van der Goes MC, Jacobs JWG, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Annals of the Rheumatic Diseases. December 1, 2013 2013;72(12):1905-1913	2
Eshuis EJ, Griffioen GH, Stokkers PC, Ubbink DT, Bemelman WA. Anti tumour necrosis factor as risk factor for free perforations in Crohn's disease? A case-control study. Colorectal Dis. May 2012;14(5):578-584	4
Esposito M, Giunta A, Mazzotta A, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: an observational long-term study. Dermatology. 2012;225(4):312-319	4
Famenini S, Wu JJ. Infliximab-induced psoriasis in treatment of Crohn's disease-associated ankylosing spondylitis: Case report and review of 142 cases. Journal of Drugs in Dermatology. 2013;12(8):939-943	6
Finckh A, Moller B, Dudler J, Walker UA, Kyburz D, Gabay C. Evolution of radiographic joint damage in rituximab-treated versus TNF-treated rheumatoid arthritis cases with inadequate response to TNF antagonists. Ann Rheum Dis. Oct 2012;71(10):1680-1685	2
Fisher MD, Watson C, Fox KM, Chen YW, Gandra SR. Dosing patterns of three tumor necrosis factor blockers among patients with rheumatoid arthritis in a large United States managed care population. Curr Med Res Opin. May 2013;29(5):561-568	2
Galloway JB, Hyrich Kl Fau - Mercer LK, Mercer Lk Fau - Dixon WG, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. 20101214 DCOM- 20110912 (1462-0332 (Electronic))	2
Galloway JB, Hyrich KL, Mercer LK, et al. The risk of serious infections in patients receiving anakinra for rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology. July 1, 2011 2011;50(7):1341-1342	5
García-Doval I, Pérez-Zafrilla B, Descalzo MÁ, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Annals of the Rheumatic Diseases. October 1, 2010 2010;69(10):1751-1755	2
Gaujoux-Viala C, Nam J, Ramiro S, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of	2

Excluded trials	Exclusion code
rheumatoid arthritis. Annals of the Rheumatic Diseases. March 1, 2014 2014;73(3):510-515	
Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. May 2005;64(5):699-703	2
Gelfand JM, Wan J, Callis Duffin K, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol. Apr 2012;148(4):487-494	2
Glintborg B, Ostergaard M Fau - Krogh NS, Krogh Ns Fau - Andersen MD, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor alpha inhibitor therapy: results from the Danish Nationwide DANBIO Registry. 20130424 DCOM- 20130618 (1529-0131 (Electronic))	2
Gomez-Reino, 2012[89]	2
Gottlieb AB, Strober B, Krueger JG, et al. An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast. Curr Med Res Opin. May 2008;24(5):1529-1538	3
Greenberg JD, Kremer Jm Fau - Curtis JR, Curtis Jr Fau - Hochberg MC, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. 20110304 DCOM- 20110421 (1468-2060 (Electronic))	2
Greenberg JD, Reed G, Decktor D, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis. Jul 2012;71(7):1134-1142	2
Guerra I, Algaba A, Perez-Calle JL, et al. Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: a report of 21 cases. J Crohns Colitis. Jun 2012;6(5):518-523	6
Haynes K, Beukelman T Fau - Curtis JR, Curtis Jr Fau - Newcomb C, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. 20130102 DCOM- 20130317 (1529-0131 (Electronic))	2
Hoes JN, Jacobs JWG, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Annals of the Rheumatic Diseases. December 1, 2007 2007;66(12):1560-1567	2
Iannone F, Gremese E, Atzeni F, et al. Longterm retention of tumor necrosis factor-alpha inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. J Rheumatol. Jun 2012;39(6):1179-1184	2
Inzinger M, Weger W, Salmhofer W, Wolf P. Differential response of chronic plaque psoriasis to briakinumab vs. ustekinumab. Acta Dermato-Venereologica. 2012;92(4):357-358	5
Johnston SS, Turpcu A Fau - Shi N, Shi N Fau - Fowler R, Fowler R Fau - Chu B-C, Chu Bc Fau - Alexander K, Alexander K. Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis. 20130812 (1532-866X (Electronic))	4
Kaufmann J, Feist E Fau - Roske A-E, Roske Ae Fau - Schmidt WA, Schmidt WA. Monotherapy with tocilizumab or TNF-alpha inhibitors in patients with rheumatoid arthritis: efficacy, treatment satisfaction, and persistence in routine clinical practice. 20130826 (1434-9949 (Electronic))	2
Kilic O, Kasapcopur O, Camcioglu Y, Cokugras H, Arisoy N, Akcakaya N. Is it safe to use anti-TNF-alpha agents for tuberculosis in children suffering with chronic rheumatic disease? Rheumatol Int. Sep 2012;32(9):2675-2679	4
Kuznar W. Meeting Coverage. Tofacitinib induced responses in patients with RA refractory to TNF inhibitors. Formulary. 2011;46(12):548-548	5
Lane MA, McDonald Jr Fau - Zeringue AL, Zeringue Al Fau - Caplan L, et al. TNF-alpha antagonist use and risk of hospitalization for infection in a national cohort of veterans with rheumatoid arthritis. 20110302 DCOM- 20110426 (1536-5964 (Electronic))	2

Excluded trials	Exclusion code
Ljung L, Simard JF, Jacobsson L, Rantapaa-Dahlqvist S, Askling J, Anti-Rheumatic Therapy S. Treatment with tumor necrosis factor inhibitors and the risk of acute coronary syndromes in early rheumatoid arthritis. Arthritis and rheumatism. Jan 2012;64(1):42-52	2
Lunt M, Watson KD, Dixon WG, Symmons PM, Hyrich KL, British Soc Rheumatology B. No Evidence of Association Between Anti-Tumor Necrosis Factor Treatment and Mortality in Patients With Rheumatoid Arthritis Results From the British Society for Rheumatology Biologics Register. Arthritis and rheumatism. Nov 2010;62(11):3145-3153	2
Mayor S. Head-to-head trial shows abatacept is as effective as adalimumab in patients with active rheumatoid arthritis. British Journal of Hospital Medicine (17508460). 2013;74(8):431-431	5
McErlane F, Foster HE, Davies R, et al. Biologic treatment response among adults with juvenile idiopathic arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). Oct 2013;52(10):1905-1913	4
Mercer LK, Davies R, Galloway JB, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology. January 1, 2013 2013;52(1):91-98	2
Nam JL, Ramiro S, Gaujoux-Viala C, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Annals of the Rheumatic Diseases. March 1, 2014 2014;73(3):516-528	2
Nam JL, Ramiro S, Gaujoux-Viala C, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Annals of the Rheumatic Diseases. March 1, 2014 2014;73(3):516-528	2
Nell-Duxneuner V, Schroeder Y, Reichardt B, Bucsics A. The use of TNF-inhibitors in ankylosing spondylitis in Austria from 2007 to 2009-a retrospective analysis. Int J Clin Pharmacol Ther. Dec 2012;50(12):867-872	4
Nguyen-Khoa BA, Goehring El Jr Fau - Alexander KA, Alexander Ka Fau - Dong W, Dong W Fau - Napalkov P, Napalkov P Fau - Jones JK, Jones JK. Risk of significant infection in rheumatoid arthritis patients switching anti-tumor necrosis factor-alpha drugs. 20120924 DCOM- 20130228 (1532-866X (Electronic))	2
Noda S, Mizuno K, Adachi M. Treatment effect of adalimumab and infliximab in Japanese psoriasis patients: results in a single community-based hospital. J Dermatol. Mar 2012;39(3):265-268	4
Otten MH, Prince FH, Twilt M, et al. Tumor necrosis factor-blocking agents for children with enthesitis-related arthritis--data from the dutch arthritis and biologicals in children register, 1999-2010. J Rheumatol. Oct 2011;38(10):2258-2263	4
Papp KA, Strober B, Augustin M, Calabro S, Londhe A, Chevrier M. PSOLAR: design, utility, and preliminary results of a prospective, international, disease-based registry of patients with psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. J Drugs Dermatol. Oct 2012;11(10):1210-1217	2
Pena-Sagredo JL, Farinas Mc Fau - Perez-Zafrilla B, Perez-Zafrilla B Fau - Cruz-Valenciano A, et al. Non-typhi Salmonella infection in patients with rheumatic diseases on TNF-alpha antagonist therapy. 20100212 DCOM- 20100331 (0392-856X (Print))	6
Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al. Interstitial Lung Disease Induced or Exacerbated by TNF-Targeted Therapies: Analysis of 122 Cases. Seminars in Arthritis and Rheumatism. 2011;41(2):256-264	6
Raaschou P, Simard JF, Holmqvist M, Askling J. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. BMJ. 2013-04-08 11:22:18 2013;346	2
Riis A, Martinsen TC, Waldum HL, Fossmark R. Clinical experience with infliximab and adalimumab in a single-center cohort of patients with Crohn's disease. Scand J Gastroenterol. Jun 2012;47(6):649-657	6
Rituximab: fatal infusion-related reactions. WHO Drug Information;25(3):245-246	5

Excluded trials	Exclusion code
Schabert VF, Watson C, Gandra SR, Goodman S, Harrison DJ, et al. Annual costs of tumor necrosis factor inhibitors using real-world data in a commercially insured population in the United States. Journal of Medical Economics (England). 2012;15:264	6
Sevcic K, Orban I, Brodszky V, Bazso A, Kiss E, et al. Experiences with tumour necrosis factor-alpha inhibitors in patients with juvenile idiopathic arthritis: Hungarian data from the National Institute of Rheumatology and Physiotherapy Registry. Rheumatology (Oxford). 2011;50:1337	6
Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewé R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Annals of the Rheumatic Diseases. January 1, 2014 2014;73(1):3-5	2
Solomon DH, Kremer JM, Fisher M, et al. Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs. 20140203 (1532-866X (Electronic))	2
Spadaro A, Lubrano E, Marchesoni A, et al. Remission in ankylosing spondylitis treated with anti-TNF-alpha drugs: a national multicentre study. Rheumatology (Oxford). Oct 2013;52(10):1914-1919	2
Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Annals of the Rheumatic Diseases. November 1, 2011 2011;70(11):1914-1920	2
Strober BE, Poulin Y Fau - Kerdel FA, Kerdel Fa Fau - Langley RG, et al. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. 20110318 DCOM- 20110531 (1097-6787 (Electronic))	6
Tocilizumab alone gives similar remission rates to combination. British Journal of Hospital Medicine (17508460);72(7):370	5
Toussirot E, Houvenagel E, Goeb V, et al. Development of inflammatory bowel disease during anti-TNF-alpha therapy for inflammatory rheumatic disease: a nationwide series. Joint Bone Spine. Oct 2012;79(5):457-463	6
Viguier M, Pages C, Aubin F, et al. Efficacy and safety of biologics in erythrodermic psoriasis: A multicentre, retrospective study. British Journal of Dermatology. 2012;167(2):417-423	6
Virkki LM, Sumathikutty BC, Aarnio M, Valleala H, Nordstroem DC, et al. Biological Therapy for Psoriatic Arthritis in Clinical Practice: Outcomes Up to 2 Years. Journal of Rheumatology. 2010;37:2362	2
Virkki LM, Valleala H, Takakubo Y, et al. Outcomes of switching anti-TNF drugs in rheumatoid arthritis--a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN). Clin Rheumatol. Nov 2011;30(11):1447-1454	2
Wakabayashi H, Hasegawa M, Nishioka Y, Sudo A, Nishioka K. Which subgroup of rheumatoid arthritis patients benefits from switching to tocilizumab versus etanercept after previous infliximab failure? A retrospective study. Mod Rheumatol. Feb 2012;22(1):116-121	6
Winthrop KL, Baddley Jw Fau - Chen L, Chen L Fau - Liu L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. 20130306 DCOM- 20130308 (1538-3598 (Electronic))	2
Yokoe I, Nishio S, Sato H, Kobayashi H. Comparison of MMP-3 levels in rheumatoid arthritis after treatment with tocilizumab or infliximab for 12 weeks. Mod Rheumatol. Dec 2011;21(6):710-714	2
Yoo DH, Hrycaj P, Miranda P, et al. A randomized, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. Annals of the Rheumatic Diseases. 2013;72(10):1613-1620	3
Yoshida K, Tokuda Y Fau - Oshikawa H, Oshikawa H Fau - Utsunomiya M, et al. An observational study of tocilizumab and TNF-alpha inhibitor use in a Japanese community	2

Excluded trials	Exclusion code
hospital: different remission rates, similar drug survival and safety. 20111024 DCOM-20111215 (1462-0332 (Electronic))	
Zorzi F, Zuzzi S, Onali S, et al. Efficacy and safety of infliximab and adalimumab in Crohn's disease: a single centre study. Aliment Pharmacol Ther. Jun 2012;35(12):1397-1407	6

Appendix F. Systematic reviews / network meta-analyses

The following Systematic Reviews and Network Meta-Analyses were detected in our update searches but were not eligible for this streamlined report.

Systematic Reviews
Zidi I, Bartegi A, Ben Amor N. Dermatologic adverse events: Golimumab, friend or foe? Pharmazie. 2011;66(1):5-10
Yang H, Epstein D, Bojke L, et al. Golimumab for the treatment of psoriatic arthritis (Structured abstract). Health Technology Assessment Database. 2011(4):87. http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011000774/frame.html
Yang H, Craig D, Epstein D, et al. Golimumab for the treatment of psoriatic arthritis: a NICE single technology appraisal. Pharmacoeconomics. Apr 2012;30(4):257-270
Wong AK, Kerkoutian S, Said J, Rashidi H, Pullarkat ST. Risk of lymphoma in patients receiving antitumor necrosis factor therapy: a meta-analysis of published randomized controlled studies. Clin Rheumatol. Apr 2012;31(4):631-636
Wevers-De Boer KVC, Heimans L, Huizinga TWJ, Allaart CF. Drug therapy in undifferentiated arthritis: A systematic literature review. Annals of the Rheumatic Diseases. 2013;72(9):1436-1444
Venson R, Wiens A, Correr CJ, Pontarolo R. Efficacy, safety and tolerability of using abatacept for the treatment of rheumatoid arthritis. Brazilian Journal of Pharmaceutical Sciences. 2012;48(4):781-791
Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol. May 2013;27(5):622-627
Townes SV, Furst DE, Thenkondar A. The impact of tocilizumab on physical function and quality of life in patients with rheumatoid arthritis: A systematic literature review and interpretation. Open Access Rheumatology: Research and Reviews. 2012;4:87-92
Ter Wee MM, Lems WF, Usan H, Gulpen A, Boonen A. The effect of biological agents on work participation in rheumatoid arthritis patients: A systematic review. Annals of the Rheumatic Diseases. 2012;71(2):161-171
Tan JY, Li S, Yang K, et al. Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: A meta-analysis. Journal of Dermatological Treatment. 2011;22(6):323-336
Strohal R, Chimenti S, Vena GA, Girolomoni G. Etanercept provides an effective, safe and flexible short-and long-term treatment regimen for moderate-to-severe psoriasis: A systematic review of current evidence. Journal of Dermatological Treatment. 2013;24(3):199-208
Strand V, Sharp V, Koenig AS, et al. Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment. Ann Rheum Dis. Jul 2012;71(7):1143-1150
Snydman DR, Toussi SS, Pan N, Walters HM, Walsh TJ. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-Inhibitors: Systematic review of the literature. Clinical Infectious Diseases. 2013;57(9):1318-1330
Shu T, Rong L, Feng F, et al. Indirect comparison of anti-TNF-(alpha) agents for active ankylosing spondylitis: Mixed treatment comparison of randomized controlled trials. Clinical and Experimental Rheumatology. 2013;31(5):717-722
Schoels MM, van der Heijde D, Breedveld FC, et al. Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement. Ann Rheum Dis. Apr 2013;72(4):583-589
Rustin MH. Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data. Br J Dermatol. Nov 2012;167 Suppl 3:3-11
Rubin DT, Panaccione R, Chao JD, Robinson AM. A practical, evidence-based guide to the use of adalimumab in Crohn's disease. Current Medical Research and Opinion (England). 2011;27:1803
Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis. Journal of Crohn's and Colitis. 2013;7(11):868-877
Rosenfeld G, Qian H, Bressler B. Post-operative complications following pre-operative infliximab use in crohn's disease patients undergoing abdominal surgery: A meta-analysis. Gastroenterology.

Systematic Reviews
2012;142(5):S248
Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis. American Journal of Gastroenterology. 2012;107:S687-S688
Rosenfeld G, Bressler B, Qian H. The effect of preoperative Infliximab therapy in Crohn's patients on post-operative complications: A meta-analysis. Inflammatory Bowel Diseases. 2011;17:S15
Remy A, Avouac J, Gossec Bernard L, Combe B. Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: A systematic literature review and meta-analysis. Clinical and Experimental Rheumatology. 2011;29(1):96-103
Nihr HSC. Inflectra (infliximab biosimilar) for ankylosing spondylitis (Structured abstract). Health Technology Assessment Database. 2013(4). http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000511/frame.html
Nihr HSC. CT-P13 (Infliximab biosimilar) for rheumatoid arthritis (Structured abstract). Health Technology Assessment Database. 2012(4). http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000740/frame.html
Nielsen OH, Loftus EV, Jess T. Safety of TNF-(alpha) inhibitors during IBD pregnancy: A systematic review. BMC Medicine. 2013;11(1)
Navarro-Millan I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. Clin Ther. Apr 2012;34(4):788-802 e783
Navarro G, Taroumian S, Barroso N, Duan L, Furst D. Tocilizumab in rheumatoid arthritis: A meta-analysis of efficacy and selected clinical conundrums. Seminars in Arthritis and Rheumatism. 2013
Narula N, Charleton D, Marshall JK. Meta-analysis: Peri-operative anti-TNF(alpha) treatment and post-operative complications in patients with inflammatory bowel disease. Alimentary Pharmacology and Therapeutics. 2013;37(11):1057-1064
Moulis G, Sommet A, Bene J, et al. Cancer risk of anti-TNF-alpha at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. PLoS One. 2012;7(11):e48991
Moots RJ, Naisbett-Groet B. The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review. Rheumatology (Oxford). Dec 2012;51(12):2252-2261
Lopez A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L. Adherence to anti-TNF therapy in inflammatory bowel diseases: A systematic review. Inflammatory Bowel Diseases. 2013;19(7):1528-1533
Kristensen LE, Jakobsen AK, Bartels EM, et al. The number needed to treat for second-generation biologics when treating established rheumatoid arthritis: A systematic quantitative review of randomized controlled trials. Scandinavian Journal of Rheumatology. 2011;40(1):1-7
Kemper AR, Van Mater HA, Coeytaux RR, Williams JW, Jr., Sanders GD. Systematic review of disease-modifying antirheumatic drugs for juvenile idiopathic arthritis. BMC Pediatr. 2012;12:29
Kamangar F, Neuhaus IM, Koo JYM. An evidence-based review of skin cancer rates on biologic therapies. Journal of Dermatological Treatment. 2012;23(4):305-315.
Hadjinicolaou AV, Nisar MK, Parfrey H, Chilvers ER, ostor AJK. Non-infectious pulmonary toxicity of rituximab: A systematic review. Rheumatology. 2012;51(4):653-662
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Singh JA, Wells Ga Fau - Christensen R, Christensen R Fau - Tanjong Ghogomu E, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. 20110217 DCOM- 20110323 (1469-493X (Electronic))

Appendix G. Evidence profiles of comparisons of targeted immune modulators

Table G-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 strength of the evidence
Abatacept compared with Adalimumab							
Outcome: ACR 50 response at 12 months							
1 / 646	Open-label RCT	Fair	NA	Direct	Similar ACR 50 responses: 46% vs. 46%	none	Low
Outcome: Radiographic progression at 12 months							
1 / 646	Open-label RCT	Fair	NA	Direct	Similar radiographic non-progression: 85% vs. 89%	none	Low
Abatacept compared with Infliximab							
Outcome: ACR 50 response at 6 months							
1 / 431	RCT	Fair	NA	Direct	Similar ACR 50 responses: 45% vs. 36%	No dose increase for Infliximab allowed	Low
Outcome: Radiographic progression							
No evidence							
Adalimumab compared with Etanercept							
Outcome: DAS28 at 6 months							
1 / 42	Open-label RCT	Fair	NA	Direct	Similar improvements on DAS28 (-2.12 vs. -2.84)	none	Insufficient
Outcome: Radiographic progression							
No evidence							

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall strength of the evidence
Adalimumab compared with Tocilizumab							
Outcome: ACR 50 response							
2 / 369	Open-label RCT	Fair	Inconsistent	Direct	Significantly fewer ACR 50 responses with Adalimumab: 28% vs. 47%; P=0.0002	none	Low
Outcome: Radiographic progression							
No evidence							
Adalimumab compared with Tofacitinib							
Outcome: ACR 20 response at 6 months							
2 / 1101	RCTs	Fair	Inconsistent	Direct	Similar ACR 20 responses: 47% vs. 52%	none	Low
Outcome: Radiographic progression							
No evidence							
Etanercept compared with Infliximab							
Outcome: ACR 20 response after 12 months							
1 / 32	open-label RCT	Fair	NA	Direct	More ACR 20 responses with Etanercept: 74% vs. 60%	Infliximab dosing lower than recommended	Insufficient
Outcome: Radiographic progression							
No evidence							
Etanercept compared with Tocilizumab							
Outcome: DAS28 at 6 months							
1 / 43	open-label RCT	Fair	NA	Direct	Similar improvements on DAS 28 (-2.12 vs. -2.84)	none	Insufficient
Outcome: Radiographic progression							
No evidence							
All other comparisons							
Outcome: Health outcomes							
No evidence							
Outcome: Radiographic progression							
No evidence							

Abbreviations: ACR: American College of Radiology; DAS28, Disease Activity Score28; EULAR, European League Against Rheumatism; NA, not applicable; RCT, randomized controlled trial; RR, relative risk.

Table G-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 strength of the evidence
All comparisons							
Outcome: Health outcomes							
				No evidence			
Outcome: Radiographic progression							
				No evidence			
Outcome: Harms							
				No evidence			

Table G-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 strength of the evidence
All comparisons							
Outcome: Health outcomes							
				No evidence			
Outcome: Radiographic progression							
				No evidence			

Table G-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 strength of the evidence
Adalimumab compared with Etanercept							
Outcome: Outcome: ACR 20 response after 12 months							
1 / 100	RCT	Poor	NA	Direct	Similar ACR 20 responses: 70% vs. 72%	None	Insufficient
Adalimumab compared with Infliximab							
Outcome: Outcome: ACR 20 response after 12 months							

1 / 100	RCT	Poor	NA	Direct	Similar ACR 20 responses: 70% vs. 75%	None	Insufficient
Number of studies/ patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of effect**	**Other modifying factors**	**Overall strength of the evidence**
Etanercept compared with Infliximab							
Outcome: Outcome: ACR 20 response after 12 months							
1 / 100	RCT	Poor	NA	Direct	Similar ACR 20 responses: 72% vs. 75%	None	Insufficient
All other comparisons							
Outcome: Health outcomes							
No evidence							
Outcome: Radiographic progression							
No evidence							

Abbreviations: ACR: American College of Radiology; NA: not applicable; RCT, randomized controlled trial

Table G-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 strength of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Table G-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 strength of the evidence
Adalimumab compared with infliximab							
Outcome: Treatment discontinuation (dose escalation or early termination)							
1 / 73	RCT (switch)	Fair	NA	Indirect	Higher rates of treatment discontinuation with Adalimumab	None	Insufficient

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall strength of the evidence
					than Infliximab (47% vs. 16%; *P*=0.003)		
Outcome: Treatment termination							
1 / 73	RCT (switch)	Fair	NA	Direct	Higher rates of treatment termination with Adalimumab than Infliximab (28% vs. 2%; *P*<0.01)	None	Insufficient
Number of studies/ patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of effect**	**Other modifying factors**	**Overall strength of the evidence**
Outcome: Quality of life (IBDQ)							
1 / 73	RCT (switch)	Fair	NA	Direct	IBDQ scores similar between groups	None	Insufficient
All other comparisons							
Outcome: Health outcomes							
No evidence							

Abbreviations: IBDQ: Inflammatory Bowel Disease Questionnaire; NA: not applicable; RCT, randomized controlled trial

Table G-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 strength of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Table G-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 strength of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Table G-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 strength of the evidence
All comparisons							
Outcome: Health outcomes							
No evidence							

Table G-10. Evidence profile of comparisons of targeted immune modulators for the treatment of plaque psoriasis in adults

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall strength 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	Low
Outcome: Quality of life							
No evidence							

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors	Overall strength of the evidence
Outcome: Harms							
1 / 903	RCT	Fair	NA	Yes	Overall harms similar between Etanercept and Ustekinumab, fewer ISRs for Etanercept	None	Insufficient
All other comparisons							
Outcome: Health outcomes							
No evidence							

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; ISR: injection site reactions; NA: not applicable; PASI: Psoriasis Area and Severity Index; RCT, randomized controlled trial; RR, relative risk

Table G-11. Evidence profile of comparisons of targeted immune modulators for the treatment of plaque psoriasis in children

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

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

Number of studies / patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall strength of the evidence
Overall of adverse events						
8 / 3581	RCTs	Fair	Consistent	Direct	**All comparisons** Overall, one trials for each comparison showed that effect estimates centered on the point of no effect, although confidence intervals are wide and a clinically important difference cannot be	Insufficient

Number of studies / patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall strength of the evidence
					ruled out.	
Withdrawal / discontinuation due to adverse events						
8 / 3606	RCTs	Fair	Consistent	Direct	**Adalimumab vs. Infliximab:** Infliximab consistently had a higher risk of discontinuation than Adalimumab **Etanercept vs. Infliximab:** Infliximab consistently had a higher risk of discontinuation than Etanercept **Adalimumab vs. Etanercept:** No difference detected. **All other comparisons:** Only one study available	Moderate Moderate Low Insufficient
9 / 12 219	Observational studies	Fair	Consistent	Direct		
Serious adverse events						
8 / 3606	RCTs	Fair	Consistent	Direct	**Abatacept vs. Infliximab:** More serious adverse events with Infliximab than Abatacept in one RCT (18.2% vs. 9.6%) **All other comparisons:** No differences detected.	Low Insufficient
Injection site / infusion reactions						
5 / 2178	RCTs	Fair	Consistent	Direct	**Abatacept vs. Adalimumab:** Lower risk for Abatacept, RR 0.41, 95% CI, 0.22 to 0.79 **Abatacept vs. Infliximab:** Lower risk for Abatacept, RR 0.28 95% CI, 0.13 to 0.60 **Adalimumab vs. Etanercept:** Lower risk for Adalimumab; however no difference cannot be ruled out, RR 0.47 95% CI, 0.23 to 0.96 **Etanercept vs. Ustekinumab:** Lower risk for Ustekinumab, RR 6.26 95% CI, 4.00 to 9.81	Low Low Insufficient Low
Mortality						
2 / 34 579	Observational studies	Fair	Consistent	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No differences in hazard ratios for death.	Low

Number of studies / patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall strength of the evidence
Serious Infections						
9 / 55 359	Observational studies	Fair	Consistent	Direct	Abatacept, Adalimumab, and Etanercept all cause less serious infections than Infliximab.	Moderate
Tuberculosis						
4 / 19 701	Observational studies	Fair	Consistent	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** increased risk of tuberculosis with Adalimumab and Infliximab compared with Etanercept	Low
Opportunistic infections						
1 / 202	Observational study	Fair	N/A	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No significant difference in odds ratio	Insufficient
Herpes zoster						
4 / 45 518	Observational studies	Fair	Inconsistent	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No differences in hazard ratios for herpes zoster	Low
Skin infections						
1 / 11 881	Observational study	Fair	N/A	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No differences in hazard ratios for skin infections	Insufficient
Septic arthritis						
1 / 11 881	Observational study	Fair	N/A	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No differences in hazard ratios for skin infections	Insufficient
Malignancy – general						
5 / 27 886	Observational studies	Fair	Inconsistent	Direct	No significant difference in the risk of malignancy between Adalimumab, Anakinra, Etanercept, and Infliximab	Low
Non-melanoma skin cancer and melanoma						
3 / 24 154	Observational studies	Fair	Inconsistent	Direct	Likely no differences between Adalimumab, Etanercept, or Infliximab	Insufficient
Cardiovascular disease adverse events						
1 / 13 171	Observational study	Fair	N/A	Direct	No significant differences between Etanercept and Infliximab in the risk of incident heart failure	Insufficient
Interstitial Lung Disease						
1 / 4200	Observational study	Fair	N/A	Direct	Comparisons of Adalimumab, Etanercept, and Infliximab showed no significant differences	Insufficient

Number of studies / patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall strength of the evidence
Combination strategies						
4 / 586	RCTs	Fair	Consistent	Direct	The combination of two antitumor necrosis factor drugs (of a different mechanism of action) substantially increased the frequency of serious adverse events, withdrawals due to adverse events, and serious infections	High

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, relative risk

Table G-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 strength 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	Overall strength of the evidence
Tocilizumab vs. Adalimumab: Efficacy in age-groups, sex: female, male; early vs. established disease						
1 / 326	RCT	Fair	NA	Direct	Differences of subgroups not statistically significant, imprecise results, no data available in absolute numbers	Insufficient

Abbreviations: RCT, randomized controlled trial

Appendix H. Placebo-controlled trials detected in searches for Update 4

We identified 97 placebo controlled trials during the abstract review process. These were not carried forward to the full-text review stage as they were no longer part of our inclusion criteria for Update 4.

Abatacept
Conaghan PG, Durez P, Alten RE, et al. Impact of intravenous abatacept on synovitis, osteitis and structural damage in patients with rheumatoid arthritis and an inadequate response to methotrexate: the ASSET randomised controlled trial. Ann Rheum Dis. Aug 2013;72(8):1287-1294
Kaine J, Gladstein G, Strusberg I, et al. Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase IIIb ALLOW study). Ann Rheum Dis. Jan 2012;71(1):38-44
Takeuchi T, Matsubara T, Nitobe T, et al. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Mod Rheumatol. Mar 2013;23(2):226-235
Wells AF, Westhovens R, Reed DM, et al. Abatacept plus methotrexate provides incremental clinical benefits versus methotrexate alone in methotrexate-naive patients with early rheumatoid arthritis who achieve radiographic nonprogression. J Rheumatol. Nov 2011;38(11):2362-2368
Adalimumab
Detert J, Bastian H, Listing J, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. Ann Rheum Dis. Jun 2013;72(6):844-850
Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. 20131220 DCOM- 20140218 (1528-0012 (Electronic))
Horneff G, Fitter S, Huppertz HI, et al. Phase III, multi-centre, randomised, double blind, Placebo-controlled study for treatment of juvenile ankylosing spondylitis (AS) with Adalimumab. Pediatric Rheumatology. 2011;9
Horneff G, Fitter S, Foeldvari I, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): Significant short term improvement. Arthritis Research and Therapy. 2012;14(5)
Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis. Aug 2012;15(4):358-365
Keystone EC, Van Der Heijde D, Kavanaugh A, et al. Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: Final 10-year data in longstanding rheumatoid arthritis. Journal of Rheumatology. 2013;40(9):1487-1497
Keystone EC, van der Heijde D Fau - Kavanaugh A, Kavanaugh A Fau - Kupper H, et al. Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. 20130902 (0315-162X (Print))
Kimball AB, Bensimon Ag Fau - Guerin A, Guerin A Fau - Yu AP, et al. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. 20101129 DCOM- 20110315 (1175-0561 (Print))
Leonardi C, Langley Rg Fau - Papp K, Papp K Fau - Tyring SK, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. 20110412 DCOM- 20110706 (1538-3652 (Electronic))
Ortonne JP, Chimenti S Fau - Reich K, Reich K Fau - Gniadecki R, et al. Efficacy and safety of adalimumab in patients with psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE. 20110804 DCOM- 20111205 (1468-3083 (Electronic))

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