Drug Class Review

Targeted Immune Modulators

Final Update 5 Report

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STRUCTURED ABSTRACT

Purpose

We systematically compared the efficacy, effectiveness, and harms (adverse events) of abatacept, adalimumab, alefacept, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab tocilizumab, tofacitinib, ustekinumab, and vedolizumab 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 2016 (January). We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data, requested dossiers of information from pharmaceutical manufacturers, and retrieved relevant citations from reference lists of included studies.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. Results indicate similar efficacy between targeted immune modulators if direct head-to-head trials were available (low or insufficient strength of evidence). Most of the comparisons 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).

For Crohn's disease, one open-label trial suggested higher discontinuation rates because of adverse events or loss of response for adalimumab than infliximab. A second open-label trial did not identify any differences in endoscopic, histological, or clinical recurrence rates following curative ileocolonic resection (insufficient strength of evidence).

For plaque psoriasis four head-to-head trials report that secukinumab is superior to ustekinumab; both secukinumab and ustekinumab are superior to etanercept; and tofacitinib is equivalent to etanercept in treating plaque psoriasis (low strength of evidence for all comparisons).

We did not find any head-to-head evidence for the treatment of ankylosing spondylitis and ulcerative colitis in adults. Likewise, no head-to-head evidence was available for juvenile idiopathic arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, or plaque psoriasis in children.

The most comparative evidence on harms was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab. Infliximab consistently had a higher risk

of serious infections and discontinuation because of adverse events than abatacept, adalimumab and etanercept (moderate strength of evidence.

Injection site or infusion reactions were less frequent for patients receiving abatacept compared with adalimumab and infliximab (low strength of evidence). Etanercept had a higher risk for injection site reactions than adalimumab, secukinumab, and ustekinumab (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.

High strength of evidence shows that the combination of 2 targeted immune modulators leads to higher risks of serious adverse events, withdrawal due to adverse events, and serious infections without additional therapeutic benefit.

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) 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 TIMs (infliximab) in 1998 and approved 16 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), abatacept (2005), rituximab (2006), natalizumab (2008), certolizumab pegol (2008), golimumab (2009), ustekinumab (2009), tocilizumab (2010), tofacitinib (2012), canakinumab (2013), apremilast (2014), vedolizumab (2014) and secukinumab (2015). 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
Apremilast	Otezla® Celgene Corporation	PDE4 inhibitor	Adult moderate to severe plaque psoriasis and psoriatic arthritis	Day 1: 10 mg tablet in AM; Day 2: 10 mg AM and 10 mg PM; Day 3: 10 mg AM and 20 mg PM; Day 4: 20 mg AM and 20 mg PM; Day 5: 20 mg AM and 30 mg PM; Day 6 and thereafter: 30 mg AM and 30 mg PM (in patients with severe renal impairment AM doses only).
Abatacept	Orencia® Bristol Myers Squibb	CD80/86–CD28 T-cell co-stimulation modulator	Rheumatoid arthritis	Intravenous infusion should be administered in 30-minutes 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. Subcutaneous injection once weekly with or without an intravenous loading dose; 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 intravenously 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.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Adalimumab	Humira® AbbVie	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)	Body weight:10 kg (22 lbs) to < 15 kg (33 lbs): 10 mg every other week. Body weight: 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week. Body weight: ≥ 30 kg (66 lbs): 40 mg every other week.
			Adult 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.
			Pediatric Crohn's disease	Pediatric patients 6 years of age and older with body weight of: 17 kg (37 lbs) to < 40 kg (88 lbs): 80 mg (2 40 mg injections on Day 1) and 40 mg 2 weeks later (on Day 15), followed by a maintenance dose of 20 mg every other week. Body weight ≥ 40 kg (88 lbs): 160 mg on Day 1 (4 injections on 1 day or 2 40 mg injections per day for 2 consecutive days); and 80 mg (2 40 mg injections) 2 weeks later (on Day 15), followed by 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.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Anakinra	Kineret® Biovitrum/ Amgen	IL-1 Inhibitor	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.
Canakinumab	Ilaris® Novartis	IL-1β Inhibitor	Systemic Juvenile Idiopathic Arthritis (2 years and older)	Body weight ≥ 7.5 kg: 4mg/kg SC injections (maximum of 300 mg) every 4 weeks.
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.
			Ankylosing spondylitis	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.
Etanercept	Enbrel® Amgen Pfizer Immunex	TNF Inhibitor	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	50 mg SC injection once weekly.
			Juvenile idiopathic arthritis (2-17 years)	Body weight ≥ 63 kg (138 pounds): 50 mg SC injection weekly Body weight <63 kg (138 pounds): 0.8 mg/kg SC injection weekly.
			Plaque psoriasis	50 mg SC injection twice weekly for 3 months, followed by 50 mg once weekly.
Golimumab	Simponi ARIA® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks in combination with methotrexate.
	Simponi® Janssen Biotech		Rheumatoid arthritis	50 mg SC injection once a month in combination with methotrexate.
			Psoriatic arthritis, ankylosing spondylitis	50 mg SC injection once a month with or without methotrexate or other DMARDs.
			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.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Crohn's disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; patients without initial response may benefit from increasing 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.
			Ulcerative colitis	*Adult and pediatric:* 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.
			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	α4 integrin inhbitor	Crohn'sdisease	300 mg intravenous infusion over one hour every 4 weeks.
			Multiple sclerosis	300 mg intravenous infusion over one hour every four weeks.
Rituximab	Rituxan® Genentech Hoffman-La Roche[h]	Anti-CD 20 antibody	Rheumatoid arthritis	2 1000 mg intravenous infusion on days 1 and 15 in combination with methotrexate. Subsequent courses administered every 24 weeks or based on clinical evaluation but not sooner than every 16 weeks.
Secukinumab	Cosentyx® Novartis	IL-17A inhibitor	Plaque psoriasis	300 mg (2 SC injections of 150 mg) at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable.
Tocilizumab	Actemra® Genentech	IL-6 receptor inhibitor	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 1 to 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.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			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 as a 60-minute single intravenous infusion 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 as a 60-minute single intravenous infusion every 2 weeks.
Tofacitinib	Xeljanz®/ Pfizer	JAK inhibitor	Rheumatoid arthritis	5 mg tablets 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.
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.
Vedolizumab	Entyvio® Takeda Pharmaceuticals America	α4β7 integrin inhibitor	Adult ulcerative colitis Adult Crohn's disease	300 mg intravenously over 30 minutes at 0, 2 and 6 weeks, then every 8 weeks thereafter.

Abbreviations: AM, ante meridiem (before noon); AS, ankylosing spondylitis; CD, cluster of differentiation; 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; PM, post meridiem (after noon); 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 and IL-17A, naturally occurring cytokines, have 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. Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that binds to human IL-1β and prevents its interaction with IL-1 receptors resulting in suppression of inflammation in patients with disorders of autoimmune origin. Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor, thus inhibits the release of proinflammatory cytokines and chemokines.

The immunosuppressant agents abatacept and alefacept exert their immune regulation by interfering with T lymphocyte activation. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of immunoglobulin G1. Alefacept is a dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen (LFA-3) and the Fc portion of human immunoglobulin G1.

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. Vedolizumab is a humanized monoclonal antibody that specifically binds to the α4β7 integrin and blocks its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), and fibronectin, but not vascular cell adhesion molecule 1 (VCAM-1). Therefore, it modulates inflammation in the gastrointestinal tract without inducing the systemic immunosuppression that characterizes anti-alpha 4 chain monoclonal antibodies, such as natalizumab.

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 oral TIM for the treatment of rheumatoid arthritis. It is the first 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.[7]
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).[8]

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.[9] 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.[10] 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.[11] 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.[11,12]

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.[13] 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 inTable 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.[14]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 TIMs should be employed.[15,16] Therapy in persons with psoriatic arthritis should take into account concomitant psoriasis of the skin.

Table 3 CASPAR classification criteria for psoriatic arthritis (2006)[17]

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

Abbreviations: CASPAR, **C**l**AS**sification criteria for the diagnosis of **P**soriatic **AR**thritis

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.[18] 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. TIMs 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.[18]

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.[19]

Treatment is aimed at reducing and maintaining remission of symptoms and inflammation and prevention complications.[19] Distal disease, limited to the region below the descending colon, may be reached by topical treatments. Mild disease may be controlled with oral and/or topical 5-aminosalicylate drugs. If the disease is resistant to these interventions or is more severe, corticosteroids are frequently used. In addition, some TIMs 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. Indications for surgery include excessive bleeding, perforation, carcinoma, and toxic colitis.

Plaque Psoriasis

Plaque psoriasis is a chronically recurring, debilitating inflammatory disease that affects the skin, scalp, and joints. It is characterized by erythrosquamous scaling lesions and ranges in severity from mild to severe. Patients with moderate to severe disease experienced significant deterioration of quality of life.[20] The exact pathogenesis of plaque psoriasis is still unknown, however pathophysiological evidence suggests that an overproduction of proinflammatory cytokines plays an important role.[21,22] In particular, tumor necrosis factor levels and interleukin-12 and interleukin-23 levels are increased in psoriatic lesions compared with healthy skin.

The severity of plaque psoriasis is most commonly classified based on the percentage of body surface area involved. Mild psoriasis is defined as affecting less than 5% of the body surface area; moderate psoriasis affects 5% to 10%; and severe psoriasis is defined as more than 10% of the body surface area affected.[20,23]

The goal of plaque psoriasis treatment is to gain control of the disease process, decrease the percentage of body surface involved, and achieve and maintain long-term remission.[24] Conventional therapy includes topical treatments (e.g., emollients, topical corticosteroids, vitamin D_3 analogues, tazarotene, coal tar, and dithranol), phototherapy (e.g., broadband ultraviolet B light, narrow band ultraviolet B light, and psoralen plus ultraviolet A light), and systemic therapy (e.g., methotrexate, cyclosporine, retinoids, and fumarates).[23] In addition, biologic agents such as adalimumab, alefacept, 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, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, ustekinumab, and vedolizumab. A 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 TIMsdiffer in their effects under real-life circumstances? This report addresses both efficacy (i.e., whether TIMs differ in their effects under ideal or highly controlled circumstances) and effectiveness. We distinguish between *efficacy* (*explanatory*) studies and *effectiveness (pragmatic)* studies by using a validated tool proposed by the Research Triangle Institute-International-University of North Carolina Evidence-based Practice Center.[25] Studies conducted in community-based settings that use less stringent eligibility criteria (i.e., broad range of population characteristics and disease severity), have long follow-up periods (i.e., greater than 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 ≥ 1000

Abbreviations: TIM, targeted immune modulator.

As equipotency among the reviewed TIMs 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 (seeTable 4); however, we also include radiographic outcomes. Many clinicians view radiographic changes as important parameters of treatment success or failure.

Appendix A provides a glossary of commonly used terms.

METHODS

Literature Search

To identify articles relevant to each key question, for Update 5 we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2013 (November) to 2016 (January) using included drugs (abatacept, adalimumab, alefacept, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, ustekinumab, vedolizumab), 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® X6, 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 ($n \geq 1000$), head-to-head observational studies with a follow-up of at least 12 weeks to augment findings from trials.

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)[26] and the National Health Service Centre for Reviews and Dissemination.[27] 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,[28] 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.

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.[29] 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 Berkman, et al., 2013, evaluating risk of bias includes assessment of study design and aggregate quality of studies.[29]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.[29]

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

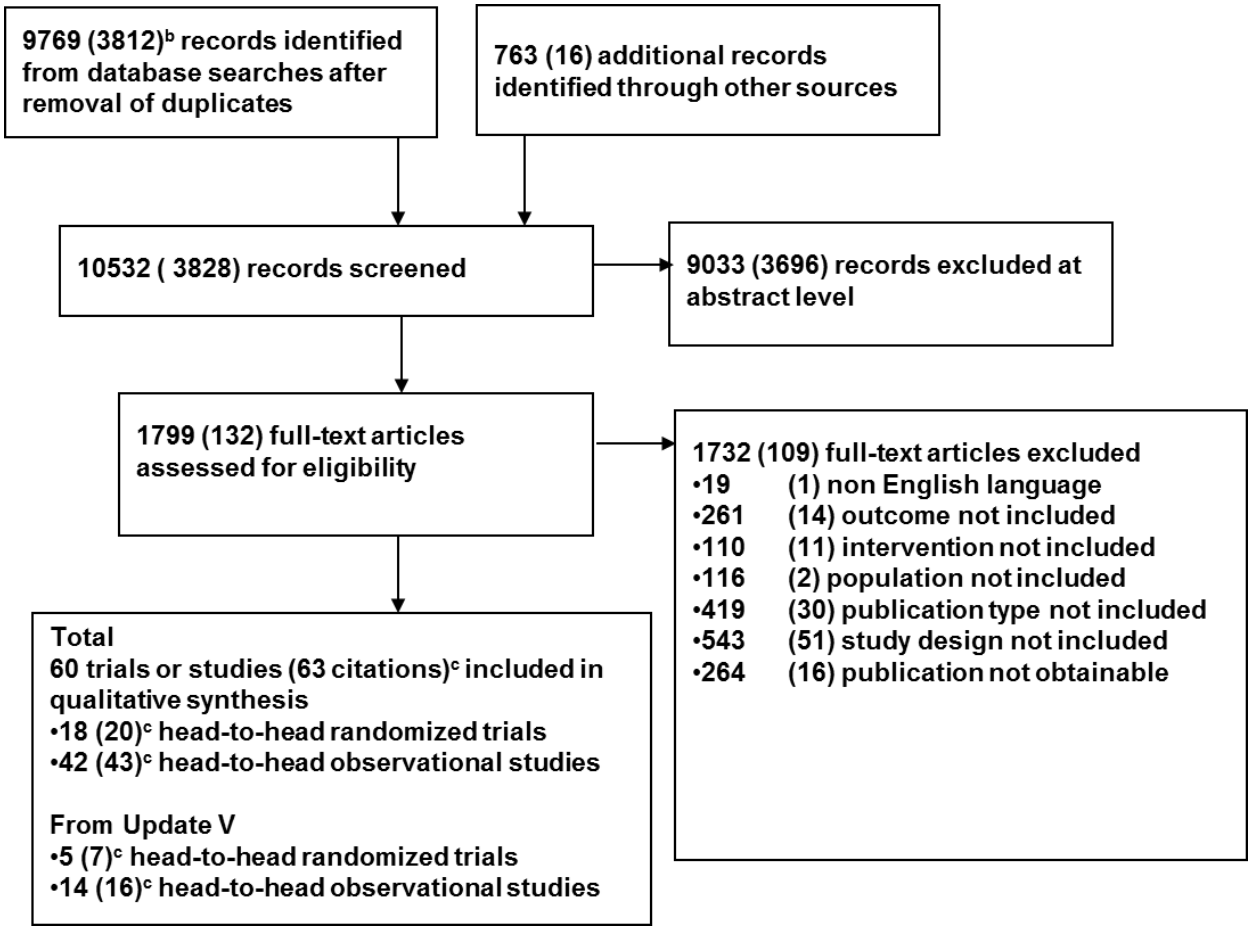
Overview

For Update 5, literature searches identified 3828 citations. In combination with previous searches, we have now identified 10 532 relevant citations in total over the history of this report. For this update, we received dossiers from 10 pharmaceutical manufacturers: Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Celgene Corporation, Genentech, Janssen Scientific Affairs, Novartis Pharmaceutical Corporation, Takeda Pharmaceuticals International Inc., and UCB Inc.

Altogether we now have evidence from 18 head-to-head randomized trials and from 42 head-to-head observational studies (in 63 publications). 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.

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.[30]
[b] Numbers in parentheses are results of the literature search new to Update 5
[c] The number of included studies differs from the number of included citations because some studies have multiple publications.

Appendix C provides a list of excluded studies and reasons for exclusions.

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?

Appendix D provides evidence profiles of the comparative effectiveness of targeted immune modulators.

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.

Summary of findings

We included 11 trials[31-41] of which 4 were open-label randomized controlled trials.[31-33,41] All but one included trials were efficacy studies, conducted in narrowly defined populations and/or limited to less than 12 months of follow-up. The only effectiveness study for rheumatoid arthritis compared abatacept, rituximab, or a TNF-inhibitor in patients who had inadequate responses to a previous TNF-inhibitor treatment.[41]

Of the 55 possible head-to-head comparisons for the approved drugs, we found direct head-to-head evidence from trials for 9 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,[31] abatacept and rituximab,[41] adalimumab and etanercept,[32] adalimumab and tofacitinib,[36] and etanercept and tocilizumab.[32] The evidence is mixed regarding differences in efficacy between adalimumab and tofacitinib.[36,37] 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.[35] 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.[34] 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.[32] 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).[33] The strength of evidence is insufficient.

A poor, open-label effectiveness trial reported similar effectiveness between abatacept, rituximab, and TNF-inhibitors in patients who failed a previous treatment with a TNF-inhibitor.[41] 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.[38-40]

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, Disease Activity Score28) combine measures of global disease activity with counts of tender and swollen joints and acute phase laboratory parameters (see Appendix E). In addition, most studies evaluated health outcomes such as quality of life, functional capacity (e.g., Short Form 36 Health Survey, Health Assessment Questionnaire Disability Index, arthritis-specific health index), or discontinuation rates due to disease worsening.

Sponsorship

All trials were funded by the pharmaceutical industry except the effectiveness trial which was supported by the Netherlands Organisation for Health Research and Development.[41]

Detailed assessment: Direct evidence on comparative effectiveness involving TNF-inhibitors

Overall, we included 10 head-to-head trials involving a TNF-inhibitor. [31-40] None of them was classified as an effectiveness study. 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, and golimumab. Included studies are summarized inTable 6.

Abatacept compared with adalimumab

The only evidence (AMPLE [Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate] 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.[31] 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 the 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.

At 2 years, American College of Rheumatology 50 (44.7% vs. 46.6%) and American College of Rheumatology 70 (31.1% vs. 29.3%) responses were still similar between patients receiving abatacept and those on adalimumab.[43] Disease activity (assessed with Disease Activity Score28, Clinical Disease Activity Index), physical functioning (Health Assessment Questionnaire Disability Index), and other patient-reported outcomes such as pain, fatigue, or the ability to perform work were also similar between treatment groups at year 2.[43,44]

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.[35] 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 (72.4% vs. 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% vs. 36.4%; *P*=NR; American College of Rheumatology 70 response 26.3% vs. 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.

Abatacept compared with TNF-inhibitors

A Dutch open-label effectiveness trial in patients who had failed TNF-inhibitor treatment compared abatacept, rituximab, and TNF-inhibitors as second-step treatments.[41] This trial enrolled 144 patients who had moderate to high disease activitiy despite previous treatment with different TNF-inhibitors. The only exclusion reason in this effectiveness trial was a contraindication for treatment (e.g., pregnancy, presence of a serious infection). Patients were randomly assigned to intravenous abatacept every 4 weeks (dosage based on body weight: patients with < 60 kg received 500mg, patients between 60 and 100 kg received 750mg, and patients with more than 100 kg 1000mg), or TNF-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab according to approved dosages). The primary outcome for effectiveness was the Disease Activity Score28 over time. We rated the study as poor quality because outcomes assessors were not blinded and the rate of cross overs and loss to follow-up was high. Overall, 42% of patients stopped their assigned medication or switched to a different medication.

At 12 months, Disease Activity Score28 scores were similar between treatment groups (3.8 for abatacept, 3.5 for TNF-inhibitors; P=not significant). Likewise, health-related quality of life measures (Health Assessment Questionnaire, Short Form 36 Health Survey did not show any statistically significant differencences between treatment groups. The strength of evidence is insufficient.

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.[32] As secondary outcomes, this study 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

2 fair trials, a double-blinded randomized controlled trial[34] and a small open-label randomized controlled trial[32] 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 Score28 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) responses 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.[32] 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

2 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.[36,37] Both trials were funded by the producer of tofacitinib, 1 of the 2 trials was a phase IIb dose-ranging study.[37]

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.[36] 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 than those on tofacitinib 5 mg or 10 mg (35.9% vs. 59.2% vs. 70.5%: *P* = NR).[37] 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).[33] Patients in this trial had confirmed rheumatoid arthritis for longer than 2 years, did not respond adequately to disease-modifying antirheumatic drugs, and were on a stable dose of methotrexate (10 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.[32] 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.Combination strategies involving TNF-inhibitors

3 trials determined the potential for additive or synergistic effects of combination therapy of 2 targeted immune modulators.[38-40] 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.[38] 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.[39] 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.[40] 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.

Detailed assessment: Direct evidence on comparative effectiveness of TIMs other than TNF-inhibitors

Abatacept compared with rituximab

The only study that addressed this comparison was a Dutch open-label effectiveness trial in patients who had failed TNF-inhibitor treatment.[41] This trial inrolled 144 patients who had moderate to high disease activitiy despite previous treatment with TNF-inhibitors. The only exclusion reason in this effectiveness trial was a contraindication for treatment (e.g., pregnancy, presence of a serious infection). Patients were randomly assigned to intravenous abatacept (n=43) every 4 weeks (dosage based on body weight: patients with < 60 kg received 500mg, patients between 61 and 100 kg received 750mg, and patients with more than 100 kg 1000mg), intravenous rituximab (n=46; 1000mg) at baseline, after 2 weeks, and optionally after 6 months, or TNF-inhibitors (see above). The primary outcome for effectiveness was the Disease Activity Score28 over time. We rated the study as poor quality because outcomes assessors were not blinded and the rate of cross overs and loss to follow-up

was high. Overall, 42% of patients stopped their assigned medication or switched to a different medication.

At 12 months, Disease Activity Score28 scores were similar between treatment groups (3.8 for abatacept, 3.4 for rituximab; P=not significant). Likewise, health-related quality of life measures (Health Assessment Questionnaire, Short Form 36 Health Survey did not show any statistically significant differencences between treatment groups. The strength of evidence is insufficient.

Targeted immune modulators combination strategies

3 trials determined the potential for additive or synergistic effects of combination therapy of 2 targeted immune modulators.[38-40] 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.[38] 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.[39] 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.[40] 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)[31] Schiff et al., 2014 (AMPLE)[43] Fleischmann et al., 2015 (AMPLE)[44]	Open-label RCT	646	12 months 24 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 Treatment response and improvements in patient-reported outcomes similar after 24 months;	Fair Fair
ABATACEPT compared with INFLIXIMAB									
Schiff et al., 2008[35]	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
ABATACEPT compared with RITUXIMAB									
Manders et al., 2015[41]	Open-label RCT	144	12 months	Abatacept vs. Rituximab vs. TNF inhibitors	DAS 28	HAQ, SF- 36	Active RA with moderate to high disease activity, had failed TNF-inhibitor; mean disease duration: 6.3 years	DAS 28, HAQ, and SF-36 scores similar for Abatacept, Rituximab, and TNF-inhibitors after 12 months	Poor
ADALIMUMAB compared with ETANERCEPT									
Kume et al., 2011[32]	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)[34]	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

Authors, Year	Study design	Number of patients	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Kume et al., 2011[32]	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)[36]	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
Fleischmann et al., 2012[37]	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[33]	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[32]	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[38]	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)[40]	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

Authors, Year	Study design	Number of patients	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Weinblatt et al., 2007[39]	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, canakinumab, 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: apremilast, adalimumab, certolizumab pegol, etanercept, golimumab,infliximab,and ustekinumab.

Summary of findings

We located 1 poor-quality randomized head-to-head trial of adalimumab, etanercept, and infliximab.[45] 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.[45] 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.[45] 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.[45] 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 for infliximab 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 thetreatment of psoriatic arthritis in children.

Summary of findings

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

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[45]	RCT	100	12 months	Adalimumab vs. Etanercept vs. Infliximab	HAQ, PASI, TJC, SJC, ACR 20, adverse events*		Adults with psoriatic arthritis with an inadequate response to DMARDs	Similar ACR 20 response rates. Similar HAQ scores	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; ACR, Americal College of Rheumatology
* Article did not distinguish between primary and secondary outcomes

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, natalizumab, and vedolizumab.

Summary of findings

We located 2, open-label, randomized, head-to-head trials; one compared switching from infliximab to adalimumab in patients with complete clinical response for at least 6 months on infliximab therapy.[46] The second study compared the risk of endoscopic, histologic, or clinical recurrence after ileocolonic resection.[47] We rated 1 study as fair-,[46] the other as poor quality.[47]In the fair-quality trial 73 patients with a satisfactory response to infliximab therapy were randomized to continue infliximab for 56 weeks or to switch to adalimumab. Significantly more patients in the adalimumab group discontinued treatment for loss of response or adverse events compared with the infliximab group. Because of an interim analysis, recruitment was stopped early before reaching the planned sample size.[46] The poor-quality trial randomized patients (n=20) after surgery to adalimumab or infliximab. After 1 year of follow-up, no statistically significant differences regarding endoscopic recurrence, histological disease activity, and clinical recurrence rates could be detected.[47] We rated this study as poor because the method of randomization was not reported, groups at baseline were substantially different regarding prognostic factors, and patients, outcome assessors, and care providers were not blinded to the treatment.The strength of evidence for this comparison is insufficient.
We did not locate any head-to-head evidence on other targeted immune modulators for Crohn's disease.

Study populations and outcome measures

All 73 randomized adult patients in the study by Van Assche et al. 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.[46] Further inclusion criteria were complete response with symptom control and a Crohn's Disease Activity Index of less than 200. The majority of patients in the fair-quality RCT received 8-weekly treatments with infliximab before entering into the trial. Some patients were on concomitant immunosuppression (17% adalimumab vs. 5% infliximab). 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 contraindications for further antitumor necrosis factor therapy were excluded from the trial. Patients randomized to the adalimumab group had been on infliximab treatment longer than patients randomized to infliximab maintenance treatment (63 vs. 32 months).[46]

The poor quality RCT randomized 20 patients within 4-6 weeks after surgery to adalimumab or infliximab.[47] Patients in the poor-quality RCT[47] underwent ileocolonic resection and were considered high risk patients for postoperative recurrence of Crohn's disease.

The main outcome in the fair-quality RCT was the proportion of patients who needed rescue therapy with steroids or anti-tumor necrosis factor dose escalation or had to terminate the treatment early. Secondary outcomes were an increase in Crohn's Disease Activity Index of more than 100 compared to baseline. 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 E) to yield a composite score between 0 and 600; scores below 150 indicate remission while scores above 450 indicate very severe illness. Response is commonly characterized by a Crohn's Disease Activity Index reduction greater than or equal to 70 points. In addition, the trial assessed quality of life measured with the Inflammatory Bowel Disease Questionnaire. C-reactive protein (CRP) was used as a marker of disease activity.[46]

The poor-quality RCT assessed endoscopic, histological and clinical recurrence of disease. For the assessment of clinical recurrence patients were evaluated with the Harvey-Bradshaw index.[48]This index is a shorter version of the Crohn's Disease Activity Index and consists of five clinical parameters.

Sponsorship

Van Assche et al.[46] 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. The study by Tursi et al. did not report sponsorship information.[47]

Detailed assessment: Direct evidence on comparative effectiveness

We included 2 open-label, randomized, head-to-head trials comparing subcutaneous adalimumab with intravenous infliximab for the treatment of Crohn's disease[46,47] Table 8 summarizes the included trials.

Adalimumab compared with infliximab

A fair-quality, open-label switch trial randomized 73 patients with ongoing infliximab maintenance therapy to continue their current infliximab regimen (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).[46] During follow-up, 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 compared with the infliximab group (28% vs. 2%, respectively; P<0.01). An increase in Crohn's Disease Activity Index of 100 or more points was observed in 28% of patients treated with adalimumab compared with 19% in the infliximab group. Median Inflammatory Bowel Disease Questionnaire scores were similar between groups throughout the study.

The poor-quality RCT reported no statistically significant differences between adalimumab- and infliximab-treated patients regarding clinical (10% vs. 10%), endoscopic (10% vs. 20%), and histological (20% vs. 30%) recurrence after 12 months.[47] The strength of evidence is insufficient.

Crohn's Disease in Children

Adalimumab and infliximab are currently approved by the US Food and Drug Administration for the treatment of Crohn's disease in children.

Summary of findings

We did not find any head-to-head randomized trials for the treatment of Crohn's disease in children.

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[46]	RCT (non-medical switch study)	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 weeks of the last 6 months with complete response	Infliximab superior to Adalimumab for treatment termination and dose escalation; no difference in IBDQ scores	Fair
Tursi et al., 2014[47]	RCT	20	12 months	Adalimumab vs. Infliximab	Endoscopic, histological and clinical recurrence after therapy		Adults with CD treated with Adalimumab or Infliximab after ileocolonic resection for 12 months; CD patients with high risk for postoperative recurrence	No statistically significant differences between Adalimumab- and Infliximab- treated groups regarding endoscopic recurrence, histological disease activity and clinical recurrence rates	Poor

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

Ulcerative Colitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis:adalimumab, golimumab, infliximab and vedolizumab

Summary of findings

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

Ulcerative Colitis in Children

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

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

Plaque Psoriasis

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

Summary of findings

We located 4 fair-quality, randomized, head-to-head trials for the treatment of moderate-to-severe plaque psoriasis; 1 of etanercept compared with ustekinumab,[49] 1 of etanercept compared with secukinumab[50], 1 of etanercept compared with tofacitinib[51], and 1 of secukinumab compared with ustekinumab.[52]

The results of the 4 trials conducted in 3 991 patients indicate that: secukinumab is superior to ustekinumab; both secukinumab and ustekinumab are superior to etanercept; and that tofacitinib is equivalent to etanercept in treating plaque psoriasis. We did not conduct any statistical comparisons across the trials (network analysis) so we can't draw any conclusions about the comparison of secukinumab or ustekinumab with tofacitinib. Nor did we locate any evidence regarding other targeted immune modulators. The strength of evidence for all the direct comparisons is low.

The 4 trials included patients with a 6 or 12 month history of moderate-to-severe plaque psoriasis resistant to systemic treatment. The average baseline Psoriasis Area and Severity Index score in the trials was between 20 [49] and 23.[50] The Psoriasis Area and Severity Index 75 results at 12 or 16 weeks from these 4 trials show that between 39.1% and 93.1% of patients achieved a response.

We did not find any comparative effectiveness studies for plaque psoriasis.

Study populations and outcome measures

The included head-to-head trials 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.

The trials assessed the Psoriasis Area and Severity Index 75 and Psoriasis Area and Severity Index 90 as one the primary outcome measures (see Appendix E). The Physician Global Assessment was also measured. The methodological quality of the trials was good or fair.

Sponsorship

All included trials were funded by the pharmaceutical industry.

Detailed assessment: Direct evidence on comparative effectiveness

We included 4 fair-quality, randomized, head-to-head trials for the treatment of moderate-to-severe plaque psoriasis Table 9 summarizes the included trials.

Etanercept compared with secukinumab

We located 1 good-quality randomized, head-to-head trial that compared etanercept with two doses of secukinumab.[50] The study was funded by the producer of secukinumab. 1,306 adult patients with moderate-to-severe plaque psoriasis of more than 6 months duration were randomized to receive either 300mg or 150mg of secukinumab (weekly at week 1, 2, 3, 4 and then every 4 weeks until week 48) or 50mg etanercept (twice weekly from baseline to week 12, then once weekly through week 51). The trial was conducted in a double-dummy design to preserve blinding. The results of this trial indicate that secukinumab is superior to etanercept in reducing the severity of plaque psoriasis. The primary outcomes (Psoriasis Area and Severity Index 75 response) at week 12 was acheived by 77.1% of patients receiving 300mg secukinumab, 67.0% of patients receiving 150mg secukinumab, and 44.0% of patients receiving 50mg etanercept. Furthermore, this Psoriasis Area and Severity Index 75 response was maintined through to week 52 in 84.3% of the patients receiving secukinumab 300mg, 82.2% of the patients receiving 150mg secukinumab, and 72.5% of the patients receiving 50mg etanercept.

Etanercept compared with tofacitinib

We located 1 good-quality randomized, 12-week head-to-head trial that compared etanercept (50mg twice weekly) with two doses of tofacitinib (5mg twice daily and 10mg twice daily) in 1 106 adult patients with moderate-to-severe plaque psoriasis of 12 or more months duration.[51] The study was funded by the producer of tofacitinib which is currently not approved for the treatment of plaques psoriasis. The aim of the trial was to show the non-inferiority of 10mg of tofacitinib twice daily compared with etanercept. The primary outcomes were a Psoriasis Area and Severity Index 75 and the Physician Global Assessment response. The results showed that a higher dose of tofacitinib is equivalent to etanercept, but a lower dose of tofacitinib is not. Specifically, after 12 weeks, 39.5% of the patients receiving 5mg of tofacitinib had achieved a Psoriasis Area and Severity Index 75 response, compared with 63.6% of the patients receiving 10mg tofacitinib and 58.8% of the patients receiving etanercept. The results for Physician Global

Assessment were similar: 47.1% achieved a response in the tofacitinib 5mg group compared with 68.2% in the tofacitinib 10mg group and 66.3% in the etanercept group.

Etanercept compared with ustekinumab

We located 1 fair-quality, randomized, single-blinded head-to-head trial that compared etanercept with ustekinumab in 903 patients with moderate-to-severe plaque psoriasis.[49] The study was funded by the producer of ustekinumab. 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 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 (90 mg) although the higher dose is recommended for patients who weigh more than 100kg. The strength of evidence is low.

Secukinumab compared with ustekinumab

We located 1 good-quality randomized, head-to-head trial that compared secukinumab with ustekinumab in adult patients with moderate-to-severe plaque psoriasis.[52]The study was funded by the producer of secukinumab. The results of this trial are currently available for up to 16 weeks of follow-up. This trial, is still ongoing and will eventually provide data up to 52 weeks. Patients received either 300mg of secukinumab at baseline and weeks 1, 2, 3, and then every 4 weeks, or 45mg (for patients $\leq$ 100kg) or 90 mg for patients over 100kg) of ustekinumab at baseline and week 4, then every 12 weeks. The trial used a double-dummy injection design to maintain blinding and the primary outcome was Psoriasis Area and Severity Index 90 response at week 16. For all outcomes secukinumab was superior to ustekinumab; for example 79.0% of secukinumab patients achieved a Psoriasis Area and Severity Index 90 response at week 16 compared with 57.6% of ustekinumab patients. The respective values for Psoriasis Area and Severity Index 75 response at week 16 were 93.1% of secukinumab patients and 82.7% of ustekinumab patients. Because results are based on preliminary data, 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

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

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 SECUKINUMAB									
Langley et al., 2014[50]	RCT	1306	52 weeks	Etanercept 50mg Secukinumab 300mg / Secukinumab 150mg / placebo / (FIXTURE only)	PASI 75	PASI 90, PASI 100, PASI 50, DLQI, itching, pain, scaling,	Adult patients with plaque psoriasis of at least 6 months duration, poorly controlled with current therapies and involving at least 10% body surface area.	Both Secukinumab doses superior to Etanercept for PASI 75	Good
ETANERCEPT compared with USTEKINUMB									
Griffiths et al., 2010[49]	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 PASI75, PGA, and PASI90	Fair

Authors, Year	Study design	Number of patients	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT compared with TOFACITINIB									
Bachelez et al., 2015[51]	RCT	1106	12 weeks	Etanercept 50mg / Tofacitinib 5mg / Tofacitinib 10mg	PASI 75	PGA PASI 90 PASI 50 itch DLQI	Adult patients with plaque psoriasis of at least 12 months duration, poorly controlled with current therapies and involving at least 10% body surface area	Tofacitinib 10mg equal to Etanercept, Tofacitinib 5mg inferior to Etanercept for PASI 75	Good
SECUKINUMAB compared with USTEKINUMAB									
Thaci et al.,2015[52]	RCT	676	16 weeks	Secukinumab 300mg / Ustekinumab 50mg or 100mg (if patient weight more than 100kg)	PASI 90	PASI 75 PASI 100 IGA DLQI pain, itch scaling	Adult patients with moderate-to-severe plaque psoriasis of at least 6 months duration.	Secukinumab superior to Ustekinumab for PASI 90	Good

Abbreviations: DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; 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?

Appendix D provides evidence profiles of the comparative risk of harms of targeted immune modulators.

Summary of findings

59 head-to-head trials or observational studies provided direct evidence on the harms associated with targeted immune modulators: 17 randomized trials [31,34-41,45,46,49-55] and data from 42 head-to-head observational studies.[56-98]

Table 10 and Table 11 describe randomized trials and observational studies providing direct evidence for this section. Most comparative evidence was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab. We did not locate any direct comparative evidence from trials or observational studies on the following targeted immune modulators: apremilast, alefacept; canakinumab; natalizumab, secukinumab, tofacitinib, or vedolizumab.

In trials, the comparative rates of overall adverse events occurring with targeted immune modulators did not differ (or any differences did not reach statistical significance; low strength of evidence).[31,34-37,41,45,46,49-52]

Overall, however, infliximab appears to have a higher risk for infections and discontinuations than other drugs. In observational studies, infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with adalimumab and etanercept (moderate strength of evidence),[62,64,92,94,99] Infliximab also had a higher comparative risk for serious infections compared with abatacept, adalimumab, and etanercept (moderate strength of evidence),[36,56,57,67,72,74,75,100,101]and opportunistic infections compared with etanercept (low strength of evidence). [90] For tuberculosis specifically, low strength evidence suggests a greater risk with adalimumab and infliximab compared with etanercept.[58,66,102,103] For herpes zoster, low strength evidence suggests no differences.[59,76,77,82]

Injection site and infusion reactions reactions were less frequent for patients receiving abatacept compared with both adalimumab and infliximab (both low strength of evidence) and greater for etanercept than adalimumab, secukinumab, and ustekinumab (low strength of evidence).[31,35,49,50]

Evidence regarding malignancies and overall mortality was sparse. Overall, no significant differences between targeted immune modulators were detected for malignancies.[41,43,50,94]and mortality.

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).[38,40,55,104]

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 more than 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 19 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).

Table 10 Summary of randomized trials with direct comparisons of adverse events in adults receiving targeted immune modulators

Authors, Year	Study design	N	Duration	Comparison	Population	Results	Quality rating
Head-to-head RCTs							
Weinblatt, et al., 2013[31]	RCT	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[35,54]	RCT	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
Manders, et al., 2015[41]	Open label RCT	144	12 months	Abatacept vs. Rituximab	Rheumatoid Arthritis	No significant differences in harms	Poor
Jobanputra, et al., 2012[53]	RCT	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[45]	RCT	100	12 months	Adalimumab vs. Etanercept 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[46]	RCT	73	12 months	Adalimumab vs. Infliximab	Crohn's Disease	No significant differences in harms	Fair
Gabay, et al., 2013[34]	RCT	325	24 weeks	Adalimumab vs. Tocilizumab	Rheumatoid Arthritis	No significant differences in harms	Fair
Van Vollenhoven, et al., 2012[36]	RCT	717	12 months	Adalimumab vs. Tofacitinib	Rheumatoid Arthritis	No significant differences in harms	Fair
Fleischmann, et al., 2012[37]	RCT	386	12 weeks	Adalimumab vs. Tofacitinib	Rheumatoid Arthritis	No significant differences in harms	Fair
Langley, et al. 2014[50]	RCT	1306	52 weeks	Etanercept vs. Secukinumab	Plaque Psoriasis	Higher risk of injection site reactions for Etanercept than Secukinumab (11% vs. 1%; RR 14.90, 95% CI, 6.70 – 33.16) No other significant differences in harms	Good

Authors, Year	Study design	N	Duration	Comparison	Population	Results	Quality rating
Bachelez, et al., 2015[51]	RCT	1106	12 weeks	Etanercept vs. Tofacitinib	Plaque Psoriasis	Higher risk of withdrawal due to adverse events for Etanercept (3%) than Tofacitinib (3% vs. 1%; RR 3.6 95% CI 1.01-12.79) Higher risk of injection site erythemas for Etanercept than Tofacitinib (5% vs. 0%; RR 36.34, 95% CI, 2.20 - 600.56) No other significant differences in harms	Good
Griffiths, et al., 2010[49]	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
Thaci, et al., 2015[52]	RCT	676	16 weeks	Secukinumab vs. Ustekinumab	Plaque Psoriasis	No significant differences in harms	Good
Head-to-head RCTs of combination strategies							
Weinblatt, et al., 2007[39]	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[55]	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[40]	RCT	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[38]	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 11 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[69]	5 212	19 118 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	No difference in HR for overall mortality	Fair
BADBIR (British Association of Dermatologists Biologic Intervention Register)						
Warren, et al., 2015[83]	3 523	6 months	Adalimumab Etanercept Infliximab Ustekinumab	Psoriasis	Infliximab has a higher risk of discontinuing drug due to adverse events than Adalimumab (HR 2.82, 95% CI, 1.79 – 4.45) Adalimumab has a higher risk of discontinuing drug due to adverse events than Ustekinumab (HR 1.67, 95% CI 1.09 to 2.56)	Fair
BNHI (Longitudinal database of Bureau of National Health Insurance), TAIWAN						
Chiu, et al., 2014[84]	2 238	NR	Adalimumab Etanercept	Rheumatoid Arthritis	Incidence rate ratio of tuberculosis was higher for Adalimumab compared to Etanercept (2.35, 95% CI 1.29-4.15) Incidence rate ratio of serious bacterial infections was higher for Adalimumab compared to Etanercept (1.83, 95% CI 1.19-2.77).	Good
Chiang, et al.,2014[93]	2 144	12 months	Adalimumab Etanercept	Rheumatoid Arthritis	Higher risk for any infections for Etanercept than Adalimumab (HR 2.04, 95% CI 1.13 to 3.61)	Good
BSRBB (British Society for Rheumatology Biologics Register) UK						
Dixon, et al., 2010[58]	10 712	34 025 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Risk for 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[57]	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
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[79]	13 784	43 798 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	No difference between the drugs in risk of basal cell carcinoma.	Fair

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
Galloway, et al., 2013[77]	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[63]	2 326	4 796 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
DCERN (Dermatology Clinical Effectiveness Research Network) US						
Yeung, et al., 2013[65]	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[67]	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 Group for the Study of Early Arthritis) 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
Hellenic Registry of Biologic Therapies, GREECE						
Flouri, et al., 2014[88]	1 208	Median follow-up 2.9-3 years	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Significantly higher incidence of serious infections with Infliximab compared to Adalimumab and Etanercept (4.0 vs. 2.7 vs.2.1 per 100 PY; p<0.001)	Good
HIRA (Health Insurance Review and Assessment Service), South Korea						
Jung, et al.,2015[87]	1 729	10 021 PY	Adalimumab Etanercept Infliximab	Mixed	Higher risk for tuberculosis with Adalimumab (IRR 3.45, 95% CI 1.82 to 6.55) and Infliximab (IRR 6.80, 95% CI 3.74 to 12.37) compared with Etanercept.	Fair
Kaiser (Kaiser Permanente Northern California) US						
Winthrop, et al., 2013[66]	8 418	20 330 PY	Adalimumab Etanercept Infliximab	Mixed	Similar incidence of tuberculosis for all 3 drugs	Poor

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
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 (Lombardy Rheumatology Network) ITALY						
Marchesoni, et al., 2009[64]	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[56]	1 064	24 months	Adalimumab Etanercept Infliximab	Rheumatic diseases	No difference in risk of serious infection between Adalimumab, Etanercept, and Infliximab	Fair
MonitorNet, Italian Society for Rheumatology (SIR) ITALY						
Scire, et al., 2013[94]	3 860	17 months	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis Spondyloarthritis	Lower discontinuation rates because of adverse events in for Adalimumab (aHR 0.66, 95% CI 0.48-0.91) and Etanercept (0.49, 95% CI 0.35-0.69) than 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
Curtis, et al 2015[89]	114 010	8.5 months	Abatacept Adalimumab Certolizumab pegol Etanercept Golimumab Rituximab Tocilizumab	Rheumatoid Arthritis	No significant differences in risk for interstitial lung disease among drugs	Good
Yun, et al., 2015[95,96]	189 326	NR	Abatacept Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Tocilizumab	Rheumatoid Arthritis	Significantly higher risk for serious infections of Etanercept (HR 1.24, 95% CI 1.07-1.45), Infliximab (HR 1.39, 95% CI 1.21-1.60), and Rituximab (HR 1.36, 95% CI 1.21-1.53) compared with Abatacept. No significant differences among other drugs.	Good

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[68]	7 734	13 296 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Incidence rate of fatal infections and fatal malignancies similar among drugs	Poor
RABBIT (rheumatoid arthritis – observation of biologic therapy register) GERMANY						
Strangfeld, et al., 2010[61]	5 120	NR	Adalimumab Anakinra Etanercept Infliximab	Rheumatoid Arthritis	Cancer recurrence was not found do be increased in patients taking Etanercept, Adalimumab, or Infliximab	Fair
Listing, et al., 2015[85]	8 908	31 378 PY 42.4 months	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	The overall risk for mortality was similar between Adalimumab and Etanercept (HR 0.76; 0.56 – 1.06) or Infliximab compared with Etanercept (HR 0.69; 0.42 – 1.13).	Good
Strangfeld, et al., 2009[82]	3 266	6 112 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
ROB-FIN (National Register for Biologic Treatment in Finland) FINLAND						
Aaltonen, et al.[86]	3 532	7 875 PY	Adalimumab Etanercept Infliximab Rituximab	Rheumatoid Arthritis	Incidence ratesof malignancies similar for all drugs.	Good
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
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

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
Baddley et al.,2014[90]	48 349	NR	Etanercept Infliximab	Mixed	Adjusted HR for opportunistic infections numerically higher for Adalimumab than Etanercept (1.8; 95% CI 0.8 to 4.0); Significantly higher for Infliximab than Etanercept (2.9; 95% CI 1.5 to 5.4)	Fair
Johnston et al.,2013[97]	4 332	Abatacept: 100 PY1772 years Adalimumab: 1772 PY Etanercept: 1932 PY Infliximab: 789 PY Rituximab: 463 PY	Abatacept Adalimumab Etanercept Infliximab Rituximab	Rheumatoid Arthritis	Significantly higher risk for infections for Infliximab than Rituximab (HR 1.62, 95% CI 1.03-2.55).	Good
SCQM-RA (Swiss Clinical Quality Management in Rheumatic Diseases) SWITZERLAND						
Du Pan, et al., 2009[62]	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
Swedish (Swedish Inpatient Register, the Swedish Outpatient Register, the Swedish Early RA Register, the Swedish National Population Registers, Swedish Tuberculosis Register, and the Swedish Biologics Register) SWEDEN						
Arkema, et al. 2015[91]	10 800	NR	Abatacept Adalimumab Anakinra Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Tocilizumab	Rheumatoid Arthritis	Crude IRs per 100,000 py for TB were highest for Infliximab (67.2 [95% CI 29.0 to 132.4]), followed by Adalimumab 52.4 [95% CI 19.2 to 114.1], Rituximab 29.0 [95% CI 0.7 to 161.7], and Etanercept 15.7 [95% CI 3.2 to 46.0]. 0 cases of TB with Abatacept, Anakinra, Certolizumab pegol, Golimumab, and Tocilizumab (less person-years investigated)	Fair
Neovius, et al. 2015[92]	9 139	20 198 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	Compared with Etanercept, discontinuation rates were higher for Adalimumab (aHR 1.26; 95% CI 1.16-1.37) and Infliximab (aHR 1.63; 95% CI 1.51-1.77). Infliximab had higher discontinuation rates than Adalimumab (aHR 1.28; 95% CI 1.18-1.40)	Good

Authors, Year	Number of patients	Follow-up	Comparison	Population	Results	Quality rating
Askling, et al., 2009[60]	6 366	25 693 PY	Adalimumab Etanercept Infliximab	Rheumatoid Arthritis	No significant difference in incidence of malignancy.	Good
National Databank for Rheumatic Diseases, US						
Wolfe, et al., 2004[80]	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[81]	13 001	49 000 PY	Adalimumab Anakinra Etanercept Infliximab	Rheumatoid Arthritis	Similar risk of overall mortality, no significant differences for lymphoma, melanoma, or non-melanoma skin cancers	Good
Veterans Affairs, Austin (Austin Automation Centre (AAC)) US						
McDonald, et al., 2010[59]	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 herpes zoster and Infliximab with a higher risk (HR 1.32, 95% CI, 0.85-2.03)	Fair
Amari, et al., 2011[78]	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
US Veterans Health Administration (VHA), US						
Curtis, et al., 2014[98]	3 152	1 year	Abatacept Adalimumab Etanercept Infliximab Rituximab	Rheumatoid Arthritis	Significantly higher risk for hospitalized bacterial infections for infliximab than Etanercept (HR2.3, 95% CI 1.3-4.0). No significant differences among other drugs	Good

Abbreviations: AE, adverse event; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; HR, hazard ratio; aHR, adjusted Hazard Ratio; IR, incidence ratio; IRR, incidence rate ratio; nbDMARD, non-biologic DMARD; NR, not reported; OR, odds ratio; PY, patient-years; RCT, randomized controlled trial; RR, relative risk; TB, tuberculosis; TNF, tumor necrosis factor.

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 F 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 13 head-to-head randomized trials with almost 7000 patients that provided evidence on general tolerability for 11 comparisons.[31,34-37,41,45,46,49-53] Table 12 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.

Overall frequency of any adverse event

We located 12 head-to-head randomized trials that provided evidence on overall adverse events for 11 comparisons.[31,34-37,41,45,46,49-52]

The majority of trials were conducted in patients with rheumatoid arthritis; only 1 trial was in patients with Crohn's disease,[46] and 4 in patients with plaque psoriasis.[49-52] The duration of trials varied from 12 weeks to 13 months and the rate of adverse events in the included trials varied from 15% to 87%,[31,45] 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, diarrhea and muscle pain.

Table 12 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 low for all the specific comparisons we present here.

Table 12 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[31,43]	1.01 (0.97 – 1.06)	0.40 (0.21 – 0.76)	0.84 (0.58 – 1.21)	0.39 (0.21 – 0.73)	Poor
Abatacept vs. Infliximab					
Schiff, et al., 2008[35]	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
Abatacept vs. Rituximab					
Manders, et al., 2015[41]	1.14 (0.65 – 2.02)	NR	NR	NR	Poor
Adalimumab vs. Etanercept					
Jobanputra, et al., 2012[53]	NR	0.83 (0.39 – 1.78)	0.86 (0.31 – 2.40)	0.47 (0.23 – 0.96)	Poor
Atteno, et al., 2010[45]	0.35 (0.08 – 1.63)	NR	NR	NR	Poor
Adalimumab vs. Infliximab					
Atteno, et al., 2010[45]	0.25 (0.06 – 1.12)	NR	NR	NR	Poor
Van Assche, et al., 2012[46]	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[34]	1.01 (0.91 – 1.11)	1.11 (0.46 – 2.66)	0.84 (0.45 – 1.58)	NR	Fair

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
Adalimumab vs. Tofacitinib					
Fleischmann, et al., 2012[37]	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[36]	0.99 (0.82 – 1.19)	0.71 (0.32 – 1.57)	0.42 (0.15 – 1.16)	NR	Fair
Etanercept vs Secukinumab					
Langley, et al. 2014[50]	0.97 (0.90– 1.05)**	1.24 (0.58 – 2.64)**	1.07 (0.61 – 1.88)**	14.90 (6.70 – 33.16)***	Good
Etanercept vs Tofacitinib					
Bachelez, et al., 2015[51]	1.05 (0.92 – 1.20)****	3.6 (1.01 – 12.79)****	0.98 (0.35 – 2.77)****	NA	Good
Etanercept vs. Ustekinumab					
Griffiths, et al., 2010[49]	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
Secukinumab vs. Ustekinumab					
Thaci, et al., 2015[52]	1.1 (0,98-1,24)	0.75 (0.17 – 3.34)	1,00 (0,42 – 2,38)	NR	Good

* 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.[46]
Abbreviations: AEs, adverse events; CI, confidence interval; NA, not applicable; 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.
** RR was calculated for Etanercept vs.Secukinumab 300 mg as approved by the FDA
*** For injection-site reactions, RR was calculated for Etanercept vs. Secukinumab combined (patients receiving Secukinumab 150 and 300 mg).
**** Patients in the etanercept group received more injections than those in the ustekinumab groups

Withdrawal / discontinuation due to adverse events

13 randomized controlled trials presented data on withdrawal due to adverse events.[31,34-37,43,45,46,49-53] We calculated the relative risk of withdrawal due to adverse events for 11 comparisons (Table 12)The majority of trials were of fair quality; two were poor and three were of good quality. The duration of trials varied from 3 to 24 months and the overall rate of withdrawal due to adverse events in the included trials ranged from 1,5% up to 20 % in smaller trials.

In one trial patients on abatacept had a statistically significant lower rate of discontinuations due to adverse events than patients on adalimumab (3.8% vs. 9.5%; relative risk: 0.4; 95% CI: 0.21-0.76) during 2 years of follow-up.[43] Another RCT reported that patients receiving etanercept had a statistically significantly higher risk to discontinue the therapy because of adverse events than patients on tofacitinib 5mg twice daily (3% vs. 1%; relative risk 3.60; 95 CI: 1.01 – 12.79). Because of low event rates, these differences need to be viewed cautiously. There was no statistically significant difference in withdrawal due to adverse events for any other comparison based on the results from randomized trials. The majority of the trials, however, was not sufficiently large to detect a statistically significant difference.

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.)

7 observational studies with more than 22 000 included patients reported on the comparative risk of discontinuation of targeted immune modulators due to adverse events.[62-64,83,92,94,99] These studies mostly included patients taking the antitumor necrosis factor drugs adalimumab, etanercept, and infliximab. Most conducted adjustment for baseline risk using Cox or propensity score modeling.

Table 13 presents the results of the included observational studies that conducted direct statistical comparisons of the targeted immune modulators adalimumab, etanercept, and infliximab in patients with rheumatoid arthritis or spondyloarthropathies 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 patients with rheumatoid arthritis. 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).[62,64,92,94,99] In a British registry of psoriasis patients the risk of discontinuation due to adverse events was also statistically significantly higher for infliximab- than for adalimumab-treated patients (hazard ratio 2.82; 95% CI 1.79-4.45). Patients taking ustekinumab were less likely to discontinue treatment due to adverse events than patients taking adalimumab (0.60 [95% CI 0.39-0.92]).[83]

Likewise, in 3 observational studies the adjusted hazard ratio for discontinuation due to adverse events favored adalimumab over infliximab (moderate strength of evidence).[62,63,94] However, these results have not been confirmed in the spondyloarthropathies subsample.[94] The comparative evidence for adalimumab and etanercept was conflicting; in 2 studies patients receiving etanercept discontinued significantly less often than patients receiving adalimumab,[63,64] and in another study the difference favored adalimumab; however this was not statistically significant (low strength of evidence).[99]

Table 13 Head-to-head comparisons of antitumor necrosis factor drugs 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)	Adalimumab versus Ustekinumab aHR (95% CI)	Quality rating
Du Pan, et al., 2009[62]	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[99]	566 patients, 2.3 years	No statistically significant difference	-	0.32 (0.15 to 0.71)* Favors Etanercept		Fair
Marchesoni, et al., 2009[64]	1064 patients, 23 months	2.09 (1.29 to 3.38) Favors Etanercept	-	No statistically significant difference		Fair
Hetland, et al., 2010[63]	4796 PY	1.5 (1.04 to 2.16) Favors Etanercept	0.56 (0.43 to 0.75)* Favors Adalimumab	-		Good
Scirè, et al., 2013[94]	3860 patients, 17 months	-	RA: 0.66 (0.48 to 0.91) Favors Adalimumab SpA: No statistically significant difference	RA: 0.49 (0.35 to 0.69) Favors Etanercept SpA: No statistically significant difference	-	Fair
Neovius, et al., 2015[92]	20 198 PY	1.26 (1.16 to1.37) Favors Etanercept	0.78 (0.71 to 0.85)* Favors Adalimumab	0.61 (0.56 to 0.66)* Favors Etanercept	-	Good
Warren, et al., 2015[83]**	3523 patients, 6 months	No statistically significant difference	0.35 (0.22 to 0.56)* Favors Adalimumab	-	1.67 (1.09 to 2.56)* Favors Ustekinumab	Fair

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; PY, patient-years; RA, rheumatoid arthritis; SpA, spondyloarthropathies
Data taken directly form publications, different models for adjustment were used.
* Direction of comparison was reversed
**Drug year was adjusted for in the analysis.

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 several comparisons (Table 12). Overall, the number of serious adverse events was low (5% 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.[35] 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 6 head-to-head trials.(Table 12) [31,35,46,49,50,53]

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) [31] 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).[35] The strength of evidence for these 2 comparisons is low. Etanercept consistently had higher risks of injections site reactions than comparator drugs. In trials, the risk of injection site reactions often were significantly higher for etanercept compared with adalimumab (relative risk 2.13, 95% CI, 1.04 to 4.35), [53] secukinumab (relative risk 14.90, 95% CI 6.70 to 33.16),[50] and ustekinumab (relative risk 6.26 95% CI, 4.00 to 9.81).[49] The strength of evidence is low.

Mortality

We located 3 publications of comparative data from observational studies on mortality.[69,70,85] In two studies, data from patients in the biologics registries was linked with mortality data from national death registries.[69,70] One study received information on vital status in patients who had missed two subsequent study visits by contacting the rheumatologist, the patient or his/her relatives or the local registration office.[85] The studies indicate that there is no statistically significant difference among the antitumor necrosis factor drugs. Specifically, 1 publication reported data from 5212 patients (19 118 patient-years) from the Swedish ARTIS (Anti-Rheumatic Therapy in Sweden biologics registry) database.[69] Overall, 179 patients died. There were no statistically significant 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 study in rheumatoid arthritis patients analyzed data from 8 908 patients (31 378 patient-years) from the German biologics register (RABBIT). [85] Overall, 463 patients died during this observation period. There were no statistically significant differences in the unadjusted hazard ratios for mortality between the antitumor necrosis factor drugs considering the ever exposed approach (adalimumab compared with etanercept: 0.94; 95% CI, 0.75 to 1.18; infliximab compared with etanercept: 1.05; 95% CI; 0.79 to 1.38). A third analysis of 29 367 patients with rheumatoid arthritis, inflammatory bowel disease, psoriatic disease, or ankylosing spondylitis conducted propensity matching to analyze 1 754 deaths and determined 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] The strength of evidence is low.

Serious infections

The number of overall serious infections was reported in 5 of the included randomized controlled trials providing direct comparative data for adalimumab and tofacitinib,[36,37] adalimumab and tocilizumab,[34]etanercept and tofacitinib,[51] and secukinumab and ustekinumab.[52] In all 5 trials very few serious infections occurred.This makes sensible comparison of the rates for the drugs using trial data impossible.

In addition, we identified 14 observational studies containing data on the comparative risk between targeted immune modulators for serious infections.[56,57,67,68,72,74,75,93,95-98,101] [86]Most of these retrospective studies used data from registries to determine the comparative risk of serious infections. 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 comparative data on abatacept, rituximab, tocilizumab, ustekinumab, and the antitumor necrosis factor drugs adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.

Table 14 present 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.[72,74,75,95-98,101]

A large retrospective observational study using Medicare data (more than 31 000 new treatment episodes) consisted of patients with rheumatoid arthritis who started a new course of treatment with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab following a previous treatment with a different targeted immune modulator. The outcome of interest was the first hospitalized infection during 12 months of follow-up.[96] Overall, 2 530 patients were hospitalized for infections, yielding a crude incidence rate of 15.3 (95% CI 14.7-15.9) infections per 100 person-years. In adjusted analyses, patients on etanercept (1.24; 95% CI 1.07-1.45), infliximab (1.38; 95% CI 1,21-1.60), and rituximab (1.36; 95% CI 1.21-1.53) had statistically significantly higher hazard ratios for serious infections than patients on abatacept.[96] No statistically significant differences could be detected among other targeted immune modulators. A subgroup analysis of patients who were hospitalized previously because of an infection, confirmed a higher risk of infliximab compared with abatacept and etanercept.[95]

Another analysis of Medicare data (more than 4 000 patients) in patients with rheumatoid arthritis who switched from anti tumor necrosis factor-inhibitors to a second-line treatment (other anti tumor necrosis factor inhibitor, abatacept, or rituximab), found a statistically significantly higher risk for serious infections for infliximab than rituximab (1.62; 95% CI 1.03-2.55).[97] Compared with rituximab, the study did not find any statististically significant differences in serious infections for abatacept, adalimumab, or etanercept.

A retrospective study using data from more than 11 000 patients with psoriasis (>22 000 patient years based on PSOLAR [Psoriasis Longitudinal Assessment and Registry]) reported numerically lower serious infection rates for patients on ustekinumab than for those on adalimumab, etanercept, or infliximab.[105]Authors, however, do not report any statistical comparisons of rates of serious infections among treatments.

The strength of evidence that infliximab has a higher risk for serious infections than abatacept, adalimumab, etanercept, and rituximab is moderate. All other comparisons are low.

Table 14 Head-to-head comparisons of antitumor necrosis factor inhibitors with one another in observational studies - adjusted hazard ratios for serious infections

Authors, Year	Adalimumab vs. Etanercept aHR (95%CI)	Adalimumab vs. Infliximab aHR (95%CI)	Etanercept vs. Infliximab aHR (95%CI)	Quality rating
Favalli et al., 2009[56]	No statistically significant difference	-	No statistically significant difference	Fair
Curtis et al., 2011[101]	-	0.52 (0.39 to 0.71) Favors Adalimumab	0.64 (0.49 to 0.84) Favors Etanercept	Fair
Galloway et al., 2011[57]	No statistically significant difference	No statistically significant difference	No statistically significant difference	Good
Grijalva et al., 2011[72]	-	1.23 (1.02 to 1.48) Favors Adalimumab	0.79 (0.68 to 0.93)* Favors Etanercept	Fair
Atzeni et al., 2012[75]	2.2 (1.1 to 4.4) Favors Etanercept	-	0.20 (0.11 to 0.37)* Favors Etanercept	Fair
Curtis et al., 2012[74]	-	0.67 (0.48 to 0.95)* Favors Adalimumab	0.66 (0.47 to 0.93)* Favors Etanercept	Fair
Thyagarajan et al., 2012[68]	No statistically significant difference	No statistically significant difference	No statistically significant difference	Poor
van Dartel et al., 2013[67]	1.83 (1.49 to 2.26) Favors Etanercept	-	0.49 (0.39 to 0.62)* Favors Etanercept	Fair
Chiang et al., 2014[93]	0.49 (0.28 to 0.88)* Favors Adalimumab	-	-	Good

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval
* Direction of comparison was reversed

Table 15 Head-to-head comparisons of antitumor necrosis factor inhibitors with abatacept in observational studies - adjusted hazard ratios for serious infections

Authors, Year	Adalimumab vs. Abatacept aHR (95%CI)	Certolizumab pegol vs. Abatacept aHR (95%CI)	Etanercept vs. Abatacept aHR (95%CI)	Golimumab vs. Abatacept aHR (95%CI)	Infliximab vs. Abatacept aHR (95%CI)	Quality rating
Curtiset al., 2011[101]	1.47 (1.04 to 2.08)* Favors Abatacept					Fair
Yun et al., 2016[96]	No statistically significant difference	No statistically significant difference	1.24 (1.07 to 1.45) Favors Abatacept	No statistically significant difference	1.39 (1.21 to 1.60) Favors Abatacept	Good

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval
* Direction of comparison was reversed

Table 16 Head-to-head comparisons of antitumor necrosis factor inhibitors with rituximab in observational studies - adjusted hazard ratios for serious infections

Authors, Year Follow-up	Adalimumab vs. Rituximab aHR (95%CI)	Certolizumab pegol vs. Rituximab aHR (95%CI)	Etanercept vs. Rituximab aHR (95%CI)	Golimumab vs. Rituximab aHR (95%CI)	Infliximab vs. Rituximab aHR (95%CI)	Quality rating
Curtis et al., 2011[101]					No statistically significant difference	Fair
Johnston et al., 2013[97 16001]	No statistically significant difference		No statistically significant difference		1.62 (1.03 to 2.55) Favors Rituximab	Good
Curtis et al., 2014 [98]			No statistically significant difference			Good
Aaltonen et al., 2015[86]	No statistically significant difference		No statistically significant difference		No statistically significant difference	Good

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval

Table 17 Head-to-head comparisons of targeted immune modulators other than antitumor necrosis factor inhibitors in observational studies - adjusted hazard ratios for serious infections

Authors, Year Follow-up	Abatacept vs. Rituximab aHR (95%CI)	Abatacept vs. Tocilizumab aHR (95%CI)	Quality rating
Johnston et al., 2013[97 16001]	No statistically significant difference		Good
Yun et al., 2016[96]	0.73 (0.65 to 0.83)* Favors Abatacept	No statistically significant difference	Good

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; NR, not reported
* Direction of comparison was reversed

Tuberculosis

We located 5 retrospective studies that reported on the comparative risk of tuberculosis in patients taking TIMs.[58,66,84,87,91] Three studies contained patients with rheumatoid arthritis,[58,84,91] 2 studies included patients with diverse indications receiving antitumor necrosis factor-alpha agents.[66,87] The larger studies provided data on 10 712 rheumatoid arthritis patients in the British Society for Rheumatology Biologics Register[58], and 10 800 rheumatoid arthritis patients in the Swedish registers.[91] The results of these 5 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 more than 10 000 rheumatoid arthritis patients treated with adalimumab, etanercept, or infliximab, 40 cases of tuberculosis occurred in more than 28 000 patient-years of follow-up (rate 95/100 000 patient-years; 95% CI, 63 to 138). A comparative analysis showed a statistically significant increased risk of tuberculosis for patients treated with adalimumab compared with those on etanercept (adjusted incidence rate ratio, 4.1; 95% CI, 1.4 to 12.4).[58] The adjusted incidence rate ratio comparing etanercept with infliximab almost reached statiscal significance (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.

In addition, data from 2 Korean studies underline the findings of a higher risk of tuberculosis with adalimumab and infliximab compared to etanercept.[84,87]

Data from Swedish registers (National Population Registers, Tuberculosis Register, Biologics Register) with 10 800 rheumatoid arthritis patients starting their first biological drug compared the risk of tuberculosis for abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab.[91] The crude incidence rates for tuberculosis per 100,000 person years were numerically highest for infliximab (67.2; 95% CI 29.0 to 132.4), followed by adalimumab 52.4 (95% CI 19.2 to 114.1), rituximab 29.0 (95% CI 0.7 to 161.7), and etanercept 15.7 (95% CI 3.2 to 46.0). In these databases, no cases of tuberculosis were seen in patients treated with abatacept, anakinra, certolizumab pegol, golimumab, and tocilizumab. Adjusted hazard ratios did not detect any statistically significant differences in the risk for tuberculosis among any of the treatments. These results, however, might be due to lack of statistical power as this study analyzed fewer patient years as the studies reported above. The strength of evidence is insufficient.

Opportunistic infections

An analysis of data on opportunistic infections from the US SABER study (SAfety Assessment of Biologic ThERapy) indicated that infliximab has a higher hazard of opportunistic infections than etanercept (aHR 2.9; 95% CI 1.5 to 5.4).[90] In the same study the difference between adalimumab and etanercept was not statistically significant (aHR 1.8; 95% CI 0.8 to 4.0). The study was large (48 349 patients) and of fair quality. Overall, 80 opportunistic infections were diagnosed in anti-tumor necrosis factor drug users; the most common infections were pneumocystis and nocardiosis/actinomycosis. The strength of evidence is low.

Herpes zoster

In 2 randomized controlled trials that reported on herpes zoster the incidence was similar for abatacept (9 cases in 2 years, 2.8%) and adalimumab (6 cases in 2 years, 1.8%),[43] and for tofacitinib 5mg (1 out of 329 in 12 weeks), tofacitinib 10mg (2 out of 330 in 12 weeks), and etanercept (2 out of 335 in 12 weeks).[51] We did not locate any other 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.[59,76,77,82] 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.[76,77,82] 1 study provided only crude rates.[59]

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.

In 3 studies adalimumab had the lowest hazard ratio of herpes zoster,[59,76,77] and this difference was significant for the comparison with infliximab in 1 study.[77] 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.[77] 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.[77] 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.[82] 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.[82] 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).

The strength of evidence for available comparisons is low.

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.[77] 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

1 observational study 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

Evidence regarding malignancies from randomized controlled trials was sparse. Several inlcuded trials reported the number of malignancies in active arms, but due to the low numbers overall, no significant differences between targeted immune modulators were detected.[41,43,50,94]

We located 6 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=31 418).[60-62,68,81,86] Overall, the studies included over 97 000 patient-years of data. Overall, there were no significant difference in the risk of malignancy between adalimumab, anakinra, etanercept, infliximab, and rituximab. Furthermore, where adjusted hazard or odds ratios 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).[60] 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.[62] 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).[68]

In a large US database of rheumatoid arthritis 6282 patients were receiving biologic therapy and there were 231 cases of cancer detected.[81] 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.[61] 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. Similarly, an analysis from Finland (ROB-FIN register plus a hospital registry) found no significant difference in the incidence rates of malignancy between the anti-tumor necrosis factor drugs adalimumab, etanercept and infliximab and rituximab in 3532 rheumatoid arthritis patients (7,875 patient-years) who had 53 cases of malignancies.[86]

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 or keratinocyte skin cancers (such as basal and squamous cell carcinomas) for patients receiving the tumor necrosis alpha antagonists adalimumab, etanercept, or infliximab.[78,79,81] 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 and the incidence of non-melanoma skin cancers in the included randomized trials was too low to provide useful comparative data.

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.[78] 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.[79,81] 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).[79] 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).[81] 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.[81] 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.[80] 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

2 retrospective cohort studies examined the comparative risk for interstistial lung disease.[89 71] 1 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. Likewise, the second study using Medicare data of more than 10 000 patients with rheumatoid arthritis did not find a statistically significant difference in the risk of interstitial lung disease in patients treated with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab.[89] Depending on the definition of the condition, however, only 16 to 59 cases of interstitial lung disease were eligible. Consequently, the study lacked power to detect clinically relevant differences in risks.The strength of evidence is insufficient.

Combination strategies in adults

We located 3 randomized controlled trials that randomized patients to a combination of targeted immune modulators (n=412).[38,40,55,104] 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).[38] 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%).[39] 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).[55] 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%.[40] 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

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 10).[34] No statistically significant or clinically meaningful difference could be determined for subgroups based on age, gender, duration of rheumatoid arthritis (< 2 vs. ≥ 2 years), and 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 18).

Detailed Assessment

Age

1 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. [34] 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

We could not find any eligible studies assessing differences in efficacy, effectiveness, or risk of harms based on racial groups. The strength of evidence is insufficient.

Gender

In 1 head-to-head trial 80% of the included patients with rheumatoid arthritis were women.[34] Gender was not a significant predictor of achieving a 70% improvement of American College of Rheumatology-criteria with either adalimumab or tocilizumab after 24 weeks. The strength of evidence 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

1 head-to-head randomized controlled trial[34] 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. The strength of evidence is insufficient.

Table 18 Summary of studies assessing subgroups

Authors, Year	Study design	N	Duration	Drug	Population	Results	Quality Rating
Age							
Gabay et al. 2013[34]	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[34]	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[34]	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 19 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, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, 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. Apremilast and tofacitinib are the only approved orally administered drugs. Infliximab, golimumab, natalizumab, rituximab, and vedolizumab require intravenous administration. Abatacept, adalimumab, anakinra, canakinumab, certolizumab pegol, etanercept, golimumab, secukinumab, 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 1 to 4 weeks, golimumab monthly, and ustekinumab every 12 weeks.

Key Question 1. Comparative Effectiveness

Rheumatoid Arthritis

Eleven trials provided head-to head evidence for the treatment of rheumatoid arthritis. Single trial evidence indicates that efficacy outcomes are similar between abatacept and adalimumab, abatacept and rituximab, 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.

A poor, open-label effectiveness trial reported similar effectiveness between abatacept, rituximab, and TNF-inhibitors in patients who failed a previous treatment with a TNF-inhibitor.[41] 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

1 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

We located 2, open-label, randomized, head-to-head trials; one fair-quality trial compared switching from infliximab to adalimumab in patients with complete clinical response for at least 6 months on infliximab therapy; the second poor-quality trial compared the risk of endoscopic, histologic, or clinical recurrence after ileocolonic resection. In the fair study, 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. In the poor study, no statistically significant differences regarding endoscopic recurrence, histological disease activity, and clinical recurrence rates following curative ileocolonic resection could be detected between the treatment groups. 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

We located 4 fair-quality, randomized, head-to-head trials for the treatment of moderate-to-severe plaque psoriasis; Based on preliminary data, secukinumab is superior to ustekinumab; both secukinumab and ustekinumab are superior to etanercept; and tofacitinib is equivalent to etanercept in treating plaque psoriasis. The strength of evidence for all the direct comparisons is low.

Key Question 2. Comparative Harms

42 trials or observational studies provided evidence on the harms associated with targeted immune modulators. We almost exclusively located evidence regarding the 3 tumor necrosis factor-inhibiting drugs adalimumab, etanercept, and infliximab. For newer targeted immune modulators such as apremilast, canakinumab, alefacept, natalizumab, secukinumab, tofacitinib, or vedolizumab harms data were completely missing.

In trials, 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). 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).

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.[106]

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. 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 19 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 randomized controlled effectiveness trial, no difference in effectiveness between abatacept, rituximab, or TNF-inhibitors in patients who had an inadequate response to a first-line TNF-inhibitor.
	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. Based on 1 head-to-head RCT, postoperative treatment with adalimumab or infliximab showed similar treatment effects.
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
	Low	Based on 1 head-to-head RCT, secukinumab is more efficacious than etanercept
	Low	Based on 1 head-to-head RCT, 10mg tofacitinib is similarly efficacious as etanercept; 5 mg tofacitinib is less efficacious
	Low	Based on preliminary data of 1 head-to-head RCT, secukinumab is more efficacious than ustekinumab
1. Comparative harms	Low	Overall adverse events for all comparisons:

Key question	Strength of evidence	Conclusion
		Based on 12 RCTs, likely no difference between TIMs
	Moderate	*Discontinuations due to adverse events*: Based on 7 observational studies, the rate is greater with infliximab than adalimumab or etanercept; the rate is greater with adalimumab than etanercept
	Insufficient	*Serious adverse events:* Based on 1 RCT, more serious adverse events with infliximab than abatacept; No differences for other comparisons
	Low	*Injection-site (infusion) reactions*: Based on 7 RCTs, lower risk for abtacept compared with adalimumab and infliximab; higher risk for etanercept than adalimumab, secukinumab, and ustekinumab
	Moderate	*Serious Infections:* Based on 5 RCTs and 8 observational studies, infliximab caused higher rates of serious infections than abatacept, adalimumab, etanercept
	Insufficient	*Based on 1 observational study, infliximab had higher rates rates of serious infections than rituximab*
	Insufficient	*Based on 1 observational study, abatacept had lower rates of serious infections than etanercept, infliximab, and rituximab*
	Insufficient	*Based on 1observational study, no differences between abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, tocilizumab*
	Low	*Mortality* Based on 3 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	Based on 1 observational study no difference among abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, rituximab, and tocilizumab
	Low	*Opportunistic infections* Based on 1 observational study, higher risk for infliximab than etanercept; no difference between adalimumab and etanercept
	Low	*Herpes zoster* *Based on 1 RCT, similar risks between abatacept and adalimumab* *Based on 1 RCT, similar risks between tofacitinib and etanercept*
	Low	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 6 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*

Key question	Strength of evidence	Conclusion
		Based on 1 observational study no difference between etanercept and infliximab
	Insufficient	*Interstitial lung disease* Based on 2 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
2. 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 mostly 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 secukinumab and ustekinumab are 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 12.01.2016

#1	Search "Arthritis, Rheumatoid"[Mesh]	97482
#2	Search Rheumatoid Arthritis[tiab]	85254
#3	Search Spondylitis, Ankylosing[Mesh]	12537
#4	Search ankylosing spondylitis[tiab]	10672
#5	Search ankylosing arthritis[tiab]	14
#6	Search "Arthritis, Psoriatic"[Mesh]	4223
#7	Search Psoriatic Arthr*[tiab]	6029
#8	Search "Crohn Disease"[Mesh]	32319
#9	Search Crohn Disease[tiab] OR Crohn's Disease[tiab]	34932
#10	Search "Colitis, Ulcerative"[Mesh]	28881
#11	Search Ulcerative Colitis[tiab]	30025
#12	Search "Arthritis, Juvenile"[Mesh]	8842
#13	Search juvenile idiopathic arthritis[tiab]	3463
#14	Search juvenile arthritis[tiab]	728
#15	Search Juvenile Chronic Arthritis[tiab]	1034
#16	Search Juvenile[ti] AND Arthritis[ti]	5570
#17	Search psoriasis[tiab]	30296
#18	Search #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	234475
#19	Search "Treatment Outcome"[Mesh]	726544
#20	Search outcome*[All Fields]	1675601
#21	Search efficacy[All Fields]	570859
#22	Search effectiveness[All Fields]	319021
#23	Search adverse[All Fields]	1668548
#24	Search safety[All Fields]	410667
#25	Search withdrawal*[All Fields]	84681
#26	Search harm[All Fields] OR harms[All Fields]	41548
#27	Search mortality[All Fields]	942762
#28	Search morbidity[All Fields]	2089884
#29	Search function*[All Fields]	2975558
#30	Search toxicity[All Fields]	552998
#31	Search complications[All Fields]	2556608
#32	Search drug discontinuation[All Fields]	1397
#33	Search Drug survival[all fields]	171
#34	Search risk of[ti]	76679
#35	Search #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19	9378929
#36	Search (#18 AND #35)	125890
#37	Search "Abatacept"[Mesh] OR "abatacept"[All Fields] OR "Orencia"[All Fields] OR 332348-12-6[rn]	2767
#38	Search "Adalimumab"[Mesh] OR "adalimumab"[All Fields] OR "Humira"[All Fields] OR 331731-18-1[rn]	4850
#39	Search "alefacept"[Supplementary Concept] OR "alefacept"[All Fields] OR "Amevive"[All Fields] OR 222535-22-0[rn]	442
#40	Search "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR "Anakinra"[All Fields] OR "Kineret"[All Fields] OR 143090-92-0[rn]	4676

#41	Search "apremilast" [Supplementary Concept] OR "apremilast"[All Fields] OR "Otezla"[All Fields] OR 608141-41-9[rn]	143
#42	Search "Certolizumab Pegol"[Mesh] OR "Certolizumab"[All Fields] OR "Cimzia"[All Fields] OR 428863-50-7[rn]	690
#43	Search "Etanercept"[Mesh] OR "etanercept"[All Fields] OR "Enbrel"[All Fields] OR 185243-69-0[rn]	6387
#44	Search "golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields] OR 476181-74-5[rn]	544
#45	Search "Infliximab"[Mesh] OR "infliximab"[All Fields] OR "Remicade"[All Fields] OR 170277-31-3[rn]	10567
#46	Search "Natalizumab"[Mesh] OR "natalizumab"[All Fields] OR "Tysabri" [All Fields] OR 189261-10-7[rn]	1692
#47	Search "Rituximab"[Mesh] OR "rituximab"[All Fields] OR "Rituxan"[All Fields] OR 174722-31-7[rn]	15179
#48	Search secukinumab [Supplementary Concept] OR secukinumab[All Fields] OR Cosentyx[All Fields] OR 1229022-83-6[rn]	149
#49	Search "tocilizumab"[Supplementary Concept] OR tocilizumab[All Fields] OR "actemra"[All Fields] OR "RoActemra"[All Fields] OR 375823-41-9[rn]	1418
#50	Search "tofacitinib" [Supplementary Concept] OR tofacitinib[All Fields] OR "janus kinase inhibitor"[all fields] OR "Xeljanz"[all fields] OR 690550[rn]	427
#51	Search "Ustekinumab"[Mesh] OR "ustekinumab"[All Fields] OR "Stelara"[All Fields] OR 815610-63-0[rn]	719
#52	Search "vedolizumab" [Supplementary Concept] OR vedolizumab[All Fields] OR Entyvio[All Fields] OR 943609-66-3[rn]	171
#53	Search "canakinumab" [Supplementary Concept] OR canakinumab[All Fields] OR ilaris[All Fields] OR acz885[all fields] OR canakinumab[all fields] OR 914613-48-2[rn]	267
#54	Search #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37	41250
#55	Search (#36 AND #54)	12270
#56	Search "Animals"[Mesh] NOT "Humans"[Mesh]	4166404
#57	Search (#55 NOT #56)	12199
#58	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]	1031477
#59	Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]	101103
#60	Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab])	94669
#61	Search "Comparative Study"[Publication Type]	1716461
#62	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]	2154765
#63	Search observational stud*[tiab]	58597
#64	Search (Multicenter[tiab] OR multicentre[tiab] OR multi-center[tiab] OR multi-centre[tiab]) AND (Study[tiab] OR analysis[tiab] OR trial[tiab])	92050
#65	Search cohort*[tiab]	341535

#66	Search nationwide study[tiab] OR nationwide trial[tiab]	1819
#67	Search Psoriasis Longitudinal Assessment and Registry[tiab] OR PSOLAR[tiab]	11
#68	Search #67 OR #66 OR #65 OR #64 OR #63 OR #62 OR #61 OR #60 OR #59 OR #58	4356025
#69	Search (#57 AND #68)	5676
#70	Search (#69) AND ("2015/10"[Date - Entrez] : "3000"[Date - Entrez])	100

Cochrane Library 13 Jan 2016

#1	[mh "Arthritis, Psoriatic"]	199
#2	[mh "Crohn Disease"]	1036
#3	[mh "Colitis, Ulcerative"]	950
#4	[mh "Arthritis, Juvenile"]	190
#5	[mh "Arthritis, Rheumatoid"]	4206
#6	[mh "Spondylitis, Ankylosing"]	452
#7	(ankylosing next (spondylitis or arthritis)):ti,ab,kw	834
#8	(juvenile near/2 arthritis):ti,ab,kw	402
#9	Psoriasis:ti,ab,kw	3824
#10	((Rheumatoid or Psoriatic) next Arthr*):ti,ab,kw	7535
#11	(crohn* next disease):ti,ab,kw	1563
#12	Ulcerative Colitis:ti,ab,kw	1725
#13	{or #1-#12}	15610
#14	[mh "Treatment Outcome"]	98415
#15	(outcome* or efficacy or effectiveness or adverse or safety or withdrawal* or harm or harms or mortality or morbidity or function* or toxicity or complications):ti,ab,kw	495445
#16	(drug next (discontinuation or survival)):ti,ab,kw	416
#17	risk of:ti	5430
#18	{or #14-#17}	499074
#19	#13 and #18	9755
#20	(abatacept or Orencia):ti,ab,kw	221
#21	(adalimumab or Humira):ti,ab,kw	875
#22	(alefacept or Amevive):ti,ab,kw	112
#23	[mh "Interleukin 1 Receptor Antagonist Protein"] or (Anakinra or Kineret):ti,ab,kw	217
#24	(apremilast or Otezla):ti,ab,kw	84
#25	(certolizumab or Cimzia):ti,ab,kw	181
#26	("TNFR-Fc fusion protein" or etanercept or Enbrel):ti,ab,kw	927
#27	(golimumab or simponi):ti,ab,kw	229
#28	(infliximab or Remicade):ti,ab,kw	1053
#29	(natalizumab or Tysabri):ti,ab,kw	183
#30	(rituximab or Rituxan):ti,ab,kw	1396
#31	(secukinumab or Cosentyx):ti,ab,kw	127
#32	(tocilizumab or actemra or RoActemra):ti,ab,kw	227
#33	(tofacitinib or "janus kinase inhibitor" or Xeljanz):ti,ab,kw	133
#34	(ustekinumab or Stelara):ti,ab,kw	163
#35	(vedolizumab or Entyvio):ti,ab,kw	38

#36	(canakinumab or acz885):ti,ab,kw	73
#37	{or #20-#36}	5328
#38	#19 and #37	2498
#39	#38 Publication Year from 2015	171

Embase (Embase.com) 13 Jan 2016

#1	'rheumatoid arthritis'/de	151371
#2	'juvenile rheumatoid arthritis'/exp	16157
#3	'ankylosing spondylitis'/exp	22216
#4	'psoriatic arthritis'/exp	13190
#5	'crohn disease'/exp	66507
#6	ulcerative colitis'/exp	54915
#7	'psoriasis vulgaris'/exp	6196
#8	(ankylosing NEXT/1 (spondylitis OR arthritis)):ab,ti	16016
#9	(juvenile NEAR/2 arthritis):ab,ti	11625
#10	psoriasis:ab,ti	42789
#11	((rheumatoid OR psoriatic) NEXT/1 arthr*):ab,ti	124234
#12	(crohn* NEXT/1 disease):ab,ti	4162
#13	ulcerative colitis':ab,ti	42810
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	330261
#15	'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	3171959
#16	'safety'/de	209397
#17	outcome*:ti OR efficacy:ti OR effectiveness:ti OR adverse:ti OR safety:ti OR withdrawal*:ti OR harm:ti OR harms:ti OR mortality:ti OR morbidity:ti OR function*:ti OR toxicity:ti OR complications:ti OR 'risk of':ti	1745717
#18	(drug NEXT/1 (discontinuation OR survival)):ti	218
#19	#15 OR #16 OR #17 OR #18	4435227
#20	#14 AND #19	85166
#21	'abatacept'/exp OR abatacept:ti OR orencia:ti	5196
#22	'adalimumab'/exp OR adalimumab:ti OR humira:ti	19019
#23	'alefacept'/exp OR alefacept:ti OR amevive:ti	1630
#24	'recombinant interleukin 1 receptor blocking agent'/exp OR anakinra:ti OR kineret:ti	5402
#25	'certolizumab pegol'/exp OR certolizumab:ti OR cimzia:ti	3535
#26	'etanercept'/exp OR 'tnfr-fc fusion protein':ti OR etanercept:ti OR enbrel:ti	22048
#27	'golimumab'/exp OR golimumab:ti OR simponi:ti	3006
#28	'infliximab'/exp OR infliximab:ti OR remicade:ti	34076
#29	'natalizumab'/exp OR natalizumab:ti OR tysabri:ti	6527
#30	'rituximab'/exp OR rituximab:ti OR rituxan:ti	49293
#31	'secukinumab'/exp OR secukinumab:ti OR cosentyx:ti	668
#32	'tocilizumab'/exp OR tocilizumab:ti OR actemra:ti OR roactemra:ti	5307
#33	'tofacitinib'/exp OR tofacitinib:ti OR 'janus kinase inhibitor':ti OR xeljanz:ti	1433
#34	'ustekinumab'/exp OR ustekinumab:ti OR stelara:ti	2526
#35	'vedolizumab'/exp OR vedolizumab:ti OR entyvio:ti	736
#36	'canakinumab'/exp OR canakinumab:ti OR acz885:ti	1359
#37	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	105541

	OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	
#38	#20 AND #37	24533
#39	'systematic review'/exp OR 'meta analysis'/exp	165269
#40	'controlled clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp OR 'placebo'/exp	788055
#41	'controlled study'/exp OR 'cohort analysis'/exp OR 'epidemiology'/de 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 'multicenter study'/exp OR 'prospective study'/exp	7112488
#42	systematic review':ti OR 'meta analysis':ti OR cohort:ti OR random*:ti OR observational:ti OR 'multi center':ti OR 'multi centre':ti OR multicenter:ti OR multicentre:ti	388838
#43	#39 OR #40 OR #41 OR #42	7411361
#44	#38 AND #43	12864
#45	'animal'/exp NOT 'human'/exp	4582704
#46	#44 NOT #45	12815
#47	#46 NOT [medline]/lim	5269
#48	#47 AND [1-10-2015]/sd NOT [13-1-2016]/sd	264

CRD Database 13 Jan 2016

1	(abatacept OR Orencia) IN HTA IN 2015	0
2	(adalimumab OR Humira) IN HTA IN 2015	1
3	(alefacept OR Amevive) IN HTA IN 2015	0
4	("Interleukin 1 Receptor Antagonist Protein" OR Anakinra OR Kineret) IN HTA IN 2015	0
5	(apremilast OR Otezla) IN HTA IN 2015	1
6	(certolizumab OR Cimzia) IN HTA IN 2015	0
7	("TNFR-Fc fusion protein" OR etanercept OR Enbrel) IN HTA IN 2015	0
8	(golimumab OR simponi) IN HTA IN 2015	0
9	(infliximab OR Remicade) IN HTA IN 2015	3
10	(natalizumab OR Tysabri) IN HTA IN 2015	0
11	(rituximab OR Rituxan) IN HTA IN 2015	2
12	(secukinumab OR Cosentyx) IN HTA IN 2015	2
13	(tocilizumab OR actemra OR RoActemra) IN HTA IN 2015	0
14	(tofacitinib OR "janus kinase inhibitor" OR Xeljanz) IN HTA IN 2015	0
15	(ustekinumab OR Stelara) IN HTA IN 2015	0
16	(vedolizumab OR Entyvio) IN HTA IN 2015	0
17	(canakinumab OR acz885) IN HTA IN 2015	0
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	9

CINAHL (Ebsco) 13 Jan 2016

S1	MH "Arthritis, Rheumatoid+"	13,476
S2	MH "Crohn Disease"	2,305
S3	MH "Colitis, Ulcerative"	1,564
S4	(MH "Arthritis, Juvenile Rheumatoid")	1,53
S5	(MH "Arthritis, Psoriatic")	776
S6	(MH "Spondylitis, Ankylosing")	1,166
S7	TI (ankylosing N1 (spondylitis OR arthritis)) OR AB (ankylosing N1 (spondylitis OR arthritis))	1,123

S8	TI ((rheumatoid OR psoriatic OR juvenile) N1 arthr*) OR AB ((rheumatoid OR psoriatic OR juvenile) N1 arthr*)	10,123
S9	TI psoriasis OR AB psoriasis	1,514
S10	TI crohn* N1 disease OR AB crohn* N1 disease	1,918
S11	TI "ulcerative colitis" OR AB "ulcerative colitis"	1,289
S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	20,776
S13	TI ((abatacept OR Orencia)) OR AB ((abatacept OR Orencia)) OR SU ((abatacept OR Orencia))	167
S14	TI ((adalimumab OR Humira)) OR AB ((adalimumab OR Humira)) OR SU ((adalimumab OR Humira))	452
S15	TI ((alefacept OR Amevive)) OR AB ((alefacept OR Amevive)) OR SU ((alefacept OR Amevive))	17
S16	TI (("Interleukin 1 Receptor Antagonist Protein" OR Anakinra OR Kineret)) OR AB (("Interleukin 1 Receptor Antagonist Protein" OR Anakinra OR Kineret)) OR SU (("Interleukin 1 Receptor Antagonist Protein" OR Anakinra OR Kineret))	150
S17	TI ((apremilast OR Otezla)) OR AB ((apremilast OR Otezla)) OR SU ((apremilast OR Otezla))	19
S18	TI ((certolizumab OR Cimzia)) OR AB ((certolizumab OR Cimzia)) OR SU ((certolizumab OR Cimzia))	76
S19	TI (("TNFR-Fc fusion protein" OR etanercept OR Enbrel)) OR AB (("TNFR-Fc fusion protein" OR etanercept OR Enbrel)) OR SU (("TNFR-Fc fusion protein" OR etanercept OR Enbrel))	943
S20	TI ((golimumab OR simponi)) OR AB ((golimumab OR simponi)) OR SU ((golimumab OR simponi))	89
S21	TI ((infliximab OR Remicade)) OR AB ((infliximab OR Remicade)) OR SU ((infliximab OR Remicade))	1,23
S22	TI ((natalizumab OR Tysabri)) OR AB ((natalizumab OR Tysabri)) OR SU ((natalizumab OR Tysabri))	288
S23	TI ((rituximab OR Rituxan)) OR AB ((rituximab OR Rituxan)) OR SU ((rituximab OR Rituxan))	1,783
S24	TI ((secukinumab OR Cosentyx)) OR AB ((secukinumab OR Cosentyx)) OR SU ((secukinumab OR Cosentyx))	21
S25	TI ((tocilizumab OR actemra OR RoActemra)) OR AB ((tocilizumab OR actemra OR RoActemra)) OR SU ((tocilizumab OR actemra OR RoActemra))	178
S26	TI ((tofacitinib OR "janus kinase inhibitor" OR Xeljanz)) OR AB ((tofacitinib OR "janus kinase inhibitor" OR Xeljanz)) OR SU ((tofacitinib OR "janus kinase inhibitor" OR Xeljanz))	52
S27	TI ((ustekinumab OR Stelara)) OR AB ((ustekinumab OR Stelara)) OR SU ((ustekinumab OR Stelara))	52
S28	TI ((vedolizumab OR Entyvio)) OR AB ((vedolizumab OR Entyvio)) OR SU ((vedolizumab OR Entyvio))	17
S29	TI ((canakinumab OR acz885)) OR AB ((canakinumab OR acz885)) OR SU ((canakinumab OR acz885))	32
S30	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	4,567
S31	S12 AND S30	2,117
S32	S31 Limiters - Clinical Queries: Therapy - High Sensitivity	1,026
S33	S31 Limiters - Special Interest: Evidence-Based Practice	162

S34	S31 AND ((MH "Systematic Review") OR (MH "Randomized Controlled Trials") OR (MH "Clinical Trials") OR (MH "Nonexperimental Studies") OR (MH "Prospective Studies") OR (MH "Double-Blind Studies") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Multicenter Studies") OR (MH "Meta Analysis"))	746
S35	TI ("systematic review" OR "meta analysis" OR metaanalysis OR random* OR observational OR cohort OR multi-center OR multicenter OR multi-centre OR multicentre) AND S31	210
S36	(TX (random* OR observational OR cohort* OR multi-center OR multicenter OR multi-centre OR multicentre OR control*) N4 (trial OR study)) AND S31	521
S37	S32 OR S33 OR S34 OR S35 OR S36	1,121
S38	S37 Limiters - Published Date: 20151001-	16
S39	S37 Limiters - Published Date: 20150601-	36

International Pharmaceutical Abstracts (Ebsco)

S1	TX (juvenile OR rheumatoid OR psoriatic) N1 arthritis	5,02
S2	TX ankylosing W1 (spondylitis OR arthritis)	411
S3	Psoriasis	2,775
S4	TX crohn* W0 disease	842
S5	TX "ulcerative colitis"	678
S6	S1 OR S2 OR S3 OR S4 OR S5	8,853
S7	TX (abatacept OR Orencia)	234
S8	TX (adalimumab OR Humira)	899
S9	TX (alefacept OR Amevive)	148
S10	TX ("Interleukin 1 Receptor Antagonist Protein" OR Anakinra OR Kineret)	256
S11	TX (apremilast OR Otezla)	20
S12	TX (certolizumab OR Cimzia)	105
S13	TX ("TNFR-Fc fusion protein" OR etanercept OR Enbrel)	1,435
S14	TX (golimumab OR simponi)	115
S15	TX (infliximab OR Remicade)	1,615
S16	TX (natalizumab OR Tysabri)	159
S17	TX (rituximab OR Rituxan)	1,456
S18	TX (secukinumab OR Cosentyx)	13
S19	TX (tocilizumab OR actemra OR RoActemra)	206
S20	TX (ustekinumab OR Stelara)	121
S21	TX (vedolizumab OR Entyvio)	10
S22	TX (tofacitinib OR "janus kinase inhibitor" OR Xeljanz)	40
S23	TX (canakinumab OR acz885)	31
S24	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	4,811
S25	S6 AND S24	2,576
S26	S25	1
S27	S25 Limiters - Published Date: 20150601-	28

Appendix C Excluded studies

During Update 5, 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
Abasolo L, Leon L, Rodriguez-Rodriguez L, et al. Safety of disease-modifying antirheumatic drugs and biologic agents for rheumatoid arthritis patients in real-life conditions. Seminars in Arthritis & Rheumatism. 2015;44(5):506-513	3
Accortt NA, Bonafede MM, Collier DH, et al. Risk of Subsequent Infection among Patients Receiving Tumor Necrosis Factor Inhibitors and Other Disease-Modifying Antirheumatic Drugs. Arthritis and Rheumatology. 2016;68(1):67-76	2
Alawneh KM, Ayesh MH, Khassawneh BY, et al. Anti-TNF therapy in Jordan: A focus on severe infections and tuberculosis. Biologics: Targets and Therapy. 2014;8:193-198.	6
Albert D A. Are all biologics the same? Optimal treatment strategies for patients with early rheumatoid arthritis: Systematic review and indirect pairwise meta-analysis. Journal of Clinical Rheumatology. 2015;21(8):398-404	6
Bardazzi F, Odorici G, Virdi A, et al. Autoantibodies in psoriatic patients treated with anti-TNF-alpha therapy. Journal der Deutschen Dermatologischen Gesellschaft. 2014;12(5):401-406	2
Berglund A, Ljungberg A, Dorange A. Higher Drug Survival Rates in Patients with Psoriasis Utilizing Etanercept Compared to Adalimumab - a Nationwide Population-Based Cohort Study in Sweden. Value Health. 2015;18(7):A416	5
Bizzi E, Petrella L, Integlia D, et al. A Network Metanalysis Comparing The Efficacy of Biologics for The Treatment of Early Rheumatoid Arthritis. Value Health. 2015;18(7):A636	5
Bounthavong M, Madkour N, Kazerooni R. Retrospective cohort study of anti-tumor necrosis factor agent use in a Veteran Population. PeerJ. 2014;2014(1):e385	6
Broe J, Solem EJ, Nielsen S, et al. Different safety profiles of biologic agents in children with juvenile idiopathic arthritis (JIA). Annals of the Rheumatic Diseases. 2014;73(Suplement 2):578-578	5
Cameron FL, Wilson ML, Basheer N, et al. Anti-TNF therapy for paediatric IBD: the Scottish national experience. Archives of disease in childhood. 2015;100(4):399-405	6
Capkin E, Karkucak M, Cosar AM, et al. Treatment of ankylosing spondylitis with TNF inhibitors does not have adverse effect on results of liver function tests: A longitudinal study. International Journal of Rheumatic Diseases. 2015;18(5):548-552	6
Carrillo MJ, Beltran R, Maldonado B, et al. Side effects in inflammatory bowel disease patients treated with biological therapy: Our experience. Journal of Crohn's and Colitis. 2013;7(Supplement 1):S157	5
Castillo Muñoz MA, Marín Gil R, Ubago Pérez R, e al. Biological therapies in the treatment of ankylosing spondylitis: a comparison of efficacy and safety between different biological inhibitors of tumour necrosis factor-alpha. Andalusian Agency for Health Technology Assessment (AETSA). 2013; ISBN 978-84-15600-28-2	1
Chen HH, Chen YM, Lai KL, et al. Factors affecting discontinuation of adalimumab and etanercept therapy in anti-TNF-naive patients with ankylosing spondylitis: Nationwide population-based cohort study. Modern Rheumatology. 2015;25(6):903-907	6
Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, et al. The Risk of Cancer in Patients With Psoriasis: A Population-Based Cohort Study in the Health Improvement Network. JAMA Dermatology. 2016;152(3):282-90	2
Cho SK, Sakai R, Nanki T, et al. A comparison of incidence and risk factors for serious adverse events in rheumatoid arthritis patients with etanercept or adalimumab in Korea and Japan. Modern Rheumatology. 2014;24(4): 572-579	2

Christensen R, Tarp S, Furst DE, et al. Efficacy and safety of infliximab or adalimumab, versus abatacept, in patients with rheumatoid arthritis: ATTEST-AMPLE network randomized trial. International Journal of Clinical Rheumatology. 2013;8(6)647-655	5
Codreanu C, Damjanov N. Safety of biologics in rheumatoid arthritis: Data from randomized controlled trials and registries. Biologics: Targets and Therapy. 2015;9:1-6	6
Codreanu C, Mogosan C, Ionescu R, et al. Biologic therapy in rheumatoid arthritis: Results from the Romanian registry of rheumatic diseases one year after initiation. Farmacia. 2014;62(6):1089-1096	6
Colombel JF, Sands B, Hanauer S, et al. Long-term Safety of Vedolizumab for the Treatment of Ulcerative Colitis or Crohn´s Disease. The American Journal of Gastroenterology. 2013;108(S1):1674	5
Curtis JR, Perez-Gutthann S, Suissa S, et al. Tocilizumab in rheumatoid arthritis: A case study of safety evaluations of a large postmarketing data set from multiple data sources. Seminars in Arthritis and Rheumatism. 2015;44(4):381-388.	6
De Pablo P, Maggs FM, Carruthers D, et al. Incidence of diabetes and effect of etanercept and adalimumab on HbA1c over 1 year: Data from a randomised trial in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2013;65:S1009	6
den Broeder AA, van Herwaarden N, van der Maas A, et al. Dose REduction strategy of subcutaneous TNF inhibitors in rheumatoid arthritis: design of a pragmatic randomised non inferiority trial, the DRESS study. BMC Musculoskelet Disord. 2013;14:299	5
Desai RJ, Thaler KJ, Mahlknecht P, et al. Comparative risk of harm associated with the use of targeted immunomodulators- A systematic review. Arthritis Care & Research (Hoboken). Dec. 2015;[E-Pub, ahead of print]; DOI: 10.1002/acr.22815	6
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Appendix D Evidence profiles of comparisons of targeted immune modulators

Table D-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			
Abatacept compared with Rituximab							
Outcome: DAS28 at 12 months							
1/144	Open-label RCT	Poor	NA	Direct	Similar improvements in DAS28 scores (-3.8 vs. -.3.9)	none	Insufficient
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 D-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 D-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			
Outcome: Harms							
				No evidence			

Table D-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 D-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 D-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 than Infliximab (47% vs. 16%; *P*=0.003)	None	Insufficient
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: Clincial improvement							
1 / 20	RCT	Poor	NA	Direct	Endoscopic, clinical and histological recurrence similar between groups	None	Insufficient

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

Table D-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			
Outcome: Harms							
				No evidence			

Table D-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			
Outcome: Harms							
				No evidence			

Table D-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			
Outcome: Harms							
				No evidence			

Table D-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: PASI 75							
1 / 903	RCT	Fair	NA	Direct	RR 1.26 (95% CI, 1.13 to 1.40) favoring Ustekinumab	None	Low
Outcome: Quality of life							
				No evidence			
Etanercept compared with secukinumab							
Outcome:PASI 75							
1/ 1306	RCT	Good	NA	Direct	Response: 77.1% (secukinumab 300mg) vs. 67.6% (secukinumab 150mg) vs. 44.0% (etanercept 50mg)	None	Low
Outcome: Quality of life							
				No evidence			
Etanercept compared with tofacitinib							
Outcome:PASI 75							
1 / 1106	RCT	Good	NA	Direct	Response: 39.5% (tofacitinib 5mg) vs. 63.6% (tofacitinib 10mg) vs. 58.8% (etanercept 50mg)	None	Low
Outcome: Quality of life							
				No evidence			
Secukinumab compared with ustekinumab							
Outcome:PASI 75							
1 / 676	RCT	Good	NA	Direct	Response: 93.1% (secukinumab) vs. 82.7% (ustekinumab)	None	Low
Outcome: Quality of life							
				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 D-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			
Outcome: Harms							
				No evidence			

Table D-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						
12 / >4000	RCTs	Fair	Consistent	Direct	**All comparisons** Overall, one trial 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 ruled out.	Low
Withdrawal / discontinuation due to adverse events						
13 / ~6 800	RCTs	Fair	Consistent	Direct	**Adalimumab vs. Infliximab:** Infliximab consistently had a higher risk of discontinuation than Adalimumab	Moderate
					Etanercept vs. Infliximab: Infliximab consistently had a higher risk of discontinuation than Etanercept	Moderate
7 / ~ 22 000	Observational studies	Fair	Consistent	Direct	**All other comparisons:** Only one study available	Insufficient
Serious adverse events						
11 / > 4000	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.	Insufficient

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall strength of the evidence
Injection site / infusion reactions						
6 / 2178	RCTs	Fair	Consistent	Direct	**Abatacept vs. Adalimumab:** Lower risk for Abatacept, RR 0.41, 95% CI, 0.22 to 0.79	Low
					Abatacept vs. Infliximab: Lower risk for Abatacept, RR 0.28 95% CI, 0.13 to 0.60	Low
					Adalimumab vs. Etanercept: Lower risk for Adalimumab; however no difference cannot be ruled out, RR 0.47 95% CI, 0.23 to 0.96	Low
					Etanercept vs. Ustekinumab: Lower risk for Ustekinumab, RR 6.26 95% CI, 4.00 to 9.81	Low
Mortality						
3 / 34 579	Observational studies	Fair	Consistent	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No differences in hazard ratios for death.	Low
Serious Infections						
5 / >50 000	Observational studies	Fair	Consistent	Direct	Abatacept, Adalimumab, Etanercept, and Rituximab all cause less serious infections than Infliximab.	Moderate
Tuberculosis						
5 / >60 000	Observational studies	Fair	Consistent	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** increased risk of tuberculosis with Adalimumab and Infliximab compared with Etanercept	Low
					No difference in risks among Abatacept, Adalimumab, Anakinra, Certolizumab pegol, Etanercept, Golimumab, Rituximab, and Tocilizumab	Insufficient
Opportunistic infections						
1 / > 40 000	Observational study	Fair	N/A	Direct	**Adalimumab vs. Etanercept vs. Infliximab:** No significant difference in odds ratio	Low

Number of studies/ patients	Design	Quality	Consistency	Directness	Magnitude of effect	Overall strength of the evidence
2 / > 45 000	Observational studies	Fair	Inconsistent	Direct	Adalimumab vs. Etanercept vs. Infliximab: No differences in hazard ratios for herpes zoster **Abatacept vs. Adalimumab:** Similar risks **Etanercept vs. Tofacitinib:** Similar risks	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						
6 / >29 000	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						
2 / > 5000	Observational study	Fair	N/A	Direct	Comparisons of Adalimumab, Etanercept, and Infliximab showed no significant differences	Insufficient
Combination strategies						
3 / 412	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; N/A, not applicable

Table D-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							
Outcome: Harms							
No evidence							

Table D-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; NA, not applicable

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

Abbreviation	Name	Condition(s) used in	General description	Range and direction
ACR 20/50/70	American College of Rheumatology, numbers refer to percentage improvement	RA, JIA, PsA	Improvement is defined by at least 20% improvement in TJC and in SJC, and at least 20% improvement in 3 of the 5 measures: ESR or CRP PhGA of disease activity PtGA of disease activity Patient assessment of pain Disability	0-100, higher is better
ACR Pedi	American College of Rheumatology Pediatric scale	JIA	See above – adapted for children	0-100, higher is better
ASAS 20/50/70	Assessment in Ankylosing Spondylitis, numbers refer to percentage improvement	AS	Improvement of 20% or more and absolute improvement of 10 units (on a scale of 0-100) in 3 of the following 4 domains: Patient global assessment - pain – function – inflammation Absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of 20% and net worsening of 10 units (on a scale of 0-100)	0-100, higher is better
BASDAI	Bath AS Disease Activity Index	AS	Six 10 cm horizontal visual analog scales to measure severity of fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative)	0-10, lower is better
BASFI	Ankylosing Spondylitis Functional Index	AS	Defining and monitoring functional ability in patients with AS	0-10, higher is better
BASMI	Bath Ankylosing Spondylitis Metrology Index	AS	Measures axial status using: cervical rotation, tragus to wall distance, lateral flexion, modified Schober's, and intermalleolar distance.	Lower is better
CAHP	Childhood Arthritis Health Profile	JIA	Three modules – the CHQ, JIA specific scales and patients characteristics	
CDAI	Crohn's Disease Activity Index	CD	Eight clinical factors, each summed after adjustment with a weighting factor. These include, Number of liquid or soft stools each day for 7 days x 2, Abdominal pain (graded from 0-3 on severity) each day for 7 days x 5, General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days x 7, Presence of complications* x 20, Taking 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 death.	For DI, 0-3, lower is better

Abbreviation	Name	Condition(s) used in	General description	Range and direction
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; CHQ, Childhood Health Questionnaire; DAS, Disease Activity Score; DI, disease index;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 F Boxed warnings of included drugs

Active ingredients (trade names)	Boxed warnings and precautions
Apremilast (Otezla®)	None listed
Abatacept (Orencia®)	None listed
Adalimumab (Humira®)	WARNING: SERIOUS INFECTIONS AND MALIGNANCY **SERIOUS INFECTIONS** Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA. Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • with a history of an opportunistic infection; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or with underlying conditions that may predispose them to infection. ***Tuberculosis****:* Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille CalmetteGuerin (BCG). Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating antituberculosis therapy is appropriate for an individual patient. Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. ***Monitoring:*** Closely monitor patients for the development of signs and symptoms of

infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA. Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections: If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

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Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults: In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 37 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), nkylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps) and hidradenitis suppurativa (HS), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.45, 1.01) per 100 patient-years among 7723 HUMIRA-treated patients versus a rate of 0.8 (0.48, 1.31) per 100 patient-years among 4598 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 50 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps and HS, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

- **Non-Melanoma Skin Cancer:** During the controlled portions of 37 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps and HS, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.11) per 100 patient-years among HUMIRA-treated patients and 0.3 (0.11, 0.63) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.
- **Lymphoma and Leukemia:** In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 37 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps and HS, 2 lymphomas occurred among 7723 HUMIRA-treated patients versus 1 among 4598 control-treated patients. In 50 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps and HS with a median duration of approximately 0.7 years, including 24,135 patients and over 39,000 patientyears of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient years. This is approximately 3-fold

	higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. ***Malignancies in Pediatric Patients and Young Adults:*** Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources including registries and spontaneous postmarketing reports. Postmarketing 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 of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) 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. The potential risk with the combination of azathioprine or 6- mercaptopurine and HUMIRA should be carefully considered.
Alefacept (Amevive®)	None listed
Anakinra (Kineret®)	None listed
Canakinumab (Ilaris®)	None listed
	WARNING: SERIOUS INFECTIONS AND MALIGNANCIES **SERIOUS INFECTIONS** Patients treated with CIMZIA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.
Certolizumab pegol (Cimzia®)	Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g. corticosteroids or methotrexate) may be at a greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

• with chronic or recurrent infection
• who have been exposed to tuberculosis
• with a history of an opportunistic infection
• who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis
• with underlying conditions that may predispose them to infection

Tuberculosis: Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating CIMZIA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating CIMZIA, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of CIMZIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision of whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during CIMZIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.
Monitoring: Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with CIMZIA. CIMZIA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with CIMZIA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.
Invasive Fungal Infections: For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and risks of antifungal therapy.

MALIGNANCIES
In the controlled portions of clinical studies of some TNF blockers, more cases of malignancies have been observed among patients receiving TNF blockers compared to control patients. During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.5 (0.4, 0.7) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.1, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.
Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with

	immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. CIMZIA is not indicated for use in pediatric patients. In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin's lymphoma among 1,319 placebo-treated patients. In the CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn's disease that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy. The potential role of TNF blocker therapy in the development of malignancies in adults is not known. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP) 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. The potential risk of using a TNF blocker in combination with azathioprine or 6 MP should be carefully considered. Cases of acute and chronic leukemia have been reported in association with post-marketing TNFblocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.
Etanercept (Enbrel®)	WARNING: SERIOUS INFECTIONS AND MALIGNANCIES **SERIOUS INFECTIONS** Patients treated with Enbrel are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. Treatment with Enbrel should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients: • With chronic or recurrent infection; • Who have been exposed to tuberculosis; • With a history of an opportunistic infection; • Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or

• With underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Enbrel. Enbrel should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with Enbrel should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Tuberculosis: Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving Enbrel, including patients who have previously received treatment for latent or active tuberculosis. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with Enbrel than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including Enbrel. Tuberculosis has developed in patients who tested negative for latent tuberculosis prior to initiation of therapy. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating Enbrel and periodically during therapy. Tests for latent tuberculosis infection may be falsely negative while on therapy with Enbrel. Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating Enbrel, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of Enbrel in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during Enbrel treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Invasive Fungal Infections: Cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including Enbrel. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric anti-fungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric anti-fungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of anti-fungal therapy. In 38 Enbrel clinical trials and 4 cohort studies in all approved indications representing 27,169 patient-years of exposure (17,696 patients) from the United States and Canada, no histoplasmosis infections were reported among patients treated with Enbrel.

MALIGNANCIES

Lymphomas: In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared to control patients. During the controlled portions of Enbrel trials in adult patients with RA, AS, and PsA, 2 lymphomas were observed among 3306 Enbrel-treated patients versus 0 among 1521 control patients (duration of controlled treatment ranged from 3 to 36 months). Among 6543 adult rheumatology (RA, PsA, AS) patients treated with Enbrel in controlled and uncontrolled portions of clinical trials, representing approximately 12,845 patient-years of therapy, the observed rate of lymphoma was 0.10 cases per 100 patient-years. This was 3-fold higher than the rate of lymphoma expected in the general U.S. population based on the Surveillance, Epidemiology, and End Results (SEER) Database. An increased rate of

	lymphoma up to several-fold has been reported in the RA patient population, and may be further increased in patients with more severe disease activity. Among 4410 adult PsO patients treated with Enbrel in clinical trials up to 36 months, representing approximately 4278 patient-years of therapy, the observed rate of lymphoma was 0.05 cases per 100 patient-years, which is comparable to the rate in the general population. No cases were observed in Enbrel- or placebo-treated patients during the controlled portions of these trials. **Leukemia**: Cases of acute and chronic leukemia have been reported in association with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia. During the controlled portions of Enbrel trials, 2 cases of leukemia were observed among 5445 (0.06 cases per 100 patient-years) Enbrel-treated patients versus 0 among 2890 (0%) control patients (duration of controlled treatment ranged from 3 to 48 months). Among 15,401 patients treated with Enbrel in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukemia was 0.03 cases per 100 patient-years. **Other Malignancies:** Information is available from 10,953 adult patients with 17,123 patient-years and 696 pediatric patients with 1282 patient-years of experience across 45 Enbrel clinical studies. For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposureadjusted rates between the Enbrel and control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general U.S. population based on the SEER database and suggests no increase in rates over time. Whether treatment with Enbrel might influence the development and course of malignancies in adults is unknown. **Melanoma and Non-melanoma skin cancer (NMSC):** Melanoma and non-melanoma skin cancer has been reported in patients treated with TNF antagonists including etanercept. Among 15,401 patients treated with Enbrel in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years. Among 3306 adult rheumatology (RA, PsA, AS) patients treated with Enbrel in controlled clinical trials representing approximately 2669 patient-years of therapy, the observed rate of NMSC was 0.41 cases per 100 patient-years vs 0.37 cases per 100 patient-years among 1521 control-treated patients representing 1077 patient-years. Among 1245 adult psoriasis patients treated with Enbrel in controlled clinical trials, representing approximately 283 patient-years of therapy, the observed rate of NMSC was 3.54 cases per 100 patient-years vs 1.28 cases per 100 patient-years among 720 control-treated patients representing 156 patient-years. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examinations should be considered for all patients at increased risk for skin cancer. **Pediatric Patients**: Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including Enbrel. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. In clinical trials of 1140 pediatric patients representing 1927.2 patient-years of therapy, no malignancies, including lymphoma or NMSC, have been reported. **Postmarketing Use**: In global postmarketing adult and pediatric use, lymphoma and other malignancies have been reported.
Golimumab, SC (Simponi®)	WARNING: SERIOUS INFECTIONS AND MALIGNANCIES **SERIOUS INFECTIONS** Patients treated with SIMPONI are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended. Treatment with SIMPONI should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating SIMPONI in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Monitoring: Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI. Discontinue SIMPONI if a patient develops a serious infection, an opportunistic infection, or sepsis. For a patient who develops a new infection during treatment with SIMPONI, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor them.

Serious Infection in Clinical Trials: In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI-treated patients and 1.3% of control-treated patients. In the controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.7 (95% CI: 3.8, 8.2) for the SIMPONI group and 4.2 (95% CI: 1.8, 8.2) for the placebo group. In the controlled Phase 2/3 trial through Week 6 of SIMPONI induction in UC, the incidence of serious infections in SIMPONI 200/100 mg-treated patients was similar to the incidence of serious infections in placebo-treated patients. Through Week 60, the incidence of serious infections was similar in patients who received SIMPONI induction and 100 mg during maintenance compared with patients who received SIMPONI induction and placebo during the maintenance portion of the UC trial. Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection.

Tuberculosis: Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMPONI and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMPONI, assess if treatment for latent tuberculosis is needed; an induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Consider anti-tuberculosis therapy prior to initiation of SIMPONI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Cases of active tuberculosis have occurred in patients treated with SIMPONI during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection. Consider tuberculosis in the differential diagnosis in patients who develop a new infection during SIMPONI treatment, especially in

patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extrapulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. In the controlled Phase 2/3 trial of SIMPONI induction through Week 6 in UC, no cases of TB were observed in SIMPONI 200/100 mg-treated patients or in placebo-treated patients. Through Week 60, the incidence per 100 patient-years of TB in patients who received SIMPONI induction and 100 mg during the maintenance portion of the UC trial was 0.52 (95% CI: 0.11, 1.53). One case of TB was observed in the placebo maintenance group in a patient who received SIMPONI intravenous (IV) induction.

Invasive Fungal Infections: If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Consider appropriate empiric antifungal therapy, and take into account both the risk for severe fungal infection and the risks of antifungal therapy while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Hepatitis B Virus Reactivation: The use of TNF blockers including SIMPONI has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants. All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF blockers, including SIMPONI, to patients who are carriers of HBV. Adequate data are not available on whether antiviral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF blockers. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blockers in this situation and monitor patients closely.

MALIGNANCIES

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which SIMPONI is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. The risks and benefits of TNF-blocker treatment, including SIMPONI, should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated nonmelanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy.

In the controlled portions of clinical trials of TNF blockers, including SIMPONI, more cases of

lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In the controlled and uncontrolled portions of these clinical trials in 2347 SIMPONI-treated patients with a median follow-up of 1.4 years, the incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).1 Through Week 60 of the UC trials, there were no cases of lymphoma with SIMPONI. Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with TNF-blocker use, including SIMPONI, in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.
Rare postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of the reported TNF blocker associated cases have occurred in patients with Crohn's disease or ulcerative colitis. The majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. The potential risk with the combination of AZA or 6-MP and SIMPONI should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF blockers cannot be excluded. During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was not elevated in the combined SIMPONI group compared with the placebo group. In the controlled and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in SIMPONI-treated patients was similar to that expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).1 In the 6-week placebo-controlled portions of the SIMPONI Phase 2/3 clinical trials in UC, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar between the SIMPONI and the placebo group. Through Week 60, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar to the general U.S. population according to the SEER database (adjusted for age, gender, and race).1 Short follow-up periods, such as those of one year or less in the studies above, may not adequately reflect the true incidence of malignancies.
It is not known if SIMPONI treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with SIMPONI, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued. Melanoma has been reported in patients treated with TNF-blocking agents, including SIMPONI. Merkel cell carcinoma has been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. In controlled trials of other TNF blockers in patients at higher risk for malignancies (e.g., patients with chronic obstructive pulmonary disease [COPD], patients with Wegener’s granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory 1-year clinical trial evaluating the use of 50 mg, 100 mg, and 200 mg of SIMPONI in 309 patients with severe persistent asthma, 6 patients developed malignancies other than NMSC in the SIMPONI groups compared to none in the control group. Three of the 6 patients were in the 200-mg

	SIMPONI group.
Golimumab, IV (Simponi Aria®)	WARNING: SERIOUS INFECTIONS AND MALIGNANCIES SERIOUS INFECTIONS Patients treated with SIMPONI ARIA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI ARIA and these biologic products is not recommended. Treatment with SIMPONI ARIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating SIMPONI ARIA in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • with a history of an opportunistic infection; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or • with underlying conditions that may predispose them to infection. **Monitoring**: Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI ARIA. Discontinue SIMPONI ARIA if a patient develops a serious infection, an opportunistic infection, or sepsis. For patients who develop a new infection during treatment with SIMPONI ARIA, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient and initiate appropriate antimicrobial therapy and closely monitor them. **Tuberculosis**: Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMPONI ARIA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMPONI ARIA, assess if treatment for latent tuberculosis is needed; An induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille CalmetteGuerin (BCG). Consider anti-tuberculosis therapy prior to initiation of SIMPONI ARIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Cases of active tuberculosis have occurred in patients treated with the subcutaneous formulation of golimumab during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection. Consider tuberculosis in the differential diagnosis in patients who develop a new infection during SIMPONI ARIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. **Invasive Fungal Infections**: If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Consider appropriate empiric antifungal therapy and take into account both the risk for severe fungal infection and the risks of antifungal therapy while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative

in some patients with active infection. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Hepatitis B Virus Reactivation: The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants. All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI ARIA, to patients who are carriers of HBV. Adequate data are not available on whether antiviral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely.

MALIGNANCIES

Malignancies in Pediatric Patients: Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which SIMPONI ARIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. Use of SIMPONI ARIA in patients under 18 years of age has not been established.

Malignancies in Adult Patients: The risks and benefits of TNF-blocker treatment including SIMPONI ARIA should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy. In the controlled portions of clinical trials of TNF-blockers including the subcutaneous formulation of golimumab more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with TNF-blocker use, including SIMPONI ARIA, in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Rare postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of the reported TNF-blocker associated cases have occurred in patients with Crohn's disease or ulcerative colitis. The majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF-blocker at or prior to diagnosis. A risk for the development for hepatosplenic T-cell

	lymphoma in patients treated with TNF-blockers cannot be excluded. Melanoma has been reported in patients treated with TNF-blocking agents, including SIMPONI ARIA. Merkel cell carcinoma has been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with chronic obstructive pulmonary disease [COPD], patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory clinical trial evaluating the use of the subcutaneous formulation of golimumab in patients with severe persistent asthma, more patients treated with golimumab reported malignancies compared with control patients. The significance of this finding is unknown. During the controlled portion of the Phase 3 trial in RA for SIMPONI ARIA, the incidence of malignancies other than lymphoma and NMSC per 100-patient-years of follow-up was 0.56 (95% CI: 0.01, 3.11) in the SIMPONI ARIA group compared with an incidence of 0 (95% CI: 0.00, 3.79) in the placebo group.
Infliximab (Remicade®)	WARNING: SERIOUS INFECTIONS AND MALIGNANCIES SERIOUS INFECTIONS Patients treated with REMICADE are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • with a history of an opportunistic infection; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or • with underlying conditions that may predispose them to infection. **Tuberculosis:** Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with REMICADE during treatment for latent tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating REMICADE and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during REMICADE treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. ***Monitoring:*** Patients should be closely monitored for the development of signs and

symptoms of infection during and after treatment with REMICADE, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with REMICADE. REMICADE should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with REMICADE should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections: For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

MALIGNANCIES

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and nonHodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

- **Lymphomas:** In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.
- **Hepatosplenic T-cell lymphoma (HSTCL)**: Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF-blockers or TNF-

	blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use REMICADE alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data. • **Skin cancer:** Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including REMICADE [see Adverse Reactions (6.2)]. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. • **Other Malignancies**: In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD. Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy.The potential role of TNF-blocking therapy in the development of malignancies is not known Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE.
Natalizumab (Tysabri®)	WARNING: PROGRESSIV MUTIFOCAL LEUKOENCEPHAOPATHY Progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability, has occurred in patients who have received TYSABRI. Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified: • Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 6 years of TYSABRI treatment. • Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil). • The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.

Table 1: Estimated United States Incidence of PML Stratified by Risk Factor

Anti-JCV Antibody Negative	TYSABRI Exposure†	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
<1/1,000	1-24 months	<1/1,000	1/1,000
	25-48 months	3/1,000	12/1,000
	49-72 months	6/1,000	13/1,000

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.
†Data beyond 6 years of treatment are limited.
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.

Infection by the JC virus is required for the development of PML. Anti-JCV antibody testing should not be used to diagnose PML. Anti-JCV antibody negative status indicates that exposure to the JC virus has not been detected. Patients who are anti-JCV antibody negative have a lower risk of PML than those who are positive. Patients who are anti-JCV antibody negative are still at risk for the development of PML due to the potential for a new JCV infection or a false negative test result. The reported rate of seroconversion in patients with MS (changing from anti-JCV antibody negative to positive and remaining positive in subsequent testing) is 3 to 8 percent annually. In addition, some patients' serostatus may change intermittently. Therefore, patients with a negative anti-JCV antibody test result should be retested periodically. For purposes of risk assessment, a patient with a positive anti-JCV antibody test at any time is considered antiJCV antibody positive regardless of the results of any prior or subsequent anti-JCV antibody testing. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay. Anti-JCV antibody testing should not be performed for at least two weeks following plasma exchange due to the removal of antibodies from the serum. There are no known interventions that can reliably prevent PML or that can adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease. PML has been reported following discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for at least six months following discontinuation of TYSABRI. Ordinarily, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI. Because of the risk of PML, TYSABRI is available only under a restricted distribution program, the TOUCH® Prescribing Program.
In multiple sclerosis patients, an MRI scan should be obtained prior to initiating therapy with TYSABRI. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML. In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on TYSABRI therapy are uncommon. Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. Withhold TYSABRI dosing immediately at the first sign or symptom suggestive of PML. For diagnosis of PML, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended. If the initial evaluations for PML are negative but clinical suspicion for PML remains, continue to withhold TYSABRI dosing, and repeat the evaluations. There are no known interventions that can adequately treat PML if it occurs. Three sessions of plasma exchange over 5 to 8 days were shown to accelerate TYSABRI clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients, alpha-4 integrin receptor binding remained high. Adverse events which may occur during plasma exchange include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although plasma exchange has not

	been studied in TYSABRI treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation. Anti-JCV antibody testing should not be performed during or for at least two weeks following plasma exchange because of the removal of antibodies from the serum. Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI treated patients who developed PML and subsequently discontinued TYSABRI. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating TYSABRI. It presents as a clinical decline in the patient's condition after TYSABRI removal (and in some cases after apparent clinical improvement) that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing treatment with TYSABRI for reasons unrelated to PML. In TYSABRI treated patients with PML, IRIS has been reported within days to several weeks after plasma exchange. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.
Rituximab (Rituxan®)	WARNING: FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) **Infusion Reactions:** Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3). **Severe Mucocutaneous Reactions:** Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous reactions has not been determined. **Hepatitis B Virus Reactivation:** Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Rituxan. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur. Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with Rituxan. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B

	regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituxan treatment. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Rituxan therapy. HBV reactivation has been reported up to 24 months following completion of Rituxan therapy. In patients who develop reactivation of HBV while on Rituxan, immediately discontinue Rituxan and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop HBV reactivation. Resumption of Rituxan in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. **Progressive Multifocal Leukoencephalopathy (PML):** JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituxan. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.
Tocilizumab (Actemra®)	WARNING: RISK OF SERIOUS INFECTIONS **SERIOUS INFECTIONS** Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA for rheumatoid arthritis. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis [see Adverse Reactions (6.1)]. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections. Do not administer ACTEMRA in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • with a history of serious or an opportunistic infection; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or • with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants. Hold ACTEMRA if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient. **Tuberculosis**: Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating ACTEMRA. Consider anti-tuberculosis therapy prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative

	for latent tuberculosis infection prior to initiating therapy. It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA. **Viral Reactivation:** Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.
Tofacitinib (Xeljanz®)	WARNING: SERIOUS INFECTIONS AND MALIGNANCY SERIOUS INFECTIONS Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster and urinary tract infection. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids. Other serious infections that were not reported in clinical studies may also occur (e.g., histoplasmosis, coccidioidomycosis, and listeriosis). Avoid use of XELJANZ in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients: • with chronic or recurrent infection • who have been exposed to tuberculosis • with a history of a serious or an opportunistic infection • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or • with underlying conditions that may predispose them to infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. XELJANZ should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. Tuberculosis: Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ. Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ. Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ. The risk of herpes zoster is increased in patients treated with XELJANZ and appears to be higher in patients treated with XELJANZ in Japan. MALIGNANIES Malignancy and Lymphoproliferative Disorders: Consider the risks and benefits of XELJANZ

	treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ [see Adverse Reactions (6.1)]. In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ. In Phase 2B, controlled dose-ranging trials in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine. Non-Melanoma Skin Cancer: Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. GASTROINTESTINAL PERFORATIONS Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known. XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation
Ustekinumab (Stelara®)	None listed
Vedolizumab (Entyvio®)	None listed