

Drug Class Review

Targeted Immune Modulators

Final Update 3 Report
Executive Summary

March 2012

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

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Targeted Immune Modulators", dated March 2012. The full report can be accessed at the following web address: <http://derp.ohsu.edu/about/final-document-display.cfm>. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 2: November 2009

Update 1: January 2007

Original Report: December 2005

The literature on this topic is scanned periodically

Update 3 Authors

Kylie J. Thaler, MD, MPH
Gerald Gartlehner, MD, MPH
Christina Kien, MSc
Megan G. Van Noord, MSIS
Sujata Thakurta, MPA:HA
Roberta C. M. Wines, MPH
Richard A. Hansen, PhD
Marian S. McDonagh, PharmD

Produced by

RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
Tim Carey, M.D., M.P.H., Director

Drug Effectiveness Review Project

Marian McDonagh, PharmD, Principal Investigator
Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Copyright © 2012 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



INTRODUCTION

Targeted immune modulators, commonly referred to as biological response modifiers or simply *biologics*, are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn’s disease, and ulcerative colitis. The US Food and Drug Administration approved the first of the biologics (infliximab) in 1998 and approved 12 additional agents since that time for treating various rheumatic conditions, inflammatory bowel diseases, and plaque psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), efalizumab (2003), abatacept (2005), rituximab (2006), natalizumab (2008), certolizumab pegol (2008), golimumab (2009), ustekinumab (2009), and tocilizumab (2010).

Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of targeted immune modulators. Included drugs are shown in Table 1.

Table 1. Included interventions

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

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Juvenile idiopathic arthritis ^b (4 years of age and older)	15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week. ≥ 30 kg (66 lbs): 40 mg every other week.
			Crohn's disease	Initial subcutaneous dose (Day 1) 160 mg (four 40 mg injections in 1 day or two 40 mg injections daily for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.
			Plaque psoriasis	80 mg initial subcutaneous dose followed by 40 mg every other week starting 1 week after initial dose.
Alefacept	Amevive [®] Astellas	CD2 antagonist	Plaque psoriasis	15 mg given once weekly as an intramuscular injection. Treatment should be continued for 12 weeks; re-treatment with an additional 12 week course may be initiated provided that CD4+ T lymphocytes counts are >250 cells/μL and a 12-week interval has passed since the end of the initial treatment cycle.
Anakinra	Kineret [®] Biovitrum/ Amgen	IL-1 receptor antagonist	Rheumatoid arthritis	100 mg daily as subcutaneous injection; dose should be decreased to 100 mg every other day in renal insufficiency.
Certolizumab pegol	Cimzia [®] UCB, Inc	TNF Inhibitor	Rheumatoid arthritis	400 mg subcutaneous injection initially and at weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
			Crohn's disease ^b	400 mg subcutaneous injection initially and at weeks 2 and 4. If response occurs 400 mg subcutaneously every 4 weeks.
Etanercept	Enbrel [®] Amgen Pfizer Immunex	TNF Inhibitor	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	50 mg once weekly as subcutaneous injection.
			Juvenile idiopathic arthritis (2-17 years) ^c	0.8 mg/kg weekly (maximum 50 mg weekly), given as 1 or 2 subcutaneous injections.
			Plaque psoriasis	50 mg given twice weekly as a subcutaneous injection for 3 months, followed by 50 mg weekly.
Golimumab	Simponi [®] Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	50 mg subcutaneous injection once a month in combination with methotrexate. ^d
			Psoriatic arthritis, ankylosing spondylitis	50 mg subcutaneous injection once a month with or without methotrexate or other DMARDs. ^e
Infliximab	Remicade [®] Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	<i>Adult:</i> 3 mg/kg intravenous induction at 0, 2, and 6 weeks with methotrexate followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treating as often as every 4 weeks.
			Crohn's disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to 10 mg/kg. <i>Pediatric</i> ^{f,g} : 5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter.

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

Abbreviations: AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

^a Approved only in Canada

^b Not approved in Canada

^c In Canada, pediatric: 4-17 years

^d Not approved in combination with methotrexate in Canada

^e Not approved in combination with methotrexate/other DMARDs in Canada

^f In United States., pediatric: 6-17 years

^g In Canada, pediatric: ≥9 years

^h Manufacturer in Canada

Note: Table 1 provides manufacturer and approved indications in the United States and Canada and dosage and administration information in the United States relative to indications covered in this report. Readers should refer to the Health Canada product monograph of individual drug products for dosing information for Canada.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

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?

METHODS

For Update 3 we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2009 (January) to 2011 (October) using included drugs, indications, and study designs as search terms. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches.

We assessed the internal validity (quality) of all studies using predefined criteria based on study design (see www.ohsu.edu/drugeffectiveness). We also determined the quality of studies to be *good*, *fair*, or *poor* based on predefined criteria. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality.

RESULTS

Overview

For Update 3, literature searches identified 1589 citations. We received dossiers from five pharmaceutical manufacturers: Abbot, Amgen, Centocor Ortho Biotech, Genentech, and UCB Inc. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 436 citations. After re-applying the criteria for inclusion, we ultimately included 78 new publications, representing 68 unique studies.

Key Question 1. Efficacy and Effectiveness

Rheumatoid Arthritis

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

We included 16 trials, 21 systematic reviews and meta-analyses, and seven observational studies. Only one randomized controlled trial was a double-blinded head-to-head trial. One study was characterized as an effectiveness trial. Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up.

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

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

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

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

Indirect comparisons of placebo-controlled randomized controlled trials suggest that etanercept is statistically significantly more efficacious than abatacept, anakinra, infliximab, and tocilizumab (range of relative risks from 2.31 to 3.30). No statistically significant differences in efficacy could be detected among adalimumab, anakinra, infliximab, and tocilizumab. The strength of evidence was low, except for the comparison of etanercept with infliximab for which the strength of evidence was moderate.

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

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

Juvenile Idiopathic Arthritis

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

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of juvenile idiopathic arthritis exists. Five randomized controlled trials provided fair evidence that abatacept, adalimumab, etanercept, infliximab, and tocilizumab are more efficacious than placebo for the treatment of juvenile idiopathic arthritis. Except for the infliximab trial, however, the highly selected study populations were likely to compromise the external validity of these studies. Some of these studies did not meet our formal eligibility criteria. Because these studies are the only available randomized controlled evidence on some drugs, we are still presenting main findings.

Ankylosing Spondylitis

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

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

Psoriatic Arthritis

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

We included two systematic reviews and meta-analyses that analyzed the same six trials of adalimumab, etanercept, and infliximab. The reviews provided comparisons between the three biologics using two different statistical methods of indirect comparisons. In addition, we included four placebo-controlled randomized controlled trials assessing the efficacy of abatacept, alefacept, golimumab, and ustekinumab. The studies ranged in duration from 12 to 22 weeks. Finally, we included one open-label registry study of adalimumab, etanercept, and infliximab for

data on quality of life. We did not find any studies on anakinra, certolizumab pegol, natalizumab, rituximab, or tocilizumab.

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

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

In addition, evidence indicated that alefacept combined with methotrexate is more efficacious than methotrexate alone and that abatacept, golimumab, and ustekinumab are more efficacious than placebo.

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

Psoriatic Arthritis in Children

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

Crohn's Disease

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

Overall, the strength of evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease was insufficient. We did not find any head-to-head randomized controlled trials or observational studies comparing one targeted immune modulator to another and evidence was insufficient to make indirect comparisons.

We included one recent, good-quality systematic review and meta-analysis of all four targeted immune modulators approved by the US Food and Drug Administration for Crohn's disease. The review assessed two outcomes, failure of remission and relapse of disease activity, and analyzed the subgroup of patients with fistulizing disease separately. Overall, the review included 27 randomized controlled trials: eight on adalimumab, seven on certolizumab pegol, seven on infliximab, and six on natalizumab.

Pooled results regarding the general efficacy of targeted immune modulators for Crohn's disease showed consistent results. Infliximab demonstrated statistically significant greater efficacy than placebo for inducing remission and preventing relapse in all patients and in healing and maintaining remission in fistulizing Crohn's disease. Natalizumab was superior to placebo in inducing remission and preventing relapse in patients with Crohn's disease. Adalimumab demonstrated statistically significant greater efficacy than placebo for inducing remission. Both single trials on evaluating the efficacy of adalimumab for maintaining response demonstrated

statistically significant greater efficacy than placebo. Certolizumab pegol was superior to placebo only in preventing relapse but there was a trend showing a greater efficacy than placebo in inducing remission. Overall, Adalimumab and certolizumab pegol were not shown to be more efficacious compared with placebo for inducing remission and healing in fistulizing Crohn's disease. In particular, the evidence from currently available trials on investigating the efficacy of targeted immune modulators in patients with fistulizing Crohn's disease was insufficient.

We did not find any evidence that met our eligibility criteria on the general efficacy of abatacept, alefacept, anakinra, etanercept, golimumab, rituximab, tocilizumab, or ustekinumab for the treatment of Crohn's disease.

Although some studies allowed stable doses of other immunomodulatory agents, no conclusive evidence exists to determine whether combination treatment of targeted immune modulators with other agents (azathioprine, 6-mercaptopurine or methotrexate) leads to clinically and statistically greater improvements than monotherapy. We did not include studies of targeted immune modulators compared with active therapies for Crohn's disease.

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

Crohn's Disease in Children

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

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

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

Ulcerative Colitis

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

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

We located one recent, good-quality systematic review and meta-analysis of targeted immune modulators for inducing remission in ulcerative colitis. This review pooled the results of

five randomized controlled trials of 5 mg/kg infliximab compared with placebo. Patients were allowed stable doses of corticosteroids in all trials. The reviewers calculated a relative risk of 0.72 (95% CI, 0.57 to 0.91) for a *failure* to achieve remission, i.e., infliximab is more efficacious than placebo.

Ulcerative Colitis in Children

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

Plaque Psoriasis

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

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

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

Key Question 2. Adverse Events

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

Evidence on the comparative risk of serious infections with targeted immune modulators was low strength. Evidence from short-term trials (median 6 months), using indirect comparison meta-analyses, indicated serious infections are less common with abatacept than with certolizumab, infliximab, and tocilizumab while certolizumab appeared to have a higher risk than

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

On the whole, a broad range of evidence did not indicate a clear increase in risk of malignancy in general with the use of targeted immune modulators. There was evidence suggesting that the risk of nonmelanoma skin cancer is increased with the use of the antitumor necrosis factor drugs adalimumab, infliximab, and etanercept (relative risk, 2.02; 95% CI, 1.11 to 3.95). Observational evidence supported these findings, although the risk estimates were somewhat lower magnitude. The strength of evidence comparing the risk of malignancy with targeted immune modulators is low strength. Although the US Food and Drug Administration issued a warning about the potential increased risk of malignancy in children, evidence in children is insufficient for making conclusions.

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

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

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

Key Question 3. Subgroups

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

Evidence on the effect of age was mixed. Indirect evidence from three studies indicated that age is not associated with greater or lesser clinical response rates or adverse events in ankylosing spondylitis, rheumatoid arthritis psoriatic arthritis, or plaque psoriasis, while two studies on rheumatoid arthritis patients found treatment response to be better in younger patients than older patients and adverse events found to be significantly higher in patients 70 years and older.

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

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

Findings in studies evaluating effectiveness and safety in patients with comorbid conditions (respiratory disease, diabetes, cardiovascular disease) are mixed. Two studies reported no differences in adverse events in patients with comorbidities while three studies reported an increased risk of the occurrence of adverse events.

SUMMARY

The main findings of this review are summarized in Table 2. The applicability of the results are limited by the scope of the key questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were often underrepresented.

Table 2. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
1. Comparative efficacy for rheumatoid arthritis	Moderate	Based on 1 randomized controlled trial, no difference in efficacy between abatacept and infliximab.
	Low	Based on 2 observational studies similar effectiveness between adalimumab and etanercept
	Low	Based on 2 observational studies, greater effectiveness of adalimumab than infliximab
	Moderate	Based on 2 trials and 5 observational studies, greater effectiveness of etanercept than infliximab.
	Low	Based on indirect comparisons, greater effectiveness of etanercept than abatacept; etanercept than anakinra; and etanercept than tocilizumab.
	Low	Based on indirect comparisons, similar efficacy between abatacept and adalimumab; abatacept and anakinra; abatacept and tocilizumab; adalimumab and anakinra; adalimumab and tocilizumab; anakinra and infliximab; anakinra and tocilizumab; and infliximab and tocilizumab.
	Insufficient	No evidence available for all other comparisons.
1. Comparative effectiveness for juvenile idiopathic arthritis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for ankylosing spondylitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for psoriatic arthritis	Low	Based on indirect comparisons and a prospective registry study, no difference in effectiveness between adalimumab, etanercept and/or infliximab.
1. Comparative effectiveness for Crohn's disease	Insufficient	No comparative evidence available.
1. Comparative effectiveness for ulcerative colitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for plaque psoriasis	Low	Based on one randomized controlled trial, ustekinumab is more efficacious than etanercept
2. Comparative harms	Low	<i>Serious Infections (as a group)</i> Less common with abatacept based on indirect comparisons and one randomized controlled trial. Certolizumab pegol associated with greater odds than adalimumab, anakinra, etanercept, golimumab, infliximab, and rituximab. The antitumor necrosis factor drugs adalimumab, etanercept, and infliximab have higher risk than DMARDs based on observational studies. Tuberculosis: risk of higher with adalimumab than etanercept based on one observational study. Herpes Zoster: risk is not increased with etanercept based on 2 observational studies, but risk with other drugs is unclear or insufficient.
	Low	<i>Malignancy:</i> Based on three observational studies and indirect comparisons, risk of non melanoma skin cancer is greater with the antitumor necrosis factor drugs adalimumab, etanercept, and infliximab than non targeted immune modulator therapy, but no increased risk of any malignancy or differences between drugs found.
	Low	<i>Overall adverse events:</i> Based on one randomized controlled trial, adalimumab has lower rate than

Key question	Strength of evidence	Conclusion
		infliximab or etanercept. Based on seven observational studies, the rate is greater with infliximab than adalimumab or etanercept. Based on one randomized controlled trial, rates similar between etanercept and ustekinumab: Injection-site reactions more frequent with etanercept than ustekinumab. In short-term trials, abatacept and anakinra have lower risk of a serious adverse event than other targeted immune modulators.
	Low	<i>Discontinuations due to adverse events:</i> Based on seven observational studies and indirect comparisons, the rate is greater with infliximab than abatacept, anakinra, etanercept and golimumab. Infusion or allergic reactions contributed to the difference in risk.
	Insufficient	<i>Children:</i> No comparative evidence available.
3. Subgroups – age	Insufficient	The evidence on the effect of age is contradicting and insufficient to draw conclusions.
3. Subgroups – sex	Insufficient	The evidence is mixed and insufficient to draw conclusions.
3. Subgroups – ethnicity	Insufficient	No direct comparisons available. Based on indirect evidence, adalimumab and ustekinumab had better efficacy than placebo in Asian patients with plaque psoriasis and rheumatoid arthritis. Based on one observational study, non white patients had increased risk of tuberculosis than white patients treated with antitumor necrosis factor drugs in patients with rheumatoid arthritis.
3. Subgroups – comorbidities	Insufficient	The evidence is mixed and was insufficient to draw conclusions.

CONCLUSION

Overall, targeted immune modulators are highly effective medications for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, and plaque psoriasis that substantially improve the burden of disease and are generally safe for short-term treatment.

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

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