



Targeted Immune Modulators

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Produced by:

The Health Resources Commission

Office for Oregon Health Policy & Research

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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, and two pharmacists. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon

Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "*Targeted Immune Modulators*", November 2009, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, "*Targeted Immune Modulators*" is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

Targeted immune modulators, commonly referred to as biological response modifiers or simply *biologics*, are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn’s disease, and ulcerative colitis. The US Food and Drug Administration approved the first of the biologics (infliximab) in 1998 and approved 9 additional agents since that time for treating various rheumatic conditions and plaque psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), efalizumab (2003), abatacept (2005), rituximab (2006), natalizumab (2008), and certolizumab pegol (2008).

Targeted immune modulators work by selectively blocking mechanisms involved in the inflammatory and immune response. Tumor necrosis factor inhibitors block specific proinflammatory mediators known as cytokines. Adalimumab, certolizumab pegol, etanercept, and infliximab target tumor necrosis factor alpha. Interleukin-1, another naturally occurring cytokine, has both immune and pro-inflammatory actions. Anakinra is a human recombinant protein and the therapeutic version of a naturally occurring cytokine that competitively blocks the interleukin-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agents abatacept, alefacept, and efalizumab exert their immune regulation by interfering with T lymphocyte activation. Genentech, the manufacturer of efalizumab (Raptiva®) has voluntarily withdrawn the drug from the United States market because of an increased risk of progressive multifocal leukoencephalopathy.

Natalizumab is a recombinant, humanized immunoglobulin G4 antibody that binds to the alpha 4 subunit of all leukocytes except neutrophils. The specific mechanisms by which natalizumab exerts its effect in Crohn's disease has not been fully defined. Because of an increased risk of progressive multifocal leukoencephalopathy, natalizumab is only available through a specialized restricted distribution program called TOUCHTM Prescribing Program. Under the TOUCHTM Prescribing Program only prescribers, infusion centers and pharmacies registered with the program are able to prescribe, distribute, and infuse the product.

Rituximab 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.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease that affects about 1% of the population worldwide. The exact etiology of rheumatoid arthritis is not completely understood, but genetic susceptibility factors have been described in certain populations. The hallmarks of the disease are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and disability in most cases. Studies have shown the importance of CD4+ T cells, B cells, and cytokines in the pathogenesis of rheumatoid arthritis. Tumor necrosis factor alpha plays a central role in the pathobiology of rheumatoid arthritis. It is an important regulator of other pro-inflammatory molecules and stimulates the secretion of matrix metalloproteinases. It also exerts a direct effect on the multiple tissues inside the joint including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. Together, its action leads to inflammation and the formation of pannus, a localized mass of tissue that causes localized joint destruction.¹

The diagnosis of rheumatoid arthritis is primarily a clinical one. Constitutional symptoms, such as fatigue and low grade fevers, are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. In a subset of patients, rheumatoid arthritis can be a devastating disease with numerous extra-articular manifestations. Severe disease may be complicated by involvement of the eyes, lungs, nerves, and the cardiovascular system.

A serum rheumatoid factor is present in up to 75% of patients with rheumatoid arthritis but is frequently negative in early disease. A more specific marker, anti-cyclic citrullinated peptide antibody, has recently been described and may be a useful marker in patients with early disease.² Treatment is aimed at controlling pain and inflammation and ultimately, slowing or arresting the progression of joint destruction. The key to successful management of rheumatoid arthritis is the early identification of the disease and the rapid institution of effective therapies.³ Methotrexate is the cornerstone of most rheumatoid arthritis treatment regimens as it has demonstrated good disease control and tolerability. However, methotrexate toxicity may limit the use of methotrexate, and many patients do not adequately respond to methotrexate monotherapy. In patients with persistent disease despite aggressive management with oral agents, biologic agents, often in combination with methotrexate, are now considered the standard of care. Lifelong therapy is usually necessary.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis is a form of arthritis that, by definition, lasts at least 6 weeks in a child under the age of 16. It is a systemic disease with a variable presentation and has 3 established subtypes: pauciarticular (<5 joints involved), polyarticular (≥ 5 joints involved), and systemic (arthritis with fever and a rash).⁵

Joint pain, stiffness, and swelling are the hallmarks of juvenile idiopathic arthritis. Children with systemic disease often present with constitutional symptoms such as fever or rash. Similar findings may be seen in polyarticular disease but are rare with pauciarticular presentation. Uveitis, an inflammatory disease of the eye, is common. Children with the most severe forms of juvenile idiopathic arthritis may have significant disability from progressive destructive arthritis. Long-term consequences of the disease include growth disturbances, deformity of the joints, and blindness.

Initial therapeutic strategies are aimed at decreasing pain and swelling and improving the child's functional status. Non-steroidal anti-inflammatory drugs are first line therapy and are usually fairly well tolerated in children. Systemic steroids are usually avoided, if possible, because of adverse effects on bone growth. However, intra-articular steroid injections can be an effective strategy, particularly if only a few joints are afflicted with active disease. As in rheumatoid arthritis, oral disease-modifying antirheumatic drugs are used next, with methotrexate being the most widely used. When the disease is resistant to oral therapies, biologic agents are indicated.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory arthritis with primary involvement of the axial skeleton and prominent involvement of the spine and sacroiliac joints. Peripheral joint disease can occur and may be destructive in some cases. The peak age of onset is in the 20s, and men are affected more frequently than women by a ratio of about 3 to 1. The onset is indolent with prominent stiffness in the low back, which is characteristically worse at night and in the early morning. The sacroiliac joints are usually the first joints involved, and the disease is characterized by progressive involvement of the spine. Enthesitis, inflammation of the insertion of ligaments and tendons on bones, is one of the hallmarks of the disease.

Existing diagnostic criteria are relatively insensitive and have limited utility in clinical practice. Ankylosing spondylitis usually presents with inflammatory back pain and stiffness in a young adult, although 20% present with peripheral joint involvement and more than 50% have joints other than the spine affected at some stage. Radiographs of the sacroiliac joints, when abnormal, can be useful in assessing the presence of ankylosing spondylitis; however, they are frequently normal in early disease. Over time, patients with ankylosing spondylitis develop progressive fusion of the spine with resultant deformity and disability.

For years non-steroidal anti-inflammatory drugs were the standard of care for the treatment of ankylosing spondylitis, as they are effective in treating pain and stiffness. However, they do not have any effect on disease progression. Traditional disease-modifying antirheumatic drugs have been used, mostly because a lack of other more effective therapies, although they are usually ineffective in treating spinal arthritis. As tumor necrosis factor has been implicated in the pathophysiology of ankylosing spondylitis, biologic agents targeting tumor necrosis factor have become a standard treatment approach.⁶ Studies are under way to assess whether treatment with these agents affects the natural history of ankylosing spondylitis.

Psoriatic Arthritis

Psoriatic arthritis is a chronic inflammatory arthritis associated with the skin disease psoriasis. In most cases, the psoriasis predates the onset of the psoriatic arthritis. The presentation, however, is highly variable. In all cases, symptoms include pain and stiffness in the affected joint as well as joint line tenderness, swelling, and sometimes loss of range of motion. Pitting of the fingernails often correlates with the extent and severity of the disease.⁷ Dactylitis, swelling of a whole digit, is a characteristic clinical finding. Enthesitis, spondylitis, sacroiliitis, and inflammatory eye disease (iritis, uveitis) may occur.

The etiology and pathogenesis of psoriasis and psoriatic arthritis are not completely understood, but genetic, immunologic, and environmental factors are all likely to play a role.⁸ The first line of treatment is non-steroidal anti-inflammatory drugs, although in most cases disease-modifying antirheumatic drugs are necessary. Corticosteroids may be used but do not have much of a role in chronic disease management in psoriatic disease. If disease continues to be active despite the use of non-steroidal anti-inflammatory drugs, methotrexate, or other oral disease-modifying antirheumatic drugs, biologics may be indicated.^{9, 10}

Crohn's Disease

Crohn's disease is a condition of the bowel causing inflammation involving the full thickness of the bowel wall. This may occur at any point from the mouth to the anus. This chronic inflammation leads to fibrosis and obstructive symptoms with sinus tracts and fistulae. Fistulizing disease is a serious complication of Crohn's disease; it is basically abnormal communication between the gut and the skin or other internal organs, with small bowel or colonic contents draining to the skin or other organs. Abdominal pain and diarrhea, with or without bleeding, are characteristic of the disease. Constitutional symptoms are very common, predominantly fatigue and weight loss. Nonspecific digestive symptoms may predate the onset of clinically overt disease. Extra-intestinal symptoms may occur and include inflammatory eye disease, arthritis, and sclerosing cholangitis. Clinical diagnosis is made on the basis of history and physical examination and is confirmed on endoscopy and biopsy of the involved segment of the GI tract. Patients with aggressive or poorly controlled disease may suffer numerous complications; these include severe hemorrhage, intestinal obstruction, perforation, development of fistulae and abscess formation, malabsorption with nutritional deficiencies, and rarely, malignancy.

Treatment is aimed at controlling the inflammation and preventing complications. Mild disease may be controlled with 5-aminosalicylate drugs or antibiotics. If the disease is resistant to these interventions or is more severe, corticosteroids are frequently used. If symptoms persist despite steroids or if the disease flares on tapering the steroids, immunomodulatory agents (azathioprine, 6-mercaptopurine, and methotrexate) often are instituted. Biologics may be warranted in patients with moderate to severe active Crohn's disease who have had inadequate response to conventional therapy. It is recommended that medical therapy be exhausted before surgical therapy is considered, except in cases of catastrophic complications such as acute colonic obstruction, massive hemorrhage, or bowel perforation.

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory bowel disease that is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain and limited to the colon and rectal areas, unlike Crohn's disease which causes inflammation deeper within the intestinal wall and can occur in other parts of the digestive system including the small intestine, mouth, esophagus, and stomach. The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Clinical diagnosis is most accurately made with colonoscopy or sigmoidoscopy.

Treatment is aimed at reducing and maintaining remission of symptoms and inflammation.¹¹ Mild disease may be controlled with oral and/or topical 5-aminosalicylate drugs. If the disease is resistant to these interventions or is more severe, corticosteroids are frequently used. In addition, infliximab has been approved by the US Food and Drug Administration for treatment of moderate to severe ulcerative colitis. Indications for surgery include excessive bleeding, perforation, carcinoma and toxic colitis. About 25% to 40% of ulcerative colitis patients must eventually have their colons removed.

Plaque Psoriasis

Plaque psoriasis is a chronically recurring, debilitating inflammatory disease that affects the skin, scalp, and joints. It is characterized by erythrosquamous skin lesions and ranges in severity from mild to severe. Patients with moderate to severe disease experience significant deterioration of quality of life.¹² The exact pathogenesis of plaque psoriasis is still unknown; however, pathophysiological evidence suggests that an overproduction of proinflammatory cytokines plays an important role.^{13, 14} In particular, tumor necrosis factor levels are increased in psoriatic lesions compared with healthy skin.

The severity of plaque psoriasis is most commonly classified based on the percentage of body surface area involved. Severe psoriasis is generally defined as more than 10% body surface area affected.¹²

The goal of plaque psoriasis treatment is to gain control of the disease process, decrease the percentage of body surface involved, and achieve and maintain long-term remission.¹⁵ Conventional therapy includes topical treatments (e.g. topical corticosteroids, calcipotriene, tazarotene), phototherapy (e.g. broadband ultraviolet B light, narrow band ultraviolet B light, psoralen plus ultraviolet A light), and systemic therapy (e.g., methotrexate, cyclosporine, acitretin). In addition, biologic agents such as adalimumab, alefacept, efalizumab, etanercept, and infliximab have been approved by the US Food and Drug Administration for the treatment of moderate to severe plaque psoriasis.

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization

- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee’s task was to evaluate

Scope and Key Questions

To identify articles relevant to each key question the EPC searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts limiting the electronic searches to “human” and “English language”; they searched sources from 1980 to 2009 (April) to delimit literature relevant to the scope of our topic.

In this report, we review the comparative effectiveness, safety, and tolerability of targeted immune modulators. Our review covers the use of these drugs in adult patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, plaque psoriasis, and pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, and plaque psoriasis.

Table 1. Targeted immune modulators

Generic name	United States trade name	Manufacturer	Route	Half-life	Onset of action	Mechanism of action	Labeled uses	Black Box warning?
Abatacept	Orencia®	Bristol Myers Squibb	IV	8-25 days	>12 days	CTLA 4-Ig	RA JIA	
Adalimumab	Humira®	Abbott	Sub Q	10-20 days	1-14 days	TNF inhibitor	RA JIA PsA AS Crohn's disease Plaque psoriasis	
Alefacept	Amevive®	Astellas	IM	11-12 days	30-60 days	CD2 antagonist	Plaque psoriasis	
Anakinra	Kineret®	Amgen	Sub Q	7-8 hours	7-21 days	IL-1 receptor antagonist	RA	
Certolizumab pegol	Cimzia®	UCB, Inc	Sub Q	14 days	2-4 weeks	TNF inhibitor	RA Crohn's	

							Disease	
Efalizumab ^a	Raptiva®	Genentech	Sub Q	6.2 days	14 days	CD11a inhibitor	Plaque Psoriasis	
Etanercept	Enbrel®	Amgen Wyeth Immunex	Sub Q	4.3 days	1-28 days	TNF inhibitor	RA JIA PsA AS Plaque psoriasis	
Infliximab	Remicade®	Centocor	IV	9.8 days	2-14 days	TNF inhibitor	RA Crohn's disease PsA AS Ulcerative colitis Plaque psoriasis	
Natalizumab	Tysabri®	Biogen-Idec	IV	7-15 days	2-4 weeks	Anti-IgG4	Crohn's disease	
Rituximab	Rituxan®	Genentech IDEC	IV	19 days	30-60 days ^b	Anti-CD 20a	RA	

The purpose of this review is to help policy makers and clinicians make informed choices about the use of targeted immune modulators. We compare the efficacy, effectiveness, and safety (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, infliximab, natalizumab, and rituximab in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

The Oregon Evidence-based Practice Center initially prepared preliminary key questions identifying the populations, interventions, and outcomes of interest, and we based the eligibility criteria for studies on these preliminary questions. Representatives of organizations participating in the Drug Effectiveness Review Project, in conjunction with experts in the fields of health policy, rheumatology, pharmacotherapy, and research methods reviewed, revised, and approved the questions and outcome measures. The participating organizations approved the following key questions:

Key Questions

KQ 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?

KQ 2. What are the comparative incidence and severity of complications associated with the use of these drugs?

KQ 3. Do the included drugs differ in effectiveness or adverse events in different age, sex, or ethnic groups, or in patients taking other commonly prescribed drugs?

Conclusions:

Limitations of the Evidence

1. The large majority of these studies was funded by the pharmaceutical industry and could be classified as efficacy trials with highly selected patients.

2. Long term data on safety is lacking. The majority of studies were of one year or less in duration with a few extending to 4 years.

Conclusions

Multiple meta-analyses and RCTs confirm the general efficacy (vs. placebo) of Abatacept, Adalimumab, Anakinra, Certolizumab, Etanercept, Infliximab, and Rituximab.

Good to fair evidence exists from meta-analyses and large randomized controlled trials that abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, infliximab, and rituximab are significantly more efficacious than placebo for the treatment of the disease entities for which they are approved for use.

The most obvious differences that might be clinically decisive for choosing a targeted immune modulator involve dosage frequency and route of administration.

KQ1: Efficacy/ Effectiveness

There is no comparative efficacy/ effectiveness evidence available for juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, or plaque psoriasis.

Rheumatoid arthritis

1. Low strength evidence suggests greater effectiveness of etanercept than infliximab.
2. Low strength evidence based on indirect comparisons suggests greater effectiveness of adalimumab, etanercept, and infliximab compared with anakinra.
3. Low strength evidence suggests there is no difference for efficacy for adalimumab vs. etanercept in rheumatoid arthritis.
4. Low strength evidence suggests there is no difference for effectiveness for abatacept vs. infliximab in rheumatoid arthritis.
5. There is insufficient evidence to determine a comparative difference for efficacy or effectiveness for all other drugs in this class for treatment of rheumatoid arthritis.

Ankylosing Spondylitis

1. Low strength evidence suggests there is no difference in effectiveness between adalimumab, etanercept and/or infliximab.

Psoriatic Arthritis

1. Low strength evidence suggests there is no difference in effectiveness between adalimumab, etanercept and/or infliximab.

KQ2: Safety/ Harms

Overall, targeted immune modulators appeared to have a good tolerability profile, although some rare but serious adverse events such as serious infections, lymphoma, leucopenia, malignancies, or demyelinations have occurred and are of concern. 196-203 Injection site or infusion reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events. In efficacy studies up to 97% of patients experienced at least 1 adverse event during the course of the study.

1. High strength evidence suggests substantially higher rates of serious adverse events for combination therapies of anakinra with etanercept and abatacept with etanercept than for monotherapies.
2. Moderate strength evidence suggests higher rates of serious adverse events (18.2% vs. 9.6%) and serious infections (8.5% vs. 1.9%) for infliximab than for abatacept.

3. Low strength evidence suggests there is no difference between etanercept and infliximab.
4. There is no evidence for all other comparisons of included drugs.
5. On August 4, 2009 the US Food and Drug Administration issued a warning about an increased risk of cancer in children and adolescents who receive anti-TNF drugs (Adalimumab, Certolizumab Pegol, Etanercept, and Infliximab).
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm>
6. Because of an increased risk of progressive multifocal leukoencephalopathy, natalizumab is only available through a specialized restricted distribution program called TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program only prescribers, infusion centers and pharmacies registered with the program are able to prescribe, distribute, and infuse the product.

KQ3: Subgroups

1. There is insufficient evidence to determine a difference for any of the included drugs based on age, gender, ethnicity or comorbidities.

Supporting Evidence

Key Question 1. Efficacy and Effectiveness

How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, or plaque psoriasis?

Rheumatoid Arthritis

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

We included 16 randomized controlled trials, 16 meta-analyses, and 7 observational studies. Only 1 randomized controlled trial was a head-to-head trial.³¹ One study was characterized as an effectiveness trial.³² Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up.

Direct Evidence

Abatacept compared with infliximab

The only double-blinded head-to-head trial, the ATTEST (Abatacept or infliximab compared with placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis) study, was a fair randomized controlled trial that compared abatacept with infliximab in patients with inadequate response to methotrexate.³¹ This study enrolled 431 patients and randomized them to abatacept (10 mg/kg every 4 weeks+ methotrexate), infliximab (3mg/kg every 8 weeks +methotrexate), or placebo. The primary outcome was assessed at 6 months followed by a double-blinded extension phase up to 1 year. No differences in efficacy were obvious between treatments at 6 months (DAS 28: abatacept -2.53, infliximab -2.25; $P=NR$) At 1 year, however, abatacept was statistically significantly more efficacious on most outcome measures than infliximab.

For example, significantly more patients on abatacept than on infliximab achieved American College of Rheumatology 20/50 responses (American College of Rheumatology 20 response 72.4 compared with 55.8%; $P < 0.001$; American College of Rheumatology 50 response 45.5 compared with 36.4%; $P < 0.001$). Likewise, health related quality of life measures (Health Assessment Questionnaire Disability Index, Short Form 36 Health Survey) improved statistically significantly more with abatacept than with infliximab treatment. It has to be noted though, that infliximab was administered at a fixed dose regimen throughout the entire study. Infliximab efficacy trials have shown that up to 30% of patients require dose increases.

Adalimumab compared with etanercept

The evidence on the comparative effectiveness of adalimumab and etanercept is limited to 1 good observational study.³⁶ In a prospective cohort study based on the Dutch Rheumatoid Arthritis Monitoring (DREAM) register, investigators compared the effectiveness of adalimumab with etanercept for the treatment of rheumatoid arthritis in a primary care based population.³⁶ Eleven rheumatology centers in the Netherlands enrolled all rheumatoid arthritis patients who had at least moderate disease activity, had failed at least 1 conventional disease-modifying antirheumatic drug and started on an anti-tumor necrosis factor drug. The choice of the treatment and dosing was at the discretion of the treating rheumatologist. The primary outcome was the DAS28 course over a 12 months follow-up, as analyzed on an intention to treat basis. Overall, 916 patients were included, 707 (77%) patients had at least 1 year follow-up. Discontinuation rates were similar in patients on adalimumab and etanercept (22% compared with 21%; $P = \text{NR}$). At study endpoint patients on adalimumab and etanercept had similar improvements of the DAS28 (-1.8 compared with -1.8; $P = \text{NR}$) and the Health Assessment Questionnaire (-0.42 compared with -0.35; $P = \text{NR}$).

Adalimumab compared with infliximab

The same prospective cohort study based on the Dutch DREAM register described above also compared the effectiveness of adalimumab with infliximab.³⁶ During the 1 year follow-up discontinuation rates were significantly higher in patients on infliximab than on adalimumab (31% compared with 22%; $P < 0.049$). At study endpoint, patients treated with adalimumab had statistically significantly better improvements on the DAS28 (-1.8 compared with -1.2; $P < 0.05$) and the Health Assessment Questionnaire (-0.42 compared with -0.26; $P < 0.05$).

Etanercept compared with infliximab

The only study for this comparisons with a randomized allocation of interventions was a fair, small ($n=32$) open-label randomized controlled trial that compared etanercept (25mg twice weekly) with infliximab (3mg/kg, weeks 0, 2, 6 and every 2 months).³³ Patients in this trial had confirmed rheumatoid arthritis for longer than 2 years, did not respond adequately to disease-modifying antirheumatic drugs, and were on a stable dose of methotrexate (10-12 mg/week). Although infliximab had a faster onset of action than etanercept, more patients on etanercept achieved American College of Rheumatology 20 response after 54 weeks (74.4% compared with 60%; $P = \text{NR}$). The same pattern existed for Health Assessment Questionnaire (-32.3 compared with -21.6; $P = \text{NR}$). The study did

not assess discontinuation rates or adverse events and did not report data on American College of Rheumatology 50 or American College of Rheumatology 70. Because the sample size of this trial was small, chance findings are likely.

In addition we identified 4 observational studies^{34-36, 40} and 1 non-randomized trial.³² With respect to the comparative efficacy of etanercept and infliximab, these studies reported similar findings as the head-to-head trial mentioned above.

For example, in the non-randomized, open-label trial, a Swedish population-based study that assessed the efficacy and safety of etanercept (n = 166), infliximab (n = 135), and leflunomide (n = 103), etanercept had significantly greater American College of Rheumatology 20 response rates at 3 months (data NR; $P < 0.02$) and 6 months (data NR; $P < 0.05$), and greater American College of Rheumatology 50 response rates at 6 months (data NR; $P < 0.005$) than infliximab.³² Comparisons at other time points, generally favored etanercept over infliximab although most differences failed to achieve statistical significance, which is probably primarily attributable to a lack of power.

The four observational studies were based on data collected for registries in the Netherlands,³⁶ Sweden,³⁵ the United Kingdom,⁴⁰ and the United States.³⁴ These studies, therefore, reflect populations that are treated in daily clinical practice. Overall, results were consistent with findings mentioned above. In all of these studies etanercept led to numerically greater response rates than infliximab after up to 3 years of follow-up. One study reported that steroid withdrawal rates did not differ between etanercept and infliximab.³⁵

The largest of these observational studies was a prospective cohort study based on the Rheumatoid Arthritis DMARD (disease-modifying antirheumatic drug) Intervention and Utilization Study program.³⁴ This multicenter (509 rheumatology practices in the United States) registry enrolled patients who required changes in their rheumatoid arthritis treatment regimens. Data on 3034 patients on etanercept and 660 patients on infliximab were available for analysis after 12 months of follow up. Etanercept-treated patients had numerically greater response rates on the modified American College of Rheumatology 20 (the modified American College of Rheumatology 20 omits erythrocyte sedimentation rate and C-reactive protein because they are infrequently measured in clinical practice) than infliximab-treated patients (etanercept + methotrexate: 43%; etanercept monotherapy: 41%; infliximab + methotrexate: 35%; infliximab monotherapy: 26%; $P = \text{NR}$).

Targeted immune modulators combination strategies

Two trials determined the potential for additive or synergistic effects of combination therapy of 2 targeted immune modulators.^{37, 38} The largest study, a 24-week randomized controlled trial, did not detect any synergistic effects of a combination treatment of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy.³⁷ Overall, 242 patients who were on stable doses of methotrexate treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept only. Furthermore, the frequency of serious adverse events was substantially higher in the combination groups (14.8% for 50 mg etanercept plus anakinra, 4.9% for 25 mg etanercept plus anakinra, and 2.5% for etanercept only; $P = \text{NR}$). Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6% compared with 7.4%; $P = \text{NR}$).

The second study, examining a combination of abatacept (2 mg/kg) and etanercept (25mg twice weekly) compared with abatacept (2mg/kg) monotherapy reached similar conclusions.³⁸ The combination was associated with increased serious adverse events but only limited additional clinical benefit.

Indirect Evidence

Because of the lack of direct head-to-head evidence for most comparisons, the EPC conducted adjusted indirect comparisons based on meta-analyses of placebo-controlled trials to compare the treatment effects of individual targeted immune modulators. We included data from published studies or from the Center for Drug Evaluation Research website. For all analyses we used only data derived from study arms at or near the recommended dosage.

chose American College of Rheumatology 50 as the outcome measure because a 50% improvement is likely to translate to a clinically significant improvement in health-related quality of life. For example, a patient with 12 swollen and 8 tender joints at baseline would need to have fewer than 6 swollen and 4 tender joints at the trial endpoint. This would be accompanied by at least a 50% improvement in at least 3 of the following 5 measures: the patient's assessment of pain, the patient's assessment of global disease activity, the physician's assessment of global disease activity, the Health Assessment Questionnaire Disability Index, and either a C-reactive protein or sedimentation rate (Westergren erythrocyte sedimentation rate).

The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.²⁶ Included targeted immune modulator-studies primarily differ in study duration, disease duration, concomitant treatments, and some other baseline characteristics. Differences in study durations did not appear to be a factor altering the effect size. The EPC included only studies of more than 3 months of study duration, however and did not limit by sample size. Most randomized controlled trials reported the onset of significant responses between 4 and 8 weeks. Treatment responses were sustained up to 2 years in open-label extension studies. Sensitivity analyses based on different study durations did not substantially change the point estimates of the treatment effect. Likewise, sensitivity analyses excluding studies without concomitant methotrexate treatment, or studies on patients with early rheumatoid arthritis, did not substantially change the point estimate. One exception was the sensitivity analysis of infliximab where removing a study on patients with early rheumatoid arthritis⁴² substantially changed the effect size. However, it was unclear if this effect was attributable to true heterogeneity or to a lesser influence of random error in this large trial. Results presented below exclude this study. Overall, diagnostic criteria and eligibility criteria appeared to be sufficiently similar to make adjusted indirect comparisons a reasonable approach. However, given the small number of studies and the subsequent lack of precision, results should still be interpreted cautiously.

Findings suggest that no substantial differences exist among the efficacy of adalimumab, etanercept, and infliximab. However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty. Confidence intervals encompass differences that would be clinically significant. More data is needed to increase the precision of these estimates.

Point estimates favor adalimumab, etanercept, and infliximab over anakinra. However, differences do not reach statistical significance in adjusted indirect comparisons which is likely attributable to a lack of power.

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

Using information from placebo- controlled trials, 5 research groups used various statistical models to produce indirect comparisons of treatment effects of targeted immune modulators.⁴³⁻⁴⁷ Overall, all but 1 study⁴⁴ concluded that anti-tumor necrosis factor drugs have similar efficacy and that anakinra is less effective than adalimumab, etanercept, and infliximab.

Placebo controlled evidence

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

Juvenile Idiopathic Arthritis

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

Direct Evidence

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of juvenile idiopathic arthritis exists that met inclusion criteria.

Indirect Evidence

We did not find any studies indirectly comparing the effectiveness of targeted immune modulators for the treatment of juvenile idiopathic arthritis that met inclusion criteria.

Placebo controlled evidence

Patients suffered from active polyarticular juvenile idiopathic arthritis and were between 4 and 17 years of age. They had active disease despite treatment with corticosteroids and methotrexate. Patients with concurrent medical conditions or systemic juvenile idiopathic arthritis were excluded from trials. Except for the infliximab trial, all studies used withdrawal designs. After a run-in period with the active drug, only patients who responded, adhered to treatment, and had no intolerable adverse events were randomized to continuing active treatment or placebo. The primary outcome measure in the randomized controlled trials was the number of patients with disease flare. Disease flare was defined as a worsening of 30% or more in at least 3 of the 6 criteria of the American College of Rheumatology Pediatric scale or the Giannini criteria. Additional outcome measures were the articular severity score, duration of morning stiffness, degree of pain, and C-reactive protein.

All studies were funded by the pharmaceutical industry.

Four randomized controlled trials provide fair evidence that abatacept (n=122),¹¹⁴ adalimumab (n=133),¹¹⁵ etanercept (n=51),¹¹⁶ and infliximab (n=122 no statistical

significance between groups)¹¹⁷ are more efficacious than placebo for the treatment of juvenile idiopathic arthritis. Except for the infliximab trial, however, the highly selected study populations are likely to compromise the external validity of these studies.

Ankylosing Spondylitis

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

Direct Evidence

No direct evidence on the comparative effectiveness of targeted immune modulators for the treatment of ankylosing spondylitis exists that meets inclusion criteria.

Indirect Evidence

One systematic review attempts to provide indirect evidence on the comparative effectiveness of adalimumab, etanercept, and infliximab for adults with ankylosing spondylitis.¹²⁴ The analysis used results from 1611 patients with ankylosing spondylitis comparing adalimumab, etanercept or infliximab compared with placebo. However, due to the heterogeneity amongst the component studies the analysis is of poor quality so was excluded.

Placebo controlled

Adalimumab

We identified 1 high quality meta-analysis on the general efficacy of adalimumab.¹²⁴ The study included information on 2 trials of adult patients with ankylosing spondylitis. Pooled results presented statistically significantly greater improvements of adalimumab- than placebo-treated patients on outcome measures at 12 weeks (all $P < 0.001$).

Assessment in Ankylosing Spondylitis 20% improvement is achieved more frequently in adalimumab patients than placebo (relative risk, 2.43; 95% CI, 1.76 to 3.35), as is the Assessment in Ankylosing Spondylitis 70% improvement (relative risk, 5.47; 95% CI, 2.43 to 12.31). Indirect comparisons did not show that adalimumab was better or worse than infliximab or etanercept.

An additional fair study, published in 3 journal articles¹¹⁹⁻¹²¹ evaluated the safety and efficacy of adalimumab (40 mg every other week) for the treatment of ankylosing spondylitis. The study lasted for 24 weeks and included 315 patients. The study was conducted in patients with moderate to severe ankylosing spondylitis and allowed concomitant treatment with disease-modifying antirheumatic drugs and corticosteroids. Results of the trial reported that significantly more patients receiving adalimumab than placebo presented clinical improvements on outcome measures at study endpoint, for example the Assessment in Ankylosing Spondylitis 20% improvement 58.2% compared with 20.6% ($P < 0.001$).

Etanercept

We identified 1 high quality meta-analysis on the general efficacy of etanercept.¹²⁴ The study included information on 5 trials of adult patients with ankylosing spondylitis. Pooled results presented statistically significantly greater improvements of etanercept- than placebo-treated patients, for example Assessment in Ankylosing Spondylitis 20% improvement is achieved more frequently in etanercept patients than placebo (relative

risk, 2.13; 95% CI, 1.73 to 2.63) as is the Assessment in Ankylosing Spondylitis 70% improvement (relative risk, 3.38; 95% CI, 2.10 to 5.45). Indirect comparisons did not show that adalimumab was better or worse than infliximab or etanercept.

An additional study not included in the meta-analysis was conducted in 356 patients over 12 weeks, [122](#), [123](#) evaluated the safety and efficacy of etanercept (50 mg once weekly or 25 mg twice weekly) for the treatment of ankylosing spondylitis. The study was conducted in patients with moderate to severe ankylosing spondylitis and allowed concomitant treatment with disease-modifying antirheumatic drugs and corticosteroids. Results of the trial reported that significantly more patients receiving etanercept than placebo presented clinical improvements on outcome measures at study endpoint. For example the primary end point, Assessment in Ankylosing Spondylitis 20% improvement response rate at week 12, was achieved by significantly more patients receiving etanercept 50 mg once weekly (74.2%) or 25 mg twice weekly (71.3%) than those receiving placebo (37.3%; $P < 0.001$).

Infliximab

We identified 1 high quality meta-analysis on the general efficacy of infliximab. [124](#) The study included information on 2 trials of adult patients with ankylosing spondylitis. Pooled results presented statistically significantly greater improvements of etanercept than placebo-treated patients on the Assessment in Ankylosing Spondylitis 20% improvement. The chances of achieving Assessment in Ankylosing Spondylitis 20% improvement at 12 weeks (relative risk, 4.11; 95% CI, 2.62 to 6.44) and Assessment in Ankylosing Spondylitis 20% improvement at 24 weeks (relative risk, 3.18; 95% CI, 1.99 to 5.08) was significantly better in the infliximab treated group ($P < 0.00001$).

Psoriatic Arthritis

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

Direct Evidence

No direct evidence on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in adults or children exists that met inclusion criteria.

Indirect Evidence

Placebo Controlled

One systematic review provides indirect evidence on the comparative effectiveness of adalimumab, etanercept, and infliximab for adults with moderate to severe plaque psoriatic arthritis. [132](#) The analysis used results from 1611 patients in with psoriatic arthritis comparing adalimumab, etanercept or infliximab compared with placebo. There were no statistical difference in the relative risk of patients achieving an American College of Rheumatology 20% response for adalimumab, etanercept, or infliximab treated patients (Adalimumab compared with etanercept [RR, 0.63; 95% CI, 0.22 to 1.81], adalimumab compared with infliximab [RR, 0.60; 95% CI, 0.30 to 1.20], and etanercept compared with infliximab [RR, 0.96; 95% CI, 0.33 to 2.76]).

Adalimumab

We identified 1 high quality meta-analysis on the general efficacy of adalimumab.¹³² The study included information on 982 adult patients with psoriatic arthritis, of which 413 were present in adalimumab compared with placebo trials. Pooled results presented statistically significantly greater improvements of adalimumab- than placebo-treated patients on all included outcome measures. Patients on adalimumab were more likely to achieve the Psoriatic Arthritis Response Criteria (RR, 2.33; 95% CI, 1.80 to 3.01) compared with placebo ($P>0.05$). In like fashion the adalimumab treated patients were more likely to achieve an American College of Rheumatology 20 response, (RR, 3.42; 95% CI, 2.08 to 5.63), American College of Rheumatology 50, (RR, 8.71; 95% CI, 4.30 to 17.66), or American College of Rheumatology 70 (RR, 15.75; 95% CI, 4.44 to 55.82) than the placebo treated patients (all $P<0.05$).

Alefacept

One phase II trial has been reported on in the literature on the use of alefacept in psoriatic arthritis.¹³⁴ The study included 185 patients suffering from moderate to severe psoriatic arthritis, which was defined as having at least 3 swollen joints and 3 tender or painful joints, who had an inadequate response to methotrexate therapy. Patients continued current methotrexate therapy and the dose had been stable for 4 weeks. The double-blinded phase of the study was 24 weeks, 12 weeks of treatment followed by 12 weeks of observation during which methotrexate treatment was continued in all participants. The dose was 15 mg every week. The alefacept group saw significantly greater response rates on American College of Rheumatology 20 than the placebo group, 54% compared with 23% ($P<0.001$). There were no significant differences in the other outcomes which included American College of Rheumatology 50/70, Psoriasis Area and Severity Index and Physician Global Assessment, though there was a trend that favored alefacept. For example, American College of Rheumatology 50/70 was achieved by 17% and 7% of the alefacept group compared with 10% and 2%, respectively, of the placebo group. Similarly, the Psoriasis Area and Severity Index 50 and a Physician Global Assessment of clear or almost clear were reported in 45% and 31% of the alefacept group compared with 31% and 24% in the placebo group.

Etanercept

We identified 1 high quality meta-analysis on the general efficacy of etanercept.¹³² The study included information on 265 adult patients with psoriatic arthritis in the 2 included etanercept trials. Pooled results presented statistically significantly greater improvements of etanercept- than placebo-treated patients on all outcome measures included. At 12 weeks the relative risk for achieving the Psoriatic Arthritis Response Criteria was 2.68 (95% CI, 1.78 to 4.04) for etanercept compared with placebo ($P<0.05$). Similarly, the etanercept treated patients were much more likely to reach an American College of Rheumatology 50 or 70 (RR, 10.68; 95% CI, 4.40 to 25.89 and RR, 14.75; 95% CI, 1.97 to 110.51, respectively) than the placebo treated patients (all $P<0.05$). Additional outcomes can be found in the individual studies of etanercept in patients with psoriatic arthritis.^{135, 136} In both fair studies patients were allowed to continue methotrexate therapy as long as it had been stable for 4 weeks prior. One study lasted 12 weeks;¹³⁵ the other trial was double-blinded for 24 weeks.¹³⁶ Both studies had the same dosing regimen of 25 mg of etanercept twice-weekly subcutaneous injections. Quality of

life was significantly improved as measured by the Health Assessment Questionnaire in both studies. Mean improvements were 83% in etanercept- compared to 3% in placebo-treated patients in the 12 week study ($P<0.0001$). In the longer study, at 24 weeks the mean improvement was 54% in the etanercept group and 6% in the placebo group ($P<0.0001$).

Infliximab

We identified 1 high quality meta-analysis on the general efficacy of infliximab.¹³² The study included information on 982 adult patients with psoriatic arthritis of which 304 were present in infliximab compared with placebo trials. Pooled results presented statistically significantly greater improvements of infliximab- than placebo-treated patients on all included outcome measures. The relative risk for achieving the Psoriatic Arthritis Response Criteria was 3.03 (95% CI, 2.27 to 4.04) for infliximab compared with placebo ($P>0.05$). In like fashion the infliximab treated patients were more likely to achieve an American College of Rheumatology 20, (RR, 5.71; 95% CI, 3.53 to 9.25); American College of Rheumatology 50, (RR, 14.73; 95% CI, 5.11 to 42.43); or American College of Rheumatology 70, (RR, 19.21; 95% CI, 3.77 to 97.87) than placebo treated patients (all $P<0.05$).

Additional outcomes were in the individual two fair studies on the use of infliximab in patients with psoriatic arthritis.¹³⁷⁻¹⁴⁰ In both studies patients were allowed to continue methotrexate therapy as long as it had been stable for 4 weeks prior. The earlier study was double-blinded for 16 weeks;¹³⁷ the other trial was double-blinded for 24 weeks with cross-over allowed at week 16 for non-responders.¹³⁸ Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, 14 and the longer study had an additional injection at week 22. Quality of life was significantly improved as measured by the Health Assessment Questionnaire in both studies. Mean improvements were 49.8% in infliximab compared to -1.6% in placebo-treated patients in the smaller study ($P<0.001$). In the bigger study, at 14 weeks the mean improvement was 48.6% in the infliximab group and an 18.4% loss in the placebo group ($P<0.001$).

Psoriatic Arthritis in Children

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in children exists that meets inclusion criteria. 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.

Direct Evidence

We did not find any head-to-head randomized controlled trials or observational studies comparing one targeted immune modulator to another that met inclusion criteria.

Indirect Evidence

Evidence was insufficient to make indirect comparisons.

Placebo controlled

Infliximab

One fair systematic review with meta-analyses¹⁵³ and 4 randomized controlled trials compared infliximab to placebo.¹⁵⁴⁻¹⁵⁷ One of these trials addressed patients with multiple draining abdominal or perianal fistulas.¹⁵⁵

The systematic review focused on the maintenance of remission in Crohn's disease patients treated with infliximab.¹⁵³ Three studies were included in the analysis. Pooled data showed that infliximab was more effective than placebo in maintenance of remission (relative risk, 2.50; 95% CI, 1.64 to 3.80; $P < 0.001$). Infliximab-treated patients also demonstrated better clinical response (relative risk, 2.19; 95% CI, 1.27 to 3.75; $P = 0.005$). Infliximab was also superior for corticosteroid-sparing effects (relative risk, 3.13; 95% CI, 1.25 to 7.81; $P = 0.01$) and for complete healing of perianal and enterocutaneous fistulas (relative risk, 1.87; 95% CI, 1.15 to 3.04; $P = 0.01$).

Two of the component trials included in the above meta-analysis reported outcomes not discussed in that analysis.^{154, 155} We therefore present those studies and the relevant outcomes.

To assess the ability of infliximab to maintain treatment response, maintenance infusions of infliximab were compared to placebo in the A Crohn's disease Clinical study Evaluating infliximab in a New long term Treatment regimen (ACCENT) I trial (multiple articles).¹⁵⁴ In this trial, 335 patients responding (CDAI ≥ 70 points) at 2 weeks to an initial infliximab infusion of 5 mg/kg were randomized to repeat infusions of placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at week 2 and 6 and then every 8 weeks thereafter until week 46. Primary outcome measures included time to loss of response (CDAI ≥ 175) and the proportion of week 2 responders in remission (CDAI < 150) at week 30. Compared to placebo, infliximab-treated patients had a significantly longer time to loss of response (46 weeks compared with 19 weeks, $P = 0.0002$) and the odds of being in remission at week 30 were nearly 3 times greater. Infliximab-treated patients also had better endoscopic healing, fewer hospitalizations, fewer surgeries, decreased corticosteroid use, fewer hours lost from work, and better quality of life scores ($P < 0.05$ for all).¹⁵⁸⁻¹⁶⁰ Additional analyses found scheduled maintenance treatment with infliximab to have better mucosal healing than episodic treatment ($P = 0.007$).¹⁶¹

The second trial compared the efficacy of infliximab to placebo in patients with enterocutaneous or perianal fistulas, a serious complication of Crohn's disease characterized by abnormal communication between the gut and the skin with small bowel or colonic contents draining to the skin surface.¹⁵⁵ In this trial (ACCENT II),¹⁵⁵ 195 patients with Crohn's disease and 1 or more draining abdominal or perianal fistulas who responded to 3 open-label 5 mg/kg infusions of infliximab were randomized to maintenance treatment with 8-week infusions of infliximab 5 mg/kg or placebo. Patients that did not respond to open-label treatment ($n = 87$) also were followed for safety. The primary outcome was defined as time to loss of response. On average, patients randomized to infliximab maintenance therapy maintained their response for more than 26 weeks longer than placebo ($P < 0.001$). At week 54, 36% of infliximab-treated patients had a complete absence of draining fistulas compared to 19% of placebo-treated patients ($P = 0.009$). At 6 weeks, infliximab also was more efficacious than placebo in a subgroup of women with rectovaginal fistulas (fistula closure 61% and 45%, respectively).¹⁶²

Compared to placebo, infliximab-treated patients had fewer hospitalizations (11 compared with 31; $P < 0.05$), fewer mean hospitalization days (0.5 compared with 2.5 days/100; $P < 0.05$), and fewer surgeries and procedures (65 compared with 126; $P < 0.05$).¹⁶³ No differences between active treatment and placebo were found in the number of fistula-related abscesses.¹⁶⁴

Two fair trials were not included in the above meta-analyses. One trial examined the efficacy of a single infusion of infliximab at doses of 5, 10, and 20 mg/kg in Crohn's disease (CDAI scores between 220 and 400).¹⁵⁶ Randomized patients were refractory to corticosteroids, mesalamine, 6-mercaptopurine, or azathioprine. This trial demonstrated significantly better efficacy of a single infusion of infliximab compared to placebo. In the 12 week multinational trial,¹⁵⁶ 108 patients randomized to infliximab 5, 10, or 20 mg/kg or placebo were assessed at 2, 4, and 12 weeks. Responders were characterized as having a CDAI reduction of 70 points or more. Quality of life with respect to bowel function (Inflammatory Bowel Disease Questionnaire) and C-reactive protein concentrations also were assessed. At 4 weeks, compared to placebo, significantly more infliximab-treated patients were characterized as CDAI responders ($P < 0.005$). Quality of life scores and C-reactive protein concentrations also were significantly better than placebo in patients treated with infliximab ($P < 0.05$ and $P < 0.01$, respectively).¹⁶⁵

The second trial evaluated the efficacy of infliximab compared with azathioprine or 6-mercaptopurine in steroid-dependent Crohn's disease patients.¹⁵⁷ Patients with active Crohn's disease despite prednisone treatment for more than 6 months were stratified and randomized to infliximab (5 mg/kg) or placebo at weeks 0, 2, and 6. Success rate (defined as percentage with CDAI < 150 and off steroids) at week 24 was superior in infliximab group (57% compared with 29%; odds ratio, 3.3; 95% CI, 1.5 to 7.4; $P = 0.003$). Patients were stratified based on whether or not they were azathioprine/6-mercaptopurine failed or naive. There was no significant interaction between treatment and stratum. Steroid resistance was less common in the infliximab group (5% compared with 23%; odds ratio, 5.1; 95% CI, 1.3 to 19.2; $P = 0.01$).

Certolizumab pegol

Three trials comparing certolizumab pegol with placebo met our eligibility criteria.¹⁴⁹⁻¹⁵² However, two were determined to be poor of quality primarily due to high rates of attrition.

The fair quality trial^{151, 152} randomized 292 patients with moderate-to-severe active Crohn's disease to certolizumab pegol (100, 200, or 400 mg) or placebo for 20 weeks. All doses of certolizumab pegol were superior to placebo for all outcomes. At all time points, certolizumab pegol produced higher response rates (≥ 100 point CDAI decrease) than placebo. Response rates for certolizumab pegol 400 mg at week 12 were 44 percent versus 35.6 percent for placebo ($P = NS$).¹⁵¹

A post hoc analysis of 290 patients assessed health-related quality of life data.¹⁵² The percentage of patients achieving remission on the Inflammatory Bowel Disease Questionnaire (defined as a score > 170 points) at week 12 was greater for all certolizumab pegol doses (100-, 200-, 400 mg) compared with placebo (38.4%, 23.6%, 38.9% compared with 23.4%, $P < 0.05$).

Adalimumab

The Crohn's Trial of the Fully Human Antibody for Remission Maintenance (CHARM) compared adalimumab to placebo.¹⁴⁵⁻¹⁴⁸ In this fair study, 884 patients with moderately to severely active Crohn's disease (CDAI \geq 220 and \leq 450) enrolled in the trial for an induction period of four weeks of which 778 were randomized to placebo, adalimumab 40 mg every second week or adalimumab 40 mg/week. At week 56, a significantly greater percentage of patients achieved remission in both adalimumab groups compared with placebo (36% and 41% compared with 12%; $P < 0.001$).¹⁴⁵ All-cause hospitalization risk was lower in the combined adalimumab group than the placebo group at 3 months (5.1% compared with 13.1%, $P < 0.01$) and 12 months (12.6% compared with 25.2%, $P < 0.01$).¹⁴⁶ The hazard ratio for all-cause hospitalization was 0.40 (95% CI, 0.26 to 0.62; $P < 0.001$) for the combined adalimumab group compared with the placebo group; the hazard ratio for hospitalization related to Crohn's disease was 0.42 (95% CI, 0.24 to 0.72; $P = 0.002$). Health reported quality of life (determined by Inflammatory Bowel Disease Questionnaire and Short Form 36 Health Survey) was better in adalimumab-treated patients.¹⁴⁷ Differences in mean Inflammatory Bowel Disease Questionnaire scores between adalimumab and placebo were statistically significant at all visits after week 4 ($P < 0.001$ for adalimumab every other week and $P < 0.05$ for adalimumab weekly). At week 56, the mean Inflammatory Bowel Disease Questionnaire score for the adalimumab groups was greater than placebo (18 points and 16 points greater for each active arm). Similar results were seen in Short Form 36 Health Survey scores across all subdomains. A subgroup analysis of 117 patients with fistulas (70 adalimumab- and 47 placebo-treated patients) showed a lower mean number of draining fistulas per day in adalimumab- than in placebo-treated patients (0.88 compared with 1.34, $P = 0.043$).¹⁴⁸

Natalizumab

A systematic review included four 12-week trials and assessed efficacy of 1, 2, or 3 infusions of natalizumab (300 mg or 3 to 4 mg/kg) with placebo.¹⁶⁶ Positive responses were seen with 1 injection of natalizumab. Furthermore, analyses suggested a trend toward increased benefits with additional injections. After 12 weeks, 3 infusions of natalizumab (4 mg/kg) compared with placebo indicated the relative risk of failure to induce remission with natalizumab was statistically significantly reduced (0.87; 95% CI, 0.78 to 0.98), as was the relative risk of failure to induce clinical response (0.85; 95% CI, 0.67 to 0.95).

One component study in the systematic review assessed quality of life.¹⁶⁸ This trial randomly assigned 248 patients to 1 of 4 treatment arms: 1 or 2 infusions of 3 mg/kg natalizumab, 2 infusions of 6 mg/kg natalizumab, or placebo. At week 6, all 3 natalizumab groups had significant improvement in mean Inflammatory Bowel Disease Questionnaire scores (155, 163, 155) compared with 145 for placebo (compared with placebo, P values were 0.008, < 0.001 , and 0.001, respectively). However, at week 12, only the 2-infusion natalizumab group was significantly better than placebo ($P = 0.021$). One randomized controlled trial (not included in the above meta-analysis) showed consistent results.¹⁶⁹ This trial, the Efficacy of Natalizumab in Crohn's disease Response and Remission (ENCORE), evaluated the efficacy of natalizumab induction therapy in patients with moderate-to-severe active Crohn's disease (CDAI \geq 220 and \leq 450). In the ENCORE trial, 309 patients were randomized to natalizumab or placebo. The

primary endpoint (response at week 8 sustained through week 12) was realized in more natalizumab than placebo patients (48% compared with 32%, $P<0.001$). Natalizumab showed significantly greater improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire score improvement at week 12 (+32.34 compared with +28.97, $P<0.001$).

We did not find any evidence on the general efficacy of abatacept, alefacept, anakinra, etanercept or rituximab for the treatment of Crohn's disease. Although some studies allowed stable doses of other immunomodulatory agents, no conclusive evidence exists to determine whether combination treatment of etanercept and infliximab with other agents (azathioprine, 6-mercaptopurine or methotrexate) leads to clinically and statistically greater improvements than monotherapy.

Pediatric Crohn's Disease

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease in children exists. In addition, no placebo-controlled trials on children with Crohn's disease met our eligibility criteria.

We identified 1 randomized controlled trial ("A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF α chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease" ortho REACH study) comparing 2 different dosing regimens of infliximab.¹⁷⁰

In this study, 112 patients with a Pediatric CDAI score greater than 30 were treated with 5 mg/kg of infliximab at weeks 0, 2, and 6. At week 10, patients who responded to treatment (88.4% of treated patients) were randomized to 5 mg/kg every 8 or 12 weeks through week 46. Pediatric patients were more likely to be in clinical response and remission at week 54 when given infliximab every 8 weeks rather than every 12 weeks.

Ulcerative Colitis

Infliximab is the only drug currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis. No evidence on the comparative effectiveness of targeted immune modulators for the treatment of ulcerative colitis exists that meets inclusion criteria. The only evidence found was in 2 studies of poor quality, primarily due to withdrawal rates of almost or more than 40% and differential rates of greater than 15 between the active and placebo groups.^{171, 172}

Ulcerative Colitis in Children

No targeted immune modulators are currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in children. There are no trials in the pediatric population of patients with ulcerative colitis at the time of our searches.

Plaque Psoriasis

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

Direct Evidence

We did not find any head-to-head trials directly comparing the efficacy and safety of one targeted immune modulator to another for the treatment of plaque psoriasis that met inclusion criteria.

Indirect Evidence

We did not find any indirect evidence on the comparative effectiveness of the targeted immune modulators for plaque psoriasis that met inclusion criteria.

Placebo controlled

Fair to good evidence from multiple placebo-controlled randomized controlled trials and meta-analyses exists on the general efficacy of adalimumab, alefacept, etanercept, and infliximab for the treatment of adults with plaque psoriasis. The EPC located 11 placebo-controlled trials that assessed the efficacy and safety of targeted immune modulators for the treatment of plaque psoriasis: 3 of adalimumab,¹⁷⁴⁻¹⁷⁶ 3 on alefacept,¹⁷⁷⁻¹⁷⁹ 4 on etanercept,¹⁸⁰⁻¹⁸³ and 1 on infliximab.¹⁸⁴ These studies on alefacept and etanercept have been pooled in meta-analyses.^{185, 186} We did not find any studies on other targeted immune modulators.

Children

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

We found 1 fair quality randomized controlled trial of etanercept in children.¹⁸⁷

In the initial phase of this trial, 211 children and adolescents aged between 4 and 17 with moderate to severe plaque psoriasis of at least 6 months duration were randomized to etanercept 0.8mg/kg/week or placebo for 12 weeks. Children receiving etanercept achieved consistently better improvement on Psoriasis Area and Severity Index, Physician Global Assessment, and the children's Dermatology Life Quality Index than those receiving placebo after 12 weeks. For example, after 12 weeks 57% of the children in the etanercept group demonstrated a Psoriasis Area and Severity Index 75 improvement compared with 11% in the placebo group ($P<0.001$). Patients who experienced a worsening of their disease during the initial double-blinded phase of the trial were eligible for "escape" to open-label etanercept. Twenty-six percent of children in the placebo group and 5% of etanercept-treated patients escaped during the first 12 weeks. One patient in the etanercept group withdrew in the first 12 weeks due to an adverse event.

Key Question 2. Adverse Events

What are the comparative incidence and severity of complications associated with the use of these drugs?

The available evidence is limited to comparisons of abatacept compared with infliximab and etanercept compared with infliximab.

Direct Evidence

Abatacept compared with infliximab

The only double-blinded head-to-head trial, the ATTEST study, also assessed the comparative safety of abatacept and infliximab.³¹ During 1 year of follow-up abatacept generally had a better adverse events profile than infliximab. The most frequently reported adverse events in both treatment groups were infections and infusion reactions (abatacept: 59.6%, infliximab: 68.5%; $P=NR$). Serious infections occurred more frequently in patients treated with infliximab than with abatacept (8.5% compared with 1.9%; $P=NR$). Likewise, more patients on infliximab than on abatacept suffered from serious adverse events (18.2% compared with 9.6%; $P=NR$). In the infliximab group 24.8% of patients experienced infusional events compared with 7.1% treated with abatacept. Overall, numerically more patients discontinued treatment in the infliximab than in the abatacept group (7.3% compared with 3.2%; $P=NR$).

Etanercept compared with infliximab

A non-randomized effectiveness trial³² and a prospective observational study³⁵ provide information on the comparative safety of etanercept and infliximab. The non-randomized trial used the adverse reaction terminology from the World Health Organization to determine adverse events.³² Overall, no significant differences in adverse events were reported between etanercept and infliximab. The overall discontinuation rates at 20 months were also similar (etanercept 21%; infliximab 25%). In both studies, however, infliximab treated patients had higher rates of withdrawal due to adverse events than patients on etanercept (data NR). Nevertheless, the evidence is insufficient to draw firm conclusions about the comparative safety of etanercept and infliximab.

Indirect Evidence

Evidence on the General Tolerability and Safety

Monotherapy

Most studies that examined the general efficacy of targeted immune modulators also determined their tolerability. In addition, some randomized controlled trials had open-label extension phases of up to 3 years.^{60, 102, 116, 204, 208, 209} Overall, targeted immune modulators appeared to have a good tolerability profile, although some rare but serious adverse events such as serious infections, lymphoma, leucopenia, malignancies, or demyelinations have occurred and are of concern.¹⁹⁶⁻²⁰³ Injection site or infusion reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events. In efficacy studies up to 97% of patients experienced at least 1 adverse event during the course of the study.

Discontinuation rates because of adverse events in patients treated with targeted immune modulators ranged from 3% to 16% and generally did not differ significantly from those in patients treated with placebo. A German retrospective, population-based cohort study reported that discontinuation rates because of adverse events, after 12 months of treatment were 16% for anakinra, 13% for etanercept, and 19% for infliximab.²¹⁰ Similarly, an uncontrolled effectiveness study including more than 6000 rheumatoid arthritis patients treated with adalimumab reported that 10.3% of patients withdrew because of adverse events over a time period of 60 weeks.¹⁹⁶

Injection site reactions (adalimumab, alefacept, anakinra, certolizumab pegol, etanercept) and infusion reactions (abatacept, infliximab, natalizumab, rituximab) were the most commonly and consistently reported adverse events. A small proportion of infusion reactions resembled anaphylactic reactions or led to convulsions and have to be considered serious adverse events. In efficacy trials of rituximab up to 32% of patients experienced infusion reactions during the first infusion. According to the US Food and Drug Administration prescription information, fatal infusion reactions have been reported for rituximab.²¹¹

In clinical trials of infliximab, 17% of patients experienced infusion reactions. These were mostly non-specific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. Nevertheless in 0.5% of all infusions severe reactions occurred.²⁰¹ Less than 2% of patients in clinical trials discontinued because of infusion reactions. Similarly, 10% of rheumatoid arthritis patients in a Japanese post-marketing surveillance of 5000 patients reported infusion reaction.²⁰³ The rates of infusion reactions reported in abatacept and natalizumab studies were 9% and 11%, respectively.

In contrast, injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity. Except for certolizumab pegol, injection site reactions were the most common reason for discontinuation due to adverse events. The mean, crude incidence of injection site reactions in randomized controlled trials and observational studies reviewed for this report was 17.5% (95% CI, 7.1 to 27.9) for adalimumab, 2.2% (95% CI, 0.4 to 3.9) for certolizumab pegol, 22.4% (95% CI, 8.5 to 36.3) for etanercept, but 67.2% (95% CI, 38.7 to 95.7) for anakinra. The higher incidence of injection site reactions for anakinra than for adalimumab and etanercept is consistent with numbers reported in the respective package inserts.²¹²⁻²¹⁴ The prescription information of alefacept reported injection site reactions in 16% of patients.²¹⁵

One large, multinational randomized controlled trial was designed primarily to evaluate the safety of anakinra over 6 months.¹⁹⁸⁻²⁰⁰ A total of 1414 patients were randomized to anakinra (100 mg) or placebo. After 6 months the rate of adverse events did not differ significantly between anakinra and placebo, except for injection site reactions (72.6% compared with 32.9%; *P* value not reported). Overall discontinuation rates (anakinra 21.6%; placebo 18.7%) and the rate of serious adverse events (anakinra 7.7%; placebo 7.8%) were also similar. However, a trend towards an increased risk of serious infections in anakinra-treated patients was apparent (2.1% compared with 0.4%; *P*=0.068). A 3-year uncontrolled extension of this study confirmed the higher rates of serious infections in patients treated with anakinra, compared with the controls during the blinded phase.²⁰⁸

The STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) study determined the safety of adalimumab in combination with standard rheumatoid therapy.⁶² At 22 weeks, there were no significant differences between adalimumab and placebo with respect to adverse events.

Long-term extension studies of randomized controlled trials and safety analyses of post-marketing surveillance reported that the incidence of adverse events does not increase over time.^{86, 99, 102, 204-207} A population-based post-marketing cohort study from Sweden reported that in 27% of patients treated with etanercept, at least 1 adverse event was reported.²¹⁶

Combination Therapy

The combination of 2 targeted immune modulators substantially increased the frequency of serious adverse events. For example, a combination of anakinra and etanercept led to a substantially higher rate of serious adverse events than etanercept monotherapy (14.8% for 50 mg etanercept plus anakinra, 4.9% for 25 mg etanercept plus anakinra, and 2.5% for etanercept only; $P=NR$).³⁷ Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6% compared with 7.4%; $P=NR$).

Similarly, 2 studies examining a combination of abatacept (2 mg/kg) and etanercept (25 mg twice weekly) compared with abatacept (2 mg/kg) monotherapy revealed that the combination was associated with a substantial increase in serious adverse events (16.5% compared with 2.8%).^{38, 111}

Specific Adverse Events

Serious infections

Because of the immunosuppressive nature of targeted immune modulators, serious infections including tuberculosis, pneumonia, osteomyelitis, sepsis, or progressive multifocal leukoencephalopathy are of special concern.

In June 2009, the manufacturer of efalizumab has voluntarily withdrawn the drug from the United States market because of an increased risk of progressive multifocal leukoencephalopathy. Progressive multifocal leukoencephalopathy is a rapidly progressive, viral infection of the central nervous system that leads to death or severe disability. A case series of more than 3000 patients treated with natalizumab for various indications did not meet our formal inclusion criteria. This study, however, estimated the risk of progressive multifocal leukoencephalopathy of roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months.²¹⁷ No evidence is available about the risk for progressive multifocal leukoencephalopathy for any of the other targeted immune modulators.

The US Food and Drug Administration has issued black box warnings or cautions in bold letters about an increased risk of infections for all targeted immune modulators.

An Italian retrospective cohort study of 1064 rheumatoid arthritis patients treated with adalimumab, etanercept, and infliximab estimated the incidence rate of infections as 35.9 per 1000 patient years.²¹⁸ Most infections were lower respiratory tract infections (34%) or skin and soft tissue infections (21%).

In efficacy trials, the incidence of serious infections was consistently higher in targeted immune modulators than in placebo-treated patients although clinically relevant differences rarely reached statistical significance due to lack of power. For example, in a large safety randomized controlled trial ($n = 1414$), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1% compared with 0.4%; $P=0.068$).¹⁹⁸⁻²⁰⁰ Similarly, a fair, uncontrolled effectiveness study of more than 6600 patients treated with adalimumab reported that 3.2% of patients suffered from serious infections during up to 60 weeks of follow-up.¹⁹⁶ Likewise, a fair meta-analysis of efficacy trials of abatacept, anakinra, and rituximab indicated an increased risk of serious infections without reaching statistical significance.²¹⁹ A good meta-analysis pooled data of more than 5000 rheumatoid arthritis patients from adalimumab and infliximab efficacy trials.²²⁰ The pooled odds

ratio for serious infections was 2.0 (95% CI, 1.3 to 3.1). The number needed to harm was 59 (95% CI, 39 to 125) within a treatment period of 3 to 12 months.

The START (Trial for Rheumatoid Arthritis with Remicade) study was a good randomized controlled trial (N=1084) conducted to assess the risk of serious infections during infliximab treatment for rheumatoid arthritis.⁹⁴ After 22 weeks of treatment patients on 3mg/kg infliximab had similar rates of serious infections as patients on placebo (relative risk, 1.0; 95% CI, 0.3 to 3.1). Patients treated with 10mg/kg infliximab had a significantly higher rate of serious infections than patients on placebo (relative risk, 3.1; 95% CI, 1.2 to 7.9).

Most long-term observational studies support these findings.^{197, 201, 221-226} The most common serious opportunistic infections were cases of tuberculosis. Other observational studies, some of which did not meet eligibility criteria for this review, reported infections with candida,²²⁷ coccidiomycosis,^{228, 229} Herpes Zoster,²³⁰ histoplasmosis,²³¹ listeriosis,²³² and pneumocystis carinii.²³³

Three retrospective database analyses^{222, 234, 235} and a prospective cohort study with a historic control group²³⁶ specifically determined the risk of tuberculosis or granulomatous infections during treatment with infliximab and etanercept. All studies reported a significant increase of risk attributable to anti-tumor necrosis factor therapy. A study of patients from the National Data Bank for Rheumatic Diseases (NDP) reported an incidence 52.5 cases per 100,000 patients years.²³⁶ Two other database analyses used the Spanish BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia)²³⁵ and different Swedish databases²²² which included data on infliximab and etanercept. Both reports indicated a substantially increased risk for tuberculosis in patients treated with etanercept or infliximab. The Swedish study reported a 4-fold increased risk of tuberculosis (relative risk, 4.0; 95% CI, 1.3 to 12) for patients on anti-tumor necrosis factor treatment compared with rheumatoid arthritis patients not exposed to etanercept or infliximab.²²²

Lymphoma and other malignancies

The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with rheumatoid arthritis.²³⁷ Data from controlled trials do not provide sufficient evidence concerning a further increase of risk attributable to targeted immune modulators or a combination of targeted immune modulators and methotrexate. A good meta-analysis pooled data of more than 5000 rheumatoid arthritis patients from adalimumab and infliximab placebo-controlled efficacy trials.²²⁰ The pooled odds ratio for malignancies was 3.3 (95% CI, 1.2 to 9.1). The number needed to harm was 154 (95% CI, 91 to 500) within a treatment period of 6 to 12 months. In this cohort authors identified 10 lymphomas in 3493 anti-tumor necrosis factor-treated patients compared with no lymphomas in 1512 patients treated with conventional rheumatoid arthritis therapy.

Several large retrospective cohort studies, using data from population-based databases, assessed the risk of malignancies during targeted immune modulators therapy. The only study that partially supported findings from the meta-analysis mentioned above was a Swedish retrospective cohort study of 1557 patients.²³⁸ Although results did not reach statistical significance, findings revealed a substantially increased relative risk of

lymphoma for patients treated with anti-tumor necrosis factor drugs compared with those on non-anti-tumor necrosis factor medications (hazard ratio, 4.9; 95% CI, 0.9 to 26.2) Various large retrospective cohort studies and a meta-analysis of individual patient data from etanercept trials²³⁹ did not detect an increased risk of hematopoietic malignancies²⁴⁰⁻²⁴³ or solid tumors.^{241 243-245} For example, a large retrospective Swedish cohort study, based on data of more than 60000 rheumatoid arthritis patients, found similar standardized incidence ratios for solid cancers (standard incidence ratio, 0.8; 95% CI, 0.4 to 1.8)²⁴⁴ and hematopoietic malignancies (relative risk, 1.1; 95% CI, 0.6 to 2.1)²⁴² between rheumatoid arthritis patients treated with anti-tumor necrosis factor medications and those on conventional therapy using both a contemporary and a historic control.

Two fair retrospective cohort studies, however detected an increased risk of skin cancers in patients treated with anti-tumor necrosis factor drugs.^{241, 246} The larger study (N=15789), reported a statistically significant association of a combination of anti-tumor necrosis factor treatment and methotrexate and non-melanoma skin cancer (hazard ratio, 1.28; 95% CI, NR; $P=0.014$).²⁴⁶

These findings, however, were not supported by a smaller retrospective cohort study that did not detect an increased incidence of squamous cell carcinoma in 1442 rheumatoid arthritis patients (4257 patient years) treated with etanercept (crude rate: 2.8 cases per 1000 patients).²⁴⁷

Cardiovascular events and congestive heart failure

No direct evidence on the comparative risk of targeted immune modulators for congestive heart failure exists. The existing evidence on the risk of cardiovascular events and congestive heart failure with anti-tumor necrosis factor therapy is mixed. A large retrospective cohort study (N=13,171) based on the National Databank for Rheumatic Diseases reported an absolute risk reduction for congestive heart failure of 1.2% (95% CI, -1.9 to -0.5; $P=NR$) for patients treated with anti-tumor necrosis factor therapy compared with those not treated with anti-tumor necrosis factor medications over a 2 year period.²⁴⁸ A retrospective cohort study based on the British Society for Rheumatology Biologics Register found that the risk for myocardial infarction is substantially reduced in patients responding to anti-tumor necrosis factor therapy after 6 months compared with non-responders (3.5 events per 1000 patient years compared with 9.4 events per 1000 patient years).²⁴⁹ Confounding by indication, however, cannot entirely be ruled out with such study designs.

By contrast, 2 retrospective cohort studies based on Medicare data reported a statistically significantly higher risk for hospitalization due to congestive heart failure in rheumatoid arthritis patients treated with anti-tumor necrosis factor drugs compared with those on methotrexate (hazard ratio, 1.70; 95% CI, 1.07 to 2.69).²⁵⁰ Similarly, a MedWatch analysis reports that half of the patients who developed new onset congestive heart failure under etanercept or infliximab treatment did not have any identifiable risk factors.²⁵¹ Indirect evidences comes from 3 trials, 2 on etanercept²⁵² and 1 on infliximab,²⁵³ that evaluated the efficacy of these drugs for the treatment of congestive heart failure. Information on the 2 etanercept studies, however, is limited to a review article.²⁵² The studies have not been published otherwise. We did not include this review article because it was not based on a systematic literature review. Nevertheless, we are briefly summarizing the findings.

Populations of these studies did not have any rheumatoid illnesses and, therefore, provide only indirect evidence. One of the 2 etanercept trials was terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.²⁵³ The package insert of infliximab issues a contraindication regarding the use in patients with congestive heart failure; the package inserts of etanercept and adalimumab emphasize precaution. Finally, 5 retrospective cohort studies could not detect statistically significant differences supporting an increased or a decreased risk for cardiovascular events or congestive heart failure between anti-tumor necrosis factor treatment and conventional rheumatoid arthritis^{249, 254-257} or Crohn's disease treatment.²⁵⁶

Other adverse events

Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but serious adverse events such as autoimmunity, demyelination, hepatotoxicity, and pancytopenia.

The infliximab package insert reports that 34% of patients treated with infliximab and methotrexate experienced transient elevations of liver function parameters.²⁶³ Severe liver injury, including acute liver failure has been reported.

Tolerability in Children

No evidence on the comparative safety of targeted immune modulators in children exists that met inclusion criteria. Furthermore, no study met our eligibility criteria for general safety.

Only minimal evidence exists on the safety of targeted immune modulators in pediatric populations. Overall, various methodological issues limit the quality and applicability of this body of evidence. A major limitation was that all studies had small sample sizes and lacked power to detect rare but potentially serious adverse events. Furthermore, except for the infliximab trial,¹¹⁷ all studies used withdrawal designs, which seriously compromise the external validity of findings. Only patients who responded, adhered to treatment, and had no intolerable adverse events were randomized to continuing active treatment or placebo. Therefore, all findings presented in the following paragraphs are subject to considerable uncertainty and should be interpreted accordingly. To provide a more realistic picture of the frequency of adverse events we focus on numbers from the open-label run-in phases that still included a less selected population than the randomized phases.

The 4 randomized controlled trials mentioned in the section on juvenile idiopathic arthritis also provided information on the general tolerability and safety of abatacept,¹¹⁴ adalimumab,¹¹⁵ etanercept,¹¹⁶ and infliximab.¹¹⁷ Generally, adverse events profiles in children were similar to those observed in adult populations. For example, in the adalimumab trial the most common adverse events were infections and injection site reactions,¹¹⁵ which were also the most commonly reported adverse events in adult populations. During the open-label run-in phase of the adalimumab and methotrexate arm (n = 85) the rate of any adverse event was 15.5 per patient year. The rate of serious adverse events was 0.1 per patient year.

Similarly, injection site reactions (39% of patients) and upper respiratory tract infections were the most commonly reported adverse events during the run-in phase of the

etanercept study. **116** Nine patients (15%) had to be hospitalized because of serious adverse events during the 2-year extension phase. **116, 209** Fifty% of the patients received etanercept up to 4 years. **270** The rate of serious adverse events in children treated over 4 years was 0.04 per patient-year. **270**

In an uncontrolled trial of etanercept (n=60), 20% of patients withdrew over a 12-months period because of adverse events including severe infections, pancytopenia, and cutaneous vasculitis. **271** In a case series based on data from a registry of children treated with etanercept in Austria and Germany (n = 322) withdrawal rates because of adverse events were substantially lower than in the trial. **118** Overall, 3.4% of etanercept-treated patients withdrew because of adverse events. Given the voluntary nature of this registry, under reporting of adverse events is possible.

Abatacept and infliximab are both administered intravenously and acute infusion reactions are a concern for both drugs. The rate of infusion reactions appeared to be greater in the infliximab study than in the abatacept study. Overall, 18% to 35% of patients treated with infliximab experienced acute infusion reactions. **117** A case series of patients (n = 11) with Crohn's disease or ulcerative colitis reported infusion reactions in 8.1% of patients. **272** By comparison, only 4% of patients on abatacept reported acute infusion reactions. **114** With respect to other adverse events, the profiles and frequencies were similar as in subcutaneously administered drugs.

On August 4th, 2009 the US Food and Drug Administration issued a warning about an increased risk of cancer in children and adolescents who receive anti-TNF drugs (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm>).

The warning is based on an investigation of cancer cases (n = 48) reported in children and adolescents with juvenile idiopathic arthritis, Crohn's disease, or other inflammatory diseases who were treated with anti-TNF drugs. About half of the cancers were lymphomas, some of which were highly malignant hepato-splenic T-cell lymphomas. Some of the malignancies were fatal. The analysis showed that an increased risk occurred after an average of 30 months of anti-TNF treatment. The Food and Drug Administration will add the new safety information as boxed warnings to the prescription information.

Key Question 3. Subgroups

Do the included drugs differ in their effectiveness or adverse events in the following subgroups: racial groups, genders, or age groups; or in patients taking other commonly prescribed drugs?

Age

Overall, the evidence of the effect of age on the effectiveness and safety of targeted immune modulators is mixed. For plaque psoriasis a pooled data analysis of 9 efficacy studies of alefacept did not show any differences in efficacy and safety in patients older than 65 years compared to younger patients during 12 weeks of treatment. **275**

This finding is supported by a pooled data analysis of 18 rheumatoid arthritis trials, 2 psoriatic arthritis trials, and 2 ankylosing spondylitis trials. **273** This analysis detected no significant differences in adverse events between elderly and younger (under 65) patients. In addition, a retrospective cohort study found no differences in discontinuation rates or mean DAS28 scores at 2 years between anti-tumor necrosis factor treated patients older than and younger than 65 years. **274**

In contrast, a prospective cohort study³⁴ (N=3694), indicated that response to treatment in rheumatoid arthritis patients treated with etanercept and infliximab was better in those younger than 65 years.³⁴ A post-marketing surveillance of 5000 rheumatoid arthritis patients reported a difference in adverse events in older patients.²⁰³ Risk factor for bacterial pneumonia in infliximab-treated patients was significantly higher in patients aged 70 years and older compared with patients in their 50's (odds ratio, 2.57; 95% CI, 1.48 to 4.46; $P<0.001$).

Racial groups

We did not identify any study specifically designed to compare the effect of targeted immune modulators in one racial group compared to another. In general, trials were conducted predominantly in white populations. No indirect evidence suggests that effectiveness or adverse events differ among races.

Gender

We did not identify any study specifically designed to compare the effects of targeted immune modulators in females compared to males. On average, study populations comprised more females than males; this fact reflects population and disease demographics and does not provide insight into treatment differences.

The available evidence is of low methodological quality and findings are mixed. One prospective observational study of rheumatoid arthritis patients treated with anti-tumor necrosis factor drugs found no significant differences in treatment response between men and women at 3 and 6 months of follow-up.²⁷⁷ The Japanese post-marketing surveillance study of infliximab, ²⁰³ reported that men were significantly more susceptible than women for bacterial pneumonia (odds ratio, 1.94; 95% CI, 1.29 to 2.93; $P=0.001$).

No other indirect evidence suggests that effectiveness or adverse events differ between females and males.

Comorbidities

Overall, the evidence of the effect of certain comorbid conditions on the efficacy and safety of targeted immune modulators is mixed. Three studies reported on rheumatoid arthritis patients with comorbid respiratory disease.^{111, 203, 276} One randomized controlled trial assigned rheumatoid arthritis patients with asthma or chronic obstructive pulmonary disease to 16 weeks of treatment with etanercept or placebo.²⁷⁶ Etanercept was associated with small increases in the incidence of serious adverse events in patients with chronic obstructive pulmonary disease; however, the relative risk was not significantly elevated (1.58; 95% CI, 0.65 to 3.87). A postmarketing surveillance of the safety of infliximab in rheumatoid arthritis patients reported a significantly higher risk factor for bacterial pneumonia in patients with comorbid respiratory disease (odds ratio, 3.90; 95% CI, 2.32 to 6.47; $P<0.001$).²⁰³ A subgroup analyses from 1 randomized controlled trial found that more adverse events were reported in rheumatoid arthritis patients with chronic obstructive pulmonary disease taking abatacept compared with placebo.¹¹¹ This was also the case for adverse events involving the respiratory system (43.2% compared with 23.5%) and serious adverse events (27% compared with 5.9%).

Three studies reported on patients with comorbid diabetes, 2 in rheumatoid arthritis patients^{111, 276} and 1 in plaque psoriasis.²⁷⁵ One trial stratified randomization of 535 rheumatoid arthritis patients by diagnosis of diabetes (with or without another comorbidity).²⁷⁶ Subjects were treated with etanercept (25 mg twice/week) or placebo for 16 weeks and to evaluate the occurrence of infections and serious adverse events. Etanercept was associated with small increases in the incidence of serious adverse events compared with placebo in patients with diabetes; however, the relative risk was not significantly elevated (1.34; 95% CI, 0.59 to 3.08).

These findings are supported by a subgroup analysis of 1 randomized controlled trial of rheumatoid arthritis patients with diabetes treated with abatacept.¹¹¹ Results indicated a slightly higher incidence of overall adverse events in diabetic patients taking abatacept compared with diabetic patients taking placebo (93.8% [n=65] compared with 90.3% [n=31]).¹¹¹ Rates of serious adverse events were higher in the abatacept group (21.5% compared with placebo 12.9%).

Results from a pooled analysis of 9 efficacy studies of alefacept for the treatment of plaque psoriasis indicated that alefacept has similar efficacy and safety in obese and diabetic patients compared to patients without these comorbidities.²⁷⁵

A post hoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, central nervous system-related events).^{198, 200} Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

No direct evidence on the comparative risk of targeted immune modulators in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, or plaque psoriasis and congestive heart failure exists. The existing evidence on the risk of cardiovascular events and congestive heart failure with anti-tumor necrosis factor therapy is mixed. A large retrospective cohort study (N=13 171) based on the National Databank for Rheumatic Diseases reported an absolute risk reduction for congestive heart failure of 1.2% (95% CI, -1.9 to -0.5; *P*=NR) for patients treated with anti-tumor necrosis factor therapy compared with those not treated with anti-tumor necrosis factor medications over a 2 year period.²⁴⁸ A retrospective cohort study based on the British Society for Rheumatology Biologics Register found that the risk for myocardial infarction is substantially reduced in patients responding to anti-tumor necrosis factor therapy after 6 months compared with non-responders (3.5 events/1000 patient years compared with 9.4 events/1000 patient years).²⁴⁹

By contrast, indirect evidence exists regarding an increased risk of worsening heart failure and mortality during anti-tumor necrosis factor alpha therapy. One trial²⁵³ evaluated efficacy of infliximab for the treatment of congestive heart failure. Infliximab was associated with higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.²⁵³ This evidence on congestive heart failure is presented in greater detail in the Key Question 2 section.

Other subgroups

We found 1 study, a case series of 131 pregnant women exposed to infliximab; however, this study did not meet our eligibility criteria.²⁷⁸ We describe it briefly because it is the only study addressing pregnant women. This study did not detect an increased risk of

adverse pregnancy outcomes compared to the general population. However, the sample size of this study was small and limitations of case series must be kept in mind. In addition, 27% of patients were lost to follow-up.

Other commonly prescribed medications

No formal drug interaction studies have been performed with any targeted immune modulators. Concurrent administration of anakinra with tumor necrosis factor-blocking agents (i.e., adalimumab, etanercept, infliximab) may be associated with an increased risk of serious infections, an increased risk of neutropenia, and no additional benefit compared to monotherapy. This evidence comes from a 24 week trial comparing concurrent treatment with anakinra and etanercept to etanercept monotherapy in patients with rheumatoid arthritis.³⁷ Patients treated with both anakinra and etanercept had a 7% rate of serious infections, compared to no infections observed in patients treated with etanercept alone. Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia. Because adalimumab and infliximab have a similar mechanism of action to etanercept, similar risks are believed to be associated with concurrent treatment with anakinra, although no formal evidence exists.

Because the majority of patients included in clinical studies received 1 or more concomitant medications (e.g., 5-aminosalicylates, antibiotics, antivirals, azathioprine, corticosteroids, folic acid, narcotics, nonsteroidal anti-inflammatory agents, and 6-mercaptopurine) with no identifiable differences in safety or tolerability, concomitant treatment with such agents is believed to be safe. One analysis of data from the first 6 months of a large, blinded, placebo-controlled safety trial of anakinra provides evidence for the risk of infections or other serious adverse events for some concomitant medications.¹⁹⁹ In this trial, no statistically significant differences were noted in the risk of infection or other serious adverse events between placebo- and anakinra-treated patients concurrently taking methotrexate or other disease-modifying antirheumatic drugs. Two patients taking anakinra and azathioprine developed serious infections compared to no patients taking azathioprine and placebo, although the number of patients taking azathioprine was deemed to be too small to draw any definitive conclusions. The adverse event profiles were similar for anakinra and placebo for patients who were or were not taking concomitant antihypertensive, antidiabetic, or statin drugs.

Concomitant administration of adalimumab and methotrexate has demonstrated a 29% to 44% reduction in the clearance of adalimumab. However, data do not suggest the need for dose adjustment of either methotrexate or adalimumab.²⁷⁹ Studies evaluating concomitant administration of methotrexate with anakinra or etanercept have not demonstrated changes in the clearance either drug. Although no formal studies have evaluated drug interactions between methotrexate and alefacept, or infliximab, concomitant administration of these agents is believed to be safe.