

Cytokine and CAM Antagonists and Related Agents Review

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Cytokine and CAM Antagonists and Related Agents Review

FDA-Approved Indications

Drug	Manufacturer	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Ankylosing Spondylitis (AS)	Plaque Psoriasis Moderate to severe in candidates for systemic therapy or phototherapy	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active Crohn's Disease	Psoriatic Arthritis (PsA)
abatacept ^a (Orencia [®]) ¹	Bristol-Myers Squibb	X	X (≥6 years)	--	--	--	--
adalimumab ^b (Humira [®]) ²	Abbott	X	X (≥4 years)	X	X	X (adults)	X
alefacept (Amevive [®]) ³	Astellas	--	--	--	X	--	--
anakinra ^c (Kineret [®]) ⁴	Amgen	X	--	--	--	--	--
certolizumab pegol (Cimzia [®]) ⁵	UCB	X	--	--	--	X (adults)	--
etanercept ^d (Enbrel [®]) ⁶	Amgen	X	X (≥2 years)	X	X	--	X
golimumab ^e (Simponi [™]) ⁷	Centocor	X	--	X	--	--	X
infliximab ^{e,f} (Remicade [®]) ⁸	Centocor	X	--	X	X	X (adults and children ≥6 years)	X
tocilizumab ^g (Actemra [®]) ⁹	Genentech	X	--	--	--	--	--
ustekinumab (Stelara [™]) ¹⁰	Centocor	--	--	--	X	--	-

^a In RA, abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. Abatacept should not be administered concomitantly with TNF antagonists or with anakinra.

^b In Crohn's Disease, adalimumab is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have a diminished response to or are intolerant to infliximab.¹¹

^c In RA, anakinra is indicated only for patients 18 years of age or older who have had an inadequate response to one or more DMARDs; may be used alone or in combination with other TNF agents.

^d In psoriatic arthritis, etanercept can be used in combination with methotrexate in patients who have failed methotrexate monotherapy. In rheumatoid arthritis, etanercept may be used with or without methotrexate.

^e In RA, infliximab and golimumab are indicated only in combination with methotrexate.

^f In Crohn's Disease, infliximab is indicated for patients who have had an inadequate response to conventional therapy; reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

^g In RA, tocilizumab is indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies.

Other Indications

infliximab (Remicade)

Ulcerative Colitis (UC): Reducing signs and symptoms, inducing and maintaining remission and mucosal healing, and eliminating corticosteroid use in patients with moderate to severe active UC who have had an inadequate response to conventional therapy.

Fistulizing Crohn's Disease: Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

Efalizumab (Raptiva®) has been voluntarily withdrawn from the US market as of June 2009 due to reports of progressive multifocal leukoencephalopathy (PML), a serious and almost always fatal brain infection caused by a virus.¹²

Overview

Cytokines and cell-adhesion molecules (CAMs) are chemical mediators involved in inflammatory processes throughout the body.

Cytokines

Cytokines are small proteins secreted in response to an immune stimulus for the purpose of mediating and regulating immunity, inflammation, and hematopoiesis. Cytokines are derived from monocytes and macrophages and induce gene expression of a number of proteins that contribute to the inflammatory response.

The actions of the various cytokines are widely varied. Cytokines are involved in fever, sleep, and anorexia, as well as in the induction of cyclooxygenase and lipoxygenases. In addition to stimulating production of other cytokines, they also increase adhesion molecule expression and activate B cells, T cells, and natural killer cells. They contribute to fibrosis and tissue degeneration associated with chronic inflammation, primarily by inducing the proliferation of fibroblasts and collagenase. The pro-inflammatory cytokines, tumor necrosis factor (TNF) and interleukin-1 (IL-1), are involved in tissue destruction in many chronic inflammatory diseases affecting various organs.¹³

TNF α and TNF β are closely related proteins recognized by the same cell surface receptor. TNF α is overproduced in the joints of patients with rheumatoid arthritis (RA) and is increased in the synovial fluid and synovium in patients with psoriatic arthritis (PsA) and in the skin of psoriatic lesions.^{14,15,16,17,18} Increased expression of TNF α has been reported in the serum, synovium, and sacroiliac joints in patients with ankylosing spondylitis (AS).^{19,20,21,22,23} TNF α also has a role in Crohn's disease.

There are two forms of IL-1, IL-1 α and IL-1 β , both of which bind to the same cell surface receptor. IL-1 is present in increased concentrations in the synovia of patients with RA.^{24,25} It promotes inflammation as well as bone and cartilage resorption and plays a major role in the promotion of rheumatic inflammation.²⁶

In psoriasis, IL-12 and IL-23 have been implicated in the pathogenesis of psoriasis.²⁷ In plaque psoriasis, over-expression of IL-12 exists. IL-12 functions to induce and sustain TH1 immune responses leading to the secretion of interferon and the homing of T cells to the skin. Interleukin-23 also is over-expressed in psoriasis plaques and functions to maintain chronic

autoimmune inflammation via the induction of IL-17, regulation of T memory cells, and direct activation of macrophages. Ustekinumab is an antagonist of IL-12 and IL-23. Tocilizumab (Actemra) is an interleukin-6 (IL-6) receptor inhibitor; IL-6 is a proinflammatory cytokine.

Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins involved in the binding of cells, usually leukocytes, to each other, endothelial cells, or the extracellular matrix. Specific signals produced in response to wounds and infection control the expression and activation of these molecules. The interactions and responses initiated by binding of these CAMs to their receptors/ligands play important roles in the mediation of the inflammatory and immune reactions that constitute one line of the body's defense against these insults.

Most of the CAMs characterized so far fall into three general families of proteins: the immunoglobulin (Ig) superfamily, the integrin family, and the selectin family. The Ig superfamily of adhesion molecules bind to integrins on leukocytes and mediate their flattening onto the blood vessel wall with their subsequent extravasation into surrounding tissue. The integrin family of CAMs consists of an α chain and a β chain that mediate cell to cell interactions, such as leukocyte adherence to the vascular endothelium. Different sets of integrins are expressed by different populations of leukocytes to provide specificity for binding to different types of CAMs expressed along the vascular endothelium. The selectin family is involved in the adhesion of leukocytes to activated endothelium. This adhesion is initiated by weak interactions followed by stronger interactions that lead to extravasation through the blood vessel walls into lymphoid tissues and sites of inflammation. Other proteins that are functionally classified as CAMs are involved in strengthening the association of T cells with antigen-presenting cells or target cells, in T cell activation, and in recirculating lymphocytes back to the circulation via the lymphatic system.

Different CAMs have been implicated in inflammatory diseases (e.g., psoriasis), fibrotic diseases (e.g., degenerative diseases of the lung, liver, and kidney), and autoimmune diseases (e.g., RA). Vascular CAM-1 has been implicated in interactions between leukocytes and connective tissue, including RA synovial tissue fibroblasts. Such interactions within the synovium contribute to RA inflammation.²⁸ In psoriatic skin, intercellular CAM-1 (ICAM-1) cell surface expression is upregulated on endothelium and keratinocytes. Activation of T lymphocytes involves the interaction between lymphocyte function-associated antigen type 3 (LFA-3) on antigen-presenting cells and CD2 on T lymphocytes. This lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis.

Treatment Guidelines

The American College of Rheumatology (ACR) updated the guidelines for the management of RA in 2008.²⁹ Biologic disease modifying antirheumatic drugs (DMARDs) should be used only after failure of nonbiologic DMARDs. The only nonbiologic agents included in these recommendations are hydroxychloroquine (Plaquenil[®]), leflunomide (Arava[®]), methotrexate, minocycline (Minocin[®]), and sulfasalazine (Azulfidine[®]). The only biologics included in the guidelines are abatacept (Orencia), adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), and rituximab (Rituxan[®]). Recommendations for the use of biologic DMARDs are separated according to disease duration (< six months and \geq six months). The use of TNF blockers (etanercept, infliximab, and adalimumab) is stratified for durations of three months or longer or three to six months. TNF blockers can be used interchangeably with methotrexate in patients with early RA who have never received DMARDs and have high disease activity. Patients with early RA and only low or moderate disease activity are not considered candidates

for biologic therapy. TNF blocker plus methotrexate is recommended for patients with high disease activity for three months or longer with poor prognosis, no barriers related to treatment cost, and no insurance restrictions to accessing medical care. Golimumab (Simponi), certolizumab pegol (Cimzia) and tocilizumab (Actemra) were not available when the ACR update was released.

A consensus statement on the biologic agents for the treatment of rheumatic diseases was developed in conjunction with the 2009 international Annual Workshop on Advances in Targeted Therapies.³⁰ Evidence for the efficacy and safety of the biologic agents for the treatment of various diseases was reviewed. Abatacept is appropriate for patients with moderate to severe RA who had an inadequate response to MTX or to at least one TNF antagonist. Use abatacept with caution in patients with a history of COPD. Anakinra has an unclear role in the treatment of RA. Tocilizumab should be used with caution in patients who have a history of intestinal ulceration or diverticulitis. Lipid parameters and complete blood counts should be monitored periodically. Statin therapy may be warranted if elevations in lipid parameters are observed. Tocilizumab is a treatment option for patients with RA who have an inadequate response to MTX or to at least one TNF antagonist. Tocilizumab may be used as monotherapy for RA. Long term safety data are need for tocilizumab. The TNF antagonists, etanercept, infliximab and adalimumab, should be used in combination with MTX for RA. Golimumab has similar efficacy in RA; however, long term safety data are needed. There appears to be no difference in efficacy among the three TNF antagonists for PsA. All three agents have efficacy data maintained for two to seven years in open-label trials for the management of AS. Ustekinumab was still investigational at the time of the consensus statement development.

In the 2009 National Institute for Health and Clinical Excellence (NICE) clinical guidelines for the management of RA in adults, patients should be treated with combination of DMARDs including methotrexate (MTX) and at least one other DMARD as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms.³¹ Once disease control is satisfactory, cautiously try to reduce drug doses to levels that still maintain disease control. Return promptly to disease-controlling dosages at the first sign of a flare. Short term glucocorticoids are a treatment option to reduce inflammation for managing flares in people with established disease or in those patients with newly diagnosed RA. Long term use of glucocorticoids should only continue when all long term complications of glucocorticoid therapy have been fully discussed and when all other treatment options including biological agents have been offered. Anakinra is not recommended for the treatment of RA. Anakinra should not be used in combination with TNF antagonists. When new drugs are added to improve disease control in a patient with established RA, consider decreasing or discontinuing their pre-existing RA treatment once disease control has been achieved. For DMARDs, monotherapy with MTX is an acceptable treatment option. When conventional DMARDs do not provide disease control, biologic agents generally add significant benefit for symptom control, function and quality of life. When TNF antagonists are used, MTX should be used in combination as the combination of biological agents plus MTX was superior to the biological agent monotherapy for symptomatic benefit with some evidence of better functional outcomes, quality of life and joint damage. The combination of biological agents plus MTX was better than MTX monotherapy in studies evaluating radiological damage in RA. Treatment with TNF antagonists should be continued for six months following initiation of therapy; an adequate response is defined as an improvement in DAS28 of 1.2 points or more.

The 2008 American Academy of Dermatology (AAD) guidelines for the management of psoriasis and psoriatic arthritis recommend patients with mild to moderate psoriatic arthritis be treated with non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular corticosteroid injections, but the use of disease-modifying antirheumatic drugs (DMARDs) including

methotrexate along with biologic agents are considered the standard of care in patients with more significant psoriatic arthritis.^{32,33} Systemic therapy for plaque psoriasis may include methotrexate, cyclosporine, acitretin (Soriatane[®] CK Convenience Kit), and the biologic agents, adalimumab, etanercept, and infliximab.³⁴ Good-quality, patient-oriented evidence supports the recommendations (class A1) for all the following drugs for the treatment of psoriasis: alefacept, adalimumab, etanercept, and infliximab. Ustekinumab was not available at the time of guideline development.

For the treatment of severe ankylosing spondylitis, adalimumab or etanercept are recommended according to the 2008 guidance from National Institute for Health and Clinical Excellence (NICE).³⁵ Patients should be assessed 12 weeks after treatment is initiated, and treatment should be only continued in the presence of an adequate response defined as a reduction of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50 percent of the pre-treatment value or by two or more units and reduction of the spinal pain VAS by 2 cm or more. The BASDAI is the most commonly used instrument to measure the inflammatory activity of ankylosing spondylitis. The BASDAI is a validated, composite index that records patients' responses to six questions relating to the five major symptoms of ankylosing spondylitis: fatigue, axial pain, peripheral pain, stiffness and enthesopathy. The BASDAI score measures fatigue, spinal pain, joint pain, swelling, areas of localized tenderness, and morning stiffness. Patients who are intolerant to either adalimumab or etanercept should try therapy with the alternative agent. NICE does not recommend infliximab for the treatment of severe ankylosing spondylitis. An update to the 2008 guidance from NICE is expected in the fall of 2010.

The 2006 American Gastroenterology Association (AGA) medical position statement on treatment of inflammatory bowel disease recommends infliximab for patients who do not achieve adequate clinical response, despite treatment with conventional therapy, for patients with fistulizing Crohn's disease or for patients with Ulcerative Colitis.³⁶ Patients who respond to induction therapy should receive maintenance therapy with infliximab. The 2006 position statement does not address adalimumab or certolizumab pegol.

The National Psoriasis Foundation consensus statement from 2008 recommends that all patients receiving systemic or biologic agents for psoriasis be screened for latent TB infection prior to initiating any immunologic therapy.³⁷ Delaying immunologic therapy until latent TB infection prophylaxis is completed is preferable. Patients with a positive tuberculin skin test should be treated with a full course of latent TB infection prophylaxis before beginning immunosuppressive or immunomodulatory treatment. However, if the patient is adhering to his prophylactic regimen and is appropriately tolerating the regimen, therapy may be started after one to two months if the clinical condition requires treatment.

Pharmacology

Cytokine Antagonists

Antagonists that bind cytokines or their receptors can block cytokine activity. Biologics, such as the IL-1 receptor antagonist, anakinra (Kineret) and anti-TNF α agents, etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), certolizumab pegol (Cimzia), and adalimumab (Humira), exert their action by neutralizing the activities of the inflammatory agents IL-1 and TNF α , respectively. Ustekinumab (Stelara) is an IL-12 and IL-23 antagonist.³⁸

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody.^{39,40} Tocilizumab binds to IL-6 receptors and has been shown to inhibit IL-6-mediated

signaling through these receptors. IL-6 is a proinflammatory cytokine which is produced by T and B cells, lymphocytes, monocytes, and fibroblasts. IL-6 is involved in a variety of immune responses including T cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in the joints affected by inflammatory process such as RA.

Despite their common ability to inhibit TNF α bioactivity, the molecular structures and mechanisms of action of anti-TNF α agents are significantly different. The TNF-binding moiety of etanercept, a fusion protein, is derived from soluble TNF receptor subunits; infliximab is a chimeric (mouse-human) monoclonal antibody to TNF while adalimumab, golimumab, and certolizumab pegol are fully human anti-TNF monoclonal antibodies.^{41,42,43}

CAM Antagonists

The CAM antagonist, alefacept (Amevive) is a T cell modulator. Alefacept interferes with the activation, reactivation, and migration of T lymphocytes. It is thought that overactivity of T cells and their subsequent trafficking into the skin eventually causes the excessive growth of skin cells that result in psoriasis.⁴⁴ Alefacept is produced by fusing the Fc portion of IgG1 with LFA-3. This fusion protein blocks the activation of T cells by antigen-presenting cells. In addition, the Fc portion of alefacept interacts with the Fc receptor on natural killer cells, which then destroy the T cell to which the LFA-3 portion of the drug is bound.

Abatacept (Orencia) is a fully recombinant fusion protein that serves as a co-stimulatory or second-signal blocker of T cell activation. It disrupts the activation pathway of T cells, causing disturbances in key mechanisms of inflammation and progressive joint destruction. By mimicking endogenous CTLA4, abatacept blocks the costimulatory signal required for optimal activation of the T cells. This leads to poorly responsive T cells and potentially cell death.

Pharmacokinetics

Drug	Half-life(days)	Bioavailability (%)
abatacept (Orencia) ⁴⁵	13 to 17	(IV)
adalimumab (Humira) ^{46,47}	10 to 20	64 (SC)
alefacept (Amevive) ⁴⁸	11.3	63 (IM)
anakinra (Kineret) ⁴⁹	0.17 to 0.25	95 (SC)
certolizumab pegol (Cimzia) ⁵⁰	14	80 (SC)
etanercept (Enbrel) ⁵¹	4.3 \pm 1.3	nd
golimumab (Simponi) ⁵²	14	53 (SC)
infliximab (Remicade) ⁵³	7.7 to 9.5	(IV)
tocilizumab (Actemra) ⁵⁴	11 to 13 days	(IV)
ustekinumab (Stelara) ⁵⁵	14.9 to 45.6	nd

nd = no data

Contraindications/Warnings

abatacept (Orencia)⁵⁶

Abatacept should not be administered to patients with known hypersensitivity to abatacept or any of its components. Patients receiving concomitant abatacept and TNF antagonist therapy experienced more infections (63 percent) and serious infections (4.4 percent) compared to patients treated with only TNF antagonists (43 and 0.8 percent, respectively). No additional efficacy was observed with concomitant administration; therefore, concurrent abatacept and TNF antagonist therapy is not recommended.

Patients should be screened for latent tuberculosis (TB) infection prior to initiating therapy with abatacept. Abatacept has not been studied in patients with a positive TB screening test; therefore, safety of abatacept in patients with latent TB is not known. Additionally, screening for hepatitis B should be performed according to published guidelines prior to initiating therapy with abatacept.

Patients with chronic obstructive pulmonary disease (COPD) reported more adverse events in clinical trials than those treated with placebo. Use caution when administering abatacept to patients with RA and COPD and monitoring for worsening of their respiratory status.

Live vaccines should not be given concurrently or within three months of discontinuation of abatacept. Patients with JIA should be brought up to date with all immunizations prior to abatacept therapy. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations.

Anaphylaxis or anaphylactoid reactions (0.074 percent) have been reported following administration of abatacept. Appropriate medical support for the treatment of hypersensitivity reactions should be available when abatacept is administered.

alefacept (Amevive)⁵⁷

Alefacept induces dose-dependent reductions in circulating CD4+ and CD8+ T lymphocyte counts; therefore, therapy with this agent should not be initiated in patients with lymphopenia. Alefacept is contraindicated for use in patients with human immunodeficiency virus (HIV).

Alefacept is contraindicated in patients with known hypersensitivity to alefacept or any components of the product.

Alefacept induces dose-dependent reductions in circulating CD4+ and CD8+ T lymphocyte counts. Alefacept should not be initiated in patients with below normal level of CD4+ T lymphocytes. Every two weeks, CD4+ T lymphocyte counts should be monitored while on alefacept. If the CD4+ T lymphocyte counts are below 250 cells/mcL, alefacept dosing should be withheld and weekly monitoring instituted. Alefacept should be discontinued if the CD4+ T lymphocyte counts remain below 250 cells/mcL for one month.

In the 24-week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 alefacept-treated patients. The incidence of malignancies was 1.3 percent (11/876) for alefacept-treated patients compared to 0.5 percent (2/413) in the placebo group

Alefacept has the potential to increase the risk of infection and reactivate latent, chronic infections. Do not administer alefacept to patients with a clinically important infection, history of chronic infections, or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection during or after a course of alefacept. New infections should be closely monitored. If a patient develops a serious infection, alefacept should be discontinued.

anakinra (Kineret)⁵⁸

Anakinra is contraindicated in patients with known hypersensitivity to *Escherichia coli*-derived proteins or any components of the product.

Concurrent use of anakinra and etanercept therapy resulted in a higher rate of serious infections in the combination arm (seven percent) compared to etanercept alone (zero percent) without an increase in ACR response rates compared to etanercept monotherapy. Combination therapy with anakinra and TNF blockers is not recommended.

Anakinra has been associated with an increased incidence of serious infections versus placebo (two versus one percent, respectively) and should be discontinued if a patient develops a serious infection. Treatment with anakinra should not be initiated in patients with active infections. Safety and efficacy of anakinra in immunosuppressed patients or in patients with chronic infections have not been evaluated.

tocilizumab (Actemra)⁵⁹

No specific contraindications have been reported for use with tocilizumab.

Patients receiving tocilizumab are at an increased risk for developing serious infections that may require hospitalization or death. Most patients in clinical trials who developed serious infections were on concurrent immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, tocilizumab should be discontinued until the infection is controlled. Infections reported included active TB (pulmonary and extrapulmonary disease), invasive fungal infections including candidiasis, aspergillosis, and pneumocystis (localized or disseminated infections), and bacterial, viral and other infections due to opportunistic pathogens. Patients should be tested for latent TB before and during treatment with tocilizumab. In patients with chronic or recurrent infections, the risks and benefits of treatment with tocilizumab should be carefully considered prior to initiating therapy with tocilizumab. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab including the possibility of TB in patients who tested negative for latent TB infection prior to initiating therapy.

Gastrointestinal perforation has been reported in clinical trials with tocilizumab, mostly as a result of complications of diverticulitis. Patients with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Tocilizumab therapy has been associated with a higher incidence of neutropenia. Tocilizumab should not be initiated in patients with a low absolute neutrophil count ($ANC < 2000/mm^3$). If the ANC during tocilizumab therapy is less than $500/mm^3$, therapy is not recommended. Monitor neutrophils every four to eight weeks. Dose modifications for tocilizumab are recommended based on ANC results.

Therapy with tocilizumab has been associated with a reduction in platelet counts. Serious bleeding associated with tocilizumab has not been reported in clinical trials. Tocilizumab should

not be initiated in patients with baseline platelet counts of $<100,000/\text{mm}^3$. If the platelet count falls to less than $50,000/\text{mm}^3$, tocilizumab is not recommended. Platelet counts should be monitored every four to eight weeks. Dosage adjustments are recommended based on platelet counts.

Elevations of liver transaminases were reported in clinical trials with tocilizumab but did not result in permanent or clinically evident hepatic injury. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs such as methotrexate were used in combination with tocilizumab. Reported elevations of ALT and AST resolved with discontinuation of tocilizumab. Therapy with tocilizumab should not be initiated in patients with baseline elevations of ALT or AST of greater than 1.5 times the upper limit of normal. If ALT or AST exceed more than five times the upper limit of normal, tocilizumab is not recommended. ALT and AST levels should be monitored every four to eight weeks. Dose modifications for tocilizumab due to elevations of ALT and/or AST are recommended.

Tocilizumab is associated with increases in lipid parameters including total cholesterol, triglycerides, LDL-cholesterol, and/or HDL-cholesterol. Lipid parameters should be assessed at approximately four to eight weeks after initiation of tocilizumab therapy and then measured every six months. Patients should be managed according to clinical guidelines for hyperlipidemia.

ustekinumab (Stelara)⁶⁰

No specific contraindications have been reported for use with ustekinumab.

Ustekinumab may increase the risk of infections and reactivation of latent infections, particularly in patients genetically deficient in IL-12/IL-23. This medication should not be given to patients with any clinically important active infection. Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Serious infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. Patients should be evaluated for tuberculosis prior to initiating therapy with ustekinumab.

Prior to initiating therapy, patients should receive all immunizations appropriate for their age.

As an immunosuppressant, ustekinumab may increase the risk of malignancy. The safety of ustekinumab in patients with a history of or a known malignancy has not been evaluated.

One case of Reversible Posterior Leukoencephalopathy syndrome (RPLS) has been reported in clinical trials with ustekinumab. RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

TNF-blocking agents – adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi) and infliximab (Remicade)^{61,62,63,64,65}

The TNF-blocking agents all have a warning stating serious and sometimes fatal infections, including bacterial, tuberculosis (TB), viral, and opportunistic invasive fungal infections have been reported with their use. Among opportunistic infections, tuberculosis including reactivation of latent TB, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and

pneumocystosis were the most commonly reported. Typically, patients present with disseminated disease rather than localized disease and are on concurrent immunosuppressants, such as methotrexate or corticosteroids plus an agent in this review. Treatment with a TNF blocker should not be initiated in patients with an active infection, and the risk/benefit ratio should be evaluated for patients with chronic or recurrent infections, exposure to TB, underlying conditions which predispose them to infections, or who have resided or traveled in areas of endemic TB or endemic mycoses. As a result, these agents must be used with caution in patients on concomitant immunosuppressive therapy and/or active or predisposition to infections. It is recommended that patients be evaluated with a TB skin test and that latent TB infections be treated prior to therapy. TNF blockers should be discontinued if a patient develops a serious infection or sepsis.

The TNF blockers also possess a warning concerning the increased incidence of lymphoma in patients receiving these agents, especially in patients with active RA. In the controlled portions of clinical trials of some TNF-blocking agents, more malignancies (excluding lymphoma and nonmelanoma skin cancer) have been observed in patients receiving those TNF blockers compared with control patients. The potential role of TNF-blocking therapy in the development of malignancies is not known.

In November 2009, the risk of lymphoma and other malignancies, some fatal, reported in children and adolescent patients treated with TNF blockers was added to the boxed warning for the TNF blockers. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range one to 84 months). Most of the patients were receiving concomitant immunosuppressants.

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Clinical trials of TNF blockers show a higher rate of serious CHF-related adverse reactions. Physicians should exercise caution when using TNF blockers in patients who have heart failure and monitor them carefully.

Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Serious infections were seen in clinical studies with concurrent use of anakinra and etanercept, with no added benefit. Due to the nature of the adverse reactions seen with this combination therapy, similar toxicities may result from combination of anakinra and other TNF blocking agents.

Treatment with agents that inhibit TNF has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis and new onset or exacerbation of seizure disorders have been observed. Exercise caution in

considering the use of TNF blockers in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with certolizumab pegol. Use caution in patients being treated with TNF blockers who have ongoing, or a history of, significant hematologic abnormalities.

The possibility exists for TNF blocking agents to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. The impact of treatment with TNF blockers on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood.

Treatment with TNF blockers may result in the formation of autoantibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with TNF blockers, treatment should be discontinued and the patient should be carefully evaluated.

adalimumab (Humira)⁶⁶

Adalimumab has no specific contraindications.

Patients using adalimumab should be monitored closely for malignancies. Recent studies show malignancies are seen more often than in controls, and lymphoma is seen more often than in the general population. Rare reports of pancytopenia and lupus have been observed in patients receiving adalimumab therapy.

Serious hypersensitivity reactions including anaphylaxis and angioneurotic edema have been reported with adalimumab therapy. If an anaphylactic or other serious allergic reaction occurs, administration should be discontinued immediately and appropriate therapy instituted.

Do not start adalimumab during an active infection. If an infection develops, monitor carefully and stop adalimumab if the infection becomes serious.

HBV reactivation has occurred with TNF-blocker therapy including adalimumab. Monitor HBV carriers during and several months after therapy. If reactivation occurs, discontinue TNF-blocker therapy and begin antiviral therapy. Safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

If cytopenia or pancytopenia develops, patients should seek immediate medical attention if symptoms develop and consider discontinuation of adalimumab.

It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating therapy. Patients on adalimumab may receive concurrent vaccinations, except for live vaccines.

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may result from combination of anakinra and other TNF blocking agents. Therefore, the combination of adalimumab and anakinra is not recommended.

certolizumab pegol (Cimzia)⁶⁷

Certolizumab pegol has no specific contraindications to its use. The prescribing information does contain the same warnings as the other TNF-blocking agents.

In 2008, a black box warning was added to the labeling for certolizumab pegol regarding an increased risk of serious infections including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. These infections have lead to hospitalization or death. Certolizumab pegol should be discontinued if a patient develops a serious infection or sepsis. Perform test for latent TB; if positive, start treatment for TB prior to starting certolizumab pegol. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. Most patients who developed serious infections were also on concurrent methotrexate or corticosteroids.

Reactions with symptoms that could be compatible with hypersensitivity reactions have been rarely reported with certolizumab pegol, including angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. If such symptoms occur, discontinue further administration of certolizumab pegol and treat appropriately. There are no data on the risks of using certolizumab pegol in patients who have experienced severe hypersensitivity reactions towards another TNF blocker.

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, and thrombocytopenia) have been infrequently reported with certolizumab pegol. Use with caution in patients being treated with certolizumab pegol who have ongoing, or a history of, significant hematologic abnormalities.

No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving certolizumab pegol. Do not administer live vaccines or attenuated vaccines concurrently with certolizumab pegol.

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF blocker, with no added benefit. Because of the nature of the adverse effects seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blockers. Therefore, the combination of certolizumab pegol and anakinra is not recommended.

Treatment with certolizumab pegol may result in the formation of autoantibodies, and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with certolizumab pegol, discontinue treatment.

The use of TNF inhibitors, including certolizumab pegol, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Use caution in considering the use of certolizumab pegol in patients with pre-existing or recent onset CNS demyelinating disorders. CNS disorders reported include seizures, optic neuritis, and peripheral neuropathy. The causal relationship to certolizumab pegol remains unclear.

etanercept (Enbrel)⁶⁸

Etanercept should not be administered to patients with sepsis or with known hypersensitivity to it or any of its components. The risks and benefits of treatment with etanercept should be

considered prior to initiating therapy in patients with chronic or recurrent infection, who have been exposed to tuberculosis, who have resided or traveled to areas of endemic tuberculosis or endemic mycoses, or with underlying conditions that may predispose them to infection such as advanced or poorly controlled diabetes.

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with etanercept. Infections have included bacterial sepsis and TB. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with etanercept. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, etanercept should be discontinued.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including etanercept. TB may be due to reactivation of latent TB infection or to new infection. Post marketing cases of TB reactivation have been reported for TNF-blockers, including etanercept. Patients should be evaluated for TB risk factors and be tested for latent TB infection prior to initiating etanercept and during treatment. Treatment of latent TB infection should be initiated prior to therapy with etanercept. Treatment of latent TB in patients with a reactive tuberculin test reduces the risk of TB reactivation in patients receiving TNF-blockers. Some patients who tested negative for latent TB prior to receiving etanercept have developed active TB. Physicians should monitor patients receiving etanercept for signs and symptoms of active TB, including patients who tested negative for latent TB infection. Tuberculosis should be strongly considered in patients who develop a new infection during etanercept treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with etanercept. The causal relationship to etanercept remains unclear.

In a small study of 48 hospitalized patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with etanercept was similar to patients treated with placebo at one month, but significantly higher after six months. Physicians should use caution when using etanercept in patients with moderate to severe alcoholic hepatitis.

Serious infections were seen in clinical studies with concurrent use of anakinra and etanercept, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may result from combination of anakinra and other TNF blocking agents.

It is recommended that JIA patients, if possible, be brought up to date with all immunization in agreement with current immunization guidelines prior to initiating therapy. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

In a randomized, placebo-controlled trial with 180 patients with Wegener's granulomatosis, etanercept-treated patients experienced more non-cutaneous solid malignancies than patients who received placebo. Clinical outcomes with etanercept plus cyclophosphamide, methotrexate and corticosteroids did not improve compared to the three drug treatment alone. Etanercept is not indicated for the management of Wegener's Granulomatosis.

golimumab (Simponi)⁶⁹

Golimumab has no specific contraindications.

The use of TNF-blockers, including golimumab, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal in some instances. Patients at risk for HBV infection should be evaluated for previous evidence of HBV infection before initiating TNF-blocker therapy. TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated in patients who develop HBV reactivation.

As with other TNF-blockers, the risks and benefits of golimumab should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer or when considering continuing a TNF-blocker in patients who develop a malignancy. In the controlled portions of clinical trials of TNF-blockers including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups.

Cases of new onset congestive heart failure (CHF) and worsening CHF have been reported with TNF-blockers.

Use of TNF-blockers has been linked with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS).

There have been post-marketing reports of pancytopenia, neutropenia, leukopenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. Caution should be exercised when using TNF-blockers, including golimumab, in patients who have significant cytopenias.

infliximab (Remicade)⁷⁰

Infliximab at doses >5 mg/kg is contraindicated in patients with moderate to severe heart failure. In a randomized study evaluating infliximab in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), infliximab treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure.

Infliximab should not be readministered to patients who have experienced a severe hypersensitivity reaction to infliximab. Additionally, infliximab should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

Infliximab contains three boxes warnings – risk of serious infections, risk of malignancies in children and adolescents, and risk of hepatosplenic T-cell lymphomas. Patients treated with infliximab are at increased risk for infections including progression to serious infections leading to hospitalization or death. Infections have included bacterial sepsis, TB, invasive fungal infections, and other opportunistic infections. Patients should be educated about the symptoms of infection, closely monitored for signs and symptoms of infection during and after treatment with infliximab, and should have access to appropriate medical care. Patients who develop an infection should be evaluated for appropriate antimicrobial therapy and for serious infections, infliximab should be discontinued.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving infliximab. Patients should be evaluated for TB risk factors and be tested for latent TB infection prior to initiating infliximab and during therapy. Treatment of latent TB infection should be initiated prior to therapy with infliximab. Treatment of latent TB in patients with a reactive tuberculin test reduces the risk of TB reactivation in patients receiving infliximab. Some patients who tested negative for latent TB prior to receiving infliximab have developed active TB. Physicians should monitor patients receiving infliximab for signs and symptoms of active TB, including patients who tested negative for latent TB infection.

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including infliximab.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with infliximab have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in postmarketing data in patients receiving infliximab.

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab. The causal relationship to infliximab therapy remains unclear.

Infliximab has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within two hours of infliximab infusion. Serum sickness-like reactions have been observed in patients after initial infliximab therapy (i.e., as early as after the second dose), and when infliximab therapy was reinstated following an extended period without infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and/or dysphagia.

In a clinical trial using infliximab in patients with moderate to severe COPD, more malignancies, with the majority being of the lung or head and neck region, were reported in the patients receiving infliximab compared to control patients. All patients had a history of heavy smoking. Providers should use caution in using infliximab in patients with moderate to severe COPD.

Patients with psoriasis should be monitored for non-melanoma skin cancers especially in those patients with a history of prolonged phototherapy treatment. Non-melanoma skin cancers were more common in patients with previous phototherapy in the maintenance trials of infliximab for the treatment of psoriasis.

Infliximab and other TNF blockers have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system (CNS) demyelinating disorders, including multiple sclerosis, and CNS manifestation of systemic vasculitis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of infliximab in patients with pre-existing or recent onset of demyelinating or seizure disorders. Discontinuation of infliximab should be considered in patients who develop significant CNS adverse effects.

Drug Interactions

abatacept (Orencia)⁷¹

Concurrent administration of a TNF α -blocker with abatacept is not recommended since concurrent therapy has been associated with an increased risk of serious infections with no additional efficacy over TNF α -blocker monotherapy. There is insufficient experience to assess the safety and efficacy of abatacept administered concurrently with anakinra; therefore, such use is not recommended.

Live vaccines should not be given concurrently with abatacept or within three months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving abatacept. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations.

adalimumab (Humira)⁷²

Adalimumab should not be used with other TNF α -blockers, although it is unknown if any adverse effects would occur. Concomitant therapy may increase the potential for infections and have an impact on the development and course of malignancies. Although not specifically evaluated, patients receiving immunosuppressives along with adalimumab may be at a greater risk of developing an infection. In studies of adalimumab, many of the serious infections occurred in patients on immunosuppressive therapy.

The clearance of adalimumab was decreased by 44 percent after multiple doses of methotrexate. No dose adjustment for either drug is needed when methotrexate (MTX) and adalimumab are used together.

Adalimumab should not be given concurrently with live vaccines.

alefacept (Amevive)⁷³

No formal drug interaction studies have been performed with alefacept.

anakinra (Kineret)⁷⁴

In a study in which patients with active RA were treated for up to 24 weeks with concurrent anakinra and etanercept therapy, a seven percent rate of serious infections was observed, which was higher than that observed with etanercept alone (zero percent). Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia. Combination therapy with any TNF-blocking agents and anakinra is not recommended.

No data are available for anakinra and the administration of live vaccines. Concurrent administration of live vaccines is not recommended.

certolizumab pegol (Cimzia)⁷⁵

Concurrent administration of anakinra and another TNF blocker has shown an increased risk of serious infections, an increased risk of neutropenia, and no added benefit compared to these medicinal products alone. Do not administer certolizumab pegol with anakinra.

Do not give live, including attenuated, vaccines concurrently with certolizumab pegol.

Interference with certain coagulation assays has been detected in patients treated with certolizumab pegol. Certolizumab pegol may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. Interference with thrombin time and prothrombin time assays has not been observed. There is no evidence that certolizumab pegol therapy has an effect on *in vivo* coagulation.

etanercept (Enbrel)⁷⁶

Concurrent or recent exposure to myelosuppressive anti-rheumatic agents (e.g., azathioprine, cyclophosphamide, leflunomide, or MTX) has been associated with pancytopenia, including aplastic anemia, in some patients treated with etanercept. Etanercept is, however, commonly given in combination with MTX.

In a study of patients with Wegener's granulomatosis, the addition of etanercept to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. Use of etanercept in patients receiving concurrent cyclophosphamide therapy is not recommended.

Patients in a clinical study who were on established therapy with sulfasalazine, to which etanercept was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either therapy alone. The clinical significance of this observation is unknown.

golimumab (Simponi)⁷⁷

When used in combination with abatacept (Orencia) or anakinra (Kineret), an increased risk of serious infections with no added benefit has been observed with other TNF-blockers in clinical RA studies. Therefore, use of golimumab with abatacept or anakinra is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab (Rituxan[®]) who received subsequent treatment with a TNF-blocker.

During chronic inflammation, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α). Consequently, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of golimumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Live vaccines should not be given concurrently with golimumab.

infliximab (Remicade)⁷⁸

Patients receiving immunosuppressives tend to have fewer infusion-related reactions to infliximab as compared to patients not receiving immunosuppressive therapy. In patients receiving immunosuppressant therapy with azathioprine, mercaptopurine, or MTX, antibody development to infliximab is lower compared to patients not receiving concurrent immunosuppression. Many serious infections during infliximab therapy have occurred in patients receiving concurrent immunosuppressives.

Rheumatoid arthritis patients who received MTX in combination with infliximab have higher serum concentrations of infliximab as compared to those who receive infliximab alone.

Combination therapy with any TNF-blocking agents and anakinra is not recommended due to the potential for increased risk of infections without any increase in efficacy as seen in clinical trials with etanercept and anakinra.

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

It is recommended that all pediatric Crohn's disease patients be brought up to date with all vaccinations prior to initiating infliximab therapy.

tocilizumab (Actemra)⁷⁹

Tocilizumab has not been studied in combination with biological DMARDs such as TNF antagonists. Tocilizumab should not be administered with live vaccines.

In infection and inflammation, the cytochrome P450 enzymes are down regulated by cytokines including IL-6. By inhibiting IL-6 signaling in RA patients by tocilizumab, CYP450 enzyme activity may be restored to higher levels than those in the absence of tocilizumab. This may increase the metabolism of CYP450 substrates. *In vitro* studies showed that tocilizumab may change the expression of many of the CYP450 enzymes responsible for drug metabolism including CYP 1A2, 2C9, 2D6 and 3A4. The effect of tocilizumab on CYP450 enzymes may be clinically relevant for CYP450 substrates with a narrow therapeutic index. Upon initiation or discontinuation of tocilizumab, patients being treated with medications metabolized via CYP450 systems may need to be monitored (e.g., warfarin) or drug concentration evaluated (e.g., theophylline, cyclosporine) and adjustments made if necessary. The effect of tocilizumab may be apparent for several weeks following the last dose.

ustekinumab (Stelara)⁸⁰

Patients who are receiving ustekinumab should not receive live vaccines. The safety of ustekinumab given with other immunosuppressive drugs or phototherapy has not been evaluated. CYP450 substrates should be monitored, as ustekinumab can alter the formation of CYP450 enzymes. This is especially important for agents with a narrow therapeutic effect, such as warfarin and cyclosporine.

Adverse Effects*In Adults*

Drug	Injection site / Infusion reaction	Infection		Headache	Nausea
		Upper respiratory	Other		
abatacept (Orencia) ⁸¹	9 (6)	5 -13	54 (48)	18 (13)	≥ 10
adalimumab (Humira) ⁸²	20 (14)	17 (13)	1/patient-year (0.9/patient- year)	12 (8)	9 (8)
alefacept (Amevive) ⁸³	16 (8)	nr	Reported	> 2	> 2
anakinra (Kineret) ^{84,85}	71 (29)	14 (17)	39 (37)	12 (9)	8 (7)
certolizumab pegol (Cimzia) ⁸⁶	reported	20 (13)	total infections 38 (30)	5 (4)	nr
etanercept (Enbrel) ⁸⁷	14-37 (10)	12-20 (< 20)	total infections 35 (32)	17-24 (13)	9-15 (10)
golimumab (Simponi) ⁸⁸	6 (2)	7 (6)	total infections 28 (25)	nr	nr
infliximab (Remicade) ⁸⁹	20 (10)	32 (25)	27-36 (18-25)	18 (14)	21 (20)
tocilizumab (Actemra) ⁹⁰	7-8 (5)	6-8 (6)	1.08/patient year	5-7 (3)	nr
ustekinumab (Stelara) ⁹¹	1-2 (<1)	4-5 (5)	27 (24)	5 (3)	nr

nr = not reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative. Incidences for placebo are indicated in parentheses.

In placebo-controlled studies, eight percent of patients receiving anakinra had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with two percent of patients in the placebo control group. Six (0.3 percent) of the anakinra-treated patients experienced neutropenia.⁹²

To investigate whether TNF- α inhibitors, together as a class, or separately as either monoclonal anti-TNF- α antibodies (adalimumab, infliximab) or a fusion protein (etanercept), are related to higher rates of herpes zoster in patients with RA, patients were enrolled in a prospective cohort.⁹³ Patients were enrolled at the initiation of treatment with etanercept, adalimumab, infliximab or anakinra, or when they changed conventional DMARD treatment. Treatment, clinical status, and adverse events were assessed by rheumatologists at fixed points during follow-up. Among the 5,040 patients receiving TNF blockers or conventional DMARDs, 86 episodes of herpes zoster occurred in 82 patients. Thirty-nine of these occurrences could be

attributed to treatment with adalimumab or infliximab, 23 to etanercept and 24 to conventional DMARDs. Adjusted for age, rheumatoid arthritis severity, and glucocorticoids use, a significantly increased risk was observed for treatment with the monoclonal antibodies. Treatment with monoclonal anti-TNF- α inhibitors (adalimumab, infliximab) may be associated with increased risk of herpes zoster, but further study is required.

In Pediatric Patients

Drug	Injection site / Infusion reaction	Infection	Headache	Nausea
abatacept (Orencia) ⁹⁴	2-4	36	≥5	≥5
adalimumab (Humira) ⁹⁵	16	45	nr	nr
etanercept (Enbrel) ⁹⁶	Reported	62	19	9
infliximab (Remicade) ⁹⁷	18	56	nr	nr

nr = not reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative.

Monitoring

Lymphocyte counts of patients receiving alefacept should be monitored every two weeks throughout the course of the 12-week dosing regimen.⁹⁸ If the CD4 T lymphocyte counts are below 250 cells/mcL, alefacept should be withheld and weekly monitoring started. Alefacept should be discontinued if the CD4+ lymphocyte count remains less than 250 cells/mcL for one month.

Tocilizumab (Actemra) requires monitoring of neutrophils, platelets, and liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] every four to eight weeks.⁹⁹ Therapy with tocilizumab may be withheld, dose reduction or maintain current therapy depending on the results. Lipid parameters should be measured after four to eight weeks of tocilizumab therapy and then every six months. Patients should be managed according to the latest lipid guidelines for hyperlipidemia.

Special Populations^{100,101,102,103,104,105,106,107,108,109}

Pediatrics

In November 2009, the boxed warning for the TNF blockers was updated to include the risk of malignancies, some fatal, associated with the use of TNF blockers in children and young adults. Approximately half of the cases were lymphoma. Some malignancies were rare and usually associated with immunosuppression and not typically observed in children and adolescents.

abatacept (Orencia)

Abatacept (Orencia) is indicated for reducing signs and symptoms of JIA in children over six years of age. Children should be brought up to date with all immunizations according to current immunization guidelines prior to initiating therapy with abatacept.

A double-blind, randomized controlled withdrawal trial enrolled 190 patients ages six to 17 years with active JIA in at least five active joints with an inadequate response or intolerance to at least one DMARD.¹¹⁰ All 190 patients were given 10 mg/kg of abatacept intravenously in the open-label period of four months. Of the 170 patients who completed the lead-in course, 47 did not respond to the treatment according to predefined American College of Rheumatology (ACR) pediatric criteria and were excluded. An ACR 30 response requires a patient to have a 30 percent reduction in the number of swollen and tender joints, and a reduction of 30 percent in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate. Of the patients who responded to abatacept, 60 were randomly assigned to receive abatacept 10 mg/kg every 28 days for six months, or until a flare of the arthritis, and 62 were randomly assigned to receive placebo at the same dose and timing. The primary endpoint was time to flare of arthritis. Flare was defined as worsening of 30 percent or more in at least three of six core variables, with at least 30 percent improvement in no more than one variable. Flares of arthritis occurred in 33 of 62 (53 percent) patients who were given placebo and 12 of 60 (20 percent) abatacept patients during the double-blind treatment ($p=0.0003$). Median time to flare of arthritis was six months for patients given placebo; insufficient events had occurred in the abatacept group for median time to flare to be assessed ($p=0.0002$). The risk of flare in patients who continued abatacept was less than a third of that for controls during that double-blind period (hazard ratio 0.31, 95% CI, 0.16-0.95). During the double-blind period, the frequency of adverse events did not differ in the two treatment groups. Adverse events were recorded in 37 abatacept recipients (62 percent) and 34 (55 percent) placebo recipients ($p=0.47$); only two serious adverse events were reported, both in controls ($p=0.50$). The manufacturer of abatacept funded the study.

adalimumab (Humira)

Adalimumab (Humira) is indicated for reducing signs and symptoms of JIA in children four years of age or older. Children should be brought up to date with all immunizations according to current immunization guidelines prior to initiating therapy with adalimumab. Patients on adalimumab may receive concurrent vaccination except live vaccines.

A randomized, double-blind, placebo-controlled, multicenter, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase enrolled patients ages four to 17 years with active JIA.¹¹¹ Patients had previously received treatment with NSAIDs underwent stratification according to methotrexate use. Patients received adalimumab 24 mg/m² of body surface area (maximum dose 40 mg) subcutaneously every other week for 16 weeks. Patients with an ACR Pedi 30 response at week 16 were randomized to adalimumab or placebo every other week in a double-blind manner for up to 32 weeks. More patients on methotrexate (94 percent, 80/85 patients) achieved ACR Pedi 30 response at week 16 compared to those not on methotrexate (74 percent, 64/86 patients). An ACR 30 response requires a patient to have a 30 percent reduction in the number of swollen and tender joints, and a reduction of 30 percent in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in Health Assessment Questionnaire (HAQ) score. ACR 50, 70, 90 and 100 responses follow accordingly. Among patients not receiving methotrexate, disease flares occurred in 43 percent of adalimumab-treated patients and 71 percent of placebo-treated patients ($p=0.03$). Among patients receiving methotrexate, flares occurred in 37 percent adalimumab-treated patients and 65 percent of placebo-treated patients ($p=0.02$). At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving

placebo; the differences between patients not treated with methotrexate who received adalimumab and those who received placebo were not significant. The most frequently reported adverse events were infections and injection site reactions.

etanercept (Enbrel)

Etanercept (Enbrel) is indicated for the treatment of JIA in children older than two years of age. Limited data on safety and effectiveness are available for etanercept in the management of moderate to severe chronic plaque psoriasis in children and adolescents.¹¹² Children should be brought up to date with all immunizations according to current immunization guidelines prior to initiating therapy with etanercept. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

A long-term, open-label extension study evaluated etanercept in 58 patients with JIA for up to eight years.¹¹³ A total of 42 of the 58 patients (72 percent) entered the fourth year of continuous etanercept treatment, and 26 patients (45 percent) entered the eighth year. Efficacy endpoints included the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), 50, 70, 90, and 100 criteria for improvement. The degree of disability in Health Assessment Questionnaire (HAQ) score was also evaluated. An ACR Pedi 70 response or higher was achieved by 100 percent of patients (n=11) with eight years of data and by 61 percent of patients (28 of 46) according to the last observation carried forward data. The overall rate of adverse events (0.12 per patient-year) did not increase with long-term exposure to etanercept.

infliximab (Remicade)

Infliximab (Remicade) is indicated in children (> six years) for the treatment of Crohn's Disease. Safety and effectiveness data for infliximab in children for the management of ulcerative colitis or plaque psoriasis are not available. Infliximab has been studied in children with juvenile rheumatoid arthritis (JRA); however, efficacy was not established in a double-blind, 14-week study with children ages four to 17 years.

The REACH study evaluated the safety and efficacy of infliximab in children with moderately to severely active Crohn's disease.¹¹⁴ Patients (n=112) received infliximab 5 mg/kg at weeks zero, two and six. Patients responding to treatment at week 10 were randomized to infliximab 5 mg/kg every eight or 12 weeks through week 46. A concurrent immunomodulator was required. Clinical response (decrease from baseline in the PCDAI score ≥ 15 points; total score ≤ 30) and clinical remission (PCDAI score ≤ 10 points) were evaluated at weeks 10, 30, and 54. At week 10, 88.4 percent patients responded to infliximab (95% CI, 82.5 to 94.3 percent) and 58.9 percent patients achieved clinical remission (95% CI, 49.8 to 68 percent). At week 54, 63.5 percent and 55.8 percent patients receiving infliximab every eight weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 33.3 percent and 23.5 percent patients receiving treatment every 12 weeks ($p=0.002$ and $p<0.001$, respectively).

Other agents

Anakinra (Kineret) is not currently FDA-approved for pediatric patients nor does the prefilled syringe permit accurate dosing lower than 100 mg. Anakinra has been studied in pediatric patients with JIA.¹¹⁵

Cytokine and CAM Antagonists and Related Agents

Safety and effectiveness of alefacept (Amevive), certolizumab pegol (Cimzia), golimumab (Simponi), tocilizumab (Actemra) and ustekinumab (Stelara) in pediatric patients have not been established.

Pregnancy

Adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, and ustekinumab are Pregnancy Category B. Abatacept and tocilizumab are Pregnancy Category C.

Dosages

Drug	Dose	Availability								
abatacept (Orencia) ¹¹⁶	<p>RA: IV infusion dose based on body weight given over 30 minutes at zero, two, and four weeks, then every four weeks thereafter</p> <table border="1"> <thead> <tr> <th><u>Body weight</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>< 60 kg</td> <td>500 mg</td> </tr> <tr> <td>60-100 kg</td> <td>750 mg</td> </tr> <tr> <td>> 100 kg</td> <td>1,000 mg</td> </tr> </tbody> </table> <p>JIA: Pediatric patients < 75 kg receive 10 mg/kg based on the patient's body weight. Pediatric patients weighing > 75 kg should be administered abatacept at the adult dose, not to exceed 1,000 mg</p>	<u>Body weight</u>	<u>Dose</u>	< 60 kg	500 mg	60-100 kg	750 mg	> 100 kg	1,000 mg	250 mg/15 mL single-dose vial (SDV)
<u>Body weight</u>	<u>Dose</u>									
< 60 kg	500 mg									
60-100 kg	750 mg									
> 100 kg	1,000 mg									
adalimumab (Humira) ¹¹⁷	<p>RA, PsA, AS: 40 mg SC every other week; MTX, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs may be continued; In RA, some patients not taking MTX may benefit from increasing the dosing frequency to 40 mg every week</p> <p>Plaque psoriasis: 80 mg SC initially (Day 1) followed by 40 mg one week later (Day 8) then 40 mg every other week starting on Day 22.</p> <p>Crohn's disease: 160 mg once followed by 80 mg at week two (Day 15), then 40 mg every other week beginning at week 4 (Day 29)</p> <p>JIA (ages four to 17 years):</p> <table border="1"> <thead> <tr> <th><u>Body weight</u></th> <th><u>Dose</u></th> </tr> </thead> <tbody> <tr> <td>15 kg to < 30 kg</td> <td>20 mg every other week</td> </tr> <tr> <td>≥ 30 kg</td> <td>40 mg every other week</td> </tr> </tbody> </table>	<u>Body weight</u>	<u>Dose</u>	15 kg to < 30 kg	20 mg every other week	≥ 30 kg	40 mg every other week	Prefilled syringes: 20 mg/0.4 mL, 40 mg/0.8 mL Single-use pen: 40 mg/0.8 mL		
<u>Body weight</u>	<u>Dose</u>									
15 kg to < 30 kg	20 mg every other week									
≥ 30 kg	40 mg every other week									
alefacept (Amevive) ¹¹⁸	Plaque psoriasis: 15 mg once weekly IM for 12 weeks	Dose pack: 15 mg SDV								
anakinra (Kineret) ¹¹⁹	<p>RA: 100 mg SC daily</p> <p>Consider 100 mg every other day for RA patients who have severe renal insufficiency or end stage renal disease (creatinine clearance < 30 mL/min).</p>	Prefilled syringe: 100 mg/0.67 mL								
certolizumab pegol (Cimzia) ¹²⁰	<p>Crohn's disease: 400 mg SC initially (given as two SC injections of 200 mg) and at weeks two and four. In patients who obtain a clinical response, the recommended maintenance dose is 400 mg SC every four weeks.</p> <p>RA: 400 mg SC initially (given as two SC injections of 200 mg) and at weeks two and four followed by 200 mg every two weeks. For maintenance dosing, 400 mg every 4 weeks may be considered.</p>	200 mg vial with 1 mL sterile water diluent Prefilled syringe: 200 mg/mL								

Dosages (continued)

Drug	Dose	Availability
etanercept (Enbrel) ¹²¹	<p>RA, PsA, AS: 50 mg SC once weekly; MTX, glucocorticoids, salicylates, NSAIDs or analgesics may be continued.</p> <p>Plaque psoriasis: 50 mg SC twice weekly for three months followed by 50 mg weekly</p> <p>JIA (ages two to 17 years): 0.8 mg/kg (up to 50 mg) SC given once weekly The 25 mg prefilled syringe is not recommended for pediatric patients weighing < 31 kg. The 50 mg prefilled syringe or SureClick autoinjector may be used for pediatric patients weighing ≥ 63 kg. Glucocorticoids, NSAIDs or analgesics may be continued. Concurrent use of higher dose etanercept with MTX has not been studied in the pediatric population.</p>	<p>Prefilled syringe: 25, 50 mg Prefilled Sureclick autoinjector: 50 mg Multiuse vial: 25 mg with 1 mL diluent</p>
golimumab (Simponi) ¹²²	<p>RA, PsA, AS: 50 mg SC once monthly; For RA, give in combination with MTX. For PsA or AS, may be given with or without methotrexate or other non-biologic DMARDs. Corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued.</p>	<p>Prefilled syringe, SmartJect autoinjector: 50 mg/0.5mL</p>
infliximab (Remicade) ¹²³	<p>RA: 3 mg/kg IV infusion, repeated at two and six weeks, then every eight weeks; for patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every four weeks. Use MTX in combination.</p> <p>AS: 5 mg/kg IV infusion at zero, two, and six weeks, then every six weeks</p> <p>Plaque psoriasis, PsA, ulcerative colitis: 5 mg/kg IV infusion at zero, two, and six weeks, then every eight weeks thereafter. May be given with or without MTX for PsA.</p> <p>Crohn's Disease (adults): 5 mg/kg IV infusion given at zero, two, and six weeks, then every eight weeks; for patients who respond and then lose their response, consider increasing to 10 mg/kg</p> <p>Crohn's Disease (pediatrics): 5 mg/kg IV infusion at zero, two, and six weeks, then every eight weeks.</p> <p>Ulcerative Colitis: 5 mg/kg IV infusion at zero, two, and six weeks, then every eight weeks.</p>	<p>100 mg/20 mL SDV Given as two-hour infusion</p>
tocilizumab (Actemra) ¹²⁴	<p>Severe RA: The starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response. Do not exceed 800 mg per infusion. Dose is administered as a 1 hour infusion.</p>	<p>80 mg/ 4 mL SDV 200 mg/ 10 mL SDV 400 mg/ 20 mL SDV</p>
ustekinumab (Stelara) ¹²⁵	<p>Psoriasis: dosing based on body weight</p> <p>For patients weighing ≤100 kg, the initial recommended dose is 45 mg followed by another dose four weeks later, followed by 45 mg every 12 weeks.</p> <p>For patients weighing ≥100 kg, the recommended dose is 90 mg initially, followed by another dose four weeks later, followed by 90 mg every 12 weeks.</p>	<p>45 mg/0.5 mL SDV 90 mg/1 mL SDV</p>

Clinical Trials

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Ankylosing Spondylitis

adalimumab (Humira)

A multicenter, randomized (2:1 ratio), double-blind, placebo-controlled study assessed the safety and efficacy of adalimumab 40 mg every other week in 315 patients with active ankylosing spondylitis.¹²⁶ Adalimumab or placebo was given for 24 weeks. At 12 weeks, the Assessment in Ankylosing Spondylitis International Working Group criteria with 20 percent improvement (ASAS 20) was achieved in 58.2 and 20.6 percent for the adalimumab and placebo groups, respectively ($p < 0.001$). The domains within the ASAS20 response criteria include measures of physical function, pain, inflammation (assessed by duration of morning stiffness), and patient's global assessment. Improvement is defined as a 20 percent improvement and ≥ 10 units of absolute change (on a 0-100 scale) in each of three domains, with no worsening of a similar amount in the fourth domain.¹²⁷ At week 12, more patients in the adalimumab group (45.2 percent) had at least 50 percent improvement in the BASDAI compared to the placebo group (15.9 percent; $p < 0.001$). Adalimumab-treated patients reported more adverse events (75 versus 59.8 percent; $p < 0.05$). The incidence of infections was similar in both groups. A total of 255 patients (82 percent) entered the two year open-label extension study and continued on adalimumab 40 mg every other week.¹²⁸ ASAS responses were maintained; 64.5 percent were ASAS20 responders, and 50.6 percent were ASAS40 responders. Adalimumab significantly improved patient-reported physical function and health-related quality of life in the three year open-label extension of the ATLAS study.¹²⁹

A closer evaluation of adalimumab on pain, fatigue and morning stiffness was performed during the ATLAS (Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis) study.¹³⁰ Pain and fatigue were assessed by the scores of the Medical Outcomes Study Short Form-36 Health Survey (SF-36) and also by total back pain and nocturnal pain using visual analog scales. Fatigue and morning stiffness were also assessed by portions of the BASDAI. At week 12, adalimumab-treated patients experienced significant improvement compared with placebo-treated patients in the SF-36 bodily pain score ($p < 0.001$), total back pain score ($p < 0.001$), nocturnal pain score ($p < 0.001$), fatigue ($p < 0.01$), and morning stiffness ($p < 0.001$). Treatment effects were maintained through 24 weeks of treatment.

In a randomized, multicenter, double-blind, placebo-controlled study, the efficacy of adalimumab and placebo were compared for reducing spinal and sacroiliac joint inflammation, as measured

by magnetic resonance imaging (MRI), in 82 patients with ankylosing spondylitis.¹³¹ Patients received adalimumab 40 mg or placebo every other week during an initial 24-week double-blind period. MRIs of both the spine and sacroiliac (SI) joints were obtained at baseline, week 12, and week 52. Spinal and SI joint inflammation were measured using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index. The spine SPARCC score in placebo-treated patients increased by a mean of 9.4 percent from baseline, compared with a mean decrease of 53.6 percent in adalimumab-treated patients ($p < 0.001$). The SI joint SPARCC score decreased by a mean of 12.7 percent from baseline in placebo-treated patients and by 52.9 percent in adalimumab-treated patients ($p = 0.017$). The response in adalimumab-treated patients was maintained at week 52. Placebo-treated patients were switched to open-label adalimumab treatment at week 24 and experienced similar reductions in spinal and SI joint inflammation by week 52.

etanercept (Enbrel)

A double-blind study recruited 40 patients with active ankylosing spondylitis symptoms despite standard therapy.¹³² Patients were randomly assigned to receive twice-weekly SC injections of etanercept 25 mg or placebo. At four months, significant improvement in symptoms, as determined by the primary composite endpoint of at least a 20 percent improvement in three of five measures of disease activity, was observed in 80 percent of etanercept patients compared to 30 percent of placebo patients ($p = 0.004$). Etanercept treatment resulted in significant improvements over baseline in four of the five measures—duration of morning stiffness, nocturnal spine pain, patient assessment of disease activity and BASFI, the Bath Ankylosing Spondylitis Functional Index ($p < 0.05$ for all comparisons to placebo)—but not for the mean swollen joint score. The etanercept group also had significant improvement in many of the secondary outcome measures, including Physician's global assessment of disease activity, chest expansion, enthesitis, ERS (erythrocyte sedimentation rate), and CRP (C-reactive protein). Placebo patients experienced a similar response to etanercept in an open-label six-month extension phase. There was no difference in the rates of adverse events between the two groups, nor were there any serious adverse events in either group.

Thirty patients with active ankylosing spondylitis refractory to NSAID therapy were randomized in double-blind fashion into two groups, receiving either etanercept 25 mg twice weekly or placebo for six weeks, after which both groups were treated with etanercept.¹³³ All patients received etanercept for a total of 12 weeks and were followed up for at least 24 weeks. At week six, 57 percent of patients treated with etanercept achieved the primary endpoint of at least a 50 percent improvement in the BASDAI compared to six percent of the placebo-treated patients ($p = 0.004$). There was ongoing improvement in all parameters in both groups throughout the period of etanercept treatment. Disease relapses occurred at an average of 6.2 weeks after cessation of etanercept. No severe adverse events, including major infections, were observed during the trial. Four patients withdrew from the study, three prior to receiving study drug and one after receiving one dose.

Two hundred seventy-seven patients with moderate to severe ankylosing spondylitis were recruited into a placebo-controlled, double-blind study of etanercept.¹³⁴ Patients were randomized to receive etanercept 25 mg or placebo twice weekly for 24 weeks. By 12 weeks, ASsessment in Ankylosing Spondylitis (ASAS) 20, the primary endpoint, was reached by 59 percent of patients in the etanercept group compared to 28 percent of patients in the placebo group ($p < 0.0001$). This rate of response was maintained, with 57 and 22 percent of patients in the etanercept and placebo groups, respectively, achieving ASAS 20 at the conclusion of the 24-week treatment period ($p < 0.0001$). All components of the ASAS, acute-phase reactant levels, and spinal mobility measures were significantly improved ($p < 0.05$ for all comparisons to

placebo). Injection-site reactions, accidental injuries, and upper respiratory tract infections are the adverse events that occurred more frequently in the etanercept group. A 168-week open-label extension of the trial enrolled 257 of the 277 patients (92 percent) to evaluate long-term safety and efficacy of etanercept treatment in patients with ankylosing spondylitis.¹³⁵ Safety endpoints included rates of adverse events, infections, and death. Of patients who received etanercept in both the clinical trial and the open-label extension, 71 percent were ASAS 20 responders at week 96, and 81 percent were responders at week 192. Placebo patients who switched to etanercept in the open-label extension showed similar patterns of efficacy maintenance. After up to 192 weeks of treatment with etanercept, the most common adverse effects were injection site reactions, headaches and diarrhea. The rate of infections was 1.1 per patient-year, and the rate for serious infections was 0.02 per patient-year. No deaths were reported.

golimumab (Simponi)

The safety and efficacy of golimumab were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 356 adult patients with active AS according to modified New York criteria for at least three months (Study AS).¹³⁶ Patients had symptoms of active disease [defined as a Bath AS Disease Activity Index (BASDAI) \geq four and Visual Analog Scale (VAS) for total back pain of \geq four, on scales of 0 to 10 centimeter] despite current or previous NSAID therapy. Patients were excluded if they had complete ankylosis of the spine or if they were previously treated with a biologic TNF-blocker. Patients were randomly assigned to golimumab 50 mg (n=138), golimumab 100 mg (n=140), or placebo (n=78) administered SC every four weeks. Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids, and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an AS assessment in Ankylosing Spondylitis (ASAS) 20 response at week 14 and was reported as 59.4 percent for golimumab 50 mg group, 60 percent for golimumab 100 mg group, and 21.8 percent for placebo treated patients ($p < 0.001$). Placebo-controlled efficacy data were collected and evaluated through week 24. ASAS 40 response rates at week 24 were 43.5 percent for golimumab 50 mg group, 54.3 percent for golimumab 100 mg group, and 15.4 percent for placebo-treated group. There was no clear evidence of improved ASAS response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). Eight golimumab-treated patients and one placebo-treated patient had markedly abnormal liver enzyme values which were transient.

infliximab (Remicade)

In a multicenter study, 70 patients with active symptoms of ankylosing spondylitis despite therapy with NSAIDs were enrolled in a placebo-controlled, double-blinded trial of infliximab 0.5 mg/kg IV given at zero, two, and six weeks.¹³⁷ The primary endpoint, a 50 percent improvement in BASDAI between baseline and week 12, was achieved by 53 percent of patients in the active therapy group and nine percent in the control group ($p < 0.05$). Significant benefit of treatment with infliximab was observed in each individual parameter of the BASDAI. Significant benefit was also observed in parameters measuring disability, spinal mobility, quality of life (QoL), and acute phase reactants. Three patients on infliximab had serious events (TB, allergic bronchial granulomatosis, transient leukopenia) and were withdrawn from the study, compared to none on placebo ($p = NS$). In a 12-week open-label extension, placebo patients who then received infliximab showed similar responses.

Of the 54 patients who completed the first year of this study, 52 continued to receive infliximab 5 mg/kg every six weeks up to week 102.¹³⁸ Forty-nine patients (71 percent of 69 enrolled patients and 94 percent of patients who started year two) completed the study up to week 102.

Improvement in signs and symptoms of ankylosing spondylitis seen during the first year of the study was sustained during the second year. Thirty (58 percent) patients achieved at least a 50 percent improvement from baseline in the BASDAI score, the primary endpoint, at week 102. Scores for other efficacy assessments were similar at weeks 54 and 102. Median CRP levels remained low at weeks 54 and 102 (3.9 and 4.3 mg/L, respectively). Side effects during the second year of the study were similar to those of the first year of treatment with infliximab.

In the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT), 357 patients with ankylosing spondylitis were randomly assigned to receive infusions of infliximab 5 mg/kg or placebo at weeks zero, two, six, 12, and 18.¹³⁹ At 24 weeks, 61.2 percent of patients in the infliximab group were ASAS 20 responders compared with 19.2 percent of patients in the placebo group ($p < 0.001$). Clinical benefit was observed in patients receiving infliximab as early as week two and was maintained over the 24-week study period. In addition, 22.4 percent of infliximab patients achieved partial remission. Patients receiving infliximab also showed significant improvements in the BASDAI, as well as the chest expansion and physical component summary score of the SF-36 short form health survey. Adverse events were reported by 82.2 percent of patients receiving infliximab and by 72 percent of patients receiving placebo. Most adverse events in both treatment groups were mild or moderate in severity. After 24 weeks of therapy in the above study, the placebo-treated ($n=78$) and the infliximab-treated ($n=201$) patients all received infliximab 5 mg/kg from week 24 to 96.¹⁴⁰ At week 102, the ASAS 20 responses for the patients initially assigned to placebo (72.1 percent) and for patients initially in infliximab (73.9 percent) were similar.

Crohn's Disease

adalimumab (Humira)

A study measured the efficacy and safety of adalimumab in the maintenance of response and remission of Crohn's Disease (CD).¹⁴¹ Patients ($n=778$) received open-label induction therapy with adalimumab 80 mg (week zero) followed by 40 mg (week two). At week four, patients were stratified by response (decrease in Crohn's Disease Activity Index [CDAI] ≥ 70 points from baseline) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly through week 56. CDAI is used in clinical trials to measure disease activity. CDAI scores of less than 150 indicate a clinical remission, and scores over 450 indicate severely active disease. The primary endpoints were the percentages of randomized responders who achieved clinical remission (CDAI score < 150) at weeks 26 and 56. The percentage of randomized responders in remission was significantly greater in the adalimumab 40 mg every other week and adalimumab weekly groups versus placebo at week 26 (40 percent, 47 percent, and 17 percent, respectively; $p < 0.001$) and week 56 (36 percent, 41 percent, and 12 percent, respectively; $p < 0.001$). There were no significant differences in efficacy between the two adalimumab groups. Adverse events requiring discontinuation occurred more frequently in the placebo group (13.4 percent) than those receiving adalimumab every week (4.7 percent) or every other week (6.9 percent). Adalimumab every other week and weekly maintenance therapies were associated with 52 percent and 60 percent relative reductions in 12-month, all-cause hospitalization risk, and 48 percent and 64 percent reductions in 12-month risk of Crohn's Disease-related hospitalization.¹⁴² Fewer Crohn's Disease-related surgeries occurred in the adalimumab every other week, weekly, and combined groups compared with placebo (0.4, 0.8, and 0.6 versus 3.8 per 100 patients, respectively; all $p < 0.05$).¹⁴³

A double-blind, placebo-controlled trial was designed to determine whether adalimumab induces remissions more frequently than placebo in 325 adult patients with Crohn's disease who have

symptoms despite infliximab therapy or who cannot take infliximab because of adverse events.¹⁴⁴ Patients were included if they had a history of Crohn's disease for four months or more that was moderate to severe at baseline (CDAI score, 220 to 450 points). Patients were randomized to receive induction doses of adalimumab, 160 mg and 80 mg, at weeks zero and two, respectively, or placebo at the same time points. The primary endpoint was induction of remission at week four. A total of 301 patients completed the trial. Remission was achieved at week four by 21 percent versus seven percent for adalimumab group versus placebo ($p < 0.001$). The absolute difference in clinical remission rates was 14.2 percentage points (95% CI, 6.7 to 21.6 percentage points). A 70-point response occurred at week four in 52 percent of patients in the adalimumab group versus 34 percent of patients in the placebo group ($p = 0.001$). Discontinuations due to adverse effects occurred in two patients in the adalimumab group and four patients in the placebo group. Serious infections were reported in four patients receiving placebo and none of the patients receiving adalimumab.

A phase III, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy of adalimumab in the healing of draining fistulas in 117 patients with active CD.¹⁴⁵ Patients were adults with moderate to severely active CD (CD activity index 220-450) for at least four months who had draining fistulas at baseline. All patients received open-label adalimumab induction therapy with 80 mg initially then 40 mg at week two. At week four, all patients were randomly assigned to receive double-blind placebo or adalimumab 40 mg every other week or weekly to week 56. Complete fistula healing/closure was defined as no drainage, either spontaneous or with gentle compression by week 56. The mean number of draining fistulas per day was significantly decreased in adalimumab-treated patients compared with placebo-treated patients during the double-blind treatment period. Of all patients with healed fistulas at week 56 (both adalimumab and placebo groups), 90 percent (28/31) maintained healing following one year of open-label adalimumab therapy (observed analysis). Complete fistula healing was sustained for up to 2 years by most patients in an open-label extension trial.

certolizumab pegol (Cimzia)

In a randomized, double-blind, placebo-controlled study, the efficacy of certolizumab pegol was evaluated in 662 adults with moderate-to-severe Crohn's disease.¹⁴⁶ Patients who had received any anti-TNF agent within the previous three months or who had had a severe hypersensitivity reaction or a lack of response to the first dose of another TNF blocker were ineligible. Patients were stratified by baseline levels of CRP (≥ 10 or < 10 mg/L), use of glucocorticoids, and use of concurrent immunosuppressive drugs. Patients were randomized to certolizumab pegol 400 mg or placebo subcutaneously at weeks zero, two, and four weeks and then every four weeks following that. Response was defined as a decrease of at least 100 points in the CDAI score at week six and 26. Remission was defined as an absolute CDAI score of 150 or less. In patients with a baseline CRP level ≥ 10 mg/L, 37 percent of patients in the certolizumab pegol group had a response at week six, as compared with 26 percent in the placebo group ($p = 0.04$). At both weeks six and 26, the corresponding values were 22 percent and 12 percent, respectively ($p = 0.05$). In the overall population, the response rates at week six for certolizumab pegol and placebo were 35 percent and 27 percent, respectively ($p = 0.02$). For both weeks six and 26, response rates were 23 percent and 16 percent for certolizumab pegol and placebo groups, respectively ($p = 0.02$). At weeks six and 26, the rates of remission in the two groups did not differ significantly ($p = 0.17$). A total of 154 assigned to placebo and 145 assigned to certolizumab pegol completed the study. Serious infections were reported in two percent of patients receiving certolizumab pegol and less than one percent of those patients who received placebo. In the certolizumab group, antibodies to the drug developed in eight percent of patients and antinuclear antibodies developed in two percent. The study was supported by the manufacturer of certolizumab pegol.

In the double-blind PRECISE-2 study, efficacy of certolizumab pegol was evaluated in 668 adults with moderate to severe Crohn's disease as maintenance therapy.¹⁴⁷ Open-label induction therapy with certolizumab pegol 400 mg subcutaneously at weeks zero, two, and four was administered. Baseline CDAI scores were 220-450. Thirty-eight percent of patients in each group were not receiving either glucocorticoids or immunosuppressives. A total of 428 patients had a clinical response at week six. Patients with a clinical response at week six were stratified by baseline CRP level and were randomized to certolizumab pegol 400 mg (n=216) or placebo (n=212) every four weeks through week 24 with two weeks of additional follow-up. The study was completed by 109 patients assigned to the placebo group and 151 patients assigned to certolizumab pegol. The response was maintained through week 26 in 62 percent of the patients with a baseline CRP level of at least 10 mg/L, who were receiving certolizumab, compared to 34 percent in the placebo group (p<0.001). Patients with a response to induction at week six and remission (defined as CDAI score ≤150) at week 26 was achieved in 48 percent and 29 percent of the certolizumab pegol and placebo groups, respectively (p<0.001). Infectious serious adverse events (including one case of pulmonary tuberculosis) were reported in three percent of patients receiving certolizumab pegol and less than one percent of the patients receiving placebo. The study was supported by the manufacturer of certolizumab pegol.

infliximab (Remicade)

ACCENT I was a randomized study of the benefit of maintenance therapy with infliximab in patients with active Crohn's disease who respond to a single infusion of infliximab.¹⁴⁸ In this study, 573 patients received infliximab 5 mg/kg IV. They were assessed two weeks later, at which time responders, defined as seeing a decrease in CDAI score of at least 70 points and 25 percent from baseline, were randomized into one of three groups: high-dose infliximab (5 mg/kg at weeks two and six followed by 10 mg/kg every eight weeks until week 46), low-dose infliximab (5 mg/kg at the same time points), or placebo. The primary endpoints were: 1) the proportion of patients who responded at week two and were in remission at week 30 and 2) the time to loss of response up to week 54. Fifty-eight percent of the patients responded to the single infusion of infliximab at two weeks. At 30 weeks, 21 percent of the placebo patients were in remission, compared to 45 percent of high-dose (p=0.0002) and 39 percent of low-dose (p=0.003) infliximab patients. Throughout the 54-week trial, the median time to loss of response was >54 weeks and 38 weeks for high- and low-dose infliximab patients, respectively, compared with 19 weeks for the placebo group (p=0.0002 and 0.002, respectively). The safety profile of infliximab was similar to other studies; the incidence of serious infections was similar across treatment groups. ACCENT I substudies showed that infliximab improved health-related quality of life.¹⁴⁹

An ACCENT II substudy examined the effect of infliximab maintenance treatment on hospitalizations, surgeries, and procedures in patients with fistulizing Crohn's disease.¹⁵⁰ After receiving infliximab 5 mg/kg at weeks zero, two, and six, patients were separately randomized at week 14 as responders (195 patients) or nonresponders (87 patients) to receive placebo or to continue with infliximab maintenance therapy every eight weeks. Among patients randomized as responders, those who received infliximab maintenance had significantly fewer mean hospitalization days (0.5 versus 2.5 days; p<0.05), mean number of hospitalizations (11/100 patient versus 31/100 patients; p<0.05), total surgeries and procedures (65 versus 126; p<0.05), inpatient surgeries and procedures (seven versus 41; p<0.01), and major surgeries (two versus 11; p<0.05), compared with those who received placebo maintenance.

Plaque Psoriasis

For this indication, the Psoriasis Area and Severity Index (PASI) is the measure of efficacy. The PASI score is a composite score that takes into consideration both the fraction of the body surface area affected and the nature and severity of psoriatic changes within the affected regions (erythema, infiltration/plaque thickness, and desquamation). The PASI 75, which reflects a 75 percent or greater improvement in symptoms, is often considered the “gold standard” and is reported when available. When the PASI is not specified, it may be useful to consider that a median reduction in PASI score of 68 percent correlates to approximately 40 percent of patients achieving the PASI 75.

adalimumab (Humira)

A multicenter, randomized, double-blind, placebo controlled trial of 147 patients with moderate to severe plaque psoriasis were treated with adalimumab 40 mg every other week, 40 mg every week, or placebo for 12 weeks and then could continue in a 48-week extension trial.¹⁵¹ Patients taking placebo were switched to adalimumab for the extension trial. After 12 weeks of adalimumab treatment, 53 percent of patients taking adalimumab every other week, 80 percent of patients taking weekly adalimumab, and four percent of patients receiving placebo achieved 75 percent improvement in PASI score ($p < 0.001$). These responses were sustained for the full 60 weeks. The study was insufficiently powered to detect rare adverse effects associated with adalimumab treatment.

A 52-week, multicenter, randomized, placebo-controlled study investigated the efficacy and safety of adalimumab 40 mg for the treatment of moderate to severe psoriasis.¹⁵² A total of 1,212 patients were randomized to adalimumab 40 mg or placebo every other week for the first 15 weeks. Patients were evaluated at week 16; 71 percent of the adalimumab-treated and seven percent of placebo-treated patients showed at least a 75 percent improvement in PASI score. During weeks 33 to 52, the percentage of patients rerandomized to placebo who lost adequate response (defined as < 50 percent improvement in the PASI response relative to baseline and at least a six-point increase in PASI score from week 33) was 28 percent compared with five percent of patients treated continuously with adalimumab.

The CHAMPION study was a 16-week study to compare adalimumab and methotrexate in 271 patients with psoriasis.¹⁵³ Patients with moderate to severe plaque psoriasis were randomized to adalimumab (80 mg subcutaneously at week zero, then 40 mg every other week, $n = 108$), methotrexate (7.5 mg orally, increased as needed and as tolerated to 25 mg weekly; $n = 110$) or placebo ($n = 53$) for 16 weeks. The primary efficacy endpoint was the proportion of patients achieving at least a 75 percent improvement in the PASI 75 after 16 weeks. After 16 weeks, the percent of patients achieving PASI 75 was 79.6 percent of adalimumab-treated patients, 35.5 percent for methotrexate ($p < 0.001$ versus adalimumab), and 18.9 percent for placebo ($p < 0.001$ versus adalimumab). Statistically significantly more adalimumab-treated patients (16.7 percent) than methotrexate-treated patients (7.3 percent) or placebo-treated patients (1.9 percent) achieved complete clearance of disease. Adverse events were similar in all the groups.

alefacept (Amevive)

A multicenter, randomized, double-blind, parallel-group study compared alefacept 10 mg and 15 mg IM and placebo IM once weekly for 12 weeks in the treatment of chronic plaque psoriasis.^{154,155} Patients were additionally followed for 12 weeks after cessation of therapy. Eligible patients included those who were older than 18 years of age, had chronic plaque

psoriasis for at least 12 months involving ≥ 10 percent body surface area, and had CD4+ T lymphocytes counts at or above the lower limit of normal. A total of 507 patients were enrolled. A significantly greater percentage of patients treated with alefacept 15 mg IM achieved ≥ 75 percent PASI reduction from baseline two weeks after the last dose compared with placebo (21 percent versus 5 percent; $p < 0.001$). Only 12 percent of patients treated with alefacept 10 mg IM reached this level of improvement ($p = \text{NS}$ versus placebo). For the 12 week follow-up after cessation of alefacept, 71 percent maintained at least 50 percent improvement in PASI throughout the follow-up time period. Alefacept was well tolerated with adverse events similar to that of placebo.

etanercept (Enbrel)

A double-blind study enrolled 583 adult patients with active, clinically stable plaque psoriasis involving at least 10 percent of body surface area, with a minimum PASI of 10 at screening and who had received or were a candidate to receive systemic psoriasis therapy or phototherapy.¹⁵⁶ During the first 12 weeks of the study, patients were randomly assigned to receive etanercept 25 or 50 mg or placebo twice weekly as subcutaneous injections. During the second 12 weeks, all patients received etanercept 25 mg twice weekly. The primary endpoint, a PASI 75 response at week 12, was achieved by 49 percent of patients in the etanercept 50 mg group, 34 percent in the 25 mg group, and three percent in the placebo group ($p < 0.0001$ for each etanercept group compared with placebo). At week 24 (after 12 weeks of open-label etanercept 25 mg twice weekly), a PASI 75 was achieved by 54 percent of patients whose dose was reduced from 50 mg to 25 mg twice weekly, by 45 percent of patients in the continuous 25 mg twice weekly group, and by 28 percent in the group that received placebo followed by etanercept 25 mg twice weekly. Etanercept was well tolerated throughout the study.

ustekinumab (Stelara) versus etanercept (Enbrel)

In the treatment of moderate to severe psoriasis, ustekinumab and etanercept were compared in a single-blind, randomized trial with 903 patients.¹⁵⁷ Patients were randomized to either ustekinumab SC 45 or 90 mg at weeks zero and four or etanercept SC 50 mg twice weekly for 12 weeks. The primary endpoint was the proportion of patients with at least 75 percent improvement in PASI at week 12. The secondary endpoint was the proportion of patients with cleared or minimal disease based on the physician's global assessment. Assessors were blinded to the treatment. The proportion of patients achieving 75 percent improvement on PASI at week 12 were 67.5 percent of ustekinumab 45 mg group, 73.8 percent of the ustekinumab 90 mg group, and 56.8 percent of the etanercept group ($p = 0.01$ and $p < 0.001$, respectively). For the physician's global assessment, 65.1, 70.6, and 49 percent of patients had cleared or minimal disease, respectively ($p < 0.001$ for both comparisons). Patients who did not have a response to etanercept were crossed over to ustekinumab therapy for 12 weeks; 48.9 percent had at least 75 percent improvement in the PASI within 12 weeks of crossover. Serious adverse events were reported in 1.9, 1.2 and 1.2 percent of the ustekinumab 90 mg and 45 mg groups and etanercept, respectively. Safety patterns were similar before and after crossover from etanercept to ustekinumab. The manufacturer of ustekinumab sponsored the study.

ustekinumab (Stelara)

Two multicenter, randomized, double-blind, placebo-controlled trials were conducted to study ustekinumab. Both studies enrolled subjects 18 years of age or older with moderate to severe plaque psoriasis who had a minimum body surface area involved of ten percent a Psoriasis Area and Severity Index (PASI) of 12 or greater, and who were candidates for phototherapy or systemic therapy. Subjects were randomized to placebo, ustekinumab 45 mg, or ustekinumab

90 mg. Subjects randomized to ustekinumab received the agent at weeks zero, four, and 16. Subjects randomized to receive placebo crossed over to ustekinumab at weeks 12 and 16. The endpoints of both trials were the proportion of subjects who achieved at least a 75 percent in PASI score from baseline to week 12 and treatment success on the Physician's Global Assessment (PGA).

PHOENIX 1 enrolled a total of 766 subjects evaluated through week 52.¹⁵⁸ At week 12, 67.1 percent of those receiving 45 mg of ustekinumab, 66.4 percent of those receiving 90 mg of ustekinumab, and 3.1 percent of those receiving placebo achieved the PASI 75 response (difference in response rate versus placebo 63.9 percent, 95% CI, 57.8-70.1, $p < 0.0001$ for 45 mg and 63.3 percent, 95% CI, 57.1-69.4, $p < 0.0001$ for 90 mg). At week 12, 59 percent of those receiving 45 mg of ustekinumab, 61 percent of those receiving 90 mg of ustekinumab, and four percent of those receiving placebo achieved a PGA score indicating "cleared" or "minimal". Of the patients initially randomized to ustekinumab at week zero who achieved a long term response (defined as 75 percent improvement in PASI 75) at weeks 28 and 40 were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment until loss of response. At week 40, long-term response had been achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group. Of these, 162 patients were randomly assigned to maintenance ustekinumab and 160 to withdrawal. At one year, PASI 75 response was better maintained in those receiving maintenance ustekinumab than those withdrawn from treatment ($p < 0.0001$). Serious adverse events were reported in 1.2 percent of patients receiving ustekinumab and 0.8 percent receiving placebo.

PHOENIX 2 enrolled a total of 1,230 subjects with moderate to severe psoriasis.¹⁵⁹ At week 12, 66.7 percent of those receiving 45 mg of ustekinumab, 75.7 percent of those receiving 90 mg of ustekinumab, and 3.7 percent of those receiving placebo achieved the PASI 75 response (difference in response rate 63.1 percent, 95% CI, 58.2-68.0, $p < 0.0001$ for the 45 mg group versus placebo and 72.0 percent, 95% CI, 67.5-76.5, $p < 0.0001$ for the 90 mg group versus placebo). At week 12, 68 percent of those receiving 45 mg of ustekinumab, 73 percent of those receiving 90 mg of ustekinumab, and four percent of those receiving placebo achieved a PGA score indicating "cleared" or "minimal".

Psoriatic Arthritis

adalimumab (Humira)

Patients with moderately to severely active PsA and a history of inadequate response to NSAIDs were randomized to receive adalimumab 40 mg or placebo SC every other week for 24 weeks.¹⁶⁰ At week 12, 58 percent of the adalimumab-treated patients achieved an ACR 20 response, a primary endpoint, compared with 14 percent of the placebo-treated patients ($p < 0.001$). At week 24, similar ACR 20 response rates were maintained and the mean change in the modified total Sharp score (TSS, a measurement of erosion and joint space narrowing) was significantly improved in patients receiving adalimumab compared to those receiving placebo ($p < 0.001$). Of the adalimumab-treated patients, 59 percent achieved a PASI 75 response at 24 weeks, compared with one percent of patients treated with placebo ($p < 0.001$). Adalimumab was generally safe and well tolerated.

Patients who completed the 24-week, double-blind, Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) study versus placebo in PsA could elect to receive open-label adalimumab 40 mg subcutaneously every other week after week 24.¹⁶¹ After 48 weeks, patients from the adalimumab arm of ADEPT ($n = 151$) had achieved ACR 20, ACR 50, and ACR

70 response rates of 56 percent, 44 percent, and 30 percent, respectively. A total of 69 patients were evaluated with PASI 50, PASI 75, PASI 90, and PASI 100 response rates are were reported as follows: 67 percent, 58 percent, 46 percent, and 33 percent, respectively. Improvements in disability, as measured by the Disability Index of the Health Assessment Questionnaire (HAQ DI), were sustained from week 24 to week 48. The HAQ DI is a self-administered questionnaire that patients can complete easily and rapidly and that gives important information about prognosis, patient status, and changes in disease course over time. Adalimumab demonstrated clinical and radiographic efficacy regardless of whether patients were receiving MTX at baseline and was generally safe and well tolerated through week 48. After two years of treatment with adalimumab 40 mg every other week, patients (n=245) continued to exhibit inhibition of radiographic progression and improvements in joint disease were maintained.¹⁶² Long term adverse effects were similar to those reported in the 24 week study with adalimumab.

In a placebo-controlled, double-blind, randomized, multicenter study, 100 patients with active PsA with an inadequate response to DMARDs were treated for 12 weeks with adalimumab 40 mg every other week or placebo.¹⁶³ The primary efficacy endpoint was the percentage of patients who met the ACR 20 core criteria at week 12. At week 12, an ACR 20 response was achieved by 39 percent of adalimumab patients versus 16 percent of placebo patients (p=0.012). At week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65 percent and 57 percent, respectively, observed at week 24. Adverse effects were similar in frequency.

etanercept (Enbrel)

Investigators randomized 205 patients with PsA to receive etanercept 25 mg or placebo twice weekly for 24 weeks.¹⁶⁴ Patients continued to receive blinded therapy in a maintenance phase until all had completed the 24-week phase, at which point they could receive open-label etanercept in a 48-week extension. At 12 weeks, 59 percent of etanercept patients achieved an ACR 20 response (the primary outcome) compared with 15 percent of placebo patients (p<0.0001); results were sustained at 24 and 48 weeks. At 24 weeks, 23 percent of etanercept patients eligible for psoriasis evaluation achieved at least a PASI 75 score, compared with three percent of placebo patients (p=0.001). Etanercept was well tolerated. This study confirmed the findings of an earlier, smaller clinical trial that was the first placebo-controlled trial of an anti-TNF medication for this indication.¹⁶⁵

In a continuation of the above study, patients were permitted to continue in an open-label extension where all patients received etanercept 25 mg twice weekly.¹⁶⁶ Radiographic progression was monitored at baseline, one, and two years using TSS method, modified to include joints frequently affected by PsA. A total of 169 patients continued therapy, 141 of them previously randomized to placebo and 70 previously randomized to etanercept, and were followed out to two years. ACR 20, PsARC, and PASI 50 criteria were met by 64 percent, 84 percent, and 62 percent, respectively, of etanercept/etanercept patients at the end of the 48-week open-label period. Placebo/etanercept patients achieved comparable results within 12 weeks that were sustained at 48 weeks (63 percent, 80 percent, and 73 percent, respectively). For the patients who initially received placebo, disease progression was inhibited once patients began receiving etanercept. Adverse effects were similar to the randomized phase.

A total of 618 patients with moderate to severe psoriasis were enrolled in a double-blind treatment with etanercept 50 mg twice weekly or placebo.¹⁶⁷ The primary endpoint, PASI 75 at

week 12, was reached by 47 percent of the etanercept group and five percent of those receiving placebo ($p < 0.0001$). Secondary endpoints were the functional assessment of chronic illness therapy fatigue (FACIT-F) scale and the Hamilton rating scale for depression (HAM-D). On the HAM-D evaluation, more patients receiving etanercept had at least a 50 percent improvement at week 12 compared with the placebo group. Fatigue was also improved in the etanercept group (mean FACIT-F improvement 5.0 versus 1.9; $p < 0.0001$).

golimumab (Simponi)

The safety and efficacy of golimumab were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA (\geq three swollen joints and \geq three tender joints) despite NSAIDs or disease-modifying antirheumatic drugs (DMARDs) therapy (Study PsA).¹⁶⁸ Patients in this study had a diagnosis of PsA for at least six months with a qualifying psoriatic skin lesion of at least two centimeters in diameter. Prior treatment with a biologic TNF-blocker was not allowed. Patients were randomly assigned to golimumab 50 mg ($n=146$), golimumab 100 mg ($n=146$), or placebo ($n=113$) given SC every four weeks. Patients were allowed to receive stable doses of concomitant MTX (\leq 25 mg/week), low dose oral corticosteroids, and/or NSAIDs during the trial. The use of DMARDs including sulfasalazine, hydroxychloroquine, cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at week 14. Placebo-controlled efficacy data were collected and evaluated through week 24. Golimumab \pm MTX, compared with placebo \pm MTX, resulted in significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ACR 20 response at Week 14 in Study PsA (ACR 20 response: 51 percent [golimumab 50 mg], 45 percent [golimumab 100 mg] versus nine percent [placebo], respectively; $p < 0.001$ for all comparisons). There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX. Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. Golimumab 50 mg treatment also resulted in significantly greater improvement in enthesitis and skin manifestations in patients with PsA. Among the 74 percent of patients in whom at least 3 percent of the body surface area was affected by psoriasis at baseline, 40 percent of those in the golimumab 50 mg group and 58 percent of those in the golimumab 100 mg group had at least 75 percent improvement in the PASI at week 14, compared with three percent of placebo-treated patients ($p < 0.001$ for both doses).

infliximab (Remicade)

IMPACT I, the Infliximab Multinational Psoriatic Arthritis Controlled Trial, was an investigator-initiated study of 104 patients with active PsA.^{169,170} Patients received placebo or infliximab 5 mg/kg at weeks zero, two, six, and 14 with open-label infliximab 5 mg/kg every eight weeks in follow-up. The primary endpoint, ACR 20 at week 16, was achieved in 69 percent of infliximab patients versus eight percent on placebo ($p < 0.001$). PASI 75 response in evaluable patients was 70.4 and zero percent in the infliximab and placebo groups, respectively ($p < 0.001$). At week 50, the same ACR 20 response was maintained.¹⁷¹ No worsening of radiographic progression was noted in approximately 85 percent of the remaining patients. At week 98, 62 percent (48/78) of infliximab-treated patients achieved an ACR 20 response.¹⁷² Among patients with baseline Psoriasis Area and Severity Index scores ≥ 2.5 , PASI 75 response was 64 percent (16/25) at week 98. The average estimated annual radiographic progression with infliximab treatment was significantly reduced versus the estimated baseline rate of progression.

IMPACT II was a randomized, double-blind study of 200 patients with active PsA who had an inadequate response to DMARDs or NSAIDs.¹⁷³ Patients received infliximab 5 mg/kg or placebo

at weeks zero, two, six, 14, and 22. Significant improvements in both ACR 20 and PASI 75 were observed as early as week two. At week 14, ACR 20 was seen in 58 percent (11 percent in placebo; $p < 0.001$) and PASI 75 response in 64 percent (two percent in placebo; $p < 0.001$). The median PASI improvement in ACR 20 responders was 87.5 percent whereas the median improvement in non-responders was 74 percent.¹⁷⁴ At week 24, 27 percent of infliximab-treated patients experienced ACR 70 versus two percent of placebo-treated patients ($p < 0.001$). At week 24, 60 percent of infliximab-treated patients experienced PASI 75 versus one percent of placebo-treated patients, and 39 percent of infliximab-treated achieved PASI 90. There were similar numbers of adverse events in each group, although there were more serious adverse events in the infliximab group (8.7 percent) than in the placebo group (6.2 percent). In a continuation of the IMPACT II trial, infliximab therapy given every eight weeks was continued for one year.¹⁷⁵ Placebo-assigned patients crossed over to infliximab at week 24. Patients randomized to infliximab who had no response or who lost response could escalate their dose to 10 mg/kg starting at week 38. Through one year of treatment, 58.9 percent and 61.4 percent of patients in the randomized infliximab and placebo/infliximab groups, respectively, achieved ACR 20; corresponding figures for PASI 75 were 50 percent and 60.3 percent. The safety profile of infliximab through week 54 was consistent with that seen through week 24. Two malignancies occurred: basal cell skin cancer (placebo) and stage I Hodgkin's lymphoma (infliximab). Radiographs of hands and feet were obtained at baseline and at weeks 24 and 54.¹⁷⁶ These were evaluated for erosions and joint space narrowing using the Sharp/van der Heijde scoring method modified for PsA. Radiographic progression, measured at week 24, was significantly less in patients initially randomized to infliximab compared with patients randomized to receive placebo ($p < 0.001$). At week 54, slower radiographic progression was observed in patients on infliximab for one year compared to patients receiving infliximab for 24 weeks ($p = 0.001$).

One hundred four patients with PsA in whom prior therapy with at least one DMARD had failed were recruited into an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial.¹⁷⁷ During the initial blinded portion of the study, patients received infusions of infliximab 5 mg/kg or placebo at weeks zero, two, six, and 14. After week 16, patients initially assigned to receive placebo crossed over to receive infliximab 5 mg/kg every eight weeks through week 50, while patients initially randomized to infliximab continued to receive active treatment at the same dose through week 50. The proportion of infliximab-treated patients who achieved the primary endpoint of an ACR 20 response at week 16 (65 percent) was significantly higher than the proportion of placebo-treated patients who achieved the response (10 percent). In addition, 46 percent of infliximab-treated patients achieved an ACR 50 response and 29 percent achieved an ACR 70 response; no placebo-treated patient achieved these endpoints. Among patients who had PASI scores of ≥ 2.5 at baseline, 68 percent of infliximab-treated patients achieved improvement of at least 75 percent in the PASI score at week 16 compared with none of the placebo-treated patients. Continued therapy with infliximab resulted in sustained improvement in articular and dermatologic manifestations of PsA through week 50. The incidence of adverse events was similar between the treatment groups.

Rheumatoid Arthritis

abatacept (Orencia)

Patients with active RA despite therapy with MTX were randomized to receive, in addition to the MTX, abatacept 2 mg/kg, abatacept 10 mg/kg, or placebo for six months.¹⁷⁸ In the 339-patient study, those treated with the higher dose of abatacept were more likely to have an ACR 20 response than were patients who received placebo (60 and 35 percent, respectively; $p < 0.001$). Significantly higher rates of ACR 50 and ACR 70 responses were seen in both active treatment groups. Abatacept was well tolerated, with an overall safety profile similar to that of placebo.

Patients with active RA and an inadequate response to at least three months of anti-TNF α therapy were randomly assigned to receive abatacept (n=258) or placebo (n=133) every two weeks for one month, then every four weeks for six months.¹⁷⁹ Patients discontinued anti-TNF α therapy before randomization but were given at least one other DMARD. After six months, the rates of ACR 20 responses were 50.4 percent in the abatacept group and 19.5 percent in the placebo group (p<0.001). The rates of ACR 50 and ACR 70 responses were also significantly higher in the abatacept group (20.3 and 10.2 percent, respectively) than in the placebo group (3.8 and 1.5 percent, p<0.003 for both comparison). At six months, significantly more patients in the abatacept group (47.3 percent) had a clinically meaningful improvement from baseline in the Health Assessment Questionnaire Disability Index (placebo 23.3 percent, p<0.001). The incidence of adverse events and serious infections were similar in each group.

Due to a lack of other data for therapy for two years with abatacept, this open-label extension study has been included. Patients completing the six-month trial were eligible to enter the long-term open-label extension trial to evaluate the safety and efficacy of abatacept during two years of the ATTAIn (Abatacept Trial in Treatment of Anti-TNF Inadequate responders) trial in patients with RA.¹⁸⁰ A total of 317 patients (218 from the abatacept and 99 from the placebo group) entered, and 222 (70 percent) completed 18 months of long-term extension treatment. The ACR 20 responses at six months and two years were 59.4 and 56.2 percent; ACR 50, 23.5 and 33.2 percent; ACR 70, 11.5 and 16.1 percent, respectively. Safety data were consistent with adverse effects reported in the six-month trial.

In a double-blind study, 652 patients with active chronic RA despite treatment with MTX were randomized to abatacept (10 mg/kg) or placebo once monthly.¹⁸¹ After six months in the abatacept in Inadequate Responders to methotrexate (AIM) study, ACR 20 (68 versus 40 percent), ACR 50 (40 versus 17 percent), and ACR 70 (20 versus seven percent) responses occurred more frequently in the active treatment group than in the group receiving placebo (p<0.05 for all comparisons). These differences were maintained at one year with ACR 20 (73 versus 40 percent), ACR 50 (48 versus 18 percent), and ACR 70 (29 versus 6 percent) responses, all occurring more frequently with abatacept (p<0.001 for all comparisons). Physician function and progression of joint damage also favored abatacept. The incidence of adverse events was similar in both groups. There was, however, a higher incidence of infusion reactions with abatacept (8.8 percent) than with placebo (4.1 percent; p<0.05). The manufacturer of abatacept, which also employs several of the authors, funded this study. At the end of one year, 539 patients remained.¹⁸² Patients who received placebo for one year were switched to abatacept and followed for one additional year with 488 patients completing the two years of evaluation. After the second year, ACR 20 scores from year two were similar to year one. Further inhibition of radiographic progression during year two of abatacept treatment was observed (57 percent reduction in mean change of total score in year two versus year one; p<0.0001), and minimal radiographic progression was observed (mean change in total score from baseline was 1.1 and 1.6 at year one and two, respectively).¹⁸³

abatacept (Orencia) versus infliximab (Remicade)

A double-blind trial compared the efficacy and safety of abatacept and infliximab in 431 adults with RA.¹⁸⁴ Patients were randomized to abatacept approximately 10 mg/kg every four weeks (n=156), infliximab 3 mg/kg every eight weeks (n=165), placebo every four weeks (n=110), and background methotrexate. The primary objective of the study was to evaluate the mean change from baseline in Disease Activity Score [based on erythrocyte sedimentation rates; DAS28 (ESR)] for the abatacept versus placebo groups at day 197. At six months, mean changes in DAS28 (ESR) were significantly greater for abatacept versus placebo (-2.53 versus -1.48, p<0.001) and infliximab versus placebo (-2.25 versus -1.48, p<0.001). At day 197, ACR 20

responses were significantly greater with abatacept versus placebo (ACR 20: 66.7 versus 41.8 percent, $p < 0.001$). ACR 20 responses were also significantly higher in the infliximab group versus placebo (ACR 20: 59.4 versus 41.8 percent, $p = 0.006$). For abatacept versus infliximab treatment at day 365, reductions in the DAS28 (ESR) were -2.88 versus -2.25. At day 365, the ACR 20 response rates were 72.4 percent for abatacept and 55.8 percent for infliximab. The DAS28-defined remission rates were 18.7 and 12.2 percent for abatacept and infliximab, respectively. Adverse events and discontinuations related to adverse events were lower with abatacept than infliximab. The manufacturer of abatacept funded the study.

adalimumab (Humira) with MTX versus placebo + MTX

The Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis (ARMADA) trial was a 24-week, double-blind study of 271 patients with active RA despite treatment with MTX.¹⁸⁵ Patients were randomly assigned to receive adalimumab 20, 40, or 80 mg or placebo SC every other week while continuing to take their long-term stable dosage of MTX. The proportion of patients achieving ACR 20 at 24 weeks was significantly greater in the adalimumab 20 mg (47.8 percent), 40 mg (67.2 percent), and 80 mg (65.8 percent) groups than in the placebo group (14.5 percent; $p < 0.001$ for all comparisons with placebo). Most patients receiving adalimumab achieved an ACR 20 response at week one. Compared with the ACR 50 response rate of 8.1 percent in the placebo group, ACR 50 response rates were higher in the groups receiving adalimumab 20 mg (31.9 percent; $p = 0.003$), 40 mg (55.2 percent; $p < 0.001$), and 80 mg (42.5 percent; $p < 0.001$). Near-remission, defined as an ACR 70 response rate, occurred in 4.8 percent of the placebo group ($p < 0.001$), 10.1 percent of the 20 mg group ($p = \text{NS}$), 26.9 percent of the 40 mg group ($p < 0.001$), and 19.2 percent of the 80 mg group ($p = 0.02$). The incidence of adverse events was similar in all groups.

A randomized trial of adalimumab evaluated 619 patients with active RA who had average disease duration of more than 10 years and who had inadequate response to MTX.¹⁸⁶ Patients received adalimumab 40 mg every other week, 20 mg every week, or placebo. All patients received stable doses of MTX. The primary efficacy end points were radiographic progression at week 52 (total Sharp score by a modified method [TSS]), clinical response at week 24 (ACR 20), and physical function at week 52 (HAQ-DI). Radiographs were assessed using a modified version of the Sharp method. Digitized images were scored by physicians who were blinded to the treatment, chronological order, and clinical response of each patient. Erosion scores were recorded for each hand/wrist and each forefoot on a six-point scale (0 = no erosions; 1 = 1 discrete erosion or ≤ 20 percent joint involvement; 2 = 2 separate quadrants with erosion or 21-40 percent joint involvement; 3 = 3 separate quadrants with erosion or 41-60 percent joint involvement; 4 = all 4 quadrants with erosion or 61-80 percent joint involvement; and 5 = extensive destruction with > 80 percent joint involvement). Joint space narrowing scores were recorded for each hand/wrist and each forefoot on a five-point scale (0 = no narrowing; 1 = up to 25 percent narrowing; 2 = 26 to 65 percent narrowing; 3 = 66 to 99 percent narrowing; and 4 = complete narrowing). To determine the modified TSS for each patient, the total erosion score (scale 0 to 230) and the joint space narrowing score (scale 0 to 168) were added (TSS scale 0 to 398). At weeks 24 and 52, adalimumab-treated patients had significantly less disease progression than placebo-treated patients. Patients receiving adalimumab plus MTX experienced significantly less radiographic progression than those taking MTX only ($p \leq 0.001$). At week 52, no new erosions were observed in significantly more patients receiving adalimumab 40 mg every other week (61.8 percent) than in those taking placebo (46 percent). In addition, joint erosion scores improved in almost twice as many patients receiving adalimumab 40 mg every other week than placebo (38.2 versus 19.3 percent, respectively). At 52 weeks, ACR 20 responses were achieved by 59 percent of patients receiving adalimumab 40 mg every other week (placebo 24 percent) and ACR 50 responses were achieved by 41.5 percent (placebo 9.5

percent). ACR 70 was achieved by 23.2 percent of patients treated with adalimumab 40 mg every other week compared to 4.5 percent in the placebo group. Physical function improved significantly more for patients receiving adalimumab 40 mg every other week than for patients on placebo ($p \leq 0.001$). The rate of adverse events was similar among patients treated with adalimumab and placebo, although the proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8 percent) than placebo (0.5 percent; $p \leq 0.002$). The most common adverse events occurring in adalimumab 40 mg and placebo treated patients, respectively, included injection-site reaction (26.1 versus 24 percent), upper-respiratory infection (19.8 versus 13.5 percent), rhinitis (16.4 versus 16.5 percent), and sinusitis (15.9 versus 13 percent). Forty-two adalimumab patients and 13 placebo patients withdrew from the study due to adverse events.

A double-blind study enrolled 799 patients with RA with active disease of less than three years duration to compare the efficacy and safety of adalimumab plus MTX versus either monotherapy over two years – the PREMIER study.¹⁸⁷ Patients had previously not received MTX. Patients were randomized to adalimumab 40 mg every other week plus MTX or either monotherapy. Co-primary end points at year one were ACR 50 and mean change from baseline in the modified TSS. The combination therapy had a superior ACR 50 response at one year (62 percent) compared to those receiving MTX (46 percent) or adalimumab monotherapy (41 percent; both $p < 0.001$). The combination group had less radiographic progression ($p \leq 0.002$), as measured by the modified TSS, at both year one and two than patients on MTX and adalimumab monotherapy. Adverse events were similar in all groups.

adalimumab (Humira) in DMARD-nonresponders

In a 26-week, double-blind, placebo-controlled trial, 544 patients with RA who had failed therapy with other DMARDs were randomized to monotherapy with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo.¹⁸⁸ After 26 weeks, patients treated with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, and 40 mg weekly had significantly better response rates than those treated with placebo: ACR 20 (35.8, 39.3, 46.0, 53.4 percent, respectively versus 19.1 percent; $p \leq 0.01$); ACR 50 (18.9, 20.5, 22.1, 35.0 percent versus 8.2 percent; $p \leq 0.05$); ACR 70 (8.5, 9.8, 12.4, 18.4 percent versus 1.8 percent; $p \leq 0.05$). Patients treated with adalimumab achieved better improvements in HAQ DI scores than those receiving placebo ($p \leq 0.01$ for all comparisons). There were no significant differences between treatment groups in the occurrence of serious adverse events, serious infections, or malignancies. Injection site reaction occurred in 10.6 and 0.9 percent of adalimumab and placebo treated patients, respectively ($p \leq 0.05$).

anakinra (Kineret)

In a 24-week extension of a 24-week, randomized, double-blind study of anakinra in 472 patients with RA, patients who had received placebo were randomized to receive anakinra 30, 75, or 150 mg SC daily.¹⁸⁹ Patients who had been initially randomized to one of the three anakinra dosages continued to receive the same dosage. Radiographs of the hands were obtained at baseline and at 24 and 48 weeks. The radiographs were evaluated using a modified TSS. The mean change in the modified TSS of 178 patients who completed 48 weeks treatment with active drug was significantly less than the change observed in the 58 patients who received placebo for 24 weeks and anakinra for 24 weeks ($p = 0.015$). Significant reductions in the second 24-week period were observed in patients receiving anakinra 75 mg/day ($p = 0.006$) and 150 mg/day ($p = 0.008$). The modified TSS was reduced significantly more during the second 24-week treatment period compared to the first ($p < 0.001$).

anakinra (Kineret) and etanercept (Enbrel) combination therapy

Two hundred forty-four patients in whom RA was active despite MTX therapy were treated with etanercept 25 SC mg twice weekly, etanercept 25 mg SC twice weekly plus anakinra 100 mg daily, or etanercept 25 mg SC once weekly plus anakinra 100 mg daily for six months in a double-blind multicenter study.¹⁹⁰ Patients had never previously received anticytokine therapy. Thirty-one percent of the patients treated with twice weekly etanercept plus anakinra achieved an ACR 50 response, compared with 41 percent of the patients treated with etanercept only (p=NS). The incidence of serious infections (zero percent for etanercept alone and 3.7 to 7.4 percent for combination therapy), injection-site reactions, and neutropenia was increased with combination therapy.

anakinra (Kineret) with MTX versus placebo + MTX

A total of 419 patients with moderate to severe active RA, despite at least six months of MTX therapy, received either placebo or anakinra 0.04 to 2 mg/kg SC daily in addition to MTX.¹⁹¹ At 12 weeks, the proportion of patients who achieved an ACR 20 response was significantly higher among those who received anakinra 1 mg/kg (46 percent; p=0.001) and 2 mg/kg (38 percent; p=0.007) than among those who received placebo (19 percent). At 24 weeks, the percentage of responders remained significantly higher among anakinra 1 mg/kg recipients (42 percent) than among placebo recipients (23 percent; p=0.004). Similar improvements in anakinra-treated subjects were noted in individual ACR components, onset of ACR 20 response, sustainability of ACR 20 response, and magnitude of ACR response. This study was supported by a grant from the manufacturers of anakinra.

In a double-blind study, 506 patients with active RA despite treatment with MTX were randomized to receive anakinra 100 mg or placebo SC daily in addition to continued treatment with MTX.¹⁹² At the first study assessment (four weeks), twice as many patients achieved an ACR 20 response with anakinra as with placebo (p<0.005). The primary outcome, ACR 20 at week 24, was achieved by 38 percent of the anakinra group and by 22 percent of the placebo group (p<0.001). A greater proportion of patients treated with anakinra also achieved ACR 50 (17 versus eight percent; p<0.01) and ACR 70 (six versus two percent; p<0.05) responses. Compared with placebo, anakinra also resulted in significant responses in individual components of the ACR response, pain, CRP levels, and ESR. The safety profile for anakinra was similar to placebo, except for more frequent mild-to-moderate injection site reactions (65 versus 24 percent). The manufacturer of anakinra supported the study.

certolizumab pegol (Cimzia)

A randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of certolizumab pegol versus placebo, plus methotrexate (MTX), in 619 patients with active RA.¹⁹³ Patients were randomized to subcutaneous certolizumab pegol 400 mg at weeks zero, two and four, and followed by 200 mg or 400 mg plus MTX, or placebo plus MTX, every two weeks for 24 weeks. The primary end point was ACR 20 response at week 24 which was achieved by 57.3 percent of the low dose certolizumab pegol group, 57.6 percent of the high dose certolizumab pegol group and 8.7 percent of the placebo-treated group (p≤0.001). Certolizumab pegol low and high dose groups also significantly inhibited radiographic progression; mean changes from baseline in mTSS at week 24 were 0.2 and -0.4, respectively, versus 1.2 for placebo (rank analysis p< or =0.01). Physical function improved rapidly with certolizumab pegol compared to placebo based on mean changes from baseline in HAQ-DI at week 24 (p≤0.001). Most adverse events were mild or moderate, with low incidence of withdrawals due to adverse events. Five patients developed tuberculosis.

A 24-week, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of certolizumab pegol 400 mg as monotherapy for 220 patients with active RA.¹⁹⁴ Patients had previously failed at least one DMARD prior to enrollment. Patients were randomized to certolizumab pegol 400 mg or placebo every four weeks. The ACR 20 response rates, the primary endpoint, were 45.5 percent for certolizumab pegol 400 mg and 9.3 percent for placebo-treated patients ($p < 0.001$). Differences for certolizumab pegol versus placebo in the ACR 20 response were statistically significant as early as week one through to week 24 ($p < 0.001$). Most adverse effects were mild or moderate with no reports of death or tuberculosis.

Certolizumab pegol plus MTX and placebo + MTX were compared in 982 patients with active RA with an inadequate response to MTX therapy alone.¹⁹⁵ The 52-week, phase III, randomized, double-blind trial evaluated ACR 20 response rates at week 24 and the mean change from baseline in the modified total Sharp score at week 52. Certolizumab pegol was given as an initial dosage of 400 mg at weeks zero, two and four, with a subsequent dosage of 200 mg or 400 mg given every two weeks, plus MTX, or placebo plus MTX. At week 24, ACR 20 response rates using nonresponder imputation for the certolizumab pegol 200 mg and 400 mg groups were 58.8 percent and 60.8 percent, respectively, as compared with 13.6 percent for the placebo group. Differences in ACR 20 response rates versus placebo were significant at week one and were sustained to week 52 ($p < 0.001$). At week 52, mean radiographic progression from baseline was reduced in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) as compared with that in placebo-treated patients (2.8 Sharp units) ($p < 0.001$ by rank analysis). Adverse effects were mild or moderate.

etanercept (Enbrel) + MTX versus MTX monotherapy

The combination of methotrexate and etanercept in active early RA (COMET) study compared remission and radiographic non-progression in patients treated with methotrexate monotherapy or combination of etanercept with methotrexate.¹⁹⁶ A total of 542 methotrexate-naïve patients with early moderate-to-severe rheumatoid arthritis for three to 24 months were randomized to methotrexate monotherapy ($n=268$) titrated up from 7.5 mg per week to a maximum of 20 mg per week by week eight or methotrexate with the same titration schedule plus etanercept 50 mg weekly ($n=274$). In the double-blind study, remission was measured with the disease activity score in 28 joints (DAS28) and radiographic non-progression measured with modified total Sharp score. Fifty percent of patients on combination therapy achieved clinical remission compared to 28 percent receiving methotrexate monotherapy (effect difference 22.05 percent, 95% CI, 13.96 to 30.15 percent, $p < 0.0001$). The manufacturer of etanercept funded the study.

etanercept (Enbrel) + MTX versus MTX monotherapy versus etanercept monotherapy

The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study evaluated the combination of etanercept plus methotrexate versus each of the single treatments in 686 patients with RA.¹⁹⁷ In the double-blind study, patients were randomized to etanercept 25 mg twice weekly, oral methotrexate up to 25 mg weekly or the combination. In the 682 patients that received study drug, the combination was more efficacious than methotrexate or etanercept alone in retardation of joint damage over 52 weeks (mean total Sharp score -0.54 [95% CI, -1.00 to -0.07] versus 2.80 [1.08 to 4.51], $p < 0.0001$, and 0.52 [-0.10 to 1.15], $p = 0.0006$; respectively). The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks. ACR-N AUC at 24 weeks was greater for the combination group compared with etanercept alone and methotrexate alone (18.3%-years [95% CI, 17.1 to 19.6] versus 14.7%-years [13.5 to 16.0], $p < 0.0001$, and 12.2%-years [11.0 to 13.4], $p < 0.0001$; respectively). The mean difference in ACR-N AUC between combination and methotrexate alone was 6.1 (95% CI, 4.5 to 7.8, $p < 0.0001$) and between etanercept and methotrexate was 2.5 (0.8 to 4.2, $p = 0.0034$).

To evaluate the clinical response between 12 and 24 weeks in subjects with RA, 12-week non-responders from the above TEMPO study were assessed at 24 weeks according to ACR response criteria. The proportion of subjects who successfully maintained response to 52 weeks was analyzed as were radiographic outcomes. Over 80 percent of the week 24 ACR 20/50/70 responders in the etanercept plus methotrexate arm sustained their response to 52 weeks.¹⁹⁸ In the etanercept arms, a delayed clinical response was not associated with increased radiographic progression at week 52. The number of patients reporting infections or adverse events was similar in all groups.

golimumab (Simponi)

The efficacy and safety of golimumab were evaluated in three multicenter, randomized, double-blind, controlled trials (Studies RA-1, RA-2, and RA-3) in 1,542 patients \geq 18 years of age.^{199,200,201} Patients had moderately to severely active RA and had been diagnosed with RA for at least three months prior to administration of study agent based on the ACR criteria. Patients were required to have at least four tender and four swollen joints. Golimumab was administered SC at doses of 50 mg or 100 mg every four weeks. Double-blinded controlled efficacy data were collected and evaluated through week 24. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to \leq 10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials. In the RA-1 study, patients had previously been treated with at least one dose of a TNF blocker. In the three RA trials, a greater percentage of patients treated with the combination of golimumab and MTX achieved ACR responses at week 14 (Studies RA-1 and RA-2) and week 24 (Studies RA-1, RA-2, and RA-3) versus patients treated with the MTX alone. ACR 20 responses for Study RA-1 were 38 percent for golimumab 100 mg (odds ratio 2.8 [95% CI, 1.6-4.7], $p=0.0001$), 35 percent for golimumab 50 mg (odds ratio 2.5 [95% CI, 1.5-4.2], $p=0.0006$), and 18 percent for placebo. For Study RA-2, ACR 20 response rates were 56.2 percent for golimumab 100 gm + MTX ($p<0.001$), 55.1 percent for the golimumab 50 mg + MTX ($p=0.001$), 44.4 percent for the golimumab 100 mg plus placebo, and 33.1 percent for placebo + MTX groups. The ACR 50 responses at week 24 for Study RA-3 were 40 percent for golimumab group and 29 percent for the MTX group. There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). In Studies RA-2 and RA-3, the golimumab monotherapy groups were not statistically different from the MTX monotherapy groups in ACR responses. In the subset of patients who received golimumab in combination with MTX in Study RA-1, the proportion of patients achieving ACR 20, 50, and 70 responses at week 14 were 40 percent, 18 percent, and 13 percent, respectively, in the golimumab 50 mg plus MTX group ($n=103$) compared with 17 percent, six percent, and two percent, respectively, in the placebo plus MTX group ($n=107$). In Study RA-2, serious adverse events and serious infections occurred in 2.3 percent and 0.8 percent of the placebo + MTX group, 3.8 percent and 0.8 percent of the golimumab 100 mg plus placebo group, 5.6 percent and 2.2 percent of the golimumab 50 mg + MTX group, and 9.0 percent and 5.6 percent of the golimumab 100 mg + MTX group, respectively.

In a multicenter, double-blind, randomized controlled trial, golimumab was evaluated in 172 patients with RA despite treatment with MTX.²⁰² Patients were randomized to one of five treatment arms: placebo plus MTX, golimumab 50 mg or 100 mg every two or four weeks plus MTX through week 48. Patients originally assigned to receive injections every 2 weeks had the interval increased to every 4 weeks starting at week 20. Patients assigned to the placebo group were given infliximab 3 mg/kg at weeks 20, 22 and 28 and then every eight weeks. MTX doses were stable throughout the study period. Seventy-five percent of patients completed the study. The primary end point was the proportion of patients achieving an ACR 20 response at week 16. The ACR 20 response rates at week 16 were 37.1 percent for placebo + MTX group, 50

percent for golimumab 50 mg every two weeks + MTX, 60 percent for golimumab 50 mg every four weeks + MTX, 79.4 percent for golimumab 100 mg every two weeks + MTX ($p < 0.001$ versus placebo), and 55.9 percent for golimumab 100 mg every four weeks + MTX. At week 20, patients who had been receiving golimumab injections every two weeks switched to injections every four weeks without an appreciable decrease in the proportion of ACR 20 responders. The patients on golimumab 100 mg + MTX had increased injection site reactions (36.1 percent) compared to the placebo group (11.8 percent). Three serious infections were reported in the golimumab groups compared to two serious infections reported in those patients who received infliximab after week 20.

The safety and efficacy of golimumab in 637 methotrexate-naïve patients with active RA in a randomized, double-blind placebo-controlled trial.²⁰³ Patients were randomized to placebo plus MTX, golimumab 100 mg plus placebo, golimumab 50 mg plus MTX or golimumab 100 mg plus MTX. Golimumab SC injections or placebo were administered every four weeks. MTX doses initially were 10 mg per week and were titrated up to 20 mg per week. The primary endpoint was the proportion of patients meeting ACR 50 response at week 24. The combination groups of golimumab 50 mg or 100 mg plus MTX in the intent-to-treat population did not show a significant difference on proportion of patients achieving ACR 50 response from the placebo plus MTX group (38.4 and 29.4 percent, respectively; $p = 0.053$). When three untreated patients were excluded in a post-hoc modified ITT analysis, the ACR 50 response showed statistically significant differences between the combined group and placebo plus MTX (38.5 percent versus 29.4 percent; $p = 0.049$) and between golimumab 50 mg plus MTX (40.5 percent; $p = 0.038$) but not golimumab 100 mg plus MTX (36.5 percent; $p = 0.177$) and placebo plus MTX. Golimumab 100 mg plus placebo was noninferior to placebo plus MTX for the ACR 50 response at week 24 (33.1 percent; 95% CI, -5.2% to -10%). The combination of golimumab plus MTX demonstrated a significantly better response compared with placebo plus MTX in most other efficacy parameters, including response/remission according to the Disease Activity Score in 28 joints.

infliximab (Remicade)

The BeST study compared clinical and radiographic outcomes of four different treatment strategies in a multicenter, randomized clinical trial.²⁰⁴ Treatment strategies were DMARD monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab. Treatment adjustments were done every three months. For patients with early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after one year than did sequential monotherapy or step-up combination therapy.

infliximab (Remicade) with MTX versus placebo + MTX

One thousand forty-nine RA patients with active disease and no prior treatment with MTX or TNF α inhibitor were randomized to one of three treatment groups: MTX+placebo, MTX+infliximab 3 mg/kg, and MTX+infliximab 6 mg/kg.²⁰⁵ MTX dosages were rapidly escalated to 20 mg/week and infliximab or placebo infusions were given at weeks zero, two, six, and every eight weeks thereafter through week 46. At week 54, the median percentage of improvement in ACR scores was higher for the MTX+infliximab 3 mg/kg (38.9 percent) and MTX+infliximab 6 mg/kg (46.7 percent) groups than for the MTX+placebo group (26.4 percent; $p < 0.001$ for both comparisons). Patients in the MTX+infliximab 3 mg/kg and MTX+ infliximab 6 mg/kg groups also showed less radiographic progression at week 54, as measured by modified TSS, than those receiving MTX alone ($p < 0.001$ for each comparison). MTX + placebo halted radiographic progression only if patients achieved remission within three months, whereas MTX + infliximab halted or minimized progression in patients with low or moderate activity, respectively.²⁰⁶

Physical function improved significantly more in the MTX + infliximab 3 mg/kg and MTX + infliximab 6 mg/kg groups than in the MTX + placebo group. Infliximab therapy was associated with a significantly higher incidence of serious infections, especially pneumonia.

In ATTRACT (Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy), a double-blind trial, 428 patients with active RA and who had received MTX for at least three months at a stable dose for at least four weeks were randomized to placebo or one of four regimens of infliximab at weeks zero, two, and six, then every four or eight weeks thereafter.²⁰⁷ At 30 weeks, ACR 20 was achieved in 50 to 60 percent of patients receiving infliximab compared with 20 percent of patients receiving placebo ($p < 0.001$ for each of the infliximab dosage regimens compared to placebo). ACR 50 was achieved in 26 to 31 percent of infliximab patients compared to five percent of patients on placebo ($p < 0.001$). Infliximab was well tolerated with no more withdrawals for adverse events or serious adverse events or infections than in the placebo group.

To evaluate the efficacy and safety of repeated administration of infliximab plus MTX over a two-year period in patients with RA who previously experienced an incomplete response to MTX, 428 such patients were randomly assigned to receive MTX plus infliximab 3 or 10 mg/kg or placebo for 54 weeks with an additional year of follow-up.²⁰⁸ The protocol was later amended to allow for continued treatment during the second year. Of 259 patients who entered the second year of treatment, 216 continued to receive infliximab plus MTX for 102 weeks. Ninety-four of these 259 patients experienced a gap in therapy of more than eight weeks before continuing therapy. Infusions were administered at weeks zero, two, and six followed by treatment every four weeks or every eight weeks at a dose of 3 or 10 mg/kg for a total of 102 weeks (including the gap in therapy). The infliximab plus MTX regimens resulted in significantly greater improvement in physical function and quality-of-life physical component scores compared with the MTX-only group. There also was stability in the quality-of-life mental component summary score among patients who received the infliximab plus MTX regimens. The proportion of patients achieving an ACR 20 response at week 102 varied from 40 to 48 percent for the infliximab plus MTX groups compared with 16 percent for the MTX-only group.

tocilizumab (Actemra)

The double-blind, parallel-group AMBITION study evaluated the efficacy and safety of tocilizumab monotherapy compared to MTX monotherapy in patients with active RA for 24 weeks.²⁰⁹ Patients had previously not failed on MTX or biological agents. Patients ($n=673$) were randomized to tocilizumab 8 mg/kg every four weeks or methotrexate starting at 7.5 mg per week and titrated to 20 mg per week within eight weeks or placebo for eight weeks followed by tocilizumab 8 mg/kg. ACR 20 response rate was the primary endpoint; ACR 20 response rate was higher in the tocilizumab group compared to MTX (69.9 versus 52.5 percent; $p < 0.001$). The DAS28 rate of less than 2.6 was better with tocilizumab (33.6 versus 12.1 percent). Serious adverse events were reported in 3.8 percent of patients receiving tocilizumab and 2.8 percent of patients receiving MTX ($p=0.5$). Serious infections were reported in 1.4 and 0.7 percent of patients receiving tocilizumab and MTX, respectively. Neutropenia (3.1 percent versus 0.4 percent) and elevated total cholesterol (≥ 240 mg/dL; 13.2 versus 0.4 percent) were reported more frequently with tocilizumab than MTX, respectively.

In a double-blind, randomized, placebo-controlled study, the efficacy in achieving ACR 20 response with tocilizumab 623 patients with moderate to severe RA was evaluated over 24 weeks.²¹⁰ Patients were randomized to tocilizumab 8 mg/kg ($n=205$), tocilizumab 4 mg/kg ($n=214$), or placebo every four weeks. Patients remained on the stable pre-study dose of MTX of 10-25 mg/week. At 24 weeks, ACR 20 response rates were 59 percent in the high dose

group, 48 percent in the low dose group, and 26 percent in the placebo group (odds ratio 4.0; 95% CI, 2.6-6.1, $p < 0.0001$ for 8 mg/kg versus placebo; odds ratio 2.6; 95% CI, 1.7-3.9; $p < 0.0001$ for 4 mg/kg versus placebo). Serious infections or infestations were reported in six patients in the 8 mg/kg group, three patients in the 4 mg/kg group and two patients in the placebo group.

In the double-blind, multicenter, randomized, controlled SATORI study, the efficacy and safety of tocilizumab monotherapy in 125 patients with active RA with an inadequate response to low dose MTX were evaluated over 24 weeks.²¹¹ Patients were randomized to tocilizumab 8 mg/kg every four weeks plus MTX placebo (tocilizumab group) or tocilizumab placebo plus MTX 8 mg/week (control group) for 24 weeks. The primary outcome measure was the ACR 20 response and the Disease Activity Score in 28 joints. After 24 weeks, 25 percent of the placebo plus MTX group and 80.3 percent in the tocilizumab group achieved ACR 20 response. The tocilizumab group showed superior ACR response criteria over control at all time points. Serious adverse events were reported in 4.7 and 6.6 percent of the placebo/MTX group and tocilizumab groups, respectively. Serious infections were reported in 1.6 and 3.3 percent of the placebo/MTX group and tocilizumab groups, respectively.

In a phase III, double-blind, randomized, multicenter study, tocilizumab was compared to placebo in 499 patients with RA who had inadequate response to one or more TNF antagonists.²¹² Patients were randomized to tocilizumab 8 mg/kg or 4 mg/kg or placebo given IV every 4 weeks with stable MTX for 24 weeks. ACR 20 response was achieved by 50 percent, 30.4 percent and 10.1 percent of patients receiving tocilizumab 8 mg/kg, 4 mg/kg or placebo, respectively (less than $p < 0.001$ both tocilizumab groups versus placebo). At week four, more patients in the high dose tocilizumab group achieved ACR 20 compared to the placebo group ($p < 0.001$). Patients responded regardless of the most recently failed anti-TNF treatment or the number of failed treatments. DAS28 remission rates at week 24 were dose related with 30.1 percent ($p < 0.001$), 7.6 percent ($p = 0.053$) and 1.6 percent of the tocilizumab 8 mg/kg, 4 mg/kg or placebo groups, respectively. The incidence of serious adverse events was higher in the placebo group (11.3 percent) compared to the tocilizumab high dose group (6.3 percent) and low dose group (7.4 percent).

In the Tocilizumab in Combination with Traditional DMARD Therapy (TOWARD) study, the efficacy and safety of tocilizumab in combination with other DMARDS were investigated in 1,220 patients with active RA.²¹³ In the phase III, double-blind, placebo-controlled, multicenter study, patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo (control group) every four weeks for 24 weeks. At week 24, the proportion of patients achieving an ACR 20 was significantly greater in the tocilizumab plus DMARD group (61 percent) than in the control group (25 percent; $p < 0.0001$). Tocilizumab also provided greater improvement in the secondary end points including ACR 50 or ACR 70 responses, the Disease Activity Score in 28 joints (DAS28), and DAS28 remission responses (DAS28 < 2.6). More adverse effects were reported in the tocilizumab group. Serious adverse effects were reported in 6.7 percent and 4.3 percent of patients in the tocilizumab and placebo groups, respectively. Elevated liver enzymes (>3xULN) were observed in 4 percent and 1 percent of the tocilizumab and placebo groups, respectively. Elevated total cholesterol levels were reported in 23 percent and six percent of the tocilizumab and placebo groups, respectively.

Ulcerative Colitis

infliximab (Remicade)

The efficacy of infliximab for induction and maintenance therapy in adults with moderate to severe active ulcerative colitis was evaluated in two randomized, double-blind, placebo-controlled studies (ACT1 and ACT2).²¹⁴ Each study had 364 patients who received either placebo or infliximab 5 or 10 mg/kg of body weight IV at weeks zero, two, and six and then every eight weeks through week 46 (ACT1) or week 22 (ACT2). Patients were followed for 54 weeks in ACT1 and 30 weeks in ACT2. By week eight in ACT1, clinical response (defined as a decrease in Mayo score of at least three points and decrease of 30 percent with a decrease in rectal bleeding measured by two scales) was seen in 69 percent, 61 percent, and 37 percent of patients receiving infliximab 5 mg, infliximab 10 mg, and placebo, respectively ($p < 0.001$ for both comparisons to placebo). In ACT2, the clinical response rates were 64 percent, 69 percent, and 29 percent ($p < 0.001$ for both comparisons to placebo). At week 30, patients receiving infliximab were more likely to have a clinical response ($p \leq 0.002$ for all comparisons). At week 52 in ACT1, the clinical response rates were 45 and 44 percent for infliximab 5 and 10 mg, respectively, compared to 20 percent in the placebo group ($p < 0.001$ for both comparisons).

Meta-Analyses

Crohn's disease

A systematic review evaluated infliximab (Remicade), adalimumab (Humira), and certolizumab (Cimzia) in the maintenance of remission in Crohn's disease.²¹⁵ Literature from 1966 to 2007 was reviewed and nine studies met inclusion criteria. Studies considered included randomized controlled trials involving patients >18 years with Crohn's disease who had a clinical response or clinical remission with a TNF-blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-blocking agent or placebo. Infliximab maintains clinical remission, maintains clinical response, has corticosteroid-sparing effects, and maintains fistula healing in patients with Crohn's disease having a response to infliximab induction therapy. There were no significant differences in remission rates between infliximab doses of 5 mg/kg or 10 mg/kg. Adalimumab maintains clinical remission, maintains clinical response, and has corticosteroid-sparing effects in patients with Crohn's disease who have responded or entered remission with adalimumab induction therapy. There were no significant differences in remission rates between adalimumab 40 mg weekly or every other week. There is evidence from one randomized controlled trial that certolizumab maintains clinical remission and maintains clinical response in patients who have responded to certolizumab induction therapy.

A systematic review found that infliximab, based on literature available through 2005, was effective in inducing clinical remission and response in patients with moderate to severe ulcerative colitis with refractory disease.²¹⁶ The need for colectomy was reduced in short-term trials with infliximab.

Another meta-analysis included 14 trials with 3,995 patients with Crohn's disease who were treated with infliximab, adalimumab or certolizumab.²¹⁷ The primary end points were clinical remission for luminal Crohn's disease and fistula closure at \geq two consecutive visits. In overall analysis, TNF blockers were effective for induction of remission at week four (mean difference, 11 percent; 95% CI, 6 to 16 percent; $p < 0.001$) and maintenance of remission at weeks 20-30 in patients who responded to induction therapy and in patients randomized before induction (mean

difference, 23 percent; 95% CI, 18 to 28 percent and mean difference, 8 percent; 95% CI, 3 to 12 percent, respectively; $p < 0.001$ for all comparisons). In the ten studies evaluating TNF blockers for fistulizing Crohn's disease ($n=776$ patients), TNF blockers were effective for fistula closure only in maintenance trials following open-label induction (mean difference, 16 percent; 95% CI, 8 to 25 percent; $p < 0.001$). In the 21 studies evaluated for safety date, TNF blockers did not increase the risk of death, malignancy, or serious infection.

Psoriasis

A systematic review evaluated the efficacy and safety of biologic agents in the treatment of plaque psoriasis.²¹⁸ Randomized, controlled, double-blind, monotherapy trials of alefacept ($n=three$), efalizumab ($n=five$), etanercept ($n=four$) and infliximab ($n=four$) with a total of 7,931 patients met inclusion criteria. Efficacy was measured by Psoriasis Area and Severity Index (PASI) 75 achievement after 10-14 weeks of treatment, using intention-to-treat analysis. All biological agents for psoriasis were efficacious ($p < 0.001$); however, there was a graded response for achievement of PASI 75: infliximab (pooled relative risk [RR]=17.40, number needed to treat [NNT]=2), etanercept (RR=11.73, NNT=3), and alefacept (RR= .70, NNT=8). The risk of one or more adverse events was evaluated by RR and number needed to harm (NNH). This was increased in the alefacept (RR=1.09, $p=0.03$, NNH=15) and infliximab (RR=1.18, $p < 0.001$, NNH=9) groups compared with placebo.

In another systematic review evaluated 24 clinical trials with 9,384 patients with moderate to severe psoriasis.²¹⁹ Sixteen double-blind trials were included. Based on PASI 75 at weeks eight to 16 in the trials, infliximab was significantly superior to all other interventions [RD 77 percent, 95% CI, 72 to 81 percent]. Adalimumab (RD 64 percent, 95% CI, 61 to 68 percent) was superior to cyclosporine (RD 33 percent, 95% CI, 13 to 52 percent), etanercept 50 mg twice weekly (RD 44 percent, 95% CI, 40 to 48 percent) and etanercept 25 mg twice weekly (RD 30 percent, 95% CI, 25 to 35 percent).

Psoriatic Arthritis

A meta-analysis evaluated the efficacy and safety of TNF blockers in the management of PsA.²²⁰ Six randomized controlled trials with 982 patients investigated adalimumab, etanercept, and infliximab. All three TNF blockers were significantly more effective than placebo on Psoriatic Arthritis Response Criteria (PsARC) and ACR 20, ACR 50, and ACR 70 ratings. There were no significant differences between TNF-alpha inhibitors and placebo in the proportions of patients experiencing withdrawal for any reason (RR 0.48, 95% CI, 0.20 to 1.18), or withdrawal due to adverse events (RR 2.14, 95% CI, 0.73 to 6.27), serious adverse events (RR 0.98, 95% CI, 0.55 to 1.77), or upper respiratory tract infections (RR 0.91, 95% C,I 0.65 to 1.28). Pooled injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR 2.48, 95% CI 1.16 to 5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR 1.03, 95% CI, 0.48 to 2.20) compared against placebo.

Rheumatoid Arthritis

A meta-analysis of 13 clinical trials with etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), or anakinra (Kineret) were included in a systematic review of the literature in the management of RA.²²¹ Efficacy was based on ACR 20 or ACR 50 response after six months of therapy. In all trials, active treatment was efficacious in comparison to placebo or methotrexate. For each treatment, the inclusion of MTX in combination improved the response. After adjustment for study-level variables, the authors found TNF α antagonists to be more efficacious

compared with anakinra ($p < 0.05$). Indirect comparisons between the three TNF α antagonists indicated no difference in efficacy. Author findings included treatment with anakinra is better than placebo; for each treatment, the use of combination MTX improves the probability of response; treatment with any of the TNF α antagonists is better than with anakinra; and all drugs in the TNF α antagonist class are no different from each other. Findings from another systematic review from 2006 were similar.²²²

A systematic review analyzed the efficacy and safety of anti-TNF drugs (infliximab, etanercept, and adalimumab) for treating RA.²²³ A total of 13 articles with 7,087 patients met inclusion criteria. All studies were at least six months in duration and evaluated response to treatment using ACR 20, ACR 50, and ACR 70. The combined relative risk to achieve a therapeutic response to treatment with recommended doses of any TNF blocker was 1.81 (95% CI, 1.43 to 2.29) with a number-needed-to-treat (NNT) of five for ACR 20, five for ACR 50, and seven for ACR 70. Overall therapeutic effects were also similar regardless of the specific TNF blocker used as well as when higher-than-recommended doses were administered. However, lower-than-recommended doses elicited low ACR 70 responses (NNT 15). For patients with an insufficient prior response to MTX, the TNF blockers plus MTX had NNT values of three for ACR 20, four for ACR 50, and eight for ACR 70. Comparisons of anti-TNF drugs plus MTX versus MTX alone in patients with no previous resistance to MTX showed somewhat lower effects. Adverse effects were more likely with TNF blockers than controls (overall combined number-needed-to-harm (NNH) 27). Patients receiving infliximab were more likely to withdraw because of adverse effects (NNH 24) and to suffer severe adverse effects (NNH 31), infections (NNH 10), and infusion reactions (NNH 9). Patients receiving adalimumab were also more likely to drop out because of side effects (NNH 47) and to suffer injection site reactions (NNH 22). Patients receiving etanercept were less likely to drop out because of side effects (NNH for control versus etanercept, 26) but more likely to experience injection site reactions (NNH 5).

A meta-analysis compared the benefits and safety of abatacept, adalimumab, anakinra, etanercept, infliximab and rituximab in patients with RA.²²⁴ ACR 50 response rates were the major outcomes evaluated. A mixed-effects logistic regression was used to provide an indirect comparison of the treatment effects between the biologics. The biologics reported higher ACR 50 rates compared to placebo (OR=3.35, 95% CI, 2.62-4.29) and a number needed to treat for benefit of 4 (95% CI, 4-6). Discontinuations due to adverse events were higher with the biologics (OR 1.39, 95% CI, 1.13-1.71), with a number needed to treat for harm of 52 (95% CI, 29-152). Anakinra was less effective than all of the other biologics, although this difference was statistically significant only for the comparison with adalimumab (OR 0.45, 95% CI, 0.21-0.99) and etanercept (OR 0.34, 95% CI, 0.14-0.81). Adalimumab, anakinra and infliximab were more likely than etanercept to lead to withdrawals related to adverse events (adalimumab OR 1.89, 95% CI, 1.18-3.04; anakinra OR 2.05, 95% CI, 1.27-3.29; and infliximab OR 2.70, 95% CI, 1.43-5.26).

Safety

A meta-analysis of nine clinical trials (three to 12 months duration involving nearly 3,500 patients) of adalimumab (Humira) and infliximab (Remicade) identified a dose-related increase in the incidence of malignancies (OR 3.3; 95% CI, 1.2 to 9.1) compared with placebo.²²⁵ Infections requiring antimicrobial therapy also occurred at a higher rate in the active treatment groups compared to placebo (OR 2.0; 95% CI, 1.3 to 3.1).

A meta-analysis of nine trials of longer than 12 weeks durations involving 3,316 patients of which 2,244 received etanercept for the treatment of RA evaluated the risk of malignancies.²²⁶ A total of 26 patients in the etanercept group (incidence rate 10.47/1,000 person-years) were diagnosed with a malignancy. In the control group, seven patients had a diagnosis of

malignancy (incidence rate of 6.66/1,000 person-years); the results were not statistically significant. A Cox's proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI, 0.79 to 4.28) for the etanercept group compared with the control group.

Summary

Cytokines and CAMs have been implicated in RA, plaque psoriasis, PsA, Crohn's disease, and ankylosing spondylitis. The development of antagonists to these mediators has yielded significant clinical benefits in those patients for whom less sophisticated treatments provide little relief.

Ankylosing Spondylitis

Etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi), and adalimumab (Humira) are indicated for ankylosing spondylitis. Although it has been established that anti-TNF α therapies are effective for symptoms of ankylosing spondylitis, it is still unclear whether they prevent structural damage.

Crohn's Disease

Adalimumab (Humira), certolizumab pegol (Cimzia), and infliximab (Remicade) are indicated in patients with Crohn's Disease. Infliximab is also indicated in reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease. Comparative data are lacking; however, adalimumab is specifically indicated for patients who are intolerant to or have a diminished response to infliximab. Certolizumab pegol is indicated for patients who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis

Traditional therapy for RA has been based on a therapeutic pyramid of increasingly efficacious and toxic medications, starting with NSAIDs. This is being supplanted by earlier, more aggressive treatment with newer agents that have improved the response rate and reduced the adverse event rate observed with older agents. The agents in this class approved for treatment of RA are etanercept (Enbrel), infliximab (Remicade), certolizumab pegol (Cimzia), golimumab (Simponi), and adalimumab (Humira). Tocilizumab (Actemra) is approved for RA with once monthly dosing for patients who have an inadequate response to one or more TNF antagonists; however, additional monitoring of neutrophils, platelets, liver enzymes, and lipid parameters are required.

Compared with the anti-TNF α agents, the uptake of the IL-1 receptor antagonist, anakinra (Kineret), has been relatively slow. This is primarily due to its inferior efficacy and higher toxicity compared with the anti-TNF α therapies. Anakinra is generally used in the 30 to 40 percent of cases in which patients fail to respond to anti-TNF α therapy. In these cases, it is given as monotherapy or in combination with MTX or other non-TNF-targeting DMARDs.

The co-stimulatory agent, abatacept (Orencia), is, like infliximab, administered at an outpatient facility. In this respect, the two agents are similar. Based on limited data from one clinical trial, abatacept may have slightly higher efficacy based on ACR 20 and better safety after one year of treatment; however further studies are warranted.

Abatacept (Orencia), etanercept (Enbrel), and adalimumab (Humira) are indicated in pediatric patients with JIA.

Plaque Psoriasis

Cytokine and CAM antagonists indicated for the treatment of psoriasis have similar efficacy. Alefacept (Amevive) is given by IM injection. Etanercept (Enbrel) and adalimumab (Humira) are given subcutaneously. Ustekinumab (Stelara) is given by subcutaneous injection by a health care professional.

When alefacept (Amevive) is effective, it often produces long-lasting remissions of psoriasis. However, peak response often does not occur until after completion of the 12-week therapeutic regimen, and only about a third of patients achieve 75 percent reduction in PASI scores. Treatment is associated with a reduction in circulating CD4 lymphocytes, but an increase in infections has not been seen.

Ustekinumab has a mechanism of action that is distinct from other DMARDs, and there have been no efforts to compare ustekinumab to other agents in this class. Ustekinumab and alefacept (Amevive) require dosing every 12 weeks once therapy is established.

Psoriatic Arthritis

Although patients with mild to moderate psoriatic arthritis may be treated with NSAIDs and/or intra-articular steroid injections, the use of DMARDs, particularly MTX, along with the biologic agents are considered the standard of care in patients with more significant psoriatic arthritis according to the 2008 AAD guidelines. MTX, TNF blockade, or the combination of these therapies is considered first-line treatment for patients with moderate to severely active PsA. The clinical trial ACR 20 efficacy data at the primary endpoint with all four FDA-approved TNF-blockers, etanercept, infliximab, golimumab, and adalimumab, for the treatment of PsA are roughly equivalent; the choice of which TNF agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration.

Ulcerative Colitis

Infliximab (Remicade) is the only agent in this category that is indicated for ulcerative colitis. Infliximab is effective in inducing clinical remission and response in patients with moderate to severe ulcerative colitis with refractory disease. Infliximab reduced the need for colectomy in short-term trials.

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