Cytokine and CAM Antagonists and Related Agents

Therapeutic Class Review (TCR)

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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	Psoriatic Arthritis (PsA)	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active Crohn's Disease	Ulcerative Colitis	Cryopyrin-Associated Periodic Syndromes (CAPS)
abatacept[a,n] (Orencia®)[1]	Bristol-Myers Squibb	X	X (≥6 years) *(IV only)*	--	--	--	--	--	--
adalimumab[b,c,n] (Humira®)[2]	Abbott	X	X (≥4 years)	X	X	X	X (adults)	X	--
anakinra[d,k] (Kineret®)[3]	Biovitrim	X	--	--	--	--	--	--	X
apremilast (Otezla®)[4]	Celgene	--	--	--	X	X	--	--	--
canakinumab[o] (Ilaris®)[5]	Novartis	--	X (≥2 years)	--	--	--	--	--	X
certolizumab pegol (Cimzia®)[6]	UCB	X	--	X (adults)	--	X (adults)	X (adults)	--	--
etanercept[e,n] (Enbrel®)[7]	Amgen	X	X (≥2 years)	X	X	X	--	--	--
golimumab[f,l] SC (Simponi™)[8]	Janssen Biotech	X	--	X	--	X	--	X	--
golimumab[f] IV (Simponi® Aria™)[9]	Janssen Biotech	X	--	--	--	--	--	--	--
infliximab[f,g] (Remicade®)[10]	Janssen Biotech	X	--	X	X	X	X (adults and children ≥6 years)	X	--

FDA-Approved Indications (continued)

Drug	Manufacturer	**Rheumatoid Arthritis (RA)**	**Juvenile Idiopathic Arthritis (JIA)**	**Ankylosing Spondylitis (AS)**	**Plaque Psoriasis** Moderate to severe in candidates for systemic therapy or phototherapy	**Psoriatic Arthritis (PsA)**	**Crohn's Disease (CD)** Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active Crohn's Disease	**Ulcerative Colitis**	**Cryopyrin-Associated Periodic Syndromes (CAPS)**
rilonacept (Arcalyst™)[11]	Regeneron	--	--	--	--	--	--	--	X
tocilizumab[h,m] (Actemra®)[12]	Genentech	X (IV and SC)	X (IV only) (≥2 years)	--	--	--	--	--	--
tofacitinib[i,j] (Xeljanz®)[13]	Pfizer	X	--	--	--	--	--	--	--
ustekinumab[p,q] (Stelara™)[14]	Janssen Biotech	--	--	--	X (adults)	X (adults)	--	--	--
vedolizumab[r,s] (Entyvio™)[15]	Takeda	--	--	--	--	--	X (adults)	X	--

IV=intravenous; SC=subcutaneous

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 patients if they have a diminished response to or are intolerant to infliximab.[16]

c. Adalimumab is indicated in moderate to severe ulcerative colitis for patients who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers.

d. 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; it may be used alone or in combination with DMARDs except TNF antagonists.

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

f. In RA, certolizumab pegol, infliximab, and golimumab (Simponi and Simponi Aria) are indicated only in combination with methotrexate.

g. 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.

h. 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 DMARDs. In RA, tocilizumab may be used alone or in combination with methotrexate or other DMARDs.

i. In RA, tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. It may be used as monotherapy or in combination with methotrexate or other DMARDs.

j. Limitation of use: tofacitinib should not be used in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine.

k. Anakinra is also approved for the treatment of Neonatal Onset Multisystem Inflammatory Disease (NOMID).

l. Golimumab subcutaneous is indicated in adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine (6-MP) for: inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, or achieving and sustaining clinical remission in induction responders.

m. Intravenous tocilizumab is indicated for both systemic and polyarticular Juvenile Idiopathic Arthritis (JIA) in children two years of age and above. Tocilizumab prefilled syringes for subcutaneous injection are not approved for JIA.

n. Abatacept, adalimumab, and etanercept are approved for the treatment of polyarticular Juvenile Idiopathic Arthritis (JIA) respectively in children 6, 4, and years of age and above.

o. Canakinumab is approved for the treatment of systemic JIA in patients aged two years and older.

p. In PsA, ustekinumab may be used alone or in combination with methotrexate.

q. Ustekinumab recently gained approval for self-administration. It should be given via subcutaneous route of administration under supervision by a physician and administered by a health care professional or by self-administration after training, if deemed appropriate.

r. Vedolizumab is approved for treatment of moderately to severely active UC in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids

s. Vedolizumab is approved for treatment moderately to severely active CD in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Rheumatoid Arthritis

Certolizumab, golimumab, tocilizumab, and tofacitinib were granted general indications for the treatment of rheumatoid arthritis (RA), while abatacept, adalimumab, etanercept, and infliximab have specific indications for reducing signs and symptoms of RA, inhibiting progression of structural damage, and improving physical function. Anakinra is indicated for reducing signs and symptoms of RA and inhibiting progression of structural damage.

Other Indications

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

In fistulizing Crohn's Disease, infliximab (Remicade) is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Anakinra (Kineret): Approved for use in pediatric patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a rare periodic fever syndrome which causes uncontrolled inflammation in multiple parts of the body beginning in the newborn period.

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 individual cytokines are widely varied, including stimulating production of other cytokines and increased 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 (IL)-1, are involved in tissue destruction in many chronic inflammatory diseases affecting various organs.[17]

TNFα and TNFß are closely related proteins recognized by the same cell surface receptor. TNFα 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.[18,19,20,21,22] Increased expression of TNFα has been reported in the serum, synovium, and sacroiliac joints in patients with ankylosing spondylitis (AS).[23,24,25,26,27] TNFα also has a role in Crohn's disease.

IL-1 plays a major role in the promotion of rheumatic inflammation.[28,29] It promotes inflammation, as well as bone and cartilage resorption, and is present in increased concentrations in the synovia of patients with RA.[30]

Over-expression of IL-12 and IL-23 have been implicated in the pathogenesis of psoriasis.[31] IL-12 induces and sustains TH1 immune responses leading to the secretion of interferon and the homing of T cells to the skin. IL-23 maintains chronic autoimmune inflammation via the induction of IL-17, regulation of T memory cells, and direct activation of macrophages. Ustekinumab (Stelara) is an antagonist of IL-12 and IL-23.

IL-6 has a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis.[32] Overproduction of IL-6 has been linked to various inflammatory, auto-immune, and malignant diseases. Tocilizumab (Actemra) is an IL-6 receptor inhibitor.

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 ß 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 followed by 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.[33] 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 2012.[34] These guidelines recommend more aggressive treatment in patients with early RA (within six months of symptom onset) since earlier treatment may provide better outcomes. ACR also provides guidance on switching between therapies. 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 biologic agents included in the guidelines are the anti-TNF agents, adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), infliximab (Remicade), and golimumab (Simponi), and the non-TNF biologics, abatacept (Orencia), rituximab (Rituxan®), and tocilizumab (Actemra). Anakinra (Kineret) was not included in the ACR recommendations due to the lack of new data and/or infrequent use. Tofacitinib (Xeljanz) was not available when these guidelines were published. Recommendations for the use of biologic DMARDs are separated according to disease duration, < six months (early RA) and ≥ six months (established RA). For each disease duration interval, the recommendations are stratified by features of poor prognosis and are further divided into levels of disease activity (low, moderate, high). Patients with early RA and only low or moderate disease activity are not considered candidates for biologic therapy. Use of an anti-TNF biologic, with or without methotrexate, is recommended for early RA in patients with high disease activity and poor prognosis; infliximab should only be used in combination with methotrexate. In patients with established RA with moderate or high disease activity after three months of methotrexate monotherapy or DMARD combination therapy, the addition of either an anti-TNF biologic, abatacept, or rituximab may be considered. If a patient still has moderate or high disease activity after three months of anti-TNF biologic therapy, ACR recommends switching to another anti-TNF agent or to a non-TNF biologic. A trial period of six months (versus three months) should be used for non-TNF agents due to the potential that a longer time period may be required to assess efficacy. If a patient has a serious adverse event due to an anti-TNF agent, the patient should be switched to a non-TNF agent. If there is an adverse event to a non-TNF agent or nonserious adverse event to an anti-TNF agent, the patient can be switched to another biologic agent, either anti-TNF or non-TNF.

A consensus statement on the biologic agents for the treatment of rheumatic diseases was developed in conjunction with the 2012 international Annual Workshop on Advances in Targeted Therapies.[35] Evidence for the efficacy and safety of the biologic agents for the treatment of various diseases was reviewed. Anti-TNF agents used in combination with methotrexate yield better results in the treatment of RA than monotherapy; adalimumab, certolizumab, etanercept, and golimumab are approved as monotherapy for RA; infliximab is only approved for use with methotrexate. There is no evidence that any one TNF antagonist should be used before another for the treatment of RA or JIA (except with systemic-onset JIA, when anakinra may be effective). There is no evidence that any one TNF antagonist is more effective than any other for the treatment of RA or AS. Indirect comparisons showed similar efficacy of abatacept compared with rituximab, tocilizumab, and golimumab in RA patients with incomplete response to TNF antagonists; however, TNF agents were more effective than abatacept in incomplete responders to methotrexate. A recent meta-analysis demonstrated that anakinra is less effective than the TNF antagonists in treating RA. Tocilizumab has not been compared directly with TNF inhibitors; however, meta-analysis comparisons show similar efficacy to other biological agents.

The Medical Letter's 2012 review for RA drugs is in agreement with the ACR guidelines and the consensus statement by the international Annual Workshop on Advances in Targeted Therapies which recommends that TNF antagonists (etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol) are typically the first-line biologic agents prescribed after an inadequate response to a DMARD; they may be given as monotherapy or in combination with methotrexate.[36] For patients who do not respond adequately to a TNF antagonist, switching to another TNF antagonist or a non-TNF biologic agent may be effective. The combination of a biologic agent with a DMARD (usually methotrexate) offers better disease control without a substantial increase in toxicity and is now commonly used to achieve remission.

Combinations are used particularly for patients with highly active disease, a long duration of disease, or with clinical features that indicate a poor prognosis. Aggressive early therapy with methotrexate and/or a biologic agent results in longer disease-free remissions, less joint destruction, and a better quality of life.

Systemic therapy for plaque psoriasis may include MTX, cyclosporine, acitretin (Soriatane® CK Convenience Kit), methoxsalen (Oxsoralen® Ultra), and the biologic agents,adalimumab, etanercept, infliximab, and ustekinumab. The American Academy of Dermatology (AAD) guidelines for the management of psoriasis and psoriatic arthritis, section six, states there is no specific sequence in which anti-TNF agents should be used in patients with moderate to severe chronic plaque psoriasis without psoriatic arthritis.[37] Monotherapy with adalimumab, etanercept, infliximab, and ustekinumab are listed as acceptable first- line agents after failure of topical therapy alone when phototherapy is not available. However, the guidelines note that in non head-to-head phase III trials of the individual agents, infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept. In patients with moderate to severe psoriatic arthritis, methotrexate, adalimumab, etanercept, golimumab, infliximab, or a combination of methotrexate plus an anti-TNF agent is considered first-line treatment. 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.[38] 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.

For the treatment of severe ankylosing spondylitis, adalimumab, etanercept, and golimumab are recommended according to the National Institute for Health and Clinical Excellence (NICE).[39,40] 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 Visual Analog Score (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. Golimumab (Simponi) was not available at the time of guideline development. In 2013, certolizumab (Cimzia) was approved for the treatment of adults with ankylosing spondylitis, and was not available at the time that the NICE guidelines were published.

The 2013 American Gastroenterology Association (AGA) medical position statement on treatment of inflammatory Crohn's Disease recommends using anti-TNF-α drugs (infliximab or adalimumab) to induce remission in patients with moderately severe Crohn's Disease (Strong Recommendation, Moderate-Quality Evidence).[41] Citing the results of the SONIC trial where the combination of infliximab and azathioprine was superior to infliximab alone in inducing remission in patients with moderately severe Crohn's Disease who had not previously received either therapy, the guideline suggests using anti-TNF drugs in combination with thiopurines over anti-TNF monotherapy to induce remission in patients who

have moderately severe Crohn's Disease (Weak Recommendation, Moderate-Quality Evidence).[42] The benefits of combination therapy remain uncertain in patients who previously failed to respond to the use of thiopurines. In the setting of corticosteroid-or anti-TNF-induced remission of patients with Crohn's Disease, the maintenance use of anti-TNF drugs is recommended (Strong recommendation, High-Quality Evidence). The data indicate that infliximab and adalimumab, as well as certolizumab, have substantial and similar benefits in the maintenance setting.

The 2009 American Gastroenterology Association (AGA) practice guidelines for the management of Crohn's Disease in adults consider anti-TNF monoclonal antibodies, infliximab, adalimumab, and certolizumab to be effective in the treatment of moderate to severely active CD in patients who have not responded to therapy with a corticosteroid or an immunosuppressive agent (grade A) or in patients in whom corticosteroid therapy is contraindicated (grade B) as induction and maintenance therapy.[43]

The 2010 ACG guidelines for Ulcerative Colitis do not address the use of adalimumab or certolizumab pegol for treatment of UC. They do, however, state infliximab is effective in maintaining and improving remission in patients with mild to moderate extensive (extends proximal to the descending colon) colitis who responded to infliximab induction regimen (Evidence A). These guidelines also state infliximab is indicated for the management of patients with severe colitis who continue to have severe symptoms despite optimal doses of oral corticosteroids. These guidelines do not address adalimumab or certolizumab pegol and in those with severe colitis who continue to have severe symptoms despite optimal doses of oral corticosteroids.[44]

In a 2012 review of drugs for inflammatory bowel disease, the TNF inhibitors infliximab, adalimumab, and certolizumab pegol, are used for treatment of moderate to severe Crohn's disease.[45] Infliximab is also indicated for treatment of moderate to severe ulcerative colitis not responsive to conventional therapies. The rates of response and remission in Crohn's disease with other TNF inhibitors appear to be comparable to those with infliximab; although, head-to-head comparisons of these agents are lacking.

PHARMACOLOGY

Cytokine Antagonists

Antagonists that bind cytokines or their receptors can block cytokine activity. Biologics, such as the IL-1 receptor antagonist, anakinra (Kineret), canakinumab (Ilaris) and rilonacept (Arcalyst), and anti-TNFα agents, adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), and infliximab (Remicade), exert their action by neutralizing the activities of the inflammatory agents IL-1 and TNFα, respectively. Ustekinumab (Stelara) is an IL-12 and IL-23 antagonist.[46] Tocilizumab (Actemra) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody.[47,48] Vedolizumab (Entyvio) is a humanized monoclonal antibody that binds to a4β7 integrin and blocks mucosal cell adhesion and inhibits the migration of T-lymphocytes into the gastrointestinal tissue.[49] Apremilast (Otezla) has a substantially different mechanism in that it is an oral phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP) PDE4 inhibition.[50] The specific mechanism by which apremilast exerts its effect is unknown.

Despite their common ability to inhibit TNFα bioactivity, the molecular structures and mechanisms of action of anti-TNFα 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.[51,52,53,54]

Cytokines secreted in response to an immune stimulus bind to receptors on cell surfaces and activate intracellular Janus kinase (JAK) proteins, which in turn activate a signaling pathway within the cell, leading to immune cell proliferation.[55,56] Over-activation of JAK can lead to inflammation and tissue destruction. Tofacitinib (Xeljanz) selectively inhibits JAK1 and JAK3, thereby blocking signaling for several cytokines, including many interleukins that are integral to lymphocyte activation, proliferation, and function. In addition, inhibition of JAK1 results in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6.

PHARMACOKINETICS

Drug	Half-life (days)	Bioavailability (%)
abatacept IV (Orencia)[57]	13.1 to 14.3	(IV)
abatacept SC (Orencia)[58]	14.3	78.6 (SC)
adalimumab (Humira)[59,60]	10 to 20	64 (SC)
anakinra (Kineret)[61]	0.17 to 0.25	95 (SC)
apremilast (Otezla)[62]	6-9 hours	73 (PO)
canakinumab (Ilaris)[63]	26	66 (SC)
certolizumab pegol (Cimzia)[64]	14	80 (SC)
etanercept (Enbrel)[65]	4.3 ± 1.3	60 (SC)
golimumab SC (Simponi)[66]	14	53 (SC)
golimumab IV (Simponi Aria)[67]	12 ±3	(IV)
infliximab (Remicade)[68]	7.7 to 9.5	(IV)
rilonacept (Arcalyst)[69]	nd	nd
tocilizumab (Actemra) adults[70]*	11 to 13 (IV)	(IV)
tocilizumab (Actemra) pediatrics[71]*	16- 23 (IV)	(IV)
tocilizumab (Actemra) adults[72]*	5 to 13 (SC)	80 (SC)
tofacitinib (Xeljanz)[73]	~0.125	74 (PO)
ustekinumab (Stelara)[74]	14.9 to 45.6	nd
vedolizumab (Entyvio)[75]	25	(IV)

nd = no data; iv=intravenous; sc=subcutaneous

* Nonlinear – concentration dependent

CONTRAINDICATIONS/WARNINGS

TNF-blocking agents – adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), and infliximab (Remicade)[76,77,78,79,80,81]

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, and pneumocystosis were the most

commonly reported. Serious bacterial infections due to *Legionella* and *Listeria* have been 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. Monitor all patients during therapy for TB even if the initial latent TB test was negative. Use of TNF blockers should be discontinued if a patient develops a serious infection or sepsis.

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. Carriers of HBV who require treatment with a TNF blocker should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of treatment. 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.

Patients at greater risk of infection may include patients older than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants, such as corticosteroids or MTX. The risks and benefits of treatments with TNF antagonists should be considered prior to initiating therapy in patients with chronic or recurrent infection, with prior exposure to tuberculosis, with a history of an opportunistic infection, or patients who have resided or traveled to areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, or patients with underlying conditions that may predispose them to infection, such as poorly controlled diabetes.

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.

Hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers has been reported in patients on TNF blockers. Nearly all of the reported TNF-blocker associated cases of hepatosplenic T-cell lymphoma (HSTCL) have occurred in patients with Crohn's disease with some occurring in ulcerative colitis patients. The majority were in adolescent and young adult males. Almost all patients had received azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis.

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 TNF blockers. Approximately half of 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). Acute and chronic leukemia have also been reported with TNF blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer. As of November 2011, the FDA is requiring manufacturers of TNF blockers to perform enhanced safety surveillance on these products.[82]

Melanoma has been reported in patients treated with TNF-blocking agents. Merkel cell carcinoma has also been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Cases of acute and chronic leukemia have been report in association with post-marketing TNF blocker use in RA and other indications.

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.

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 (CNS) 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 the use of TNF blockers in patients with pre-existing or recent-onset CNS 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.

abatacept (Orencia)[83]

Abatacept should not be administered to patients with known hypersensitivity to abatacept or any of its components. In clinical trials, patients receiving concomitant abatacept (via intravenous administration) 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. Serious infections including sepsis and pneumonia have been reported in patients receiving abatacept. In clinical studies, the safety experience for abatacept was similar for both subcutaneously and intravenous administered dosages.

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 prior to initiating therapy with abatacept according to published guidelines.

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

adalimumab (Humira)[84]

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. A higher rate of non-melanoma skin cancer has been reported among patients receiving adalimumab compared to control patients in some clinical trials. Patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA photochemotherapy treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab.

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 or abatacept and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse reactions seen with these combination therapy, similar toxicities may result from combination of anakinra or abatacept and other TNF blocking agents. Therefore, the combination of adalimumab with abatacept or anakinra is not recommended.

Development of autoantibodies and the rare development of a lupus-like syndrome have been reported following use of adalimumab. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with adalimumab, treatment should be discontinued.

anakinra (Kineret)[85]

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. In patients with NOMID, if anakinra discontinuation is contemplated, the risk of NOMID flare upon discontinuation of therapy should be weighed against the potential risk of continued treatment.

apremilast (Otezla)[86]

Apremilast is contraindicated in patients with known hypersensitivity to any components of the product.

Apremilast is associated with an increased risk of depression. Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with apremilast in patients with a history of depression and/or suicidal thoughts or behavior.

During clinical trials, apremilast was associated with weight decrease. Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of apremilast.

canakinumab (Ilaris)[87]

Canakinumab is contraindicated in patients with known hypersensitivity to any components of the product. Canakinumab blocks IL-1 which may interfere with immune response to infections. Treatment with medications that work through inhibition of IL-1 has been associated with an increased risk of serious infections. Canakinumab has been associated with an increased incidence of serious infections. Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Discontinue treatment with canakinumab if a patient develops a serious infection and do not administer it to patients during an active infection requiring medical intervention. Live vaccines should not be given concurrently with canakinumab. Prior to initiation of therapy with canakinumab, patients should receive all recommended vaccinations.

certolizumab pegol (Cimzia)[88]

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

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. Some of these reactions occurred after the first administration of certolizumab pegol. 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.

Patients treated with certolizumab pegol may receive vaccinations, except for live or live attenuated vaccines. In clinical trials, similar proportions of patients developed protective levels of anti-vaccine antibodies between certolizumab pegol and placebo treatment groups; however, patients receiving certolizumab pegol and concomitant methotrexate had a lower humoral response compared with patients receiving certolizumab pegol alone. The clinical significance of this is unknown. No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving 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. A higher risk of serious infections was also observed in combination use of TNF blockers with abatacept and rituximab. Because of the nature of the adverse events observed with this combination therapy, similar toxicities may also result from certolizumab pegol in this combination. Certolizumab pegol should not be used in combination with other biological DMARDs.

Hepatitis B virus reactivation can occur with certolizumab pegol so it is recommended to test for HBV infection before starting therapy. Monitor HBV carriers during and several months after therapy. If reactivation occurs, certolizumab pegol should be stopped and anti-viral therapy started.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including certolizumab pegol. TB may be due to reactivation of latent TB infection or to new infection. Patients should be evaluated for TB risk factors and be tested for latent TB infection prior to initiating certolizumab pegol and during treatment. Treatment of latent TB infection should be initiated prior to therapy with certolizumab pegol. 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 certolizumab pegol have developed active TB. Physicians should monitor patients receiving certolizumab pegol for signs and symptoms of active TB, including patients who tested negative for latent TB infection. Anti-tuberculosis therapy should also be considered prior to initiation of certolizumab pegol in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. 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 TB, or who have had close contact with a person with active TB.

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.

Lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with TNF blockers, including certolizumab pegol. Certolizumab pegol is not indicated in pediatrics.

etanercept (Enbrel)[89]

Etanercept is contraindicated in patients with sepsis. Etanercept should not be given to patients with a 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 due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens have been reported with TNF blockers. 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.

Cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including etanercept.

Treatment with TNF blockers, including etanercept, has been associated with rare (<0.1 percent) cases of new onset or exacerbation of central nervous system demyelinating disorders. Cases of transverse myelitis, optic neuritis, multiple sclerosis, Guillain-Barré syndromes, other peripheral demyelination neuropathies, and new onset or exacerbation of seizure disorders have been reported in post-marketing experience with etanercept.

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.

Malignancies including lymphoma, acute and chronic leukemia, and non-melanoma skin cancers have been reported in patients receiving etanercept and other TNF blocking agents. Merkel cell carcinoma has been reported infrequently in patients treated with etanercept.

Autoantibodies formation and the rare development of a lupus-like syndrome or autoimmune hepatitis have been reported in patients receiving etanercept. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with etanercept, treatment should be discontinued, and the patient should be evaluated.

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 or abatacept 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 or abatacept and other TNF blocking agents.

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-blocking agents have occurred, including very rare cases (<0.01 percent) with etanercept. In some instances, hepatitis B 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. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-blocker therapy to prevent HBV reactivation.

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.

In two clinical trials evaluating the use of etanercept for the treatment of heart failure, one study suggested higher mortality in the etanercept-treated patients compared to placebo. There have been post-marketing reports of worsening of CHF, with and without precipitating factors, in patients taking etanercept. New onset CHF (<0.1 percent) has been reported, including in patients without known pre-existing cardiovascular disease. Use etanercept with caution in patients with a history of CHF.

golimumab (Simponi, Simponi Aria)[90,91]

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, (e.g., surface antigen positive). HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal in some instances. Patients should be tested for HBV infection before initiating golimumab. 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. Leukemia has also been reported.

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

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) and peripheral demyelinating polyneuropathy. Discontinue golimumab if these disorders develop.

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.

Reports of severe hepatic reactions, including acute liver failure, have been reported in patients receiving TNF blockers. In phase three trials of golimumab in patients with RA, PsA, and AS through 16 weeks, ALT elevations $\geq$ five times the upper limit of normal (ULN) occurred in 0.2 percent of golimumab patients and 0.2 percent of control patients.

Combination therapy with golimumab and abatacept or anakinra is not recommended due to a greater infection risk without additional clinical benefit as observed with other TNF blockers.

Use caution when switching between one biologic DMARD including golimumab to another as overlapping biologic activity may increase the risk of infection.

Hypersensitivity reactions including anaphylaxis to golimumab have been reported. If an anaphylactic or other serious allergic reaction occurs, administration of golimumab should be discontinued immediately and appropriate therapy instituted.

infliximab (Remicade)[92]

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, including *Legionella* and *Listeria*. 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 adolescents treated with TNF blockers, including infliximab.

Rare post-marketing 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.

Infliximab has been associated with adverse outcomes in patients with heart failure and should be used in patients with heart failure only after consideration of other treatment options. There have been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease.

In a clinical trial using infliximab in patients with moderate to severe COPD, an increase in malignancies, 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.

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in post-marketing data in patients receiving infliximab. If jaundice and/or marked liver enzyme elevations greater than five times the upper limit of normal develop, infliximab should be discontinued, and the liver enzyme elevation evaluated. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury.

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 (e.g., as early as after the second dose), and when infliximab therapy was reinstituted 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 RA, Crohn's disease, and psoriasis clinical trials, re-administration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefit-risk of re-administration of infliximab after a period of no-treatment, especially as a re-induction regimen given at weeks zero, two, and six, should be carefully considered. If infliximab maintenance therapy for psoriasis is interrupted, infliximab should be restarted as a single dose followed by maintenance therapy.

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 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.

Combination therapy with infliximab and abatacept or anakinra is not recommended due to a greater infection risk without additional clinical benefit as observed with other TNF blockers.

When switching between biological DMARDs, use caution since overlapping biological activity may further increase the risk of infection. The concomitant use of infliximab with other biological agents is not recommended.

It is recommended that live vaccines not be given concurrently with infliximab. Caution is advised when administering live vaccines to infants born to mothers treated with infliximab during pregnancy since infliximab is known to cross the placenta and has been detected in infants up to six months of age.

Other therapeutic infectious agents (e.g., BCG bladder instillation for the treatment of cancer) could result in infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab.

Treatment with infliximab 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 infliximab, discontinue treatment.

rilonacept (Arcalyst)[93]

Rilonacept blocks IL-1 which may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept. Discontinue treatment with rilonacept if a patient develops a serious infection and do not initiate treatment with rilonacept in patients with active or chronic infections.

Rare hypersensitivity reactions have been associated with rilonacept administration. If a hypersensitivity reaction occurs, discontinue administration of rilonacept. Live vaccines should not be given concurrently with rilonacept. Prior to initiation of therapy with rilonacept, patients should receive all recommended vaccinations.

Patients should also be monitored for changes in their lipid profiles and provided with medical treatment if warranted.

tocilizumab (Actemra)[94]

Tocilizumab should not be administered to patients with known hypersensitivity to tocilizumab. Patients receiving tocilizumab are at an increased risk for developing serious infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens that may lead to 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, invasive fungal infections, 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. Tocilizumab should not be initiated in patients with active infections, including localized infections. The risk and benefits of tocilizumab therapy should be considered prior to initiation of therapy. Patients with higher infection risks include those with chronic or recurrent infection, exposure to TB, history of serious or an opportunistic infection, with a history of travel or residence in areas of endemic TB or endemic mycoses, or those with underlying conditions that may predispose them to infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

Cases of viral reactivation of herpes zoster have been reported. Patients who tested positive for hepatitis were excluded from clinical trials of tocilizumab.

Gastrointestinal (GI) 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 and thrombocytopenia. Tocilizumab should not be initiated in patients with a low absolute neutrophil count (ANC< 2,000/mm^3) or platelet counts of <100,000/mm^3. Therapy is not recommended if the ANC during tocilizumab therapy is less than 500/mm^3 or platelet count falls to less than 50,000/mm^3. Monitor neutrophils and platelets four to eight weeks after the start of therapy and every three months thereafter. Dose modifications for tocilizumab are recommended based on ANC and 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 alanine aminotransferase (ALT) and aspartate aminotransferase (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. Tocilizumab is not recommended if ALT or AST exceed more than five times the upper limit of normal. Monitor ALT and AST levels four to eight weeks after start of therapy and every three months thereafter. When clinically indicated, other liver function tests, such as bilirubin, should be considered. Dose modifications for tocilizumab due to elevations of ALT and/or AST are recommended. Patients with active hepatic disease or hepatic impairment should not receive tocilizumab.

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.

The effect that tocilizumab has on the development of malignancies and demyelinating disorders is unknown, but malignancies, multiple sclerosis, and chronic inflammatory demyelinating polyneuropathy

were reported during clinical trials. Prescribers should exercise caution in considering the use of tocilizumab in patients with pre-existing or recent onset demyelinating disorders.

Hypersensitivity reactions, including anaphylaxis, have been reported during tocilizumab infusions (0.2 percent) and with subcutaneous injections (0.7 percent). Anaphylaxis with intravenous administration has resulted in death. Reactions have occurred with a range of doses, sometimes as early as the first dose, and even in patients who have received premedication.

Tocilizumab has not been studied in combination with other biological DMARDS including TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators. Combination therapy should be avoided as there is a possibility of increased immunosuppression and increased risk of infection.

tofacitinib (Xeljanz)[95]

Boxed warnings include increased risk of serious and sometimes fatal bacterial, mycobacterial, fungal, and viral infections in those treated with tofacitinib. Most commonly reported serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infections. Active TB was also reported. TB screening and appropriate treatment prior to initiation of tofacitinib treatment is recommended. Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with tofacitinib. The impact of tofacitinib on chronic viral hepatitis reactivation is unknown as patients who screened positive for hepatitis B or C were excluded from clinical trials. Tofacitinib should not be initiated in patients with an active infection, including localized infections. The risk and benefits of treatment should be considered when prescribing tofacitinib in patients with a history of chronic, recurrent, or serious infection, prior exposure to TB, or a comorbid condition that predisposes them to infection.

A boxed warning also exists regarding the increased risk of malignancies, including lymphoma. The most common types of malignancies reported were lung and breast cancer. Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.

Ten events of GI perforations were identified (in 4,791 patients) in clinical trials with tofacitinib in RA patients. Tofacitinib should be used with caution in patients who may be at increased risk for GI perforation, such as a history of diverticulitis. New onset of abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Treatment with tofacitinib has been associated with decreases in lymphocyte, neutrophil, and red blood cell counts. It is recommended that tofacitinib not be initiated in patients with a lymphocyte count <500 cells/mm3, an ANC <1,000 cells/mm^3, or a hemoglobin level <9 g/dL. In patients receiving tofacitinib, lymphocyte counts should be obtained at baseline and every three months thereafter. Neutrophil and hemoglobin should be monitored at baseline, four to eight weeks after initiation of therapy, and every three months thereafter.

Tofacitinib was associated with an increased incidence of elevated liver enzymes. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is

suspected, the administration of tofacitinib should be interrupted until this diagnosis has been ruled out. Treatment with tofacitinib is not recommended in patients with severe hepatic impairment.

Dose dependent increases in total cholesterol, LDL-C, and HDL-C were observed in clinical trials. Increases occurred within one to three months of the start of tofacitinib therapy and remained stable thereafter with continued treatment. No evidence for an increase in cardiovascular risk has been observed. Lipid assessments should be performed approximately four to eight weeks following initiation of therapy, and patients should be managed according to clinical guidelines (e.g., National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia.

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. Live vaccines should not be given concurrently. Immunizations should be updated consistent with current immunization guidelines prior to initiating tofacitinib therapy.

Treatment with tofacitinib is not recommended in patients with severe hepatic impairment.

ustekinumab (Stelara)[96]

Ustekinumab (Stelara) is contraindicated in patients with a history of clinically significant hypersensitivity to ustekinumab or to any of the excipients. Serious allergic reactions including angioedema and anaphylaxis have been reported with ustekinumab. Discontinue use of ustekinumab and institute appropriate therapy.

Ustekinumab may increase the risk of infections and reactivation of latent infections. Patients genetically deficient in IL-12/IL-23 are vulnerable to disseminated infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 with ustekinumab will be susceptible to these types of infections. During clinical trials for the treatment of psoriasis, serious infections diagnosed included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, and sepsis. In the psoriatic arthritis trials, serious infections included cholecystitis. Ustekinumab 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. Diagnostic tests to screen for these infections should be considered, as dictated by clinical circumstances. Patients should be evaluated for tuberculosis prior to initiating therapy with ustekinumab. Do not administer ustekinumab to patients with active TB. Consider initiation of anti-TB therapy prior to ustekinumab therapy for patients with a past history of latent TB or active TB or those in who an adequate course of treatment cannot be confirmed. Prior to initiating therapy, patients should receive all age-appropriate immunizations.

As an immunosuppressant, ustekinumab may increase the risk of malignancy. There have been reports of multiple rapidly appearing cutaneous squamous cell carcinomas in patients who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving ustekinumab should be monitored for non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy, and those with a history of psoralen plus ultraviolet light (PUVA) treatment should be followed closely. The safety of ustekinumab in patients with a history of or a known malignancy has not been evaluated. Ustekinumab has not been studied beyond two years of use.

One case of reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in clinical trials with ustekinumab. RPLS is a neurological disorder that 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.

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

BCG vaccines should not be given during treatment with ustekinumab or for one year prior to initiating treatment or for one year after discontinuation. Use caution when administering live vaccines to household contacts of patients receiving ustekinumab due to the potential risk of viral shedding from the household contacts and transmission to the patient. Non-live vaccinations received during ustekinumab therapy may not elicit an immune response sufficient to prevent disease.

Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergy immunotherapy, particularly for anaphylaxis.

vedolizumab (Entyvio)[97]

Vedolizumab is contraindicated is in patients with a history of hypersensitivity to vedolizumab or to any of the excipients. Treatment with vedolizumab is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding vedolizumab in patients who develop a severe infection while on treatment.

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system. While no cases of PML were identified among patients with at least 24 months of vedolizumab exposure, a risk of PML cannot be ruled out. Monitor patients on vedolizumab for any new onset, or worsening, of neurological signs and symptoms.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)[98,99,100]

The FDA has determined that a REMS was necessary for tocilizumab (Actemra) to ensure the benefits of the drug outweigh the potential risks of serious infections, gastrointestinal perforations, hypersensitivity reactions, including anaphylaxis, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders and malignancies. Physicians are advised to discuss the risks that may be associated with tocilizumab with patients and their caregivers. In addition, the Actemra Medication Guide must be provided to patients being treated with tocilizumab.

A REMS program is in place for ustekinumab (Stelara) to mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS). A communication plan informs specified prescribers and dispensing pharmacists of the risks associated with ustekinumab (Stelara). In addition, a medication guide must be distributed to each patient who fills a prescription for ustekinumab (Stelara).

The FDA required a REMS program as part of the approval of tofacitinib (Xeljanz). The goal of the Xeljanz REMS program is to inform healthcare providers and patients about the serious risks associated with

tofacitinib treatment. A medication guide should be dispensed with each Xeljanz prescription and information letters will be distributed to likely prescribers of tofacitinib.

DRUG INTERACTIONS

abatacept (Orencia)[101]

Concurrent administration of a TNFα-blocker with abatacept is not recommended since combination therapy has been associated with an increased risk of serious infections with no additional efficacy over TNFα-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)[102]

Adalimumab should not be used with anakinra, abatacept, or other TNFα-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.

anakinra (Kineret)[103]

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.

apremilast (Otezla)[104]

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. The use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended.

canakinumab (Ilaris)[105]

No formal drug interaction studies have been conducted with canakinumab. However, concomitant use of canakinumab with TNF blockers should be avoided because of the potential for an increased risk of infections.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab so live vaccines should not be given concurrently with canakinumab.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation which may occur during canakinumab treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to be adjusted as needed.

certolizumab pegol (Cimzia)[106]

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 in combination with biological DMARDs or other TNF-blocker therapies.

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)[107]

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. The use of etanercept with cyclophosphamide is not recommended.

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.

Live vaccines should not be given concurrently with etanercept.

Serious infections were seen in clinical studies with concurrent use of anakinra or abatacept and etanercept, with no added benefit.

golimumab (Simponi, Simponi Aria)[108,109]

When used in combination with abatacept (Orencia) or anakinra (Kineret), an increased risk of serious infections with no added therapeutic benefit has been observed with other TNF blockers in clinical RA studies. Therefore, use of golimumab with abatacept or anakinra is not recommended.

During chronic inflammation, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα). 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)[110]

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 or abatacept 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. The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including infliximab, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

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.

It is recommended that therapeutic infectious agents (e.g., BCG in bladder cancer) not be given concurrently with infliximab.

rilonacept (Arcalyst)[111]

No formal drug interaction studies have been conducted with rilonacept. However, concomitant use of rilonacept with TNF blockers should be avoided because of the potential for an increased risk of infections.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation which may occur during rilonacept treatment. This may cause an interaction with

CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to be adjusted as needed.

tocilizumab (Actemra)[112]

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.

tofacitinib (Xeljanz)[113]

Tofacitinib exposure is increased when coadministered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole), and with coadministration of drugs that are both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19 (e.g., fluconazole). The dose of tofacitinib should be reduced to 5 mg once daily in patients taking these medications. In contrast, potent inducers of CYP3A4 (e.g., rifampin) decrease tofacitinib exposures and concomitant use is not recommended.

There is a risk of added immunosuppression when tofacitinib is coadministered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use with potent immunosuppressives has not been studied in RA.

ustekinumab (Stelara)[114]

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.

BCG vaccines should not be given during treatment with ustekinumab or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to patient. Non-live vaccinations received during ustekinumab therapy may not elicit an immune response sufficient to prevent disease. Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Use caution in patients receiving or who have received allergy immunotherapy and monitor for anaphylaxis.

Ustekinumab in combination with immunosuppressive agents or phototherapy has not been evaluated.

vedolizumab (Entyvio)[115]

Concomitant use of vedolizumab with natalizumab should be avoided because of the potential for an increased risk of PML and other infections.

Concomitant use of vedolizumab with TNF blockers should be avoided because of the potential for an increased risk of infections.

Live vaccines may be administered concurrently with vedolizumab only if the benefits outweigh the risks.

ADVERSE EFFECTS

In Adults

Drug	Injection site/ Infusion reaction	Infection		Headache	Nausea
		Upper respiratory	Other		
abatacept (Orencia)[116,117]	9 (6) IV - 2.5% (18/721) SC - 2.6% (19/736)	5-13	Total Infections 54 (48) Serious Infections 3 (1.9)	18 (13)	reported
adalimumab (Humira)[118]	20 (14)	17 (13)	serious infections 4.7/100 p/yr (2.7/100 p/yr)	12 (8)	9 (8)
anakinra (Kineret)[119,120]	71 (29)	14 (17)	39 (37)	12 (9)	8 (7)
apremilast (Otezla)[121]	na	0.6 (0.6)	nr	4.8 (1.8)	7.4 (1.4)
canakinumab (Ilaris)[122]	6.8	reported	37.8	14	14
certolizumab pegol (Cimzia)[123]	reported	18-20 (13)	total infections in Crohn's patients 38 (30) total infections in RA patients 0.91/ p/yr (0.72/ p/yr)	5 (with MTX; 4 with MTX alone)	nr
etanercept (Enbrel)[124]	15-43 (6-11)	17-65 (17-30)	total infections 27-81 (28-39) serious infections 1.4 (0.8)	nr	nr
golimumab (Simponi)[125]	SC - 6 (2)	SC- 16 (13)	SC - serious infections 5.7/100 p/yr (4.2/100 p/yr)	nr	nr
golimumab (Simponi Aria)[126]	IV - 2 (1)	IV - 13 (12)	IV - serious infections 4.07/100 p/yr	nr	nr
infliximab (Remicade)[127]	20 (10)	32 (25)	27-36 (18-25)	18 (14)	21 (20)
rilonacept (Arcalyst)[128]	11 (3)	6 (1)	34 (27)	nr	4 (13)
tocilizumab (Actemra)[129]	SC – 7.1-10.1 (2.4-4.1)	nr	nr	nr	nr
tocilizumab (Actemra)[130]	IV - 7-8 (5)	5-8 (6)	serious infections 3.6/100 p/yr (1.5/100 p/yr)	5-7 (2-3)	nr

In Adults (continued)

Drug	Injection site/ Infusion reaction	Infection		Headache	Nausea
		Upper respiratory	Other		
tofacitinib (Xeljanz)[131]	na	4.5 (3.3)	serious infections 1.7/100 p/yr (0.5/100 p/yr) 20 (18)	4.3 (2.1)	reported
ustekinumab (Stelara)[132]	1-2 (<1)	4-5 (5)	serious infections 0.01/ p/yr (0.02/ p/yr)	5 (3)	nr
vedolizumab (Entyvio)[133]	4 (3)	7 (6)	0.85/p/yr (0.7/p/yr)	12 (11)	9 (8)

nr = not reported na = not applicable p/yr= patient-year

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. 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.[134] Neutrophil counts should be obtained prior to initiating anakinra, while on therapy, monthly for three months, and thereafter quarterly for a period up to one year.

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.[135] 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
abatacept (Orencia)[136]	2-4	36
adalimumab (Humira)[137]	16	45
anakinra (Kineret) [138]	16	total infections 2.3 infections/patient-year in first six months of therapy 1.7 infections/patient year after the first six months of therapy
etanercept (Enbrel)[139]	reported	reported

In Pediatric Patients (continued)

Drug	Injection site/ Infusion reaction	Infection
infliximab (Remicade)[140]	18	65-68
tocilizumab (Actemra)[141]	16 - SJIA 20.2 - PJIA	total infections 163.7/100 patient years - SJIA 345/100 patient-years - PJIA (287/100 patient-years)

nr = not reported

PJIA = polyarticular juvenile idiopathic arthritis; SJIA = systemic juvenile idiopathic arthritis

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

Monitoring

In patients receiving tofacitinib, lymphocyte counts should be obtained at baseline and every three months thereafter. Neutrophil counts should be obtained at baseline and after four to eight weeks of treatment and every three months thereafter. Hemoglobin should be checked at baseline and after four to eight weeks of treatment and every three months thereafter. Routine liver tests should also be performed along with lipid assessments approximately four to eight weeks following initiation of therapy.[142]

Tocilizumab (Actemra) requires monitoring of neutrophils, platelets, and liver enzymes (ALT and AST) after four to eight weeks and every three months thereafter.[143] Therapy with tocilizumab may be withheld, dose reduced, 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. Patients with an absolute neutrophil count (ANC) below 2,000/mm^3, platelet count below 100,000/mm^3, or ALT or AST above 1.5 times the upper limit of normal should not initiate therapy with tocilizumab.

SPECIAL POPULATIONS[144,145,146,147,148,149,150,151,152,153,154,155,156,157]

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.[158] 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. Of the 190 enrolled patients, 153 patients entered the long term extension phase. By day 589 (≥21 months), the percentage of patients reaching various ACR criteria in the double-blind and long-term extension phases were the following: ACR Pedi 30 (90 percent), ACR Pedi 50 (88 percent), ACR Pedi 70 (75 percent), ACR Pedi 90 (57 percent), and ACR Pedi 100 (39 percent).[159] Similar response rates were observed by day 589 among patients previously treated with placebo. Among patients who had not achieved an ACR Pedi 30 response at the end of the open-label lead-in phase and who proceeded directly into the long term extension phase, 73 percent, 64 percent, 46 percent, 18 percent, and five percent achieved ACR Pedi 30, Pedi 50, Pedi 70, Pedi 90, and Pedi 100 responses, respectively, by day 589. Tuberculosis and malignancies were not reported during the long term extension phase.

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, multi-center, 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.[160] Patients had previously received treatment with NSAIDs underwent stratification according to methotrexate use. Patients received adalimumab 24 mg/m^2 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.

anakinra (Kineret)

Anakinra (Kineret) is approved for use in pediatric patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a rare periodic fever syndrome which causes uncontrolled inflammation in multiple parts of the body beginning in the newborn period. The pre-filled syringe does not permit accurate dosing lower than 20 mg. Anakinra has been studied in pediatric patients with JIA.[161]

In a long-term, open-label and uncontrolled study ,43 NOMID patients 0.7 to 46 years of age were treated for up to 60 months.[162] Patients were given an initial dose of anakinra 1-2.4 mg/kg, which was titrated by 0.5 to 1 mg/kg increments to control signs and symptoms of disease to a maximum of 10 mg/kg daily. The actual maximum dose studied was 7.6 mg/kg/day. The average maintenance dose was 3 to 4 mg/kg daily. The dose was given once daily, in general, but, for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Improvements occurred in all individual disease symptoms comprising the DSS and the estimated changes from baseline in DSSS were -3.5 (95% CI -3.7 to -3.3) which was seen as early as Month 3 and continued through Month 60. In addition, improvements in serum markers of inflammation (serum amyloid A [SAA], hsCRP, and ESR levels) were also evident. For 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra therapy. Upon withdrawal of treatment, the median time until disease flare criteria were met was five days.

canakinumab (Ilaris)

The CAPS trials with canakinumab included a total of 23 pediatric patients with an age range from four years to 17 years. The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., Serum Amyloid A and C-Reactive Protein). Overall, the efficacy and safety of canakinumab in pediatric and adult patients were comparable. The safety and effectiveness of canakinumab in CAPS patients under 4 years of age has not been established.

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.[163] 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.[164] 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 and for the treatment of ulcerative colitis. Safety and effectiveness data for infliximab in children for the management of psoriatic arthritis 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.[165] 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).

rilonacept (Arcalyst)

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with rilonacept at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24 weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult subjects. Safety and effectiveness in pediatric patients below the age of 12 have not been established.

tocilizumab (Actemra)

Tocilizumab is indicated for polyarticular and systemic juvenile idiopathic arthritis in children ages two years and older.

Tocilizumab was assessed in a three-part study in children two to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to MTX or inability to tolerate

MTX.[166] Patients had at least six months of active disease, with at least five joints with active arthritis and/or at least three active joints having limitation of motion. JIA subtypes at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of MTX was permitted but disease-modifying antirheumatic drugs (DMARDs), other than MTX, or other biologics (e.g., TNF antagonists or T-cell costimulation modulator) were not permitted.

Part I of the study was a 16-week active tocilizumab treatment lead-in period (n=188), part II, a 24-week randomized double-blind placebo-controlled withdrawal period, and part III, a 64-week open-label period. Patients weighing 30 kg or more received tocilizumab 8 mg/kg IV once every four weeks. Patients weighing less than 30 kg received either tocilizumab 8 mg/kg or 10 mg/kg IV in a randomized 1:1 ratio every four weeks. At the end of part I, 91 percent of patients taking background MTX in addition to tocilizumab and 83 percent of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 and entered the blinded withdrawal period (part II).

In part II, patients (ITT, n=163) were randomized to tocilizumab (same dose as in Part I) or placebo in a 1:1 ratio that was stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in part II until week 40 or until they showed JIA ACR 30 flare criteria (relative to week 16) and the subject qualified for escape. The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the six core outcome variables worsening by at least 30 percent with no more than one of the remaining variables improving by more than 30 percent relative to week 16. Tocilizumab-treated patients experienced fewer disease flares compared to placebo-treated patients (26 percent [21/82] versus 48 percent [39/81]; with an adjusted difference in proportions of -21 percent, 95% CI: -35 to -8 percent).

The efficacy of tocilizumab was assessed in active systemic JIA in a 12-week randomized, double-blind, placebo-controlled, parallel group study in children aged two and older. One hundred and twelve patients, treated with or without MTX, were randomized 2:1 to receive to tocilizumab (n=75) or placebo (n=37). Every two weeks, patients less than 30 kg received tocilizumab or placebo infusions at 12 mg/kg and those above 30 kg received tocilizumab or placebo infusions at 8 mg/kg. The primary endpoint was the proportion of patients at week 12 with at least a 30 percent improvement in American College of Rheumatology Juvenile Idiopathic Arthritis (JIA ACR 30) in three of six core outcome variables compared to baseline and absence of fever during the preceding seven days. After six weeks patients who achieved a JIA ACR 70 response could begin corticosteroid tapering. The JIA ACR 30 response rates with absence of fever at week 12 were 85 percent for tocilizumab and 24 percent for placebo, with a weighted difference between the tocilizumab and placebo response rates stratified for weight, disease duration, background oral corticosteroid dose, and background methotrexate (MTX) use of 62 percent (95% CI: 45 to 78 percent).[167]

Efficacy and safety of tocilizumab in patients with systemic JIA were evaluated in a randomized, double-blind, placebo-controlled, phase III study with 56 Japanese children with JIA ages two to 19 years.[168] Patients had disease refractory to conventional treatment. Patients were given tocilizumab 8 mg/kg every two weeks for six weeks in an open-label manner. Patients with ACR Pedi 30 response and C-reactive protein (CRP) of less than 5 mg/L were randomized in a double-blind manner to placebo or continuation of tocilizumab for 12 weeks or until withdrawal for rescue medication. At the end of the open-label lead-in phase, ACR Pedi 30, 50, and 70 responses were achieved by 51 (91 percent), 48 (86 percent), and 38 (68 percent) patients, respectively. A total of 43 patients continued to the double-blind phase. In the tocilizumab group, 80 percent (n=16/20) maintained ACR Pedi 30 response and CRP less

than 15 mg/L compared to 17 percent (n=4/23) of patients receiving placebo. In the open-label extension phase to 48 weeks, ACR Pedi 30, 50, and 70 responses were achieved by 47 (98 percent), 45 (94 percent), and 43 (90 percent) of 48 patients, respectively. Serious adverse events were anaphylactoid reaction, gastrointestinal hemorrhage, bronchitis, and gastroenteritis.

Safety and effectiveness of certolizumab pegol (Cimzia), golimumab (Simponi), tofacitinib (Xeljanz), and ustekinumab (Stelara) in pediatric patients have not been established.

Inhibition of TNFα during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Pregnancy

Adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, and ustekinumab are Pregnancy Category B. Abatacept, apremilast, canakinumab, rilonacept, tocilizumab, tofacitinib, and vedolizumab are Pregnancy Category C.

Hepatic/Renal Impairment

Anakinra is substantially excreted by the kidneys. Consider every other day administration in patients with severe renal insufficiency or end stage renal disease (CrCL < 30 mL/min).

The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment.

Tofacitinib dose should not exceed 5 mg once daily in patients with moderate hepatic impairment. Tofacitinib is not recommended in severe hepatic impairment. Tofacitinib dose should not exceed 5 mg once daily in patients with moderate or severe renal impairment.

Other

There have been reports of hypoglycemia following initiation of etanercept (Enbrel) therapy in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

DOSAGES

<table>
<tr><th>Drug</th><th>Dose</th><th>Availability</th></tr>
<tr><td>abatacept (Orencia)[169,170]</td><td>RA: IV infusion:
IV dose based on body weight given over 30 minutes at zero, two, and four weeks, then every four weeks thereafter
<table>
<tr><th>Body weight</th><th>IV Dose</th></tr>
<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>
</table>
RA: subcutaneous injection
Following a single IV loading dose, the first dose of 125 mg SC should be given within one day. 125 mg SC is given weekly thereafter. SC therapy may be initiated without the IV loading dose. If transitioning from IV therapy to SC, the first SC dose may be given instead of the next IV dose.
JIA: Pediatric patients < 75 kg receive 10 mg/kg IV 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</td><td>250 mg/15 mL single-dose vial (SDV)
125 mg/mL prefilled syringe for subcutaneous injection</td></tr>
<tr><td>adalimumab (Humira)[171]</td><td>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
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.
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). The initial dose of 160 mg may be given as four injections of 40 mg on one day or given as 80 mg given on two consecutive days.
UC: Initial dose: 160 mg (four 40 mg injections in one day [Day 1]) or two 40 mg injections per day for two consecutive days. These are followed by a second dose of 80 mg two weeks later (Day 15). Maintenance dose: Two weeks later (Day 29) begin 40 mg every other week. Only continue in patients with UC who have evidence of clinical remission by eight weeks (Day 57) of therapy.
JIA (ages four to 17 years):
<table>
<tr><th>Body weight</th><th>Dose</th></tr>
<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>
</table></td><td>Prefilled syringes:
20 mg/0.4 mL,
40 mg/0.8 mL
Single-use pen:
40 mg/0.8 mL
Psoriasis Starter Package:
4x40 mg prefilled pens

Crohn's Disease Starter Package:
6x40mg prefilled pens</td></tr>
</table>

Dosages (continued)

Drug	Dose	Availability
anakinra (Kineret)[172]	**RA**: 100 mg SC daily Consider 100 mg every other day for RA patients who have severe renal insufficiency or end stage renal disease (creatinine clearance < 30 mL/min). **CAPS (NOMID):** initiate at 1-2 mg/kg daily. Adjust in increments of 0.5-1 mg/kg to a maximum of 8 mg/kg to control active inflammation. Dose may be divided into twice daily administrations.	Prefilled syringe: 100 mg/0.67 mL Graduated syringe allows for doses between 20 and 100 mg
apremilast (Otezla)[173]	**PsA:** Initial titration: Day 1- 10 mg in morning, Day 2- 10 mg in morning and 10 mg in evening, Day 3- 10 mg in morning and 20 mg in evening, Day 4- 20 mg in morning and 20 mg in evening, Day 5- 20 mg in morning and 30 mg in evening Maintenance Dose: 30 mg twice daily **Plaque psoriasis**: Initial titration: Day 1- 10 mg in morning, Day 2- 10 mg in morning and 10 mg in evening, Day 3- 10 mg in morning and 20 mg in evening, Day 4- 20 mg in morning and 20 mg in evening, Day 5- 20 mg in morning and 30 mg in evening Maintenance Dose: 30 mg twice daily	30 mg tablets Two week starter pack containing 10 mg, 20 mg and 30 mg tablets
canakinumab (Ilaris)[174]	**CAPS:** 150 mg SC for patients with body weight greater than 40 kg 2 mg/kg SC for patients with body weight ≥15 kg and ≤40 kg 3 mg/kg SC for patients 15 to 40 kg with an inadequate response All CAPS doses should be administered every eight weeks. **SJIA:** 4 mg/kg SC for patients with body weight ≥7.5 kg All SJIA doses should be administered every four weeks.	Vial: Single use vial containing 180 mg of canakinumab reconstituted to 150 mg/ml
certolizumab pegol (Cimzia)[175]	**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. **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 four weeks may be considered. **PsA:** 400 mg (given as two SC injections of 200 mg) initially and at weeks two and four, followed by 200 SC mg every two weeks or 400 mg SC every four weeks **AS:** 400 mg (given as two SC injections of 200 mg each) initially and at weeks two and four, followed by 200 mg SC every two weeks or 400 mg SC every four weeks	200 mg vial with 1 mL sterile water diluent Prefilled syringe: 200 mg/mL
etanercept (Enbrel)[176]	**RA, PsA AS**: 50 mg SC once weekly; MTX, glucocorticoids, salicylates, NSAIDs or analgesics may be continued. **Plaque psoriasis**: 50 mg SC twice weekly for three months followed by 50 mg weekly **JIA**: Patients weighing ≥ 63 kg: 50 mg SC given once weekly. Patients weighing < 63 kg : 8 mg/kg weekly with a maximum of 50 mg per week, Glucocorticoids, NSAIDS or analgesics may be continued. Higher doses of etanercept have not been studied in the pediatric population.	Prefilled syringe: 25, 50 mg Prefilled SureClick autoinjector: 50 mg Multiuse vial: 25 mg with 1 mL diluent

Dosages (continued)

Drug	Dose	Availability
golimumab (Simponi, Simponi Aria)[177,178]	**RA, PsA, AS**: subcutaneous injection 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. **UC:** subcutaneous injection 200 mg SC at week zero, followed by 100 mg SC at week two and then 100 mg SC every four weeks. **RA**: IV infusion (Simponi Aria) 2 mg/kg as an IV infusion over 30 minutes at weeks zero and four, then every eight weeks thereafter.	Prefilled syringe for subcutaneous injection: 50 mg/0.5 mL 100 mg/1 mL SmartJect autoinjector* for subcutaneous injection: 50 mg/0.5mL 100 mg/1 mLVials (Simponi Aria): 50 mg/4 mL for IV infusion (dilute before administration)
infliximab (Remicade)[179]	**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. **AS**: 5 mg/kg IV infusion at zero, two, and six weeks, then every six weeks **Plaque psoriasis, PsA**: 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. **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 **Crohn's Disease (pediatrics)**: 5 mg/kg IV infusion at zero, two, and six weeks, then every eight weeks. **Ulcerative Colitis (adults and pediatrics)**: 5 mg/kg IV infusion at zero, two, and six weeks, then every eight weeks.	100 mg/20 mL SDV Given as two-hour infusion
rilonacept (Arcalyst)[180]	**CAPS:** Adults: Loading dose: 320 mg SC (two doses at different sites) Maintenance dose: 160 mg SC weekly Pediatrics (12 to 17 years): Loading dose: 4.4 mg/kg SC Maintenance dose: 2.2 mg/kg SC weekly	Vial: Single use vial containing 220 mg of rilonacept

* The SmartJect autoinjector has specific instructions. Patients are instructed not to use the SmartJect autoinjector without training from a health care professional.

Dosages (continued)

Drug	Dose	Availability
tocilizumab (Actemra)[181]	**RA (adults):** IV infusion starting dose 4 mg/kg one-hour IV infusion every four weeks followed by an increase to 8 mg/kg every four weeks based on clinical response. Do not exceed 800 mg per infusion. **RA (adults):** subcutaneous injection In patients < 100 kg starting dose is 162 mg SC every other week, followed by an increase to every week based on clinical response. In patients ≥ 100 kg 162 mg SC every week When transitioning from IV to SC, administer the first SC dose instead of the next scheduled IV dose. May be used as monotherapy or concomitantly with MTX or other DMARDs. **Polyarticular JIA (ages 2 to 17 years):** For patients weighing < 30 kg: 10 mg/kg IV over one hour every four weeks. For patients weighing > 30 kg: 8 mg/kg IV over one hour every four weeks. May give alone or in combination with MTX. **Systemic JIA (ages 2 to 17 years):** For patients weighing less than 30 kg: 12 mg/kg IV over one hour every two weeks. For patients weighing > 30 kg: 8 mg/kg IV over one hour every two weeks. May give alone or in combination with MTX. SC administration is not approved for PJIA or SJIA. Dose modifications: see prescribing information for details on dose modifications for liver enzyme elevation, low absolute neutrophil count (ANC), low platelet count, or infection.	80 mg/ 4 mL SDV 200 mg/ 10 mL SDV 400 mg/ 20 mL SDV 162 mg/ 0.9 mL prefilled syringe†
tofacitinib (Xeljanz)[182]	**RA:** 5 mg orally twice daily with or without food. May be used as monotherapy or in combination with MTX or other nonbiologic (DMARDs). Dose modifications: Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia with specific details in the prescribing information. Dosage should be reduced to 5 mg once daily in patients with moderate or severe renal insufficiency, moderate hepatic impairment, or those receiving potent or multiple moderate inhibitors of CYP3A4.	5 mg tablets
ustekinumab (Stelara)[183]	**Psoriasis:** Dose is based on body weight. Given under supervision by a physician and administered by a health care professional or by self administration after training, if deemed appropriate. For patients weighing ≤100 kg, the initial recommended dose is 45 mg SC followed by another dose four weeks later, followed by 45 mg SC every 12 weeks. For patients weighing ≥100 kg, the recommended dose is 90 mg SC initially, followed by another dose four weeks later, followed by 90 mg SC every 12 weeks. **PsA:** 45 mg SC followed by another dose four weeks later, followed by 45 mg every 12 weeks, for patients with co-existent moderate-to-severe plaque psoriasis weighing >100 kg, the recommended dose is 90 mg SC initially, followed by another dose four weeks later, followed by 90 mg SC every 12 weeks	45 mg/0.5 mL SDV 90 mg/1 mL SDV 45 mg/0.5 mL prefilled syringe 90 mg/1 mL prefilled syringe
vedolizumab (Entyvio)[184]	**Crohn's Disease**: 300 mg administered by a healthcare professional by IV infusion at weeks zero, two and six and then every eight weeks thereafter. **Ulcerative Colitis:** 300 mg administered by a healthcare professional by IV infusion at weeks zero, two and six and then every eight weeks thereafter.	Vial: Single use vial containing 300 mg of vedolizumab

† Subcutaneous tocilizumab can be self-administered after proper training by a healthcare professional.

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 and/or 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.[185] 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 $\geq$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.[186] 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.[187] ASAS responses were maintained; 64.5 percent were ASAS20 responders, and 50.6 percent were ASAS40 responders.

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.[188] 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. Adalimumab significantly improved patient-reported physical function and health-related quality of life in the three-year open-label extension of the ATLAS study.[189]

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.[190] 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.

certolizumab pegol (Cimzia)

RAPID-axSpA is an ongoing multicenter, Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial in patients with axial spondyloarthritis (axSpA), including patients with ankylosing spondyloarthritis (AS).[191] While all patients met the criteria for axSpA, at least 50 percent of the patients had to meet the modified New York (mNY) criteria for radiographic diagnosis of AS. Patients were randomized to placebo or certolizumab pegol (CZP) 400 mg SC at weeks zero, two, and four (loading dose) followed by either CZP 200 mg SC every two weeks or CZP 400 mg every four weeks. The doses were administered by unblinded, trained personnel at each site. All patients received injections every two weeks, either CZP or placebo, to maintain blinding. Patients were stratified by prior TNF inhibitor exposure. Patients assigned to placebo who did not achieve an Assessment of Spondyloarthritis International Society 20 (ASAS20) response at weeks 14 and 16 underwent mandatory escape at week 16 and were randomized to active treatment in a double blind fashion. Clinical primary endpoint was ASA20 response at week 12, defined as an improvement of $\geq$20 percent and $\geq$ 1 unit on a zero to 10 scale in greater than or equal to three of the following: Patients Global Assessment of Disease Activity (PTGADA), Pain assessment (total spinal pain on a zero to ten scale), Function (represented by a Bath Ankylosing Spondylitis Functional Index (BASFI), Inflammation (mean of BASDAI questions relating to morning stiffness) and no deterioration (worsening of >20 percent or 1 unit on a zero to 10 scale) in the remaining area. A total of 325 patients were randomized to one of the three treatment arms. Of these, 178 patients (54.8 percent) met the mNY criteria for AS. Concomitant therapy with NSAIDS and DMARDs was allowed on the trial. Improvements in ASAS20 at week 12 in the AS subpopulation were 56.9 percent for CZP 200 mg every two weeks and 64.3 percent for CZP 400 mg every four weeks compared to 36.8 percent for placebo ; $p<0.05$. The most common infectious adverse events were nasopharyngitis (8.8 percent CZP versus 6.5 percent placebo) and upper respiratory tract infections (four percent CZP versus 2.8 percent placebo). The most common non-infectious adverse events were headache (6.2 percent CZP versus 6.5 percent placebo) and increased blood creatine phosphokinase (5.1 percent CZP versus 1.9 percent placebo). Increases in creatine phosphokinase were transient, and resolved spontaneously despite continued CZP therapy. No elevations were associated with an ischemic cardiac event or resulted in study discontinuation.

etanercept (Enbrel)

A double-blind study recruited 40 patients with active ankylosing spondylitis symptoms despite standard therapy.[192] 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, enthesis, 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.[193] 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.[194] 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.[195] 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)

GO-RAISE study: 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).[196] Patients had symptoms of active disease [defined as a Bath AS Disease Activity Index (BASDAI) ≥ four and Visual Analog Scale (VAS) for total back pain of ≥ 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 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 that 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.[197] 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.[198] 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.[199] 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.[200] 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).[201] 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] $\geq$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.[202] 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).[203]

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.[204] 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.[205] 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 two 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.[206] 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.[207] 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 l 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.[208] 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.[209]

An ACCENT II substudy examined the effect of infliximab maintenance treatment on hospitalizations, surgeries, and procedures in patients with fistulizing Crohn's disease.[210] 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.

vedolizumab (Entyvio)[211]

Three randomized, double-blind, placebo controlled clinical trials (CD Trials I, II, and III) were conducted to evaluate the safety and efficacy of vedolizumab in adult patients with moderately to severely active CD (CDAI score of 220 to 450). Enrolled patients in the US had over the previous five year period an inadequate response or intolerance to immunomodulator therapy (e.g., thiopurines [azathioprine or mercaptopurine] or methotrexate) and/or an inadequate response, loss of response, or intolerance to one or more TNF blockers. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five year period the patients were corticosteroid dependent or had an inadequate

response or intolerance to corticosteroids. Patients that had ever received natalizumab and patients that had received a TNF blocker in the past 60 days were excluded from enrollment.

In CD Trial I, 368 patients were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo by intravenous infusion at Week Zero and Week Two with efficacy assessments at Week Six. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through Week Six. At baseline, patients were receiving corticosteroids (49 percent), immunomodulators (35 percent), and/or aminosalicylates (46 percent). A total of 48 percent of the patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. The median baseline CDAI score was 324 in the vedolizumab group and 319 in the placebo group. In the trial a statistically significantly higher percentage of patients treated with vedolizumab achieved clinical remission (defined as CDAI ≤150) as compared to placebo (15 percent versus seven percent, p=0.041) at Week Six. The difference in the percentage of patients who demonstrated clinical response (defined as a ≥100 point decrease in CDAI score from baseline), was however, not statistically significant at Week Six.

In CD Trial II, 416 patients were randomized in a double-blind fashion (1:1) to receive either vedolizumab 300 mg or placebo at Weeks Zero, Two and Six and efficacy assessments occurred at Weeks Six and Ten. The trial enrolled a higher number of patients who had over the previous five year period had an inadequate response, loss of response, or intolerance to one or more TNF blockers (76 percent) than CD Trial I. Concomitant aminosalicylates, corticosteroids, and immunomodulators were permitted through Week Ten. At baseline, patients were receiving corticosteroids (54 percent), immunomodulators (34 percent), and aminosalicylates (31 percent). The median baseline CDAI score was 317 in the vedolizumab group and 301 in the placebo group. For the primary endpoint of clinical remission at Week Six, treatment with vedolizumab did not result in statistically significant improvement over placebo.

In CD Trial III, 461 patients who had a clinical response to vedolizumab at Week Six were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week Six: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks or placebo every four weeks. Concomitant aminosalicylates and corticosteroids were permitted through Week 52 and efficacy assessments were conducted at Week 52. Concomitant immunomodulators were permitted outside the US but were not permitted beyond Week Six in the US. At Week Six, patients were receiving corticosteroids (59 percent), immunomodulators (31 percent), and aminosalicylates (41 percent). A total of 51 percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. At Week Six, the median CDAI score was 322 in the vedolizumab every eight week group, 316 in the vedolizumab every four week group, and 315 in the placebo group. Patients who had achieved clinical response at Week Six and were receiving corticosteroids were required to begin a corticosteroid tapering regimen at Week Six. In the trial a greater percentage of patients in groups treated with vedolizumab as compared to placebo (39 percent versus 22 percent, p=0.001) were in clinical remission at Week 52. A greater percentage of patients in groups treated with vedolizumab as compared to placebo (44 percent versus 30 percent, p=0.013) had a clinical response at Week 52. The vedolizumab every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen and is not the recommended dosing regimen.

Cryopyrin-Associated Periodic Syndromes (CAPS)

anakinra (Kineret) [212]

The efficacy of anakinra was evaluated in a prospective, long-term, open-label and uncontrolled study which incorporated a withdrawal period in a subset of 11 patients. This study included 43 Neonatal-Onset Multisystem Inflammatory Disease (NOMID) patients 0.7 to 46 years of age treated for up to 60 months. Patients were given an initial anakinra dose of 1–2.4 mg/kg body weight. During the study, the dose was adjusted by 0.5 to 1 mg/kg increments to a protocol-specified maximum of 10 mg/kg daily, titrated to control signs and symptoms of disease. The average maintenance dose was 3 to 4 mg/kg daily. In general, the dose was given once daily, but for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Mean change in DSSS score was -3.5 (95 percent confidence interval [-3.7 to -3.3]) at month 3-6 and -3.5 (95 percent confidence interval (-3.8 to -3.1)) at month 60. For the 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra therapy.

canakinumab (Ilaris) [213]

The efficacy and safety of canakinumab for the treatment of CAPS was demonstrated in a 3-part trial in patients in 31 patients nine to 74 years of age with the Muckle-Wells Syndrome (MWS) phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received canakinumab 150 mg and patients weighing 15 to 40 kg received 2 mg/kg. Part one was an eight week open-label, single-dose period where all patients received canakinumab. Patients who achieved a complete clinical response and did not relapse by week eight were randomized into part two, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed part two or experienced a disease flare entered part three, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part one, a complete clinical response was observed in 71 percent of patients one week following initiation of treatment and in 97 percent of patients by Week eight. In part two 16 patients were randomized to the placebo group and 15 were randomized to the canakinumab group. A total of 13 patients (81 percent) of the patients randomized to placebo flared as compared to none of the patients randomized to canakinumab. The 95 percent confidence interval for treatment difference in the proportion of flares was 53 percent to 96 percent. At the end of part two, all 15 patients treated with canakinumab had absent or minimal disease activity and skin disease. CRP and SAA values subsequently normalized in the placebo group after reintroduction of canakinumab in part three.

rilonacept (Arcalyst)[214]

The safety and efficacy of rilonacept for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS (Familial Cold Autoinflammatory Syndrome) and MWS phenotypes of CAPS. Part A was a six week, randomized, double-blind, parallel-group period comparing rilonacept at a dose of 160

mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a nine week, patient-blind period during which all subjects received rilonacept 160 mg weekly, followed by a nine week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on rilonacept 160 mg weekly or to receive placebo Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment. The patients in the rilonacept group had a larger reduction than the placebo (-2.4 versus -0.5 (95 percent confidence interval -2.4 to -1.3)) in the mean symptom score in Part A. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on rilonacept (0.9 versus 0.1 (95 percent confidence interval -1.3 to -0.4)).

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.[215] 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.[216] 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 re-randomized 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.[217] 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.

apremilast (Otezla)

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2) enrolled a total of 1257 subjects 18 years of age and older with moderate to severe plaque psoriasis.[218] Subjects were allowed to use low-potency topical corticosteroids on the face, axilla and groin. Subjects with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to apremilast 30 mg BID or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved (Psoriasis Area and Severity Index) PASI-75 at Week 16 and the proportion of subjects who achieved a (Physician Global Assessment) sPGA score of clear (0) or almost clear (1) at Week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19 percent (median 21 percent), the mean baseline PASI score was 19.07 (median 16.80), and the proportion of subjects with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70 percent and 29.8 percent, respectively. In both studies (PSOR-1 and PSOR-2), the PASI-75 and sPGA were statistically significantly higher in the apremilast group when compared to placebo (PSOR-1 PASI-75 33.1 percent versus 5.3 percent and sPGA 21.7 percent versus 3.9 percent, PSOR-1 PASI-75 28.8 percent versus 5.8 percent and sPGA 20.4 percent versus 4.4 percent [p values < 0.05]).

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.[219] 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.[220] 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 group, 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.[221] 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 to 70.1, p<0.0001 for 45 mg and 63.3 percent, 95% CI, 57.1 to 69.4, p<0.0001 for 90 mg). At week 12, a total of 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. Long-term safety data demonstrated consistent adverse effects over three years.[222]

PHOENIX 2 enrolled a total of 1,230 subjects with moderate to severe psoriasis.[223] 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 to 68.0, p<0.0001 for the 45 mg group versus placebo and 72.0 percent, 95% CI, 67.5 to 76.5, p<0.0001 for the 90 mg group versus placebo). At week 12, a total of 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.[224] 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 ($p<0.001$). An ACR 20 response requires a patient to have a 20 percent reduction in the number of swollen and tender joints, and a reduction of 20 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 30, 50, 70, 90, and 100 responses follow accordingly. 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 (n=313) 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.[225] 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 and results 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.[226] 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.[227] 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.

apremilast (Otezla)

The safety and efficacy of apremilast was evaluated in three randomized, double-blind, placebo-controlled, multicenter trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1,493 adult patients with active psoriatic arthritis (PsA) (three swollen joints and three tender joints) despite prior or current treatment with DMARD therapy were randomized.[228] Patients enrolled in these studies had a diagnosis of PsA for at least six months. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10 percent could be TNF-blocker therapeutic failures). Across the three studies, patients were randomly assigned to placebo (n=496), apremilast 20 mg (n=500), or apremilast 30 mg (n=497) given orally twice daily. Titration was used over the first five days. Patients were allowed to receive stable doses of concomitant methotrexate [MTX (25 mg/week)], sulfasalazine, leflunomide, low dose oral corticosteroids, and/or NSAIDs during the trial. The patients who were therapeutic failures of greater than three agents for PsA (small molecules or biologics), or more than one biologic TNF blocker were excluded. The primary endpoint was the percentage of patients achieving ACR 20 response at Week 16. In all three studies (PsA-1, PsA-2, and PsA-3), the week ACR 20 response was statistically significantly higher in the apremilast group when compared to placebo (PsA-1 38 percent versus 19 percent, PsA-2 32 percent versus 19 percent and PsA-3 41 percent versus 18 percent [$p < 0.05$]).

certolizumab pegol (Cimzia)

RAPID-PsA is a phase 3, double-blind, placebo-controlled study of certolizumab in patients with psoriatic arthritis.[229] A total of 409 adult ($\geq$ 18 years) patients were randomized to one of three arms: placebo, certolizumab pegol (CZP) 200 mg SC every two weeks, or CZP 400 mg every four weeks. Patients on the active treatment arms also received a loading dose of CZP 400 mg SC at weeks 0, 2, and 4 and then preceded on to the assigned maintenance dose arms. The drug was administered by investigators at each site using a blinded prefilled syringe. Patients at each site were stratified by prior exposure to TNF inhibitor. Placebo patients who failed to achieve a 10 percent improvement from baseline in both swollen and tender joints at weeks 14 and 16 underwent mandatory escape to active treatment in a blinded manner. A total of 59 (43.4 percent) of placebo patients were re-randomized to CZP treatment at week 16. The primary clinical endpoint of the study was ACR20 response at week 12. The radiographic primary endpoint of the trial was change from baseline to week 24. Concomitant DMARDS were used by 70.2 percent of patients at baseline through week 24. At week 12, significantly more patients in the CZP 200 mg SC every two weeks and CZP 400 mg SC every four weeks achieved an ACR20 response compared to placebo patients (58 percent, 51. 9 percent versus 24.3 percent, $p<0.001$ for both). Patients treated with CZP 200 mg SC every two weeks demonstrated greater reduction in radiographic progression compared to placebo-treated patients at week 24 as measured by change in baseline in total modified total Sharp score (mTSS) (0.18 in placebo group compared with -0.02 in CZP 200 mg SC every two weeks group (95 percent confidence interval: -0.38–0.04). Patients treated with CZP 400 mg SC every four weeks did not demonstrate greater inhibition of radiographic progression compared with placebo-treated patients at week 24. The most common non-infectious adverse events were diarrhea (3.6 percent CZP versus 2.9 percent placebo) and headache (3.6 percent CZP versus 1.5 percent placebo). The most common infectious adverse effects were nasopharyngitis (8.7 percent CZP versus 7.4 percent placebo) and upper respiratory tract infection (7.8 percent CZP versus 5.1 percent placebo).

etanercept (Enbrel)

Investigators randomized 205 patients with PsA to receive etanercept 25 mg or placebo twice weekly for 24 weeks.[230] 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.[231]

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.[232] 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.[233] 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)

GO-REVEAL: 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 (≥ three swollen joints and ≥ three tender joints).[234] 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 (≤ 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 and was reported as: 51 percent (golimumab 50 mg), 45 percent (golimumab 100 mg) versus nine percent (placebo), respectively; p<0.001 for all comparisons. Among secondary endpoints, 52 percent of patients administered golimumab 50 mg and 61 percent of patient receiving golimumab 100 mg, achieved ACR 20 at week 24 versus 12 percent in the placebo group (p<0.001). 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 three 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). A two-year follow-up of the GO-REVEAL trial indicated sustained responses at two years.[235] At week 104, patients originally randomized to golimumab 50 mg had an ACR20 response of 67.1 percent and patients originally randomized to golimumab 100 mg had an ACR20 response of 69.9 percent. Through week 104, 23 (six percent) of patients discontinued golimumab because of an adverse event. Serious adverse events were reported for 16 (6.5 percent) and 18 (eight percent) of patients receiving golimumab 50 mg and 100 mg, respectively. There were six serious infections but, when assessed according to patient-years follow-up, no increase in the incidence of serous infection was observed for either golimumab arm. This analysis was, however, limited by the relatively short duration of placebo treatment and the small number of patients. No patient developed active TB through week 104, including the 44 patients who received TB prophylaxis secondary to detection of latent TB at time of trial participation screening. Eight patients were diagnosed with a malignancy during the two-year time frame (one colon cancer, one prostate cancer, two squamous cell lung cancers, and four basal cell carcinomas). When assessed by patient-years of follow-up, the incidence of malignancies for golimumab-treated patients was numerically higher compared to patients receiving placebo (95 percent confidence interval 0.00-0.74). Again, the authors note the analysis was limited by small sample size and the short period of placebo follow-up. When the number of malignancies (excluding the non melanoma skin cancers) in the trial were compared to the expected rates in the general U.S. population, the numbers were not statistically significantly different.

infliximab (Remicade)

IMPACT I, the Infliximab Multinational Psoriatic Arthritis Controlled Trial, was an investigator-initiated study of 104 patients with active PsA.[236,237] 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.[238] No worsening of radiographic progression was noted in approximately 85 percent of the remaining patients. At week 98, 62 percent (48/78 patients) of infliximab-treated patients achieved an ACR 20 response.[239] Among patients with baseline Psoriasis Area and Severity Index scores ≥2.5, PASI 75 response was 64 percent (16/25 patients) 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.[240] 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.[241] 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.[242] 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.[243] 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.[244] 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 $\geq$ 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.

ustekinumab (Stelara)

A total of 927 adult patients with active PsA ($\geq$ 5 swollen joints and $\geq$ 5 tender joints) were enrolled in two randomized, double-blind, placebo-controlled studies.[245,246] Patients in both trials had ongoing symptoms despite therapy with NSAIDs or DMARDs. In study one (PSUMMIT 1 trial), 615 patients were randomized to placebo, 45 mg SC ustekinumab, or 90 mg SC ustekinumab at weeks zero and four and every 12 weeks thereafter. Patients with prior history of treatment with an anti-TNF inhibitor were excluded from this trial. Early escape was allowed at week 16 for patients on placebo or ustekinumab 45 mg if they had a less than five percent improvement from baseline in both tender and swollen joints. Primary efficacy endpoint was the proportion of patients with ACR20 at week 24. A significantly higher proportion of patients in the ustekinumab groups than in the placebo group achieved an ACR20 response at week 24 (difference in response rate 19.6 percent, 95% CI, 10.8 to 28.5, p<0.0001 for the 45 mg group

versus placebo and 26.7 percent, 95% CI, 17.8 to 35.6, p<0.0001 for the 90 mg group versus placebo). ACR20 treatment effects at week 24 were numerically lower for patients receiving concomitant methotrexate than for those patients who were not but tests of significance were not reported. The most common adverse events in the ustekinumab-treated patients were nasopharyngitis (4.6 percent), upper respiratory tract infection (3.4 percent), and headache (3.4 percent). In PsA Study 2 (n=312), the trial design was identical to the PSUMMIT 1 trial except PsA Study 2 included patients who had been previously treated with an anti-TNF agent (58 percent of study participants). Seventy percent of the patients previously treated with an anti-TNF agent had discontinued their anti-TNF treatment for lack of efficacy or intolerance. The ACR20 response at week 24 in this trial was 44 percent in patients receiving ustekinumab 45 mg, 44 percent in patients receiving ustekinumab 90 mg, and 20 percent for patients receiving placebo. Responses were similar in patients regardless of prior anti-TNF exposure.

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.[247] 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-TNFα 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.[248] Patients discontinued anti-TNFα 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.[249] 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.[250] 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.[251] 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).[252]

The efficacy and safety of abatacept in MTX-naïve patients with early RA was investigated in a double-blind phase III study.[253] Patients had RA for less than two years and had a mean DAS28 of 6.3. Inclusion criteria also required patients to have erosions and be seropositive for rheumatoid factor and/or anti-CCP2 that are associated with poor radiologic outcomes. Patients were randomized to abatacept 10 mg/kg plus MTX (n=256) or placebo plus MTX (n=253). The co-primary endpoints were the portion of patients achieving disease activity score in 28 joints (DAS-28)-defined remission and joint damage progression measured by Genant-modified Sharp total score at one year. After one year, a significantly greater proportion of abatacept plus MTX-treated patients achieved remission (41.4 versus 23.3 percent; $p<0.001$). Less radiographic progression occurred in the combination treatment group (mean change in total Sharp score: 0.63 versus 1.06; $p=0.04$). Adverse effects were comparable between groups for frequency of adverse effects, serious adverse events, serious infections, and malignancies.

The efficacy and safety of abatacept administered subcutaneously (SC) in 1,457 RA patients who had an inadequate response to MTX was studied in a randomized, double-blind, double-dummy, non-inferiority study (Study SC-I).[254] Patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive abatacept 125 mg SC injections weekly, after a single IV loading dose of abatacept based on body weight or abatacept IV on days one, 15, 29, and every four weeks thereafter. Patients continued taking their current dose of MTX from the day of randomization. The main outcome measure was ACR 20 at six months. The pre-specified non-inferiority margin was a treatment difference of -7.5 percent. The percent of patients achieving ACR response in the abatacept SC and IV treatment arms at six months was as follows: ACR 20 (76 percent SC, 76 percent IV); ACR 50 (52 percent SC, 50 percent IV); ACR 70 (26 percent SC, 25 percent IV). Non-inferiority of abatacept SC relative to IV infusions of abatacept with respect to ACR 20 responses up to six months of treatment was demonstrated. No major differences in ACR responses were observed between IV and SC treatment groups in subgroups based on weight categories.

abatacept (Orencia) versus infliximab (Remicade)

A double-blind trial compared the efficacy and safety of abatacept and infliximab in 431 adults with RA.[255] 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.

abatacept(Orencia) versus adalimumab (Humira)

AMPLE (Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate) was a phase 3, randomized, prospective study.[256] Patients with active RA (n=646) who had never received a biologic agent and had an inadequate response to methotrexate were randomized to abatacept 125 mg SC weekly or adalimumab 40 SC biweekly, both given in combination with methotrexate for the two-year study period. Patients were not blinded, but the independent clinical assessors, as well as the radiologists interpreting the radiographs, were blinded with regard to each patient's treatment. The primary endpoint was treatment inferiority based on ACR20 at one year. Other comparisons measured were radiographic response (of the hands and feet taken at baseline and on day 365), as well as overall safety. At one year, 274 (86.2 percent) of the abatacept-treated patients and 269 (82 percent) of the adalimumab-treated patients completed the study. The main reasons for discontinuation were lack of efficacy (3.8 percent of abatacept-treated patients versus 4.6 percent of adalimumab-treated patients) and adverse events (3.5 percent of abatacept-treated patients versus 6.1 percent of adalimumab-treated patients). The proportion of patients achieving an ACR20 response at one year was 64.8 percent (95 percent confidence interval 59.5 percent to 70.0 percent) in the abatacept group and 63.4 percent (95 percent confidence interval 58.2 percent to 68.6 percent) in the adalimumab group. The difference in ACR20 response rates between groups was 1.1 percent (95 percent confidence interval -6.5 percent to 8.7 percent), demonstrating noninferiority of abatacept compared to adalimumab. The rate of radiographic non progression from baseline to one year was observed to be 84.8 percent in the abatacept group and 88.6 percent in the adalimumab group (difference between groups was 4.1 percent (95 percent confidence interval -1.5 percent to 9.6 percent). The rate of serious adverse events was 10.1 percent in the abatacept group and 9.1 percent in the adalimumab group. Discontinuations due to adverse effects occurred at almost twice the rate in the adalimumab group (6.1 percent) than in the abatacept group (3.5 percent). The incidences of infection (63.2 percent versus 61.3 percent) and malignancies (1.6 percent versus 1.2 percent) were similar between the two groups; however, the rate of autoimmune events was higher in the abatacept group (3.1 percent) compared to the adalimumab group (1.2 percent). Statistical analyses were not reported on these safety measures. Local injection site reactions occurred in significantly fewer patients in the abatacept group than in the adalimumab group (3.8 percent versus 9.1 percent, 95 percent confidence interval -9.13 percent to -1.62 percent, p=0.006). A follow-up publication reported 79.2 percent of abatacept and 74.7 percent of adalimumab patients completed year two of the AMPLE trial. At year two, efficacy outcomes, including radiographic results, remained comparable between groups and with year one results. The ACR20 at year two were 59.7 percent for abatacept and 60.1 percent for adalimumab. Overall, the rates of adverse events and serious adverse events were similar between the two groups; however, there were more

serious infections with adalimumab (3.8 percent versus 5.8 percent), including two cases of tuberculosis with adalimumab. There were fewer discontinuations due to adverse events (3.8 percent versus 9.5 percent) or serious adverse events (1.6 percent versus 4.9 percent) in the abatacept group. Injection site reactions occurred less frequently with abatacept (4.1 percent versus 10.4 percent).[257]

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.[258] 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=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.[259] Patients received adalimumab 40 mg every other week, 20 mg every week, or placebo. All patients received stable doses of MTX. The primary efficacy endpoints 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≤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≤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.[260] Patients had previously not received MTX. Patients were randomized to adalimumab 40 mg every other week plus MTX or either monotherapy. Co-primary endpoints 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≤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.[261] 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≤0.01); ACR 50 (18.9, 20.5, 22.1, 35.0 percent versus 8.2 percent; p≤0.05); ACR 70 (8.5, 9.8, 12.4, 18.4 percent versus 1.8 percent; p≤0.05). Patients treated with adalimumab achieved better improvements in HAQ DI scores than those receiving placebo (p≤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≤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.[262] 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.[263] Patients were naive to 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.[264] 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.[265] 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) versus placebo

The FAST4WARD (eFficAcy and Safety of cerTolizumab pegol - 4 Weekly dosAge in RheumatoiD arthritis) study was a 24-week, multicenter, double-blind trial that evaluated the efficacy and safety of certolizumab pegol as monotherapy in patients with active RA.[266] Patients who had not received a biologic therapy for RA within six months and had previously failed at least one DMARD (n=220) were randomized 1:1 to receive certolizumab pegol 400 mg or placebo every four weeks. ACR 20 response at week 24, the primary endpoint, was 45.5 percent for certolizumab pegol and 9.3 percent for placebo (p<0.001). Most adverse events in both groups were mild or moderate. There were no reports of tuberculosis, opportunistic infections, malignancy, demyelinating disease, or congestive heart failure in either group. However, two cases (1.8 percent) of serious infection and two (1.8 percent) cases of benign tumors were reported in the certolizumab pegol group. This study was funded by the manufacturer of certolizumab pegol.

certolizumab pegol (Cimzia) + MTX versus MTX monotherapy

RAPID 2 was a 24-week, phase III, multicenter, double-blind study that evaluated the efficacy and safety of subcutaneous certolizumab pegol plus MTX compared with placebo plus MTX.[267] Patients (n=619) with active adult-onset RA were randomized 2:2:1 to certolizumab pegol 400 mg at weeks zero, two, and four followed by 200 mg or 400 mg plus MTX, or placebo plus MTX, every two weeks for 24 weeks. The primary endpoint, ACR 20 response at week 24, 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 ($p \leq 0.001$). 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 $p \leq 0.01$). Physical function improved rapidly with certolizumab pegol compared to placebo based on mean changes from baseline in HAQ-DI at week 24 ($p \leq 0.001$). Most adverse events were mild or moderate, with low incidence of withdrawals due to adverse events. Five patients treated with certolizumab pegol developed tuberculosis. The RAPID 2 study was fully funded by the manufacturer of certolizumab pegol.

Certolizumab pegol plus MTX and placebo plus MTX were compared in 982 patients with active RA with an inadequate response to MTX therapy alone.[268] 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.[269] 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.

The COMET study continued to evaluate the outcomes of patients who completed the first year of the two year study.[270] The original combinations group either continued etanercept plus methotrexate (n=111) or received etanercept monotherapy (n=111) in year two. The original methotrexate group received either methotrexate plus etanercept (n=90) or continued methotrexate monotherapy (n=99) in

year two. Efficacy endpoints were DAS28 remission and radiographic nonprogression at year two. DAS28 remission was achieved by 62/108 patients of the etanercept plus methotrexate group continuous group, 54/108 patients for the etanercept plus methotrexate group then switched to etanercept only, 51/88 patients of the methotrexate group switched to combination therapy, and 33/94 patients in the methotrexate monotherapy group (p<0.01 for the etanercept plus methotrexate for two year group, and methotrexate monotherapy for year one then combination therapy for year two versus the methotrexate monotherapy for two years group). The proportions of subjects achieving radiographic nonprogression (n=360) were 89/99 of the combination therapy over two years group, 74/99 of the combination therapy then etanercept monotherapy group, 59/79 methotrexate then combination therapy group, and 56/83 methotrexate monotherapy over two years group (p<0.01 versus each of the other groups). No new safety issues or differences in serious adverse events were reported.

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

The TEMPO study evaluated the combination of etanercept plus methotrexate versus each of the single treatments in 686 patients with RA.[271] 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.[272] 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) subcutaneous

GO-AFTER: This was a phase III, multicenter, double-blind trial that included 461 patients with moderately to severely active rheumatoid arthritis who had previously received TNF-α therapy.[273] Eligible patients had been treated with at least one dose of a TNFα inhibitor previously. Patients continued stable doses of methotrexate, sulfasalazine, hydroxychloroquine, oral corticosteroids, and NSAIDs. Patients were randomized to receive subcutaneous injections of placebo (n=155), 50 mg golimumab (n=153), or 100 mg golimumab (n=153) every four weeks. The primary endpoint was achievement of ACR 20 at week 14. At week 16, patients who did not achieve ACR 20 were given rescue therapy and changed treatment from placebo to 50 mg golimumab, or from 50 mg to 100 mg golimumab. At week 14, 18 percent of patients on placebo, 35 percent of patients on 50 mg golimumab (odds ratio 2.5 [95% CI, 1.5 to 4.2], p=0.0006), and 38 percent of patients on 100 mg golimumab (OR 2.8 [95% CI, 1.6 to 4.7], p=0.0001)

achieved ACR 20. Serious adverse events were recorded in seven percent of patients on placebo, five percent on 50 mg golimumab, and three percent on 100 mg golimumab.

GO-FORWARD: This was a phase III, multicenter, double-blind, placebo controlled-trial.[274] All patients were diagnosed with moderate to severe RA and had been on a stable MTX dose of 15-25 mg/week immediately prior to screening. Patients (n=444) were randomized to receive placebo plus MTX, golimumab 100 mg SC plus placebo, golimumab 50 mg SC plus MTX, or golimumab 100 mg SC plus MTX every four weeks. Primary endpoints were proportion of patients that achieved ACR 20 at week 14 and the change from baseline in the HAQ-DI at week 24. The proportion of patients who achieved an ACR 20 response at week 14 was 33.1 percent in the placebo/MTX group, 44.4 percent (p=0.059) in the golimumab 100 mg/placebo group, 55.1 percent (p=0.001) in the golimumab 50 mg/MTX group and 56.2 percent (p<0.001) in the golimumab 100 mg/MTX group. At week 24, median improvements from baseline in HAQ-DI scores were 0.13, 0.13 (p=0.240), 0.38 (p<0.001), and 0.50 (p<0.001), respectively. At week 52, the ACR 20 response rates were 44 percent for the placebo/MTX group, 45 percent for the golimumab 100 mg plus placebo, 64 percent for the golimumab 50 mg/MTX, and 58 percent for the golimumab 100 mg/MTX group.[275] The golimumab 100 mg/MTX group had a higher rate of serious adverse effects and infections. A two-year follow-up of this trial reported that 392 patients continued from week 52 through week 104. Clinical improvement was maintained through week 104; 75 percent of golimumab 50 mg +MTX patients achieved an ACR 20 response and 72 percent of patients randomized to golimumab 100 mg + methotrexate achieved an ACR20 response. Incidences of serious infections were 2.24, 4.77, and 5.78 per 100 patient-years of follow-up for golimumab 50 mg + MTX, golimumab 100 mg + placebo, and 100 mg + MTX, respectively.[276]

GO-BEFORE: This study evaluated 637 patients with moderately to severely active RA who were MTX-naive and had not previously been treated with a biologic TNF blocker.[277,278] Patients were randomized to receive MTX, golimumab 50 mg SC plus MTX, golimumab 100 mg SC plus MTX, or golimumab 100 mg SC monotherapy. For patients receiving MTX, the MTX dose was 10 mg per week beginning at week zero and increased to 20 mg per week by week eight. Golimumab dose or placebo was administered every four weeks. The use of other DMARDs or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an 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 non inferior 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.

In a multicenter, double-blind, randomized controlled trial, golimumab was evaluated in 172 patients with RA despite treatment with MTX.[279] 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 four 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 endpoint 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.

golimumab (Simponi Aria) intravenous + MTX versus placebo + MTX

GO FURTHER was a 24-week randomized, double-blind, placebo-controlled, multicenter, phase III trial.[280] Patients (n=592) 18 years of age and older with moderately to severely active RA despite concurrent MTX therapy and had not previously been treated with a biological TNF blocker. Patients were diagnosed by the ACR criteria and had at least six swollen and six tender joints. Patients were randomized 2:1 to receive golimumab 2 mg/kg IV at weeks zero, four, and every eight weeks thereafter (n=395) in addition to MTX (15-25 mg/kg) or placebo (n=197) in addition to MTX (15-25 mg/kg). Both groups had similar baseline demographics and 81 percent were women and 80 percent were Caucasian. The primary endpoint of the trial was the percentage of patients achieving a 20 percent ACR improvement by week 14. At week 14, 231 of 395 (58.5 percent) patients in the golimumab + MTX group and 49 of 197 (24.9 percent) patients in the placebo + MTX group achieved a 20 percent ACR improvement (95% CI: 25.9 to 41.4; $p<0.001$). The most common adverse effects at week 14 were infections and infestations with 24.3 percent in the golimumab and 20.8 percent in the placebo group.

infliximab (Remicade)

The BeST study compared clinical and radiographic outcomes of four different treatment strategies in a multicenter, randomized clinical trial.[281] 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. After five years, initial combination therapy resulted in significantly less joint damage progression, reflecting the earlier clinical response.[282]

infliximab (Remicade) with MTX versus placebo + MTX

One thousand forty-nine RA patients with active disease and no prior treatment with MTX or TNFα inhibitor were randomized to one of three treatment groups: MTX+placebo, MTX+infliximab 3 mg/kg, and MTX+infliximab 6 mg/kg.[283] 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.[284] 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.[285] At 30 weeks, ACR 20 was achieved in 50 to 60 percent of patients receiving infliximab compare 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.[286] 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) intravenous

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.[287] Patients had previously not failed on MTX or biological agents. Patients (n=673) were randomized to tocilizumab 8 mg/kg IV 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 in the OPTION study.[288] Patients were randomized to IV 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 to 6.1, p<0.0001 for 8 mg/kg versus placebo; odds ratio 2.6; 95% CI, 1.7 to 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.[289] Patients were randomized to IV tocilizumab 8 mg/kg every four weeks plus placebo or placebo plus MTX 8 mg/week 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 MTX group and tocilizumab groups, respectively. Serious infections were reported in 1.6 and 3.3 percent of the 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.[290] Patients were randomized to IV tocilizumab 8 mg/kg or 4 mg/kg or placebo given IV every four 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 TOWARD, the efficacy and safety of tocilizumab in combination with other DMARDS were investigated in 1,220 patients with active RA.[291] In the phase III, double-blind, placebo-controlled, multicenter study, patients remained on stable doses of DMARDs and received IV 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 endpoints including ACR 50 or ACR 70 responses, the 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 were observed in four percent and one 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.

The ROSE trial evaluated efficacy of tocilizumab in patients with moderate to severe active RA and inadequate clinical response to DMARDs.[292] Safety-related outcomes were also analyzed. In a 24-week, double-blind trial, patients with moderate to severe active RA and inadequate clinical response to DMARD therapy were randomized 2:1 to IV tocilizumab 8 mg/kg (n=412) or placebo (n=207) every four weeks while continuing background DMARD in both groups. The primary endpoint of ACR50 response at week 24, was higher with tocilizumab versus placebo (30.1 versus 11.2 percent; p<0.0001). Percentages of ACR20 and ACR50 responders were significantly higher with tocilizumab versus placebo as early as week-4 and continued to week 24; more patients in the tocilizumab arm also achieved ACR70 responses beginning at week-8 compared to the placebo group (p<0.01). A substudy examining early response to therapy showed improved patient global assessment of disease activity (p=0.005) and pain (p=0.01) and DAS28 (p=0.007) with tocilizumab versus placebo at day-7. Safety findings were consistent with the known tocilizumab safety profile; rates of serious infections (per 100 patient-years) were 7.87 (95% CI 4.30 to 13.2) and 1.20 (95% CI 0.03 to 6.66) in the tocilizumab and placebo groups, respectively.

ADACTA was a randomized, double-blind, multicenter controlled phase four trial that compared IV tocilizumab monotherapy versus SC adalimumab monotherapy for adults with rheumatoid arthritis (diagnosed for at least six months) who were intolerant to methotrexate or for whom continuation of methotrexate was deemed inappropriate.[293] The study enrolled 326 patients who were randomized 1:1 (163 assigned to tocilizumab and 162 assigned to adalimumab). Patients previously treated with a biologic DMARD were excluded. Patients received either tocilizumab 8 mg/kg IV every four weeks plus placebo SC every two weeks or adalimumab 40 mg SC every two weeks plus placebo IV every four weeks for 24 weeks. The primary efficacy endpoint was change in disease activity score using 28 joints (DAS28; using erythrocyte sedimentation rate) from baseline to week 24. Key secondary efficacy endpoints were proportion of patients achieving a DAS28 of 3.2 or lower, a DAS28 of less than 2.6, ACR 20, 50, 70 responses, European League Against Rheumatism (EULAR) good response at week 24, and EULAR good or moderate response at week 24. A total of 24 of 163 (15 percent) of patients in the tocilizumab group and 28 of 163 (17 percent) of patients in the adalimumab group withdrew early from the study. Safety reasons for withdrawal included adverse events (nine with tocilizumab and 10 with adalimumab) and death (two for tocilizumab-one death was deemed unrelated to tocilizumab and one death was ruled possibly related to tocilizumab although the cause of death was not known and the patient had multiple cardiac comorbidities). Other reasons for withdrawal included insufficient treatment response (seven for tocilizumab, 14 for adalimumab), treatment refusal (three for tocilizumab, six for adalimumab), and failure to return (three for tocilizumab). The primary endpoint, mean change of DAS28 from baseline to week 24, was significantly greater with tocilizumab (-3.3) than with adalimumab (-1.8; difference -1.5, 95 percent confidence interval -1.8 to -1.1; p<0.001). Secondary endpoints at week 24 demonstrated significantly more patients in the tocilizumab group than in the adalimumab group had a DAS28 of 3.2 or less (p<0.001), a DAS28 of less than 2.6 (p<0.001), and ACR 20 (p=0.0038), 50 (p=0.002), 70 (p=0.0023) responses. EULAR responses were also more common in the tocilizumab group compared with the adalimumab group (EULAR good p<0.001; EULAR good or moderate p<0.001). The rates of adverse events were similar in each group, 82.1 percent for tocilizumab versus 82.7 percent for adalimumab. The most commonly reported adverse events were upper respiratory tract infections (11.1 percent for tocilizumab and 10.5 percent for adalimumab), nasopharyngitis (10.5 percent for tocilizumab versus 8 percent for adalimumab), and worsening of rheumatoid arthritis symptoms (6.8 percent for tocilizumab versus 9.9 percent with adalimumab). Incidence of serious adverse events was also similar between the groups; serious infections were the most common and were reported at similar proportions in both groups (23 in the tocilizumab group and 21 in the adalimumab group) with no specific type of infection

predominating. More patients treated with tocilizumab than adalimumab needed dose modification or interruption because of adverse events, these were most commonly related to infections or laboratory abnormalities. The study sponsor, Hoffman-LA Roche, parent company of Genentech, designed the study, collected, analyzed, and interpreted the data, as well as wrote the report; the lead authors had full access to all the data.

tocilizumab (Actemra) subcutaneous

SUMMACTA: Study SC-1 was a randomized, double-blind, active-controlled, multicenter, non-inferiority study comparing tocilizumab 162 mg SC administered every week to tocilizumab 8 mg/ kg IV every four weeks in patients >18 years of age with moderate to severe active RA.[294,295] A total of 1,262 patients with moderate to severe active RA diagnosed according to ACR criteria who had at least four tender and four swollen joints at baseline were randomized 1:1 to receive tocilizumab SC or IV in combination with non-biologic DMARD(s). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. The pre-specified non-inferiority margin was a treatment difference of 12 percent or less. At week 24, 69 percent of the per protocol population who received tocilizumab SC had an ACR20 compared to 73.4 percent of the patients who received tocilizumab IV. The weighted difference (95% CI) was -4 percent (-9.2, 1.2), demonstrating non-inferiority of tocilizumab SC administration to IV administration.

MUSASHI: This was a double-blind, double-dummy, parallel-group, comparative study of tocilizumab SC 162 mg every two weeks to tocilizumab IV 8 mg/kg every four weeks in Japanese patients.[296] Patients were 20-75 years of age and had RA for ≥ six months, diagnosed 1987 ACR criteria. Inclusion criteria included: an inadequate response of ≥12 weeks to any synthetic DMARD (MTX, salazosulfapyridine, bucillamine and leflunomide), biologic DMARD (infliximab, etanercept and adalimumab) or immunosuppressant (e.g., tacrolimus); ≥ 8 tender joints; ≥ 6 swollen joints; and an erythrocyte sedimentation rate (ESR) of ≥ 30 mm/hour or a C-reactive protein level of ≥ 1.0 mg/dL. Patients (n=346) were randomized 1:1 into each treatment group and received drugs. No DMARDs or immunosuppressants were allowed during the study, although low dose corticosteroids and an NSAID were permitted. The primary endpoint was the ACR20 response rate at week 24, with a prespecified tocilizumab SC to tocilizumab IV noninferiority margin of 18 percent. At week 24, the per protocol ACR20 response was achieved in 79.2 percent (95% CI, 72.9-85.5) of the tocilizumab SC group and in 88.5 percent (95% CI, 83.4-93.5) of the tocilizumab IV group; and the weighted difference was −9.4 percent (95% CI, −17.6 to −1.2).

Study (SC-II) was a randomized, double-blind, placebo controlled, multicenter study in patients with active RA comparing tocilizumab 162 mg SC administered every other week to placebo.[297] Subjects were >18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline, and an inadequate response to their existing DMARD therapy. Patients (n=656) were randomized 2:1 to tocilizumab 162 mg SC every other week or placebo, in combination with non-biologic DMARD(s). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. In SC-II, 61 percent of patients treated with tocilizumab 162 mg SC every other week achieved an ACR20 response compared to 32 percent of placebo-treated patients in the intent to treat population with a weighted difference (95% CI) of 30 percent (22, 37).

tofacitinib (Xeljanz)

Solo Study: A six-month, randomized, double-blind, monotherapy study in 610 patients with moderate to severe active RA who had an inadequate response to a DMARD (non-biologic or biologic).[298] Patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo. At the Month-3 visit, all patients on placebo were switched to tofacitinib 5 or 10 mg twice daily. Primary efficacy endpoints were ACR20, Health Assessment Questionnaire-Disability Index (HAQ-DI), and DAS28 <2.6 at Month-3. A greater proportion of patients on tofacitinib 5mg or 10 mg had ACR20 responses compared to placebo (59.8 and 65.7 versus 26.7 percent, respectively; p≤0.05 for both). ACR50 and ACR70 responses were consistent with the ACR20 results. ACR20, ACR50, and ACR70 responses were numerically higher for tofacitinib 10 mg compared 5 mg at all time points; the differences between the dosages were most pronounced for ACR70. The differences in HAQ-DI from placebo were similar between the 5 mg and 10 mg dose groups (0.5 and 0.57, versus 0.19, respectively; p<0.0001 for both). ACR20 and HAQ-DI efficacy responses were observed starting at Week 2 and were maintained throughout the study. The proportion of patients achieving DAS28-4(ESR) <2.6 at Month-3 was numerically but not statistically significantly greater for both tofacitinib dosages (5.6 and 8.7 versus 4.4 percent, respectively).

Scan, Sync, and Standard Studies: Three 12-month double-blind Phase 3 studies included patients with moderate to severe active RA who had an inadequate response to a non-biologic DMARD, including methotrexate (MTX).[299] In the Scan study, patients (n=797) received tofacitinib 5 or 10 mg twice daily or placebo added to background MTX treatment; Sync study patients (n=792) received tofacitinib 5 or 10 mg twice daily or placebo added to background DMARDs; Standard study patients (n=717) received tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. The co-primary endpoints for all three studies were the proportion of patients who achieved an ACR20 response at Month-6, changes in HAQ-DI at Month-3, and rates of DAS28-4(ESR) < 2.6 at Month-6. In the studies 45 to 49 percent of placebo patients were considered nonresponders (e.g. those not reaching ACR20) and were switched to tofacitinib 5 mg or 10 mg twice daily at Month-3. At the end of Month-6, all placebo patients were switched to tofacitinib 5 mg or 10 mg twice daily. ACR20 response rate was greater in patients treated with tofacitinib 5 mg or 10 mg compared with placebo (47.3 to 61.8 percent and 51.5 to 52.7 percent versus 25.3 to 31.2 percent, respectively). Placebo patients rapidly responded after advancing to tofacitinib. The proportion of patients who achieved ACR20 response was similar in the tofacitinib treatment groups and the adalimumab treatment group (51.5 and 52.6, versus 47.3 percent, respectively). ACR50 response rates were greater in the tofacitinib 5 mg treatment group than in the adalimumab treatment group at Month-3 (p≤0.05); although at Month-6 neither dose of tofacitinib was statistically significantly different to adalimumab. ACR70 response rates were better in both tofacitinib dose groups than in the adalimumab group at Month-6 (p≤0.0019). The changes from baseline in HAQ-DI were similar or better for tofacitinib 5 mg or 10 mg than that seen for adalimumab group during the entire treatment period (0.56 and 0.64 versus 0.51, respectively). The proportion of patients achieving DAS28-4(ESR) <2.6 at the primary time point was statistically significantly different from the placebo group for both tofacitinib dose groups across the Phase 3 background DMARD studies (p-value <0.05). The proportions for the tofacitinib 10 mg dose group were notably greater than for the 5 mg dose group.

The Scan study also assessed progression of structural damage using modified Total Sharp Score (mTSS) at Month-6; no progression in mTSS was defined as ≤0.5 unit increase from baseline. At baseline treatment groups were similar in degree of damage as shown on x-ray and their estimated annual rate of progression. Changes in mean mTSS at Month-6 for tofacitinib 5mg and 10 mg and placebo were 0.12,

0.06, and 0.47, respectively; this represented approximately 74 and 87 percent reductions relative to placebo, respectively. The difference compared to placebo was statistically significant for the 10 mg dose (p=0.0376) at Month-6; but not for the 5 mg dose (p=0.0792). Reductions continued through Month-12. The proportion of patients with no progression of mTSS for both tofacitinib doses (88.8 percent for 5 mg, 86.9 percent for 10 mg) was statistically greater than placebo (77.7 percent) at Month-6. Effect of tofacitinib on inhibition of the progression of structural damage was maintained for up to 12 months.

Step Study: The Step Study was a six-month phase 3 trial in 399 patients with moderate to severe active RA who had an inadequate response to at least one TNF-inhibitor biologic agent.[300] These patients received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX treatment. At Month 3, all patients on placebo treatment were switched to tofacitinib 5 mg or 10 mg twice daily. The primary endpoints were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) < 2.6 at Month-3. ACR20 response rate for tofacitinib 5 mg and 10 mg and placebo were 41.7, 48.01, and 24.4 percent, respectively. Changes from baseline in HAQ-DI were 0.43, 0.46, and 0.18, respectively. Proportion of patients with DAS28 < 2.6 were 8.8, 6.7, and 1.7 percent, respectively. The authors noted that the magnitudes of these improvements tended to be lower in this trial than in the other background DMARD studies, which was expected for patients with biologic DMARD refractory RA.

Ulcerative Colitis

adalimumab (Humira)

Study UC-I, was a randomized, double-blind, placebo-controlled study in 390 TNF-blocker naive adults with moderate to severe active UC (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants including corticosteroids, azathioprine, or 6-mercaptopurine (6-MP).[301] Patients were randomized to one of three treatment groups, which included placebo or one of two different regimens of adalimumab. Concomitant stable doses of aminosalicylates and immunosuppressants, including corticosteroids, azathioprine, and 6-MP were permitted. The placebo group received doses at weeks 0, two, four, and six. The first treatment group, (160/80), received adalimumab 160 mg adalimumab at week 0 and 80 mg at week two, and the second treatment group, (80/40), received adalimumab 80 mg at week 0 and 40 mg at week two. After week 2, patients in both treatment groups received 40 mg every other week. Induction of clinical remission was defined as a Mayo score ≤ 2 with no individual subscores > 1) at week eight. A total of 18.5 percent of subjects receiving adalimumab 160/80 mg achieved a clinical remission at eight weeks compared to 9.2 percent of subjects receiving placebo. This is a treatment difference of 9.3 percent; 95% CI 0.9-17.6 percent, which is statistically significant (p<0.05) using a pairwise comparison of proportions. In the adalimumab 80/40 mg group and the placebo group at week eight, there was no statistically significant difference in clinical remission. Study UC-II, was a randomized, double-blind, placebo-controlled study in 518 TNF-blocker naive adult patients with moderate to severe active UC (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP or who had lost response or were intolerant to TNF blockers.[302] Forty percent of patients had previously used another TNF blocker. Patients were randomized to either placebo or adalimumab. Concomitant stable doses of aminosalicylates and immunosuppressants, including corticosteroids, azathioprine, and 6-MP were permitted. Subjects received either placebo at weeks zero, two, four, and six or an initial dose of adalimumab 160 mg at week zero and 80 mg at week two. After week two, patients received 40 mg every other week. Induction of clinical remission was defined as a Mayo score ≤ 2 with no individual

subscores > 1) at week eight. Clinical remission at week 52 and sustained clinical remission (defined as clinical remission at both weeks eight and 52) were evaluated. A total of 16.5 percent of subjects receiving adalimumab 160/80 mg achieved a clinical remission at eight weeks compared to 9.3 percent of subject receiving placebo. This is a treatment difference of 7.2 percent with a 95% CI 1.2-12.9 percent. The rate of sustained clinical remission was 8.5 percent for adalimumab 160/80 mg and 4.1 percent for placebo for a treatment difference of 4.4 percent; 95% CI 0.1-8.6 percent. Both the rate of induction of clinical remission at eight weeks and the rate of sustained clinical remission for adalimumab 160/80 mg were statistically significant $p<0.05$ using a pairwise comparison of proportions. Rates of clinical remission at week 52, were 17.3 percent for adalimumab compared to 8.5 percent for placebo (treatment difference: 8.8 percent; 95% CI, 2.8-14.5 percent; $p<0.05$).The safety profile with adalimumab in patients with ulcerative colitis was reported as similar to the profile seen in patients with rheumatoid arthritis.

golimumab (Simponi)

The phase three portion of the PURSUIT-SC trial was a randomized, double-blind, placebo-controlled, six week induction trial in 771 patients ≥ 18 years of age with moderate to severely active ulcerative colitis (Mayo score 6-12).[303] Subjects also had an endoscopy subscore of 2 or 3 on a 3-point scale, and were corticosteroid dependent, or had an inadequate response or failed to tolerate at least one of the following: aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine (6-MP). Subjects were randomized to the following subcutaneous treatments at week 0 and week two: placebo at both weeks, 200 mg followed by 100 mg, or 400 mg followed by 200 mg. The primary endpoint was the percent of responders at week six, defined as a decrease from baseline in the Mayo score by ≥ 30 percent and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time). Stable doses of oral aminosalicylates, oral corticosteroids (less than 40 mg/day), azathioprine, 6-MP, and/or methotrexate (MTX) were permitted. Patients who received TNF inhibitors previously were excluded. Fifty-two percent of patients receiving golimumab 200 mg/100 mg had a response at week six compared to 30 percent of patients on placebo for a treatment difference of 22 percent (95% CI, 14-30 percent), $p<0.0001$. There was no additional benefit in the 400 mg/ 200 mg group and the 100 mg 50 mg group did not show a response. PURSUIT-M was a randomized, double-blind, placebo-controlled, 54-week maintenance trial in 463 patients ≥ 18 years of age with moderate to severely active ulcerative colitis who achieved a clinical response with golimumab induction at six weeks and who tolerated therapy.[304] Subjects were randomized to placebo, golimumab 50 mg or 100 mg subcutaneously every four weeks. Concomitant oral aminosalicylates, azathioprine, 6-MP, and/or MTX were permitted if doses were stable. Corticosteroid dosage was tapered at the start of treatment. The clinical response was assessed every four weeks and the primary endpoint was the percent of patients maintaining a clinical response through week 54. Fifty-one percent of patients receiving golimumab 100 mg (n=154) maintained a clinical response through week 54 as compared to 31 percent of placebo patients (n=156) for a treatment difference of 19 percent (95% CI, 8-30 percent), $p<0.001$.

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).[305] 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 ($p\leq0.002$ 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).

vedolizumab (Entyvio)

Two randomized, double-blind, placebo controlled trials (UC Trials I and II) were conducted to evaluate the safety and efficacy of vedolizumab in adult patients with moderately to severely active UC.[306] Severely active UC was defined in both trials as a Mayo score of six to 12 with endoscopy subscore of two or three. Enrolled patients in the US had over the previous five year period an inadequate response or intolerance to immunomodulator therapy (e.g., thiopurines [azathioprine or mercaptopurine]) and/or an inadequate response, loss of response, or intolerance to a TNF blocker. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five year period the patients were corticosteroid dependent or had an inadequate response or intolerance to corticosteroids. Patients that had ever received natalizumab and patients that had received a TNF blocker in the past 60 days were excluded from enrollment.

In UC Trial I, patients (n=374) were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo by intravenous (IV) infusion at Week Zero and Week Two. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through Week Six and efficacy assessments were conducted at Week Six. A total of 39 percent of patients had an inadequate response, loss of response, or intolerance to TNF blocker therapy and 18 percent only had an inadequate response, inability to taper or intolerance to prior corticosteroid treatment. The median baseline Mayo score was nine in the vedolizumab group and eight in the placebo group. In UC Trial I, a greater percentage of patients treated with vedolizumab compared to patients treated with placebo (47 percent versus 26 percent, $p<0.001$) achieved clinical response at Week Six. A greater percentage of patients treated with vedolizumab compared to patients treated with placebo (17 percent versus five percent, $p=0.001$) also achieved clinical remission and improvement of endoscopic appearance of the mucosa (25 percent versus 41 percent, $p=0.001$) at Week Six.

In UC Trial II, 373 patients who had a clinical response to vedolizumab at Week Six were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week Six: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks or placebo every four weeks. Concomitant aminosalicylates and corticosteroids were permitted through Week 52 and efficacy assessments occurred at week 52. Concomitant immunomodulators were permitted outside the US but were not permitted beyond Week Six in the US. At Week Six, patients were receiving corticosteroids (61 percent), immunomodulators (32 percent) and aminosalicylates (75 percent). A total of 32 percent of patients had an inadequate response, loss of response or intolerance to a TNF blocker therapy. At Week Six, the median Mayo score was eight in all three groups. Patients who had achieved clinical response at Week Six and were receiving corticosteroids were required to begin a corticosteroid tapering regimen at Week Six. In the trial, a greater percentage of patients in groups treated with vedolizumab as compared to

placebo (42 percent versus 16 percent, p<0.001) achieved clinical remission at Week 52 and maintained clinical response (57 percent versus 24 percent, p <0.001). In addition, a greater percentage of patients in groups treated with vedolizumab as compared to placebo were in clinical remission at both Weeks Six and 52 (21 percent versus nine percent, p <0.001), and had improvement of endoscopic appearance of the mucosa at Week 52 (52 percent versus 20 percent, p<0.001). The vedolizumab every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen and is not the recommended dosing regimen.

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.[307] 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.[308] 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.[309] The primary endpoints were clinical remission for luminal Crohn's disease and fistula closure at ≥ 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, 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.[310] 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=0.70, 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.[311] 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).

A systematic literature review and meta-analysis compared the efficacy of psoriasis treatments.[312] Randomized controlled trials evaluating PASI were identified and evaluated for quality. PASI responses were modeled using a mixed-treatment comparison, which enabled the estimation of the relative effectiveness of several treatments. A total of 22 trials were included. TNF inhibitors were most likely to achieve PASI 75, with a mean relative risk (RR) of 15.57 (95% CI, 12.46 to 19.25) versus mean RRs of 9.24 (95% CI, 5.33 to 13.91) for systemic and 5.65 (95% CI, 3.74 to 7.97) for T-cell therapies. Infliximab (81 percent) and adalimumab (71 percent) had greater probabilities of achieving PASI 75 than etanercept (50 percent), although dosage was an important determinant of outcome.

Psoriatic Arthritis

A meta-analysis evaluated the efficacy and safety of TNF blockers in the management of PsA.[313] 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% CI, 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.[314] 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 MTX. For each treatment, the inclusion of MTX in combination improved the response. After adjustment for study-level variables, the authors found TNFα antagonists to be more efficacious compared with anakinra (p<0.05). Indirect comparisons between the three TNFα 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 TNFα antagonists is better than with anakinra; and all drugs in the TNFα antagonist class are no different from each other. Findings from another systematic review from 2006 were similar.[315]

A systematic review analyzed the efficacy and safety of anti-TNF drugs (infliximab, etanercept, and adalimumab) for treating RA.[316] 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.[317] 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 to 6). Discontinuations due to adverse events were higher with the biologics (OR 1.39, 95% CI, 1.13 to 1.71), with a number needed to treat for harm of 52 (95% CI, 29 to 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 to 0.99) and etanercept (OR 0.34, 95% CI, 0.14 to 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 to 3.04; anakinra OR 2.05, 95% CI, 1.27 to 3.29; and infliximab OR 2.7, 95% CI, 1.43 to 5.26).

A meta-analysis evaluated the efficacy and safety of using the TNF antagonists including adalimumab, etanercept, and infliximab in the treatment of adults with RA.[318] A total of 21 randomized, placebo-controlled trials were included. A total of 1,524 patients with adalimumab, 1,116 patients received infliximab, and 1,029 patients received etanercept, and 2,834 patients received placebo with or without MTX in all groups. Efficacy was compared using ACR 20, ACR 50, and ACR 70 criteria. In the short term trials (12 to 30 weeks), etanercept had the highest risk ratios for reaching ACR 20 and ACR 50: 2.94 (95% CI, 2.27 to 3.81) and 5.28 (95% CI, 3.12 to 8.92), respectively. ACR 70 achievement was highest with adalimumab (5.36; 95% CI, 3.76 to 7.64). Over long-term treatment (one to three years), adalimumab demonstrated the highest risk ratios for ACR 20 (1.85 [95% CI, 1.07 to 3.19]), ACR 50 (2.8 [95% CI, 1.16 to 6.77]), and ACR 70 (3.23 [95% CI, 1.37 to 7.61]). No significant differences were observed between the active treatments and placebo.

A systematic review of 16 randomized controlled trials comparing the efficacy of anti-TNF agents with placebo at 24 weeks in patients who have had an inadequate response to MTX was performed.[319] Relative efficacy was estimated using Bayesian mixed treatment comparison (MTC) models. Three different outcome measures were used: ACR20 and ACR50 response and the percentage improvement in Health Assessment Questionnaire (HAQ) score. All anti-TNF agents showed significantly improved efficacy over placebo. The results also provide evidence of some differences in efficacy among the agents. Etanercept was favored over infliximab and golimumab, and certolizumab was favored over infliximab and adalimumab. ACR results indicate improved efficacy of certolizumab over golimumab. On HAQ analysis, adalimumab, certolizumab, etanercept and golimumab appear superior to infliximab, and etanercept shows improved efficacy compared with adalimumab.

A total of 18 published trials and one abstract were included in a meta-analysis examining the efficacy of a biological agent in RA at six months in patients with an incomplete response to methotrexate or an anti-TNF biologic.[320] In patients with incomplete response to methotrexate, anti-TNF agents had the same probability of reaching an ACR50 compared to non-anti-TNF biologicals taken together (OR 1.30, 95 % CI 0.91 to 1.86). However, when compared to specific biological agents, anti-TNFs demonstrated a higher probability of reaching an ACR50 than abatacept (OR 1.52, 95 % CI 1.0 to 2.28), but not in comparison to rituximab and tocilizumab. In patients with prior incomplete response to anti-TNF agents, rituximab demonstrated a higher probability of achieving an ACR50 than tocilizumab (OR 2.61, 95% CI 1.10 to 6.37), but no significant differences existed between golimumab and other biologicals.

A meta-analysis including similarly designed double-blind, randomized, placebo-controlled trials over an 18-year period compared the response of tocilizumab and other biologic agents in patients with RA who had inadequate response to DMARD therapy.[321] Biologic agents included abatacept, rituximab, etanercept, infliximab, adalimumab, and tocilizumab. The endpoint of interest was ACR20/50/70 response criteria at 24 to 30 weeks. The effectiveness of tocilizumab appeared to be comparable to that of other biologic agents for ACR20 and ACR50 responses but greater for ACR70. Specifically, tocilizumab had greater ACR70 responses than both TNF-alpha inhibitors (RR=1.8; credible interval [CrI]=1.2, 2.6) and abatacept (RR=2; CrI=1.3, 3.1).

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.[322] 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.[323] 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.

A systematic review of the TNF antagonists to evaluate the risk of infection and malignancy in patients with plaque psoriasis and psoriatic arthritis included randomized, placebo-controlled trials of etanercept,

infliximab, adalimumab, golimumab, and certolizumab.[324] A total of 20 studies with 6,810 patients were included. The odds ratios for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% CI, 1.05 to 1.33) and 0.7 (95% CI, 0.4 to 1.21), respectively. The odds ratio for malignancy was 1.48 (95% CI, 0.71 to 3.09) and 1.26 (95% CI, 0.39 to 4.15) when nonmelanoma skin cancer was excluded. In the short term, the authors concluded that there is a small risk of overall infection with the TNF antagonists. No evidence of an increased risk of serious infection or malignancy was observed in the short-term trials.

SUMMARY

Cytokines and CAMs have been implicated in RA, plaque psoriasis, psoriatic arthritis, 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

Adalimumab (Humira), etanercept (Enbrel), golimumab (Simponi), certolizumab pegol (Cimzia), and infliximab (Remicade) are indicated for ankylosing spondylitis. Although it has been established that anti-TNFα 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), infliximab (Remicade), and vedolizumab (Entyvio) 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 as well as the treatment of children age six years and older. Comparative data are lacking; however, adalimumab is specifically indicated for patients who are intolerant to or have a diminished response to infliximab. Certolizumab pegol and vedolizumab (Entyvio) are indicated for patients who have had an inadequate response to conventional therapy.

Cryopyrin-Associated Periodic Syndromes (CAPS)

Canakinumab (Ilaris) and rilonacept (Arcalyst) are both indicated for CAPS associated with FCAS and MWS while anakinra (Kineret) is indicated for CAPS associated with Neonatal-Onset Multisystem Inflammatory Disease (NOMID).

Juvenile Idiopathic Arthritis

Abatacept (Orencia), adalimumab (Humira), and etanercept (Enbrel) are respectively indicated for polyarticular Juvenile Idiopathic Arthritis (JIA) in children six, four, and two years of age and above. Tocilizumab (Actemra) is indicated for polyarticular and systemic Juvenile Idiopathic Arthritis (JIA) in children two years of age and older. Canakinumab (Ilaris) is indicated for systemic JIA in children two years of age and older.

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 adalimumab (Humira), etanercept (Enbrel), certolizumab pegol (Cimzia), golimumab (Simponi, Simponi Aria), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), anakinra (Kineret), and tofacitinib (Xeljanz).

Compared with the anti-TNFα 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-TNFα therapies. Anakinra is given as monotherapy or in combination with MTX or other non-TNF-targeting DMARDs.

Infliximab (Remicade) is administered at an outpatient facility as an IV infusion. Abatacept (Orencia) and tocilizumab (Actemra) may be administered either IV in an outpatient facility for RA or may be administered as a SC injection for RA. Abatacept (Orencia) for JIA must be administered IV for JIA in an outpatient facility.

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

Tofacitinib (Xeljanz) is a Janus kinase (JAK) inhibitor. This oral option for RA is not approved for first-line therapy.

The American College of Rheumatology (ACR) 2012 guidelines for the management of RA recommend more aggressive treatment in patients with early RA (within six months of symptom onset) since earlier treatment may provide better outcomes. In patients with established RA with moderate or high disease activity after three months of MTX monotherapy or DMARD combination therapy, the addition of either an anti-TNF biologic, abatacept, or rituximab maybe considered. If a patient still has moderate or high disease activity after three months of anti-TNF biologic therapy, ACR recommends switching to another anti-TNF agent or to a non-TNF biologic.

The 2012 consensus statement on the biologic agents for the treatment of rheumatic diseases from the international Annual Workshop on Advances in Targeted Therapies states that anti-TNF agents used in combination with methotrexate yield better results in the treatment of RA than monotherapy; most anti-TNF agents are approved as monotherapy for RA, except infliximab, which is only approved for use with methotrexate. There is no evidence that any one TNF antagonist should be used before another one can be tried for the treatment of RA or JIA (except with systemic-onset JIA, when anakinra may be effective). There is no evidence that any one TNF antagonist is more effective than any other for the treatment of RA or AS.

Plaque Psoriasis

Cytokine and CAM antagonists indicated for the treatment of psoriasis have similar efficacy. The American Academy of Dermatology (AAD) states there is no specific sequence in which anti-TNF agents should be used in patients with moderate to severe chronic plaque psoriasis without psoriatic arthritis. However, the guidelines note that in non-head-to-head phase III trials of the individual agents, infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept.

Etanercept (Enbrel), adalimumab (Humira), and ustekinumab (Stelara) are given subcutaneously. Infliximab (Remicade) is given by IV infusion. Apremilast (Otezla) is an oral tablet given twice daily.

Ustekinumab (Stelara) has a mechanism of action that is distinct from other DMARDs. Ustekinumab requires 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 AAD. 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 six FDA-approved TNF blockers, adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), and ustekinumab (Stelara) 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. Apremilast (Otezla) is a recently approved oral tablet for psoriatic arthritis that has not been included in the current guidelines.

Ulcerative Colitis

Infliximab, (Remicade), adalimumab, (Humira), golimumab (Simponi), and vedolizumab (Entyvio) are indicated for treating ulcerative colitis. Infliximab is effective in inducing clinical remission and response in patients with moderate to severe ulcerative colitis with refractory disease. Adalimumab and golimumab are approved for inducing and sustaining clinical remission in adult patients with moderate to severe active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. Golimumab is also approved in patients who have failed to respond to oral aminosalicylates and who cannot tolerate immunosuppressants or aminosalicylates. Vedolizumab (Entyvio) is approved for moderate to severe disease after trial or intolerance to a TNF blocker, immunomodulator, or corticosteroid. The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers. Use of Infliximab reduced the need for colectomy in short-term trials.

Other Indications

Anakinra (Kineret) is approved for use in pediatric patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a rare periodic fever syndrome which causes uncontrolled inflammation in multiple parts of the body beginning in the newborn period.

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