# Monoclonal Antibodies in Rheumatic Diseases

*Candice Yuvienco, MD, and Stuart Schwartz, MD*

**An increased understanding of the** immunopathogenesis of rheumatic diseases has dramatically improved the identification of therapeutic targets within the inflammation cascade. These targets include cytokines, B cells, and molecules involved in T cell interactions, which have been pivotal in the initiation and perpetuation of the immune response. Disordered regulation of cytokines, particularly **tumor necrosis factor-alpha (TNF-alpha)**, **interleukin 1 (IL-1)**, and **interleukin-6 (IL-6)** has been well-recognized in inflammatory disorders.[1] Successful isolation of these molecules through advances in biotechnology has led to effective therapies, thus revolutionizing treatment of diseases such as **rheumatoid arthritis (RA)**, **psoriatic arthritis (PSA)**, **ankylosing spondylitis (AS)**, **autoinflammatory syndromes, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)**, and **systemic lupus erythematosus (SLE)**.

Monoclonal antibodies are among these targeted biologic therapies, of which there are now eight in established clinical use for rheumatic disease indications (Table 1): infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), golimumab (Simponi®), tocilizumab (Actemra®), rituximab (Rituxan®), canakinumab (Ilaris®), and recently approved in 2011, belimumab (Benlysta®).[2-27]

Pivotal trials of TNF-inhibitors (infliximab, adalimumab, certolizumab, and golimumab) have proven efficacious in early and longstanding RA, with clinical improvement based on **American College of Rheumatology (ACR)** response criteria. Improvement in functional outcomes, quality of life, and inhibition of radiographic structural damage has been demonstrated. Infliximab, adalimumab, and golimumab have also established efficacy for PSA and AS.

Conventional **disease-modifying anti-rheumatic drug (DMARD)** therapy remains the cornerstone of treatment for RA, particularly **methotrexate (MTX)**. In clinical trials directly comparing MTX with biologics, both were similarly effective. However, improvement began earlier with biologic treatment than with MTX therapy. Inhibition of radiographic progression was more robust with biologics, a finding believed to occur because TNF-inhibitors directly reduce osteoclast activity.[28] Combination therapy with MTX and TNF-inhibitors has consistently proven superior to either given as monotherapy.[2,3,8,9,14]

There are no head-to-head comparison trials of TNF-inhibitors to support the use of one agent over another based on efficacy; they have all been proven effective. Nevertheless, differences in route of administration and dosing intervals may influence the choice of agent. Switching among TNF-inhibitors to overcome inadequate response or poor tolerability appears beneficial in some patients.[29] However, not all patients with RA respond to or tolerate TNF-inhibitors. Additional agents have subsequently emerged which target different cytokines or cells (tocilizumab for IL-6, or rituximab for B cells respectively), offering alternative treatment options for difficult to control cases.

## Emerging Clinical Use

Newer applications for existing monoclonal antibodies have evolved. Rituximab, originally indicated for the treatment of lymphoma, was found in the RAVE trial not to be inferior to daily cyclophosphamide treatment to induce remission in severe ANCA-associated vasculitis and may be superior in relapsing disease.[30] The **cryopyrin-associated periodic syndromes (CAPS)**, particularly Muckle Wells and Familial Cold Autoinflammatory Syndrome, typically manifest in the pediatric population but occasionally present in adults. These syndromes have clinical manifestations which include: urticarial-like rash, fever, central nervous system inflammation, arthropathy, and amyloidosis. These syndromes respond dramatically to canakinumab, an anti-IL-1 biologic agent.[25]

Belimumab has been recently approved by the FDA as the first new therapeutic agent for SLE in more than 50 years.

## Mechanism of Action

### Cytokine-directed therapies:

TNFα plays a central role in the pathogenesis of RA and other inflammatory disorders, mediating both inflammation and articular damage.[1] It is produced primarily by monocytes, macrophages, and B cells, and is inhibited by the monoclonal antibodies infliximab, adalimumab, golimumab, and certolizumab. Blocking TNFα reproducibly inhibited production of other proinflammatory cytokines such as IL-1 and IL-6, confirming that TNFα functions early on in the inflammatory cascade. Furthermore, its blockade reduced leukocyte recruitment to the inflamed joints[1]. Certolizumab has a **PEG (polyethylene glycol)** moiety that prolongs its half-life, which may contribute to preferential distribution to inflamed tissues.[11]

Interleukin-6 is overexpressed in synovial tissue in RA joints, and is a major inducer of the acute phase response. IL-6 activates intracellular signaling that ultimately leads to chronic synovial inflammation. Tocilizumab inhibits IL-6 by competitively binding to its receptor.[19] In CAPS, a cryopyrin mutation leads to the overproduction of the inflammasome, a multiprotein complex that produces IL-1beta. Canakinumab inhibits IL-1beta thereby preventing these autoinflammatory syndromes.[25]

### B-cell directed therapies:

RA has a complex pathophysiology in part mediated by self-perpetuating B cell clones, a population of cells that may explain disease persistence. In ANCA associated vasculitis, the number of activated peripheral blood B lymphocytes correlates with disease activity.[30] Rituximab is directed against the CD20 antigen on the B cell membrane causing B cell depletion. This results in a decline of autoantibodies such as rheumatoid factor and anti-cyclic citrullinated peptide in RA, and ANCA in vasculitis.[30,31] Rituximab suppresses the immune response since B cells are no longer available to present antigen to T cells or produce pro-inflammatory molecules.

Belimumab neutralizes **B lymphocyte stimulator (BlyS)**, a potent B cell survival factor. SLE patients have elevated BlyS levels which correlate with their autoantibody titers and disease activity. Inhibition of this factor results in apoptosis of autoreactive B cells.[32,33]

**Table 1. Description of the monoclonal antibodies, their indications, mechanism of action, dosing, and corresponding pivotal trials**

| DRUG (year approved by US FDA) | FDA-approved rheumatic disease indication | Description | Mechanism of action | Usual dose range, route and frequency of administration | Pivotal Trials |
|---|---|---|---|---|---|
| infliximab Remicade® (1998) | RA[a], PSA[b], AS[b] | Chimeric | Inhibits TNFα | 3-10 mg/kg IV infusion every 8 weeks after initial loading 5 mg/kg used for PSA, AS | ATTRACT[2], ASPIRE[3], IMPACT 1[4] IMPACT 2[5], Braun[6] |
| adalimumab Humira® (2002) | RA[a,b], PSA[b], AS[b] | Human | Inhibits TNFα | 40 mg SC every other week, can increase to weekly | Van De Putte[7], ARMADA[8], PREMIER[9], ATLAS[10] |
| certolizumab Cimzia® (2008) | RA[a,b] | PEG-linked humanized Fab | Inhibits TNFα | 200 SC mg every 2 weeks or 400 mg every 4 weeks after initial loading | RAPID 1[11], RAPID 2[12], FAST4WARD[13] |
| golimumab Simponi® (2009) | RA[a], PSA[b], AS | Human | Inhibits TNFα | 50 mg SC once monthly | GOBEFORE[14], GOFORWARD[15], GOAFTER[16], GOREVEAL[17], GORAISE[18] |
| tocilizumab Actemra® (2010) | RA[a,b,c] | Humanized | Inhibits IL-6 | 4-8 mg/kg IV infusion every 4 weeks | OPTION[19], TOWARD[20], RADIATE[21], AMBITION[22] |
| rituximab Rituxan® (2006) | RA[a,c] | Chimeric | Depletes B cells | 1000 mg IV infusion repeated 2 weeks later, then every 24 weeks[d,e] | DANCER[23] REFLEX[24] |
| canakinumab Ilaris® (2009) | CAPS | Human | Inhibits IL-1 | 150 mg SC every 8 weeks (adults and children ≥4 years old, >40 kg) | Lachmann[25] |
| belimumab Benlysta® (2011) | SLE | Human | Inhibits BLYS | 10 mg/kg every 2 weeks x 3, then every 4 weeks | BLISS 52[26], BLISS 76[27] |

[a] for moderate to severe RA in combination with methotrexate, [b] can be used as monotherapy, [c] for patients with inadequate response to one or more TNF-inhibitor/s, [d] premedicate prior to each infusion with glucocorticoid, antihistamine, and acetaminophen, [e] dose recommendation for RA, with dosing interval based on clinical response

**Abbreviations:** FDA: Food and Drug Administration; RA: rheumatoid arthritis; PSA: psoriatic arthritis; AS: ankylosing spondylitis; CAPS: cryopyrin-associated periodic syndromes; SLE: systemic lupus erythematosus; PEG: polyethylene glycol; Fab: antigen-binding region of antibody; TNFα: tumor necrosis factor-alpha; IL-1: inerleukin-1; BLYS: B lymphocyte stimulator; IV: intravenous; SC: subcutaneous; mg: milligrams; kg: kilograms.

## Safety and Risks

TNFα plays a key role not only in the pathogenesis of inflammatory diseases but also in normal immune homeostasis, host defense, and tumor growth control. As a result, there has been guarded optimism as to the long-term safety of TNF-inhibitors. Clinical trials uncovered the most common adverse events among thousands of patients, and determined that TNF-inhibitors are generally well tolerated. RA itself is associated with an increased risk of infection, lymphoma, and CHF, complicating assessments of these adverse events while on biologic therapy or other immunosuppressants.[29] Safety concerns with the use of TNF-inhibitors are summarized in Table 2, and for non-TNF-inhibitors in Table 3.

## General Advisory on the Use of TNF Inhibitors

Decisions to use TNF-inhibitors should always be made on an individual basis, including consideration of all comorbidities, and with clear discussion of the risks and benefits.

Patient and physician vigilance with monitoring for infection is essential,

**Table 2. Safety concerns with the use of TNF inhibitors**

| | |
|---|---|
| Serious infections (requiring intravenous antibiotics and/or hospitalization) | Serious, sometimes fatal infections from bacterial, mycobacterial, fungal, viral, or other opportunistic pathogens have been reported.[34-37] |
| Tuberculosis (TB) | Cases of reactivation or new TB infection have been observed, both pulmonary and disseminated forms. Majority of cases were in countries with high TB incidence rate. TB activation is likely a class effect of TNF inhibitors.[29,34-37] |
| Opportunistic infections | Histoplasmosis, coccidioidomycosis, aspergillosis, candidiasis, listeriosis, some of these were disseminated, often while on concomitant immunosuppressants.[34-37] |
| Hepatitis B virus (HBV) reactivation | In chronic carriers, cases of HBV reactivation were seen, the majority in patients who received concomitant immunosuppresants.[34-37] |
| Demyelinating disease | Rare cases of new-onset/exacerbations of demyelinating disorders of the central (multiple sclerosis, optic neuritis) or peripheral nervous system (Guillain-Barre syndrome) have occurred. Some were temporally related to TNF-inhibitor therapy.[29,34-37] |
| Immunogenicity | All TNF-inhibitors are foreign proteins that may induce formation of antibodies which may affect safety and efficacy. Antibodies can neutralize the action of these drugs and may cause hypersensitivity reactions. Lower drug doses are more immunogenic than higher doses; chimeric agents (mouse-human structure) are more immunogenic than human monoclonal antibodies; use of concomitant immunosuppressive treatment such as MTX may reduce the magnitude of the immunogenic response.[29,34] |
| Congestive heart failure | New-onset/worsening of existing heart failure were observed, likely to be a class effect of TNF inhibitors; conflicting data suggested that treatment with TNF inhibitors is associated with decreased prevalence of CHF.[29] |
| Lupus-like syndrome | Antinuclear and anti-DNA antibody formation have occurred, as well as rare cases of lupus-like syndrome. Most cases were promptly reversible upon withdrawal of medication.[29] |
| Neoplasia, lymphoma | There have been several reports of lymphoma.[29,34-37] Confounding this relationship is the independently increased risk of lymphoma in advanced/more severe RA.[29] In some trials, there were more cases of malignancy seen in those who received TNF inhibitors versus the control groups.[34,35] |
| Infusion/injection site reactions | These may be consequences of antibody formation to the drug.[29,34] Patients who developed antibodies to infliximab were more likely to have infusion reactions, the majority of which were mild.[34] Injection site reactions were most commonly erythema, pain, and swelling. |
| Hematologic events | Postmarketing reports revealed pancytopenia, leukopenia, neutropenia, aplastic anemia, thrombocytopenia.[34-37] |
| Hepatotoxicity | Severe hepatic reactions were seen, including acute liver failure reports. Elevated transaminases have occurred, however many patients were also on potentially hepatotoxic medications such as methotrexate.[34,36] |

with decisions on discontinuation and re-initiation closely reevaluated.

Avoid live vaccines.[29,34-39]

Closely monitor concomitant immunosuppressive/DMARD treatment to limit adverse effects such as hepatotoxicity or hematologic toxicity.[29]

Screening for latent TB by purified protein derivative (PPD) placement is essential, and appropriate treatment should be given accordingly prior to initiation of TNF-inhibitors. If active TB is present, TNF-inhibitor therapy should be delayed until treatment is complete.[29] Monitor all patients for active TB during treatment even if initial PPD is negative, as de novo TB cases have occurred.[29]

Patients at risk for Hepatitis B infection should be screened prior to initiation of TNF-inhibitors. Those with evidence of prior infection should have close monitoring for clinical and laboratory signs of reactivation throughout and after discontinuation of therapy.[29,34-37]

Table 4 summarizes the absolute contraindications to and precautions with the use of TNF-inhibitors. Similar vigilance and precautions should be undertaken with use of the non-TNF-inhibitor monoclonal antibodies (rituximab, tocilizumab, canakinumab, belimumab), particularly with regard to infections, malignancy, demyelinating disorders, pregnancy. Avoidance of live vaccines is emphasized.

## Conclusion

The last decade has witnessed the dynamic growth of an effective therapeutic arsenal for a number of chronic inflammatory disorders. Monoclonal antibodies now play an important role in treating rheumatic disease offering significant improvement in clinical, functional, and radiographic outcomes.

**Table 3. Safety concerns of non-TNF inhibitor monoclonal antibodies**

| | |
|---|---|
| TOCILIZUMAB | • The most common adverse event was infections, including skin and subcutaneous infections.[21,22] Serious and opportunistic infections have occurred.[19,20,21,22,38] |
| | • Gastrointestinal perforations complicating diverticulitis, reversible neutropenia and thrombocytopenia, and infusion reactions were seen.[21,38] |
| | • Aminotransferase elevations, elevations in total cholesterol and low-density lipoprotein levels were reported, however there were no symptoms of hepatitis or cardiovascular events.[21,22] |
| RITUXIMAB | • Infusion reactions were common adverse events, especially after the first infusion; use of IV steroid prior to infusion reduced these reactions.[23,24,39] |
| | • Most infections reported in RA patients were mild to moderate, and largely upper respiratory or urinary tract infections.[23,24] |
| | • There was a slight increase in serious infections compared to placebo in the REFLEX trial (5.2 for rituximab versus 3.7 for placebo per 100 patient-years).[24] |
| | • Immunogenicity with development of human anti-chimeric antibodies has occurred, but was not associated with increased infusion reactions.[39] |
| | • Rare cases of progressive multifocal leukoencephalopathy cases have been reported.[39] |
| CANAKINUMAB | • There were no reported deaths or life-threatening adverse events.[25] |
| | • Vertigo was reported in a small percentage, and 34% developed infections.[25] |
| | • There were no cases of malignancy, opportunistic infections, autoantibodies to canakinumab, autoimmune or demyelinating adverse events.[25] |
| BELIMUMAB | • Overall adverse events in studies of belimumab in SLE patients demonstrated that rates of serious infections were comparable across treatment groups, and rate of opportunistic infections were stable over time.[40] |
| | • Malignancies were seen, however no pattern or increase in any particular type of malignancy was identified in the belimumab group.[40] |

**Table 4. Absolute contraindications and precautions with use of anti-TNF therapy**

| ABSOLUTE CONTRAINDICATIONS | PRECAUTIONS |
|---|---|
| Active, latent, untreated tuberculosis | Chronic or recurrent infection |
| Active serious infection/sepsis | Hepatitis C, hepatitis B infection/ carrier |
| Active or recent history of malignancy other than successfully treated non-melanoma skin cancer | Malignancy in remission |
| Demyelinating disease | Human immunodeficiency virus infection |
| Live vaccines | Pregnancy |
| Lymphoma | Lactation |
| Known anaphylaxis to product | Systemic lupus erythematosus |
| Combination with anakinra or abatacept, which increases risk of infection without increase in benefit | Lupus-like syndrome |
| CHF class III/IV | CHF class I/II |

TNF: tumor necrosis factor; CHF: congestive heart failure
Modified from: Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum*. 2005 Jun;34(6):819-36.

TNF inbibitors have become the first line treatment in rheumatoid arthritis for methotrexate failures. Rituximab and tocilizumab are presently reserved for TNF failures. Despite their significant expense and unique safety profile, monoclonal antibodies have dramatically improved the management of several rheumatic diseases.

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*Candice Yuvienco, MD, is a fellow of Rheumatology at Rhode Island Hospital.*

*Stuart Schwartz, MD, is a Clinical Associate Professor of Medicine at the Warren Alpter Medical School of Brown University.*

## Correspondence

Stuart Schwartz, MD
2 Dudley St., Suite 370
Providence, RI 02905
e-mail: SSchwartz@Lifespan.org