Biologic Therapies:
Clinical Implications for Rheumatologists, Gastroenterologists, Allied Health Practitioners
Spondyloarthritis: Therapeutic Implications of Advances in Pathogenesis

Three prevalent forms of inflammatory arthritis include rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Although they share certain characteristics, they are distinguished by the specific sites of joint inflammation associated with each: the synovium in RA; the bone, enthesis, and synovium in PsA; and the bone and enthesis in AS. The location of inflammation is an important factor to consider when making treatment decisions. For example, an agent that is effective for peripheral synovitis may not have the same level of therapeutic response in axial disease or enthesitis.

Osteoclast precursors as a biomarker

Osteoclast precursors are monocyte effector cells in the circulation. An abundance of osteoclast precursors is observed in patients with certain phenotypes of erosive immune-mediated inflammatory disorders, namely RA, PsA, and psoriasis (see Figure 1). Of note, osteoclast precursors are strikingly high in a subset of patients with psoriasis without musculoskeletal signs and symptoms who later develop inflammatory arthritis, which suggests that osteoclast precursors may be useful as a biomarker for susceptibility to arthritis in this population.

Therapeutic targets

Th17 represents a therapeutic target for joint destruction associated with T cell activation. Other logical therapeutic targets include IL-23 (a perpetuator of the Th17 phenotype), IL-17, IL-21, dendritic cells that express IL-23, and dendritic cell specific transmembrane protein (DC-STAMP).

Anti-p40 antibody was associated with an improvement in the American College of Rheumatology (ACR) 20 response compared with placebo in patients with PsA, but the ACR20, ACR50, and ACR70 response achieved was somewhat inferior to that of other biologic agents tested in randomized, placebo-controlled trials, and typically lower than that achieved in the treatment of plaque psoriasis.

Dendritic cell specific transmembrane protein is a 7-transmembrane protein that is present on monocytes. Its role in osteoclastogenesis is as a regulator of cell to cell fusion in the formation of a polykaryon. When a monocyte forms an osteoclast, it must form a multinucleated cell, called a polykaryon. DC-STAMP is critical to polykaryon formation.

DC-STAMP may therefore be a therapeutic target; DC-STAMP antibodies added to culture have been shown to prevent polykaryon formation. DC-STAMP is but one signaling pathway required for osteoclast formation and activation. Osteoclast activation can also be blocked at RANK or in accessory pathways downstream of RANK, such as Syk. Molecules that bind to Syk have shown impressive efficacy in the treatment of RA.

Osteoblasts and osteoclasts offer different therapeutic targets. The Wnt signaling pathway is a critical pathway responsible for osteoblast formation and development of new bone. The Dick-
kof (DKK) family of proteins acts as inhibitors of the Wnt pathway and may interfere with new bone formation by interrupting osteoblast differentiation. DKK-1 is highly elevated in patients with RA, which may explain the relative absence of bone reparative response associated with RA.

The effect of TNF inhibition on new bone formation has been a concern, but two phase 3 clinical trials with etanercept and adalimumab revealed no decline in radiographic progression (when compared to progression in a historical cohort). New models of AS consider that osteoproliferation may be uncoupled from inflammation, such that new bone formation may be influenced by pathways that are separate from those that regulate bone resorption. The possibility that TNF may actually inhibit new bone formation has also been suggested, and in this scenario, TNF blockade may actually promote the development of a pathologic bone formation phenotype.

**Biologics and Systemic Vasculitis**

The investigation of biologic agents to treat vasculitis is ongoing. The use of biologic agents must be evaluated in the context of standard therapies, as no biologic agent has been proven to be effective in this patient population.

Theoretical advantages and objectives with the use of biologic agents in vasculitis are the reduction in the toxicity of therapy, the reduction in the incidence of disease relapse, and the induction of disease remission permitted by specific immunologic targeting. Of concern, however, is that such specific targeting may be insufficient to modulate the disease and reduce the potential for disease-specific toxicities.

In considering the use of a biologic agent for a patient with systemic vasculitis, several issues must be contemplated, including the goals of treatment, the effectiveness of current standard therapy, and clinical data on biologic agents drawn from the particular form of vasculitis being treated. For this discussion, these issues will be examined in the settings of Wegener’s granulomatosis and giant cell arteritis.

**Wegener’s granulomatosis**

Wegener’s granulomatosis is a potentially life-threatening disease, and protection of patient survival is the first priority. Because of the effectiveness of current treatment options, the goals may be broadened to include the following:

1) Induction of remission, defined as the absence of disease activity;

2) Avoidance of disease relapse, defined as the return of disease activity after achieving remission; and

3) Minimization of therapeutic toxicity.

The current treatment approach to Wegener’s granulomatosis is based on two phases: an induction phase in which active disease is placed into remission and a maintenance of remission phase (see Figure 2). Wegener’s granulomatosis is a disease that has a wide spectrum of severity ranging from localized upper airway disease to acute multisystem disease involvement. The choice of therapy has traditionally been based on the degree of disease severity, with cyclophosphamide induction followed by less toxic maintenance therapy (eg, methotrexate, azathioprine, mycophenolate mofetil) for severe disease and methotrexate for induction and maintenance of less severe active disease.

These regimens have been proven to prolong survival and to induce remission in more than 85% of patients, but relapse occurs in 50% to 75% of patients and therapy is potentially toxic. As a result, other treatment options, particularly biologic agents, have been investigated.

Interfering with the pathway leading to granulomatous inflammation may represent a therapeutic strategy in Wegener’s granulomatosis. Information gleaned from other human diseases and murine models indicates that CD4+ T cells with the Th1 cytokine pattern play an important role in the initiation and maintenance of granuloma formation. The primacy of this cytokine pattern in Wegener’s granulomatosis has been supported by evidence gained from the laboratory.

Based on these data, therapies that interrupt TNF production generated initial excitement in Wegener’s granulomatosis. However, a clinical trial of 180 patients randomized to etanercept or placebo failed to support the use of this agent for the induction or maintenance of remission in patients with Wegener’s granulomatosis.7 There were six malignancies documented in patients receiving etanercept (none with placebo); all malignancies occurred in patients receiving concurrent cyclophosphamide. Although this occurred in a small population, it raises caution against the use of cyclophosphamide concurrently with any anti-TNF agent.

An open-label trial of infliximab in 32 patients with Wegener’s granulomatosis or microscopic polyangiitis achieved an 88% remission rate, but all patients were also receiving standard therapy concomitantly.9 The rate of relapse was 18%, the mortality rate was 6%, and 21% of patients’ experienced serious infections. In the absence of a sufficiently powered trial, the efficacy of other anti-TNF agents cannot be determined. Current evidence, however, does not support the use of any anti-TNF agent in Wegener’s granulomatosis.

Another avenue for intervention in Wegener’s granulomatosis is interference with T-cell activation. Abatacept is an agent that acts on this pathway, although there is currently no experience...
with it in the treatment of Wegener’s granulomatosis. A clinical trial of abatacept in the treatment of mild, relapsing Wegener’s granulomatosis by the Vasculitis Clinical Research Consortium is ongoing.

B-cell–depleting therapies were first explored based on the rationale of interfering with the production of antineutrophil cytoplasmic antibodies (ANCA). The role of ANCA in disease pathogenesis remains unclear, although bodies of evidence from the laboratory have supported a means through which ANCA-induced neutrophil-mediated vascular injury might occur. Two open-label studies of rituximab combined with glucocorticoids in patients with refractory ANCA-associated vasculitis resulted in undetectable levels of B cells and induction of remission in all patients. All patients remained in remission as long as B lymphocytes were depleted; 10% to 20% relapsed in association with a return of B cells and ANCA. Although ANCA production declined in all patients, it remained positive in up to 40% of patients, which raises the possibility that rituximab may exert its action through other mechanisms.

In addition to its potential efficacy, important questions that remain with B-cell–depleting therapy are whether its effects differ between organs and whether any disease impact occurs through ANCA or other B-cell–dependent mechanisms. These questions are being explored through the ongoing Rituximab in ANCA-associated Vasculitis (RA VE) trial.

**Giant cell arteritis**

Giant cell arteritis is the most common form of vasculitis, and it carries many phenotypes. It is most commonly associated with cranial disease (temporal arteritis) and a risk of loss of vision, but it also includes polymyalgia rheumatica and potential involvement of large vessels of the aorta and its branch vessels.

Treatment goals for giant cell arteritis are to prevent serious morbidity or mortality, reduce symptoms that affect quality of life, lessen disease relapse, and avoid therapeutic toxicity. Prednisone and aspirin remain the standard treatments (see Figure 3). Relapse, however, occurs in 75% to 90% of treated patients, and toxicity is common.

The introduction of biologic therapies offered great potential, particularly in the inhibition of TNF. However, Hoffman et al. found no difference between placebo and infliximab on relapse through week 22 in patients with newly diagnosed giant cell arteritis, all of whom also received standard doses of prednisone. More patients randomized to infliximab had infection than placebo recipients. This finding was replicated in a placebo-controlled study of infliximab in patients with newly diagnosed polymyalgia rheumatica, all of whom were also treated with prednisone. Intervention with T-cell activation, as with abatacept, is a potential therapeutic target in giant cell arteritis. The T cell is one cell that appears to play a role in the pathogenesis of giant cell arteritis. Activated T cells in the arterial wall secrete cytokines that initiate and maintain granulomatous inflammation. Granulomas in the vessel wall, formed by interferon-gamma-producing CD4+ T cells and macrophages, are a characteristic feature of giant cell arteritis.

**PsA: QOL Issues and the Role of Biologics**

Up to 30% of patients with psoriasis can have inflammatory joint disease or arthritis.

Features that distinguish PsA from RA are seronegativity and associated dactylitis and enthesitis. The arthritis in a patient with PsA can range from mild nondestructive disease to a severely rapid and destructive arthropathy. In addition to joint involvement, the tendons, ligaments, and bone are affected in PsA (see Table 1).

**Table 1. Psoriatic arthritis conditions**

<table>
<thead>
<tr>
<th>Musculoskeletal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Dactylitis/sausage digits</td>
<td></td>
</tr>
<tr>
<td>Enthesitis</td>
<td></td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td></td>
</tr>
<tr>
<td>Sacroiliitis/spondylitis</td>
<td></td>
</tr>
</tbody>
</table>

**Cutaneous and extraarticular manifestations**

<table>
<thead>
<tr>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail pitting</td>
</tr>
<tr>
<td>Onycholysis</td>
</tr>
<tr>
<td>Conjunctivitis/iritis/uveitis</td>
</tr>
</tbody>
</table>

**Radiographic characteristics**

| Erosions                       |
| Pencil-in-cup deformity        |
| Ray distribution               |
| Osteolysis                     |
| Nonmarginal asymmetric syndesmophytes |
| Asymmetric sacroiliitis        |

Novel applications are being used in various disease states, including PsA, to assess the impact of disease on QOL and to measure patient preferences associated with health-related QOL.

**Measuring QOL**

In public health and in medicine, the concept of health-related QOL refers to a person or group’s perceived physical and mental health over time. Tracking health-related QOL in different populations can identify subgroups with poor physical or mental health and can help guide interventions to improve their health. Quality of life has not been a standard outcome measure in the recent past in studies of biologic therapies. However, as the bar is being raised regarding how much treatment effect can be gained...
with biologic agents, an effort is being made to quantify more outcomes measures for patients suffering from PsA.

Health-related QOL is a measure of the effects of chronic illness with the goal of obtaining a better understanding of how an illness interferes with a person’s day-to-day life. Patients with arthritis have significantly worse QOL than those without arthritis; they report twice the number of unhealthy days and three times as many days with limitations in activity monthly. Scores on health-related QOL and life satisfaction questionnaires are similar between patients with RA and PsA despite greater peripheral joint damage, inflammation, and physical disability associated with RA. This suggests that the QOL impact of skin disease in patients with PsA is more profound than previously believed.

The Patient Reported Outcomes Measurement Information System (PROMIS) is a cooperative network of seven institutions and the National Institutions of Health that was designed to quantify patient-reported symptoms (eg, pain, fatigue, aspects of health-related QOL) in clinical practice across several disease states. Perceived changes in such symptoms is often the best way that patients can judge the effectiveness of treatments.

Instruments that measure health-related QOL must be valid, reliable, and responsive to change. Patient-recorded QOL outcomes scales can be general or disease-specific. Examples of general health measures are the SF-36, the Euro-QOL, the Nottingham Health Profile, and the Health Assessment Questionnaire (HAQ), which is a measure of disease activity and long-term disability. Instruments specific to PsA include the PsA QOL, the expanded HAQ (HAQ-SK), and the Psoriatic Arthritis Response Criteria (PsARC).

**Willfulness to pay as a measure of impact**

A novel technique to further extrapolate on the QOL issues is the concept of willfulness to pay. This is a method to measure the value of stated preferences in terms of dollars, with a higher willingness to pay associated with stronger preference. It is being used increasingly in health care to gauge the impact of a chronic disease on health-related QOL. Willingness to pay is able to have the patient take all the possible factors (education, severity of illness, income, beliefs) that are important to them and balance this in their ultimate decision for a health benefit or risk.

A recent study was done to validate this in a cohort of psoriatic arthritis patients. The impact of psoriasis on health-related QOL was measured in 59 patients with PsA using eight QOL domains: intimacy, physical comfort, social comfort, self-care, ability to work, ability to concentrate, ability to sleep, and emotional health. Nearly 90% of patients were willing to pay to fully restore physical function. Also, the emotional, sleep, and work domains were considered important to cure by a majority.

**References**

Benefits and Risks of Biologics in Inflammatory Bowel Disease: Critical Management Decisions

The treatment goals in inflammatory bowel disease (IBD) are to manage symptoms, which entails induction of remission (rapid control of symptoms) and maintenance of remission. Other goals are to change the natural history of the disease through endoscopic remission, thereby improving long-term outcomes; minimize complications from treatment; and reduce the need for surgeries and hospitalizations.

Prior to the era of biologic therapies, less than 40% of treated patients with Crohn’s disease achieved remission, and approximately one-third had high disease activity. Furthermore, toxicities associated with several classes of nonbiologic agents (e.g., corticosteroids, methotrexate) preclude their long-term use.

Four biologic agents have been approved for the treatment of Crohn’s disease:
- Infliximab, a chimeric mouse (25%)-human (75%) IgG1 monoclonal antibody;
- Adalimumab, a fully human IgG1 monoclonal antibody;
- Certolizumab pegol, a humanized Fab fragment of the anti-TNF antibody that is linked to two polyethylene glycol molecules;
- Natalizumab, a humanized antibody to alpha 4 beta 7 integrins.

Randomized controlled trials have shown that anti-TNF therapy is effective in patients for moderate to severe Crohn’s disease. In several trials, remission and maintenance of remission was achieved significantly more often in patients assigned to anti-TNF therapy (infliximab, adalimumab, and certolizumab) than in placebo recipients.1-5 The trials also showed significant improvement in maintenance of remission with biologic agents as well as lower rates of Crohn’s disease-related hospitalizations, consistent with an improvement in the natural history of the disease.

The potential mechanisms for secondary loss of response to anti-TNF therapy are the formation of neutralizing antibodies, increased clearance of biologic agents, and noninflammatory complications of the bowel.

About one-third of patients with Crohn’s disease treated with infliximab will require dose escalation.2 In patients with secondary failure to infliximab, response rates of about 80% are obtained with dose escalation, a rate similar to that with placebo. About one-third of patients who do not achieve remission with adalimumab at week 4 will need escalation from every other week to weekly therapy to achieve and maintain remission.6

In patients who initially responded to infliximab therapy but lost responsiveness, switching them to adalimumab achieved significant clinical response and remission rates compared with placebo.7 However, the absolute likelihood of response to a second anti-TNF agent is lower than the response in treatment-naïve patients.3,5

Loss of response to anti-TNF therapy should prompt an investigation to confirm ongoing active inflammation, as not all recurrent symptoms are caused by disease activity. If the presence of inflammation is documented, measurement of antibodies is warranted. Switching treatments within the anti-TNF class is reasonable if antibodies are present. Dose escalation is reasonable if antibodies and serum drug levels are absent. Switching to natalizumab is reasonable if antibodies are absent and serum drug levels are adequate.

Factors involved in the choice of therapy

Choosing between biologic therapies is complicated because different trial designs, patient populations, and definitions of response and remission prevent valid comparisons of results. Taking into consideration the heterogeneity in the definition of response, all clinical trials of TNF inhibitors have resulted in a fairly uniform response rate of approximately 60% at week 4.

With efficacy established for the biologic agents in the treatment of Crohn’s disease, attention shifts to selecting the best treatment and improving outcomes.

Risk of immunogenicity

Immunogenicity is a concern with the use of biologics. Factors that contribute to immunogenicity are the molecular sequence and structure of the agent, the treatment regimen (ongoing or episodic), and concomitant therapy. Episodic therapy with long intervals between infliximab infusions is associated with the formation of anti-infliximab antibodies (ATIs). The development of ATIs correlates with an increased risk of infusion reactions, lower serum concentrations of infliximab, and a shorter duration of response.1,8-10 The formation of ATIs is approximately halved by concomitant use of immunosuppressive agents.1,8-11 Therefore, it is now clear that azathioprine, methotrexate, or 6-mercaptopurine should be used concomitantly with infliximab, and that administering infliximab on a scheduled basis with the recommended induction regimen will reduce formation of ATIs.

Antibody formation is not unique to infliximab. In the treatment of patients with rheumatoid arthritis, anti-adalimumab antibodies developed in 1% of patients on methotrexate and 12% of patients not on methotrexate. In another trial, 8% of patients developed antibodies to certolizumab pegol and a similar proportion of patients form antibodies when treated with natalizumab.

“Step up” or “top down” strategies

Two competing strategies for the treatment of Crohn’s disease are the “step up” and “top down” strategies. The step up strategy is the traditional practice in which steroids are used for induction of disease remission; thiopurine or methotrexate is added for maintenance of remission. Once steroid dependence or failure is encountered, a biologic agent is added. The top down strategy starts with a combination of a thiopurine, methotrexate, and a biologic agent, with use of corticosteroids if loss of response occurs (see Figure 1).

A top down strategy starting with infliximab and azathioprine was superior to a step up strategy at inducing remission without corti-
costeroids and without bowel surgery in patients with Crohn’s disease diagnosed in the previous 4 years. Relapse happened later for patients who started with infliximab and azathioprine than in those who started on steroids. Serious adverse events were similar in each treatment group. The rate of pancreatitis was not significantly different between groups, and all cases of pancreatitis occurred in patients on azathioprine. The top down strategy was associated with a non-significant trend toward more eczema and rash.

**Selecting therapy**

The choice of biologic agent accounts for efficacy and toxicity as well as patient preference and the willingness to cooperate with treatment. Although efficacy in achieving and maintaining remission between TNF inhibitors appears similar in controlled clinical trials, deciphering toxicity in IBD is complicated by the use of concomitant medications, side effects that may be related to the disease itself, the under-recognition of adverse events during controlled trials and clinical practice, and the uncertain reliability of the information.

Three biologic agents — infliximab, natalizumab, and certolizumab — are infusion therapies. Adalimumab, in contrast, can be self-administered, and although it offers greater convenience, it also requires the patient to fill the prescription. The patient’s willingness to accept the potential adverse events in exchange for clinical benefits must also be considered in the choice of treatment. In a survey of patients with chronic active disease, greater risk acceptance correlated with greater symptom improvement (see Figure 2).

**The Role and Risks of Natalizumab in the Treatment of IBD**

Natalizumab may be considered for difficult-to-treat patients with Crohn’s disease. It is approved for treating moderately to severely active Crohn’s disease. The benefit-to-risk ratio of natalizumab appears favorable in appropriately selected patients. Contraindications include hypersensitivity (if severe), active infection, and a history of progressive multifocal leukoencephalopathy.

Natalizumab has been shown effective for induction and maintenance of remission, and it is steroid sparing. In patients in whom anti-TNF agents had failed, the remission rate was 17% with natalizumab versus 5% with placebo ($P < 0.05$). In two large clinical studies, the incidence of all-cause and Crohn’s disease-related hospitalizations was reduced significantly in the natalizumab group in treatment-naive patients and anti-TNF failures. Progressive multifocal leukoencephalopathy (PML) is an infectious disease caused by the JC virus. The infection is asymptomatic, occurs in childhood, and remains latent; however, immunosuppressive medications have been associated with reactivation of the virus. If not recognized early, PML is almost uniformly fatal.

Seven cases of PML have been confirmed among the 39,000 patients worldwide who have been treated with natalizumab, only one of whom was being treated for Crohn’s disease. This patient received eight doses of natalizumab, was taking azathioprine concurrently, and had a history of reduced white blood cell counts. Natalizumab distribution is restricted to pharmacies and infusion centers certified through the monitoring program developed in accordance with the US Food and Drug Administration. Figure 3 shows the timeline for natalizumab marketing approvals.

**The Potential Role for Biologic Agents in the Management of Nonalcoholic and Alcoholic Fatty Liver Disease**

Nonalcoholic fatty liver disease represents a wide spectrum of liver disease, ranging from steatosis (relatively benign fatty liver) to nonalcoholic steatohepatitis (NASH) and cirrhosis. Only a minority with nonalcoholic fatty liver progress to NASH, and few of those progress to cirrhosis. The histologic picture of alcoholic fatty liver disease is much the same as nonalcoholic fatty liver disease (accumulation of fat in liver cells, inflammation of the liver, necrosis of liver cells, and possibly fibrosis), but the progression from alcoholic liver disease to hepatitis and cirrhosis is much greater. Whereas about 1% of patients with nonalcoholic...
steatosis will progress over their lifetime to cirrhosis and liver-related death, alcoholic hepatitis will progress to cirrhosis and one-fifth will die from liver-related injury. However, the prevalence of nonalcoholic steatohepatitis is much higher than that for alcoholic hepatitis.

**Alcoholic fatty liver: The rationale for biologics**

The basis for the use of biologic agents in alcoholic fatty liver disease lies in the histology of liver injury. The Kupffer cell is the resident macrophage in the liver. These cells are the critical controllers of the stellate cell, which can cause scarring and cirrhosis when activated. Alcohol abuse increases the production of reactive oxygen species and endotoxemia, upregulating nuclear factor kappa beta to increase the production of TNF, leading to bacterial translocation and oxidative tissue injury.

Tumor necrosis factor signaling through activation of Kupffer cells is crucial to the development of hepatotoxicity. The liver is normally resistant to TNF, but Kupffer cells undergo priming and activation during alcoholic steatohepatitis to increase production of TNF and sensitization to TNF. Nearly all experimental models of liver disease are associated with elevated levels of plasma or tissue TNF.

The Kupffer cell is critical in activating the cytokine response in alcoholic liver disease. By inactivating Kupffer cells through the administration of gadolinium chloride, ethanol-induced increases in AST can be blunted. Fatty liver, inflammation, and fibrosis have been prevented by knocking out TNF-R1 and by administration of TNF-alpha antibodies.

**Clinical data with biologics in alcoholic fatty liver**

Etanercept and infliximab have been studied in alcoholic liver disease. A standard dose of infliximab results in reductions in ALT and total bilirubin, but mortality in severe alcoholic hepatitis was increased with the addition of infliximab to steroids compared with steroids alone.

In a placebo-controlled study of etanercept in patients with alcoholic hepatitis, six doses of etanercept over 30 days increased mortality significantly at 30 days but not at 60 days relative to placebo.

Pentoxifylline, an inhibitor of TNF synthesis, appears to be the most promising of the biologic agents in the treatment of alcoholic fatty liver disease. In addition to inhibiting cytokine synthesis, it decreases blood viscosity and improves renal microcirculation. In severe alcoholic hepatitis, pentoxifylline was associated with a significant 40% reduction in mortality compared with placebo. The difference in mortality occurred after 2 to 3 weeks of therapy and was due to a reduction in the development of hepatorenal syndrome.

**Nonalcoholic fatty liver disease: The rationale for biologics**

The basis for the use of biologic agents in nonalcoholic fatty liver disease lies in adipocyte production and release of cytokines as fat mass increases. In addition to TNF, the release of non-TNF cytokines, such as transdermal growth factor-beta and IL-8, has an important role in the genesis of nonalcoholic fatty liver disease.

When administered to animals on a methionine-choline deficient diet, anti-TNF therapy produced significant reductions in the percentage of steatotic cells, inflammation, necrotic focus, fibrosis, and activated stellate cells compared with placebo.

In experimental nonalcoholic fatty liver disease, infliximab decreased total liver fat and levels of TNF, IL-8, and other cytokines. Inhibition of TNF-alpha using pentoxifylline reduced ALT significantly with a reduction in insulin resistance in patients with nonalcoholic steatohepatitis.

**No current role for biologics**

Biologic agents have no proven value in alcoholic fatty liver disease, at least in the doses studied, and the safety data are concerning. In nonalcoholic fatty liver disease (NAFLD), their role is muted since lifelong therapy would be required unless patients lose a substantial amount of weight. Although invasive, the only therapy that interrupts the natural history of NAFLD is bariatric surgery.

**References**

16. Adachi Y, Bradford BU, Gao W, et al. Inactivation of Kupffer cells prevents early hepatic necrosis when activated. Alcohol abuse increases the production of TNF, leading to the resident macrophage in the liver. These cells are the critical controllers of the stellate cell, which can cause scarring and cirrhosis when activated. Alcohol abuse increases the production of reactive oxygen species and endotoxemia, upregulating nuclear factor kappa beta to increase the production of TNF, leading to bacterial translocation and oxidative tissue injury.

Tumor necrosis factor signaling through activation of Kupffer cells is crucial to the development of hepatotoxicity. The liver is normally resistant to TNF, but Kupffer cells undergo priming and activation during alcoholic steatohepatitis to increase production of TNF and sensitization to TNF. Nearly all experimental models of liver disease are associated with elevated levels of plasma or tissue TNF.

The Kupffer cell is critical in activating the cytokine response in alcoholic liver disease. By inactivating Kupffer cells through the administration of gadolinium chloride, ethanol-induced increases in AST can be blunted. Fatty liver, inflammation, and fibrosis have been prevented by knocking out TNF-R1 and by administration of TNF-alpha antibodies.

**Clinical data with biologics in alcoholic fatty liver**

Etanercept and infliximab have been studied in alcoholic liver disease. A standard dose of in infliximab results in reductions in ALT and total bilirubin, but mortality in severe alcoholic hepatitis was increased with the addition of infliximab to steroids compared with steroids alone.

In a placebo-controlled study of etanercept in patients with alcoholic hepatitis, six doses of etanercept over 30 days increased mortality significantly at 30 days but not at 60 days relative to placebo.

Pentoxifylline, an inhibitor of TNF synthesis, appears to be the most promising of the biologic agents in the treatment of alcoholic fatty liver disease. In addition to inhibiting cytokine synthesis, it decreases blood viscosity and improves renal microcirculation. In severe alcoholic hepatitis, pentoxifylline was associated with a significant 40% reduction in mortality compared with placebo. The difference in mortality occurred after 2 to 3 weeks of therapy and was due to a reduction in the development of hepatorenal syndrome.

**Nonalcoholic fatty liver disease: The rationale for biologics**

The basis for the use of biologic agents in nonalcoholic fatty liver disease lies in adipocyte production and release of cytokines as fat mass increases. In addition to TNF, the release of non-TNF cytokines, such as transdermal growth factor-beta and IL-8, has an important role in the genesis of nonalcoholic fatty liver disease.

When administered to animals on a methionine-choline deficient diet, anti-TNF therapy produced significant reductions in the percentage of steatotic cells, inflammation, necrotic focus, fibrosis, and activated stellate cells compared with placebo.

In experimental nonalcoholic fatty liver disease, infliximab decreased total liver fat and levels of TNF, IL-8, and other cytokines. Inhibition of TNF-alpha using pentoxifylline reduced ALT significantly with a reduction in insulin resistance in patients with nonalcoholic steatohepatitis.
Immunology of Biologic Agents for Nonimmunologists

The immune system is an integrated system composed of the innate immune system and the adaptive immune system. Even though they are distinct systems, they are intimately linked. The innate immune response can be defined by several principles:

- It has no memory, so when assaulted, it responds as it did to previous assaults.
- The response occurs early and rapidly through quick mobilization of its cellular elements — macrophages, polymorphonuclear leukocytes, dendritic cells, and the soluble components that complement acute-phase proteins.
- It operates by expressing the germ-line encoded receptors.
- It does not recognize every antigen; instead, it recognizes highly conserved structures.

The role of the immune system is to protect against outside invasion. It does this by detecting danger in the form of infection, chemical insults (eg, environmental and self-inflicted toxins), and physical damage (eg, tissue injury, cell death).

In the case of an insult that punctures the skin, the first layer of defense is the epithelium, which contains molecules (eg, beta defensins) that have antibacterial properties. Bacteria also reside in the subcutaneous space for insults that penetrate the epithelium. Dendritic cells in the epithelium (Langerhans cells in the epidermis) have a system of pattern recognition receptors, such as pathogen-associated molecular pattern (PAMP) receptors. When stimulated, dendritic cells secrete cytokines (eg, tumor necrosis factor, IL-1, IL-6). These cytokines serve as an early warning signal to the immune system. Resident tissue macrophages respond to this danger signal by accumulating at the injury site. The cytokines prepare the endothelium to allow the invasion of more inflammatory cells by upregulating the endothelium’s adhesion molecules (selectins and integrins). They further upregulate the microbicidal activity of the resident phagocytic cells to allow them to kill the invader bacteria. This cytokine response occurs within a matter of hours, producing inflammation and erythema.

If the innate immune system fails, it must recruit additional defenses, such as natural killer cells (see Figure 1). The acute phase response is an innate defense that involves increases in the production of acute-phase proteins in the serum, one being C-reactive proteins, which have the ability to bind to certain bacterial recognition agents and activate fibrinogen, haptoglobin, and serum amyloid A, among others.

If infection persists despite the efforts of the innate immune system, elements of the adaptive immune system are recruited. Remaining bacteria migrate to the regional lymph nodes, where they interact with the adaptive immune system.

The adaptive immune response is a delayed response to a specific antigen, demonstrating the features of specificity and memory, two elements lacking in innate immunity. The two types of adaptive immune response are cell-mediated and humoral. Whenever adaptive immunity is elicited, it creates cells that have immunologic memory to react quickly should the invader attack again. Antigens are taken up by macrophages and presented to helper T cells.

Both antibodies and T cells have unique surface receptors. Each cell bears its own type of receptor that responds to a different type of antigen. When an antigen enters a cell, transport molecules called major histocompatibility complex (MHC) molecules within the cell attach themselves to the cell’s surface, where they present the antigen to helper T cells so that the T cell can bind to the presented antigen. A second costimulatory signal is essential to activate the T cell. These costimulatory signals are members of the B7 family and are expressed constitutively by T cells and react to ligands on antigen-presenting cells.

---

<table>
<thead>
<tr>
<th>Innate Immunity (immediate: 0-4 hours)</th>
<th>Recruitment by preformed, nonspecific effectors</th>
<th>Removal of infectious agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early induced response (early: 4-96 hours)</td>
<td>Recruitment of effector cells</td>
<td>Recognition, activation of effector cells</td>
</tr>
<tr>
<td>Adaptive immune response</td>
<td>Transport of antigen to naive</td>
<td>Recognition by naive</td>
</tr>
</tbody>
</table>
After the antigen has migrated to the regional lymph nodes and has found the appropriate helper T cells, which have become activated, the final step in the adaptive response is deployment. One limb of the activated T cell forms active effector cells, which recognize cytokines and chemokines emanating from the area of infection, and another limb of the activated T cells turns into memory cells, which recognize the infection should it recur.

At the same time, B cells that have differentiated in the bone marrow migrate to the lymph nodes and search for the antigens that have migrated from the skin. On the surface of every B cell are Y-shaped antibodies called immunoglobulins (IgG, IgM, IgD, IgA, and IgE) that have the capacity to recognize larger pieces of the antigen. This is part of the humoral immune response. The antibody binds to the antigen at the arms of the “Y.” Activated B cells secrete cytokines such as macrophages, T cells, and dendritic cells. These cytokines and proteins cause inflammation and joint destruction in the patient with rheumatoid arthritis (RA). An important pathogenic inflammatory cytokine produced directly by activated B cells is IL-6, which has a number of biological activities. Interleukin-6 is found in the highest concentration of all the cytokines released by B cells. It is active in many tissues including those of the liver, bone, immune cells, fat, muscle, and kidney.

## Role of the Allied Health Professional in use of Biologic Therapies for RA

Each limb of the immune system is a potential target for immune-based therapies. The infusible biologic agents with indications in rheumatology are infliximab, abatacept, and rituximab (see Table 1).

### Table 1. Indications for TNF inhibitors

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>Yes</td>
<td>In trials</td>
<td>Yes</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>No</td>
<td>Yes</td>
<td>In trials</td>
</tr>
</tbody>
</table>

### Infliximab

Infliximab is an antibody that neutralizes the biological activity of TNF-alpha by binding to its soluble and transmembrane forms and inhibiting TNF-alpha binding.

### Abatacept

Abatacept is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7. Abatacept is a selective costimulation modulator as it inhibits the costimulation of T cells.

Ordinarily, full T cell activation requires the following:

1) Binding of the T-cell receptor to the antigen-MHC complex on the APC, and
2) A costimulatory signal provided by the binding of the T cell’s CD28 protein to the B7 protein on the APC.

Abatacept, which contains a high-affinity binding site for B7, works by binding to the B7 protein on antigen-presenting cells and preventing them from delivering the costimulatory signal to T cells, thus preventing the full activation of T cells.

### Rituximab

Rituximab is a chimeric monoclonal antibody against the protein CD20, which is widely expressed on B cells, from early pre-B cells to later in differentiation. Rituximab destroys B lymphocytes, and thus, it is used to treat diseases that are characterized by having too many B cells, overactive B cells, or dysfunctional B cells.

### Contraindications to the use of biologic disease-modifying antirheumatic drugs

Active infection and pneumonitis are contraindications to the use of biologics. Others are prior lymphoproliferative disease diagnosed and/or treated in the past 5 years, moderate to severe heart failure (New York Heart Association Class III-IV), acute hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (or chronic HBV or HCV infection for those with significant liver injury), and multiple sclerosis or demyelinating disorders.

In patients scheduled for surgery, the American College of Rheumatology recommends holding the medication for 1 week before and after surgery. An attempt should be made to schedule the surgery in the middle of the infusion cycle (eg, week 4 for those on infliximab).

### Considerations before starting anti-TNF therapy

#### Hepatitis screening

Rare reactivation of hepatitis B has occurred in chronic carriers of the virus; evaluate all patients prior to initiation and during treatment in patients at risk for hepatitis B infection.

#### Malignancy screening

Confirm that appropriate cancer screening is complete. Use of anti-TNF therapies may affect defenses against malignancies; the impact on the development and course of malignancies is not fully defined. An increased risk of lymphoma has been noted in clinical trials.

#### Tuberculosis

Data have associated TNF inhibitors with tuberculosis (TB) reactivation, so patients should be evaluated for latent TB infection with a tuberculin skin test before starting therapy. If results are positive, TB therapy should be initiated before administering TNF inhibitors. Some patients who test negative prior to therapy will develop active TB infection; therefore, it is imperative to monitor for TB infection in all patients.
Infections
Serious and potentially fatal infections have been reported including bacterial sepsis and tuberculosis. Patients should be assessed for active infection prior to every infusion.

Vaccination update
All vaccines should be brought up to date before starting anti-TNF therapy. Immunosuppressed patients should not receive live vaccines.

Pregnancy test
Anti-TNF therapy has not been studied in pregnancy, so use of these therapies during pregnancy should be avoided.

Nervous system disorders (demyelinating disease)
Demyelinating disease, such as multiple sclerosis, seizures, or inflammation of the nerves, have occurred in rare cases. Symptoms include numbness or tingling, problems with vision, weakness in arms and legs, and dizziness. Patients should be screened for these types of symptoms prior to beginning therapy.

Congestive heart failure (CHF)
An echocardiogram or examination to rule out signs and symptoms of CHF should be performed prior to initiating anti-TNF therapy. Administration of anti-TNF agents has been linked to worsening or new onset CHF.

Additional considerations
Specific TNF inhibitors have additional factors to consider before starting therapy:
- Abatacept should not be used in combination with anakinra or TNF-blocking agents.
- Baseline measures of immunoglobulins are recommended because rituximab can deplete IgM and sometimes IgG.
- Although evidence does not indicated an increased frequency of TB in patients with lymphoma treated with rituximab, it is often used concomitantly with methotrexate, so TB screening should be up to date.

Monitoring therapy with biologic agents
Abatacept
Six infusions of abatacept (5 months of treatment) may be required before its full effect is observed. A joint count and health assessment questionnaire can help measure efficacy without the need for a blood draw. Because patients must present to the office every 4 weeks for abatacept treatments, it provides an opportunity to assess for new or subtle symptoms.

Monitoring is recommended approximately every 3 months. This frequency allows clinicians to obtain a disease activity score with three variables (DAS28-3), which requires a sedimentation rate evaluation.

Rituximab
Monitoring patients on rituximab is unlike monitoring patients on other biologics. Following rituximab infusion, 90% of the patient’s B cells are depleted, although patients may not report an improvement in RA symptoms for 6 weeks.

Management of Infusion-Related Issues
The ability to generate an adverse reaction to infusible biologic agents depends in part on the amount of antihuman protein contained. The immune system reacts to these antibodies as a foreign antigen and creates its own antibodies. Adverse effects are classified in three categories (see Figure 2).

Infusion reactions to biologics can be either acute (occurring within 24 hours, most commonly 10 minutes to 4 hours) or delayed (occurring after 24 hours, most commonly 5 to 7 days). Acute reactions are classified based on their severity (mild to moderate or severe). Mild to moderate reactions can consist of a change in systolic blood pressure (SBP) of less than 20 mm Hg, headache, dizziness, pruritus, nausea, and palpitations. Severe reactions are those causing a change in systolic BP of more than 40 mm Hg, flushing, fever, and shortness of breath with wheezing.

Delayed reactions mimic serum sickness and are often associated with joint pain, mild fever, headache, myalgia, and skin rash.

Infusion reactions may have a hypersensitivity basis, but these are rare. The clinical manifestations of anaphylactic acute infusion reactions include bronchospasm and urticaria. Without these symptoms, the reaction is probably not allergic.

Infliximab
In five studies of patients with RA, infusion reactions to infliximab occurred in 15% to 20% of patients and in 3% of infusions.1-5 Most reactions were mild with only 0.5% severe. Approximately 0.4% of reactions were delayed.2 Reactions were similar for trials in patients with Crohn’s disease (Table 2).6-10

Management of acute infusion reactions
The severity of the reaction guides the management strategies for acute infliximab infusion reactions. Slowing the rate of infusion decreases the opportunity for immune complexes to form. With hemodynamic changes (eg, hypotension), stopping the infusion may be necessary. Medications such as acetaminophen (for fever) and diphenhydramine (for pruritus or mild allergy) can be used on a symptomatic basis.
For more severe reactions, methylprednisolone or hydrocortisone have been recommended. For anaphylactic reactions, epinephrine is advised.

Monitoring vital signs is important. The frequency of monitoring depends on the severity of the reaction, which can range from every 10 minutes with mild reactions to every 2 minutes with very severe reactions.

Once the reaction is stable, the infusion can be reattempted at a lower rate, following treatment with IV or oral diphenhydramine, 25 to 50 mg, and oral acetaminophen, 650 mg. Start with an infliximab test dose of 10 mL/hr for 15 minutes then gradually increase it to 125 mL/hr over 3 hours. A protocol has been developed for effectively managing infliximab infusion reactions.11

<table>
<thead>
<tr>
<th>Study, disease</th>
<th>Pts</th>
<th>Infusions</th>
<th>Infusion reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maini1</td>
<td>340</td>
<td>100%</td>
<td>20% pts 10%</td>
</tr>
<tr>
<td>Maini2</td>
<td>259</td>
<td>100%</td>
<td>3% 2%</td>
</tr>
<tr>
<td>St Clair4</td>
<td>751</td>
<td>100%</td>
<td>15%-20% pts 0</td>
</tr>
<tr>
<td>Westhoven5</td>
<td>721</td>
<td>100%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kugathasan6</td>
<td>86</td>
<td>100%</td>
<td>24% pts</td>
</tr>
<tr>
<td>Baert7</td>
<td>125</td>
<td>100%</td>
<td>487 27% pts</td>
</tr>
<tr>
<td>Cheifetz8</td>
<td>165</td>
<td>100%</td>
<td>479 6.1%</td>
</tr>
<tr>
<td>Farrell9</td>
<td>53</td>
<td>100%</td>
<td>199 28% pts</td>
</tr>
<tr>
<td>Hanauer10</td>
<td>573</td>
<td>100%</td>
<td>2863 3%-6%</td>
</tr>
</tbody>
</table>

**Premedication: Evidence for and against**

Preinfusion treatment with antihistamines or acetaminophen to reduce the likelihood of infusion reactions is controversial. Diphenhydramine pretreatment provided no benefit to patients with previous infliximab infusion reactions.12

Investigators developed a protocol for patients with prior severe infusion reactions in which patients were treated with oral diphenhydramine and oral acetaminophen 90 minutes before the infusion, in addition to oral prednisone (or alternatively IV hydrocortisone or IV methylprednisolone) 20 minutes before the infusion.13 This protocol allowed successful retreatment of three of four patients with severe acute reactions and all patients with prior mild or moderate acute reactions.

**Glucocorticoid pretreatment**

Glucocorticoid pretreatment may be reasonable in RA patients with prior moderate to severe infliximab infusion reactions or comorbidities, or when changing to another infusable biologic is not an option.

Preinfusion treatment with IV hydrocortisone has been shown to reduce the development of antibodies to infliximab and the incidence of subsequent infusion reactions.14 Use of daily low-dose glucocorticoids has been found by some to be associated with fewer treatment-limiting immediate infusion reactions to infliximab but should not be used solely for this purpose.15 Pre-infusion treatment with IV betamethasone, however, was not found to reduce the risk of infliximab infusion reactions.16

**Anti-infliximab antibodies**

Infliximab infusion reactions are often attributed to anti-infliximab antibodies (ATIs). Their true incidence is unknown because measurement of ATIs depends on analytical technique, timing of sampling, dosing regimen, circulating drug, and concomitant therapy.

Development of ATIs has been associated with a greater risk of infusion reactions and tends to limit the long-term efficacy of infliximab.17 Hanauer et al18 showed that infusion reactions occurred in 16% of patients who were positive for ATIs compared with 8% who were negative. Higher titers of ATIs have also been associated with a greater frequency of infusion reactions.

Anti-infliximab antibodies can develop at any time but are more likely to occur with sporadic infusions. Maser et al19 found that compared with scheduled infusions of infliximab, episodic infusions were associated with a greater rate of ATIs (39% vs 16%; \( P = 0.036 \)) and infusion reactions (50% vs 21%; \( P = 0.018 \)). The development of ATIs was reduced only by scheduled maintenance treatment. Patients receiving other immunosuppressive therapy (eg, methotrexate) are much less likely to develop ATIs.19-23

Even when treatment is optimized to avoid ATIs through scheduled maintenance or by concomitant immunomodulator therapy, approximately one-half of patients still need dose adjustment to treat recurrent symptoms and about one-fifth lose response.

**Rituximab**

Rituximab infusion reactions are easily managed medically with acetaminophen and diphenhydramine before the first administered dose of rituximab. Additional doses of acetaminophen, hydrocortisone, and diphenhydramine can be used if fever or any type of bronchospastic symptom occurs. If rigors occur, they can be managed with meperidine. Most symptoms such as bronchospasm, rigor, fever, and hypotension will resolve if treatment is delayed for 30 minutes after additional medications.

If a side effect occurs, recommendations are to stop the infusion for approximately 30 minutes, add IV saline, then resume the infusion at a rate one step slower than the rate at the time of the reaction. If the reaction abates, slowly increase the rate.

Emery et al24 showed that premedication with IV glucocorticoids significantly reduced both the incidence and severity of acute infusion reactions in rituximab recipients.

**Mechanism is multifactorial**

Antichimeric antibodies are very rarely encountered in rituximab recipients. Rather, the mechanism of rituximab infusion reactions appears to be multifactorial. A cytokine release syndrome has been described in which increases in IL-6 and TNF-alpha have been documented in patients with non-Hodgkin’s lymphoma and chronic lymphocytic leukemia who have been treated with rituximab.25 Hypersensitivity reactions are also possible. In patients with Hodgkin’s lymphoma, some patients have developed tumor lysis syndrome.
Abatacept

Abatacept is a human fusion protein that has the ability to prevent the costimulation of T cells. The FDA classifies abatacept infusion reactions as peri-infusional (within 24 hours) and acute infusion events (within the first hour). The incidence of peri-infusional reactions is 22.8% and the incidence of acute infusion reactions is 8.9%. Treatment discontinuation due to infusion reactions is 0.6%. Most abatacept infusion reactions are mild to moderate in severity. The most common effects are dizziness, headaches, and nausea.

**Uncertain mechanism**

The mechanism of abatacept infusion reactions is uncertain. The immunogenicity potential is very low: antiabatacept antibodies have been observed in only 1.7% of infusions, with antibody titers being slightly higher with missed doses or long intervals between infusions.

**References**


