Safety and Efficacy of the Biologic Response Modifiers

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The treatment of rheumatoid arthritis (RA) was revolutionized in the late 1990s when biologic response modifiers (BRMs) were introduced into clinical practice. BRMs differ from other disease-modifying treatments because, as their name suggests, they modify the body's normal immune response by interfering with substances that trigger inflammation, the process at the center of RA. Unlike previous anti-inflammatory agents, however, BRMs grew out of new techniques that enabled drug developers to isolate the primary inflammatory mediators of RA and engineer specific, targeted blockers.

BRMs can be categorized into 4 general groups based on mechanism of action: (1) the tumor necrosis factor–alpha (TNF-α) inhibitors (adalimumab, etanercept, and infliximab); (2) the interleukin-1 (IL-1) inhibitor (anakinra); (3) the anti-CD20 antibody (rituximab); and (4) the selective T-cell costimulation modulator (abatacept) (Table I). Although some of these drugs have demonstrated significant benefits over the traditional disease-modifying antirheumatic drugs (DMARDs), concerns over their long-term efficacy and safety remain.[1]

TNF-α INHIBITION

TNF-α inhibitors are indicated for the treatment of active RA, usually after a traditional DMARD (usually methotrexate) has proven insufficient. In addition, they have been approved for the treatment of psoriatic arthritis and ankylosing spondylitis.[2-4] Adalimumab and etanercept are delivered by subcutaneous (SC) injection; infliximab is administered as an intravenous (IV) infusion.[5]

Infliximab is approved for use with methotrexate in RA. Both adalimumab and etanercept have been approved as monotherapy for RA and may be added to or replace preexisting DMARD therapy. Either can be used in methotrexate-naive patients. Most randomized, controlled trials, however, suggest that therapy combining a TNF-α inhibitor with methotrexate produces better clinical responses than TNF-α inhibitor monotherapy.[5]

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Adalimumab

Adalimumab monotherapy has demonstrated significant, sustained RA improvement in patients for whom traditional DMARD therapy has failed.[6] In a 26-week trial in which 544 patients were randomly assigned to receive adalimumab monotherapy at dosages of 20 mg every other week, 20 mg weekly, 40 mg every other week, or 40 mg weekly, response rates were significantly better than placebo for all dosing regimens.[6] At trial's end, the various dosing regimens, respectively, produced American College of Rheumatology (ACR) 20 response rates of 36%, 39%, 46%, and 53%, compared with 19% for placebo; ACR 50 response rates of 19%, 21%, 22%, and 35%, compared with 8% for placebo; and ACR 70 response rates of 9%, 10%, 12%, and 18%, compared with 2% for placebo.[6]

Over the course of the study, 12% of adalimumab-treated patients tested positive for antibodies to the drug, though positivity did not appear to affect the pattern or frequency of adverse events.[6] In another study, patients treated with adalimumab and concomitant methotrexate had a lower rate of antibody development than patients treated with adalimumab monotherapy (1% versus 12%).[7]

Adalimumab has proven more effective when used in combination with methotrexate than when used as monotherapy. The 2-year, multicenter, randomized, double-blind premier study found that the 2 treatments combined were clinically and radiographically superior to either treatment alone.[8] After 1 year of treatment, the primary end point of the study, an ACR 50 response rate, was achieved by 62% of the patients receiving combination therapy, compared with 41% receiving adalimumab monotherapy and 46%

receiving methotrexate monotherapy. At the end of year 2, the ACR 50 response was sustained in the combination treatment group and remained statistically superior to responses in either monotherapy treatment arm.

Etanercept

Etanercept has been shown to be effective compared with placebo in terms of ACR response rates.[9] In a 6-month, randomized, controlled trial involving 234 subjects, the 25-mg dose resulted in an ACR 20 response rate of 59%, compared with 11% in the placebo group, and an ACR 50 response rate of 40%, compared with 5% in the placebo group.[9] Non-neutralizing antibodies to etanercept developed in 1 patient (in the 10-mg group) in this study[9] and in roughly 3% of those receiving etanercept in a study involving 632 patients treated with either oral methotrexate or SC etanercept, 10 or 25 mg.[10]

The multicenter Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) demonstrated the benefits of combination therapy with etanercept and methotrexate over either agent alone. In this double-blind, randomized, controlled trial, 686 patients with RA were randomly assigned to receive treatment with etanercept (25 mg twice weekly), or methotrexate (up to 20 mg/wk), or a combination of etanercept and methotrexate.[11] After 3 years, not only were ACR 20, ACR 50, and ACR 70 response rates significantly higher with combination therapy than with either drug alone, but compared with either monotherapy, combination therapy was associated with significant improvement in disability. (Table II).[12]

A significantly higher proportion of patients receiving combination therapy completed 3 years of the study compared with those receiving either monotherapy (57% versus 48% and 39% of the etanercept and methotrexate groups, respectively). Discontinuations due to adverse events were not significantly different among the 3 treatment groups.[12]

Infliximab

At dosages of 3 or 10 mg/kg every 4 or 8 weeks, infliximab combined with methotrexate was more effective than methotrexate plus placebo in a 54-week study of 428 patients with active RA.[13] The ACR 20 response rates ranged from 42% (with 3 mg/kg every 8 weeks) to 59% (achieved both with 10 mg/kg every 8 weeks and 10 mg/kg every 4 weeks). The ACR 50 response rate in the group receiving 3 mg/kg every 8 weeks (21%) was significantly lower than those in the groups receiving 10 mg/kg every 8 weeks or every 4 weeks (39% and 38%, respectively).[13] A follow-up study found that infliximab combined with methotrexate inhibits the progression of structural damage in patients with early RA and may provide long-term benefits.[14]

Following completion of the study, antibodies to infliximab were detected in roughly 9% of analyzable blood samples, distributed across all treatment groups.[15] At doses lower than 3 mg/kg, antibodies have been observed in roughly 50% of treated patients.[16]

Adverse Events

Serious infections, malignancies, and injection site or infusion reactions have been observed with all 3 TNF-α inhibitors.[11,17] In addition, all 3 have been associated with at least some instances of demyelination, autoimmune disease, deleterious effects on patients with heart failure, liver disease, and sepsis.[18]

Postmarketing surveillance has revealed that at least 70 of 147,000 patients who received infliximab treatment for RA or Crohn disease developed tuberculosis (TB) after treatment. Of these patients, 56% had extrapulmonary disease and 24% had disseminated disease.[17] Of the estimated 102,000 patients who have been treated with etanercept, 9 have developed TB.[17] Occurrence of TB was observed early in the clinical development of adalimumab, which prompted the institution of TB screening prior to patient enrollment in clinical trials.[11] In 2006, 34 cases of TB associated with adalimumab treatment had been reported, and an estimated 10,050 patients had been treated with the drug.[19] Product labeling for infliximab and adalimumab now recommends screening for latent TB before initiating therapy. It is commonly recommended that such screening precede the initiation of treatment with etanercept as well.[17] Similarly, TNF-α inhibitors should not be used in patients with hepatitis B infection, as viral reactivation is possible.[5]

Opportunistic infections (including histoplasmosis, listeriosis, coccidioidomycosis, and *Pneumocystis carinii* pneumonia) and nonopportunistic infections have been associated with TNF-α inhibitors.[17,18] Clinicians are advised to be on the alert for these serious potential complications of TNF-α inhibitor therapy.

A greater number of lymphomas have been observed among patients with RA using TNF-α inhibitors than among patients in control groups.[2-4] There is also some evidence that TNF-α inhibitor therapy raises the risk of lung cancer among smokers and patients with chronic obstructive pulmonary disease.[5] Three-year data from the TEMPO trial, however, showed no significant difference in the number of malignancies reported within the 3 arms of the study, and no cases of lymphoma were reported.[20]

Mild to moderate injection site reactions have occurred with the subcutaneously administered TNF-α inhibitors, adalimumab and etanercept. The intravenously infused infliximab has been associated with infusion reaction, though less commonly.[5]

Since TNF-α antagonists, regardless of dose, have been shown to exacerbate multiple sclerosis,[21] physicians are reluctant to prescribe these drugs to patients with RA and comorbid demyelinating syndromes. A small number of neurologic events suggestive of demyelination have occurred during TNF-α inhibitor therapy and been

Table I. BRMs Currently Approved for RA Treatment

Mechanism of Action	Drug	Approved use	Precautions
Anti-CD20 action	Rituximab	Monotherapy for active RA with inadequate response to TNF-α inhibitors, or supplemental RA therapy for use with methotrexate	Infusion reactions are common. Safety with TB infection is unknown. Vaccinations for pneumonia and influenza prior to administration. Associated with progressive multifocal leukoencephalopathy and hepatitis B reactivation with fulminant hepatitis.
IL-1 inhibition	Anakinra	Monotherapy for active RA when traditional DMARD therapy has failed, or supplemental RA therapy for use with traditional DMARDs other than TNF-α inhibitors	Injection-site reaction is not uncommon. Associated adverse events include serious infection. Safety in patients with lymphoma or other malignancies has not been established.
Selective T-cell costimulation modulation	Abatacept	Treatment of active RA with inadequate response to traditional DMARD or TNF-α inhibitor therapy. Use as monotherapy or in combination with a traditional DMARD (not any TNF-α or IL-1 inhibitor).	Use with other BRMs could elevate risk of infection. TB screening prior to initiating therapy is recommended.
TNF-α inhibition	Adalimumab Etanercept	Monotherapy for active RA or supplemental RA therapy for use with traditional DMARD	May develop antidrug antibodies. Associated adverse events include infection, malignancy, and injection site or infusion reactions. Demyelination, autoimmune disease, and worsening heart failure have been reported.
	Infliximab	Supplemental RA therapy to be used with methotrexate	

RA = rheumatoid arthritis; TNF-α = tumor necrosis factor alpha; TB= tuberculosis; IL-1 = interleukin-1; DMARD = disease-modifying antirheumatic drug; BRMs = biologic response modifiers.

reported to the Adverse Events Reporting System of the US Food and Drug Administration (FDA).[5] These reports were associated more often with etanercept than with infliximab, and all partially or completely resolved upon drug discontinuation.[5] Likewise, some patients receiving TNF-α inhibitor therapy have developed lupus-like autoimmune syndromes, which required that therapy be stopped.[5]

Infliximab at doses of 10 mg/kg is associated with worsening heart failure and mortality, particularly in patients with moderate to severe heart failure (New York Heart Association class III-IV). Although there is little evidence that infliximab 5 mg/kg or the other TNF-α inhibitors exacerbate heart failure, controlled studies of these agents tend to exclude patients with heart failure.[5]

IL-1 INHIBITION

Anakinra is indicated for the treatment of active RA in patients for whom traditional DMARD therapy has proven insufficient. It can be used alone or in combination with DMARDs other than TNF-α inhibitors.[22] Anakinra is supplied in single-use, prefilled syringes containing 0.67 mL (100 mg) of the drug and administered daily by SC injection.[22]

Anakinra has been shown to produce significant improvement in symptoms, signs, and laboratory parameters within 16 weeks and to slow radiographic progression in RA.[5] In a multicenter, double-blind, randomized, controlled trial involving 906 patients with active RA, the addition of anakinra to a stable methotrexate regimen produced significant improvements over placebo.[23] The patients had been using methotrexate for at least 6 months at dosages ranging from 10 to 25 mg. An initial analysis of the first 501 patients who completed 24 weeks of the trial showed that those receiving anakinra achieved ACR 20, ACR 50, and ACR 70 response rates of 38%, 17%, and 6%, respectively, compared with 22%, 8%, and 2% in the placebo group. The most frequently reported adverse event was injection site reaction.[23]

Like the TNF-α inhibitors, anakinra is associated with serious infection, though it does not appear to be associated with increased incidence of TB.[5] Its safety in patients with lymphoma or other malignancies has not been established.[5] It has been studied as a treatment for patients with severe

Table II. Key Efficacy Findings in the Tempo Trial: Three-Year Data[12]

Treatment	ACR 20 (%)	ACR 50 (%)	ACR 70 (%)	DAS (Mean)	DAS 28 (% remission)	HAQ (Mean % Improvement)	CRP (Mean % Improvement)
Etanercept	72	46	24	3	21	37	50
Methotrexate	68	43	22	3	19	33	41
Combination	85	67	49	2	40	56	72

TEMPO = Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; ACR = American College of Rheumatology response rates; DAS = disease activity score; DAS 28 = 28-joint disease activity score; HAQ = Health Assessment Questionnaire; CRP = C-reactive protein.
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lupus arthritis, and preliminary case studies suggest that it is well tolerated and may lead to clinical and serologic improvement in such patients.[24]

ANTI-CD20 THERAPY

The FDA has approved rituximab for the treatment of RA in patients who have had an inadequate response to TNF-α inhibitors.[25] It can be used alone or in combination with methotrexate.[5] Rituximab is administered as two 1000-mg IV infusions separated by 2 weeks. Methylprednisolone 100 mg IV or its equivalent is administered 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.[5,25]

In a multicenter, double-blind, controlled trial, 520 patients with active RA and an inadequate response to 1 or more TNF-α inhibitors were randomly assigned to receive background methotrexate with either IV rituximab or placebo.[26] At 24 weeks, significantly more rituximab-treated patients than placebo-treated patients demonstrated ACR 20 response rates ACR 50 response rates and ACR 70 response rates. Although rituximab depleted peripheral CD20 B cells, mean immunoglobulin levels remained within normal ranges.[26]

Most adverse events were mild or moderate in severity and fewer than 40% in both placebo and treatment groups were determined to be related to the study treatment. In fact, more patients receiving placebo than receiving rituximab experienced serious adverse events. There were no deaths recorded during the 24-week double-blind portion of the study.[26]

An earlier randomized, double-blind, controlled trial involving 465 patients with active RA had found that rituximab was effective and well tolerated when added to methotrexate therapy independent of concomitant glucocorticoid therapy, though the latter improved tolerance of the first rituximab infusion.[27]

The adverse event most frequently associated with rituximab is infusion reaction, which usually occurs with the first infusion (35%) and subsides with the second (10%). The risk of activating latent TB infection with rituximab is unknown. Since rituximab depletes B cells, patients should be vaccinated for pneumonia and influenza prior to its use.[5]

In February 2006, the labeling for rituximab was updated to include reports of serious viral infection, including progressive multifocal leukoencephalopathy (PML), associated with use of the drug by patients with cancer. The FDA has also received reports of 2 deaths from PML in patients being treated with rituximab for systemic lupus erythematosus (an off-label use of the drug).[28] Hepatitis B reactivation with fulminant hepatitis has also been reported in patients receiving rituximab.[25]

SELECTIVE T-CELL COSTIMULATION MODULATION

To date, the only selective costimulation modulator to be approved in the United States is abatacept, which is indicated for the treatment of active RA in patients who have had an inadequate response to traditional DMARD or TNF-α inhibitor therapy. It can be used alone or in combination with a traditional DMARD, but not with any TNF-α or IL-1 inhibitor.[5,29]

Abatacept is administered under medical supervision as an IV infusion over a period of 30 minutes at a dose of 10 mg/kg.[5,29] Following the first infusion, it is administered 2 weeks and 4 weeks later, then every 4 weeks thereafter.[29]

A 12-month, multicenter, randomized, controlled, double-blind trial involving 339 patients with active RA despite methotrexate therapy showed that, at 1 year, abatacept produced ACR 20 response rates of 63%, ACR 50 rates of 42%, and ACR 70 rates of 21% versus 36%, 20%, and 8% for those treated with placebo. Abatacept treatment was associated with significant reduction in disease activity and improvement in physical function. Over the course of the year, it was found to be generally well tolerated and safe.[30]

A multicenter, randomized, controlled, double-blind trial involving 345 patients, 322 of whom completed the study, evaluated the efficacy and safety of abatacept in patients with active RA and an inadequate response to at least 3 months of TNF-α inhibitor therapy.[31] At 6 months, patients treated with abatacept achieved ACR 20 response rates of 50%, ACR 50 response rates of 20%, and ACR 70 response rates of 20%, compared with 20%, 4%, and 2% in the placebo group.[31]

Improvement was even greater in the phase III, 1-year Abatacept in Inadequate Responders to Methotrexate study, a multicenter trial involving 652 patients with active RA despite methotrexate treatment.[32] At 1 year, ACR 20, ACR 50, and ACR 70 response rates were 73%, 48%, and 29% for abatacept versus 40%, 18%, and 6% for placebo.

Patients treated with abatacept also demonstrated significant slowing of structural damage progression compared with patients treated with placebo. Total mean changes in structural damage progression were 1.21 for abatacept and 2.32 for placebo from a baseline score of 45.[32]

Although abatacept was well tolerated and improved physical function and disease outcomes in combination with traditional DMARDs, when combined with other BRMs, it was associated with an increase in serious adverse events.[33]

The risk of activating latent TB with abatacept therapy is unknown.[5] Until the risk is better understood, TB screening is recommended prior to initiating therapy.[5]

NEW DIRECTIONS

Although TNF-α and IL-1 inhibition greatly advanced the treatment of RA, many cases remained refractory despite such an approach. However, over the past year, certain novel treatments have demonstrated clinical efficacy and acceptable toxicity profiles, bringing new hope for better response and sustained improvement to patients with intractable disease.

AUTHOR'S DISCLOSURE STATEMENT

Dr. Markenson reports he has received grant/research support, is on the speakers' bureaus of, and is a consultant to the following: Abbott Laboratories; Amgen USA Inc; Bristol-Myers Squibb Company; Genentech, Inc; and Wyeth Pharmaceuticals.

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