Selective T-Cell Costimulation Modulation: A New Approach to Treating Rheumatoid Arthritis

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Rheumatoid arthritis (RA) affects 2.1 million adults in the United States, roughly 1% of the population.[1] Characterized by chronic inflammation of the joints and progressive joint damage, RA disables, within 20 years, 80% of those it affects and reduces average life expectancy by up to 18 years.[2]

Although the traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, and the biologic agents that target tumor necrosis factor alpha (TNF-α) or B cells have made tremendous inroads in reducing disability associated with RA, many people have either no response or inadequate or unsustained responses to these agents.[3] For these patients, a new class, selective T-cell costimulation modulators, offers hope in the battle against this persistent, incurable disease. Abatacept is the first of such drugs to be approved by the US Food and Drug Administration for treatment of active RA.[3]

THE ROLE OF SELECTIVE T-CELL COSTIMULATION MODULATION

Abatacept is indicated for the treatment of active RA in patients who have had an inadequate response to traditional DMARD or TNF-α inhibitor therapy.[4] It can be used as monotherapy or in combination with traditional DMARDs, but not with other biologic agents, because acceptable safety has not been demonstrated and costs are prohibitive.[4] It is administered as a 30-minute intravenous (IV) infusion at doses of about 10 mg/kg. After the initial infusion, it is administered 2 weeks and 4 weeks later, then every 4 weeks thereafter.[4]

Abatacept functions to inhibit T-cell activation.[4] Activated T cells trigger the autoimmune and inflammatory processes of RA, producing proinflammatory cytokines, stimulating other immune system cells, and leading to production of metalloproteinases and inflammatory mediators that result in bone and cartilage degradation.[5,6]

Abatacept blocks 1 of the 2 signals required for T-cell activation following antigen recognition.[5] The first of these is antigen specific and requires binding of the T-cell receptor to the peptide-major histocompatibility complex on the antigen-presenting cell (APC). The second is not antigen specific and results from binding of the costimulatory ligand on the T cell, CD28, with costimulatory receptors CD80 and CD86 (also termed, respectively, B7-1 and B7-2) on the surface of APCs.[5-7] The off-switch is cytotoxic T-lymphocyte–associated antigen (CTLA) 4, a regulatory cell-surface protein expressed on T cells hours or days after cell activation. Competitively binding to CD80 and CD86, CTLA4 prevents these receptors from interacting with CD28, thereby blocking the second signal necessary for full T-cell activation and proliferation.[5-7]

Abatacept (also known as CTLA4-lg) is a genetically engineered protein constructed by fusing CTLA4 to the heavy-chain constant region of human immunoglobulin (Ig) G1. Abatacept mimics the action of CTLA4, binding to CD80 and CD86 on the APC and thus preventing the delivery of the second costimulatory signal required for optimal T-cell activation.[5-7] Notably, in vitro studies suggest that abatacept's inhibitory effect on T-cell activation reduces cytokine production without depleting T cells.[5]

As Monotherapy

In a 3-month pilot study by Moreland and colleagues,[8] abatacept was administered as monotherapy, at doses of 0.5, 2, or 10 mg/kg, for RA that was inadequately controlled by at least 1 DMARD. After 85 days of treatment, 53% of the patients who received the higher dose experienced a 20% improvement based on American College of Rheumatology (ACR) criteria (an ACR 20 response rate), and the treatment was generally well tolerated. *(Continued on page 13)*

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When Methotrexate Is Insufficient

Following the Moreland study, Kremer and colleagues[6] conducted a 6-month, double-blind, randomized, controlled trial investigating the effectiveness of abatacept in conjunction with background methotrexate in patients who had active RA despite having taken 10 to 30 mg methotrexate weekly for at least 6 months. The study population consisted of 339 patients between the ages of 18 and 65 whose methotrexate dose had been stable for at least 28 days before enrollment. Other than methotrexate, DMARDs were discontinued throughout the study. Patients were, however, allowed to continue taking corticosteroids at stable doses of 10 mg or lower per day as well as nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients were randomly assigned to receive placebo plus methotrexate, abatacept 2 mg/kg plus methotrexate, or abatacept 10 mg/kg plus methotrexate. Placebo or abatacept was delivered by intravenous (IV) infusion over 30 minutes on days 1, 15, 30, and then monthly for the next 5 months. A total of 259 patients completed the study: 78 were treated with methotrexate plus placebo, 82 with methotrexate plus 2 mg/kg abatacept, and 99 with methotrexate plus 10 mg/kg abatacept.

At 6 months, the group given 10 mg/kg abatacept achieved a significantly higher proportion of ACR 20 responses than the methotrexate-plus-placebo group (60% versus 35.3%). Although the ACR 20 response rate of the group given 2 mg/kg abatacept was not significantly higher than that of the methotrexate-plus-placebo group (41.9%), both abatacept treatment groups achieved significantly higher ACR 50 and ACR 70 response rates than that group. For methotrexate plus placebo, methotrexate plus abatacept 2 mg/kg, and methotrexate plus abatacept 10 mg/kg, ACR 50 rates were 11.8%, 22.9%, and 36.5%, respectively, and ACR 70 rates were 1.7%, 10.5%, and 16.5%. At both dosages, abatacept was well tolerated, with a safety profile similar to that of placebo.

Similar efficacy and safety data were presented in 12-month findings[9] from this phase IIb trial. At 12 months, an additional 24 patients had dropped out of the trial. Of the 90 patients receiving methotrexate plus abatacept 10 mg/kg who completed the trial, 62.6% achieved an ACR 20 response, 41.7% achieved an ACR 50 response, and 20.9% achieved an ACR 70 response, versus 36.1%, 20.2%, and 7.6%, respectively, for those who received methotrexate plus placebo. There were no significant differences in ACR 20 responses between the groups receiving methotrexate plus 2 mg/kg abatacept and methotrexate plus placebo, which confirmed that the 2-mg/kg dose of abatacept was suboptimal. Again, over the course of the study, abatacept was found to be well tolerated and safe.

In another year-long, multicenter, randomized, double-blind, controlled trial involving 652 patients with active RA despite at least 3 months' treatment with methotrexate, abatacept produced even higher ACR response rates.[10] Patients were randomly assigned to receive either a once-monthly infusion of abatacept 10 mg/kg or placebo in conjunction with methotrexate treatment. At 1 year, ACR 20, ACR 50, and ACR 70 response rates were 73.1%, 48.3%, and 28.8% for abatacept versus 39.7%, 18.2%, and 6.1% for placebo. The overall incidence of adverse events was similar in the abatacept and placebo groups.

After Inadequate Response to TNF-α Inhibitors

Genovese and colleagues[3] conducted a randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of abatacept in patients with active RA, who had had an inadequate response to at least 3 months' treatment with a TNF-α inhibitor. Researchers randomly assigned patients to receive abatacept 10 mg/kg or placebo in a 30-minute IV infusion on days 1, 15, and 29, and every 28 days thereafter through day 141. Patients discontinued TNF-α inhibitor therapy at least 28 days prior to randomization but continued using the oral, nonbiologic DMARD or the IL-1 inhibitor anakinra, which they had been taking for at least 3 months before enrollment at a dosage that had remained stable for at least 28 days.

A total of 223 patients in the abatacept group and 99 in the placebo group completed the 6-month study. The abatacept group achieved ACR 20, ACR 50, and ACR 70 responses of 50.4%, 20.3%, and 10.2% versus 19.5%, 3.8%, and 1.5% in the placebo group.

Discontinuations due to adverse events were uncommon and similar in both abatacept and placebo groups. Acute infusion reactions, which were usually mild or moderate in intensity, were more frequent in the abatacept group than in the placebo group. Antibodies against abatacept developed in only 3 of 234 patients administered the drug. Abatacept did not increase the risk of inducing antinuclear antibodies or anti–double-stranded DNA antibodies.

With Other Biologic Therapies

Weinblatt and colleagues[11] conducted a phase IIb pilot study to evaluate the safety and efficacy of abatacept in combination with etanercept in patients with active RA despite at least 3 months of etanercept 25 mg twice weekly. A total of 121 patients were randomly assigned to receive abatacept 2 mg/kg or placebo while continuing to take etanercept. Since, while this study was ongoing, a separate trial[9] established that an effective dose of abatacept was 10 mg/kg, all patients were given the higher dose during the study's open-label, long-term extension.[11] The initial trial and its long-term extension were conducted at 40 centers in the United States between February 26, 2001, and October 13, 2004.

At 1 year, there were only nonsignificant differences between ACR response rates in the group receiving abatacept 2 mg/kg plus etanercept and the group receiving placebo plus etanercept: ACR 20, ACR 50, and ACR 70 response rates were 48.2%, 28.2%, and 9.4% for the abatacept group, compared with 30.6%, 16.7%, and 5.6% for the placebo plus etanercept group. Although all

patients began receiving abatacept at a fixed dose approximating 10 mg/kg with the start of the long-term extension for the most part ACR response rates were maintained through the end of the study.

Although the incidence of adverse events in this study was generally low, the combination of abatacept and etanercept elevated the rate of adverse events, including serious adverse events and infections. This finding is consistent with data from a large-scale phase III safety trial of abatacept in patients with RA receiving background biologic or nonbiologic DMARDs,[12] which demonstrate that combining abatacept with another biologic agent produces a less favorable safety profile and no increase in benefit.

The latter was a 1-year, multicenter, double-blind, randomized, controlled trial involving adults with active RA who had been using at least 1 DMARD for at least 3 months prior to study entry.[12] With continued background RA therapy, a total of 1441 patients were treated with either abatacept or placebo by IV infusion on days 1, 15, and 29, and every 4 weeks thereafter until they had received 14 doses. Methotrexate was the most frequently used synthetic and etanercept the most frequently used biologic DMARD. Stable, low doses of oral corticosteroids and stable doses of NSAIDs were allowed.

In combination with synthetic DMARD therapy, abatacept was well tolerated and improved physical function as well as reported disease outcomes. The adverse event profile was similar to that of abatacept in other methotrexate combination trials. In conjunction with biologic DMARDs, however, abatacept was associated with an increase in the rate of serious adverse events, including infections and neoplasms.

The primary aim of this study was to evaluate the safety of abatacept used with background biologic versus synthetic DMARD therapy. Abatacept tended to be less beneficial—in terms of physical function, reported pain, and global assessment—for patients receiving biologic DMARDs. Similar observations were made when other biologic DMARDs, such as etanercept and anakinra, were used in combination.[13] The use of abatacept in combination with other biologic DMARDs, therefore, is specifically proscribed in current US labeling.[4,12]

Precautions

Patients with chronic obstructive pulmonary disease (COPD) who have been treated with abatacept have had more adverse events than patients treated with placebo.[12,14] When abatacept is used to treat RA in patients with comorbid COPD, respiratory status should be closely monitored.[14] Live attenuated vaccines should not be administered within 3 months of abatacept therapy. Since the risk of activating latent tuberculosis (TB) with abatacept therapy is unknown,[14] it is recommended that patients undergo TB screening before starting abatacept therapy.[14]

A PROMISING STRATEGY

New biologic agents targeting different immunologic processes and cytokine cascades that underlie RA offer clinical benefit for patients whose RA is refractory to traditional DMARD or TNF-α inhibitor therapy. Since abatacept, with its novel mechanism of action, can be used as monotherapy or in combination with synthetic DMARDs by such patients, it is a valuable therapeutic to add to the armamentarium of antirheumatic medications.

AUTHOR'S DISCLOSURE STATEMENT

Dr. Strand reports she is a consultant to Abott Immunology, Amgen USA Inc, Astellas, AstraZeneca, Bayhill, Biogen Idec, CanFite, Centocor, Cypress Biosciences, Inc, Dainippon Sumitomo, Genelabs, Genentech, Human Genome Sciences, Novartis, Omeros, Pfizer, Pharmacopeia, Proprius, Rigel, Roche, Sanofi-Aventis, Schering-Plough, Serono, SKK, UCB, Wyeth-Ayerst, and Xdx; she is on the advisory boards of Abbott Laboratories, Amgen USA Inc, Biogen Idec, BMS, CanFite, Centocor, Chelsea, Novartis, Roche, Pfizer, Schering-Plough, and UCB; and is on the speakers' bureaus of Abbott Laboratories, Amgen USA Inc, Centocor, and Pfizer Inc.

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