T-Cell Agents in the Treatment of Rheumatoid Arthritis

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Abstract

T cells play a prominent role in the pathogenesis of rheumatoid arthritis. Abatacept is the first FDA approved agent for rheumatoid arthritis that blocks the activation of T cells by interrupting the interaction between the CD28 ligand on the T cell and the CD80/86 ligand on the antigen presenting cell. Inhibition of T cell activation has pleotropic effects that lowers the downstream production of multiple cytokines. In clinical trials, abatacept is effective in treating the signs and symptoms of rheumatoid arthritis as well as in inhibiting structural damage. It has a favorable safety profile and can be used in patients who may have co-morbidities that preclude the use of anti-TNF agents. While no direct head to head trials exist, a study in which both abatacept and infliximab were compared to an identical control population, suggested that the efficacy of the two drugs was similar but that there were fewer adverse effects with abatacept than with infliximab. Abatacept is an important addition to the therapeutic repertoire available to treat rheumatoid arthritis. Available data support its use as a first line agent to treat patients who have had and inadequate response to methotrexate.

The role of T cells, in general, and CD4+ T cells, in particular, have long been recognized as central in the pathogenesis of rheumatoid arthritis (RA). Strong support for this concept comes from a variety of clinical and experimental observations. First and foremost, the strong association of RA with specific genes of the major histocompatibility complex implies an antigen recognition event involving T cells. CD4+ T cells are abundant in rheumatoid synovium, where they are found in proximity to antigen presenting cells. Ablation of the CD4 population by human immunodeficiency virus (HIV) results in remission of well-established RA and reconstitution after highly active antiretroviral therapy (HAART) therapy results in recurrence of disease. Antibodies to CD4 favorably affect murine models of arthritis although this success has not been reproduced in humans.

In the past decade, the management of RA has been dramatically changed by the introduction of therapies that are directed against cytokines secreted by activated macrophages and lymphocytes. Multiple agents that inhibit the biologic effects of tumor necrosis factor (TNF) have been shown to be highly effective in treating the signs and symptoms of RA, as well as in preventing the accrual of structural damage. While anti-TNF agents in combination with methotrexate (MTX) have become the new standard of care for RA, there are still large, unmet needs in RA therapeutics.

If the desired outcome for patients with RA is an American College of Rheumatology ACR50 or low disease activity score (DAS), the reality is that less than 50% of patients receiving anti-TNF agents will achieve this goal. Furthermore, many patients who initially respond to anti-TNF agents will lose response over time, due to either antibody-mediated drug resistance or the emergence of pathways of inflammation that are TNF independent. Others will need to discontinue drug agents because of adverse effects associated with TNF inhibition, most notably infections. Finally, some patients are not eligible for TNF inhibition because of comorbidities, including tuberculosis (TB), viral or opportunistic infections, lymphoma, or recent solid tumors.
Abatacept—Selective Costimulation Modulator

Mechanism of Action
Abatacept (Orencia®, Bristol-Myers Squibb) is a selective T-cell costimulation modulator that blocks the activation of T cells by interrupting the interaction between the CD28 ligand on the T cell and the CD80/86 ligand on the antigen presenting cell (Fig. 1). This “second signal” is necessary in addition to a “first signal,” the interaction between the T-cell receptor and the MHC-antigen complex on the antigen presenting cell. The abatacept molecule is constructed as a fusion protein between an immunoglobulin and the extracellular portion of cytotoxic T-lymphocyte antigen 4 (CTLA-4). This molecule binds with high affinity to the CD80/86, preventing it from binding to CD28. Without this binding, T-cell activation cannot occur.

Inhibition of T-cell activation is an “upstream” event that has profound consequences for “downstream events,” including the generation of the cytokines TNF, IL-1 and IL-6, as well as B-cell activation. Unlike anti-TNF agents, which effectively ablate a small portion of the immune system, abatacept results in a more global dampening of a variety of immune mechanisms, including TNF production.

Approved Indications
Abatacept is indicated for reducing the signs and symptoms of RA, to include inducing a major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderate to severely active disease. This agent may be used as monotherapy or in combination with disease modifying arthritic drugs (DMARDS) other than TNF antagonists.

Dosing
Abatacept is administered based on the body weight of patients, with dose stratification for weights of under 60 kg, 60 to 100 kg, and more than 100 kg. Doses are given at weeks 0, 2, and 4 (loading dose), with subsequent infusions on a monthly basis. Both of these features—weight-based dosing and loading dose—make sense to this investigator as an intelligent way to administer a biologic agent. Of the anti-TNF agents, only infliximab can make this claim, and certolizumab is given with a loading dose but does not have weight-based dosing. The infusion is relatively short (30 to 45 minutes), and premedication is not needed. Both of these features are also advantageous to the practitioner.

Efficacy in Clinical Trials
Clinical efficacy has been demonstrated in three populations and evaluated in separate trials: early methotrexate naïve patients in the AGREE trial (Abatacept Study to Gauge Remission and Joint Damage Progression in Methotrexate Naïve Patients with Early Erosive Rheumatoid Arthritis), methotrexate inadequate responders in the AIM (Abatacept in Inadequate Responders to Methotrexate) study, and TNF-inadequate responders in the ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) trial. Long-term extension data from AIM is now available that demonstrates sustained clinical efficacy, with maintenance of ACR scores for over 5 years (Fig. 2). Retention rates from the clinical trials are remarkably high, with retention rates of 72.4% through year 5 of the AIM extension, with only 5.0% withdrawing due to lack of efficacy. Radiographic data through 5 years in AIM shows maintenance of radiographic protection, with linear increases in Sharp scores at rates below those seen with methotrexate plus placebo (Fig. 3).

While abatacept shows significant inhibition of structural damage, the results are less striking than those seen for anti-TNF agents. Nonetheless, nearly half of the patients show no radiographic damage over 5 years. Furthermore, the increase in structural damage that is seen does not result in loss of function as evidenced by a change in the Health Assessment Questionnaire (HAQ) scores.

Safety
The safety profile of abatacept is reassuring, with low rates of both serious adverse events (SAEs) and major infections. In the 2-year extension data from the AIM trial, the rates of significant adverse events was similar to the rates seen in the placebo group and fell well within the ranges reported for patients receiving anti-TNF therapies. Initial concerns about an increased incidence of lung cancer have not proved to be warranted. The rates of malignancies in the published clinical trials of abatacept, including total malignancies, breast, colorectal, lung, and lymphoma, do not differ from the background rates seen in patients with RA.

Time Course of Response
Abatacept works quickly in responders. In the AGREE study, meaningful changes in the ACR core components were seen once a month, and, by month 2, a greater than 50% improvement was observed for tender joint counts (TJCs) and swollen joint counts (SJCs) in 56.4% and 57.1% of the abatacept plus MTX group, respectively, versus 35.6% and 41.6%, respectively, for MTX alone. By month 12, a greater than 70% improvement in TJCs and SJC s were seen in 72.4% and 78.4% of the abatacept plus MTX group, respectively. By month 4, patients receiving abatacept = MTX demonstrated meaningful improvements in all of the ACR core components, including the patient-reported outcomes.

Comparison with Other Agents
One of the problems facing the clinician in choosing among the many available biologic agents to treat RA is the absence of a head-to-head comparison trial between agents. To my knowledge, the only such trial compared Orencia® at standard weight-based dosing plus MTX to infliximab at a dose of 3 mg/kg plus MTX, over a
12-month period. Although both trial drugs were significantly more effective than placebo plus MTX, the changes in DAS were greater for abatacept than for infliximab. Furthermore, there was an increase in patient response from month 6 to month 12 with abatacept, while the infliximab patients did not show further improvement from months 6 to 12.

Infliximab responders who were crossed over to abatacept for months 12 to 24 demonstrated further improvement. Abatacept also showed a better safety profile, with SAEs of 9.6% versus 18.2% for infliximab. Discontinuations due to AEs were 3.2% for abatacept versus 7.3% for infliximab. In the infliximab treated group, TB and other opportunistic infections were seen, whereas there was no TB or opportunistic infection seen in the abatacept treated group.\textsuperscript{12,13}

A similar conclusion was reached by Yazici and colleagues in a meta-analysis comparing safety and efficacy for published clinical trials. In this study, investigators calcu-
lated indices of efficacy and safety based on the number of patients that needed to be treated to demonstrate clinical improvement (NNT, numbers needed to treat) and the number of patients that needed to be treated to produce a significant adverse event (NNH, numbers needed to harm). They called these indices “patients needed to help” and “patients needed to harm.” In this analysis, the NNT for abatacept to achieve DAS 20, 50, or 70 or to achieve DAS remission was virtually identical to the numbers seen for etanercept or adalimumab and far lower than those seen for infliximab.

**Conclusions and Recommendations**

Several points and recommendations can be made that positively position abatacept as an important agent of a new class of drugs in the management of rheumatoid arthritis:

1. Abatacept is a novel agent that works by inhibiting the “second signal” needed for T-cell activation. Through blockade of T-cell activation, abatacept secondarily inhibits “downstream” generation of cytokines, including TNF, IL-1, and IL-6, resulting in a broad dampening of inflammation.

2. The clinical efficacy of abatacept is comparable to anti-TNF agents and, in one comparison trial, proved to be superior to infliximab at standard doses.

3. The safety profile of abatacept is excellent, with fewer SAEs than anti-TNF agents, based upon Cochran analysis of clinical trial data.

4. Abatacept can be used in patients with co-morbidities that preclude the use of anti-TNF agents.

5. Abatacept is administered with a dose based upon weight and with a loading dose. The infusions are fast, do not require pre-medication, and result in few adverse reactions. Responders may show improvement as soon as in 1 month and, in responders, improvement is seen in all ACR core components by month 4.

6. Patients who respond to abatacept tend to maintain their clinical responses over time, with little evidence of tachyphylaxis or antibody-mediated drug resistance.

7. Inhibition of radiographic progression falls short of that seen with anti-TNF agent but is robust and quite adequate to prevent loss of function.

8. Abatacept should be strongly considered as first-line therapy of patients with early RA who do exhibit an incomplete response to MTX, as well as in patients who do not respond to one or more anti-TNF agents or who are TNF ineligible.

9. With the introduction of newer agents that inhibit other cytokines, such as IL-6 and IL 12/23 or B cells, head-to-head trials are needed to establish the relative efficacy of these treatments in comparison to T-cell costimulatory blockade.

**Disclosure Statement**

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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