Efficacy results from pivotal clinical trials with abatacept

A.L. Rozelle, M.C. Genovese

Division of Immunology and Rheumatology, Stanford University, California, USA.

Andrew L. Rozelle, MD, PhD; Mark C. Genovese, MD.

Please address correspondence to: M. Genovese, MD, Stanford University, Division of Immunology and Rheumatology, 1000 Welch Road #203, Palo Alto, CA 94304, USA. E-mail: genovese@stanford.edu

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ABSTRACT

Rheumatoid arthritis (RA) is a prevalent systemic disease that causes significant joint dysfunction and disability. Dramatic improvements in the management of RA have been achieved with the use of biologic therapies aimed at cytokines, and B and T lymphocytes. Abatacept, a soluble receptor-IgG fusion protein that interferes with T-cell co-stimulation, has now been shown to improve symptoms, signs and function in RA, while also slowing radiographic progression. The degree of improvement in these measures is comparable to that seen with other biologic agents. Abatacept is effective in a range of RA patients that are encountered in clinical practice, namely methotrexate-inadequate responders, as well patients with inadequate responses to tumor necrosis factor inhibitors and patients with co-morbidities common in an aging population. When used for up to 2 years, abatacept appears to be safe and remains efficacious, although there is a trend toward increased infection rates when used in combination with other biologic therapies, as well as a trend toward more adverse events when used in a background of chronic obstructive pulmonary disease.

Backed by these data, ongoing extensions of these trials, and additional new studies, abatacept represents the first co-stimulation modulator approved for RA, and is a welcome addition to the biologic therapies available for the management of this disease.

Introduction

Rheumatoid arthritis (RA) is a prevalent systemic disease that causes significant joint dysfunction and disability. Research focused on understanding the pathogenesis of RA has implicated lymphocytes, both B and T cells, as well as cells of the granulocytic lineage – including mast cells, monocytes and macrophages. The latter secrete inflammatory mediators like tumor necrosis factor (TNF)-α and interleukin (IL)-1; blockade of each of these has provided effective therapies for this disease. The importance of B cells in RA is demonstrated by the fact that immunoglobulins, including rheumatoid factor and antibodies to citrullinated peptide antigens, are associated with more severe radiographic disease and extra-articular manifestations. Importantly, this role for B cells has been confirmed with the demonstration that B-cell targeted therapy, such as with rituximab, is an effective treatment.

In addition to the aforementioned players, a role for T cells is indicated by their presence in the rheumatoid synovium. Furthermore, major histocompatibility complex (MHC)-II encoding alleles of the HLA-DR4 and DR1 families confer strong susceptibility to the disease among Caucasian patients. Optimal T-cell activation requires dual stimulation through both the peptide-loaded MHC II molecule:T-cell receptor interaction and the binding of CD80/CD86 family members on the antigen presenting cell to members of the CD28 family of co-stimulators on the T cell. As a likely natural safety mechanism against unchecked T-cell stimulation, expression of the inhibitory receptor cytotoxic T-lymphocyte-associated antigen (CTLA)-4 is up-regulated on the T-cell membrane within hours of stimulation. CTLA-4, also a CD28 family member, binds to receptors of the CD80/CD86 family with high affinity and avidity, holding T-cell activation in check. This strategy of immune regulation is mimicked by the new biologic agent abatacept, a recombinant protein consisting of the extra-cellular portion of the CTLA-4 receptor fused to the Fc portion of immunoglobulin (Ig)G1, and modified to avoid complement activation. Blockade of T-cell co-stimulation with abatacept has been shown to be effective in several animal models of autoimmune disease, including psoriasis, lupus, and RA. Clinical trials in

RA have demonstrated both its safety and its efficacy, and it has recently become a new addition to the growing list of biologic therapies for this disease.

Early clinical trials with abatacept

Initial studies of abatacept in RA were performed in patients with longstanding erosive disease refractory to methotrexate (1). A Phase IIb trial comparing two doses of abatacept with placebo showed significant improvements in the symptoms and signs of RA, as well as in physical function. In this study, 339 patients with long-standing active disease despite the use of methotrexate were assigned randomly to receive either placebo or abatacept at a dose of 2 mg/kg or 10 mg/kg. Infusions were given on Days 1, 15 and 30, and every 28 days thereafter until 6 months. The primary outcome was a 20% improvement in the American College of Rheumatology (ACR) criteria (ACR20 response; this outcome measure represents a ≥ 20% improvement in both the tender and swollen joint counts, as well as in ≥ 3 or more of the 5 following criteria: patient global assessment, physician global assessment, visual analog pain scale, functional/disability, and erythrocyte sedimentation rate or C-reactive protein).

This outcome was achieved by a significantly higher proportion of patients receiving the 10 mg/kg dose (60.0%) than placebo (35.3%). Furthermore, ACR50 and ACR70 responses at 6 months were met by a significantly higher proportion of patients receiving abatacept than placebo, and the percentages achieving all three response levels were comparable to those seen in the initial trials of TNF inhibitors when added to methotrexate in a similar RA population. Patients receiving the lower dose (2 mg/kg) also responded in greater numbers than those receiving placebo, although the percentages were not statistically significant. Detailed analysis showed that for the 10 mg/kg dose, significant differences from placebo in the proportion of patients achieving ACR20, 50 and 70 responses and clinically important improvements (≥ 0.22 units) in the modified Health Assessment Questionnaire (m-HAQ) were seen by 2 months; an extension of this trial to 12 months showed that the percentage of responders continued to increase quarterly through this entire period (2).

The AIM trial

These encouraging results were followed by a large Phase III trial called '**A**batacept in **I**nadequate responders to **M**ethotrexate' (AIM), which was composed of roughly 650 patients assigned to either 10 mg/kg abatacept or placebo who were then followed over 1 year (3). The patients enrolled in this study were again representative of a large portion of the RA population seen in everyday practice, with the majority of patients being females, age 50 or higher, who suffered from long-standing (~9 years) seropositive, erosive disease that was responding inadequately to methotrexate.

Three primary objectives – significant improvement in the ACR20 response at 6 months, clinically significant improvement (≥ 0.3 units) in the Health Assessment Questionnaire Disability Index (HAQ-DI) score at 1 year, and a significant reduction in the rate of structural damage at 1 year – were met in all groups receiving abatacept. The percentages of patients achieving ACR 20, 50 and 70 responses at 6 and 12 months were slightly higher than in the Phase II studies, with 73%, 48% and 29% achieving these responses, respectively, at 1 year. Statistically significant responses in AIM were actually seen as early as 15 days after the start of infusions; these consisted mainly of decreased pain and improved patient and physician assessments of disease activity. The percentages of responders reached near maximum by 90 days, but did continue to increase compared with placebo through the entire length of the study. Significant clinical improvement in physical function as measured by the HAQ-DI was achieved by 64% of patients receiving the active drug compared with 39% receiving placebo, with once again near maximal responses achieved by 90 days and then continuing through the year.

The patients studied in the AIM trial exhibited high disease activity at baseline, as measured by the Disease Activity Score (DAS)28 (mean = 6.4); at 6 and 12 months significant percentages of the patients receiving abatacept had achieved remission (score < 2.6) on this scale (14.8% and 23.8%, respectively, as opposed to 2.8% and 1.9% of the placebo group). Although the addition of other disease-modifying anti-rheumatic drugs (DMARDs) was allowed between 6 and 12 months, the continued improvement in patients receiving active drug during this period is not likely to have been affected by this relaxing of the study protocol, as additional DMARDs were given to only a small number of patients, and to fewer patients receiving the active study drug than to those receiving placebo. Furthermore, the percentage of responders in the placebo group did not increase during this period. Improvement with abatacept was robust, with ACR70 responses being maintained for up to 9 consecutive months.

Preliminary data on a 1-year open-label extension of AIM were made available at the 2006 ACR annual meeting in Washington, DC (4, 5). A non-responder analysis (with all discontinued patients considered as non-responders) of the intent-to-treat population confirms and underscores the AIM data, as improvements in both the ACR response and physical function as measured by the HAQ-DI appeared to be sustained through 2 years. When these data are analyzed in an as-observed fashion, the percentages of ACR 20, 50 and 70 responders increased slightly during the second year of treatment.

The ATTAIN trial

Despite the success of the TNF inhibitor agents in treating RA over the last decade, a significant proportion of patients seen in clinical practice have inadequate responses to these medications, even when used in combination with high doses of MTX and/or other DMARDs. The utility of abatacept in such a group was studied in the '**A**batacept **T**rial in the **T**reatment of **A**nti-TNF **IN**adequate Responders' (ATTAIN), which randomized nearly 400 patients with an inadequate clinical response

to TNF inhibition to receive either 10 mg/kg abatacept or placebo in addition to continued use of a background DMARD (6). Infusions were given on a similar schedule to those in AIM, and the study was designed to measure at 6 months the primary endpoints of the ACR 20 response as well as improvement in physical function as measured by the HAQ-DI. Patients were largely similar to those studied in AIM, having long-standing (11–12 years) seropositive and active (DAS28 = 6.5) disease. In addition, all patients had failed at least a 3-month trial of either infliximab or etanercept.

The ATTAIN trial met both of its primary endpoints, as patients receiving the active drug achieved ACR20, 50 and 70 responses at significantly higher percentages (50%, 20% and 10%, respectively) than those receiving placebo (20%, 4% and 1%, respectively). Similar to AIM, statistically significant differences in the percentages of responders were seen as early as 15 days from study initiation, and they continued to increase throughout the 6-month period. Significant improvements in physical function, as measured by the HAQ-DI, were also seen by 15 days, with percentages increasing to involve 47% of patients receiving the study drug compared with 23% of those receiving placebo at 6 months. Furthermore, the magnitude of improvement in individual responders was greater in those receiving abatacept compared with placebo (0.45 units *vs*.. 0.1 units, respectively).

A significantly greater proportion of patients receiving abatacept versus those on placebo achieved clinical remission as measured by a DAS28 score of < 2.6 (10% *vs*. 1%), although these figures, like the ACR responses, were generally lower that those seen at 6 months in the AIM trial (15% DAS28-defined remission and 29%, 48% and 73% of patients achieving ACR20, 50 and 70 responses, respectively). These differences may indicate that the patients studied in ATTAIN had more refractory disease, although they could also simply reflect a generally higher placebo response in AIM. Preliminary data from an 18-month, open-label extension of the ATTAIN trial indicate that the ACR response improvements, as well as the proportion of patients reaching a low disease activity score or DAS28-defined remission, are maintained – and possibly continue to increase – through consecutive 6-month periods extending to 2 total years of treatment (7).

Abatacept and the progression of radiographic damage

Although the trials discussed here report a robust efficacy for abatacept in treating the symptoms and disability caused by RA, another important outcome measure used daily in clinical practice is progression of radiographic damage. AIM was the only one of these trials to study this outcome measure. Nearly all (92%) patients had radiographs of the hands and feet taken at study entry and at completion (at 1 year), and the progression of erosions and joint space narrowing was measured. Patients had moderately destructive disease at study onset as measured by the Genant-modified Sharp score, a scale that assigns equal weight to both erosions and joint space narrowing. Mean and median scores for patients in the treatment arms were slightly lower than for the placebo group at study onset (mean scores 44.5 *vs*. 44.9 in the study drug versus placebo groups, respectively, and median scores 31.9 *vs*. 33.4, respectively, out of a total possible score of 290). At 1 year, the progression of structural damage was around 50% lower in the treatment group as measured by this scale, with patients receiving abatacept progressing by a median score of 0.25 and those receiving placebo progressing by a median of 0.53.

Further data regarding these radiographic responses to abatacept were reported at the 2006 ACR annual meeting (8). The reduction in radiographic progression in patients receiving abatacept is underscored by data from the extension phase of the AIM trial, which indicates that 56% and 50% of these patients have no progression at all (total score ≤ 0) at years 1 and 2, respectively, when treated with abatacept. In addition, nearly half (45%) of patients who did progress during the first year showed no additional damage during the second year.

The ASSURE trial and the safety of abatacept

Safety is a primary concern in the consideration of any new therapy or class of therapies. The AIM trial suggested a slightly higher rate of serious adverse events (SAEs; 15% *vs*. 11.9%) and discontinuation due to adverse events (AEs; 4.2% *vs*. 1.8%) in the abatacept versus placebo groups, respectively, although the most frequently reported events (headache, nasopharyngitis and nausea) did not differ between the two groups. These trends were not seen in ATTAIN, in which similar percentages of patients in the abatacept and placebo groups experienced SAEs (10.5% *vs*. 11.3%, respectively) and discontinued the drug because of them (3.5% *vs*. 3.8%, respectively) between the two groups. Importantly, both trials suggested a slightly higher rate of infection for patients receiving abatacept versus placebo (3.9% *vs*. 2.3%, respectively, for AIM, and 38% *vs*. 32%, respectively, for ATTAIN), although a trend toward serious infection with abatacept versus placebo was seen only in AIM (2.5% *vs*. 0.9%, respectively). Infections were mostly bacterial, and included both the upper and lower respiratory tract; no cases of tuberculosis or opportunistic infection were seen in either study.

The safety of abatacept in combination with other DMARDs was studied as a primary outcome for a large number of patients in the **A**batacept **S**tudy of **S**afety in **U**se with other **R**A th**E**rapies' (ASSURE) trial (9). This study randomized 1441 patients on background DMARD therapy, of whom 10.7% were receiving biologic agents, to receive abatacept at 10 mg/kg every 4 weeks or placebo for 1 year. The incidence of AEs and SAEs was similar between the abatacept and placebo groups (90% *vs*. 87% AEs, and 13% *vs*. 12% SAEs, respectively), as were discontinuations due to AEs (5% *vs*. 4%, respectively). Among patients who were taking both a background biologic DMARD agent and abatacept, however, there was a trend toward more SAEs (22% *vs*. 11–12% in groups taking background biologic agents plus

placebo or background non-biologics plus abatacept) and discontinuations due to SAEs. The incidence of serious infections was higher in the abatacept group (2.9% *vs*. 1.7%), and this trend appeared to increase in magnitude when the group taking both biologic DMARDs and abatacept was examined (5.8% serious infection rate *vs*. 1.6% and 2.6% in groups taking background biologic plus placebo and background non-biologic plus abatacept, respectively). Again, most serious infections involved the upper respiratory tract, and there were no observed cases of opportunistic organisms or tuberculosis. Infections were largely treatable and did not lead to discontinuation of the study drug or fatality.

Another characteristic of ASSURE that should be helpful in daily practice is that it included patients with chronic diseases that are often encountered in the clinic (6–7% of patients had diabetes mellitus [DM], 6% had asthma, 4% had chronic obstructive pulmonary disease [COPD], and 1–2% had congestive heart failure [CHF]). Among the group of patients with COPD, AEs and SAEs were more common in those receiving abatacept (AE incidence 43.2% *vs*. 23.5% in abatacept *vs*. placebo groups, respectively; SAE incidence 27% *vs*. 5%, respectively). Most AEs were of a respiratory nature, including exacerbation of COPD, cough and dyspnea, while the infection rate was similar between the abatacept and placebo groups (59.5% and 58.8%, respectively).

An additional study was presented at the late-breaking session of the 2006 ACR annual meeting. The study was entitled: "The efficacy and safety of abatacept or infliximab in RA patients with an inadequate response to MTX: results from a 1-year double-blind, randomized, placebo-controlled trial." This study investigated the magnitude of the treatment effect and the safety of abatacept, infliximab or placebo over a 6-month time frame, and subsequently looked at abatacept or infliximab over an entire year of use. Abatacept was dosed similarly to the previously mentioned studies, approximating 10 mg/kg every 4 weeks, while infliximab was dosed at 3 mg/kg every 8 weeks following the initial dosing at 0, 2 and 6 weeks. The primary endpoint was a reduction in the mean DAS28 scores. Through 6 months, efficacy appeared to be similar between abatacept and infliximab, with both agents statistically better than placebo. Further improvement was observed at 12 months with abatacept (10, 11). Safety data suggested that there were fewer SAEs with abatacept than infliximab at both 6 and 12 months (10).

Conclusion

The clinical trials of abatacept in RA described here have led to the addition of a new agent to the therapies available to clinicians for the management of this disease. Thus far, abatacept appears to reduce the symptoms and signs, improve function and reduce disability, and inhibit radiographic progression in patients with RA. Perhaps the greatest attribute is its effectiveness in those patients who have had an inadequate response to TNF inhibition, as this serves a large unmet need. Outstanding issues to be addressed include its long-term efficacy as well as the long-term safety of continued use. Close study of additional safety data as more patients receive the drug is warranted, as would be expected from any new therapy.

Key points box

- Treatment options for patients with rheumatoid arthritis (RA) have been greatly improved by the introduction of the biologic anti-tumor necrosis factor (TNF) agents. However, not all patients with RA respond to these agents, while others lose their response to treatment over time
- Abatacept is a selective modulator of T-cell co-stimulation that targets the interaction of CD80/CD86 on the antigen-presenting cell with CD28 on the T cell, by mimicking the action of cytotoxic T-lymphocyte-associated antigen-4
- The efficacy of abatacept has been evaluated in a number of randomized, placebo-controlled Phase II and Phase III trials of patients with RA, including patients with an inadequate response to methotrexate (MTX) or anti-TNF therapy
- Following either 6 months or 1 year of double-blind treatment, abatacept significantly reduced the signs and symptoms of RA and improved physical function versus placebo in patients who were inadequate responders to either MTX or anti-TNF, with responses becoming apparent as early as 15 days into treatment
- Results of open-label extensions from the Phase III studies show that these improvements were maintained through 2 years of abatacept treatment
- During a Phase III trial enrolling MTX-inadequate responders, radiographic progression at 1 year was significantly lower in abatacept- versus placebo-treated patients; reductions in progression were sustained after 2 years of abatacept treatment
- The demonstrated efficacy of abatacept was associated with acceptable safety and tolerability. Longer-term follow-up will now be necessary in order to establish whether these attributes are maintained in patients receiving ongoing treatment

References

1. KREMER JM, WESTHOVENS R, LEON M *et al*.: Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003; 349: 1907-15.
2. KREMER JM, DOUGADOS M, EMERY P *et al*.: Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a Phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 2263-71.
3. KREMER JM, GENANT HK, MORELAND LW *et al*.: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; 144: 865-76.

4. KREMER JM, WESTHOVENS R, RUSSELL A *et al.*: Long-term efficacy of abatacept through 2 years of treatment in rheumatoid arthritis patients in the AIM trial. *Arthritis Rheum* 2006; 54 (Suppl.): S427, Abstract 506.
5. LUGGEN M, EMERY P, LI T, MCCANN T, TENG J, SCHIFF M: Abatacept provided clinically meaningful improvements in multiple aspects of health related quality of life (HR-QoL) and physical function through 2 years of treatment in patients with active rheumatoid arthritis (RA): results from the AIM and ATTAIN trials. *Arthritis Rheum* 2006; 54 (Suppl.): S423, Abstract 980.
6. GENOVESE MC, BECKER JC, SCHIFF M *et al.*: Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005; 353: 1114-23.
7. GENOVESE MC, SCHIFF M, LUGGEN M *et al.*: Sustained efficacy and safety through 2 years in patients with rheumatoid arthritis (RA) in the long-term extension of the ATTAIN trial. *Arthritis Rheum* 2006; 54 (Suppl.): S244, Abstract 498.
8. GENANT HK, PETERFY C, WESTHOVENS R *et al.*: Non-progression of structural damage over 2 years with abatacept in rheumatoid arthritis patients with an inadequate response to methotrexate in the AIM trial. *Arthritis Rheum* 2006; 54 (Suppl.): S408, Abstract 940.
9. WEINBLATT M, COMBE B, COVUCCI A, ARANDA R, BECKER JC, KEYSTONE E: Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and non-biologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006; 54: 2807-16.
10. SCHIFF M, KEISERMAN M, CODDING *et al.*: The efficacy and safety of abatacept or infliximab in RA patients with an inadequate response to MTX: results from a 1-year double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2006; 54: (Abstract no. 12) 4117.
11. BRISTOL-MYERS SQUIBB: Summary of product characteristics. 2007; Accessed on 21 August 2007; Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/orencia/H-701-PI-en.pdf.