



Abatacept for the Treatment of Rheumatoid Arthritis: A Review

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting synovial joints. Patients with persistent, active disease have traditionally been treated with disease-modifying antirheumatic drugs (DMARDs) (eg, methotrexate) or biologic agents (eg, tumor necrosis factor [TNF] antagonists). However, patients may discontinue these treatments due to toxicity, infection, or lack of efficacy. Two additional biologic therapies—rituximab and abatacept—are currently available for TNF-antagonist inadequate responders. Abatacept is also indicated for inadequate responders to traditional DMARDs.

Objectives: The aims of this review was to provide an overview of the issues surrounding the treatment of RA patients experiencing inadequate responses to current treatment and to discuss the current and future impact of abatacept on the RA treatment armamentarium.

Methods: The MEDLINE, EMBASE, and BIOSIS databases were searched (search dates: January 1, 2000–September 19, 2007) using the terms *abatacept* or *CTLA-4* or *Orencia* with *rheumatoid arthritis*. Full text articles in English were selected for relevance, and only articles presenting primary clinical trial data from randomized, placebo-controlled, clinical trials of abatacept were included. This review focused on the Phase III trials of abatacept in methotrexate and/or TNF-antagonist inadequate responders, as these trials had the largest number of patients and the longest study durations.

Results: The literature search initially yielded 848 papers. A total of 12 articles fulfilled the inclusion criteria. Abatacept is a novel agent that has been reported to reduce the signs and symptoms of RA in patients with active RA with an inadequate response to DMARDs and/or TNF-antagonist treatment. In both of these patient populations, treatment with abatacept was found to provide clinically meaningful health-related quality-of-life benefits, such as improvements in physical function, activity limitation, sleep, and fatigue. Abatacept was reported to have a consistent safety and tolerability profile, with a low rate (3.5%–4.2%) of discontinuation due to adverse events.

Conclusion: The efficacy and tolerability data from Phase III clinical trials suggest that abatacept is an effective and generally well tolerated treatment option for RA patients with an inadequate response to methotrexate and/or

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Key words: abatacept, selective costimulation modulator, rheumatoid arthritis, inadequate responders, methotrexate, tumor-necrosis factor antagonists.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory disease occurring in ~3 of 10,000 adults worldwide and in ~1% of the adult population in the United States.¹ Although RA affects a wide range of synovial joints, the most commonly involved are those of the hands, knees, and feet.²

The American College of Rheumatology (ACR) guidelines for the treatment of RA recommend that all patients with a diagnosis of RA be treated with disease-modifying antirheumatic drugs (DMARDs) within 3 months of diagnosis.³ Traditional DMARDs, such as methotrexate, are frequently used as first-line treatment for in the management of moderate-to-severe RA.⁴ The primary reason reported for discontinuation of traditional DMARD treatment has been adverse events (AEs),^{5–9} with studies reporting that 43% to 53% of patients permanently discontinued treatment due to tolerability issues.^{5,10} Patients may also experience a lack of efficacy with traditional DMARD treatment.^{5,10} This was found in a retrospective study of 760 patient medical records, in which up to 47% of patients discontinued DMARD treatment due to an inadequate response.¹⁰ There are still no data available to predict factors that will influence lack of tolerability or an inadequate response to traditional DMARD treatment.¹¹

In the past decade, biologic DMARDs, such as the tumor necrosis factor (TNF) antagonists (eg, etanercept, infliximab, and adalimumab), have become firmly established as effective treatments for RA patients with an inadequate response to traditional DMARDs.^{12–14} The anti-interleukin–1 receptor antagonist anakinra is also an alternative treatment option for these patients.¹⁵ However, as with traditional DMARDs, some patients (20%–40%) who are treated with TNF antagonists do not respond to treatment^{16–18} or may respond initially to treatment, but are unable to sustain the response over time.¹⁹

The definition of an inadequate response to RA treatment continues to evolve, and attempts to clarify the definition have generally been in the context of clinical trial data.²⁰

In clinical trials, the identification of an adequate responder is most commonly based on stringent measures, such as ACR response rates.²¹ The ACR response rates measure the signs and symptoms of RA based on a number of assessments, including the number of swollen and tender joints, physician and patient global assessments of disease activity, and the patient's assessment of pain.³ Measurements of ACR response also include laboratory assessments of acute-phase reactants and physical function, the latter of which is evaluated using the Health Assessment Questionnaire (HAQ).³ The overall response rate represents a discontinuous measure of treatment response and

is scored as either ACR 20, 50, or 70, reflecting a 20%, 50%, or 70% improvement, respectively.³

A second method of assessing clinical improvements uses the Disease Activity Score 28 (DAS28).²² The DAS28 is a continuous measure of disease activity that combines information based on how many of 28 joints are swollen and tender. Patients' general health and the acute phase response (the erythrocyte sedimentation rate or C-reactive protein [CRP] concentration) are also factored.²² The DAS28 is scored on a scale ranging from 0 to 9.4, and the absolute level of disease activity can be selected as a clinically meaningful goal for therapeutic intervention.²³ A DAS28 >5.1 indicates high-disease activity, >3.2 to ≤5.1 is classified as moderate-disease activity, <3.2 is defined as the threshold for a low-disease activity state, and <2.6 as the threshold for remission.²³

Using the described measurements of disease activity, the ACR guidelines state that an inadequate response is defined as repetitive flares of RA, ongoing disease activity after 3 months of maximal treatment, or progressive joint damage.³ In routine clinical practice, it is generally up to the practitioner to decide if the patient is experiencing an inadequate response to a course of treatment. Patients should be periodically assessed for levels of disease activity, as conventionally measured by tender joint counts, swollen joint counts, and the DAS28.

Validated responses to patient-oriented measures, such as the HAQ Disability Index (HAQ-DI) and the Medical Outcomes Survey Short Form-36 (SF-36), are also valuable assessment tools and must be considered to determine patient response to treatment.²⁴ The HAQ-DI is a self-assessment questionnaire, which measures physical impairment and is scored from 0 to 3 (0 = no difficulty and 3 = unable to perform); a change of ≥0.22 units is considered to be clinically meaningful.²⁵ Health-related quality of life can be assessed using the self-reported SF-36, which is scored from 0 to 100 (a score of 100 indicates perfect quality of life)²⁶; a 5- to 10-point change is considered to be a clinically meaningful improvement.²⁷

For a rheumatologist in the day-to-day clinic setting, the management of patients experiencing an inadequate response to treatment can be problematic. If a patient has an inadequate response to a TNF antagonist, the rheumatologist may switch the patient to a different TNF-antagonist agent. Currently available data indicate that switching between TNF antagonists to overcome inadequate efficacy or poor tolerability may be beneficial.²⁸ However, patients who fail to respond to their first TNF antagonist may show an adequate response to a second TNF antagonist.^{28–32} In addition, in patients who had previously discontinued TNF-antagonist treatment, the reasons for discontinuing a second TNF antagonist may be related to the reasons for discontinuation of the first TNF antagonist.²⁸ Alternatively, instead of switching between TNF antagonists, the rheumatologist may choose to increase the dose or shorten the administration interval to improve a patient's response; however, there is still no concrete evidence as to whether these are effective measures.³³ Furthermore, to date, no large controlled clinical trials have effectively assessed the benefits of switching between TNF antagonists.

Two alternative biologic DMARDs are currently available—rituximab and abatacept. Rituximab is a chimeric anti-CD20 monoclonal antibody that selectively depletes CD20+ B cells and is indicated for use in combination with methotrexate.³⁴ Abatacept is a selective T-cell costimulation modulator that may be used as a monotherapy or in combination with a nonbiologic DMARD.³⁵ Rituximab and abatacept are both approved in the United States for the treatment of patients with an inadequate response to TNF-antagonist treatment.^{34,35} Abatacept is also approved for use in patients who have an inadequate response to traditional DMARDs, such as methotrexate.

Abatacept is a fully soluble human fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen (CTLA)-4 linked to the Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1, which has been modified to avoid complement fixation. The mechanism of action of abatacept differs from that of methotrexate, TNF antagonists, and rituximab in that it selectively modulates the activation of T cells.^{35–37} To become fully activated, T cells require 2 signals. Initially, antigens are processed and presented to the T cell by antigen-presenting cells (APCs).³⁷ After antigen recognition, a secondary costimulatory signal is needed to promote full T-cell activation.³⁸ One of the most well characterized costimulatory pathways is the engagement of CD80/CD86 on APCs with CD28 on T cells.^{37,39} Employing the high-binding avidity of CTLA-4 for CD80/CD86 on APCs, abatacept selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation (**Figure**). By targeting the activation of T cells, an upstream event in the immune cascade that underlies RA, abatacept has the potential to impact multiple downstream aspects of RA immunopathogenesis, such as the production of cytokines, autoantibodies, and inflammatory proteins.⁴⁰

The purpose of this review was to provide an overview of the clinical trial data of abatacept, with a focus on Phase III trial data, in patients with an inadequate response to methotrexate and/or TNF antagonists and to discuss the current and future impact of abatacept on the RA treatment armamentarium.

METHODS

A search was performed using the MEDLINE, EMBASE, and BIOSIS databases (search dates: January 1, 2000–September 19, 2007) for literature using the terms *abatacept* or *CTLA-4* or *Orencia* with *rheumatoid arthritis*. Full text articles in English were selected for relevance, and only articles presenting primary clinical trial data from randomized, placebo-controlled clinical trials of abatacept were selected.

ABATACEPT CLINICAL TRIAL DATA

The literature search initially yielded 848 papers. Of these, 15 papers were excluded, as they were not written in English (no primary abatacept randomized,

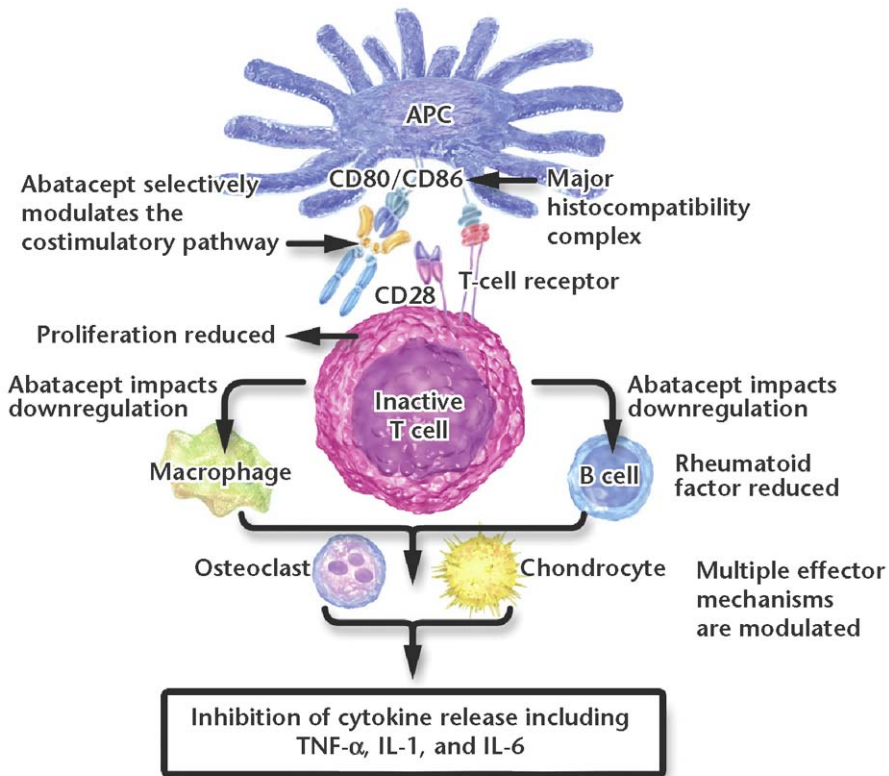


Figure. Mechanism of action of abatacept. APC = antigen-presenting cell; TNF = tumor necrosis factor; IL = interleukin.

placebo-controlled clinical trials were among these excluded papers). Of the remaining 833 papers, 4 were excluded because they were case studies and 247 because they were reviews, leaving 582 primary papers. A total of 549 papers were excluded because they did not describe randomized, placebo-controlled, clinical trial data or did not present data in patients with RA. Of the remaining 33 papers, all of which presented randomized, placebo-controlled clinical trial data in patients with RA, 21 were excluded because they presented clinical data from RA therapies other than abatacept. Therefore, a total of 12 articles fulfilled the inclusion criteria and were included in this article. This review focused mainly on the Phase III trials, as these trials had the largest population of study patients and the longest study duration.

Abatacept was the first biologic RA treatment studied in patients with an inadequate response to methotrexate and/or TNF antagonists.^{41,42} The efficacy and tolerability of abatacept in these patient populations have been assessed in several randomized, double-blind, placebo-controlled studies in patients

aged ≥ 18 years with active RA that was diagnosed according to the ACR and/or American Rheumatism Association (ARA) criteria.^{41–47} A summary of the trials outlined in this review is given in **Table I**.^{41,44,46}

Use of Abatacept in Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate

Clinical Efficacy

The Phase III Abatacept in Inadequate responders to Methotrexate (AIM) trial was a 1-year, multicenter, randomized, double-blind, placebo-controlled study, which examined the efficacy and tolerability of abatacept in patients with moderate-to-severe RA and an inadequate response to methotrexate.⁴⁴ Patients were defined as having an inadequate response if they had *persistent RA*, which was defined as: ≥ 10 swollen joints, ≥ 12 tender joints, and CRP protein levels of ≥ 10.0 mg/L, despite methotrexate treatment (≥ 15 mg/wk for ≥ 3 months). The primary end points of the study were a 20% improvement in ACR response criteria (ACR 20) at 6 months, clinically meaningful improvements (≥ 0.3 units)²⁵ in physical function as measured by the HAQ, and change from baseline in joint erosion, as measured by the Genant-modified Sharp scale score at 1 year.^{48,49} Erosions were scored on an 8-point scale (0–3.5, where 0 = normal and 3 and upwards = severe) at: 10 locations in the hand, 4 in the wrist,⁵⁰ and 6 in the foot.⁴⁸ The joint-space narrowing is scored on a 9-point scale (0–4, where 0 = normal and 4 = ankylosed or dislocated) at: 10 locations in the hand, 3 in the wrist,⁵⁰ and 6 in the foot.⁴⁸ The total score is calculated by the sum of the erosion plus joint-space narrowing score.

Physicians who performed the efficacy and tolerability assessments were blinded to treatment group assignment. An intent-to-treat approach was used for data analysis, including all patients who received ≥ 1 dose of study medication. Using a centralized randomization system, a total of 433 patients were randomized to receive abatacept (10 mg/kg as a standardized dose via IV infusion) plus methotrexate (15 mg/wk, or 10 mg/wk if the patient had a history of toxicity) and 219 to receive placebo plus methotrexate. Abatacept was administered on days 1, 15, and 29, and then every 28 days up to and including day 337. Baseline demographic and clinical characteristics were well matched across treatment groups. A total of 89% of the abatacept group and 74% of the placebo group completed 1 year of treatment. A higher proportion of the placebo group discontinued the study compared with the abatacept group (26% vs 11%). Lack of efficacy was the most common reason for discontinuation in the placebo group compared with the abatacept group (18% vs 3%), and AEs were the most common reason for discontinuation in the abatacept group compared with the placebo group (4% vs 2%, respectively).

Investigators reported that abatacept treatment was associated with statistically significant improvements in the signs and symptoms of RA compared with placebo, as assessed by ACR responses and the DAS28, in this active-disease patient population.⁴⁴ Following 6 months of treatment, improvements

Table 1. Overview of abatacept clinical trials used in this review.

Trial	Design	Dose	Patients	Primary Objectives
Kremer et al, 2006 ⁴⁴ (AIM)	Phase III, 1-year, randomized, double-blind, placebo-controlled trial with parallel administration	Abatacept 10 mg/kg as a standardized dose (500 mg for patients <60 kg, 750 mg for patients 60–100 kg, and 1 g for patients >100 kg) or placebo by IV infusion on a background of methotrexate	Patients with active RA receiving methotrexate Double-blind: Abatacept + methotrexate n = 433 Placebo + methotrexate n = 219	To compare the efficacy of abatacept + methotrexate versus placebo + methotrexate in patients with active RA
Genovese et al, 2005 ⁴¹ (ATTAIN)	Phase III, 6-month, randomized, double-blind, placebo-controlled trial with parallel administration	Abatacept 10 mg/kg as a standardized dose (500 mg for patients <60 kg, 750 mg for patients 60–100 kg, and 1 g for patients >100 kg) or placebo by IV infusion	Patients with active RA who had been treated with TNF-antagonist treatment for ≥3 months and were designated as TNF-antagonist treatment failures due to inadequate efficacy Double-blind: Abatacept + DMARDs n = 258 Placebo + DMARDs n = 133	To determine the efficacy and safety of abatacept in patients with active RA on background DMARDs who had failed TNF-antagonist treatment

(continued)

Table I. (Continued)

Trial	Design	Dose	Patients	Primary Objectives
Weinblatt et al, 2006 ⁴⁶ (ASSURE)	Phase III, 1-year, randomized, double-blind, placebo-controlled trial with parallel administration	Abatacept 10 mg/kg as a standardized dose (500 mg for patients <60 kg, 750 mg for patients 60–100 kg, and 1 g for patients >100 kg) or placebo by IV infusion	Patients with active RA with or without comorbid medical conditions receiving nonbiologic DMARDs and/or biologic treatment approved for RA Double-blind: Abatacept + DMARDs n = 959 Placebo + DMARDs n = 482	To summarize the incidence of AEs, SAEs, and discontinuations due to AEs during 1 year of combined treatment with abatacept and ≥ 1 DMARD and/or biologics approved for RA in patients with active RA with or without comorbid medical conditions

AIM = Abatacept in Inadequate responders to Methotrexate; RA = rheumatoid arthritis; ATTAIN = Abatacept Trial in Treatment of Anti-TNF Inadequate responders; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; ASSURE = Abatacept Study of Safety in Use with other RA therapies; AE = adverse event; SAE = serious adverse event.

in ACR 20, 50, and 70 response rates were all statistically significant in favor of abatacept versus placebo (ACR 20, 68% vs 40%; ACR 50, 40% vs 17%; ACR 70, 20% vs 7%; all, $P < 0.001$). The improvements in ACR responses were sustained over time, with statistically significant differences maintained in the abatacept group compared with the placebo group at 1 year (ACR 20, 73% vs 40%; ACR 50, 48% vs 18%; ACR 70, 29% vs 6%; all, $P < 0.001$). A DAS28 score < 2.6 has been shown to be indicative of clinical remission according to ARA criteria.⁵¹ In the AIM trial, 6-month data revealed a statistically significantly higher percentage of patients in the abatacept group having a DAS28 score < 2.6 compared with placebo (14.8% vs 2.8%; $P < 0.001$).⁴⁴ Similar to the ACR response rates, the proportion of the abatacept group experiencing statistically significant improvements in DAS28 scores increased from 6 to 12 months compared with patients in the placebo group, (6 months, 14.8% vs 2.8%; 12 months, 23.8% vs 1.9% [both, $P < 0.001$]).

In the AIM trial, at 12 months, the abatacept group had a statistically significant inhibition of structural damage progression, with a decrease of ~50% from baseline in Genant-modified Sharp scores compared with placebo. The mean (median) change from baseline in erosion score was 0.63 (0.0) for abatacept versus 1.14 (0.27) for placebo ($P = 0.029$ for median change). The mean (median) change in the joint-space narrowing score was 0.58 (0.0) for abatacept versus 1.18 (0.0) for placebo ($P = 0.009$ for median change). The mean (median) change in total score was 1.21 (0.0) for abatacept versus 2.32 (0.53) for placebo ($P = 0.012$ for median change).⁴⁴

Use of Abatacept in Rheumatoid Arthritis Patients with an Inadequate Response to Tumor Necrosis Factor Antagonists

Clinical Efficacy

An important patient population with limited treatment options is that of patients with an inadequate response to TNF antagonists. These patients typically have progressed substantially through the RA treatment paradigm and might be receiving concurrent DMARD treatment.^{35,41}

The Phase III Abatacept Trial in Treatment of Anti-TNF INadequate responders (ATTAIN) was a 6-month, randomized, double-blind, placebo-controlled study.⁴¹ It was the first trial to evaluate the efficacy and tolerability of a biologic agent for the treatment of patients with RA with an inadequate response to TNF antagonists.

As in the AIM study, patients were randomized to receive either abatacept (10 mg/kg via IV infusion) or placebo in a 2:1 ratio using a centralized randomization system.⁴¹ Abatacept was administered on days 1, 15, and 29, and every 28 days thereafter, up to and including day 141. All patients had to have been taking a stable background dose of an oral DMARD or anakinra for ≥ 28 days and were allowed to continue to receive their current background DMARD medication throughout the study. Stratification according to TNF antagonist use was applied as follows: those receiving TNF-antagonist treatment at the

time of screening (current users) versus those who had previously failed TNF-antagonist treatment (former users). Current users of TNF antagonists had their TNF-antagonist treatment withdrawn before randomization. During the washout period, the number of tender and swollen joints and CRP concentrations were assessed to determine whether there was any disease flare in this patient population prior to randomization. No statistically significant changes were observed in either measure, indicating that no flare occurred and that these patients actually were experiencing an inadequate response to their TNF-antagonist treatment and had persistent RA. An intent-to-treat population that included all randomized patients who received ≥ 1 dose of study drug was used for efficacy analyses. All study personnel were blinded to treatment group.

A total of 258 patients were randomized to abatacept and 133 to placebo (all patients continued to receive ≥ 1 background DMARD), with 223 (86.4%) and 99 patients (74.4%), respectively, completing the study. The primary reason for discontinuation in both treatment groups was lack of efficacy (5.4% and 20.3% for the abatacept and placebo groups, respectively). Baseline demographic and clinical characteristics did not differ significantly across treatment groups. Patients in the ATTAIn trial had active disease at baseline, with long-standing RA as evidenced by an average disease duration of ~ 12 years (a slightly longer disease duration than typical trial populations of patients with an inadequate response to methotrexate, such as in the AIM trial⁴⁴). This was reflected in high mean counts of tender and swollen joints (tender joints, 31 and 33, for abatacept and placebo, respectively; swollen joints, 22 for both groups). In addition, patients had impaired physical function, as seen in low HAQ-DI scores (1.8 for both groups), high DAS28 scores (6.5 for both groups), and elevated CRP concentrations (4.6 mg/dL and 4.0 mg/dL for abatacept and placebo, respectively), which are all consistent with active disease.

The ATTAIn trial found that abatacept treatment was associated with statistically significant improvements in the signs and symptoms of RA over 6 months compared with placebo-treated patients, as assessed by ACR responses and DAS28.⁴¹ The improvements in the ACR response rates for the ATTAIn trial were statistically significant for abatacept versus placebo at 6 months: ACR 20, 50.4% versus 19.5% ($P < 0.001$); ACR 50, 20.3% versus 3.8% ($P < 0.001$); and ACR 70, 10.2% versus 1.5% ($P = 0.003$). These statistically significant improvements were evident in both current and former users of TNF-antagonist treatment (both, $P < 0.001$), which suggests that the time between discontinuation of TNF-antagonist treatment and the initiation of abatacept treatment did not impact the level of benefit achieved.

In addition to the improvements in ACR scores, a statistically significantly higher percentage of patients in the abatacept group achieved a DAS28 score indicative of clinical remission (ie, DAS28 < 2.6) after 6 months of treatment compared with the placebo group (10.0% vs 0.8%; $P < 0.001$).⁴¹

A summary of the clinical efficacy after abatacept treatment in patients with an inadequate response to methotrexate and in those not responding

adequately to TNF antagonists, as found in the AIM⁴⁴ and ATTAIN⁴¹ trials, respectively, is shown in **Table II**.

Improvements in Health-Related Quality of Life with Abatacept

Abatacept treatment has been found to be associated with clinically meaningful improvements in all 8 subscales of the SF-36, including the physical and the mental component summary scores (PCS and MCS, respectively) in inadequate responders to both methotrexate and TNF antagonists in the AIM and ATTAIN trials, respectively.^{41,44,52,53} These clinically meaningful improvements were also statistically significant in favor of abatacept compared with placebo at the respective study end points. In addition, both statistically and clinically significant improvements in physical function were seen with abatacept treatment in both patient populations.^{41,44}

After 1 year of treatment in the AIM trial, abatacept was associated with significantly improved patients' physical function, as measured by the HAQ-DI.⁴⁴ Clinically meaningful improvements in physical function (denoted by an improvement of ≥ 0.3 units from baseline²⁴) were achieved in 64% of the abatacept group compared with 39% of the placebo group.⁴⁴ Improvements in 5 of the 8 subscales of the SF-36 were seen as early as day 29 in the abatacept group.⁵² At 6 months, the abatacept group had clinically significant improvements (as defined by a reduction of 3 units on the SF-36 scale), which were also statistically significant compared with the placebo group in all 8 subscales of the SF-36, including the PCS ($P < 0.001$) and MCS ($P = 0.009$). These improvements were sustained over 1 year of treatment and were statistically significant for the abatacept group (PCS, $P < 0.001$; MCS, $P = 0.038$).⁴⁴ At year 1, there were also statistically significant improvements for the abatacept group compared with the placebo group with regard to change from baseline in activity limitation (-8.4 vs -4.5 ; $P < 0.001$), fatigue severity (-25.9 vs -17.3 ; $P = 0.003$), and sleep problems (-10.4 vs -7.2 ; $P = 0.019$).⁵⁴ At year 1, a statistically significantly higher proportion of the abatacept group compared with the placebo group had improvements in daily activity (58.7% vs 44.5%; $P = 0.001$), fatigue (69.1% vs 51.1%; $P < 0.001$), and sleep (58.0% vs 46.7%; $P = 0.005$). These improvements were defined as being clinically meaningful, as they exceeded the minimal clinically important differences (MCIDs) for activity limitation, fatigue, and sleep (4, 10, and 6, respectively). Improvements in fatigue for the abatacept group were observed as early as day 29 in the AIM trial.⁵²

In the ATTAIN trial, 47% of the patients in the abatacept group achieved clinically meaningful improvements in physical function compared with 23% of patients in the placebo group ($P < 0.001$).⁴¹ Patients in the ATTAIN trial were functioning between 1 and 2 SDs below the norm in terms of health-related quality of life (HRQoL).⁵³ At 6 months, the abatacept group had statistically significantly greater improvements compared with the placebo group in all 8 subscales of the SF-36, including the PCS and MCS ($P < 0.001$ and $P < 0.01$, respectively).⁴¹ These improvements in the abatacept group were also clini-

Table II. Efficacy findings in the Abatacept in Inadequate responders to Methotrexate (AIM)⁴⁴ and Abatacept Trial in Treatment of Anti-TNF Inadequate responders (ATTAIN)⁴¹ clinical trials.

Trial	ACR Responders (% of Responders)			DAS28 (% of Patients)		Inhibition of Structural Damage,* (Mean [SD] Change)			Frequency of Adverse Events (% of Patients)	
	20	50	70	Remission (DAS28 <2.6)	LDAS (DAS28 ≤3.2)	Erosion Score	JSN Score	Total Score	Adverse Events	Serious Adverse Events
AIM— 6 months abatacept	67.9 [†]	39.9 [†]	19.8 [†]	14.8 [†]	30.1 [†]	—	—	—	—	—
AIM— 6 months placebo	39.7	16.8	6.5	2.8	10.0	—	—	—	—	—
AIM— 1 year abatacept	73.1 [†]	48.3 [†]	28.8 [†]	23.8 [†]	42.5 [†]	0.63 (1.8) [‡]	0.58 (1.5) [§]	1.21 (2.9)	87.3	15.0
AIM— 1 year placebo	39.7	18.2	6.1	1.9	9.9	1.1 (2.81)	1.2 (2.58)	2.3 (5.04)	84.0	11.9
ATTAIN— 6 months abatacept	50.4 [†]	20.3 [†]	10.2 ^{†¶}	10.0 [†]	17.1 [†]	—	—	—	79.5	10.5
ATTAIN— 6 months placebo	19.5	3.8	1.5	0.8	3.1	—	—	—	71.4	11.3

ACR = American College of Rheumatology; DAS28 = Disease Activity Score 28; LDAS = low disease-activity state; JSN = joint-space narrowing. *Erosions were scored on an 8-point scale (0–3.5) and joint-space narrowing scored on a 9-point scale (0–4). Total score is the sum of erosion and joint-space narrowing score.

[†]*p* < 0.001 versus placebo.

[‡]*p* = 0.029 versus placebo.

[§]*p* = 0.009 versus placebo.

^{||}*p* = 0.012 versus placebo.

[¶]*p* = 0.003 versus placebo.

cally meaningful. At 6 months, greater and statistically significant reductions in activity limitation were reported for the abatacept group compared with the placebo group (-7.4 vs -1.3 ; $P < 0.001$). Significant reductions in fatigue severity (-22.3 vs -5.3 ; $P < 0.001$) and sleep problems (-9.8 vs -2.1 ; $P < 0.001$) were also noted.⁵⁴ At 6 months, a higher proportion of the abatacept group compared with the placebo group had clinically meaningful improvements, which were statistically significant in favor of abatacept in activity limitation (53.1% vs 31.1%; $P < 0.001$), fatigue (58.5% vs 37.1%; $P < 0.001$), and sleep (58.9% vs 37.9%; $P < 0.001$), as defined by improvements exceeding the MCIDs of 4, 10, and 6, respectively.⁵⁴ Across both the AIM and ATTAIn trials, rapid improvements in HRQoL outcomes, such as fatigue, were observed as early as 4 and 2 weeks, respectively, which support the suggestion that clinically meaningful changes are provided to patients.^{52,53}

Improvements in HRQoL seen with abatacept have a strong correlation with clinical responses: the greatest improvements in HRQoL (SF-36) were observed in patients achieving a higher ACR response, while the smallest improvements in HRQoL were observed in patients who failed to achieve an ACR 20 response.⁵² This illustrates the positive relationship between the level of ACR improvement and improvements in HRQoL measurements and suggests that the clinical efficacy seen with abatacept may translate into tangible benefits for the patient.

Safety Profile and Tolerability of Abatacept

The tolerability of abatacept has been studied in 5 trials, including the AIM and ATTAIn trials and an additional Phase III trial, the Abatacept Study of Safety in Use with other RA therapies (ASSURE) trial. This trial was designed to encompass a wide range of RA patients receiving a variety of nonbiologic and biologic background RA therapies, a patient population that is regularly encountered in routine clinical practice.⁴⁶

A tolerability analysis³⁵ performed by the drug manufacturer included data from the AIM, ATTAIn, and ASSURE trials, along with 2 other 1-year, Phase IIb, randomized, placebo-controlled clinical trials: abatacept in combination with etanercept⁴⁷ in etanercept inadequate responders and abatacept plus methotrexate in patients who had an inadequate response to methotrexate.⁴³ These were placebo-controlled trials of abatacept, which had a double-blind period of 6 months (258 and 133 patients in the abatacept and placebo groups, respectively) or 12 months (1697 and 856 in the abatacept and placebo groups, respectively), with a total of 1955 patients in the abatacept group and 989 in the placebo group. Data from this analysis indicate that abatacept was generally well tolerated in patients with an inadequate response to methotrexate or to TNF antagonists when used in combination with nonbiologic background DMARDs.

The most commonly reported AEs, which occurred in $\geq 3\%$ of all patients and $\geq 1\%$ more frequently in abatacept-treated patients were: headache (18%), nasopharyngitis (12%), dizziness (9%), and cough (8%).³⁵ Infections were reported in

54% of the abatacept group and 48% of the placebo group, and the overall frequencies of malignancies were similar in both groups (1.3% and 1.1%, respectively). In the double-blind periods (1955 patients in the abatacept group), a total of 4 cases of lung cancer (0.2%) were reported in the abatacept group compared with 0 cases in the placebo group. In the cumulative period (placebo-controlled and uncontrolled, open-label trials), a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 of lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (a total of 3827 patient-years). Although the role of abatacept in the development of malignancies is unknown, patients with active RA are at a greater risk for the development of lymphoma (~3.5-fold higher than expected in an age- and gender-matched general population based on the Surveillance, Epidemiology and End Results Database [National Cancer Institute, Bethesda, Maryland]).

The ASSURE trial was a 1-year, randomized, double-blind, placebo-controlled study, designed to investigate the safety of abatacept in patients receiving background biologic/nonbiologic DMARDs. A total of 1231 patients with active RA, despite receiving biologic/nonbiologic DMARDs (≥ 1 medication for ≥ 3 months) were included and received abatacept or placebo. Abatacept was administered as an IV infusion, at a dose of 10 mg/kg, according to weight range, on days 1, 15, 29 and every 4 weeks thereafter. Patients continued to receive background biologic/nonbiologic therapy throughout the trial.

Investigators reported that when comparing the abatacept-treated patients in the subgroups receiving background biologic and nonbiologic treatment, there was an increase in discontinuations, AEs, and serious AEs in the biologic-background-treatment subgroup.⁴⁶ Serious infections in the abatacept-treated patients in the biologic versus nonbiologic subgroup were 5.8% vs 2.6%, respectively. These findings are consistent with previous trials that attempted to combine 2 biologic agents.^{35,47} In a trial that investigated the efficacy and safety of abatacept in combination with etanercept, 16.5% of patients receiving these 2 biologic therapies experienced serious AEs, compared with 2.8% patients in the etanercept plus placebo group.⁴⁷ Serious infections were experienced by 3.5% and 0% patients, in the etanercept plus abatacept and etanercept plus placebo groups, respectively. Based on the evidence from that trial and the results of the ASSURE trial,⁴⁶ abatacept used concurrently with another biologic is not recommended.³⁵

Pulmonary AEs, such as the exacerbation of chronic obstructive pulmonary disease (COPD), have been noted in clinical trials with biologic DMARDs, such as TNF antagonists.^{55,56} In the ASSURE trial, 37 patients with COPD were treated with abatacept and 17 patients with COPD were administered placebo.⁴⁶ A total of 43% of abatacept-treated patients experienced a respiratory disorder AE, such as exacerbation of COPD, compared with 24% placebo-treated patients. Therefore, patients with RA and COPD should be monitored closely when receiving abatacept.³⁵

It has been recommended that RA patients treated with TNF antagonists should be screened for latent tuberculosis.⁵⁷ Prior to randomization in the AIM

trial, all patients were evaluated for latent tuberculosis infection.⁴⁴ Patients who were positive for the purified protein derivative test were excluded from the trial. Since abatacept has not been studied in patients with a positive tuberculosis screening examination, the tolerability of abatacept in individuals with latent tuberculosis infection is unknown. Additional long-term data are needed to ascertain if there is a link between abatacept treatment and an increase in the relative risk of tuberculosis.

The safety and tolerability profile of abatacept has been found to be consistent throughout treatment over 1 year.³⁵ However, further observations in routine clinical practice are required to fully document the long-term safety and tolerability data.

Reports of acute infusion-related events (AEs occurring <1 hour after the start of the infusion), which were assessed in Phase III trials only, were reported in 9% of abatacept-treated patients compared with 6% of placebo-treated patients. However, <1% of the abatacept group discontinued due to an acute infusion-related event.³⁵

DISCUSSION

Rheumatologists and patients currently have a variety of options available for the treatment of RA. Patients are generally prescribed traditional DMARDs as first-line treatment.³ However, discontinuation rates are generally high (~40% to 50%) and are primarily associated with either a lack of efficacy or safety issues. Biologic DMARD therapies, such as TNF antagonists, have provided clinical benefits to these patients and, therefore, offer valuable alternative treatment options. However, it has been reported that 20% to 40% of patients have an inadequate response to TNF antagonists, and switching between these agents, increasing the dose, or decreasing the administration interval may not be effective in all patients.³³ There are also no clear guidelines available on the effective management of inadequate responders to TNF antagonists.

Before the approval of rituximab and abatacept, patients deemed to have an inadequate response to TNF-antagonist treatment had limited future treatment options. Abatacept is indicated either as a monotherapy or in combination with other nonbiologic DMARDs in patients with an inadequate response to methotrexate, as well as TNF antagonists. Abatacept provides a valuable treatment option for use in adult patients with moderate-to-severe RA who have not benefited from previous methotrexate or TNF-antagonist treatment.

The clinical profile of abatacept, as assessed by multiple measures of clinical efficacy in Phase III clinical trials, indicates that this recent addition to the RA treatment paradigm provides significant clinical benefit and a consistent safety profile in patients who have experienced an inadequate response to methotrexate and for those who have not responded to TNF antagonists. Notable benefits with abatacept in both patient populations include clinically meaningful improvements in HRQoL (eg, fatigue) within the first month of treatment, as well

as in the durability of the clinical response and safety profile seen with treatment. By improving HRQoL, abatacept might also provide benefits for patients with RA with previous inadequate responses to standard treatment. Long-term studies are needed to continually assess the efficacy, HRQoL, and tolerability of abatacept and to further support the findings outlined in this review.

In this analysis, there were no stringent predefined inclusion and exclusion criteria used to select the studies. Only randomized, double-blind, placebo-controlled primary abatacept clinical data were included, and papers were only included if they were written in English. These inclusion criteria could potentially have introduced bias into the search results, as only published full manuscripts were selected, thereby excluding abstracts. In addition, the quality and validity of the included publications were not assessed.

The findings from long-term extension periods of the AIM⁵⁸ and ATTAIN⁵⁹ trials will be published in the near future (both presenting 2-year data), adding to the long-term efficacy and safety experience of abatacept. A Phase IIIb, randomized, double-blind, placebo-controlled, parallel-assignment study of abatacept or infliximab in combination with methotrexate in controlling disease activity in patients with RA having an inadequate response to methotrexate has now been completed.⁶⁰ Even though this study was not designed to specifically compare the efficacy of abatacept with infliximab, this is the first trial to incorporate 2 biologic treatment arms in a single study.

Other recently completed, but as yet unpublished, abatacept trials include an evaluation of the tolerability of abatacept in children and adolescents with active polyarticular juvenile RA.⁶¹ Trials assessing abatacept treatment in early RA are also being conducted.⁶² Other ongoing trials include the evaluation of the tolerability and efficacy of abatacept in populations other than in the United States that have an inadequate response to methotrexate, such as Korean and Japanese patients with RA.^{63–65} The results of these trials and use in routine clinical practice will add to the current knowledge regarding the efficacy and safety data already available on abatacept.

CONCLUSION

The efficacy and tolerability data from Phase III clinical trials suggest that abatacept is an effective and generally well tolerated treatment option for RA patients with an inadequate response to methotrexate and/or TNF antagonists.

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