

# Critical appraisal of efficacy and safety of abatacept in the treatment of refractory rheumatoid arthritis

Lisa M Lundquist<sup>1</sup>

Sabrina W Cole<sup>2</sup>

Jill M Augustine<sup>1</sup>

<sup>1</sup>Mercer University College of Pharmacy and Health Sciences, Atlanta, GA, <sup>2</sup>Wingate University School of Pharmacy, Wingate, NC, USA

**Abstract:** Rheumatoid arthritis is a chronic, progressive, autoimmune disease that leads to significant disability and premature mortality. Various treatment options are available, but the foundation of treatment includes nonbiologic and biologic disease-modifying antirheumatic drugs. The incidence of patients with rheumatoid arthritis refractory to first-line agents is estimated to be at least 20%. Abatacept, a T cell costimulation modulator, is the first agent to interfere with full T cell activation by competing with CD28 for binding of CD80 and CD86, which results in decreased secretion of proinflammatory cytokines and autoantibody production. Current American College of Rheumatology treatment guidelines recommend abatacept for patients with at least moderate disease activity and a poor prognosis demonstrating an inadequate response to other agents. Several key Phase III trials have been conducted to evaluate the efficacy and safety of abatacept in patients with an inadequate response to methotrexate or anti-tumor necrosis factor alpha therapy. Response rates in all trials showed statistically significant improvements compared with placebo according to American College of Rheumatology criteria for disease improvement. The most common adverse event report in patients receiving abatacept was infection; however, the frequency of adverse events was similar to placebo. Abatacept is a safe and effective rheumatoid arthritis treatment for patients with an inadequate response to methotrexate or anti-tumor necrosis factor alpha therapy.

**Keywords:** abatacept, rheumatoid arthritis, treatment refractory, biologic, disease-modifying antirheumatic drugs

## Introduction

Rheumatoid arthritis, a chronic, progressive, autoimmune disease, is characterized by destructive synovitis, joint swelling, and joint tenderness, and causes pain, stiffness, inflammation, and limitation in the motion and function of multiple joints. Many patients with rheumatoid arthritis develop progressive destructive disease that leads to significant disability and premature mortality.<sup>1</sup> An estimated 0.5%–1% of the adult population in developing countries is affected by rheumatoid arthritis, with the average age increasing over time to an average of approximately 67 years in 1995 from 63 years in 1965.<sup>2–4</sup> It is estimated that 1.3 million (0.6%) adults have rheumatoid arthritis in the US.<sup>2</sup>

The 1987 Revised Criteria for the Classification of Rheumatoid Arthritis, published by the American College of Rheumatology (ACR) have come under scrutiny in recent years given their limited sensitivity and specificity and failure to identify patients with early characteristics of rheumatoid arthritis.<sup>1,3,5</sup> A joint working group of the ACR and the European League Against Rheumatism was convened to develop new classification criteria to identify individuals with early-stage disease, and those

Correspondence: Lisa M Lundquist  
Mercer University College of Pharmacy  
and Health Sciences, 3001 Mercer  
University Drive, D-110, Atlanta,  
GA, USA 30341-4155  
Tel +1 678 547 6308  
Fax +1 678 547 6315  
Email [lundquist\\_lm@mercer.edu](mailto:lundquist_lm@mercer.edu)

criteria were published in 2010.<sup>1</sup> The revisions were intended to identify patients with earlier stages of the disease, given that recognition and early therapeutic intervention improves clinical outcomes and reduces the accrual of joint damage and disability.<sup>1,3</sup> A comparison of the classification criteria is detailed in Table 1.

While the exact etiology of rheumatoid arthritis is not known, once the autoimmune inflammatory process begins in the synovial tissue, a cascade of events occurs at the cellular level. Antigen-presenting cells (eg, activated macrophages, activated B cells) lead to activation of T cells that are predominant in the tissue of the synovium, and the subsequent result of T cell activation is the secretion of cytokines that drives further synovial proliferation.<sup>3,4,6</sup> T cells stimulate overproduction of the interleukin-1, interleukin-6, and tumor necrosis factor alpha (TNF- $\alpha$ ) cytokines which are key factors in the inflammatory process of rheumatoid arthritis. The inflammatory process in the synovial tissue results in proliferation of synovial tissue and synovitis, thus leading to overproduction of synovial fluid and invasion of pannus into the surrounding bone and cartilage. This process leads to the clinical picture of rheumatoid arthritis, with deformation and disability due to damage to the bone and cartilage and destruction of the joint.

The disease-modifying antirheumatic drugs (DMARDs) provide the foundation of treatment for rheumatoid

arthritis and combinations of DMARDs with nonsteroidal anti-inflammatory drugs or glucocorticoids are used frequently in clinical practice.<sup>7</sup> Current treatment guidelines from the ACR note that there are more than 170 possible dual-DMARD and triple-DMARD combinations among the recommended nonbiologic DMARDs, methotrexate, leflunomide, hydroxychloroquine, minocycline, and sulfasalazine. However, the following combinations are included in the treatment guidelines, given the strength of the evidence supporting their use: methotrexate plus hydroxychloroquine, methotrexate plus sulfasalazine, methotrexate plus leflunomide, sulfasalazine plus hydroxychloroquine, and sulfasalazine plus hydroxychloroquine plus methotrexate. The recommended regimen is individualized and based on disease duration, disease activity, and prognosis (ie, active disease with high tender and swollen joint counts, radiographic erosions, elevated rheumatoid factor and/or anticyclic citrullinated peptide antibodies, elevated erythrocyte sedimentation rate, and/or elevated C-reactive protein concentration). However, methotrexate or leflunomide monotherapy is recommended initially regardless of these factors.

The use of the biologic DMARDs, ie, abatacept, adalimumab, etanercept, infliximab, and rituximab, should be reserved for patients who have failed treatment with nonbiologic DMARDs.<sup>7</sup> Although other biologic DMARDs are available, (eg, anakinra, certolizumab, golimumab) they are

**Table 1** Comparison of 1987 and 2010 classification criteria for rheumatoid arthritis<sup>1,5</sup>

ACR 1987 criteria	ACR/EULAR 2010 criteria
<ol style="list-style-type: none"> <li>Morning stiffness lasting at least 1 hour before maximal improvement</li> <li>Arthritis in 3 or more joint areas with simultaneous soft tissue swelling or fluid</li> <li>Arthritis in at least 1 of the following: wrist, metacarpophalangeal, or 6 weeks proximal interphalangeal joints</li> <li>Symmetrical joint swelling</li> <li>Subcutaneous nodules</li> <li>Positive rheumatoid factor</li> <li>Radiographic changes consistent with RA</li> </ol>	<ol style="list-style-type: none"> <li>Joint involvement               <ol style="list-style-type: none"> <li>1 large joint (0)</li> <li>2–10 large joints (1)</li> <li>1–3 small joints (with or without involvement of large joints) (2)</li> <li>4–10 small joints (with or without involvement of large joints) (3)</li> <li>&gt;10 joints (at least 1 small joint) (5)</li> </ol> </li> <li>Serology (at least 1 test result is needed for classification)               <ol style="list-style-type: none"> <li>Negative RF and negative ACPA (0)</li> <li>Low-positive RF or low-positive ACPA (2)</li> <li>High-positive RF or high-positive ACPA (3)</li> </ol> </li> <li>Acute-phase reactants (at least 1 test result is needed for classification)               <ol style="list-style-type: none"> <li>Normal CRP and normal ESR (0)</li> <li>Abnormal CRP or abnormal ESR (1)</li> </ol> </li> <li>Duration of symptoms               <ol style="list-style-type: none"> <li>&lt;6 weeks (0)</li> <li>≥6 weeks (1)</li> </ol> </li> </ol>
Four of the seven criteria must be present and criteria 1–4 must have been present for at least 6 weeks	A score ≥6 classifies a patient as having RA

**Note:** Patients with erosive disease with a history of prior fulfillment of the 2010 criteria should be classified as having RA, as well as, patients with longstanding disease, including those whose disease is inactive who have previously fulfilled the 2010 criteria. Adapted with permission from: (1) Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum.* 2010;62:2569–2581. © 2010, American College of Rheumatology; (2) Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31:315–324. © The American Rheumatism Association.

**Abbreviations:** ACPA, anticyclic citrullinated peptide antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor.

excluded from the ACR treatment guidelines due to their limited use in patients with rheumatoid arthritis or are not recommended for patients beginning or resuming treatment. The choice of biologic DMARD should be determined by disease duration, disease activity, and prognosis. Combination therapy using the biologic DMARDs is not recommended due to a lack of supporting evidence of their enhanced efficacy and the propensity toward increased rates of adverse reactions. Abatacept and rituximab should be reserved for patients with a poor prognosis who have demonstrated an inadequate response to the combination of methotrexate and DMARDs or sequential administration of other nonbiologic DMARDs with at least moderate disease activity for use of abatacept and high disease activity for use of rituximab.

Historically, the goal for therapeutic management has been symptomatic relief, but goals of treatment have evolved into clinical remission, given the significant advancements in recent years using multiple biologic therapies.<sup>8–10</sup> Although treatment guidelines reserve use of biologic agents for patients who have demonstrated an inadequate response to other therapies, there is no consensus definition of rheumatoid arthritis remission, and the terms “refractory rheumatoid arthritis” or “inadequate response” are debated in the rheumatology community.<sup>4,8,9,11–15</sup> Although the possibility of a state of complete remission of rheumatoid arthritis is widely accepted, until recently, specific criteria for making such a claim were not defined. A working group of the ACR (formerly the American Rheumatism Association) published criteria defining clinical remission in 1981.<sup>12</sup> Pinals et al noted that complete and partial remission were used to describe the total absence of and reduced disease activity, respectively, although there was a lack of consensus and clarity of clinical and radiographic disease activity. There continues to be a lack of consistency with the use of terminology regarding remission, inadequate response, and failure of therapeutic regimens.

The definition of improvement in rheumatoid arthritis has traditionally been recognized by the ACR20, ie, 20% improvement in tender and swollen joint counts and 20% improvement in at least three of the ACR core set measures, ie, pain, patient and physician global assessment, self-assessed physical disability, and acute-phase reactant.<sup>16</sup> This definition was developed in response to widespread use of multiple definitions for improvement and corresponded closely with the clinical impression of a patient's improvement because it emphasizes joint counts. However, recent developments in therapeutic options have resulted in dramatic reductions in disease activity. Revisions to the ACR20 allowed for more stringent criteria

for improvement, such as ACR50 and ACR70 with 50% and 70% improvement, respectively.<sup>10</sup> The disease activity score in 28 joints (DAS28) is used in clinical trials as well as in practice to describe disease activity and guide treatment decisions. The score is calculated from the results of a joint examination based on joint characteristics (ie, swollen and/or tender) at the shoulder, elbow, wrist, metacarpophalangeal joint, proximal interphalangeal joint, and knee.

With clinical remission of rheumatoid arthritis being a realistic and attainable goal, the definition of remission was revised to incorporate more stringent clinical markers and patient-reported outcomes.<sup>9</sup> The criteria for remission are detailed in Table 2.

With inconsistency in the definition of inadequate response to therapeutic options for the treatment of rheumatoid arthritis, an estimation of patients refractory to first-line nonbiologic and biologic DMARDs is difficult. However, it is suggested that at least 30% of patients treated with a TNF- $\alpha$  inhibitor do not respond (primary failure) or demonstrate a diminished clinical response during treatment after an initial benefit (secondary failure).<sup>11,13,17</sup> The remaining therapeutic options for these patients include treatment with a B cell-depleting agent (ie, rituximab) or administration of a T cell costimulation antagonist (ie, abatacept). This review will focus on literature evaluating the role of abatacept in patients with rheumatoid arthritis refractory to other treatment options.

## Pharmacology, mechanism of action, and pharmacokinetics

Activation of T cells is dependent on antigen-presenting cells, such as activated B cells and macrophages, and costimulation,

**Table 2** American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis<sup>9</sup>

### Boolean-based definition:

At any time point, patient must satisfy all of the following:

- Tender joint count  $\leq$  1
- Swollen joint count  $\leq$  1
- C-reactive protein  $\leq$  1 mg/dL
- Patient global assessment  $\leq$  1 (on a 0–10 scale)

### Index-based definition:

At any time point, patient must have a

- Simplified disease activity index score  $\leq$  3.3

[Defined as the sum of the following: tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale) and C-reactive protein concentration (mg/dL)]

**Note:** Reproduced with permission from: Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum*. 2011;63:573–586. © 2011, American College of Rheumatology.

such as by CD80 and CD86.<sup>4,18</sup> The prevention of full T cell activation may limit the joint destruction characterized by rheumatoid arthritis. Abatacept, a recombinant soluble fusion protein, consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 linked to the modified Fc portion of human immunoglobulin G1 and has a high affinity to CD28. Abatacept is the first agent to target and thus interfere with full T cell activation by competing with CD28 for binding of CD80 and CD86.<sup>4,18–20</sup> The immunopathology of rheumatoid arthritis and role of abatacept for the treatment of rheumatoid arthritis is depicted in Figure 1.

In vitro studies of abatacept demonstrate a decrease in T cell proliferation and production inhibition of TNF- $\alpha$ , interferon gamma, and interleukin-2; however, the effect of these mechanisms in the clinical picture of rheumatoid arthritis is not known.<sup>18</sup> While decreases in serum concentrations of soluble interleukin-2 receptor, interleukin-6, rheumatoid factor, C-reactive protein, matrix metalloproteinase-3, and TNF- $\alpha$  have been observed with approximate doses of 10 mg/kg, their clinical relevance is unknown.

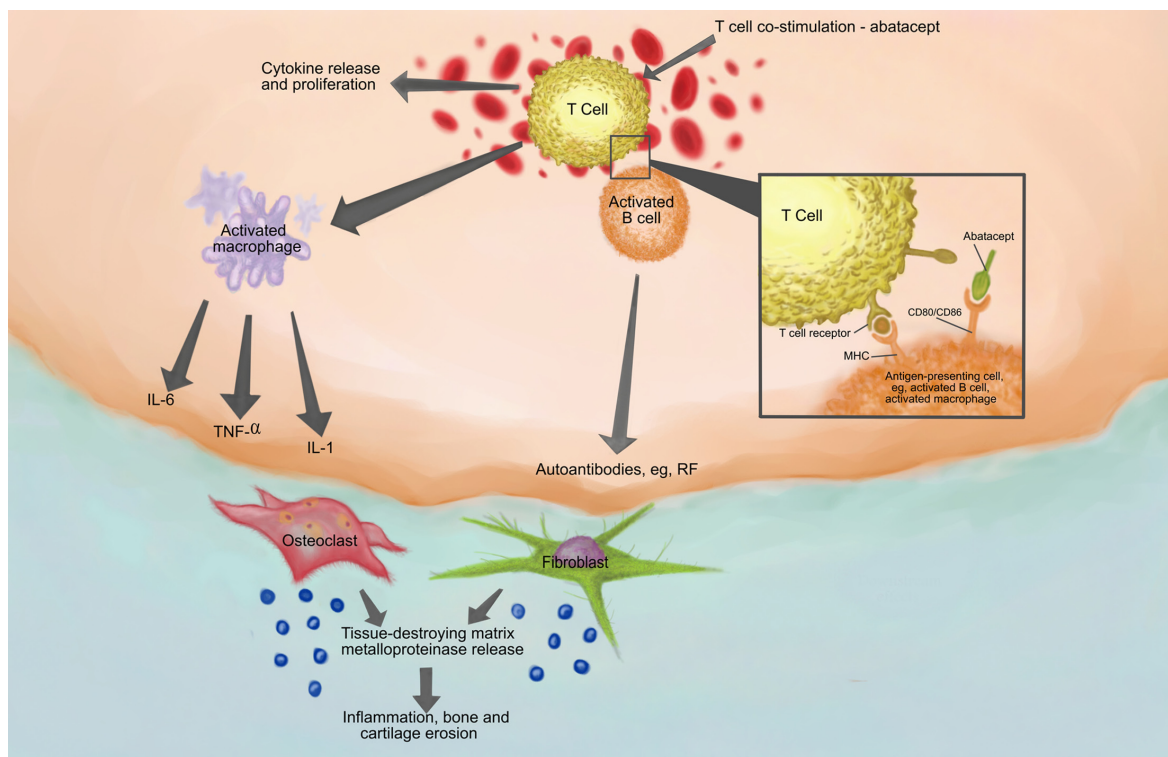
In a small pharmacokinetic study of 13 healthy subjects and 14 subjects with rheumatoid arthritis, the pharmacokinetic parameters of abatacept appeared to be similar.<sup>18</sup> Each healthy subject received a single dose of 10 mg/kg, whereas subjects with rheumatoid arthritis received multiple infusions

of 10 mg/kg, each administered on days 1, 15, 30, and then monthly. The pharmacokinetic parameters are detailed in Table 3. Following multiple injections of abatacept in patients with rheumatoid arthritis, steady-state concentration was achieved by day 60, with a mean trough concentration of 24 (1–66  $\mu\text{g/mL}$ ), and no systemic accumulation was observed with continuation of monthly doses of 10 mg/kg.

Abatacept clearance was not affected by the confounding factors of age, gender, or concomitant administration of methotrexate, nonsteroidal anti-inflammatory drugs, corticosteroids, or TNF- $\alpha$  inhibitors. The effect of renal or hepatic impairment on the pharmacokinetic profile of abatacept has not been formally evaluated. Given the relationship between increase in clearance and increase in body weight, abatacept is dosed according to weight ranges (ie, <60 kg, 60–100 kg, and >100 kg).

## Efficacy studies

A multicenter, multinational, randomized, double-blind, placebo-controlled, Phase II trial examined the efficacy of abatacept (also known as CTLA-4Ig) compared with belatacept (LEA29Y) and placebo.<sup>21</sup> Belatacept is a useful comparator because its molecule is based on abatacept. Belatacept has a similar mechanism of action to abatacept, except that it has a two-fold greater binding affinity for CD80 and a four-fold greater binding affinity for CD86. Belatacept



**Figure 1** Immunopathology of rheumatoid arthritis and mechanism of abatacept in the treatment of rheumatoid arthritis.

**Abbreviations:** IL, interleukin; TNF- $\alpha$ , tumor necrosis factor alpha; RF, rheumatoid factor.



**Table 3** Pharmacokinetic parameters of abatacept in healthy subjects and subjects with rheumatoid arthritis<sup>18</sup>

Pharmacokinetic parameter	Healthy subjects following a single dose of 10 mg/kg, n = 13 Mean (range)	Subjects with RA after multiple doses of 10 mg/kg, n = 14 Mean (range)
Peak concentration (µg/mL)	292 (175–427)	295 (171–398)
Terminal half-life (days)	16.7 (12–23)	13.1 (8–25)
Systemic clearance (mL/h/kg)	0.23 (0.16–0.30)	0.22 (0.13–0.47)
Volume of distribution (L/kg)	0.09 (0.06–0.13)	0.07 (0.02–0.13)

**Note:** Adapted from the Pharmacokinetics Table 3 in the full prescribing information for Orencia.<sup>18</sup>

**Abbreviation:** RA, rheumatoid arthritis.

was chosen as a comparator to determine the preliminary efficacy of the blockade of CD80 and CD86. Two hundred and sixteen patients received either placebo, abatacept 0.5 mg/kg, 2 mg/kg, or 10 mg/kg, or belatacept 0.5 mg/kg, 2 mg/kg, or 10 mg/kg. Only two infusions of the study medication were given to patients prior to being assessed for efficacy. To be enrolled in the study, patients had to meet the ACR criteria for rheumatoid arthritis and be in functional class I, II, or III, be aged 18–65 years with disease duration of less than 7 years, have greater than 10 swollen joints, greater than 12 tender joints, and have been treated unsuccessfully with at least one classic DMARD. Patients were excluded if a positive serum or urine pregnancy test was obtained within 72 hours prior to starting the study medication or if nursing. Patients were allowed to continue treatment with low-dose corticosteroids or nonsteroidal anti-inflammatory drugs. Patients were assessed on efficacy using the ACR20, ACR50, and ACR70 criteria and on safety. Patients, who received either agent had an increased dose-response achievement of ACR20 (abatacept 2 mg/kg 43%, abatacept 10 mg/kg 52%; belatacept 0.5 mg/kg 35%, belatacept 2 mg/kg 44%, and belatacept 10 mg/kg 61%). More patients who received abatacept 2 mg/kg or 10 mg/kg had an improvement in their ACR50 and ACR70 scores (abatacept 2 mg/kg 19% and 12%; abatacept 10 mg/kg 16% and 8%, respectively) compared with belatacept 0.5 mg/kg (8% and 0%), 2 mg/kg (10% and 3%) or 10 mg/kg (12% and 3%). The authors concluded that an abatacept dose of 10 mg/kg should be utilized in other clinical trials because it showed efficacy in patients with refractory rheumatoid arthritis while maintaining a good safety profile.<sup>21</sup>

A second, 6-month, randomized, double-blind, placebo-controlled study compared the safety and efficacy of

abatacept 2 mg/kg and abatacept 10 mg/kg with that of placebo.<sup>22</sup> Three hundred and thirty-nine patients received weight-based dosing of abatacept or placebo in addition to stable doses of methotrexate. Patients were included if they met the ACR criteria for diagnosis of rheumatoid arthritis, had active disease (defined by  $\geq 10$  swollen joints and  $\geq 12$  tender joints), had a C-reactive protein level  $> 1$  mg/dL, and had been treated with methotrexate for at least 6 months. Patients who were receiving another DMARD were required to undergo a washout period of all other DMARDs. Patients who were pregnant or nursing were excluded from this study. After 6 months of study medication, 60% of patients who received abatacept 10 mg/kg had a positive response to ACR20 as compared with 41.9% of patients who received abatacept 2 mg/kg or 35.3% of patients who received placebo, which was found to be significantly higher for patients receiving 10 mg/kg compared with patients receiving 2 mg/kg and placebo ( $P < 0.001$ ). Researchers determined that there was a statistically significant higher percentage of patients who reached ACR50 and ACR70 in the 10 mg/kg group (36.5% and 16.5%, respectively) when compared with placebo (11.8% and 1.7%,  $P < 0.001$ ). There was also a significantly higher percentage of patients in the 2 mg/kg group who reached ACR50 and ACR70 after 6 months (22.9% and 10.5%) compared with placebo ( $P < 0.05$ ).<sup>22</sup>

This study was continued for an additional 6 months<sup>23</sup> to continue monitoring of safety and efficacy in this patient population. Patients who received abatacept 10 mg/kg showed significant improvement in disease severity as compared with placebo. Fifty-six percent of patients on abatacept achieved an ACR20 response for up to one year as compared with 34.5% of patients who received placebo ( $P < 0.001$ ). However, there was no statistically significant difference in ACR20 responses in patients who received abatacept 2 mg/kg as compared with placebo after one year of treatment. Patients who received abatacept 10 mg/kg also had significantly higher ACR50 and ACR70 response rates compared with placebo after one year of treatment ( $P = 0.02$  and  $P = 0.003$ , respectively).<sup>23</sup>

Several key Phase III trials have been conducted to evaluate the efficacy of abatacept.<sup>24–28</sup> To evaluate efficacy, ACR20, ACR50, and ACR70 responses were used as the primary and/or secondary endpoints for these trials. The percentage of patients who achieved an ACR20, ACR50, and ACR70 response in the initial trial periods can be found in Table 4 and percentages for the long-term follow-up trials can be found in Table 5. AIM (Abatacept in Inadequate responders to Methotrexate) was a one-year multicenter, multinational,

**Table 4** American College of Rheumatology responses in key abatacept trials

Trial	Endpoint	Group	Patients randomized	ACR20 (% patients)	ACR50 (% patients)	ACR70 (% patients)
AIM <sup>24</sup>	24 weeks	Abatacept	433	67.9	39.9	19.8
		Placebo	219	39.7	16.8	6.5
ATTAIN <sup>26</sup>	24 weeks	Abatacept	258	50.4	20.3	10.2
		Placebo	133	19.5	3.8	1.5
ATTEST <sup>28</sup>	24 weeks	Abatacept	156	66.7	40.4	20.5
		Infliximab	165	59.4	37.0	24.2
		Placebo	110	41.8	20.0	9.1

**Abbreviations:** ACR, American College of Rheumatology; AIM, Abatacept in Inadequate responders to Methotrexate; ATTAIN, Abatacept Trial in Treatment of Anti-TNF Inadequate responders; ATTEST, Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis.

randomized, double-blind, placebo-controlled trial<sup>24</sup> with an additional two years of open-label follow-up.<sup>25</sup> The primary endpoint of this trial was the proportion of patients with an ACR20 response. Secondary objectives included the proportion of patients with an ACR50 and ACR70 response. Patients were eligible for the trial if they were 18 years of age, had had rheumatoid arthritis for at least one year, met the ACR criteria for rheumatoid arthritis, and had active and persistent disease despite methotrexate treatment. Patients who were on another DMARD (other than methotrexate) underwent a washout period at least 28 days before randomization. Patients were allowed to be on low-dose corticosteroids (10 mg of prednisone or less). Initially, patients were randomized to abatacept 10 mg/kg or placebo in addition to methotrexate. In the blinded trial, 652 patients were randomized. This trial found that all patients who received abatacept had statistically significant improvement in ACR after 6 months ( $P < 0.001$ ) as well as improvement in ACR50 and ACR70 responses. After 6 months of treatment, all ACR responses continued to improve in patients who received abatacept while ACR response remained unchanged in patients who received placebo. After one year, patients on abatacept had increased ACR20 responses compared with patients on placebo ( $P < 0.001$ ), and ACR50 responses improved ( $P < 0.001$ ) as well as ACR70 responses ( $P < 0.001$ ).<sup>24</sup>

After one year of treatment, patients were eligible to enroll in a long-term open-label trial which allowed addition of other

biologic and nonbiologic DMARDs to their regimen.<sup>25</sup> In the one-year follow-up trial, all patients ( $n = 539$ ) received a fixed dose of 10 mg/kg abatacept, even if they were previously placed in the placebo group. In order to preserve blinding from the previous study, patients who originally received placebo did not receive a loading dose of abatacept, which contradicts normal practice whereby all patients who are started on abatacept would receive a loading dose. Patients who originally received abatacept maintained an ACR response after 2 years. For patients who initially received placebo, ACR20, ACR50, and ACR70 responses quickly increased to percentages similar to those who initially received abatacept.<sup>25</sup>

ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate responders) was a 6-month, randomized, double-blind, placebo-controlled trial<sup>26</sup> which examined the safety and efficacy of abatacept in patients with active rheumatoid arthritis with an inadequate response to at least 3 months of anti-TNF- $\alpha$  therapy. The primary and secondary endpoints of this trial were the proportion of patients with an ACR20, ACR50, or ACR70 response, as well as other efficacy scores. All patients were required to have an inadequate response to either etanercept or infliximab and to have discontinued these medications for at least 28 or 60 days, respectively, prior to randomization. Patients were stratified according to use of anti-TNF- $\alpha$  therapy (former versus current use), then randomized to receive abatacept or placebo. In the blinded study, 393 patients underwent randomization. After 6 months

**Table 5** American College of Rheumatology responses in key long-term follow-up trials

Trial	Endpoint	Initial group	Patients enrolled in longer-term trial	ACR20 (% patients)	ACR50 (% patients)	ACR70 (% patients)
AIM <sup>25</sup>	2 years	Abatacept	385	80.3	55.6	34.3
		Placebo	162	78.1	58.1	31.9
ATTAIN <sup>27</sup>	2 years	Abatacept	218	56.2	33.2	16.1
		Placebo	99	51.5	32.3	13.1
ATTEST <sup>28</sup>	52 weeks	Abatacept	147	72.4	45.5	26.3
		Infliximab	152	55.8	36.4	20.6

**Abbreviations:** ACR, American College of Rheumatology; AIM, Abatacept in Inadequate responders to Methotrexate; ATTAIN, Abatacept Trial in Treatment of Anti-TNF Inadequate responders; ATTEST, Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis.

of treatment, ACR20 responses from patients who received abatacept were significantly higher than responses from patients who received placebo (67.9% versus 39.7%, respectively,  $P < 0.001$ ). Statistically significant higher rates were seen for ACR50 (39.9% versus 16.9%) and ACR70 (19.8% versus 6.5%) in patients who received abatacept compared with placebo ( $P < 0.001$  and  $P = 0.003$ , respectively).<sup>26</sup>

In the 18-month long-term follow-up to ATTAIN,<sup>27</sup> 317 patients who completed the initial trial were allowed to continue in this trial. Similar to the AIM follow-up trial, all patients who initially received placebo were changed to abatacept and did not receive a loading dose (in order to protect blinding). Patients were asked to continue to not use any anti-TNF- $\alpha$  therapy; however, other DMARDs were acceptable. Response rates for ACR20, ACR50, and ACR70 were maintained through 2 years in patients who were initially randomized to the abatacept group (56.2%, 33.2%, and 16.1%, respectively). The ACR20, ACR50, and ACR70 response rates for patients who initially received placebo achieved similar rates to those who had received abatacept after one year of treatment (51.5%, 32.3%, and 13.1%, respectively).<sup>27</sup>

ATTEST<sup>28</sup> (Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis) was a Phase III, multicenter, randomized, double-blind, placebo-controlled trial which examined the efficacy of abatacept compared with infliximab and placebo in treatment groups over one year. The primary endpoint was to evaluate a reduction in disease activity as measured by the DAS28. Additional secondary endpoints included the proportions of patients who had an ACR20, ACR50, and ACR70 response. Patients were eligible for the study if they met the ACR criteria for rheumatoid arthritis, were at least 18 years of age, had had rheumatoid arthritis for at least one year, and had an inadequate response to methotrexate. Four hundred and thirty-one patients were randomized to receive abatacept 10 mg/kg, infliximab 3 mg/kg, or placebo. Patients continued on the randomized study medication for 6 months, then all patients were switched to abatacept (with blinding being preserved similar to other follow-up trials). Significant reductions in DAS28 were greater in patients who received abatacept ( $P < 0.001$ ) or infliximab ( $P < 0.001$ ) when compared with placebo at the end of 6 months (abatacept  $-2.53$ , infliximab  $-2.25$ , placebo  $-1.48$ ). After one year, patients who initially received abatacept still had a greater reduction in DAS28 compared with patients who received infliximab ( $-2.88$  versus  $-2.55$ ).

Researchers found that by the end of 6 months, ACR20, ACR50, and ACR70 responses were significantly greater in

patients who received abatacept or infliximab when compared with placebo. It was noted that the onset of response (as assessed using the ACR20 responses) was more rapid in patients receiving infliximab compared with patients who received abatacept. Researchers also noted that abatacept and infliximab had similar responses by the end of 6 months. However, during the following 6 months (when all patients received abatacept), patients who had initially received abatacept had their responses maintained while patients who initially received infliximab responses were lower at the end of one year.<sup>28</sup>

A 6-month, multinational, randomized, double-blind, double-dummy study compared the safety and efficacy of subcutaneous abatacept and intravenous abatacept (ACQUIRE).<sup>29</sup> In total, 1457 patients with rheumatoid arthritis and an inadequate response to methotrexate were randomized to receive 125 mg subcutaneous abatacept or 10 mg/kg intravenous abatacept. In order to maintain blinding, the subcutaneous abatacept group received intravenous placebo therapy and the intravenous abatacept group received subcutaneous placebo therapy. The primary endpoint of this study was the proportion of patients in each group that achieved an ACR20 response after 6 months. Secondary objectives included the proportion of patients with an ACR50 and ACR70 response. Patients were included in the study if they met the 1987 ACR criteria for rheumatoid arthritis, had active disease, had had an inadequate response to methotrexate within the past 3 months, and did not have active tuberculosis disease. Patients were able to be on methotrexate and low-dose oral corticosteroids at the same dosage at randomization, and changes were not permitted during the first 6 months. All other DMARDs were discontinued at least 4 weeks prior to the start of the trial. At month 6, 74.8% of patients treated with subcutaneous abatacept compared with 74.3% of patients treated with intravenous abatacept achieved an ACR20 response. Similar response rates were seen for the proportion of patients who achieved an ACR50 (50.2% subcutaneous versus 48.6% intravenous) and ACR70 (25.8% subcutaneous versus 24.2% intravenous). This study confirmed the noninferiority of subcutaneous abatacept compared with intravenous abatacept.<sup>29</sup>

## Safety and tolerability

Safety information has been included in all clinical trials,<sup>21–28</sup> as well as an additional safety-focused trial.<sup>30</sup> For each trial, patients were monitored for safety as long as they received at least one dose of the study medication. The follow-up trials detailed safety for patients until the end of the trial.

ASSURE<sup>30</sup> (the Abatacept Study of Safety in Use with other Rheumatoid arthritis therapies) strictly examined the adverse events that occurred with all patients who received at least one dose of the study medication. The trial was a one-year, multinational, multicenter, randomized, double-blind, two-arm, parallel-dosing trial. Patients enrolled met the 1987 ACR criteria for diagnosis of rheumatoid arthritis, were at least 18 years of age, had active disease despite receiving other DMARDs, had received at least one biologic and/or nonbiologic DMARD for at least two months, and at a stable dose for at least 28 days prior to the start of the trial. Patients were excluded from the trial if they had unstable or uncontrolled renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, or neurologic disease, an autoimmune disorder other than rheumatoid arthritis, active or chronic bacterial infection, active herpes zoster infection, hepatitis B or C virus infection, or active or latent tuberculosis. Pregnant and nursing women were also excluded. In total, 1441 patients were randomized to receive abatacept 10 mg/kg or placebo. In this trial, patients were allowed to remain on other biologic and nonbiologic DMARDs and were only allowed to change (either medication or dosages) 3 months after enrollment in the trial. Due to addition of background medication, patients were also stratified based on use of any biologic DMARDs. Overall, 90% of patients in the abatacept group and 87% of patients in the placebo group experienced an adverse event. Similar percentages of patients experienced a serious adverse event in the abatacept and placebo groups (13% and 12%, respectively). Medication discontinuation due to adverse events was very low in both groups (5% and 4%). Discontinuation due to a serious adverse event was also very low in both groups (2.3% and 1.5%). In this trial, five patients in the abatacept (0.5%) and four patients in the placebo group (0.8%) died during the one-year trial. One death in the placebo group (from *Pneumocystis carinii* pneumonia) was deemed related to the study medication by the study investigator, who was blinded to therapy. All other deaths in the abatacept and placebo groups were deemed either unlikely to be related or unlikely to be unrelated to the study medication.<sup>30</sup>

The most frequent serious adverse event reported in both treatment groups was infection (abatacept 56% and placebo 54.1%). Upper respiratory infections and nasopharyngitis were the most frequent infections reported in the abatacept and placebo groups (15% for both groups and 10% for both groups, respectively). In patients who received a background nonbiologic DMARD, patients who received abatacept had a higher frequency of serious infection compared with patients

who received placebo (2.6% versus 1.7%). In patients taking a background biologic agent, those who received abatacept had a higher frequency of serious infection compared with patients who received placebo (5.8% versus 1.6%). Reported infections included cellulitis, intestinal abscess, infective bursitis, and pyelonephritis.<sup>30</sup>

The overall incidence of malignancies was similar for both the abatacept and placebo groups (3.5%). The most common type of neoplasm reported was skin carcinoma, primarily basal cell or squamous cell, followed by breast and lung cancer (three patients for each type). The rate of autoimmune disorders was similar in both treatment groups (abatacept 3.3% and placebo 3.1%). Reported autoimmune disorders included keratoconjunctivitis sicca and vasculitis. The rate of infusion-related events was similar in both groups. Acute infusion-related events were reported in 10% of the abatacept group compared with 7.1% in the placebo group and peri-infusional events were similar between the groups (abatacept 24.3% and placebo 20.3%). Overall, a small number of patients discontinued the study medication from an acute infusion or peri-infusional events (abatacept 0.6% and placebo 0.2%).<sup>30</sup>

In Table 6, patients with an adverse event, serious adverse event, discontinuation due to a serious adverse event, and deaths for the AIM, ATTAIN, and ATTEST trials are reported. The respective number of patients with reported serious infections, malignancies, and autoimmune disorders are included in the table.

The AIM, ATTAIN, and ATTEST trials<sup>24–28</sup> have shown that patients who receive abatacept need to be monitored for malignancies, autoimmune disorders, and serious infections. Some malignancies that were reported by the trials include basal cell carcinoma, squamous cell carcinoma, lung neoplasm, and lymphoma. Only 32 patients among the three trials experienced an autoimmune disorder. Some of the autoimmune disorders reported were psoriasis, vasculitis, keratoconjunctivitis sicca, systemic lupus erythematosus, cutaneous vasculitis, erythema nodosum, and Sjogren's syndrome. Some of the serious infections reported in the trials included pneumonia, acute bronchitis, cellulitis, urinary tract infection, and sepsis.

Overall, abatacept was found to be a relatively safe medication for use in patients with refractory rheumatoid arthritis. In each study, there was a high percentage of patients who experienced an adverse event. However, a small percentage of patients discontinued the study medication due to a serious adverse event. Also, 17 of 2712 patients (0.6%) died during these trials.



**Table 6** Number of patients reported with adverse events reported in abatacept trials

	AIM trial <sup>24,25</sup>		ATTAIN trial <sup>26,27</sup>		ATTEST trial <sup>28</sup>		
	Abatacept plus MTX (n = 593) <sup>25</sup>	Placebo plus MTX (n = 219) <sup>24</sup>	Abatacept plus DMARDs (n = 357) <sup>27</sup>	Placebo (n = 133) <sup>26</sup>	Abatacept plus MTX (n = 156)	Infliximab plus MTX (n = 165)	Placebo plus MTX (n = 110)
Patients with AE, n (%)	550 (92.6)	184 (84.0)	329 (92.2)	95 (71.4)	139 (89.1)	154 (93.3)	92 (83.6)
Patients with SAE, n (%)	149 (25.1)	26 (11.9)	103 (28.9)	15 (11.3)	15 (9.6)	30 (18.2)	13 (11.8)
Discontinuation due to SAE, n (%)	24 (4.0)	3 (1.4)	18 (5.0)	2 (1.5)	4 (2.6)	6 (3.6)	0 (0.0)
Deaths, n (%)	3 (0.5)	1 (0.5)	2 (0.6)	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)
Serious infections, n (%)	43 (7.2)	2 (0.9)	25 (7.0)	3 (2.3)	3 (1.9)	14 (8.5)	3 (2.7)
Malignancies, n (%)	14 (2.3)	2 (0.9)	11 (3.0)	NR	1 (0.6)	2 (1.2)	1 (0.9)
Autoimmune disorders, n (%)	15 (2.5)	0 (0.0)	15 (4.2)	NR	2 (1.3)	1 (0.6)	1 (0.9)

**Abbreviations:** AE, adverse events; AIM, Abatacept in Inadequate responders to Methotrexate; ATTAIN, Abatacept Trial in Treatment of Anti-TNF Inadequate responders; ATTEST, Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis; SAE, serious adverse events; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NR, not reported.

## Quality of life

In addition to safety benefits and tolerability, one outcome that can influence patient satisfaction is quality of life. In patients with an inadequate response to methotrexate, health-related quality of life was examined in patients receiving abatacept in the AIM trial.<sup>31</sup> The Short Form (SF)-36 Health Survey was used to assess health-related quality of life, with higher scores representing better health. The Health Assessment Questionnaire was utilized to assess physical functioning, and the visual analog scale was utilized to assess fatigue. By day 29, the abatacept group was statistically better in five of the eight SF-36 domains, and by day 169 all eight SF-36 domains were significantly better for the abatacept group. Physical function had statistically improved by day 57 for patients receiving abatacept and the fatigue score declined (indicating improvement) from baseline significantly more in the abatacept group by day 29. The authors concluded that abatacept in addition to methotrexate treatment for rheumatoid arthritis provided improvements in patients over a range of health-related quality of life domains, including physical function and fatigue.<sup>31</sup>

The impact on quality of life was explored in patients with an inadequate response to anti-TNF therapy in the ATTAIN trial.<sup>32</sup> The SF-36, Health Assessment Questionnaire, and visual analog fatigue scale were utilized to assess patient quality of life. By 6 months, the quality of life in patients receiving abatacept improved significantly based on the Health Assessment Questionnaire, visual analog scale, and SF-36 scores. The authors concluded that patients with an inadequate response to anti-TNF therapy had significantly increased quality of life after 6 months of treatment with abatacept compared with placebo.<sup>32</sup>

In a simulation model, the cost-effectiveness of abatacept was assessed in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate.<sup>33</sup> The simulation model was designed to depict progression of functional disability over time in women 55–64 years of age. Functional disability was stated in terms of the Health Assessment Questionnaire-Disability Index (HAQ-DI), which ranges from 0 (no limitation in activities of daily living) to 3 (complete inability to perform these activities). Cost-effectiveness was expressed in terms of incremental costs per quality-adjusted life-year (QALY) gained over 10 years and a lifetime. The estimated mean HAQ-DI at baseline was 1.7 and was 1.9 at 10 years for patients who received abatacept plus methotrexate. Abatacept was estimated to result in a mean gain of 1.2 QALYs per patient over 10 years compared with methotrexate alone. The mean cost-effectiveness of abatacept over 10 years was estimated to be \$47,910 per QALY gained. The authors acknowledged their assumption of sustained benefit of abatacept-treated patients beyond 6 months, but concluded that abatacept is cost-effective in patients with rheumatoid arthritis who are inadequate responders to methotrexate.<sup>33</sup>

## Conclusion

ACR 2008 guidelines for use of biologic DMARDs in the treatment of rheumatoid arthritis suggest that abatacept should be reserved for patients with a poor prognosis who have demonstrated an inadequate response to other treatment options and maintain at least moderate disease activity. Abatacept offers a novel mechanism of action in the treatment of rheumatoid arthritis. Abatacept has a high affinity for CD28 and prevents full activation of T cells, which prevents inflammation and joint destruction.

Efficacy of abatacept in patients with an inadequate response to methotrexate or anti-TNF- $\alpha$  therapy (ie, etanercept or infliximab) has been evaluated in several Phase III clinical trials. In the AIM study, patients receiving abatacept 10 mg/kg had improvement in ACR20, ACR50, and ACR70 responses, which continued to improve following 6 months of treatment, while patients receiving placebo did not have an increase in ACR response. Similarly, more patients receiving abatacept in the ATTAIn study had an improvement in ACR response compared with patients receiving placebo. The ATTEST study evaluated the efficacy of abatacept compared with infliximab or placebo, and more patients receiving abatacept had reductions in DAS28 compared with patients receiving infliximab or placebo. These data support that abatacept is an effective therapy for patients who have demonstrated a poor response to methotrexate, infliximab, or etanercept. Abatacept represents a proven effective treatment for refractory rheumatoid arthritis with an established safety profile. The role of abatacept in clinical practice is reserved for patients with an inadequate response to other nonbiologic and biologic DMARDs. Further studies should be conducted to evaluate sustained benefits and safety data.

## Acknowledgment

The authors wish to acknowledge Brian D Cole for his medical illustrating.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum.* 2010;62:2569–2581.
- Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis Rheum.* 2008;58:15–25.
- Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. *Lancet.* 2010;376:1094–1108.
- Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet.* 2007;370:1861–1874.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31:315–324.
- Choy EHS, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med.* 2001;344:907–916.
- Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:762–784.
- Paulus HE, Egger MJ, Ward JR, et al. Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. *Arthritis Rheum.* 1990;33:477–484.
- Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum.* 2011;63:573–586.
- American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. *Arthritis Rheum.* 2007;57:193–202.
- Sheeran T, Chalam V, Gomez-Reino JJ. Treatment alternatives after inadequate response to a tumor necrosis factor- $\alpha$  inhibitor. *European Musculoskeletal Review.* 2009;4:22–23.
- Pinals RS, Masi AT, Larson RA. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum.* 1981;24:1308–1315.
- Lutt JR, Deodhar A. Rheumatoid arthritis. *Drugs.* 2008;68:591–606.
- Cohen SB, Cohen MD, Cush JJ, et al. Unresolved issues in identifying and overcoming inadequate response in rheumatoid arthritis: weighing the evidence. *J Rheumatol.* 2007;35 Suppl 2:S4–S30.
- Furst DE, Keystone EC, Kirkham B, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. *Ann Rheum Dis.* 2008;67 Suppl III:iii2–iii25.
- Felson DT, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 1995;38:727–735.
- Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Res Ther.* 2009;11 Suppl 1:S1–S12.
- Orencia [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2009.
- Ostor AJK. Abatacept: a T-cell co-stimulation modulator for the treatment of rheumatoid arthritis. *Clin Rheumatol.* 2008;27:1343–1353.
- Lundquist LM. Abatacept: a novel treatment for rheumatoid arthritis. *Expert Opin Pharmacother.* 2007;8:2371–2379.
- Moreland LW, Alten R, Van de Bosch F, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum.* 2002;46:1470–1479.
- Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA-4Ig. *N Engl J Med.* 2003;349:1907–1915.
- Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept. *Arthritis Rheum.* 2005;52:2263–2271.
- 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;144:865–876.
- Kremer JM, Genant HK, Moreland LW, et al. Results of a two-year follow-up study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum.* 2008;58:953–963.
- Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor  $\alpha$  inhibition. *N Engl J Med.* 2005;353:1114–1123.
- Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. *Ann Rheum Dis.* 2008;67:547–554.
- Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomized, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis.* 2008;67:1096–1103.
- Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a Phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum.* 2011;63:2854–2864.

30. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs. *Arthritis Rheum.* 2006;54: 2807–2816.
31. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis.* 2007;66:189–194.
32. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. *Rheumatology.* 2006;45:1238–1246.
33. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. *Rheumatology.* 2008;47:535–541.

#### Open Access Rheumatology Research and Reviews

#### Publish your work in this journal

Open Access Rheumatology Research and Reviews is an international, peer-reviewed, open access journal, publishing all aspects of clinical and experimental rheumatology in the clinic and laboratory including the following topics: Pathology, pathophysiology of rheumatological diseases; Investigation, treatment and management of rheumatological

diseases; Clinical trials and novel pharmacological approaches for the treatment of rheumatological disorders. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/open-access-rheumatology-research-and-reviews-journal>

Dovepress