

ORIGINAL ARTICLE

Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition

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ABSTRACT

BACKGROUND

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A substantial number of patients with rheumatoid arthritis have an inadequate or unsustained response to tumor necrosis factor α (TNF- α) inhibitors. We conducted a randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of abatacept, a selective costimulation modulator, in patients with active rheumatoid arthritis and an inadequate response to at least three months of anti-TNF- α therapy.

METHODS

Patients with active rheumatoid arthritis and an inadequate response to anti-TNF- α therapy were randomly assigned in a 2:1 ratio to receive abatacept or placebo on days 1, 15, and 29 and every 28 days thereafter for 6 months, in addition to at least one disease-modifying antirheumatic drug. Patients discontinued anti-TNF- α therapy before randomization. The rates of American College of Rheumatology (ACR) 20 responses (indicating a clinical improvement of 20 percent or greater) and improvement in functional disability, as reflected by scores for the Health Assessment Questionnaire (HAQ) disability index, were assessed.

RESULTS

After six months, the rates of ACR 20 responses were 50.4 percent in the abatacept group and 19.5 percent in the placebo group ($P < 0.001$); the respective rates of ACR 50 and ACR 70 responses were also significantly higher in the abatacept group than in the placebo group (20.3 percent vs. 3.8 percent, $P < 0.001$; and 10.2 percent vs. 1.5 percent, $P = 0.003$). At six months, significantly more patients in the abatacept group than in the placebo group had a clinically meaningful improvement in physical function, as reflected by an improvement from baseline of at least 0.3 in the HAQ disability index (47.3 percent vs. 23.3 percent, $P < 0.001$). The incidence of adverse events and peri-infusional adverse events was 79.5 percent and 5.0 percent, respectively, in the abatacept group and 71.4 percent and 3.0 percent, respectively, in the placebo group. The incidence of serious infections was 2.3 percent in each group.

CONCLUSIONS

Abatacept produced significant clinical and functional benefits in patients who had had an inadequate response to anti-TNF- α therapy.

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RHEUMATOID ARTHRITIS IS A CHRONIC disease that leads to inflammation and progressive joint damage.¹ Current therapies target the inflammatory consequences of autoimmune activation with the use of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and biologic DMARDs, which inhibit inflammatory cytokines such as tumor necrosis factor α (TNF- α).² Despite the efficacy of agents such as TNF- α inhibitors, a substantial proportion of patients have no response,³⁻⁵ have an unsustained response,⁶ or form antibodies against the drugs.⁷ There are currently no clinically proven treatment options for patients with an inadequate response to anti-TNF- α therapy.

Abatacept is the first in a new class of agents for the treatment of rheumatoid arthritis that selectively modulate the CD80 or CD86-CD28 costimulatory signal required for full T-cell activation.^{8,9} CD80 or CD86 on the surface of an antigen-presenting cell binds to CD28 on the T cell, facilitating T-cell activation. In the normal sequence of events, the naturally occurring inhibitory molecule cytotoxic T-lymphocyte antigen 4 (CTLA4) is induced on the surface of the T cell. CTLA4 has a markedly greater affinity for CD80 or CD86 than does CD28, thus outcompeting CD28 for CD80 or CD86 binding.¹⁰ Abatacept is a recombinant fusion protein comprising the extracellular domain of human CTLA4 and a fragment of the Fc domain of human IgG1,¹¹ which has been modified to prevent complement fixation. Abatacept, like CTLA4, competes with CD28 for CD80 and CD86 binding and thereby can be used to selectively modulate T-cell activation.⁹

The efficacy of abatacept has been reported in two phase 2 studies.^{8,12} In patients with active rheumatoid arthritis and an inadequate response to methotrexate, abatacept in combination with methotrexate led to significant improvements in signs and symptoms, physical function, and the quality of life over a period of 12 months.^{12,13} Given the novel mechanism of action of abatacept and the recognized role of T cells in rheumatoid arthritis, selective modulation of costimulation represents a rational therapeutic approach in patients with an inadequate response to anti-TNF- α therapy. We therefore initiated the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN), a six-month, randomized, double-blind, placebo-controlled study, to assess the efficacy and safety of abatacept in patients with active rheumatoid arthri-

tis and an inadequate response to anti-TNF- α therapy who were receiving background DMARDs.

METHODS

PATIENTS

Eligible patients met the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, were at least 18 years of age, had had rheumatoid arthritis for at least one year,¹⁴ and had an inadequate response to anti-TNF- α therapy with etanercept, infliximab, or both at the approved dose after at least three months of treatment. This study was initiated before the use of adalimumab became widespread. Patients who had adverse events while receiving anti-TNF- α therapy but who discontinued treatment primarily because of a lack of efficacy were also eligible.

Two groups of patients were enrolled: those receiving anti-TNF- α therapy at the time of screening (current users) and those who had previously received such therapy (former users). All users were required to stop taking etanercept or infliximab for at least 28 or 60 days, respectively, before undergoing randomization.

At randomization, patients had to have at least 10 swollen joints, at least 12 tender joints, and C-reactive protein levels of at least 1 mg per deciliter (upper limit of the normal range, 0.5). Patients had to have been taking an oral DMARD or anakinra for at least 3 months, and the dose had to have been stable for at least 28 days. Use of oral corticosteroids (no more than 10 mg of prednisone or its equivalent per day) was allowed if the dose had been stable for at least 28 days. Changes in the doses of background DMARDs were not permitted except to avoid adverse effects.

STUDY PROTOCOL

Patients were randomly assigned in a 2:1 ratio to receive abatacept or placebo and were stratified according to the use of anti-TNF- α therapy at the time of enrollment (former vs. current use). To ensure balanced treatment-group assignments, no more than two thirds of randomized patients were permitted to be either current or former anti-TNF- α users. There was a central randomization system, and the randomization schedule was generated by the drug-management group within Bristol-Myers Squibb. A total of 89 sites participated, and a median of 3 patients were enrolled per site (range, 1 to 16); there was no stratification according to site.

Patients received a fixed dose of abatacept, approximating 10 mg per kilogram of body weight, or placebo; patients weighing less than 60 kg received 500 mg of abatacept, those weighing 60 to 100 kg received 750 mg, and those weighing more than 100 kg received 1000 mg. Study medication was administered in a 30-minute intravenous infusion on days 1, 15, and 29 and every 28 days thereafter, up to and including day 141. The drug was prepared by pharmacists or other qualified personnel who had no interaction with the patients. Medication was administered intravenously in a blinded fashion by qualified personnel. All clinical assessments of response were performed in a blinded fashion by the same trained assessors throughout the study.

This study was approved by the institutional review boards and independent ethics committees at participating sites and was carried out in accordance with the ethics principles of the Declaration of Helsinki. All patients provided written informed consent before randomization. The academic authors had full access to the data and certify the veracity and completeness of the data and the data analysis.

MEASURES OF CLINICAL EFFICACY

There were two primary end points: the proportion of patients with an ACR 20 response and the proportion of patients with an improvement of at least 0.3 from baseline in the Health Assessment Questionnaire (HAQ) disability index (exceeding the minimal clinically important change of 0.22¹⁵) at six months. An ACR 20 response indicates a decrease of at least 20 percent in the number of both tender and swollen joints (68 joints were assessed for tenderness, and 66 joints were assessed for swelling) as well as a 20 percent improvement in at least three of the following: the patient's global assessment of disease activity; the patient's assessment of pain; physical function, as assessed by the HAQ disability index; the physician's global assessment of disease activity; and the C-reactive protein level.¹⁶

Secondary objectives included a 50 percent and 70 percent improvement in the ACR response (ACR 50 and ACR 70, respectively) at six months. Changes in disease activity were assessed with the use of the Disease Activity Score 28 (DAS28).^{17,18} Clinical remission was defined by a DAS28 of less than 2.6,¹⁹ and a low level of disease activity was defined by a DAS28 of 3.2 or less.²⁰ The mean

improvement in physical function at six months was based on the change from baseline in the HAQ disability index. Changes from baseline in the health-related quality of life were assessed by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36)²¹ at six months. The SF-36 consists of 36 items, 35 of which are aggregated to evaluate eight dimensions of health: physical function, pain, general and mental health, vitality, social function, and physical and emotional health. Scores on the eight subscales were aggregated to derive the physical-component summary score and the mental-component summary score. Scores on each subscale can range from 0 to 10, and the summary scores can range from 0 to 100, with higher scores indicating better health.

SAFETY ASSESSMENTS

Patients were monitored for adverse events, serious adverse events, and clinically significant changes in vital signs and laboratory tests. Both the severity of adverse events and their relation to the study treatment were noted by the investigator.

IMMUNOGENICITY TESTING

The immunogenicity of abatacept was assessed with the use of two validated, direct-format enzyme-linked immunosorbent assays. One assay measured the response to the whole molecule (anti-abatacept assay), whereas the second assay measured the response to the CTLA4 portion alone. Samples were obtained at baseline (day 1); days 29, 85, and 169; and 85 days after the last dose of abatacept.

STATISTICAL ANALYSIS

All efficacy analyses included all randomized patients who received at least one dose of study medication. The statistical power of the study with respect to the two primary end points of the ACR 20 response and the HAQ response was 96 percent and 87 percent, respectively, at a two-sided alpha level of 5 percent, to detect absolute differences of 20 percent and 18 percent, respectively. No interim analyses were planned or conducted. For the primary analyses of the ACR 20 and HAQ responses, the proportion of patients who had a response at six months was summarized according to the treatment group. A two-sided Cochran-Mantel-Haenszel chi-square test (with stratification according to baseline anti-TNF- α use [current or former]) was used to compare response rates in the abatacept group with those in the placebo group at the 0.05

level of significance. For the analyses of ACR 20 and HAQ responses, all patients who discontinued treatment were subsequently considered not to have had a response. The primary and the multiple secondary end points were tested in a prespecified sequence after the use of a closed testing procedure, thus controlling the overall type I error rate at the 0.05 level. All reported P values are two-sided.

Mean changes from baseline in the DAS28, HAQ disability index, and the scores for the eight individual subscales as well as the physical- and mental-component summary scores of the SF-36 were compared between treatment groups with the use of analysis of covariance after adjustment for the baseline assessments. For patients who discontin-

ued treatment, the last observation was carried forward in subsequent analyses.

Safety was evaluated according to the frequency of adverse events, changes in laboratory values, and abnormal clinical findings. P values for safety comparisons were obtained with the use of a chi-square test or, where appropriate, Fisher's exact test.

RESULTS

RANDOMIZATION AND OUTCOME

From December 10, 2002, to June 2, 2004, 258 patients were randomly assigned to and treated with abatacept and 133 were assigned to and received

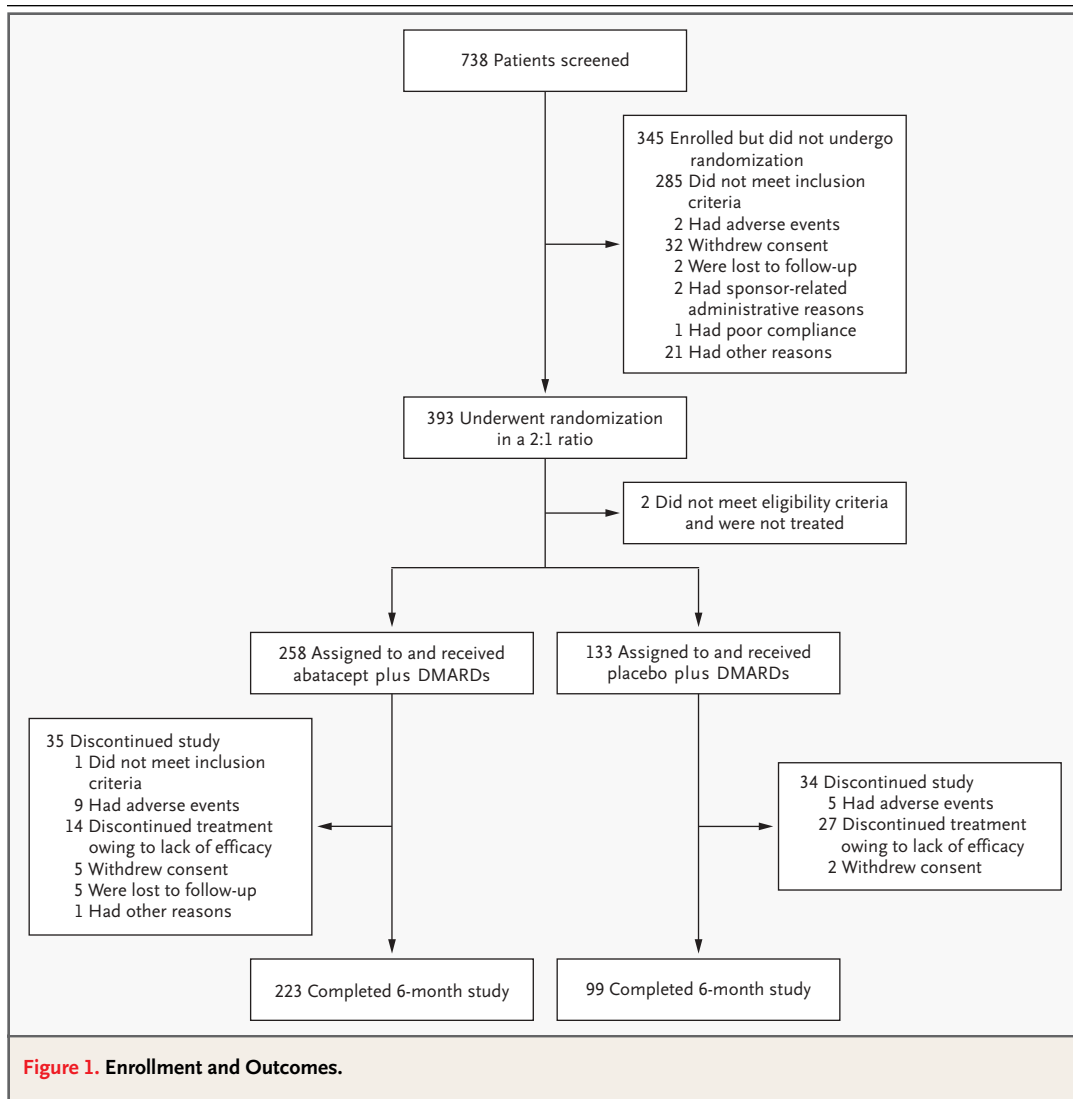


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Abatacept (N=258)	Placebo (N=133)
Age — yr	53.4±12.4	52.7±11.3
Weight — kg	78.2±19.0	78.2±21.0
Female sex — %	77.1	79.7
Race — no. (%)†		
White	248 (96.1)	124 (93.2)
Black	9 (3.5)	5 (3.8)
Other	1 (0.4)	4 (3.0)
Geographic region — no. (%)		
North America	189 (73.3)	99 (74.4)
Europe	69 (26.7)	34 (25.6)
Duration of disease — yr	12.2±8.5	11.4±8.9
Use of anti-TNF- α therapy — no. (%)‡		
Current	98 (38.0)	55 (41.4)
Former	160 (62.0)	78 (58.6)
Anti-TNF- α therapy — no. (%)		
Etanercept	83 (32.2)	53 (39.8)
Infliximab	175 (67.8)	80 (60.2)
Adalimumab	6 (2.3)	2 (1.5)
Medications at randomization — no. (%)		
Methotrexate	195 (75.6)	109 (82.0)
Azathioprine	7 (2.7)	3 (2.3)
Penicillamine	1 (0.4)	0
Gold	0	1 (0.8)
Hydroxychloroquine	23 (8.9)	12 (9.0)
Chloroquine	0	1 (0.8)
Leflunomide	23 (8.9)	11 (8.3)
Sulfasalazine	18 (7.0)	13 (9.8)
Anakinra	7 (2.7)	3 (2.3)
NSAIDs	181 (70.2)	95 (71.4)
Corticosteroids	181 (70.2)	86 (64.7)
Methotrexate dose at baseline — mg/wk	15.2±5.3	14.4±6.1
Median corticosteroid dose at baseline — mg/day§	5.0	5.0
No. of tender joints¶	31.2±13.0	32.8±13.4
No. of swollen joints¶	22.3±10.2	22.0±10.0
Pain score	70.8±19.8	69.9±19.0
Physical-function score**	1.8±0.6	1.8±0.6
Global assessment of disease activity		
Patient	69.2±19.7	69.7±20.3
Physician	68.8±17.7	67.3±16.8
DAS28	6.5±0.9	6.5±0.8
C-reactive protein — mg/dl	4.6±4.0	4.0±3.6
Positive for rheumatoid factor — no. (%)	189 (73.3)	97 (72.9)

* Plus-minus values are means \pm SD. NSAIDs denotes nonsteroidal antiinflammatory drugs, and DAS28 Disease Activity Score 28.

† Race was self-reported.

‡ Current users were those receiving anti-TNF- α therapy at enrollment; former users were those who had discontinued etanercept or infliximab at least 28 or 60 days, respectively, before enrollment.

§ The doses are based on all patients who received maintenance corticosteroids. On day 169, the median dose of prednisone remained 5 mg per day in both groups.

¶ A total of 68 joints were assessed for tenderness and 66 were assessed for swelling.

|| A 100-mm visual-analogue scale was used, in which higher values indicated more severe pain or abnormalities.

**Scores for the Stanford Health Assessment Questionnaire (HAQ) can range from 0 to 3, with higher scores indicating greater disease activity.

placebo (Fig. 1). A total of 322 patients completed 24 weeks of therapy: 223 (86.4 percent) in the abatacept group and 99 (74.4 percent) in the placebo group. Lack of efficacy (based on the discretion of the patient and the investigator) was the main reason for discontinuation in both groups (5.4 and 20.3 percent, respectively) (Fig. 1).

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Baseline demographic and clinical characteristics were similar in the two groups (Table 1). Patients had active disease at baseline as evidenced by high mean counts of tender and swollen joints, scores for the HAQ disability index, C-reactive protein levels, and the DAS28 (Table 1). The percentages of current and former anti-TNF- α users were similar in the abatacept and placebo groups (38.0 percent and 41.4 percent, respectively; and 62.0 percent and 58.6 percent, respectively).

CLINICAL EFFICACY

Improvement in the Signs and Symptoms

At six months, the rate of ACR 20 responses was significantly higher in the abatacept group than in the placebo group (50.4 percent vs. 19.5 percent, $P < 0.001$) (Fig. 2A). The rates of responses in the abatacept group were significantly higher than those in the placebo group from day 15 onward and progressively increased during the six-month study period (Fig. 2B). The rates of ACR 50 and ACR 70 responses were also significantly higher in the abatacept group than in the placebo group at six months (rate of ACR 50 response, 20.3 percent vs. 3.8 percent, $P < 0.001$; rate of ACR 70 response, 10.2 percent vs. 1.5 percent, $P = 0.003$) (Fig. 2A).

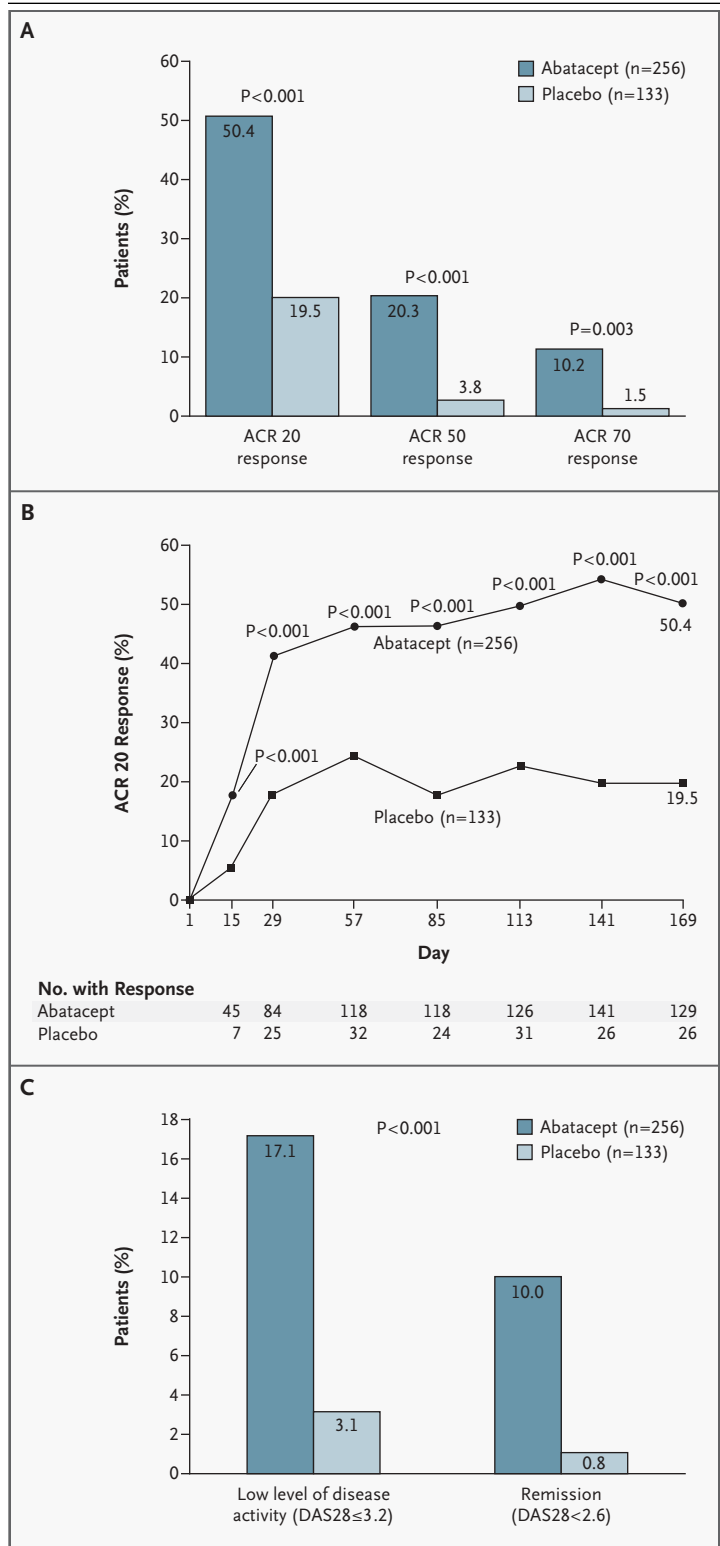


Figure 2. Signs and Symptoms of Disease.

Panel A shows the rates of ACR 20, ACR 50, and ACR 70 responses at six months. Panel B shows the rates of ACR 20 responses at each post-baseline visit during the six-month study. The numbers below the panel are the numbers of patients with a response who were assessed. Panel C shows the rates of low levels of disease activity and remission at six months as defined with the use of the DAS28. Two patients in the abatacept group were excluded from the efficacy analysis because of a protocol violation.

Among both current and former users of anti-TNF- α therapy, the rates of ACR 20 responses were significantly higher in the abatacept group than in the placebo group ($P < 0.001$ for both comparisons).

Current users of anti-TNF- α agents had such therapy withdrawn before undergoing randomization. We assessed the changes in C-reactive protein levels and in the numbers of swollen and tender joints in current and former anti-TNF- α users in the placebo group during the study. We found no significant increase in the number of swollen joints (mean joint count, 20 at screening, 21 at randomization, and 17 on day 29 after randomization), tender joints (mean joint count, 29 at screening, 30 at randomization, and 27 on day 29 after randomization), or C-reactive protein levels (data not shown) during the washout period or subsequently.

Rates of remission (as defined by a DAS28 of less than 2.6) at six months were also significantly higher in the abatacept group than in the placebo group (10.0 percent vs. 0.8 percent, $P < 0.001$) (Fig. 2C). Furthermore, 17.1 percent of patients in the abatacept group had a low level of disease activity at six months (as defined by a DAS28 of 3.2 or less), as compared with 3.1 percent of patients in the placebo group ($P < 0.001$).

Improvement in Physical Function

At six months, significantly more patients in the abatacept group than in the placebo group had a clinically meaningful improvement in physical function (defined by an improvement in the HAQ disability index of at least 0.3 from baseline) (47.3 percent vs. 23.3 percent, $P < 0.001$) (Fig. 3A). Significant improvements were achieved by the time of the first measurement on day 15 in the abatacept group, as compared with the placebo group (data not shown). At six months, the abatacept group also had greater mean improvements from baseline in the HAQ disability index (0.45 vs. 0.11, $P < 0.001$).

Improvement in Health-Related Quality of Life

As compared with the placebo group, the abatacept group had significantly greater improvements from baseline in scores for all eight physical and mental subscales of the SF-36 (Fig. 3B). The improvements in scores for all subscales were considered clinically meaningful (as reflected by an increase of at least 3 points).²² As compared with the placebo group, the abatacept group also had significant improvements in the physical-component

and mental-component summary scores ($P < 0.001$ and $P < 0.01$, respectively) (Fig. 3B).

SAFETY

The rates of discontinuation because of adverse events and serious adverse events were low and similar in the abatacept and placebo groups (3.5 percent and 3.8 percent, respectively; and 2.7 percent and 1.5 percent, respectively) (Table 2). The rates of adverse events and serious adverse events were also similar in the abatacept and placebo groups (79.5 percent and 71.4 percent, respectively; and 10.5 percent and 11.3 percent, respectively) (Table 2). The incidence of serious infections (Table 2) was 2.3 percent in both groups, and no unusual or opportunistic infections were seen.

Infections were more frequent in the abatacept group than in the placebo group (37.6 percent vs. 32.3 percent, $P = 0.30$), with nasopharyngitis, sinusitis, upper respiratory tract infection, and bronchitis being reported most frequently. Most infections were mild to moderate in intensity. The rates of discontinuation due to infection were 0.8 percent in the abatacept group and 1.5 percent in the placebo group ($P = 0.61$). One patient treated with abatacept died of a myocardial infarction and congestive heart failure. This event was not considered by the investigator to be related to the study drug.

Abatacept treatment did not increase the risk of inducing antinuclear antibodies or anti-double-stranded DNA antibodies. A total of 7.5 percent of patients in the abatacept group and 11.3 percent of patients in the placebo group were negative for antinuclear antibodies at baseline and became positive during the study. The respective values for anti-double-stranded DNA antibodies were 1.7 percent and 9.4 percent.

Acute infusion reactions were more frequent in the abatacept group than in the placebo group (5.0 percent vs. 3.0 percent, $P = 0.35$), with dizziness (1.6 percent vs. 0 percent, $P = 0.30$) and headache (1.2 percent vs. 0.8 percent, $P = 1.0$) being the most commonly reported events. Infusion reactions were usually mild or moderate in intensity. There were no severe or very severe acute infusion reactions in either group.

IMMUNOGENICITY

Antibodies against abatacept developed in only 3 of 234 patients (1.3 percent). In one patient, the response was against the immunoglobulin portion of the molecule, and in two patients the responses

were against the CTLA4-binding portion of the molecule. All of these responses showed low-level reactivity.

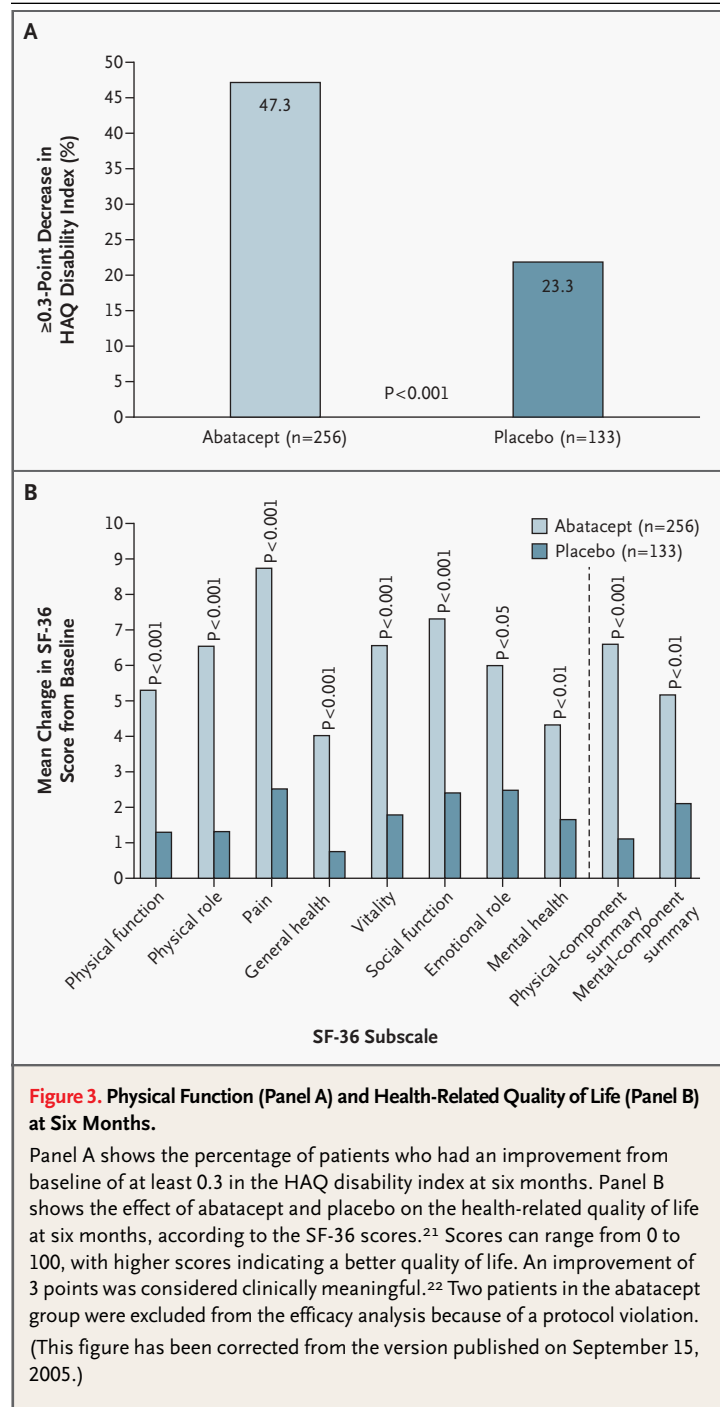
DISCUSSION

The treatment of rheumatoid arthritis has improved in the past decade, owing in part to the more aggressive use of DMARDs and the introduction of TNF- α inhibitors. Despite these improvements, unmet needs remain, especially for patients who have not had an adequate response to TNF- α inhibition.

We evaluated the efficacy and safety of abatacept in patients with active rheumatoid arthritis who had an inadequate clinical response to anti-TNF- α therapy. These patients had long-standing disease, evidence of clinically significant disease activity, and moderate-to-severe disability. We found clinically meaningful and statistically significant improvements in this refractory population. At six months, all primary and secondary outcomes were improved in the abatacept group as compared with the placebo group. Clinical improvements in ACR 20 and HAQ responses were seen at day 15, and the rates increased over the six-month study period. In addition, the efficacy of abatacept was similar regardless of whether patients were receiving anti-TNF- α therapy at the time of screening or had a history of such therapy. Abatacept therapy also induced significant improvements in physical function and scores for all eight subscales of the SF-36.

The incidence of infection was slightly higher in the abatacept group than in the placebo group, but no specific infection was clearly more frequent, and the intensity of infections appeared similar in the two groups. There were no significant differences in the proportions of patients discontinuing treatment as a result of infection or in the incidence of serious infections. There was a low incidence of serious infusion reactions, and abatacept treatment did not appear to increase the incidence of autoimmunity.

Approximately one third of current users of anti-TNF- α therapy (etanercept or infliximab) had a washout period before undergoing randomization. This could have invoked an artificial flare or worsening of disease. However, there was no evidence of such a flare in patients who had a washout period and were randomly assigned to placebo, indicating that these patients were not benefiting from TNF- α inhibition and that the significant improvement observed after randomization



to abatacept reflected treatment of active baseline disease.

Abatacept belongs to a new class of selective costimulation modulators. The efficacy of this agent may in part be explained by its novel mechanism of action at the level of the T cell. By modulating events upstream of T-cell activation, abatacept has the

Table 2. Adverse Events.

Adverse Event	Abatacept (N=258)	Placebo (N=133)	P Value
	<i>number (percent)</i>		
Death	1 (0.4)*	0	1.0
Serious adverse events	27 (10.5)	15 (11.3)	0.81
Serious infections†	6 (2.3)	3 (2.3)	0.97
Limb abscess	1 (0.4)	0	1.0
Diverticulitis	1 (0.4)	0	1.0
Peridiverticular abscess	1 (0.4)	0	1.0
Pneumonia	1 (0.4)	0	1.0
Bacterial pneumonia	1 (0.4)	0	1.0
Influenzal pneumonia	1 (0.4)	0	1.0
Streptococcal sepsis	1 (0.4)	0	1.0
Acute sinusitis	0	1 (0.8)	0.34
Osteomyelitis	0	1 (0.8)	0.34
Pharyngitis	0	1 (0.8)	0.34
Sepsis	0	1 (0.8)	0.34
Staphylococcal abscess	0	1 (0.8)	0.34
Any adverse event‡	205 (79.5)	95 (71.4)	0.08
Most frequent adverse events§			
Headache	32 (12.4)	7 (5.3)	0.03
Nasopharyngitis	20 (7.8)	8 (6.0)	0.53
Nausea	17 (6.6)	9 (6.8)	0.95
Sinusitis	16 (6.2)	5 (3.8)	0.31
Upper respiratory tract infection	15 (5.8)	10 (7.5)	0.51
Diarrhea	15 (5.8)	7 (5.3)	0.82
Bronchitis	15 (5.8)	6 (4.5)	0.59
Back pain	13 (5.0)	7 (5.3)	0.92
Discontinuations	35 (13.6)	34 (25.6)	0.003
Adverse events	9 (3.5)	5 (3.8)	0.89
Serious	7 (2.7)	2 (1.5)	
Lack of efficacy	14 (5.4)	27 (20.3)	<0.001
Withdrawal of consent	5 (1.9)	2 (1.5)	1.0
Lost to follow-up	5 (1.9)	0	0.17
Other	2 (0.8)	0	0.55
Death	0	0	—

* One patient died of myocardial infarction and congestive heart failure, an event considered by the investigator to be unrelated to the study drug (this patient had previously discontinued the study to undergo coronary-artery bypass surgery and valve replacement).

† One patient in the abatacept group and two patients in the placebo group had two serious infections.

‡ Events were defined as any new or worsening illness, sign, symptom, or clinically significant abnormality in a laboratory test noted by the investigator during the course of the study, regardless of the cause.

§ The most frequent adverse events were those occurring in at least 5 percent of patients in either group, including the related and unrelated events (but not rheumatoid arthritis).

potential to affect multiple downstream pathways.²³ Our data suggest that, in addition to playing a key role in the activation of naive T cells that orchestrate early disease,¹ costimulation continues to play a role in the pathogenesis of established, long-standing disease.

Our results provide evidence that abatacept is clinically efficacious and has an acceptable safety profile in patients with rheumatoid arthritis and an inadequate response to anti-TNF- α therapy. Abatacept may thus represent a potential new treatment for patients with rheumatoid arthritis, including those who have had an inadequate response to anti-TNF- α therapy.

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Dr. Genovese reports having served as a consultant for Abbott, Amgen, Genentech, and Bristol-Myers Squibb and as a speaker for Abbott and Amgen and receiving grant support from Abbott, Biogen IDEC, Bristol-Myers Squibb, and Human Genome Services. Drs. Becker, Natarajan, Li, Aranda, and Hagerty are employees of Bristol-Myers Squibb and have stock options in the company. Dr. Hagerty is involved in patent licensing with Bristol-Myers Squibb. Dr. Schiff reports having served as a consultant for and receiving grant support from Bristol-Myers Squibb. Dr. Luggen reports having received grant support from Biogen IDEC, Bristol-Myers Squibb, and Genentech. Dr. Sherrer reports having served as a consultant for Abbott, Amgen, and Bristol-Myers Squibb and as a speaker for Abbott, Amgen, and Wyeth and receiving grant support from Abbott, Amgen, Bristol-Myers Squibb, and Genentech. Dr. Kremer reports having received grant support and consulting and speaking fees from Bristol-Myers Squibb. Dr. Birbara reports having served as a speaker for Merck and Pfizer. Dr. Box reports having served as a consultant for Bristol-Myers Squibb. At the time of submission, Dr. Nuamah was an employee of Bristol-Myers Squibb and had stock options in the company. Dr. Dougados reports having served as a speaker for and receiving grant support from Bristol-Myers Squibb.

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CORRECTION

Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition

Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition . On page 1121, in Figure 3B, the key was incorrectly labeled. The light blue bars represent abatacept, and the dark blue bars placebo. We regret the error.