Annals of Internal Medicine | ARTICLE

Effects of Abatacept in Patients with Methotrexate-Resistant Active Rheumatoid Arthritis

A Randomized Trial

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Background: The selective co-stimulation modulator abatacept demonstrated efficacy for treating rheumatoid arthritis in early clinical studies.

Objective: To evaluate the effects of abatacept in patients with persistent, active rheumatoid arthritis despite methotrexate treatment.

Design: One-year, multicenter, randomized, double-blind, placebo-controlled trial (November 2002 to October 2004).

Setting: 116 centers worldwide.

Patients: 652 patients with active rheumatoid arthritis despite methotrexate treatment.

Intervention: Once-monthly infusion of a fixed dose of abatacept, approximately 10 mg/kg of body weight, or placebo.

Measurements: Co-primary end points were a 20% improvement in American College of Rheumatology (ACR) response criteria (ACR 20) at 6 months, clinically meaningful improvements in physical function, and change from baseline in joint erosion score at 1 year.

Results: Four hundred thirty-three and 219 patients were randomly assigned to abatacept or placebo, respectively, and 385 (89%) and 162 (74%), respectively, completed 1 year of treatment. In a modified intention-to-treat analysis, 6-month ACR 20, ACR 50, and ACR 70 responses were 67.9% for abatacept versus 39.7% for placebo (difference, 28.2 percentage points [95% CI, 19.8 to 36.7 percentage points]), 39.9% for abatacept versus 16.8% for placebo (difference, 23.0 percentage points [CI, 15.0 to 31.1 percentage points]), and 19.8% for abatacept versus 6.5% for placebo (difference, 13.3 percentage points [CI, 7.0 to 19.5 percentage points]), respectively. At 1 year, the responses increased to 73.1% for abatacept versus 39.7% for placebo (difference, 33.4 percentage points [CI, 25.1 to 41.7 percentage points]), 48.3% for abatacept versus 18.2% for placebo (difference, 30.1 percentage points [CI, 21.8 to 38.5 percentage points]), and 28.8% for abatacept versus 6.1% for placebo (difference, 22.7 percentage points [CI, 15.6 to 29.8 percentage points]), respectively ($P < 0.001$ for all). Physical function significantly improved in 63.7% versus 39.3% of patients ($P < 0.001$). At 1 year, abatacept statistically significantly slowed the progression of structural joint damage compared with placebo. Abatacept-treated patients had a similar incidence of adverse events (87.3% vs. 84.0%; difference, 3.3 percentage points [CI, −2.5 to 9.1 percentage points]) and a higher incidence of prespecified serious infections (2.5% vs. 0.9%; difference, 1.6 percentage points [CI, −0.3 to 3.6 percentage points]) and infusion reactions (acute, 8.8% vs. 4.1%; difference, 4.7 percentage points [CI, 0.9 to 8.4 percentage points]; peri-infusional, 24.5% vs. 16.9%; difference, 7.6 percentage points [CI, 1.2 to 14.0 percentage points]) compared with placebo recipients.

Limitations: The study involved only 1 group of patients over 1 year.

Conclusions: Abatacept statistically significantly reduced disease activity in patients with rheumatoid arthritis and an inadequate response to methotrexate. Longer treatment in different patient populations is needed to establish its appropriate role in rheumatoid arthritis.

Ann Intern Med. 2006;144:865-876. www.annals.org
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ClinicalTrials.gov identifier: NTC00048568.

Rheumatoid arthritis is characterized by synovial membrane hyperplasia and inflammatory cell infiltrate, including activated T cells (1). T cells contribute to the initiation and perpetuation of rheumatoid arthritis immunopathology, leading to inflammation and, ultimately, joint destruction. Activated T cells proliferate and induce monocytes, macrophages, and synovial fibroblasts to produce proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6 (1), and stimulate osteoclastogenesis and matrix metalloproteinase secretion (2), as well as immunoglobulin production by B cells (3). The central role of activated T cells in rheumatoid arthritis immunopathology makes T-cell activation a rational therapeutic target.

T cells require 2 signals for full activation: an antigen-specific signal (signal 1) and a co-stimulatory signal (signal 2) (4). One of the best-characterized co-stimulatory pathways is the engagement of CD80 or CD86 on antigen-presenting cells with CD28 on T cells (5). In the normal immune response, endogenous cytotoxic T-lymphocyte antigen-4 (CTLA-4) downregulates CD28-mediated T-cell activation by binding to CD80 or CD86 with higher avidity than CD28 (6).

Abatacept is a soluble, recombinant, fully human fu-

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Context

Abatacept, an agent that selectively modulates the co-stimulatory signal required for T-cell activation, may benefit some patients with rheumatoid arthritis.

Contribution

This 1-year, randomized, double-blind trial compared once-monthly infusions of abatacept with placebo in 652 patients with symptomatic rheumatoid arthritis despite ongoing methotrexate treatment. Compared with placebo recipients, patients who received abatacept more often had improved physical function, more frequently met standard response criteria, and less often had radiographic progression of joint damage. They also had serious infections (2.5% vs. 0.9%) and infusion reactions more often.

Implications

Adding abatacept can reduce disease activity in patients with rheumatoid arthritis and an inadequate response to methotrexate.

—The Editors

sion protein, comprising the extracellular domain of CTLA-4 and the Fc portion of IgG1, modified to prevent complement fixation. Abatacept is the first in a new class of agents for treating rheumatoid arthritis that selectively modulate the co-stimulatory signal required for full T-cell activation. A phase IIa study of patients with rheumatoid arthritis and an inadequate response to disease-modifying antirheumatic drugs showed the efficacy of abatacept as monotherapy (7). In a phase IIb study of abatacept plus methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate, signs and symptoms of rheumatoid arthritis, physical function, and health-related quality of life statistically significantly improved over 1 year (8, 9).

We present findings from the phase III, 1-year Abatacept in Inadequate Responders to Methotrexate (AIM) trial, which was designed to further evaluate the safety and clinical efficacy of abatacept plus methotrexate and to assess the effects of abatacept on the radiographic progression of structural damage.

METHODS

The institutional review boards or independent ethics committees approved a common clinical protocol for each site, and we performed the study in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent to the study protocol before randomization.

Patients

Eligible patients were at least 18 years of age, had had rheumatoid arthritis for at least 1 year, and met the American Rheumatism Association criteria for rheumatoid arthritis (10). Rheumatoid arthritis was persistent and active despite methotrexate treatment. All patients must have been treated with methotrexate (≥15 mg/wk) for 3 months or longer, with a stable dose for 28 days before enrollment. We required patients to undergo a washout of all other disease-modifying antirheumatic drugs at least 28 days before randomization. We allowed corticosteroid use, with dosages equal to 10 mg of prednisone or less per day, stabilized for 25 days before randomization.

At randomization, we required patients to have 10 or more swollen joints, 12 or more tender joints, and C-reactive protein levels of 10.0 mg/L or greater (normal range, 1.0 mg/L to 4.0 mg/L) while receiving methotrexate. We required tuberculin skin testing before randomization. We excluded patients with a positive tuberculin skin test result unless they had completed treatment for latent tuberculosis before enrollment.

Study Design

Our 1-year, multicenter, multinational, randomized, double-blind, placebo-controlled study aimed to compare the efficacy and safety of abatacept versus placebo in combination with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate treatment. We used a central randomization system, and the Drug Management Group within Bristol-Myers Squibb, Princeton, New Jersey, generated the randomization schedule. Stratification per site was not performed. Patients were randomly assigned in a 2:1 ratio to receive either a fixed dose of abatacept, approximately 10 mg/kg of body weight, or placebo. Patients weighing less than 60 kg, 60 to 100 kg, or more than 100 kg received 500 mg, 750 mg, or 1000 mg of abatacept, respectively. We administered study medication by 30-minute intravenous infusion on days 1, 15, and 29 and then every 28 days up to and including day 337. No premedication was required.

The protocol specified that all patients were to receive methotrexate, 15 mg or more per week, although methotrexate at 10 mg per week was acceptable if the patient had a history of toxicity. During the first 6 months, we did not allow adjustments in methotrexate dose, except in cases of toxicity. We permitted use of stable dosages of nonsteroidal anti-inflammatory drugs and corticosteroid dosages equal to 10 mg of prednisone or less per day. Between 6 and 12 months, we allowed the following adjustments, as the investigator deemed necessary: 1) adjustment in methotrexate dose, 2) addition of 1 other disease-modifying antirheumatic drug (hydroxychloroquine, sulfasalazine, gold, or azathioprine), or 3) adjustment in corticosteroid dose equal to 10 mg of prednisone or less per day. However, investigators were blinded to treatment group assignment throughout the 1-year study.

Clinical Efficacy Measures

Our 3 primary objectives were to evaluate the proportion of patients in each group with a 20% improvement in American College of Rheumatology (ACR) response crite-

Table 1. **Outcome Measures for Assessing Response to Treatment of Rheumatoid Arthritis***

Measurement (Reference)	Outcome Measured	Measurement Scale and Clinically Meaningful Differences (Reference)
ACR response criteria (14)	Categorical physician, patient, and laboratory assessment of improvements in disease activity in response to treatment	ACR 20, ACR 50, and ACR 70: 20%, 50%, and 70% improvements, respectively, in the components of the ACR criteria Major clinical response: ACR 70 maintained for 6 consecutive months Extended major clinical response: ACR 70 maintained for 9 consecutive months
DAS28 (15)	Continuous physician, patient, and laboratory assessment of current disease activity levels, as well as improvements in disease activity in response to treatment	Scale of 0–10: high disease activity, ≥5.1; low disease activity, ≤3.2; remission, <2.6; minimum clinically important improvement, ≥1.2
HAQ-DI (16)	Patients' self-assessment questionnaire of 8 subscales relating to physical disability	Scale of 0–3 (no disability = 0, completely disabled = 3): minimum clinically important improvement, ≥0.22 (11)†
SF-36 (17)	Patients' self-assessment questionnaire measuring mental and physical aspects of health-related quality of life, consisting of 8 subscales and the MCS‡ and PCS‡	Scale of 0–100 (worst = 0, best = 100): minimum clinically meaningful improvement, ≥3 units (18, 19)
Genant-modified Sharp score (12, 13)	Assessment of changes in structural damage, scored independently by 2 specially trained radiologists blinded to treatment group assignment and chronological order of radiography	Erosion score: 8-point scale scored in 0.5-point increments (0 [normal] to 3.5 [severe]): maximum achievable normalized erosion score, 145 Joint-space narrowing score: 9-point scale scored in 0.5-point increments (0 [normal] to 4.0 [ankylosed]): maximum achievable normalized joint-space narrowing score, 145 Total score: combination of erosion and joint-space narrowing scores; maximum achievable normalized score, 290

* ACR = American College of Rheumatology; DAS28 = Disease Activity Score 28; HAQ-DI = Health Assessment Questionnaire Disability Index; MCS = mental component summary; PCS = physical component summary; SF-36 = Medical Outcomes Study Short Form-36 Health Survey.
† A HAQ-DI response was defined as an improvement from baseline of ≥0.3 unit.
‡ MCS and PCS are derived from a weighted linear combination of the 8 individual subscales of the SF-36.

ria (ACR 20) at 6 months, the proportion of patients in each group with clinically significant improvement (≥0.3 unit) in the Health Assessment Questionnaire Disability Index (HAQ-DI) score (11) at 1 year, and the radiographic progression of joint erosions (assessed by comparing changes from baseline in the Genant-modified Sharp score) (12, 13) at 1 year.

Table 1 summarizes the outcome measures used to assess the response to treatment.

Secondary objectives included assessing ACR 50 and ACR 70 responses at 6 months and all ACR responses at 1 year. In addition, we determined the proportions of patients achieving a major clinical response and a protocol-defined extended major clinical response at 1 year. We also assessed changes in disease activity by using the Disease Activity Score 28 (DAS28) (20, 21).

We assessed improvements in physical function over 1 year by using the HAQ-DI, which measures physical function during daily activities (22). We evaluated changes in health-related quality of life by using the Medical Outcomes Study Short Form-36 Health Survey (SF-36) (17), which evaluates physical and mental health status (**Table 1**) (18, 19).

Physicians blinded to treatment group assignment performed assessments at enrollment and at every visit before treatment administration on days 1, 15, and 29; every 28 days up to and including day 169 (6 months); and on days 225, 281, and 365 (1 year).

Radiographic Evaluation

We performed standardized radiography of the hands or wrists and feet at baseline and at 1 year or upon early termination (if applicable). Two independent expert readers who were blinded to treatment group assignment, chronological order of radiography, and patients' clinical response assessed all radiographic images for changes in erosion and joint-space narrowing by using the Genant-modified Sharp scoring system.

Safety and Immunogenicity

We monitored all patients who received at least 1 dose of the study medication for adverse events, serious adverse events, infusion reactions, clinical laboratory test abnormalities, and clinically significant changes in vital signs. Adverse events were self-reported by the patient and elicited by general questioning and examination at each visit. We attributed an adverse event to the study treatment on the basis of the investigator's opinion, and we deemed an event as serious by standard regulatory definition. An external safety advisory panel, consisting of 5 physicians (3 rheumatologists, 1 oncologist, and 1 infectious disease expert), assessed overall safety in a blinded fashion by using reports of adverse events and laboratory results on a quarterly basis. We obtained serum samples before infusions on days 1, 29, 85, 169, 281, and 365 or 28 days after the last dose of the study medication in patients who discontinued

before 1 year. We assessed immunogenicity by immunoassay to measure the antibody response to the entire abatacept molecule and also specifically to the CTLA-4 portion of the molecule (7).

Statistical Analysis

The protocol estimated that 680 patients would need to be enrolled to randomly assign 540 patients. We based sample sizes on a 5% level of significance (2-tailed). The study had 99% power to detect a difference of 20% in ACR 20 between the 2 groups. On the basis of the hierarchical testing procedure for the co-primary measures, this sample size allowed us to detect an 18% difference in HAQ-DI response rate between the 2 groups, with 98% power, and a treatment effect of 60% reduction from placebo (assuming an increase of 1.27 units in placebo for the change from baseline), with 90% power, for change from baseline in the Genant-modified Sharp erosion score. We based the assumptions on the findings of a phase IIb study of patients with rheumatoid arthritis who were using abatacept (8, 9).

We performed all efficacy and safety analyses on a modified intention-to-treat population, defined as all randomly assigned patients who received at least 1 dose of study medication. We based all statistical tests on a 2-sided 5% level of significance and used SAS software, version 8.2 (SAS Institute, Cary, North Carolina), for all analyses.

For the co-primary analyses of ACR 20 at 6 months and HAQ-DI responses at 1 year, we used a 2-sided, continuity-corrected chi-square test to compare the responses of the abatacept group with those of the placebo group. We imputed missing data for patients who discontinued as nonresponders subsequent to the discontinuation; thus, we based these analyses on the full modified intention-to-treat denominator. We performed additional sensitivity analyses to assess the effect of the imputation of missing data. These include a "modified worst-case" analysis, where we imputed missing data for placebo recipients who discontinued for reasons other than lack of efficacy by using their last observed response, and a "worst-case" analysis, where we imputed missing data for placebo recipients who discontinued as responders. In both cases, however, we still imputed missing data for abatacept recipients as nonresponders. We performed additional longitudinal analyses by using the generalized estimating equations to assess the treatment effect over time. We used all available data, and the longitudinal analysis assumes that data were missing completely at random and were not dependent on current or future responses. The models included treatment, visit day, and treatment-by-visit interaction as fixed effects, and we used an unstructured covariance to account for within-patient correlation over time (23, 24).

We used a rank-based analysis of covariance (25) to compare the changes from baseline in Genant-modified Sharp scores between treatment groups at 1 year. The model included the ranks for score changes as the dependent variable, with treatment group as a main effect, and the ranks for baseline scores as additional covariates. Midranks were assigned for ties. The primary radiographic analyses included all observed data at baseline and at 12 months. We imputed missing annual radiographic data with linear extrapolation for discontinued patients on the basis of the baseline value and the on-treatment assessment at the time of discontinuation, provided that both assessments were available. Summary statistics and a cumulative probability plot were provided for changes from baseline in the Genant-modified Sharp scores at 1 year by treatment group assignment. We performed additional sensitivity analyses to assess the effect of missing annual radiographic data. These included analysis with imputed 12-month values for patients with missing annual assessments on the basis of the responses predicted by the data observed across both treatment groups, clustering patients with similar baseline radiographic scores. In addition, we also performed a "graded worst-case" imputation, where we imputed missing data for abatacept and placebo recipients with progressively worst outcomes and progressively best outcomes, respectively.

To avoid multiple testing, we used a prespecified sequential testing procedure for co-primary end points. We made comparisons only if all preceding co-primary end points were statistically significant, according to the following hierarchy: ACR 20 response at 6 months; functional performance at 1 year, as measured by the HAQ-DI; and change in erosion, by using the Genant-modified Sharp score, at 1 year.

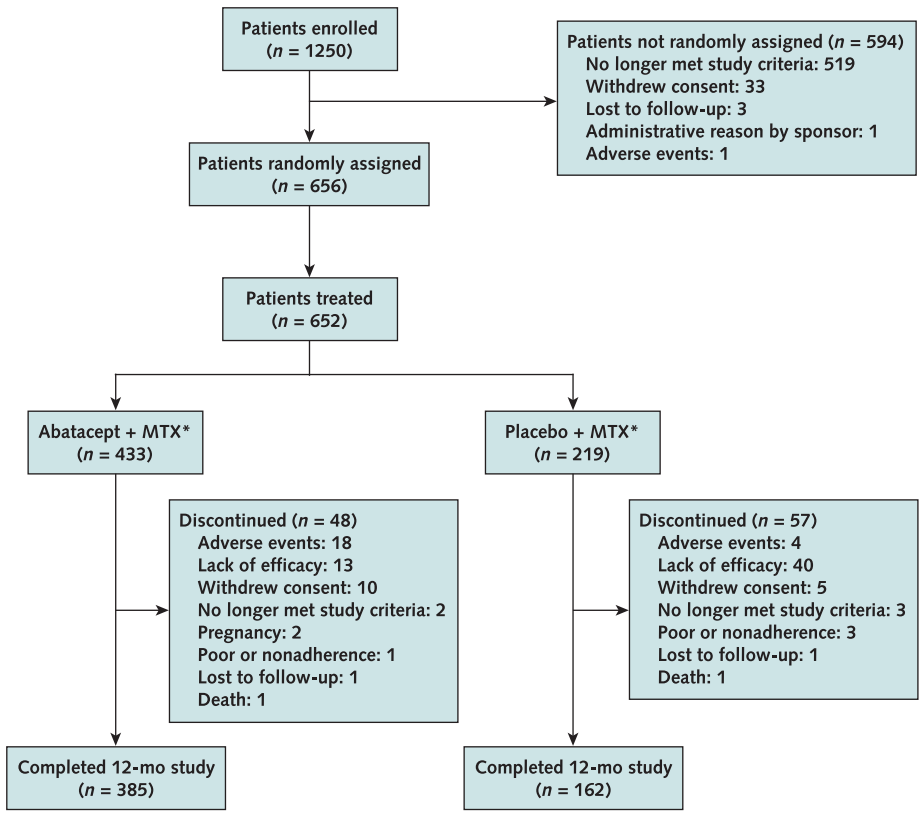
The analysis of covariance with the last observation carried forward (LOCF) approach was the prespecified method for the comparisons between treatment groups of mean changes from baseline in the HAQ-DI and the 8 subscales and the physical and mental component summaries of the SF-36. However, because the limitations of the LOCF approach could yield substantial bias in treatment effects (26), and also on the basis of editorial advice, we used a longitudinal linear mixed-effects model in the comparisons of these end points. We used all available data, and the longitudinal analysis assumes that data were missing at random and were not dependent on current or future responses. The models included treatment, visit day, and treatment-by-visit interaction as fixed effects, and we used an autoregressive (1) covariance to account for within-patient correlation over time (23).

For DAS28, we used a 2-sided, continuity-corrected chi-square test to compare the responses of the abatacept group with those of the placebo group. We summarized the incidence of adverse events by treatment and used 95% CIs for the comparisons between treatment groups.

Role of the Funding Source

This trial was sponsored by Bristol-Myers Squibb. The funding source helped design the study in consultation with the authors and provided statistical support for data

Figure 1. **Study flow diagram.**



*MTX = methotrexate. Nine abatacept-treated patients and 5 placebo recipients from 1 site were excluded from all efficacy analyses before unblinding due to nonadherence but were included in all safety analyses.

analysis. Interpretation of the data was aided by the funding biostatisticians, with input from the authors. The funding source was not involved in the decision to submit the article for publication.

Results

Patient Characteristics

We enrolled 1250 patients with rheumatoid arthritis, and we randomly assigned 652 of them to treatment with abatacept ($n = 433$) or placebo ($n = 219$) plus methotrexate (**Figure 1**). The most frequent reason for exclusion was if a patient no longer met the study entry criteria. Baseline demographic or clinical characteristics did not notably differ between treatment groups (**Table 2**). Because of adherence issues identified during the study, we excluded patients from 1 site from all efficacy analyses before unblinding but included them in the safety analysis.

More patients in the abatacept group (89%) than in the placebo group (74%) completed 1 year of treatment (**Figure 1**). Lack of efficacy was the most common reason for discontinuation in the placebo group (18% vs. 3%). Adverse events were the most common reasons for discontinuation in the abatacept group (4% vs. 2%). Fewer patients discontinued the study during months 7 through 12 in the abatacept group than in the placebo group (4% vs. 5%, respectively).

During the study, the background methotrexate dosage was stable and similar in both groups (approximately 15 mg/wk), as were nonsteroidal anti-inflammatory drug and corticosteroid dosages. Between 6 and 12 months, 15 (3.7%) abatacept-treated patients versus 25 (14.4%) placebo recipients received additional disease-modifying antirheumatic drugs (azathioprine, 2 [0.5%] patients vs. 3 [1.7%] patients; sulfasalazine, 8 [2.0%] patients vs. 12 [6.9%] patients; hydroxychloroquine, 5 [1.3%] patients vs. 6 [3.5%] patients; $P < 0.001$).

Clinical Efficacy

ACR Responses and Major Clinical Response

The ACR 20 scores statistically significantly improved at 6 months with abatacept (67.9% for abatacept vs. 39.7% for placebo; $P < 0.001$; difference, 28.2 percentage points [95% CI, 19.8 to 36.7 percentage points]) (**Figure 2**, *A*). At 6 months, ACR 50 responses were 39.9% versus

Table 2. **Baseline Characteristics***

Characteristics	Abatacept + Methotrexate Group (n = 433)	Placebo + Methotrexate Group (n = 219)
Age, *y*	51.5 (12.9)	50.4 (12.4)
Weight, *kg*	72.3 (17.5)	70.2 (16.1)
Women, %	77.8	81.7
White, %	87.5	88.1
Geographic region, %		
North America	21.5	21.0
South America	40.0	42.5
Europe	33.0	30.6
Other	5.5	5.9
Disease duration, *y*	8.5 (7.3)	8.9 (7.1)
Methotrexate dose, *mg/wk*	16.1 (3.6)	15.7 (3.5)
Tender joints, *n*	31.0 (13.2)	32.3 (13.6)
Swollen joints, *n*	21.4 (8.8)	22.1 (8.8)
Pain (100-mm VAS)	63.3 (21.1)	65.9 (20.6)
Physical function (HAQ-DI)	1.7 (0.7)†	1.7 (0.6)
Patient global assessment (100-mm VAS)	62.7 (21.2)	62.8 (21.6)
Physician global assessment (100-mm VAS)	68.0 (16.0)	67.4 (17.0)
CRP level, *mg/L*	33 (31)	28 (25)
Rheumatoid factor, %	81.8	78.5
Baseline radiographic score		
Erosion score	21.7 (18.1)	21.8 (18.6)
Joint-space narrowing score	22.8 (20.2)	23.0 (20.4)
Total score	44.5 (37.3)	44.9 (37.7)
Baseline median score (range)		
Erosion score	16.6 (0.0–112.2)	16.7 (0.3–95.8)
Joint-space narrowing score	16.2 (0.0–108.8)	16.6 (0.0–94.3)
Total score	31.9 (0.5–221.0)	33.4 (2.3–190.1)
Antirheumatic medications at enrollment, *n (%)*		
Methotrexate	433 (100.0)	219 (100.0)
Other disease-modifying antirheumatic drugs	53 (12.2)	19 (8.7)
Biologics	1 (0.2)	0
Corticosteroids	312 (72.1)	150 (68.5)
NSAIDs	370 (85.5)	181 (82.6)
Other	1 (0.2)	0

* Data are reported as means (SDs), unless otherwise indicated. CRP = C-reactive protein; HAQ-DI = Health Assessment Questionnaire Disability Index; NSAID = nonsteroidal anti-inflammatory drug; VAS = visual analogue scale.
† n = 431.

16.8% (difference, 23.0 percentage points [CI, 15.0 to 31.1 percentage points]) and ACR 70 responses were 19.8% versus 6.5% (difference, 13.3 percentage points [CI, 7.0 to 19.5 percentage points]) for abatacept versus placebo, respectively ($P < 0.001$ for both) (**Figure 2**, *B and C*).

Between 6 and 12 months, all ACR responses continually improved in patients receiving abatacept, while responses in placebo recipients were largely unchanged from month 6. At 1 year, ACR 20 responses had increased to 73.1% versus 39.7% (difference, 33.4 percentage points [CI, 25.1 to 41.7 percentage points]), ACR 50 responses were 48.3% versus 18.2% (difference, 30.1 percentage points [CI, 21.8 to 38.5 percentage points]), and ACR 70 responses were 28.8% versus 6.1% (difference, 22.7 percentage points [CI, 15.6 to 29.8 percentage points]) for abatacept recipients versus placebo recipients, respectively ($P < 0.001$ for all) (**Figure 2**, *A to C*). Post hoc analyses of the abatacept group showed that the proportion of patients with ACR 50 and ACR 70 responses statistically significantly increased from 6 months to 12 months ($P < 0.001$ for 6 months vs. 12 months). Of the abatacept-treated patients with an ACR 70 response at 1 year, 45% maintained the response for 6 consecutive months (major clinical response overall, 14.2%) and 21% maintained the response for 9 consecutive months (extended major clinical response overall, 6.1%).

In the modified worst-case and worst-case sensitivity analyses, we observed an ACR 20 response at 6 months in more patients in the abatacept group (68% in both cases) than in the placebo group (40% in the modified worst-case and 57% in the worst-case analyses). An additional longitudinal analysis confirmed the significant increase in ACR 20 response for abatacept versus placebo ($P < 0.001$) and, more specifically, at day 15 ($P = 0.008$). This early response was largely driven by rapid improvements in pain and by patients' and physicians' assessments of disease activity, which were statistically significant from day 15 onward compared with placebo (data not shown). Longitudinal analyses also demonstrated significant increases in ACR 50 and ACR 70 responses with abatacept compared with

placebo at 1 year ($P < 0.001$). The **Appendix Table** (available at www.annals.org) provides results related to the individual components of the ACR.

Physical Function

At the start of the study, patients' physical function was considerably impaired (HAQ-DI score of 1.7 in both groups) (**Table 2**). At 1 year, physical function clinically significantly improved in statistically significantly more abatacept-treated patients (11) than placebo recipients (63.7% vs. 39.3%; $P < 0.001$; difference, 24.4 percentage points [CI, 15.9 to 32.9 percentage points]) (**Figure 2**, *D*).

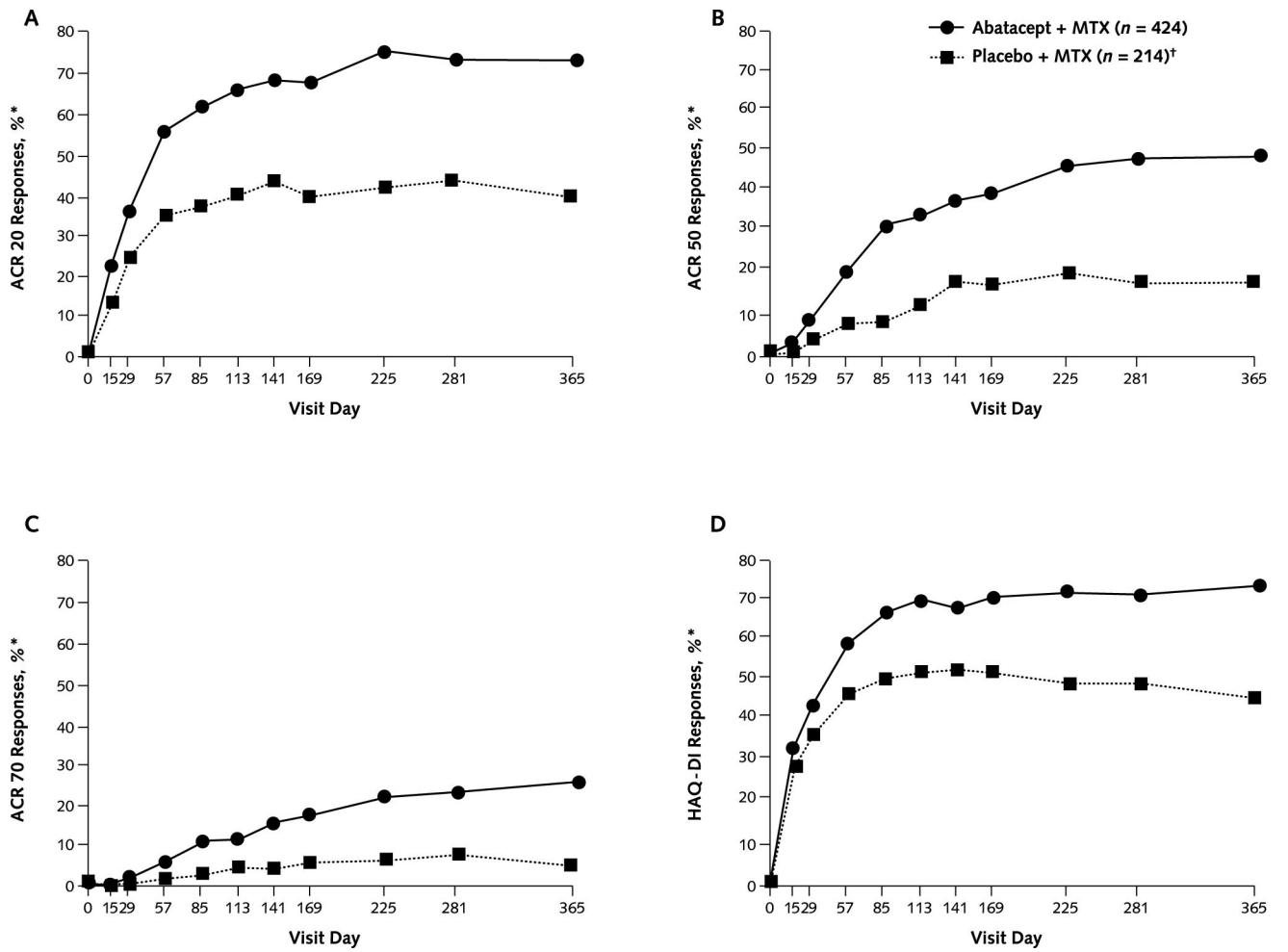
In the modified worst-case sensitivity analysis, more patients in the abatacept group (64%) had an HAQ-DI response at 1 year than those in the placebo group (42%). In the worst-case analysis, similar proportions in both treatment groups (64%) had an HAQ-DI response. However, because of the extreme nature of the response imputation rule, the resulting high response rate in the placebo group does not represent an observable placebo response rate. The longitudinal analysis using the generalized estimating equations confirmed the significant increase in the proportion of patients with an HAQ-DI response for abatacept versus placebo ($P < 0.001$).

When we used the longitudinal linear mixed-effects approach, the mean improvement from baseline in the HAQ-DI was statistically significantly better in abatacept-treated patients than in placebo recipients at both 6 months and 1 year ($P < 0.001$). Results were consistent with the LOCF approach.

Radiographic Progression

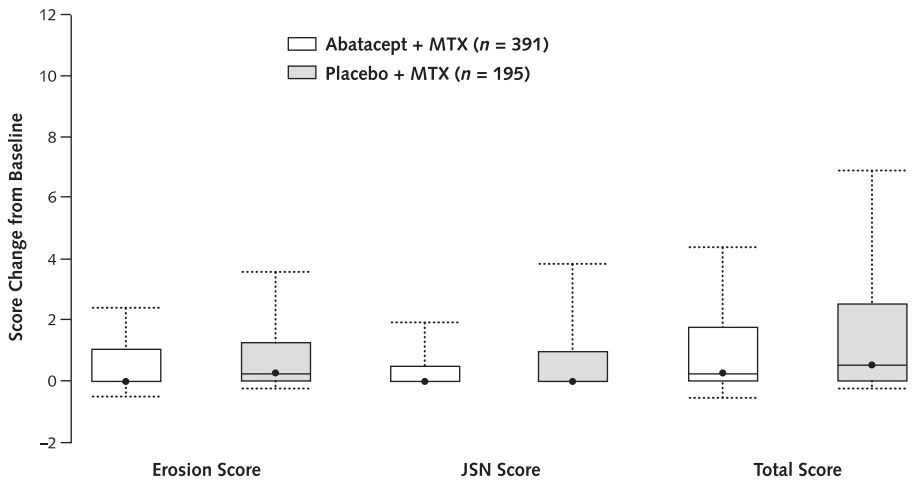
We collected radiographic data for 586 (92%) randomly assigned patients at baseline and at 1 postbaseline

Figure 2. **Improvements in signs and symptoms of disease and physical function.**



A–C. American College of Rheumatology (*ACR*) 20 (*panel A*), ACR 50 (*panel B*), and ACR 70 (*panel C*) responses over 1 year in all patients who received at least 1 dose of the study medication. **D.** The percentage of patients who achieved a Health Assessment Questionnaire Disability Index (*HAQ-DI*) response (≥0.3-unit improvement from baseline in HAQ-DI) was determined over 1 year. MTX = methotrexate. *Intention-to-treat population where all dropouts were considered to be ACR nonresponders subsequent to their dropout. †Because of adherence issues identified during the study, patients from 1 site were excluded from all efficacy analyses before unblinding but were included in the analysis of safety.

Figure 3. **Slowing of radiographic structural damage progression at 1 year.**



Interquartile range changes from baseline in Genant-modified Sharp erosion, joint-space narrowing (*JSN*), and total scores were evaluated at 1 year or at early termination (if applicable). The median (*solid circles*), interquartile range, and 10th and 90th percentiles (*dotted lines*) are shown. Data shown are from all randomly assigned and treated patients with baseline and follow-up radiography. MTX = methotrexate.

time point. Baseline erosion, joint-space narrowing, and total scores were similar between the groups (**Table 2**). At 1 year, abatacept-treated patients demonstrated statistically significant slowing of structural damage progression compared with placebo recipients, with an approximately 50% reduction in change from baseline in Genant-modified Sharp scores compared with that of placebo. The median change from baseline in erosion score was 0.0 (25th and 75th percentiles, 0.0 and 1.0, respectively) for abatacept versus 0.27 (25th and 75th percentiles, 0.0 and 1.3, respectively) for placebo ($P = 0.029$; **Figure 3**). Median changes in the joint-space narrowing and total scores were similar between the groups. The median change in joint-space narrowing score was 0.0 (25th and 75th percentiles, 0.0 and 0.5, respectively) for abatacept versus 0.0 (25th and 75th percentiles, 0.0 and 1.0, respectively) for placebo ($P = 0.009$) (**Figure 3**). The median change in total score was 0.25 (25th and 75th percentiles, 0.0 and 1.8, respectively) for abatacept versus 0.53 (25th and 75th percentiles, 0.0 and 2.5, respectively) for placebo ($P = 0.012$) (**Figure 3**). The mean change from baseline was 0.63 for abatacept versus 1.14 for placebo in erosion score, 0.58 for abatacept versus 1.18 for placebo in joint-space narrowing score, and 1.21 for abatacept versus 2.32 for placebo in total score.

The sensitivity analysis suggested that the few missing data did not statistically significantly affect the robustness of slowing the progression of structural damage. For the sensitivity analysis, in which we imputed missing 1-year radiographic values, the median changes in total score were 0.26 (interquartile range, 0.00 to 1.84) and 0.53 (interquartile range, 0.00 to 3.14) in the abatacept and placebo groups, respectively. These changes for both treatment groups were the same as those in the primary analysis, with differences observed only in the 75th percentile and a more notable increase in the placebo group. In the graded worst-case sensitivity analyses, in which several imputations increasingly favored placebo, the trend for the benefit of abatacept was maintained compared with that of placebo, even in the extreme case (data not shown).

Disease Activity

Patients exhibited high baseline disease activity (DAS28 of 6.4 for both groups [15]). At 6 months and 12 months, 30.1% and 42.5% of the abatacept group, respectively, had a DAS28 of 3.2 or less, compared with 10.0% and 9.9% of the placebo group, respectively ($P < 0.001$). Abatacept induced DAS28 less than 2.6 in 14.8% of abatacept recipients versus 2.8% of placebo recipients at 6 months and in 23.8% of abatacept recipients versus 1.9% of placebo recipients at 1 year ($P < 0.001$).

Health-Related Quality of Life

When we used the linear mixed-effects approach, both the physical ($P < 0.001$) and mental ($P = 0.009$) component summaries significantly improved from baseline to 6 months (increase of ≥3 units) (18, 19) in the abatacept group compared with the placebo group. At 1 year, both summary scores for patients treated with abatacept were still significant (physical component summary, $P < 0.001$; difference, 3.8 [CI, 2.4 to 5.2]; mental component summary, $P = 0.038$; difference, 1.76 [CI, 0.1 to 3.4]). Results were also significant at both 6 months and 1 year with the LOCF approach.

Safety and Immunogenicity

Safety

The overall incidence of adverse events was similar in both the abatacept and placebo groups (87.3% vs. 84.0% [CI, −2.5 to 9.1 percentage points]) (**Table 3**). The most

frequently reported adverse events (>5% in either group) included headache, nasopharyngitis, and nausea. More patients discontinued because of adverse events in the abatacept group than in the placebo group (4.2% vs. 1.8%) (**Table 3**).

The incidence of serious adverse events increased with abatacept treatment; rates of discontinuation due to serious adverse events were similar between the groups (**Table 4**). The most frequently reported serious adverse events were musculoskeletal, primarily related to hospitalizations for rheumatoid arthritis flares or elective surgery for rheumatoid arthritis.

The incidence of infection reported as a serious adverse event was higher with abatacept than with placebo (**Table 4**). Discontinuations due to serious infections were similar between groups (2 discontinuations [0.5%] for abatacept vs. 1 discontinuation [0.5%] for placebo). More patients in the abatacept group than in the placebo group had prespecified infections that met the criteria for a serious adverse event (a subset of all serious adverse events). We observed an increase in cases of pneumonia with abatacept treatment versus placebo treatment (**Table 4**). One abatacept-treated patient reported an enlarged lymph node, which revealed histologic findings on biopsy compatible with possible tuberculosis; however, the patient did not experience any symptom of tuberculosis and we found no bacterial evidence of tuberculosis. One case of unconfirmed tuberculosis was reported in the placebo group. Two deaths due to infections occurred. One abatacept-treated patient with underlying pulmonary disease, characterized by a history of tuberculosis, asbestos exposure, and pulmonary fibrosis, died of bronchopneumonia, pulmonary aspergillosis, and *Pseudomonas aeruginosa* septicemia. A placebo recipient died after *P. aeruginosa* pneumonia, sepsis, and multiorgan failure.

The incidence of neoplasms (benign or malignant) and hematologic disorders was similar in both groups. A large B-cell lymphoma of the thyroid on a background of Hashimoto thyroiditis was reported in 1 patient receiving abatacept, and 1 endometrial carcinoma was reported in a patient receiving placebo.

No major autoimmune disorders, such as multiple sclerosis or lupus, were reported (**Tables 3** and **4**).

More infusion reactions (acute and peri-infusional) occurred with abatacept than with placebo (**Table 4**). Two patients discontinued because of severe acute infusion reactions. One patient experienced hypersensitivity (rash and chest pain) after the second infusion; the second patient experienced severe hypotension during the fourth infusion. Both events resolved shortly after cessation of infusions. Severe peri-infusional events were infrequent.

Immunogenicity

Six patients (1.4%) demonstrated antibody reactivity to abatacept. The pattern of ACR 20 responses in these patients was similar before and after the time of antibody response, and no patient had a hypersensitivity reaction.

Table 3. **Adverse Events**

Adverse Event	Abatacept + Methotrexate Group (*n* = 433), *n (%)*	Placebo + Methotrexate Group (*n* = 219), *n (%)*
Death	1 (0.2)	1 (0.5)
Total adverse events*	378 (87.3)	184 (84.0)
Related to study drug	214 (49.4)	104 (47.5)
Discontinuations due to adverse events	18 (4.2)	4 (1.8)
Most frequently reported adverse events (>5%)†		
Headache	76 (17.6)	26 (11.9)
Nasopharyngitis	66 (15.2)	25 (11.4)
Nausea	52 (12.0)	24 (11.0)
Diarrhea	47 (10.9)	21 (9.6)
Upper respiratory tract infection	47 (10.9)	21 (9.6)
Dizziness	40 (9.2)	16 (7.3)
Back pain	40 (9.2)	12 (5.5)
Influenza	31 (7.2)	12 (5.5)
Cough	29 (6.7)	13 (5.9)
Dyspepsia	27 (6.2)	10 (4.6)
Pharyngitis	26 (6.0)	10 (4.6)
Hypertension	24 (5.5)	3 (1.4)
Fatigue	23 (5.3)	15 (6.8)
Urinary tract infection	22 (5.1)	11 (5.0)
Upper abdominal pain	19 (4.4)	13 (5.9)
Sinusitis	18 (4.2)	15 (6.8)
Bronchitis	18 (4.2)	12 (5.5)

* Includes all adverse events from day 1 of treatment through 56 days after treatment. A list of adverse events reported by fewer than 5% of patients is available from the authors upon request.
† Does not include worsening rheumatoid arthritis.

Table 4. **Serious and Infusional Adverse Events and Serious Infections**

Variable	Abatacept + Methotrexate Group (*n* = 433), *n (%)*	Placebo + Methotrexate Group (*n* = 219), *n (%)*	Difference (95% CI), *percentage points*
Serious adverse events	65 (15.0)	26 (11.9)	3.2 (–2.3 to 8.6)
Related to study drug	15 (3.5)	1 (0.5)	
Discontinuations due to serious adverse events	10 (2.3)	3 (1.4)	
Musculoskeletal and connective tissue disorders*	20 (4.6)	10 (4.6)	
Infections	17 (3.9)	5 (2.3)	
Nervous system disorders	6 (1.4)	4 (1.8)	
Cardiac disorders	4 (0.9)	2 (0.9)	
Neoplasms (benign, malignant, and unspecified)	4 (0.9)	2 (0.9)	
Acute infusional adverse events†	38 (8.8)	9 (4.1)	4.7 (0.9 to 8.4)
Peri-infusional adverse events†	106 (24.5)	37 (16.9)	7.6 (1.2 to 14.0)
Serious infections (prespecified)‡	11 (2.5)	2 (0.9)	1.6 (–0.3 to 3.6)
Pneumonia	4 (0.9)	1 (0.5)	
Bronchopneumonia	2 (0.5)	0	
Cellulitis	1 (0.2)	1 (0.5)	
Sepsis	1 (0.2)	1 (0.5)	
Abscess	1 (0.2)	0	
Bacterial arthritis	1 (0.2)	0	
Bronchopulmonary aspergillosis	1 (0.2)	0	
Acute pyelonephritis	1 (0.2)	0	
Tuberculosis§	1 (0.2)	1 (0.5)‖	
Limb abscess	0	1 (0.5)	

* Includes rheumatoid arthritis.
† Acute infusional events occurred within 1 hour of the start of the infusion; peri-infusional events occurred within 24 hours of the start of the infusion.
‡ A subset of overall infections classified as serious adverse events, prespecified as those serious infections that may be associated with use of immunomodulatory drugs.
§ Unconfirmed.
‖ Not reported as a serious infection.

DISCUSSION

The phase III AIM study confirmed and extended the findings of a phase IIb study in a similar patient population (8, 9) by demonstrating that abatacept, with background methotrexate, is effective in reducing the signs and symptoms of rheumatoid arthritis and improving physical function and health-related quality of life. The study also demonstrated that abatacept slows the progression of structural damage in patients with moderate-to-severe disease and an inadequate response to methotrexate treatment.

We observed a rapid and sustained increase in all ACR responses through 1 year with abatacept. Both pain and self-assessment of disease activity statistically significantly improved in abatacept-treated patients, as early as day 15 in some patients. A total of 28.8% of abatacept-treated patients exhibited an ACR 70 response at 1 year, and a statistically significant number of these patients maintained their ACR 70 response for 6 and 9 consecutive months. Statistically significant proportions of patients in the abatacept group had DAS28 less than 2.6 or 3.2 or less at 6 months, and scores continued to increase through 1 year. The increasing efficacy observed during 1 year of abatacept treatment was not due to the allowance of additional medications during the second half of the study. Few abatacept-treated patients received additional disease-modifying antirheumatic drugs (3.7% for abatacept vs. 14.4% for placebo) during months 7 through 12 of treatment.

We believe that our study is the first to demonstrate that abatacept statistically significantly slows the progression of structural damage. One-year radiographic data, from 92% of patients, indicate that the progression of structural damage was reduced by approximately 50% with abatacept compared with placebo. Additional sensitivity analyses to assess the effect of imputation suggest that the few missing data (8%) did not statistically significantly affect these findings. Abatacept demonstrated this protective effect in a wide range of patients, including those with relatively long-standing disease, with irreversible damage and highly progressed lesions. These findings correspond well with the observed improvements in clinical and functional end points. We should note that the actual degree of progression in both groups was relatively low in our study, although the primary end point of reduction in the progression of erosion was met and was statistically significant for abatacept versus placebo. The clinical relevance of the finding may require additional long-term observations in patients with rheumatoid arthritis who receive abatacept for prolonged periods of time.

Our safety findings were consistent with those of a previous phase IIb abatacept study in a similar patient population (8, 9). Other than headache and nasopharyngitis, which were more frequent with abatacept, the incidence of the most commonly reported adverse events was similar for both treatment groups. Discontinuations due to adverse events occurred in only 4.2% of patients receiving abatacept compared with 1.8% of those receiving placebo. Serious adverse events occurred in 15% of abatacept-treated patients and 11.9% of placebo recipients.

Prespecified serious infections occurred in 2.5% of patients receiving abatacept and 0.9% of patients receiving

placebo. One case of aspergillosis occurred in the abatacept group. One case of tuberculosis was reported in each group; however, neither case of tuberculosis was confirmed bacteriologically. We included patients who were from countries where tuberculosis is endemic; however, as recommended with antitumor necrosis factor agents used for treating rheumatoid arthritis, which have shown an increased incidence of tuberculosis, we screened all patients by tuberculin skin test before study entry. We excluded patients with a positive antituberculin skin test result, and therefore, comparison of the rates of tuberculosis with the early experience of antitumor necrosis factor agents, in which routine tuberculin skin testing was not performed, would not be appropriate. Additional longer-term information is needed to determine whether an increased relative risk for tuberculosis or other opportunistic infection is associated with the use of this agent. Increases in hematologic and hepatic abnormalities and malignant conditions were not associated with abatacept treatment. In addition, no major autoimmune diseases were reported (for example, lupus or demyelination), as observed with anticytokine therapies (27).

These findings should be considered within the context of our study's limitations. The trial's 1-year duration precludes the determination of whether longer-term treatment will be associated with the emergence of other possible toxicities. Detection of a range of toxicities will require more widespread study in more patients. Furthermore, we examined the safety and efficacy of abatacept in only 1 subset of the patient population with rheumatoid arthritis—those with an inadequate response to methotrexate. An additional phase III study of abatacept in patients with rheumatoid arthritis and an inadequate response to antitumor necrosis factor-α therapy demonstrated statistically significant clinical benefits with a similar safety and tolerability profile (28). Our current trial assessed the effects of abatacept in patients with established rheumatoid arthritis (mean duration of about 9 years) and was not designed to investigate the effects of abatacept in early disease. Further studies of abatacept in the longer-term treatment of patients with rheumatoid arthritis and varying disease and treatment histories are required to substantiate the efficacy and safety findings with abatacept to date.

The data from the phase IIb trial (8, 9) and the larger, optimal-dose, phase III investigation indicate that the strategy of selective T-cell inhibition by abatacept provides consistent and statistically significant additional therapeutic value for treating patients with rheumatoid arthritis and an inadequate response to methotrexate. Abatacept treatment is, thus, an alternative strategy to inhibit tumor necrosis factor-α in these patients, although the relative merits of each approach may require several years to determine via information derived from large databases or registries.

In our study, the clinical benefits seen with the fixed dosage of abatacept encompassed clinical and radiographic efficacy, statistically significant and clinically meaningful improvements in patients' physical function and health-related quality of life, and a consistent safety profile. Observations of the slowing of radiographic progression by abatacept, which we believe that our study is the first to demonstrate, as well as the safety and clinical findings, are expected to be extended with longer-term observations in this and other patient populations. Overall, abatacept seems to be a rational and effective treatment strategy for patients with rheumatoid arthritis who have an inadequate response to weekly methotrexate.

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Grant Support: By Bristol-Myers Squibb.

Potential Financial Conflicts of Interest: *Employment:* T. Li (Bristol-Myers Squibb), Z. Ge (Bristol-Myers Squibb), J.-C. Becker (Bristol-Myers Squibb); *Consultancies:* J.M. Kremer (Bristol-Myers Squibb), H.K. Genant (Bristol-Myers Squibb, Amgen, Wyeth, Novartis, Lilly, Roche), L.W. Moreland (Bristol-Myers Squibb), A.S. Russell (Bristol-Myers Squibb), P. Emery (Amgen, Schering-Plough, Centocor, Bristol-Myers Squibb), R. Westhovens (Schering-Plough, Bristol-Myers Squibb); *Honoraria:* J.M. Kremer (Bristol-Myers Squibb), H.K. Genant (Bristol-Myers Squibb, Amgen, Wyeth, Novartis, Lilly, Roche), L.W. Moreland (Bristol-Myers Squibb), P. Emery (Wyeth, Roche), R. Westhovens (Schering-Plough, Bristol-Myers Squibb); *Stock ownership or options (other than mutual funds):* T. Li (Bristol-Myers Squibb), Z. Ge (Bristol-Myers Squibb), J.-C. Becker (Bristol-Myers Squibb); *Grants received:* J.M. Kremer (Bristol-Myers Squibb), H.K. Genant (Bristol-Myers Squibb, Amgen, Wyeth, Novartis, Lilly, Roche), L.W. Moreland (Bristol-Myers Squibb); *Patents pending:* J.-C. Becker (Bristol-Myers Squibb).

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Appendix Table. **Mean Change from Baseline in American College of Rheumatology Core Component at Year 1***

Variable	Adjusted Mean Improvement from Baseline to 12 Months		Difference (95% CI)
	Abatacept + Methotrexate Group (n = 384)†	Placebo + Methotrexate Group (n = 161)†	
Swollen joints, *n*	–16.1 ± 0.35	–11.5 ± 0.54	–4.6 (–5.88 to –3.35)
Tender joints, *n*	–22.5 ± 0.55	–16.3 ± 0.85	–6.2 (–8.20 to –4.22)
Patient pain (100-mm VAS)	–35.8 ± 1.17	–23.2 ± 1.81	–12.6 (–16.9 to –8.39)
Patient global assessment (100-mm VAS)	–35.8 ± 1.12	–24.2 ± 1.72	–11.6 (–15.7 to –7.58)
Physician global assessment (100-mm VAS)	–49.1 ± 0.93	–34.3 ± 1.44	–14.8 (–18.2 to –11.5)
Physical function (HAQ score)	–0.68 ± 0.03	–0.50 ± 0.05	–0.18 (–0.29 to –0.07)
CRP level, *mg/L*	–18.3 ± 0.9	–8.2 ± 1.4	–10.1 (–13.5 to –6.7)

* Analysis of covariance model with treatment as a factor and baseline as a covariate. Data are means (± SE) unless otherwise noted. HAQ = Health Assessment Questionnaire; VAS = visual analogue scale.
† Results are based on an analysis of complete cases only; patients from 1 site were excluded from the efficacy analysis because of adherence issues.