

Treatment of Rheumatoid Arthritis With the Selective Costimulation Modulator Abatacept

Twelve-Month Results of a Phase IIb, Double-Blind, Randomized, Placebo-Controlled Trial

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Objective. To determine the clinical efficacy, safety, and immunogenicity of abatacept (CTLA-4Ig), a selective costimulation modulator, in patients with rheumatoid arthritis (RA) that has remained active despite methotrexate (MTX) therapy.

Methods. This was a 12-month, multicenter, randomized, double-blind, placebo-controlled study. A total of 339 patients with active RA despite MTX therapy were randomly assigned to receive 10 mg/kg abatacept (n = 115), 2 mg/kg abatacept (n = 105), or placebo (n = 119). This report focuses on the results observed at month 12 of a phase IIb trial.

Results. A significantly greater percentage of patients treated with 10 mg/kg abatacept met the American College of Rheumatology 20% improvement criteria

(achieved an ACR20 response) at 1 year compared with patients who received placebo (62.6% versus 36.1%; $P < 0.001$). Greater percentages of patients treated with 10 mg/kg abatacept also achieved ACR50 responses (41.7% versus 20.2%; $P < 0.001$) and ACR70 responses (20.9% versus 7.6%; $P = 0.003$) compared with patients who received placebo. For patients treated with 10 mg/kg abatacept, there were also statistically significant and clinically important improvements in modified Health Assessment Questionnaire scores compared with patients who received placebo (49.6% versus 27.7%; $P < 0.001$). Abatacept at a dosage of 10 mg/kg elicited an increase in rates of remission (Disease Activity Score in 28 joints of <2.6) compared with placebo at 1 year (34.8% versus 10.1%; $P < 0.001$). The incidence of adverse events was comparable between the groups, and no significant formation of neutralizing antibodies was noted.

Conclusion. Abatacept was associated with significant reductions in disease activity and improvements in physical function that were maintained over the course of 12 months in patients with RA that had remained active despite MTX treatment. Abatacept was found to be well tolerated and safe over the course of 1 year. Abatacept in combination with MTX has the potential to play an important role in future RA therapy.

Rheumatoid arthritis (RA) is a complex autoimmune disease that may lead to joint destruction, disability, and poor quality of life (QOL). While experimental models of RA pathogenesis show that multiple pathways and cell types are involved (1–3), there is

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increasing evidence to suggest that activated T cells may play a fundamental role in the immunopathology of RA (3). T cells are thought to underlie the autoimmune and inflammatory components of RA by directly influencing other cell types through cell-to-cell contact and the production of immunomodulatory cytokines. Consequently, targeting T cell activation is a rational approach for the treatment of RA.

One of the initial steps in T cell activation is antigen recognition through the T cell receptor. Following antigen recognition, T cells require costimulation to become fully activated. One of the best-characterized costimulatory pathways is the engagement of CD80/CD86 on antigen-presenting cells (APCs) with CD28 on T cells. This produces a positive costimulatory signal and promotes full T cell activation (2). While naive T cells are classically thought to be more dependent on a costimulatory signal than activated T cells, there is increasing scientific evidence that autoimmune effector T cells also require a costimulatory signal for their maintenance (4,5). There are several other pathways involved in T cell activation, some of which optimize T cell activity and some of which cause down-regulation. CTLA-4 is a well-defined down-regulator of T cell activation and has a much higher binding avidity with CD80/CD86 than does CD28. Its expression is increased on the T cell surface 24–48 hours after T cell activation.

Abatacept (CTLA-4Ig) is a soluble recombinant fusion protein comprising the extracellular domain of human CTLA-4 and a fragment of the Fc domain of human IgG1, which has been modified to prevent complement fixation. Abatacept employs the high binding avidity of CTLA-4 for CD80/CD86 on APCs to competitively bind CD80/CD86. This prevents these molecules from engaging CD28 on T cells and selectively modulates this costimulatory pathway, preventing full T cell activation.

Abatacept has previously shown efficacy in pre-clinical studies involving many animal models of autoimmune disease (6,7) and allograft rejection (8). The preliminary efficacy and safety of abatacept in the treatment of RA were first evaluated using abatacept as monotherapy in a dose-finding pilot study of patients with active early RA that was refractory to disease-modifying antirheumatic drugs (DMARDs) (9). Patients who were treated with abatacept at 0.5 mg/kg, 2 mg/kg, or 10 mg/kg for 85 days experienced improvements in disease activity as demonstrated by dose-dependent increases in the percentages of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) (10). A subsequent phase IIb trial compared abatacept (2 mg/kg or 10

mg/kg) plus methotrexate (MTX) with MTX alone in patients with RA that was active despite continued MTX treatment. Six-month data from this trial demonstrated that 10 mg/kg abatacept plus MTX in patients with active RA effectively controlled the signs and symptoms of RA and also improved patients' physical function and QOL (11). The 2 mg/kg dose of abatacept was found to be suboptimal at 6 months. One-year improvements in aspects of QOL have been recently reported (12).

We present herein the 12-month findings from this phase IIb, double-blind, randomized, placebo-controlled trial. The trial enabled us to evaluate the sustained beneficial effects of abatacept by assessing the extended efficacy and safety profiles of the drug in this patient population.

PATIENTS AND METHODS

Patients. Patients enrolled in this study met the ACR (formerly, the American Rheumatism Association) criteria for the diagnosis of RA (functional classes I, II, or III) (13), had active disease defined by ≥ 10 swollen and ≥ 12 tender joints, had a C-reactive protein (CRP) level > 1 mg/dl, and had been treated with MTX (10–30 mg/week) for at least 6 months with a stable dosage for 28 days prior to enrollment. Before entering the study, patients were required to undergo a washout of all other DMARDs excluding MTX. Levels of corticosteroids were reduced to the equivalent of ≤ 10 mg/day prednisone and stabilized for ≥ 28 days prior to day 1. Pregnant or nursing women were excluded from the trial.

Study protocol. This was a randomized, double-blind, placebo-controlled study of 12 months' duration. Patients were randomly assigned in a ratio of 1:1:1 to receive 10 mg/kg abatacept, 2 mg/kg abatacept, or placebo using a central randomization procedure. This study was approved by the Institutional Review Board/Independent Ethics Committee and was carried out in accordance with the ethical principles of the Declaration of Helsinki.

Treatment administration. Abatacept (2 mg/kg or 10 mg/kg) or placebo was infused intravenously over a 30-minute period on days 1, 15, and 30 and every 30 days thereafter.

Concomitant therapy. The protocol mandated that patients be treated with MTX at a level deemed by the physician to be appropriate for each patient (10–30 mg/week) for the duration of the study. Standardization of the dosage of MTX at entry into the trial was designed to facilitate interpretation of the effects of adding abatacept treatment. For the first 180 days of the trial, no adjustments in the dosage of MTX were allowed except in cases of hepatotoxicity. Between days 180 and 360, the following adjustments were allowed based on the clinical judgment of the investigator: 1) changes in MTX dosage, provided the dosage was < 30 mg/week; 2) the addition of another DMARD (hydroxychloroquine, sulfasalazine, gold, or azathioprine); and 3) adjustment in corticosteroids equivalent to ≤ 10 mg/day prednisone.

Clinical assessment. Assessments were carried out 28 days prior to the start of the study by physicians blinded to the treatment group, and before treatment administration on treatment days 1, 15, 30, 60, 90, 120, 150, 180, 240, 300, 330, and at one posttreatment time point—day 360 (12 months).

Efficacy. Disease activity. This report is focused on the results observed at month 12 of a phase IIb trial in which the primary efficacy end point was an ACR20 response at 6 months (10). Secondary end points were ACR50 and ACR70 responses (14) and improvements in individual components of the ACR core data set (15). Pain and global assessment of disease activity (patient's and physician's) were evaluated using a 0–100-mm visual analog scale (VAS). The proportions of patients having low disease activity and experiencing remission were also determined by a post hoc analysis using the Disease Activity Score in 28 joints (DAS28) (16), which assessed the number of swollen and tender joints, CRP levels, and the patient's global assessment of disease activity (as measured on a VAS). DAS28 values range from 2 to 10, where a value of <2.6 is indicative of remission and a value of <3.2 is indicative of low disease activity (17).

Physical function. Physical function was determined using the modified Health Assessment Questionnaire (M-HAQ) (18), which evaluates physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. A responder analysis was carried out to evaluate the percentage of patients who achieved a clinically meaningful improvement in M-HAQ scores (≥ 0.22 units) (19); an improvement of ≥ 0.22 units represents an accepted threshold of the minimum clinically important difference. The percentages of patients with no disability (an M-HAQ score of zero) were compared between the groups.

Adverse events (AEs) and immunogenicity testing. All patients were monitored for AEs, serious AEs, clinical laboratory test result abnormalities, and significant changes in vital signs. A serious AE was defined as an AE that was fatal or life threatening, resulted in or prolonged hospitalization, resulted in persistent or significant disability or incapacity, resulted in an overdose, resulted in the development of drug dependency or drug abuse, or was an important medical event. Serious AEs could also include cancer or congenital anomalies/birth defects. Patients were monitored for acute hypersensitivity reactions both during and following the administration of treatment. In addition, immunogenicity was assessed by measuring the antibody response to abatacept and also specifically to the CD80/CD86 binding portion of the molecule (CTLA4-T). Serum samples were obtained on days 1, 30, 90, 180, 270, and 360. Antiabatacept antibody levels were determined by enzyme-linked immunosorbent assay as described previously (9).

Statistical analysis. A sample size of 107 patients per treatment group was calculated to yield 94% power to detect a difference of 25% in ACR20 responses between the 2 abatacept groups and the placebo group at the 5% significance level (2-tailed), adjusted for a discontinuation rate of 15%. The ACR20 response rate in the placebo group was assumed to be 25%. All statistical analyses were carried out on the intent-to-treat (ITT) population, defined as all patients who received at least 1 treatment infusion.

Baseline demographics and disease history were analyzed using descriptive statistics. Differences in ACR20, ACR50, and ACR70 response rates on day 360 were analyzed by comparing each abatacept treatment group with the placebo group using a Dunnett-adjusted chi-square test. ACR response rates at other time points were compared between each abatacept treatment group and the placebo group using a chi-square test unadjusted for multiple comparisons. Differences in percentage change from baseline to the last observation carried forward

(LOCF) for all ACR core components were analyzed using analysis of covariance with the baseline value as the covariate and without adjustment for multiple comparisons. Fisher's exact tests were used to compare the incidence of AEs between the abatacept treatment groups and the placebo group. For all other end points, discrete variables were analyzed using chi-square tests, and all continuous variables were analyzed by *t*-tests unadjusted for multiple comparisons. All statistical tests were conducted at the 5% significance level (2-tailed).

When ACR response rates were assessed, all patients who discontinued from the study due to worsening RA disease (lack of efficacy) were considered nonresponders from that time point. However, patients who discontinued for other reasons had their last observations carried forward.

The Kaplan-Meier analysis of the time to discontinuation was used to estimate the cumulative proportion of patients who discontinued during the study. Three such analyses were carried out for patients who discontinued due to lack of efficacy, as a result of an AE, or for any reason. The differences in time to discontinuation between the 2 abatacept groups and the placebo group were compared using log rank tests.

RESULTS

Baseline characteristics. Three hundred thirty-nine patients were recruited and randomly assigned to 1

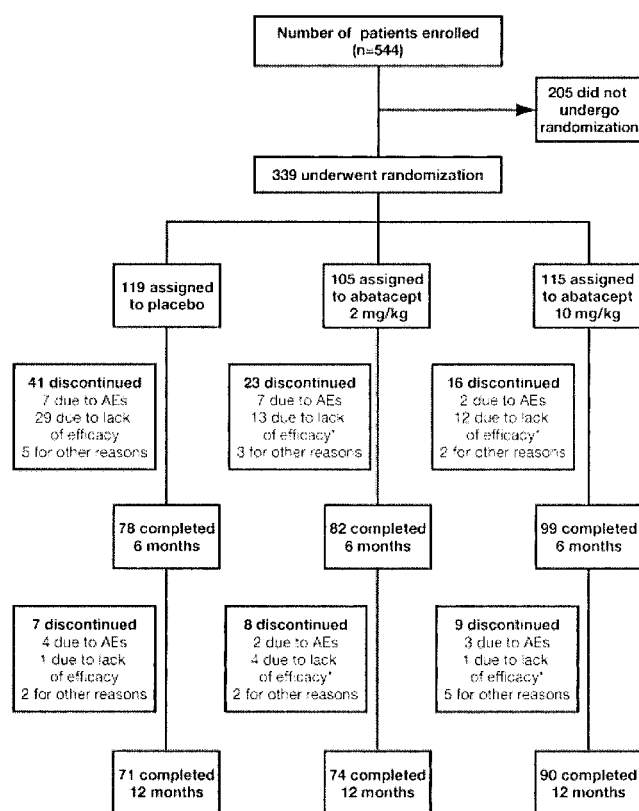


Figure 1. Patient disposition from enrollment to completion of the 12-month study. * = $P < 0.05$ versus placebo plus methotrexate. AEs = adverse events. Adapted, with permission, from ref. 11.

Table 1. Patient characteristics at baseline in the intent-to-treat population*

	Placebo + MTX (n = 119)	2 mg/kg abatacept + MTX (n = 105)	10 mg/kg abatacept + MTX (n = 115)
Age, mean (range) years	54.7 (23–80)	54.4 (23–80)	55.8 (17–83)
Weight, mean (range) kg	79.9 (44–140)	78.7 (48–187)	77.8 (40–144)
Female, %	66	63	75
Race, no. (%)			
White	104 (87)	91 (87)	100 (87)
Black	3 (3)	0	6 (5)
Other	12 (10)	14 (13)	9 (8)
Disease duration, years	8.9 ± 8.3	9.7 ± 8.1	9.7 ± 9.8
Tender joints†	29.2 ± 13.0	28.2 ± 12.0	30.8 ± 12.2
Swollen joints†	21.8 ± 8.8	20.2 ± 8.9	21.3 ± 8.4
Pain, 0–100-mm VAS‡	65.2 ± 22.1	64.5 ± 22.3	62.1 ± 21.4
Physical function, M-HAQ score 0–3§	1.0 ± 0.6	1.0 ± 0.5	1.0 ± 0.5
Patient's global assessment, 0–100-mm VAS‡	62.8 ± 21.6	59.4 ± 23.7	60.1 ± 20.7
Physician's global assessment, 0–100-mm VAS‡	63.3 ± 15.5	61.0 ± 16.7	62.1 ± 14.8
CRP level, mg/dl	3.2 ± 3.2	3.2 ± 2.6	2.9 ± 2.8
DAS28, 2–10	5.5 ± 0.87	5.4 ± 0.82	5.5 ± 0.63
Medications prior to enrollment, %			
MTX	99.2	98.1	99.1
Other DMARDs	21.0	18.1	16.5
Corticosteroids	67.2	67.6	60.0
MTX dosage during study, mg/week	15.8 ± 4.1	15.8 ± 4.5	15.0 ± 4.4

* Except where indicated otherwise, values are the mean ± SD. MTX = methotrexate; VAS = visual analog scale; M-HAQ = modified Health Assessment Questionnaire; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; DMARDs = disease-modifying antirheumatic drugs.

† Sixty-eight joints were assessed for tenderness and 66 joints were assessed for swelling.

‡ High VAS scores were indicative of more severe abnormalities.

§ Low scores indicate low disease activity and high scores indicate greater disease activity.

of 3 groups: 115 to the 10 mg/kg abatacept plus MTX group, 105 to the 2 mg/kg abatacept plus MTX group, and 119 to the placebo plus MTX group (Figure 1). Patients were mainly white women, ages 17–83 years, with RA that was inadequately controlled with other DMARDs including MTX (Table 1). All patients had comparable demographic and disease characteristics (duration of RA, number of tender joints, number of swollen joints, pain, and physical function) (Table 1). The use of MTX, oral corticosteroids, and other DMARDs prior to the study was similar among the groups (Table 1).

Patient disposition. Five hundred forty-four patients were enrolled in the trial, and 339 were randomly assigned to receive treatment. During the course of the trial, 48 patients in the placebo group discontinued, compared with 31 and 25 patients in the 2 mg/kg and 10 mg/kg abatacept groups, respectively. A total of 90 patients (78.3%) in the 10 mg/kg abatacept group, 74 (70.5%) in the 2 mg/kg abatacept group, and 71 (59.7%) in the placebo group completed 360 days of therapy (Figure 1). A Kaplan-Meier analysis of the time to discontinuation (for any reason) indicated that there was a significant difference in discontinuation rates between the 10 mg/kg abatacept and placebo groups ($P < 0.01$ by

log rank test). The significant difference in discontinuation rates between these 2 groups applied to patients who discontinued due to lack of efficacy alone ($P < 0.01$ by log rank test). However, there was no statistical difference between the 10 mg/kg abatacept and placebo groups among those who discontinued due to AEs. While the cumulative proportion of patients discontinuing in the 2 mg/kg abatacept group was lower than that in the placebo group (regardless of the reason for discontinuation), these differences were not statistically significant.

Clinical efficacy. Signs and symptoms; ACR response rates. Patients who had been treated with 10 mg/kg abatacept once a month showed significant improvements in disease severity compared with those who had received placebo, as demonstrated by statistically significant differences between these groups in the percentage of patients who achieved an ACR20 response up to 1 year (Figure 2A). This response was significant compared with placebo from day 60 (56.5% versus 34.5%; $P < 0.001$), with significance being sustained at each visit up to and including day 360 (62.6% versus 36.1%; $P < 0.001$). No significant differences in ACR20 responses were observed in the 2 mg/kg abatacept group relative to placebo (Figure 2A), confirming this dose to be suboptimal.

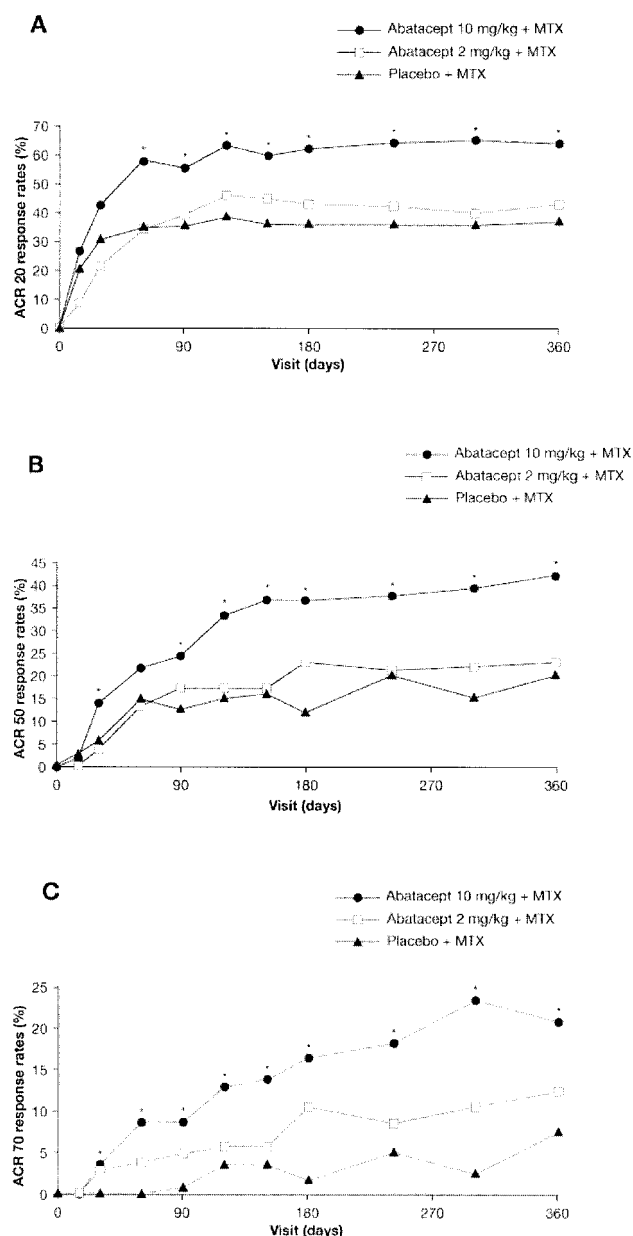


Figure 2. Percentages of patients meeting the American College of Rheumatology 20%, 50%, and 70% improvement criteria (achieving ACR20 [A], ACR50 [B], and ACR70 [C] responses) at each visit from day 1 through day 360 (12 months). Values are the mean. * = $P < 0.05$ versus placebo, by prespecified analysis. MTX = methotrexate.

ACR50 response rates were highest in the 10 mg/kg abatacept group compared with the placebo group, beginning on day 30 (13.9% versus 5.9%; $P = 0.039$), increasing over time, and again becoming statistically significant continuously from 90 days (24.3%

versus 12.6%; $P = 0.02$) to 1 year (41.7% versus 20.2%; $P < 0.001$) (Figure 2B). ACR70 response rates were also highest in the 10 mg/kg abatacept group compared with the placebo group from day 30 (3.5% versus 0%; $P = 0.04$) and were statistically significantly higher with abatacept treatment than with placebo at every visit thereafter until 12 months (20.9% versus 7.6%; $P = 0.003$) (Figure 2C). Compared with the placebo group, statistically significant differences were observed in mean percentage improvements from baseline for the 10 mg/kg abatacept group in each component of the ACR core set (tender and swollen joints, CRP level, pain, patient's and physician's global assessments, and physical function) at 1 year ($P < 0.05$) (Table 2).

Signs and symptoms; remission rates. Treatment with 10 mg/kg abatacept led to an increase in remission rates (defined as a DAS28 of <2.6) up to 1 year (Figure 3A). In patients treated with 10 mg/kg abatacept, this increase was statistically significant compared with the placebo plus MTX group from day 90 onward ($P = 0.022$). At months 3, 6, and 12, the remission rates for the ITT population were 17.4%, 26.1%, and 34.8% ($P < 0.001$ versus placebo group), respectively, in the 10 mg/kg abatacept group and 7.6%, 9.2%, and 10.1%, respectively, in the placebo group. Similar results were obtained when patients were assessed for evidence of low disease activity (defined as a DAS28 of <3.2). Among the patients treated with 10 mg/kg abatacept, there was an increase over 1 year in the proportion with low disease activity. At months 3, 6, and 12, the proportions of patients with low disease activity were 29.6%, 40%, and 49.6%, respectively. The rates of low disease activity in the placebo group at those same time points were 18.5%, 19.3%, and 21.9%, respectively, and the rates in the 2 mg/kg abatacept group were 22.9%, 30.5%, and 28.6%, respectively. There were statistically significant differences in low disease activity rates between the 10 mg/kg abatacept and placebo groups ($P < 0.05$ at all time points), but the differences between the 2 mg/kg abatacept and placebo groups were not statistically significant.

Physical function assessed by the M-HAQ. Physical function, assessed by the M-HAQ, was also shown to be statistically significantly improved in the 10 mg/kg abatacept group compared with the placebo group (Table 2). At baseline, the mean M-HAQ summary score was 1.0 for all groups. Significant differences in the mean percentage improvements in physical function were observed from day 30 onward between the 10 mg/kg abatacept group and the placebo group. In addition, when an analysis of responders (patients whose M-HAQ

Table 2. Changes in individual components of the ACR core set at day 360 (1 year) in the intent-to-treat population*

Component	Placebo (n = 119)	2 mg/kg abatacept (n = 105)	10 mg/kg abatacept (n = 115)
No. of tender joints			
Baseline value	29.2 ± 13.0	28.2 ± 12.0	30.8 ± 12.2
Mean improvement, %	30.0	43.6	66.4
<i>P</i> versus placebo	–	0.033	<0.001
No. of swollen joints			
Baseline value	21.8 ± 8.8	20.2 ± 8.9	21.3 ± 8.4
Mean improvement, %	36.2	46.4	59.7
<i>P</i> versus placebo	–	0.093	<0.001
Pain, 0–100-mm VAS			
Baseline value	65.2 ± 22.1	64.3 ± 22.3	62.6 ± 20.6
Mean improvement, %	12.6	26.2	44.9
<i>P</i> versus placebo	–	0.071	<0.001
Patient's global assessment, 0–100-mm VAS			
Baseline value	62.8 ± 21.6	59.4 ± 23.7	60.1 ± 20.7
Mean improvement, %	2.0	16.0	41.0
<i>P</i> versus placebo	–	0.260	0.012
Physician's global assessment, 0–100-mm VAS			
Baseline value	63.3 ± 15.5	61.0 ± 16.7	62.1 ± 14.8
Mean improvement, %	24.1	37.9	53.5
<i>P</i> versus placebo	–	0.004	<0.001
Physical function, M-HAQ score 0–3			
Baseline value	1.0 ± 0.5	1.1 ± 0.5	1.0 ± 0.5
Mean improvement, %	10.3	22.9	42.3
<i>P</i> versus placebo	–	0.087	<0.001
CRP level, mg/dl			
Baseline value	3.2 ± 3.2	3.2 ± 2.6	2.9 ± 2.8
Mean improvement, %	–31.3	11.0	27.6
<i>P</i> versus placebo	–	0.006	<0.001

* Shown are baseline values (mean ± SD) for individual components of the American College of Rheumatology (ACR) core set and mean percentages of improvement from these baseline values at day 360. Mean percentages of improvement are calculated as the average of the changes in the individual patient data and not as differences between group means. Analyses are based on the intent-to-treat population. See Table 1 for other definitions.

scores improved from baseline by ≥ 0.22 units) was conducted, statistically significantly more patients in the 10 mg/kg abatacept group achieved clinically important improvements in M-HAQ scores as early as 30 days after treatment. The effect was further improved at 6 months (58.3% with 10 mg/kg abatacept plus MTX versus 33.6% with placebo plus MTX; $P < 0.001$) and was sustained at 1 year (49.6% versus 27.7%; $P < 0.001$) (Figure 3B). Furthermore, at 6 months, a higher proportion of patients receiving abatacept plus MTX achieved an M-HAQ score of zero compared with patients receiving placebo plus MTX (20.0% versus 7.6%; $P < 0.01$), and this improvement over placebo was sustained at 1 year (15.7% versus 7.6%; $P = 0.05$).

The fact that the M-HAQ response rate appeared to drop slightly toward the end of the study was the result of this being a conservative statistical analysis, since all patients who dropped out were considered nonresponders. A similar analysis either using the LOCF

method or limited to only those patients with observed data confirmed that improvement in physical function was maintained through the end of the study.

AEs. Abatacept was well tolerated, and the safety profile of both doses of abatacept was similar to that of placebo over 1 year (Table 3). The most frequently reported AEs in the 10 mg/kg and 2 mg/kg abatacept treatment groups (seen in at least 5% of patients, and excluding worsening of RA) were nasopharyngitis (14.8% and 18.1%, respectively), headache (14.8% and 16.2%, respectively), and nausea (13.9% and 11.4%, respectively). Arthralgia was also frequently reported by patients in the 2 mg/kg abatacept group (16.2%). The AEs most frequently reported by patients treated with placebo (excluding worsening of RA) were headache (15.1%), nausea (14.3%), cough (12.6%), and nasopharyngitis (9.2%). For the 10 mg/kg abatacept treatment group, the most frequently reported AEs considered related to the study drug were nasopharyngitis (6.1%

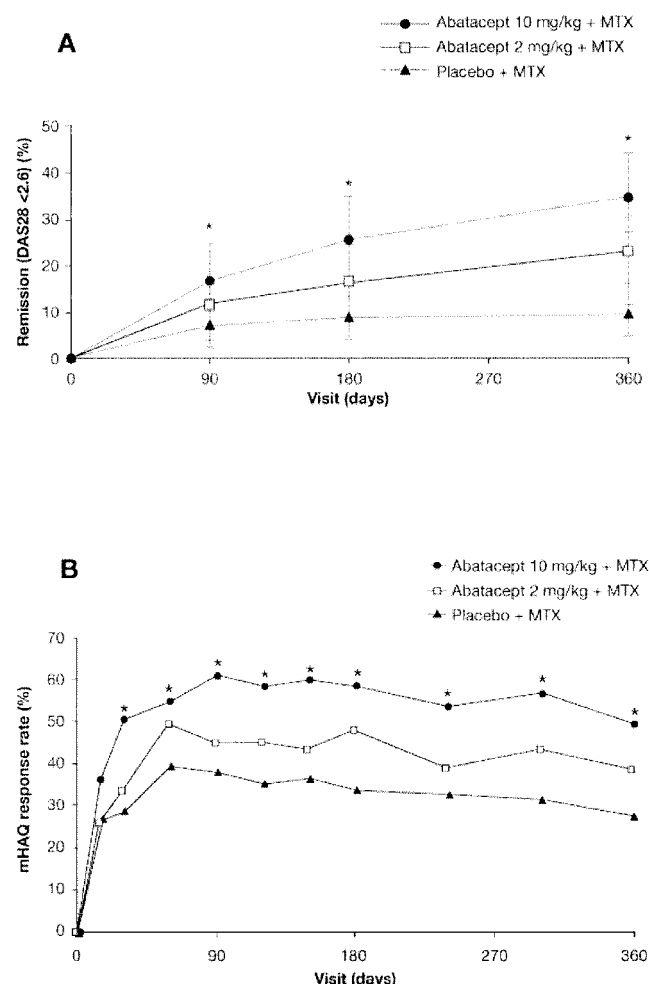


Figure 3. A, Impact of abatacept (10 mg/kg or 2 mg/kg) plus methotrexate (MTX) on rates of remission (defined as a Disease Activity Score in 28 joints [DAS28] of <2.6) at visit days 1, 90, 180, and 360. Values are the mean $\pm$ SD. Treatment with 10 mg/kg abatacept led to an increase in remission rates up to 1 year. * = $P < 0.05$ versus placebo. B, Percentages of patients attaining clinically meaningful improvement (defined as ≥ 0.22 units in scores on the modified Health Assessment Questionnaire [M-HAQ]) at each visit from day 1 through day 360 (12 months). At baseline, the mean M-HAQ summary score was 1.0 for all groups. Values are the mean. * = $P < 0.05$ versus placebo.

versus 3.4% with placebo), nausea (5.2% versus 5.9% with placebo), and headache (5.2% versus 6.7% with placebo) (Table 3). Serious AEs were less common in the 10 mg/kg abatacept group (12.2%) than in the 2 mg/kg abatacept and placebo groups (18.1% and 16%, respectively). Serious AEs in the 10 mg/kg abatacept, 2 mg/kg abatacept, and placebo groups included chest

pain (0.9%, 3.8%, and 0%, respectively), myocardial infarction (0.9%, 0%, and 0.8%, respectively), and gastrointestinal disorder (0.9%, 0%, and 0%, respectively).

No apparent pattern was observed in the types of serious AEs reported. In addition, there was no apparent relationship between serious AEs and the number of infusions. The frequency of drug-related serious AEs did not differ between the 10 mg/kg abatacept and placebo groups (1.7% for both).

No abatacept-related deaths, cancers, opportunistic infections, or atypical presentations of infections were observed during this 12-month trial. An opportunistic infection (a pulmonary infection due to *Cryptococcus*) was reported in 1 patient who received placebo, which resulted in the patient's withdrawal from the study. One atypical presentation of an infection, consisting of sepsis and an infected hip joint prosthesis, was reported in a patient who received placebo. This patient also withdrew from the study. Malignancies included 1 case of bladder cancer, 2 cases of basal cell carcinoma, and 1 neoplasm in the 10 mg/kg abatacept group; and 1 case each of endometrial cancer, squamous cell carcinoma, and malignant melanoma in the placebo group. The malignancies reported by patients in the 10 mg/kg abatacept group were considered by the investigators to be unrelated to the study drug.

Immunogenicity testing. No patients were shown to seroconvert for antiabatacept antibodies directed at the whole molecule; however, 2 patients produced antibodies against the CTLA4-T portion. In 1 of these patients, the antibody response was transient and only present at a single measurement. The other patient discontinued participation in the study after withdrawing consent, and therefore no followup data for this patient are available. In these patients, there was no evidence of toxicity associated with the development of these antibodies.

DISCUSSION

The results of this double-blind, placebo-controlled trial demonstrated that abatacept plus MTX provided sustained clinical benefits over 1 year as measured by significant improvements in ACR responses and functional disability (measured by the M-HAQ) in RA patients having an inadequate response to MTX. These findings are consistent with the previously reported 6-month observations (11), and they extend them to 1 year. There were fewer discontinuations in either of the abatacept-treated groups than in the placebo-treated

Table 3. AEs and discontinuations at day 360 (1 year) in the intent-to-treat population*

	Placebo + MTX (n = 119)	2 mg/kg abatacept + MTX (n = 105)	10 mg/kg abatacept + MTX (n = 115)
AEs			
Death†	0	1	0
Serious AEs	19 (16)	19 (18.1)	14 (12.2)
Serious AEs related to study drug	2 (1.7)	5 (4.8)	2 (1.7)
Most frequent AEs‡			
Nasopharyngitis	11 (9.2)	19 (18.1)	17 (14.8)
Headache	18 (15.1)	17 (16.2)	17 (14.8)
Nausea	17 (14.3)	12 (11.4)	16 (13.9)
Cough	15 (12.6)	10 (9.5)	15 (13.0)
Diarrhea	9 (7.6)	10 (9.5)	13 (11.3)
Upper respiratory tract infection	9 (7.6)	10 (9.5)	13 (11.3)
Dyspepsia	7 (5.9)	12 (11.4)	10 (8.7)
AEs related to study drug			
Nasopharyngitis	4 (3.4)	3 (2.9)	7 (6.1)
Nausea	7 (5.9)	6 (5.7)	6 (5.2)
Headache	8 (6.7)	6 (5.7)	6 (5.2)
Cough	3 (2.5)	2 (1.9)	6 (5.2)
Upper respiratory tract infection	1 (0.8)	2 (1.9)	5 (4.3)
Malignancies§	3	0	4
Total discontinuations	48 (40.3)	31 (29.5)	26 (22.6)
AEs	11 (9.2)	9 (8.6)	6 (5.2)
Lack of efficacy	30 (25.2)	17 (16.2)	13 (11.3)
Withdrawal of consent	6 (5.0)	2 (1.9)	5 (4.3)
Lost to followup	0	2 (1.9)	1 (0.9)
Other	1 (0.8)	0	1 (0.9)
Death	0	1 (1.0)	0

* Values are the number (%) of patients. AEs = adverse events; MTX = methotrexate.

† On study day 271, 28 days after the last infusion, a patient died as a result of multisystem organ failure, ischemia of the extremities, postoperative nonsustained ventricular tachycardia, and left ventricular hypertrophy following coronary artery bypass grafting surgery. No autopsy was performed. The investigator reported the death as unrelated to the investigational drug.

‡ Not including rheumatoid arthritis.

§ Considered by the investigator to be unrelated to study medication.

group for any reason, including lack of efficacy. Because the clinical responses at 12 months were clearly superior for the 10 mg/kg dose compared with the 2 mg/kg dose, this study supports the use of the higher-dose regimen in the treatment of RA. In addition, the improvements in ACR50 and ACR70 response rates in patients receiving the 10 mg/kg dose continued for the duration of this 1-year trial. Post hoc analysis also demonstrated a significant proportion of patients experiencing low disease activity and remission as measured by the DAS28 cutoffs.

This study also demonstrated that 10 mg/kg abatacept in combination with MTX leads to sustained, significant, and clinically meaningful long-term improvements in physical function. In fact, mean improvement in physical function was >3-fold greater in the 10 mg/kg abatacept group than in the placebo group. Greater numbers of patients experienced zero disability in the 10 mg/kg abatacept group than in the placebo group.

The overall incidence of AEs, including serious AEs, was similar in the abatacept and placebo groups. Fewer numbers of patients discontinued due to AEs in either of the abatacept groups than in the placebo group.

The clinical efficacy observed in this trial is supportive of the concept that T cells play an important role in the immunopathology underlying RA. By targeting full T cell activation through modulation of a key costimulatory signal, the chronic inflammatory process can be effectively reduced. Despite recent advances in RA therapy, some patients do not respond to existing agents or may not be candidates for them, while others are unable to tolerate them. Therefore, there is still significant room for novel therapies with mechanisms of action different from those of existing agents. As the first in a novel class of agents, the selective costimulation modulators, abatacept has the potential to play an important role in the future treatment of patients with RA.

REFERENCES

1. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nat Immunol* 2003;423:356–61.
2. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. *Nat Rev Drug Discov* 2003;2:473–88.
3. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001;344:907–16.
4. Schweitzer AN, Sharpe AH. Studies using antigen-presenting cells lacking expression of both B7-1 (CD80) and B7-2 (CD86) show distinct requirements for B7 molecules during priming versus restimulation of Th2 but not Th1 cytokine production. *J Immunol* 1998;161:2762–71.
5. Chang TT, Jabs C, Sobel RA, Kuchroo VK, Sharpe AH. Studies in B7-deficient mice reveal a critical role for B7 costimulation in both induction and effector phases of experimental autoimmune encephalomyelitis. *J Exp Med* 1999;190:733–40.
6. Finck B, Linsley PS, Wofsy D. Treatment of murine lupus with CTLA4Ig. *Science* 1994;265:1225–7.
7. Webb LM, Walmsley MJ, Feldmann M. Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2. *Eur J Immunol* 1996;26:2320–8.
8. Lin H, Bolling SF, Linsley PS, Gordon D, Thompson CB, Turka LA. Long-term acceptance of major histocompatibility complex mismatched cardiac allografts induced by CTLA4Ig plus donor-specific transfusion. *J Exp Med* 1993;178:1801–6.
9. Moreland LW, Alten R, van den Bosch F, Appelboom T, Leon M, Emery P, 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;46:1470–9.
10. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
11. Kremer JM, Westhovens R, Leon M, di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907–15.
12. Emery P, Russell A, Williams GR, Li T, Nuamah I, Becker JC, et al. CTLA4-Ig, a co-stimulation blocker, maintains health-related quality of life improvement in patients with active rheumatoid arthritis using methotrexate over one year [abstract]. *Ann Rheum Dis* 2003;62 Suppl 1:350.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
14. Felson DT, Anderson JJ, Lange ML, Wells G, LaValley MP. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum* 1998;41:1564–70.
15. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729–40.
16. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
17. URL: <http://www.das-score.nl/www.das-score.nl/howto1.htm>.
18. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346–53.
19. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993;20:557–660.