Results of a Two-Year Followup Study of Patients With Rheumatoid Arthritis Who Received a Combination of Abatacept and Methotrexate

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Objective. To evaluate the efficacy, radiographic changes, and safety of abatacept and methotrexate therapy through 2 years in a long-term extension of a previously published 1-year study.

Methods. Patients who received placebo during year 1 were switched to abatacept. Patients taking abatacept continued to take it. Efficacy and safety were assessed through 2 years.

Results. Of 539 patients enrolled in the initial 1-year study, 488 completed 1 year of the long-term extension (2% discontinued for lack of efficacy). At 2 years, patients taking abatacept had maintained their responses on the American College of Rheumatology (ACR) improvement criteria and the Disease Activity Score in 28 joints (DAS28; using the C-reactive protein [CRP] level), as well as their physical function (according to the Health Assessment Questionnaire [HAQ] disability index [DI]) and health-related quality of life (HRQOL; assessed with the Short Form 36 [SF-36] health survey), that were observed at the end of the double-blind period (year 1 versus year 2 values were 81.9% versus 80.3% for ACR 20% improvement, 25.4% versus 30.9% for a DAS28 [CRP] of <2.6, 71.8% versus 66.8% for the HAQ DI, and 9.7 versus 10.6 and 7.3 versus 7.2, respectively, for the mean change in the physical and mental components summary scores of the SF-36). In the abatacept group, post hoc analysis demonstrated further inhibition of radiographic progression during year 2 (57% reduction in mean change of total score in year 2 versus year 1; \( P < 0.0001 \)), and minimal radiographic progression was observed (mean change in total score from baseline was 1.1 and 1.6 at year 1 and 2, respectively). Rates of adverse events (AEs) and severe AEs were consistent throughout the cumulative period.

Conclusion. The improvements in signs and symptoms, physical function, and HRQOL observed after 1 year of abatacept treatment were maintained through 2 years of treatment. This durability was accompanied by a safety profile consistent with that in the double-blind portion of the study. Radiographic pro-
pression was further inhibited in year 2 compared with year 1, suggesting an increasing effect of abatacept on the inhibition of structural damage in year 2.

Disease-modifying antirheumatic drugs (DMARDs) are the mainstay of treatment for patients with rheumatoid arthritis (RA) (1,2), with methotrexate (MTX) often considered the standard for patients with moderate to severe disease (3,4). However, many patients fail to show adequate improvement and often continue to experience flares that necessitate additional treatment (5).

Abatacept is the first in a class of agents for the treatment of RA that selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T cell activation (6). The mechanism of action of abatacept is fundamentally different from that of other biologic DMARDs, such as tumor necrosis factor (TNF) antagonists or B cell–depleting agents. Abatacept is a soluble fusion protein that consists of the extracellular domain of human CTLA-4 linked to the modified Fc (hinge C1 α2 and C113 domains) portion of human IgG1.

The efficacy and safety of abatacept in patients with active RA have been demonstrated in 2 distinct populations: those with an inadequate response to MTX (7–9) and those with an inadequate response to anti-TNF agents (10). The efficacy of abatacept in patients with an inadequate response to MTX has been demonstrated in clinical trials, both as a monotherapy (11) and in combination with MTX (8,9). The phase III randomized, double-blind, placebo-controlled Abatacept in Inadequate Responders to MTX (AIM) trial confirmed the clinical benefits of abatacept in a larger population of patients with an inadequate response to MTX (7). In that trial, a fixed dose of abatacept of ~10 mg/kg and MTX provided significant improvements over 1 year in the signs and symptoms of RA, inhibition of radiographic progression, and significant and clinically meaningful improvements in physical function and health-related quality of life (HRQOL) compared with placebo (7). The present study addressed the efficacy, radiographic outcomes, and safety of abatacept through 2 years in patients previously studied in the AIM trial through 1 year.

PATIENTS AND METHODS

Patients. Patients eligible for inclusion in the open-label, long-term extension portion of the AIM trial were required to have met the inclusion criteria of the multicenter, multinational, randomized, double-blind, placebo-controlled trial described in detail previously (7) and to have completed 1 year of treatment under double-blinded conditions.

Study design. All patients who enrolled in the long-term extension portion of the trial, including patients originally randomized to the placebo group during the double-blind portion, received a fixed dose of ~10 mg/kg abatacept, in addition to background MTX. Patients who weighed <60 kg, 60–100 kg, or >100 kg received 500, 750, or 1,000 mg abatacept, respectively. During the long-term extension portion, abatacept was administered as a 30-minute intravenous infusion every 28 days. In order to maintain blinding, patients who originally received placebo during the double-blind portion did not receive a loading dose at 15 days following reallocation to abatacept. No premedication was required. Adjustments to background DMARDs and other concomitant medications were permitted during the long-term extension portion at the discretion of the investigator, based on the clinical status of the patient. Prior to the start of the double-blind portion, all patients were screened for tuberculosis using tuberculin skin testing. Patients who had a positive test result were excluded unless they had completed treatment for latent tuberculosis before enrollment. Both the double-blind portion and the long-term extension portion of the study were approved by the appropriate institutional review boards or independent ethics committees. All patients provided written informed consent.

Clinical efficacy measures. During the long-term extension portion, efficacy assessments were performed quarterly, with the exception of the radiographic analyses, which were performed at the 2-year time point. For all assessments, baseline was defined as day 1 of the study.

Signs and symptoms. Signs and symptoms were recorded using the American College of Rheumatology (ACR) criteria for 20%, 50%, and 70% improvement in disease activity (ACR20, ACR50, and ACR70 responses) (12). The proportion of patients achieving a major clinical response (MCR; maintenance of an ACR70 response for 6 continuous months) and the proportion of patients maintaining an ACR70 response for 9 continuous months were evaluated. Disease activity was evaluated using the Disease Activity Score in 28 joints (DAS28), based on the C-reactive protein level (CRP). Low disease activity was defined by a DAS28 (CRP) of ≤3.2 (13), with remission defined as a DAS28 (CRP) of <2.6 (14).

Radiographic assessment. Structural damage progression was evaluated on day 729 or upon early withdrawal (if applicable) and was compared with that on radiographs obtained at baseline and year 1 visits. Patients were evaluated for radiographic progression in year 1 regardless of any study drug discontinuation. Patients who discontinued abatacept during the open-label portion of the study were asked to return for radiographic assessment in year 2; radiographs were obtained upon discontinuation from the study in patients who were unwilling or unable to return at 2 years.

Joints in the hands, wrists, and feet were assessed radiographically for changes in erosion, joint space narrowing (JSN), and their combination (total score), using the Genant-modified Sharp scoring system (7,15–17). The erosion score was determined from 14 sites in each wrist and hand, and 6 joints in each foot (scored using an 8-point scale from 0 to 3.5 based on the size of the erosions and area of the bone). The JSN score was determined from 13 sites in each wrist and hand,
and 6 sites in each foot (scored using a 9-point scale from 0 to 4). The maximum possible normalized total score was 290 using this scoring system. Assessments were made at a central reading facility by 2 independent expert readers who were blinded to treatment group assignment, chronologic order of the radiographs, and the patients’ clinical responses.

**Assessment of physical function and HRQOL.** The Health Assessment Questionnaire (HAQ) disability index (DI) was used to assess improvements in physical function (18). A clinically meaningful improvement or HAQ DI response was defined as a reduction in the baseline HAQ DI score of ≥0.3 units (19). HRQOL was assessed using the validated Short Form 36 (SF-36) health survey, which includes 4 physical subscales (physical function, physical role, bodily pain, and general health) and 4 mental subscales (vitality, social function, emotional role, and mental health) (20). Weighted linear combinations of the 8 individual subscales were used to generate the physical and mental component summary (PCS and MCS, respectively) scores (20). Additional health-related outcomes also were assessed, namely, sleep quality and fatigue. Sleep quality was assessed using the Medical Outcomes Study Sleep-Related Quality of Life (SRIQ) Scale (21), which measures different aspects of sleep problems, including sleep disturbance, sleep quantity, and sleep quality. The scores range from 0 to 100, with higher scores reflecting more problems. The patient’s assessment of fatigue severity was measured using a 0–100-mm visual analog scale (VAS) (22).

**Safety assessments.** Routine safety assessments were performed monthly when patients were scheduled to receive abatacept and included all reported adverse events (AEs), serious AEs (SAEs), clinically significant changes in vital signs and physical examination findings, and abnormal findings on laboratory tests. An AE was defined as any new or worsening illness, sign, symptom, or clinically significant abnormality on laboratory testing noted by the investigator during the course of the trial, regardless of cause. An SAE was defined as an AE that was either fatal, life-threatening, resulted in persistent or significant disability or incapacity, was cancer, was a congenital anomaly or birth defect, resulted in an overdose or the development of drug dependency or drug abuse, or was an important medical event. Acute infusional AEs were defined as AEs that occurred within 1 hour following the start of the abatacept infusion. AEs and SAEs were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) classification, version 8.0 (previously published safety data from the AIM trial through 12 months were analyzed using the MedDRA classification, version 7.0 [7]). AEs included those volunteered by the patients, those elicited by general questioning and examination at the time of each visit, and those retrospectively reported subsequent to the time of the event.

**Statistical analysis.** Patients who received at least 1 infusion of abatacept during the long-term extension portion (the intent-to-treat [ITT] population) were included in the efficacy analyses. Efficacy measures were assessed using either protocol-prespecified analyses or post hoc as-observed analyses. The prespecified analyses were performed on the ITT population using either data from all patients randomized and treated (with those who discontinued considered nonresponders [nonresponder analysis]) or as-observed data (using only patients with data available at the visit of interest [as-observed analysis]). Post hoc analyses were also performed on the ITT population using as-observed data.

Nonresponder analyses of ACR and HAQ DI responses were performed in addition to post hoc as-observed analyses. Protocol-prespecified as-observed analyses of the following measures were performed: DAS28 (CRP) mean change, SF-36, fatigue, and sleep quality. Post hoc as-observed analyses of low disease activity state (LDAS) and DAS28 (CRP)–defined remission were also performed. MCR and the proportion of patients who maintained an ACR70 response for 9 continuous months were assessed using nonresponder analyses. Efficacy assessments were presented by original randomization group; however, no formal statistical comparisons were performed between the treatment groups.

For radiographic assessments, patients who discontinued the study with missing data at year 2 of the long-term extension period had assessments imputed with linear extrapolation, in which data from 3 time points were used: baseline, year 1, and time of discontinuation. A comparison of mean change in radiographic progression was made between treatment groups. Exploratory analyses of radiographic scores were also performed. A nonparametric analysis of covariance model, with baseline as a covariate and treatment as a main effect, was used to compare the difference between treatment groups at years 1 and 2. A signed rank test was performed to compare the rate of radiographic progression during year 1 versus year 2. A linear mixed model for changes from baseline, with terms for treatment (time dependent), baseline, and days (365 and 729) as fixed effects, was used to account for repeat measures and allocation of all patients to abatacept. This analysis was used to compare the intercept of radiographic progression for abatacept versus placebo through 2 years of treatment.

All patients who received at least 1 infusion of study drug were studied for drug safety. During the long-term extension period, all patients were pooled into 1 group regardless of treatment assignment during the double-blind period. Data presented from the double-blind period are based on all patients who received at least 1 dose of study medication during the 12-month double-blind period. Data presented from the cumulative study (double-blind and long-term extension periods) are based on all patients who were originally randomized to receive abatacept and received at least 1 dose of abatacept, plus all patients who were originally randomized to receive placebo and entered the long-term extension (and subsequently received at least 1 dose of abatacept). Incidence rates and frequencies were calculated for AEs, SAEs, infections, and serious infections. Rarer events, including those defined as malignant neoplasms and autoimmune manifestations, were described using frequencies only. Incidence rates were calculated as the number of patients with the event of interest, divided by the total exposure time for the specified treatment period. A patient’s contribution to the exposure time ended at the time of the first occurrence of the AE. Incidence rates are expressed per 100 patient-years of exposure. P values less than 0.05 were considered significant.
RESULTS

Patient randomization. Of the 385 abatacept-treated and 162 placebo-treated patients who completed 1 year of treatment under double-blind conditions, a total of 539 (378 and 161, respectively) were enrolled and treated in the long-term extension period of study (Figure 1).

A total of 488 of the 539 patients (90.5%) completed the first year of the long-term extension period (Figure 1). Fifty-one of the 539 enrolled and treated patients (9.5%) discontinued the study drug (Figure 1). The mean time of exposure to abatacept during the cumulative double-blind and long-term extension periods was 22.7 months, representing 628.9 patient-years of exposure.

Baseline characteristics and demographics. For the population of patients entering the long-term extension, baseline and clinical characteristics were similar among the 2 original treatment groups at randomization (Table 1). The majority of patients were white women, with a mean duration of RA of 8.5 years. At baseline, the mean ± SEM Genant-modified total Sharp scores were 45.2 ± 35.1 and 47.3 ± 38.1 in the original abatacept and placebo groups, respectively (based on all patients who entered the long-term extension period and underwent radiography on day 365).

Concomitant medications. The concomitant anti-rheumatic medications taken most frequently by patients in the original abatacept and placebo groups at any time during the long-term extension period were MTX (100% and 99.4%), nonsteroidal antiinflammatory drugs (89.2% and 89.4%), and corticosteroids (79.4% and 76.4%). Eleven patients (2.9%) from the original abatacept group added a DMARD during the long-term extension period (1 patient added 2 DMARDs). These

Table 1. Baseline demographic and clinical characteristics of the patients in the open-label long-term extension of the AIM trial*

<table>
<thead>
<tr>
<th></th>
<th>Abatacept plus MTX (n = 378)†</th>
<th>Placebo plus MTX (n = 161)‡</th>
<th>Total (n = 539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51.4 ± 12.8</td>
<td>49.5 ± 11.5</td>
<td>50.8 ± 12.4</td>
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<tr>
<td>Weight, kg</td>
<td>72.1 ± 17.7</td>
<td>68.6 ± 13.4</td>
<td>71.1 ± 16.6</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>77.2</td>
<td>84.5</td>
<td>79.4</td>
</tr>
<tr>
<td>Race, % white</td>
<td>87.8</td>
<td>86.3</td>
<td>87.4</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8.4 ± 7.3</td>
<td>8.8 ± 6.9</td>
<td>8.5 ± 7.2</td>
</tr>
<tr>
<td>No. of tender joints</td>
<td>31.0 ± 13.0</td>
<td>33.0 ± 13.9</td>
<td>31.6 ± 13.3</td>
</tr>
<tr>
<td>No. of swollen joints</td>
<td>21.7 ± 8.9</td>
<td>22.4 ± 8.6</td>
<td>21.9 ± 8.8</td>
</tr>
<tr>
<td>Erosion score</td>
<td>25.0 ± 17.8</td>
<td>25.3 ± 19.4</td>
<td>25.1 ± 18.3</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td>20.2 ± 18.3</td>
<td>22.0 ± 19.9</td>
<td>20.7 ± 18.8</td>
</tr>
<tr>
<td>Total Genant-modified Sharp score</td>
<td>45.2 ± 35.1</td>
<td>47.3 ± 38.1</td>
<td>45.8 ± 36.0</td>
</tr>
<tr>
<td>Pain assessment, 100-mm VAS</td>
<td>63.6 ± 20.9</td>
<td>65.7 ± 19.9</td>
<td>64.2 ± 20.6</td>
</tr>
<tr>
<td>Physical function (HAQ DI)</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Patient’s global assessment, 100-mm VAS</td>
<td>63.0 ± 20.9</td>
<td>61.7 ± 21.6</td>
<td>62.6 ± 21.1</td>
</tr>
<tr>
<td>Physician’s global assessment, 100-mm VAS</td>
<td>68.6 ± 15.3</td>
<td>67.9 ± 16.6</td>
<td>68.4 ± 15.7</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>3.2 ± 3.1</td>
<td>2.5 ± 2.1</td>
<td>3.0 ± 2.9</td>
</tr>
<tr>
<td>Rheumatoid factor, % positive</td>
<td>82.5</td>
<td>82.0</td>
<td>82.0</td>
</tr>
<tr>
<td>Duration of morning stiffness, minutes</td>
<td>98.4 ± 61.2‡</td>
<td>84.1 ± 59.0</td>
<td>94.1 ± 60.8</td>
</tr>
<tr>
<td>DAS28 (CRP)</td>
<td>6.4 ± 0.8</td>
<td>6.3 ± 0.8</td>
<td>6.4 ± 0.8</td>
</tr>
</tbody>
</table>

* Except where indicated otherwise, values are the mean ± SD. AIM = Abatacept in Inadequate Responders to Methotrexate; MTX = methotrexate; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index; CRP = C-reactive protein; DAS28 (CRP) = Disease Activity Score in 28 joints based on CRP levels.
† Based on initial randomization group.
‡ Assessed in 377 patients.
were hydroxychloroquine (4 patients), sulfasalazine (4 patients), chloroquine (3 patients), and leflunomide (1 patient). Six patients (3.7%) from the original placebo group added a DMARD during the long-term extension portion of the study. These were sulfasalazine (3 patients), leflunomide (2 patients), and hydroxychloroquine (1 patient).

Signs and symptoms. In the original abatacept group, the improvements in ACR20, ACR50, and ACR70 responses observed following 1 year of treatment under double-blind conditions (7) were maintained for 2 years. At years 1 and 2 of the nonresponder analyses, ACR20 responses were 81.9% and 80.3%, ACR50 responses were 54.0% and 55.6%, and ACR70 responses were 32.4% and 34.3%, respectively (Figure 2A). For patients originally randomized to receive placebo, the ACR20, ACR50, and ACR70 responses were similar to those observed in the original abatacept group at year 2 (80.3% versus 78.1%, 55.6% versus 58.1%, and 34.3% versus 31.9% for the abatacept versus placebo...
The second year was similar for the erosion and JSN effect of the combination of abatacept and MTX during the second year of treatment (Figure 3). The rate of progression in the total score was significantly lower during the second year (total score was 1.07 versus 0.21, and 0.45 versus 0.24, respectively). A post hoc analysis comparing the mean change in radiographic progression during year 1 versus year 2. The rate of radiographic progression with abatacept treatment was shown to be significantly lower during year 2 (P < 0.0001). The rate of radiographic progression during year 2 was 57% lower than during year 1 (mean ± SD change in total score from baseline to year 1 1.1 ± 2.9 and 2.4 ± 5.1 in the abatacept and placebo groups, respectively; change in total score from year 1 to year 2 1.6 ± 3.7 in the abatacept group). At year 1, there were 328 patients in the abatacept group and 144 in the placebo group. At year 2, there were 324 patients in the abatacept group and 143 in the placebo group. MTX = methotrexate.

Figure 3. Mean change in total score from baseline in patients in the long-term extension period. Radiographs of the hands and feet were obtained at baseline and at 1 and 2 years, or upon early withdrawal from the study. Paired radiographs were independently scored by 2 readers for erosion, joint space narrowing, and total score using the Genant-modified Sharp scoring system. All patients received a fixed dose of abatacept in the open-label period after year 1 (~10 mg/kg once every 28 days). The signed rank test was used to compare the mean change in total score during year 1 versus year 2. The rate of radiographic progression with abatacept treatment was shown to be significantly lower during year 2 (P < 0.0001). The rate of radiographic progression during year 2 was 57% lower than during year 1 (mean ± SD change in total score from baseline to year 1 1.1 ± 2.9 and 2.4 ± 5.1 in the abatacept and placebo groups, respectively; change in total score from year 1 to year 2 1.6 ± 3.7 in the abatacept group). At year 1, there were 328 patients in the abatacept group and 144 in the placebo group. At year 2, there were 324 patients in the abatacept group and 143 in the placebo group. MTX = methotrexate.

Physical function and HRQOL. For the nonresponder analyses, the proportion of patients who achieved a clinically meaningful improvement in physical function (improvement of ≥0.3 units in the HAQ DI scores (mean changes for year 1 versus year 2 for total score, erosion score, and JSN score were 1.07 versus 0.46, 0.62 versus 0.21, and 0.45 versus 0.24, respectively). Based on the results of a linear mixed model comparing the intercept of radiographic progression over the 2-year period, 2 years of abatacept treatment was shown to be significantly better than 1 year of placebo followed by 1 year of abatacept (total score P < 0.01, erosion score P < 0.001, JSN score P < 0.05).

Linear extrapolation of the rate of radiographic progression (total score) in the placebo group at year 1 provided an estimated mean progression in the total score of 4.8 units at year 2. Compared with this extrapolated mean change in total score for the placebo group at 2 years, the original abatacept group demonstrated a mean change of 1.55 units over 2 years (Figure 3) and a reduction of ~70% in the expected progression from year 1.
score) or a HAQ DI response was maintained for 2 years of abatacept treatment. Of the 376 and 160 patients in the original abatacept and placebo groups, 66.8% and 63.1%, respectively, demonstrated a meaningful HAQ DI response for physical function at 2 years. Patients in the original placebo group demonstrated HAQ DI responses comparable to those of the original abatacept group at 2 years (73.2% versus 68.8% for the abatacept

Figure 4. Improvements in physical function and health-related quality of life through 2 years of treatment. A, Proportion of patients who entered the open-label long-term extension period of the study with a clinically meaningful response on the Health Assessment Questionnaire (HAQ) disability index (DI). Response was defined as an improvement of 0.3 units from baseline. Responses were based on the intent-to-treat (ITT) population of patients with data available at the visit of interest (post hoc as-observed analysis). Data are presented with 95% confidence intervals. B, Mean change in physical component summary (PCS) and mental component summary (MCS) scores from baseline to year 1 and from baseline to year 2 in all patients who entered the open-label period. C, Mean change from baseline in the individual subscales of the Short Form 36 (SF-36) and the PCS and MCS at year 2. All patients received an abatacept dose of 10 mg/kg and methotrexate (MTX) upon entry into the open-label period. Patients who received placebo and MTX during the initial double-blind period were reallocated to receive abatacept on day 365. All data were based on a prespecified analysis scheme, using the ITT population of patients with data available at the visit of interest (as-observed analysis). Horizontal line in B and C indicates a minimal clinically important difference (MCID) of 3 units. See Figure 2 for other definitions.
versus placebo group). The mean change in the HAQ DI score from baseline to year 2 was −0.73 in both groups. For the post hoc as-observed analysis, maintenance of response with abatacept treatment was also observed through 2 years (Figure 4A).

For the original abatacept group, the mean improvement from baseline (day 1) in the PCS score was 9.7 at the end of the double-blind period (year 1) and was stable at 10.6 at year 2. The mean improvement in the MCS score was 7.3 at year 1 and 7.2 at year 2 (Figure 4B). At 2 years, patients in the original placebo group experienced improvements that were similar to those observed in patients who had received abatacept for 2 years (Figure 4B). Clinically meaningful improvements exceeding 3 units (23) were observed in all 8 subscales of the SF-36, including the PCS and MCS scores (Figure 4C), for the original abatacept and placebo groups at year 2.

Improvements in sleep quality (assessed using the SPI) and fatigue also were maintained through 2 years of abatacept treatment. For patients in the original abatacept group, mean improvements from baseline in the SPI were 10.8 at year 1 and 10.9 at year 2 (deemed to be clinically meaningful) (24); mean changes in fatigue were 28.0 at year 1 and 30.9 at year 2, more than twice the minimal clinically important difference of 10 units (25). At year 2, patients who received abatacept for 1 year in the long-term extension period experienced improvements in both the SPI and fatigue VAS score that were comparable to those in patients who had received abatacept for 2 years (SPI 11.8; fatigue VAS 30.9) (Figures 4A–C).

Safety. Adverse events. Table 2 presents a summary of the safety results for patients enrolled in the AIM trial who received at least 1 dose of abatacept.

<table>
<thead>
<tr>
<th></th>
<th>Abatacept plus MTX, days 1–365 (n = 433)†</th>
<th>Abatacept plus MTX, days 1–729 (n = 593)‡</th>
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<tr>
<td>Patients with AEs, no. (%)</td>
<td>380 (87.8)</td>
<td>550 (92.6)</td>
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<tr>
<td>No. of AEs/100 patient-years</td>
<td>300.2</td>
<td>257.7</td>
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<tr>
<td>Discontinuations due to AEs, no. (%)</td>
<td>19 (4.4)</td>
<td>38 (6.4)</td>
</tr>
<tr>
<td>Patients with SAEs, no. (%)</td>
<td>68 (15.7)</td>
<td>149 (25.1)</td>
</tr>
<tr>
<td>No. of SAEs/100 patient-years</td>
<td>17.7</td>
<td>16.3</td>
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<tr>
<td>Discontinuations due to SAEs, no. (%)</td>
<td>10 (2.3)</td>
<td>24 (4.0)</td>
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<tr>
<td>Patients with infections, no. (%)§</td>
<td>244 (56.4)</td>
<td>400 (67.3)</td>
</tr>
<tr>
<td>No. of infections/100 patient-years§</td>
<td>90.9</td>
<td>77.6</td>
</tr>
<tr>
<td>Patients with serious infections, no. (%)§</td>
<td>17 (3.9)</td>
<td>43 (7.2)</td>
</tr>
<tr>
<td>No. of serious infections/100 patient-years§</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Deaths, no. (%)</td>
<td>1 (0.2)</td>
<td>3 (0.5)</td>
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</table>

* AIM = Abatacept in Inadequate Responders to Methotrexate; MTX = methotrexate; AEs = adverse events; SAEs = serious adverse events.
† All patients who received at least 1 dose of study medication during the double-blind period of the study.
‡ All patients who were randomized to receive placebo and entered the long-term extension period (and subsequently received 1 dose of study medication).
§ All infections were classified by system organ class of infections and infestations using the Medical Dictionary for Regulatory Activities, version 8.0.

Throughout the cumulative study period of the AIM trial, a total of 550 abatacept-treated patients experienced AEs at an incidence rate of 257.7 per 100 patient-years. This is consistent with the rate of AEs reported in the double-blind period alone (300.2 per 100 patient-years). The types and incidences (rate or frequency) of the most commonly reported AEs were similar to those reported in the double-blind period. The incidence of acute infusional events was low and was consistent with that in the double-blind period.

SAEs were reported in 149 abatacept-treated patients at an incidence rate of 16.3 per 100 patient-years for the cumulative study period, which is again comparable to the rate reported in the double-blind period alone (17.7 per 100 patient-years) (Table 2). Excluding worsening of arthritis, the most frequent SAEs were osteoarthritis, pneumonia, basal cell carcinoma, and chest pain, all of which occurred in >0.5% of patients during the cumulative study period.

Three deaths were reported during the 2 years of the AIM trial: 1 during the double-blind period (bronchopulmonary aspergillosis) and 2 during the long-term extension period (myocardial ischemia and postproce-
durational complications in 1 patient and lobar pneumonia in the other).

**Infection.** During the cumulative study period, infections and serious infections (classified as infections and infestations according to MedDRA version 8.0) occurred at an incidence rate of 77.6 and 4.3 per 100 patient-years, respectively. The rates of infections and serious infections in the cumulative study period remained similar to those reported during the double-blind period, during which event rates of 90.9 and 4.2 per 100 patient-years, respectively, were reported. The most frequent serious infections in the cumulative study period were pneumonia, acute bronchitis, cellulitis, and urinary tract infection. Discontinuations due to infections and infestations during the cumulative double-blind and long-term extension periods occurred in only 7 patients (1.2%).

**Malignancy.** Fourteen malignant neoplasms were reported during the cumulative study period. The most frequently reported malignant event was basal cell carcinoma, which was reported by 6 patients. Lung neoplasm and lymphoma were reported by 2 patients each. The remaining events were endometrial cancer, myelodysplastic syndrome (reported by 1 patient each), and 2 events of squamous cell carcinoma.

**Autoimmune disease.** In the cumulative study period, 15 of all abatacept-treated patients experienced possible autoimmune symptoms or disorders, the most frequently reported of which was psoriasis (7 patients). Vasculitis was reported in 3 patients, keratoconjunctivitis sicca was reported in 2 patients, and cutaneous vasculitis, erythema nodosum, Sjögren’s syndrome, and systemic lupus erythematosus (SLE) were reported in 1 patient each. Most of the events were considered to be of mild or moderate intensity, excluding the case of SLE, which was considered severe at the time of diagnosis on day 667, 14 days after the last abatacept infusion.

**DISCUSSION**

Over the lifespan of the disease, patients with RA typically experience progressive disability and joint destruction, which occur over 10–20 years (25). This chronic disease requires long-term treatment, with durable clinical and radiographic benefits.

Data presented here support and extend the findings of the 1-year, double-blind, placebo-controlled period of the AIM trial (7). Improvements in signs and symptoms of RA, physical function, and HRQOL observed after 1 year of treatment with abatacept and MTX were maintained through the first year of open-label treatment (comparable to a cohort study). This durability was matched by a safety profile consistent with that in the double-blind period, with no unique safety events observed in the long-term extension period.

Similar to the double-blind period of the study, a low rate of discontinuation was reported during the 1-year long-term extension period of the AIM trial, with a retention rate of 90.5% reported at 2 years. Discontinuations due to lack of efficacy were also low (2%). Sustained improvements were observed for all efficacy, HRQOL, and radiographic assessments during the second year of treatment. Once they started active treatment in the long-term extension period, patients originally randomized to the placebo group rapidly began to exhibit efficacy that was comparable to that seen in patients who had received abatacept throughout the study. For the ACR20 and HAQ DI responses, these improvements were observed by the first quarterly assessment during the long-term extension period.

During the double-blind period of the AIM trial (7), post hoc analyses demonstrated that the proportion of patients with ACR50 and ACR70 responses was significantly increased from 6 to 12 months (P < 0.001), indicating increasing improvement in the signs and symptoms over the course of treatment. Through 2 years of therapy, sustained ACR20, ACR50, ACR70, and HAQ DI responses were observed, regardless of the analysis performed, demonstrating the durability of response to abatacept over time. Similar responses were observed with both types of analysis used in this study, confirming the consistency of the data. At 2 years, approximately one-third of all patients experienced an MCR. Improvements in the proportion of patients with low disease activity, i.e., DAS28 (CRP) ≤3.2, and remission, i.e., DAS28 (CRP) <2.6, also were maintained through 2 years in patients who received abatacept, as assessed by the post hoc as-observed analysis. It is notable that the 95% CIs for the percentage of patients with as-observed LDAS were not shown to overlap at 12 versus 24 months in patients started on abatacept at baseline, supporting the increased clinical benefits provided by abatacept through 2 years.

Although these findings may be tempered by the open nature of the observations after 1 year, they are consistent with the statistically significant improvements observed during the double-blind period of the trial between 6 and 12 months. To our knowledge, abatacept is the first biologic or nonbiologic DMARD to demonstrate improvements in clinical parameters between 6 months and 2 years of treatment in a combination of
blinded and open-label observation periods. In this respect, in open-label, long-term studies, MTX failed to show incremental improvements after the first 6 months of treatment (26,27).

The AIM trial was the first to examine the effect of abatacept on radiographic progression in patients with active RA who had an inadequate response to MTX. Patients treated with abatacept for 2 years demonstrated further inhibition in the progression of structural damage, with a significantly greater effect during year 2 compared with year 1, suggesting an increased effect of the combination of abatacept and MTX on reducing structural damage in the second year. A detailed description of radiographic progression in this trial through 2 years of treatment will be presented elsewhere.

The sustained efficacy described above was associated with long-lasting and clinically meaningful improvements in patient-centered outcomes, such as all 8 subscales of the SF-36, as well as the physical and mental components summary scores. Following 2 years of abatacept treatment, patients’ quality of life and sleep quality approached US population norms, with PCS and MCS scores of 41.2 and 48.5, respectively (population norm 50), and SPI scores of 31.3 (norm 29). Improvements in fatigue also were sustained with abatacept treatment.

The safety profile of abatacept reported after 2 years of this study is consistent with that observed during the 1-year double-blind period, in which the overall frequency of AEs was comparable to that seen in patients treated with placebo (7). AEs were easily recognized and managed, with a low frequency of discontinuations due to AEs reported throughout the 2-year study period. The incidence rates of AEs observed in this study fell within the range reported for RA patients receiving anti-TNF therapy (28–30). However, due to differences between trials (e.g., inclusion criteria, background medication, or patient numbers), direct comparisons are difficult to interpret.

Data presented here should be interpreted in the context of the limitations of this study, which currently presents data through 2 years of treatment with abatacept. At initial randomization in the trial, patients had active disease, with joint counts that have become typical for inclusion in these trials (mean ± SEM tender joints 31.6 ± 13.3 and mean ± SEM swollen joints 21.9 ± 8.8). However, they may not represent typical patients with RA found in clinical practice, who normally have lower joint counts. Therefore, the extent of improvement we describe may not be applicable to these patients. In addition, the SF-36 data presented here are shown in the context of US norms for PCS and MCS scores, even though this was a multinational study. These were mainly used to illustrate the relevance of the changes.

The findings of this study demonstrate that when administered with MTX, a fixed dose of abatacept of ~10 mg/kg provides durable clinical efficacy and acceptable safety and tolerability in RA patients with an inadequate response to MTX. There were meaningful benefits to HRQOL and inhibition of radiographic progression through 2 years of treatment. For many of the assessments, including disease activity and radiographic progression, post hoc analyses showed sustainability of response and improvements of effects in year 2 compared with year 1. When combined with the significant efficacy and safety demonstrated previously in RA patients receiving background MTX (7–9) and in those with an inadequate response to anti-TNF therapy (10), these data demonstrate sustained and even more robust responses with abatacept in the second year of treatment, which was not seen in other open-label trials. While these 2-year treatment results are encouraging, further observations of both safety and efficacy are needed over longer treatment intervals in order to determine if the clinical responses described here can be sustained or if unexpected safety events emerge over time.

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AUTHOR CONTRIBUTIONS

Dr. Kremer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


Statistical analysis. Genant, Teng, Becker.

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