Safety and Efficacy of the Selective Costimulation Modulator Abatacept in Patients with Rheumatoid Arthritis Receiving Background Methotrexate: A 5-year Extended Phase IIB Study

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ABSTRACT. ***Objective.*** To evaluate the safety and efficacy of abatacept plus methotrexate (MTX) over 5 years in patients with rheumatoid arthritis.

Methods. Patients were randomized to abatacept 10 or 2 mg/kg or placebo, plus MTX. Patients completing the 1-year, double-blind period entered the longterm extension, where all patients received a fixed dose of abatacept ~10 mg/kg. We describe safety analyses for all patients who received at least 1 dose of abatacept and efficacy analyses for the original ~10 mg/kg abatacept-treated group, over 5 years.

Results. Of the 235 abatacept- or placebo-treated patients completing the double-blind period, 219 entered the longterm extension; 130 (59.4%) were continuing at Year 5. No unexpected safety events were observed during the longterm extension compared with the double-blind period. Incidence rates of adverse events (AE) and serious AE were 489.7 and 20.0/100 patient-years in Year 1 versus 374.9 and 18.9/100 patient-years in the cumulative period, respectively. Using exploratory analyses, improvements observed at Year 1 in the 10 mg/kg group were maintained at Year 5, as assessed by ACR responses (ACR20 = 77.1% vs 82.7%; ACR50 = 53.0% vs 65.4%; ACR70 = 28.9% vs 40.4% at Years 1 and 5, respectively) and disease activity (Low Disease Activity State = 48.2% vs 58.5%; Disease Activity Score-28-defined remission = 25.3% vs 45.3% at Years 1 and 5, respectively).

Conclusion. Abatacept maintained the efficacy observed at Year 1 over 5 years of treatment, and demonstrated consistent safety and tolerability. These data, along with relatively high retention rates, support the longterm clinical benefit provided by selective T cell costimulation modulation. Clinical trial registry: ClinicalTrials.gov; clinical trial registration number: NCT00254293. (J Rheumatol First Release March 1 2009; doi:10.3899/jrheum.080813)

Key Indexing Terms:
ABATACEPT RHEUMATOID ARTHRITIS T CELL LONGTERM SAFETY

Chronic diseases, such as rheumatoid arthritis (RA), require treatments that not only provide durable efficacy, but are also safe and well tolerated. Recent advances in the understanding of RA immunopathology have facilitated the development of novel biologic therapies that provide an additional therapeutic option to standard disease modifying antirheumatic drug (DMARD) therapy. There is increasing evidence that T cells play a fundamental role in the upstream initiation and perpetuation of the pathological immune response in RA, resulting in downstream inflammation and joint destruction[1]. The important role of T cells as orchestrators of the immune response in RA makes T cell activation a rational therapeutic target for treatment of this disease.

Abatacept is a fully human soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte antigen-4 (CTLA-4) linked to the modified Fc portion of human immunoglobulin G1, which has been modified to prevent complement fixation. Abatacept selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T cell activation[2]. The mechanism of

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action of abatacept is fundamentally different from that of other biologic DMARD, such as tumor necrosis factor (TNF) antagonists or B cell-depleting agents.

This Phase IIb study demonstrated the safety and efficacy of abatacept plus methotrexate (MTX) over 1 year of double-blind (DB) treatment in patients with RA and an inadequate response to MTX[3,4], and confirmed ~10 mg/kg to be the most effective dose. Subsequent Phase III studies verified the efficacy and safety of abatacept both in patients with an inadequate response to MTX[5] and in patients with an inadequate response to anti-TNF agents[6]. We describe the safety, tolerability, and efficacy of abatacept ~10 mg/kg over 5 years of treatment in the continuing open-label longterm extension (LTE) of a Phase IIb study.

We report on the safety and tolerability of all patients who received at least 1 dose of abatacept over 5 years, and the efficacy and health-related quality of life (HRQOL) of patients who had received ~10 mg/kg abatacept over 5 years in this continuing open-label extension of a Phase IIb study.

MATERIALS AND METHODS

Patients. All patients who completed the 1-year, DB period of this study (clinical trial registration number: NCT00254293)[3,4] were eligible to enter the open-label LTE period.

Study protocol. The primary objectives of the LTE study period were to assess the longer-term safety and tolerability of abatacept combined with MTX, and to assess the efficacy and HRQOL of a fixed dose (~10 mg/kg) of abatacept. This trial was approved by the Institutional Review Boards/Independent Ethics Committees and was carried out in accord with the ethical principles of the Declaration of Helsinki. All patients gave their written, informed consent.

Patients who completed the 1-year DB period (abatacept 10 and 2 mg/kg and placebo groups) and enrolled into the LTE period were reallocated to a fixed dose of abatacept ~10 mg/kg, in addition to background MTX. During the LTE period, abatacept was infused once a month, intravenously over a 30-minute period. Abatacept treatment was weight-tiered as follows; < 60 kg, 500 mg; 60–100 kg, 750 mg; > 100 kg, 1 g. No premedication was required prior to these monthly infusions but could have been administered at the discretion of the investigator. Up to 2 consecutive infusions, if required, could be skipped for safety reasons.

Patients were not permitted to take other biologic DMARD during this study, and were not eligible to enter the study if they had required treatment for *Mycobacterium tuberculosis* in the past 3 years.

Safety evaluation. Adverse events. Safety and tolerability assessments were performed once a month, on scheduled visit days. All patients who received at least 1 dose of abatacept (10 or 2 mg/kg) were evaluated for safety, including patients originally randomized to placebo who subsequently received abatacept ~10 mg/kg during the LTE period. For the original placebo group, only adverse events (AE) occurring during the LTE period while receiving ~10 mg/kg abatacept therapy were recorded.

Safety assessments, including all reported AE, serious AE (SAE), discontinuations due to AE, deaths, clinically significant changes in vital signs, physical examination and clinical laboratory test abnormalities, were classified using the *Medical Dictionary for Regulatory Activities*, version 8. Patients were monitored for acute infusional reactions (defined as those occurring within 1 hour of the start of infusion).

Efficacy evaluation. Signs and symptoms. Efficacy parameters were assessed on a quarterly basis. The 2 mg/kg abatacept dose was included in the DB period dose-finding study, but was not considered the optimal recommended dose and therefore was not pursued. Efficacy data are presented at 6-monthly intervals. Unlike the safety analyses performed in this study, efficacy data are presented only for those patients who were originally randomized to the abatacept 10 mg/kg group and then entered the LTE period.

Efficacy outcome measures included a 20%, 50%, or 70% improvement in the American College of Rheumatology (ACR) criteria[7] (ACR20, ACR50, ACR70, respectively); and the proportions of patients achieving Low Disease Activity State [LDAS; Disease Activity State (DAS28) ≤ 3.2] and achieving DAS28-defined remission [DAS28 C-reactive protein (CRP) < 2.6][8].

Physical function and quality of life evaluation. Improvements in physical function were assessed using the modified Health Assessment Questionnaire (mHAQ)[9]. Clinically meaningful improvements were defined as a reduction in mHAQ score of ≥ 0.3 units from baseline[10] (exceeding the minimum clinically important difference for this measure of ≥ 0.22 units); patients experiencing such an improvement were termed mHAQ responders.

HRQOL was assessed using the Medical Outcomes Study Short Form-36 (SF-36), which includes a physical component summary (PCS; derived from subscales of physical function, role–physical, bodily pain, and general health) and a mental component summary (MCS; derived from subscales of vitality, social function, role–emotional, and mental health)[11]. Clinically meaningful improvements were defined as an increase of at least 3 points from baseline[10,12].

Statistical analysis. Baseline demographic data and clinical characteristics were analyzed descriptively for all patients who entered the LTE. A collective analysis of the safety data for all patients in the LTE period, regardless of original randomized group, was carried out. Data presented for the DB period are based on all patients who received at least 1 dose of study medication. Data presented for the cumulative study period (DB plus LTE periods) are based on all patients who were originally randomized to abatacept and received at least 1 dose (10 or 2 mg/kg) of study drug, plus all patients who were originally randomized to placebo and then entered the LTE period (subsequently receiving at least 1 dose of abatacept ~10 mg/kg). Incidence rates and frequencies were calculated for AE, SAE, infections, serious infections, and total malignancies. Incidence rates were calculated as the number of patients with the event of interest, divided by the total exposure for the specified treatment period. A patient's contribution to the incidence rate of each AE ended at the time of the first occurrence of that AE. Incidence rates were expressed per 100 patient-years of exposure.

Patients who were originally randomized to the 10 mg/kg abatacept group and who received at least one infusion of abatacept during the LTE period (the intent-to-treat population) were the only patients included in the efficacy analyses. Efficacy measures were assessed using exploratory analyses of as-observed data, using only patients with data available at the visit of interest.

RESULTS

Baseline demographics and characteristics. Baseline demographics and clinical characteristics for those patients who entered the LTE period were comparable between treatment groups and were similar to patients who entered the 1-year DB period, as reported[3]. The majority of patients were Caucasian women with mean disease durations ranging from 8.2 (SD 8.4) to 9.9 (SD 10.1) years for the patients randomized to 10 or 2 mg/kg of abatacept or placebo, respectively. Patients assigned to each of the 3 study groups had active disease, with similar tender and swollen joint counts.

Patient disposition. Of the 235 patients who completed the DB period, 219 (84, 68, and 67 patients originally randomized to the abatacept 10 and 2 mg/kg and placebo groups,

respectively) were enrolled and treated in the LTE period. Overall, a total of 130 (59.4%) patients completed 4 years of therapy in the LTE [91 and 39 patients originally randomized to the abatacept 10 or 2 mg/kg and placebo groups, respectively (Figure 1)]. Of the 84 patients originally randomized to abatacept 10 mg/kg, 53 (63%) patients remained in the study and therefore received ~10 mg/kg over a period of 5 years.

Safety. Adverse events. Table 1 provides a summary of safety data for all patients who received at least 1 dose of abatacept (10 or 2 mg/kg) for the DB versus the cumulative (DB plus LTE) study periods.

Over the cumulative study period, a total of 283/287 (98.6%) abatacept-treated patients experienced AE at an incidence rate of 374.9/100 patient-years, similar to the incidence of AE reported in the DB period (489.7/100 patient-yrs; Table 1). The types and incidence rate of the most commonly reported AE in the cumulative period (excluding those defined as musculoskeletal disorders) in the combined abatacept dose group were similar to those reported in the DB period; these included nasopharyngitis [87 (30.3%) patients; 12.6/100 patient-yrs], upper respiratory tract infection [66 (23.0%) patients; 8.4/100 patient-yrs], cough [64 (22.3%) patients; 8.3/100 patient-yrs], headache [68 (23.7%) patients; 8.8/100 patient-yrs], nausea [44 (15.3%) patients; 5.2/100 patient-yrs], and diarrhea [57 (19.9%) patients; 6.9/100 patient-yrs]. The incidence of acute infusion reactions during the cumulative study period was low, and consistent with the DB period.

Analysis of only those patients who were originally randomized to the 10 mg/kg abatacept group showed a decrease in the incidence of AE between the DB and cumulative study periods (531.4 vs 374.9/100 patient-yrs, respectively).

Serious AE occurred in 132 (46.0%) abatacept-treated patients at an incidence rate of 18.9/100 patient-years for the cumulative study period; these rates were similar to those reported in the DB period alone (20.0/100 patient-yrs; Table 1). Aside from progression of arthritis, the most frequent SAE that occurred in > 1% of abatacept-treated patients over 5 years were chest pain and basal cell carcinoma [6 (2.1%) patients each], osteoarthritis and cholelithiasis [5 (1.7%) patients each], and dyspnea, pulmonary embolism, deep vein thrombosis, myocardial infarction and hip arthroplasty [4 (1.4%) patients each].

Five deaths were reported over 5 years of treatment; one during the DB period (malignant lung neoplasm), 3 during the LTE period (lung adenocarcinoma; severe dyspnea and cardiorespiratory failure), and one posttreatment (chest pain, following coronary artery bypass graft surgery). The patient who died of malignant lung neoplasm (DB period) had a history of smoking, and the patient who died of severe dyspnea during the LTE period was a current smoker. The remaining 3 patients who died had no history of smoking. All 5 deaths were considered unlikely to be related or unrelated to study medication by the investigator.

Infections. Infections and serious infections occurred at an incidence rate of 94.2 and 2.1/100 patient-years in the DB period, and at a rate of 77.3 and 3.0/100 patient-years over the cumulative study period, respectively. The most frequent serious infections that occurred during the cumulative study period were pneumonia and diverticulitis reported in 3 patients each (1.0%) and abscess, bacterial arthritis, celluli-

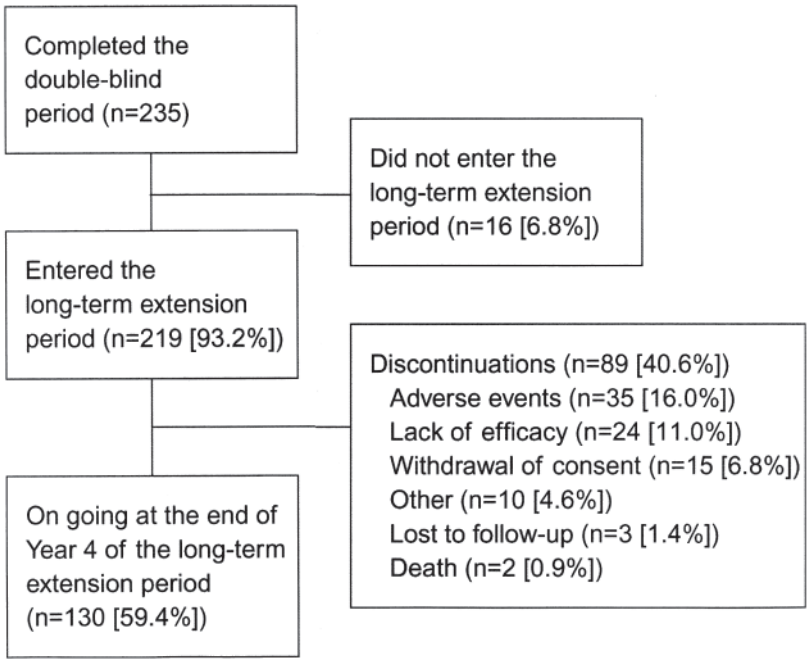


Figure 1. Patient disposition during the open-label longterm extension period.

Table 1. Safety summary during the double-blind and cumulative study periods. Data are event/100 patient-years (95% CI) unless otherwise specified.

	Double-blind Study Periods* Abatacept 10 and 2 mg/kg Groups, 1 year	Cumulative Study Period† All Treatment Groups Combined, 5 years
Deaths, n (%)	1 (0.5)	5 (1.7)
Discontinuations due to AE, n (%)	18 (8.2)	49 (17.1)
Discontinuations due to SAE, n (%)	9 (4.1)	32 (11.1)
AE events/100 pt-yrs	489.7 (425.46, 561.03)	374.9 (332.48, 421.20)
SAE events/100 pt-yrs	20.0 (14.03, 27.74)	18.9 (15.78, 22.37)
Infections/100 pt-yrs	94.2 (78.06, 112.58)	77.3 (67.58, 87.94)
Serious infections/100 pt-yrs	2.1 (0.57, 5.38)	3.0 (1.97, 4.35)
Malignancies/100 pt-yrs	2.1 (0.57, 5.38)	1.5 (1.07, 2.93)

* All patients who received at least 1 dose of study medication during the double-blind period. † All patients who were randomized to abatacept (10 and 2 mg/kg) and received 1 dose of study medication, plus all patients who were randomized to placebo and entered the open-label longterm extension period (and subsequently received 1 dose of study medication. AE: adverse event, SAE: serious adverse event.

tis, and sinusitis, reported in 2 patients each (0.7%). There were no occurrences of opportunistic infection or *M. tuberculosis* reported during the cumulative study period.

Malignancies. Malignancies, including those previously reported as causes of death, were reported at a total incidence rate of 1.5/100 patient-years during the cumulative study period; 10 non-melanoma skin cancers and 7 solid organ malignancies were reported in 14 (4.9%) patients. The most frequently reported malignant event was basal cell carcinoma [6 (2.1%) patients]. In addition, squamous cell carcinoma was reported in 3 (1.0%) patients; small-cell lung cancer and squamous cell carcinoma of the skin were reported in one (0.3%) patient each. The remaining events, also reported in one patient each, were bladder cancer, breast cancer, ovarian cancer, lung adenocarcinoma, metastatic lung cancer, and malignant lung neoplasm.

Autoimmune disease. In the cumulative study period, a total of 12 abatacept-treated patients experienced possible autoimmune symptoms or disorders, the most frequent of which was psoriasis [6 (2.1%) patients]. Cutaneous vasculitis was reported in 2 patients, while rheumatoid vasculitis, erythema nodosum, vasculitis, sicca syndrome, and multiple sclerosis were all reported in one patient each.

Clinical efficacy. ACR responses. In the original abatacept 10 mg/kg group, the improvements in ACR20, ACR50, and ACR70 responses observed following 1 year of DB treatment were maintained at Year 5. At Years 1 and 5, ACR20 responses were 77.1% (95% CI 68.1, 86.1) and 82.7% (95% CI 72.4, 93.0), respectively; ACR50 responses were 53.0% (95% CI 42.3, 63.7) and 65.4% (95% CI 52.5, 78.3); and ACR70 responses were 28.9% (95% CI 19.2, 38.7) and 40.4% (95% CI 27.0, 53.7; Figure 2A).

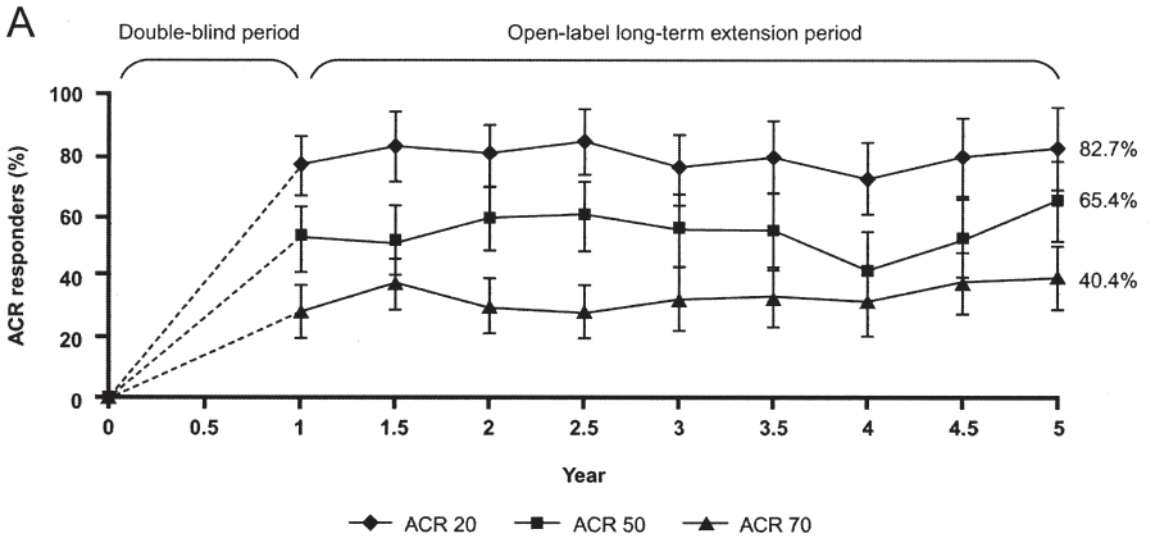
Disease activity. The proportion of patients achieving LDAS or DAS28 (CRP)-defined remission increased over 5 years of abatacept treatment (Figure 2B). In the original abatacept 10 mg/kg group at Years 1 and 5, respectively, LDAS was experienced by 48.2% (95% CI 37.4, 58.9) and 58.5% (45.2, 71.8) of patients and DAS28 (CRP)-defined remission by 25.3% (95% CI 15.9, 34.7) and 45.3% (95% CI 31.9, 58.7) of patients.

Physical function and HRQOL. The proportion of patients achieving a mHAQ response (clinically meaningful improvement ≥ 0.3 units in mHAQ) was maintained over 5 years of abatacept treatment. Of the patients originally randomized to abatacept 10 mg/kg, 52.8% (95% CI 39.4, 66.3) demonstrated a meaningful mHAQ response in physical function at Year 5, compared with 54.8% (95% CI 44.1, 65.4) after Year 1. The mean change from baseline in the mHAQ at Year 5 was –0.47 (SD 0.07).

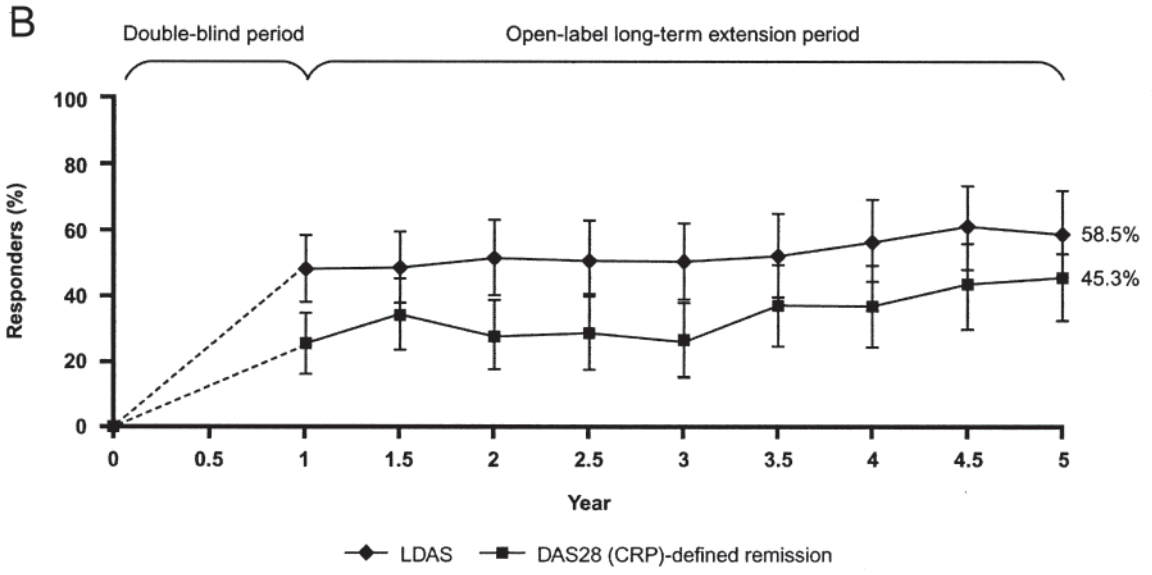
Improvements in HRQOL were also sustained over 5 years of abatacept treatment. For the original abatacept 10 mg/kg group, the mean improvement from baseline (Day 1) in PCS was 9.7 (95% CI 7.6, 11.8) at the end of the DB period (Year 1; mean score 40.6, SD 11.04) and was stable at 9.7 (95% CI 6.64, 12.74) at Year 5 (mean score 41.7, SD 12.09). The mean improvement in the MCS was 6.1 (95% CI 3.68, 8.42) at Year 1 (mean score 52.3, SD 9.92) and 5.4 (95% CI 2.59, 8.17) at Year 5 (mean score 50.8, SD 10.7). At Year 5, clinically meaningful improvements, exceeding 3 units, were observed for both summary scores, PCS and MCS, and in all 8 subscales of the SF-36 (mean change from baseline was 8.8, 10.2, 9.5, 6.5, 7.5, 8.7, 7.7, and 4.3 for physical function, role–physical, bodily pain, general health, vitality, social function, role–emotional, and mental health, respectively) for the original abatacept 10 mg/kg group.

DISCUSSION

The findings from these longterm analyses demonstrate that abatacept ~10 mg/kg provides consistent safety and tolerabili-



As-observed population (n)	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Year 5
Abatacept 10 mg/kg group	83	73	66	63	63	60	59	55	52



As-observed population (n)	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Year 5
Abatacept 10 mg/kg group	83	73	72	67	64	60	60	56	53

Figure 2. A. The proportion of patients originally randomized to the 10 mg/kg abatacept group who achieved ACR20, ACR50, and ACR70 responses over time. B. The proportion of patients originally randomized to the 10 mg/kg abatacept group experiencing Low Disease Activity State (DAS28 CRP ≤ 3.2) and DAS28-defined remission (DAS28 CRP < 2.6) by visit day. Responses are based on the intent-to-treat population for patients with data available at the visit of interest (as-observed analysis). Broken line represents the double-blind period; data are presented with 95% confidence intervals.

ty in combination with sustained efficacy in patients with RA and an inadequate response to MTX, over 5 years of treatment.

Safety assessments over 5 years of cumulative abatacept treatment indicate that the patterns and rates of AE were comparable to those seen in the 1-year DB period. The safety results for abatacept treatment during the 1-year DB and the cumulative study periods were consistent with previous reports[3,4,13], and are representative of RA populations receiving MTX[14]. AE were generally manageable, with a low frequency of serious infections and no opportunistic infections in the LTE period. Compared with the general population, patients with RA have an elevated risk of developing malignancies, specifically lung cancer and lymphoma[15,16]. An analysis of clinical trial experience with abatacept, encompassing ~8400 person–years of exposure, showed that the observed incidence rates of total malignancy, breast cancer, and lymphoma compared with the DB period remained unchanged and that overall incidence rates of cancer were consistent with expectation based on comparator RA cohorts treated with DMARD[17].

The incidence rates of AE, SAE, and serious infections were found to be within the range of those previously reported in clinical trials of patients with RA treated with anti-TNF therapies. Due to variations in study design, including inclusion criteria, number of randomized patients, and background medication, direct comparisons between independent trials should be interpreted with caution[18-21].

In this study, efficacy data were assessed using post-hoc as-observed analyses. Although as-observed data are vulnerable to dropout of patients who respond less well to treatment, they are more relevant over the long term, following only those patients who actually continue therapy in the study. In this trial, a relatively high retention rate was observed over 5 years, with roughly 10% of patients discontinuing per year. Despite the discontinuation of a small proportion of patients, improvements in ACR responses and the proportion of patients achieving LDAS and DAS28 (CRP)-defined remission at Year 1 were maintained over 5 years. Of the abatacept-treated patients remaining in the trial at Year 5, 40% had achieved an ACR70 response, and approximately 45% had reached DAS28 (CRP)-defined remission.

The sustained efficacy described above was associated with clinically meaningful, sustained improvements in patient-centered outcomes. Analysis of mHAQ responses showed that abatacept 10 mg/kg provided clinically meaningful improvements in physical function that were maintained through 5 years of treatment. Similarly, clinically meaningful improvements in all 8 subscales of the SF-36 as well as the PCS and MCS were sustained over 5 years. Following 5 years of ~10 mg/kg abatacept treatment, patients' HRQOL approached population norms, with PCS and MCS scores of 41.7 and 50.8, respectively (population norms, PCS 49, MCS 50)[11,22].

The safety and efficacy improvements observed over time are reflected in the good retention rate of this study. About 60% of the patients originally randomized to receive abatacept ~10 mg/kg remained in the study over 5 years, corresponding to a relatively low yearly discontinuation rate of 10%. High retention rates of 90.5% over 2 years of the LTE period were also observed in the AIM (Abatacept Inadequate responders to Methotrexate) trial[23].

Our findings should be interpreted within the context of the design of this clinical trial. At initial randomization, patients had active disease with joint counts that are now typical for inclusion in randomized controlled trials — baseline scores in the abatacept 10 mg/kg group for tender joints and swollen joints were mean 30.4 ± SD 11.4 and mean 21.2 ± SD 7.6, respectively. However, we recognize that these patients may not represent typical patients with RA found in clinical practice, who often present with lower joint counts. Conversely, we also recognize that achieving a response in a patient population that has a high disease activity and high tender and swollen joint counts at baseline may be more challenging. Further observations, of larger patient populations over longer periods, including patients with concomitant diseases, are required to confirm these data.

The findings from this study demonstrate that, administered with MTX, a fixed dose of abatacept ~10 mg/kg provides durable acceptable safety, tolerability, and clinical efficacy in patients with RA and an inadequate response to MTX. In the AIM trial of abatacept in a similar patient population (with active RA and an inadequate response to MTX), a reduction in the rate of progression of structural damage was demonstrated[5]. When combined with the acceptable safety and favorable efficacy demonstrated previously in abatacept-treated patients with RA and an inadequate response to MTX[3,5], as well as in those with an inadequate response to anti-TNF therapy[24], these data support the longterm use of abatacept for the treatment of RA in routine clinical practice.

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