Safety and Efficacy of Adalimumab in Treatment of Patients with Psoriatic Arthritis Who Had Failed Disease Modifying Antirheumatic Drug Therapy

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ABSTRACT. ***Objective.*** To demonstrate the safety and efficacy of adalimumab for the treatment of active psoriatic arthritis (PsA) in patients with an inadequate response to disease modifying antirheumatic drugs (DMARD).

Methods. In a placebo controlled, double-blind, randomized, multicenter study, patients were treated for 12 weeks with subcutaneous injections of adalimumab 40 mg every other week (eow) or placebo, followed by a period of open-label treatment with adalimumab 40 mg eow. The primary efficacy endpoint was the percentage of patients who met the American College of Rheumatology (ACR20) core criteria at Week 12. Secondary efficacy measures included the modified Psoriatic Arthritis Response Criteria (PsARC) and assessments of disability, psoriatic lesions, and quality of life. For missing data, nonresponder imputation was used for ACR and PsARC scores and last observation carried forward for other measures.

Results. A total of 100 patients received study drug (51 adalimumab, 49 placebo). At Week 12, an ACR20 response was achieved by 39% of adalimumab patients versus 16% of placebo patients ($p = 0.012$), and a PsARC response was achieved by 51% with adalimumab versus 24% with placebo ($p = 0.007$). At Week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After Week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at Week 24. Serious adverse events had similar frequencies during therapy with placebo (4.1%), blinded adalimumab (2.0%), and open-label adalimumab (3.1%). No serious infections occurred during adalimumab therapy.

Conclusion. In this study of patients who had active PsA and a previous, inadequate response to DMARD therapy, adalimumab was well tolerated and significantly reduced the signs, symptoms, and disability of PsA during 12 weeks of blinded and 12 weeks of open-label therapy. Adalimumab also improved psoriasis in these patients. (First Release April 15 2007; J Rheumatol 2007;34:1040–50)

Key Indexing Terms:
ADALIMUMAB TUMOR NECROSIS FACTOR PSORIASIS
PSORIATIC ARTHRITIS DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Psoriatic arthritis (PsA) is an inflammatory arthropathy that occurs in 10%–30% of the 4.5 million patients with psoriasis in the United States[1]. For most patients, skin manifestations predate arthritis, typically by many years[2]. PsA is usually characterized by flares and remissions[3], and in some patients may be as severe and debilitating as rheumatoid arthritis (RA)[4,5]. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, disability, and a reduced life expectancy[6-9].

The goal of treatment for PsA is to reduce the signs and symptoms of arthritis, inhibit structural damage to joints, improve psoriasis, and improve patient quality of life. Traditional interventions for moderate to severe PsA have included nonsteroidal antiinflammatory drugs (NSAID) and nonbiologic disease modifying antirheumatic drugs (DMARD). In controlled clinical trials, several DMARD have been found to have some degree of efficacy in PsA[10]. A meta-analysis of published, well controlled studies found that, of the traditional DMARD, only high-dosage parenteral methotrexate (MTX) and sulfasalazine had demonstrated efficacy in PsA[11]. Despite the limited amount of supporting evi-

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dence, many patients with PsA are currently treated with traditional, nonbiologic DMARD such as sulfasalazine or MTX.

The proinflammatory cytokine tumor necrosis factor (TNF) is present in increased concentrations in affected joints of patients with PsA[12,13], and has been found to have elevated biologic activity in lesional skin, compared with uninvolved skin in patients with psoriasis[14]. Serum TNF concentrations have been found to correlate with psoriatic disease severity[15]. An important role of TNF in psoriatic disease has been convincingly established by studies of the currently available TNF antagonists — adalimumab, etanercept, and infliximab — all of which have been shown to significantly reduce the signs and symptoms of psoriasis and arthritis, inhibit radiographic progression, and improve quality of life in patients with PsA[16-20].

Adalimumab (Humira®; Abbott Laboratories, Abbott Park, IL, USA) is a fully human anti-TNF monoclonal antibody. In ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial), a 24-week study of patients with moderate to severe PsA who were intolerant of or unresponsive to NSAID, treatment with adalimumab significantly improved arthritis, psoriasis, disability, and quality of life, and inhibited radiographic progression of joint damage[20]. At Week 24 in ADEPT, 57% of adalimumab-treated patients had achieved a 20% improvement according to the American College of Rheumatology core criteria (ACR20 response), versus 15% of placebo-treated patients ($p < 0.001$). For patients with psoriasis involving at least 3% of body surface area at the ADEPT baseline, a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) was achieved at Week 24 by 59% of patients treated with adalimumab, versus 1% treated with placebo ($p < 0.001$).

At about the same time as ADEPT, another Phase III randomized placebo controlled trial was conducted to test the efficacy and safety of adalimumab for patients with active PsA. The design of this second study differed from that of ADEPT in that: (1) its patients were required to have had an inadequate response of arthritis to previous DMARD therapy; (2) the double-blind period lasted 12 rather than 24 weeks; (3) it did not include radiographic assessments; and (4) the treatment groups were smaller than in ADEPT. The results of this randomized placebo controlled trial of adalimumab therapy in PsA, and of the subsequent 12 weeks of open-label therapy with adalimumab, are reported here.

MATERIALS AND METHODS

Study design. A double-blind, Phase III, randomized placebo controlled multicenter study was conducted to demonstrate the safety and efficacy of adalimumab in the treatment of moderately to severely active PsA in patients who had had an inadequate response to DMARD therapy. Following a screening period of up to 14 days, patients were stratified by DMARD use at baseline (yes/no), then randomized in a 1:1 ratio to receive a subcutaneous injection of adalimumab 40 mg every other week (eow) or placebo for 12 weeks. Patients were randomized in blocks of 4 using an interactive voice-response system. Patients who completed the blinded phase could elect to receive open-label therapy with adalimumab 40 mg eow, the first 12 weeks of which are reported here. Study drug was provided in prefilled syringes containing a 0.8 ml solution of adalimumab (50 mg/ml) or matching placebo (Abbott Laboratories). Study visits occurred at baseline and Weeks 2, 4, 8, 12, 14, 18, and 24 for safety and efficacy assessments.

The study was conducted at 16 sites in Canada and the United States. The protocol was approved at each site by an independent ethics committee or institutional review board and was conducted in accord with the International Conference on Harmonization good clinical practice standards; US Food and Drug Administration regulations governing clinical study conduct; ethical principles originating from the Declaration of Helsinki (1989 revision); and all applicable local laws and customs. All participants provided written informed consent after the nature and purpose of the study had been explained and before any study procedure was initiated.

Patients. Eligible patients were male or female, at least 18 years of age, and in generally good health based on medical history, physical examination, laboratory profile, chest radiograph, and a 12-lead electrocardiogram. At study entry, patients were required to have had ≥ 3 swollen joints and ≥ 3 tender or painful joints, and either an active cutaneous lesion of chronic plaque psoriasis or a documented history of chronic plaque psoriasis diagnosed by the investigator or a dermatologist. All patients enrolled in the study were receiving concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response, as defined by the investigator. Oral corticosteroids were allowed during the trial if the dosage did not exceed the equivalent of prednisone 10 mg/day and had been stable during the 4 weeks preceding the baseline visit. Concomitant treatment with MTX or other DMARD, with the exception of cyclosporine and tacrolimus (oral or topical) received within 4 weeks of the baseline visit, was allowed if the patient had received a minimum of 3 months of therapy and the dosage had been stable during the 4 weeks preceding the baseline visit. The maximum allowable MTX dosage was 30 mg/week. A purified protein derivative skin test was required for all participants. For patients with evidence of a previous tuberculosis infection, a documented history of treatment for latent tuberculosis was required, or such treatment had to have been initiated before the first dose of study drug.

Patients were excluded if they had a history of previous anti-TNF therapy; intravenous infusions or intraarticular injections of corticosteroids within 4 weeks of baseline; topical psoriasis therapies (e.g., keratolytics, coal tar, anthralin) within 2 weeks of baseline (although medicated shampoos and low-potency topical steroid use on the palms, soles of the feet, axilla, and groin area were allowed); ultraviolet A (UVA) phototherapy, including psoralen and UVA, or use of a tanning booth within 2 weeks of the baseline visit; or oral retinoids within 4 weeks of the baseline visit, alefacept or siplizumab within 12 weeks, or any other biologic or investigational therapy within 6 weeks of the baseline visit. Patients were excluded if they were currently using or likely to need antiretroviral therapy.

Patients with persistent or severe infections or a history of active tuberculosis, or who had an active nonpsoriatic skin disease that could interfere with the assessment of target lesions, were excluded. Additional exclusion criteria were a significant history of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease; neurologic symptoms suggestive of central nervous systemic demyelinating disease; and a history of malignancy other than carcinoma *in situ* of the cervix or adequately treated nonmetastatic squamous or basal cell skin carcinoma.

Measures of efficacy and safety. The primary efficacy variable was the ACR20 response rate at Week 12[21]. The total number of assessed joints was 78 for the tender joint count (TJC) and 76 for the swollen joint count (SJC)[20]. Joints or regions examined were those routinely examined in RA plus the first carpal metacarpal phalangeal joints (n = 2) and the distal interphalangeal joints of the toes (n = 8). Hips were excluded from the SJC. Patients were evaluated for dactylitis of the hands and feet [total score 0–60, with each digit rated 0 (absent) to 3 (severe)], and enthesitis of the proximal insertion of the Achilles tendon and plantar fascia [total score 0–4, with each insertion rated 0 (enthesitis absent) or 1 (enthesitis present)]. Other efficacy measures included patient's assessment of pain during the previous week, patient's global assessment of disease activity during the previous 24 hours, and physician's global assessment of disease activity (current PsA activity), each using a visual analog scale of 0–100 mm[21].

Secondary efficacy measures of arthritis and quality of life included the ACR50 and ACR70 response rates, the modified Psoriatic Arthritis Response Criteria (PsARC)[19,22]; the disability index of the Health Assessment Questionnaire (HAQ-DI) score[23]; the Short Form-36 Health Survey (SF-36) and its Physical and Mental Component Summary (PCS and MCS) scores[23]; and the 13-item fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT-F) measure[24]. Psoriasis-related assessments were the target lesion assessment, the physician's global assessment for psoriasis, and the Dermatology Life Quality Index (DLQI)[25]. The target lesion assessment evaluated target lesions for erythema, induration, and scaling, each on a scale of 0 (best) to 5 (worst), with a total plaque score of 0–15. Psoriasis-related assessments were conducted only for patients with a lesion that, at baseline, was ≥ 2 cm diameter and had a plaque score ≥ 6.

Post-hoc analyses of ACR response rates at Week 12 were performed for treatment group subsets defined according to the following indicators: MTX use at baseline (yes/no), DMARD use at baseline (yes/no), NSAID use at baseline (yes/no), corticosteroid use at baseline (yes/no), baseline rheumatoid factor (RF) positive or negative, baseline C-reactive protein (CRP) concentration ≥ 1 or < 1 mg/dl, and male or female.

The safety of adalimumab was assessed by measuring vital signs at every study visit, performing routine hematologic and clinical chemistry blood tests and urinalyses throughout the study, and recording adverse events (AE) throughout the study. Serological tests for RF and antinuclear antibodies were performed only at baseline visits.

Statistical analyses. To provide ≥ 90% power to detect a difference in responses at $\alpha = 0.05$ for a projected Week 12 ACR20 rate of 60% for the adalimumab group and 25% for the placebo group, ≥ 50 patients per group were needed. For efficacy and safety analyses, the intention-to-treat (ITT) population was defined as all patients who received at least one dose of study medication. After Week 12, the ITT population for the placebo arm was defined as those patients who received at least one dose of open-label adalimumab. All statistical tests were 2-sided, and comparisons were performed with $\alpha = 0.05$ unless stated otherwise.

The percentages of patients who achieved an ACR20 response in each group at Week 12 were compared using the Cochran-Mantel-Haenszel test, with baseline DMARD use as the stratification factor. ACR20 response rates at timepoints other than Week 12 and ACR50 and ACR70 rates at all timepoints were analyzed using Fisher's exact test and combining baseline DMARD use categories. PsARC responses and comparisons of the numbers of patients in the physician global assessment of psoriasis disease activity categories "Clear" and "Minimal" with the numbers in other categories were analyzed using the Cochran-Mantel-Haenszel test, with baseline DMARD use as the stratification factor. The mean changes from baseline in the HAQ-DI, target lesion response, DLQI, FACIT-F, and SF-36 scores, as well as patient's assessment of pain, patient's global assessment of disease activity, and physician's global assessment of disease activity, were compared (adalimumab vs placebo) using a 2-way analysis of variance model that included factors for baseline DMARD use and treatment. For missing data, nonresponder imputation (i.e., missing responses were counted in the nonresponder category) was used for analysis of ACR and PsARC responses, and last observation carried forward was used for all other efficacy measures. Statistical significance was not determined for comparisons involving results after Week 12.

Adverse events were summarized by incidence and severity. Fisher's exact test was used to compare the incidences of reported adverse events in each group.

RESULTS

Between June 30, 2003, and March 1, 2004, 102 patients were enrolled, 100 of whom received study drug (51 adalimumab, 49 placebo; Figure 1). Two patients randomized to placebo never received study drug: one because of withdrawn consent, and the other because the initial evaluation indicated the patient was not in generally good health. Overall, 96 patients (50 adalimumab, 46 placebo) completed the 12-week, double-blind, placebo controlled portion of the study. The one patient from the adalimumab arm who did not complete the blinded period was allowed to enter the open-label extension. Of the 97 patients enrolled in the extension study, 92 completed 12 weeks of open-label adalimumab treatment (Figure 1).

Overall, the baseline demographic data, medication usage, and disease severity characteristics were similar between treatment groups and representative of long-standing, predominantly polyarticular PsA. The mean CRP concentration and percentage of patients with a negative RF test were statistically significantly greater in the placebo group (Table 1). RF titers were only modestly elevated in the RF-positive patients (Table 1). In the adalimumab arm, RF-positive and RF-negative patients were similar in terms of the mean scores at baseline for dactylitis (2.6 vs 3.0, respectively) and enthesitis (0.8 vs 0.9), as well as the percentages of patients whose baseline dactylitis score and enthesitis score were both zero (30.0% vs 24.4%). At baseline, 62 patients (32 adalimumab, 30 placebo) had evaluable target lesions and were therefore eligible for psoriasis evaluations (Table 1).

Efficacy at Week 12

ACR response rates and core ACR assessments. At Week 12, 39% of adalimumab patients achieved an ACR20 response, compared with 16% of placebo patients ($\Delta = 23\%$, 95% CI 5%–41%, $p = 0.012$). Statistically significantly more adalimumab than placebo patients also achieved ACR50 (25% vs 2%; $p = 0.001$) and ACR70 (14% vs 0%; $p = 0.013$) responses at Week 12 (Figure 2). Reductions in the ACR components of pain, patient and physician global assessments of disease activity, and physical function (HAQ-DI) were all statistically significantly greater at Week 12 for adalimumab versus placebo patients (Table 2). Patients in the adalimumab group had a numerically greater mean reduction in CRP concentration at Week 12, compared with placebo patients (–0.5 vs 0.0; $p = 0.051$). The mean reductions in SJC and TJC were numerically greater in the adalimumab group (–5.7 for SJC and –9.7 for TJC) compared with the placebo group (–1.9 for SJC and –6.2 for TJC), but the differences were not statistically significant (Table 2).

The ACR20 response rate was greater for adalimumab than placebo by Week 2 (Figure 3A), with the difference becoming statistically significant by Week 4 ($p = 0.001$). Statistically significant differences in the response rates were first observed at Week 4 for ACR50 ($p \leq 0.05$; Figure 3B) and Week 12 for ACR70 ($p \leq 0.05$; Figure 3C). For adalimumab patients, the Week 12 ACR20/50/70 response rates were similar for those who at baseline were receiving MTX compared to those who were not; were versus were not receiving a DMARD; were versus were not receiving an NSAID; and were versus were not receiving oral corticosteroids (data not shown). In addition, they were similar for patients who were RF-positive (40/30/10; n = 10) versus RF-negative (39/24/15;

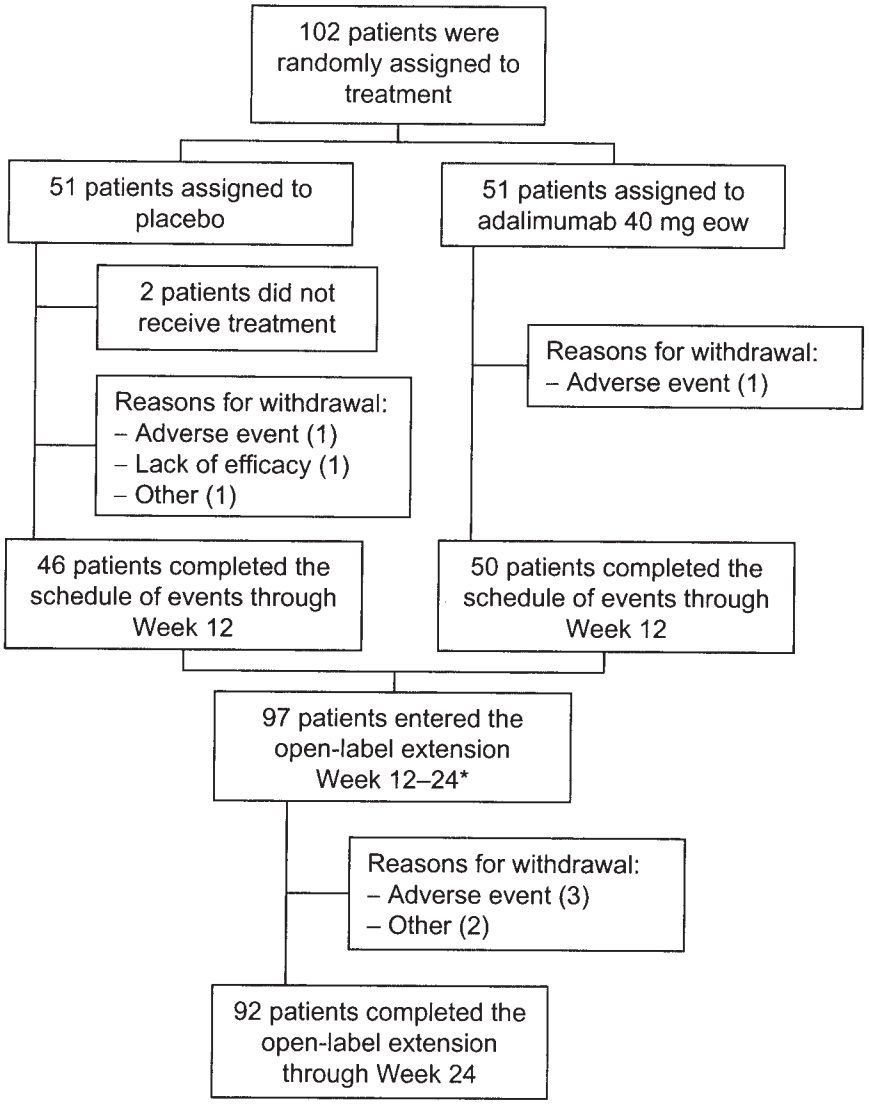

Figure 1. Patient disposition. *One patient discontinued the blinded trial because of diverticulitis, but was allowed to enter the open-label extension. eow: every other week.

n = 41), and for those who had a baseline serum CRP concentration ≥ 1 mg/dl (47/27/7; n = 15) versus < 1 mg/dl (36/25/17; n = 36). The Week 12 ACR20 response rate for adalimumab was greater for the 29 men (52%) than for the 22 women (23%).

PsARC, dactylitis, and enthesitis assessments. Efficacy of adalimumab in treating the signs and symptoms of PsA-associated musculoskeletal disease was assessed via several additional measures (Table 2). At Week 12, the PsARC response rate for the adalimumab group (51%) was statistically significantly greater than for the placebo group (24%) ($p = 0.007$). At Week 12, adalimumab led to numerically greater mean reductions, compared with placebo, in the dactylitis score (mean change –2.4 for adalimumab vs –1.4 for placebo; $p > 0.05$) and the enthesitis score (–0.5 vs –0.2; $p > 0.05$).

Psoriasis assessments. At Week 12, the mean target lesion score had decreased from baseline by 3.7 units for adalimumab patients compared with 0.3 units for placebo patients ($p \leq 0.001$; Table 2). At Week 12, the physician global assessment for psoriasis was "Clear" or "Minimal" for significantly more adalimumab patients (40.6%, 13/32) than placebo patients (6.7%, 2/30) ($p = 0.002$; Table 2).

Quality of life assessments. At Week 12, significant mean improvements from baseline in the Physical Functioning ($p = 0.027$), Bodily Pain ($p = 0.007$), General Health ($p = 0.017$), and Mental Health ($p = 0.009$) domains of the SF-36 were observed for adalimumab compared with placebo (data not shown). Numerically greater mean improvements were also observed for adalimumab, compared with placebo, in the Vitality domain ($p = 0.070$), and the Role–Physical, Social

Table 1. Baseline demographic and clinical characteristics.

Characteristic	Placebo, N = 49	Adalimumab 40 mg eow, N = 51
Age, yrs	47.7 ± 11.3	50.4 ± 11.0
Male, n (%)	25 (51.0)	29 (56.9)
Caucasian, n (%)	46 (93.9)	50 (98.0)
Weight, kg	88.5 (21.1)	91.5 (22.5)
Rheumatoid factor-negative, n (%)*	48 (98.0)	41 (80.4)
Duration of psoriasis, yrs	13.8 ± 10.7	18.0 ± 13.2
Duration of psoriatic arthritis, yrs	7.2 ± 7.0	7.5 ± 7.0
Moll and Wright subtype, n (%)		
Symmetric polyarthritis	41 (83.7)	42 (82.4)
Asymmetric oligoarthritis	7 (14.3)	5 (9.8)
Distal interphalangeal arthropathy	0	3 (5.9)
Spondylitis	1 (2.0)	1 (2.0)
Arthritis mutilans	0	0
Dactylitis (overall severity)	2.5 ± 4.3	2.9 ± 5.1
Enthesitis (total sites)	1.0 ± 1.3	0.9 ± 1.2
Medications		
Use of previous DMARD, n (%)	49 (100)	51 (100)
Use of DMARD at baseline, n (%)	33 (67.3)	33 (64.7)
Mean no. of previous DMARD, n	2.1 ± 1.3	1.7 ± 0.9
Use of previous methotrexate, n (%)	39 (79.6)	41 (80.4)
Use of methotrexate at baseline, n (%)	23 (46.9)	24 (47.1)
Use of previous NSAID, n (%)	48 (98.0)	46 (90.2)
Use of NSAID at baseline, n (%)	42 (85.7)	37 (72.6)
Use of previous oral corticosteroids, n (%)	15 (30.6)	10 (19.6)
Use of oral corticosteroids at baseline, n (%)	9 (18.4)	4 (7.8)
Core ACR Assessments		
Swollen joint count (0–76)	18.4 ± 12.1	18.2 ± 10.9
Tender joint count (0–78)	29.3 ± 18.1	25.3 ± 18.3
Patient assessment of pain (0–100 mm VAS)	49.1 ± 23.5	43.3 ± 23.4
Patient global assessment of disease activity (0–100 mm VAS)	46.3 ± 24.6	42.9 ± 22.4
Physician global assessment of disease activity (0–100 mm VAS)	57.1 ± 16.2	52.5 ± 17.1
HAQ-DI (0–3)	1.0 ± 0.7	0.9 ± 0.5
C-reactive protein, mg/dl†,	1.6 ± 1.7	1.0 ± 1.0
median (range)	0.9 (0.0–7.0)	0.7 (0.0–4.5)
Quality of life assessments		
SF-36 Physical Component Summary score (0–100)	32.7 ± 11.3	34.9 ± 9.2
FACIT-F score (0–52)	31.1 ± 12.3	34.5 ± 10.9
Target lesion assessments	n = 30	n = 32
Target lesion, n (%)	30 (61.2)	32 (62.7)
Target lesion score (0-15)	8.1 ± 2.3	7.9 ± 1.8
Dermatology Life Quality Index acore (0–30)	6.2 ± 5.8	7.6 ± 6.3
Physician global assessment for psoriasis (“Clear” or “Almost clear”), n (%)	0	1 (3.1)

Values are mean ± SD unless otherwise noted. * $p \leq 0.01$ based on a Fisher’s exact test; the median RF value for the 10 RF-positive adalimumab patients was 48.5 international units (IU)/ml (range 15–336; 9 patients ≤ 93 IU/ml); the RF value for the RF-positive placebo patient was 18.0 IU/ml. † $p \leq 0.05$ based on analysis of variance with baseline DMARD use and treatment as factors. P values not calculated for medication related categories; elsewhere, $p > 0.05$ unless otherwise indicated. ACR: American College of Rheumatology; DMARD: disease-modifying antirheumatic drugs; eow: every other week; FACIT-F: 13-item fatigue scale of the Functional Assessment of Chronic Illness Therapy measure; HAQ-DI: Health Assessment Questionnaire Disability Index; NSAID: nonsteroidal antiinflammatory drugs; SF-36: Short Form 36 Health Survey; VAS: visual analog scale.

Functioning, and Role–Emotional domains (all $p > 0.10$) of the SF-36 (data not shown). At Week 12, numerically greater mean improvements were observed for adalimumab versus placebo in the SF-36 PCS scores (5.7 vs 2.8; $p = 0.082$) and to a lesser degree in the MCS (1.1 vs –0.6; $p = 0.242$) (Table 2).

During the first 12 weeks of therapy, the FACIT-F scores of the 2 treatment groups improved by similar amounts, although each increased by < 4 units, the amount needed to be clinically meaningful (Table 2)[24]. The adalimumab group exhibited a numerically greater improvement in the DLQI from baseline

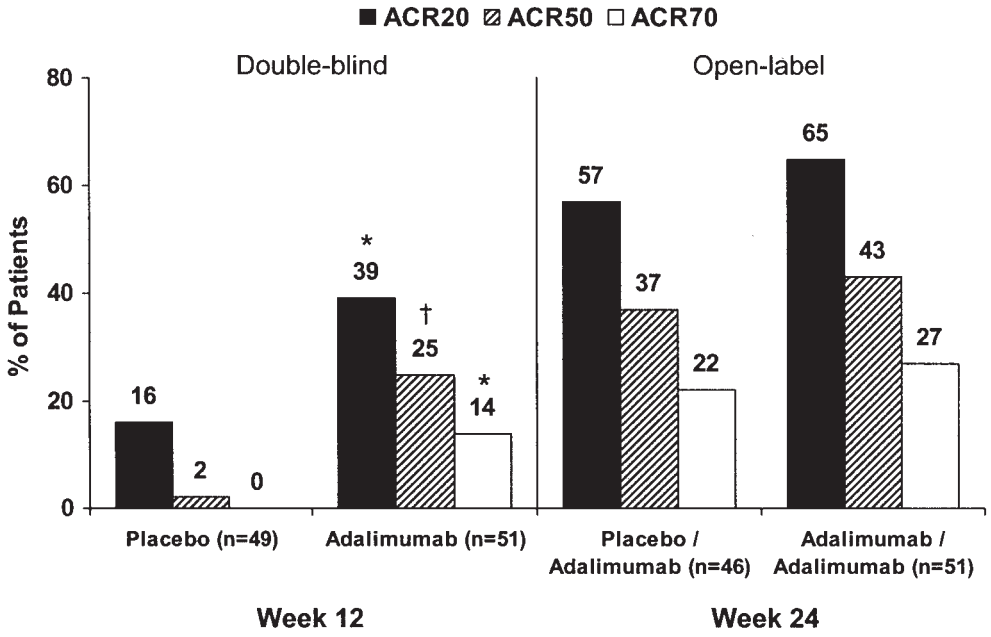

Figure 2. Percentages of patients with PsA who met ACR criteria for 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvements in arthritis at Weeks 12 and 24. *$p < 0.05$ vs placebo; †$p \leq 0.001$ vs placebo, based on Fisher's exact test combining baseline DMARD use categories. P values not calculated for results beyond Week 12. Missing responses were counted in the nonresponder category.

to Week 12 versus placebo, with mean changes from baseline of –3.4 versus –1.7 ($p = 0.171$; Table 2).

Efficacy at Week 24

Arthritis assessments during the open-label period. After 24 weeks of therapy (12 weeks double-blind plus 12 weeks open-label), the ACR20/50/70 response rates for the 51 adalimumab patients were 65%, 43%, and 27% (n = 51), indicating that their arthritis continued to improve beyond Week 12. For the 46 patients who had initially received placebo and started adalimumab at Week 12, rapid improvement occurred during open-label therapy, with ACR20/50/70 rates of 57%, 37%, and 22% observed at Week 24 (Figures 2 and 3). During open-label treatment, scores for the components of the ACR core criteria — SJC, TJC, patient's assessment of pain, and patient and physician assessments of disease activity — continued to improve for adalimumab patients and showed a markedly increased rate of improvement for placebo patients, with similar total improvements observed for the 2 groups at Week 24 (Table 2). PsARC responses were observed at Week 24 in 70% of patients in the placebo/adalimumab group and 75% in the adalimumab arm (Table 2). The mean changes in the HAQ-DI scores from baseline to Weeks 12 and 24 were –0.1 and –0.4 for the placebo/adalimumab group, and –0.3 and –0.3 for patients in the adalimumab arm (Table 2). By Week 24, mean CRP concentrations had decreased from baseline by 1.3 mg/dl for patients in the placebo/adalimumab group and 0.5 mg/dl for patients in the adalimumab arm (Table 2).

Psoriasis assessments during the open-label period. From Week 12 to Week 24, the percentages of patients who had achieved physician global assessments of "Clear" or "Minimal" increased by 43 percentage points (from 6.7% to 50.0%) for placebo patients treated with open-label adalimumab, and by 16 percentage points (from 40.6% to 56.3%) for patients in the adalimumab arm (Table 2). From Week 12 to Week 24, target lesion scores decreased by 4.4 and 0.8 for patients from the placebo and adalimumab arms, respectively, resulting in total improvements from baseline of 4.7 and 4.5 (Table 2).

Quality of life assessments during the open-label period. After Week 12, the SF-36 PCS score began to improve markedly for adalimumab patients from the placebo arm, and continued to improve for patients from the adalimumab arm, resulting in mean increases from baseline to Week 24 of 11.7 and 8.6, respectively (Table 2). By Week 24, a small mean improvement was observed in the SF-36 MCS score for patients from each arm (Table 2). For patients from the placebo and adalimumab arms, the mean improvements in the FACIT-F scores from baseline to Week 24 were 5.6 and 2.9, respectively, and the mean changes in the DLQI were –3.9 and –3.5 (Table 2).

Adverse events through Week 12. The incidence of AE reported during the 12 weeks of double-blind therapy was statistically significantly lower for adalimumab (52.9%) compared to placebo (79.6%) ($p \leq 0.01$; Table 3). The incidences of AE attributed to study drug during the first 12 weeks were 27.5% for adalimumab and 28.6% for placebo. The incidences of AE

Table 2. Changes from baseline in secondary efficacy measurements.

Assessment	Week 12			Week 24	
	Placebo, n = 49	Adalimumab, n = 51	p*	Placebo/ Adalimumab, n = 46	Adalimumab/ Adalimumab, n = 51
Core ACR assessments					
Swollen joint count (0–76)	–1.9 ± 11.5	–5.7 ± 13.7	0.140	–9.4 ± 13.9	–9.1 ± 11.3
Tender joint count (0-78)	–6.2 ± 10.3	–9.7 ± 17.3	0.231	–19.3 ± 14.5	–15.7 ± 17.0
Patient assessment of pain (0–100 mm VAS)	0.2 ± 23.1	–15.4 ± 25.6	0.002	–24.8 ± 24.4	–19.6 ± 25.4
Patient global assessment of disease activity (0-100 mm VAS)	–0.4 ± 24.9	–14.8 ± 24.5	0.004	–19.8 ± 25.9	–20.6 ± 24.0
Physician global assessment of disease activity (0–100 mm VAS)	–9.7 ± 18.2	–21.4 ± 22.4	0.005	–32.3 ± 20.9	–33.5 ± 19.5
HAQ-DI (0–3)	–0.1 ± 0.3	–0.3 ± 0.5	0.010	–0.4 ± 0.4	–0.3 ± 0.5
C-reactive protein, mg/dl	0.0 ± 1.4	–0.5 ± 1.2	0.051	–1.3 ± 1.5	–0.5 ± 0.8
Additional PsA assessment					
PsARC, n (%)†	12 (24)	26 (51)	0.007	32 (70)	38 (75)
Psoriasis assessments					
Target lesion score (0–15)	n = 30	n = 32		n = 30	n = 32
	–0.3 ± 3.1	–3.7 ± 3.3	< 0.001	–4.7 ± 3.5	–4.5 ± 3.3
Physician global assessment for psoriasis	n = 30	n = 32		n = 26	n = 32
("Clear"/"Minimal"), n (%)†	2 (6.7)	13 (40.6)	0.002	13 (50.0)	18 (56.3)
Dermatology Life Quality Index score (0–30)	n = 28	n = 32		n = 26	n = 32
	–1.7 ± 5.3	–3.4 ± 4.5	0.171	–3.9 ± 6.4	–3.5 ± 5.1
Quality of life assessments					
SF-36 PCS (0–100)	n = 45	n = 49		n = 40	n = 50
2.8 ± 7.1	2.8 ± 7.1	5.7 ± 8.5	0.082	11.7 ± 9.1	8.6 ± 7.4
SF-36 MCS (0–100)	n = 45	n = 49	0.242	n = 40	n = 50
	–0.6 ± 7.8	1.1 ± 7.4		0.3 ± 9.7	1.9 ± 8.2
FACIT-F score (0–52)	n = 46	n = 49		n = 41	n = 50
	2.3 ± 6.7	2.6 ± 7.1	0.783	5.6 ± 9.2	2.9 ± 8.0

Values are mean change from baseline (± SD), unless otherwise noted. * p values for differences between treatment groups are based on a 2-way analysis of variance model with treatment group and baseline DMARD use as factors, unless otherwise noted. † Based on Cochran-Mantel-Haenszel mean score test with baseline DMARD use as the stratification factor. FACIT-F: 13-item fatigue scale of the Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire Disability Index; MCS: Mental Component Summary; PCS: Physical Component Summary; PsARC: modified Psoriatic Arthritis Response Criteria; SF-36: Short Form-36 Health Survey; VAS: visual analog scale.

reported during the first 12 weeks by ≥ 5% of patients in either group were similar, with the exception of "psoriasis aggravated" and "psoriatic arthropathy aggravated," which were reported statistically significantly more frequently by placebo-treated patients (Table 3).

During the first 12 weeks, most AE were mild or moderate, and there were 3 serious AE and 3 AE that led to study discontinuation (Table 3). Two serious AE occurred in placebo patients, both of whom required hospitalization, one for intravenous antibiotic treatment of a sublingual abscess, and the other for excision of a benign periganglioma neoplasm. The only adalimumab patient who experienced a serious AE during the first 12 weeks was hospitalized for treatment of diverticulitis, and discontinued study medication. This patient was allowed to continue in the open-label phase. Two placebo patients discontinued study medication, one because of aggravated psoriatic arthropathy, and the other because of injection-site reaction. All three patients recovered from their AE. The incidence of infectious AE to Week 12 was greater in the placebo group (32.7% vs 17.6%). The only serious infectious AE occurred in a placebo patient. Changes in laboratory values and vital signs were not clinically significant. One placebo patient had elevations of aspartate aminotransferase and alanine transaminase (ALT) concentrations > 3 times the upper limit of normal that resolved spontaneously prior to open-label adalimumab. During the first 12 weeks, there were no cases of tuberculosis, granulomatous infection, demyelination, drug induced lupus, congestive heart failure, or malignancy and there were no deaths.

Adverse events Weeks 12–24. During the open-label period of study, the rates of AE (54.6%), serious AE (3.1%), and AE leading to discontinuation of adalimumab (6.2%) were consistent with those observed during the double-blind period (Table 3). The 3 serious AE comprised one case of renal failure associated with rhabdomyolysis and 2 cases of noncutaneous cancer (see below). During the open-label period, there were no serious infectious AE, and the overall rate of infectious AE (29.9%) was similar to that observed for all patients (placebo and adalimumab) during the blinded period (25.0%; Table 3). During the open-label period, 2 additional types of AE were reported in ≥ 5% of all patients: cough (n = 6, 6.2%) and nasopharyngitis (n = 5, 5.2%). One patient from the adalimumab arm had an ALT elevation > 3 times upper limit of normal in the open-label extension that resolved following

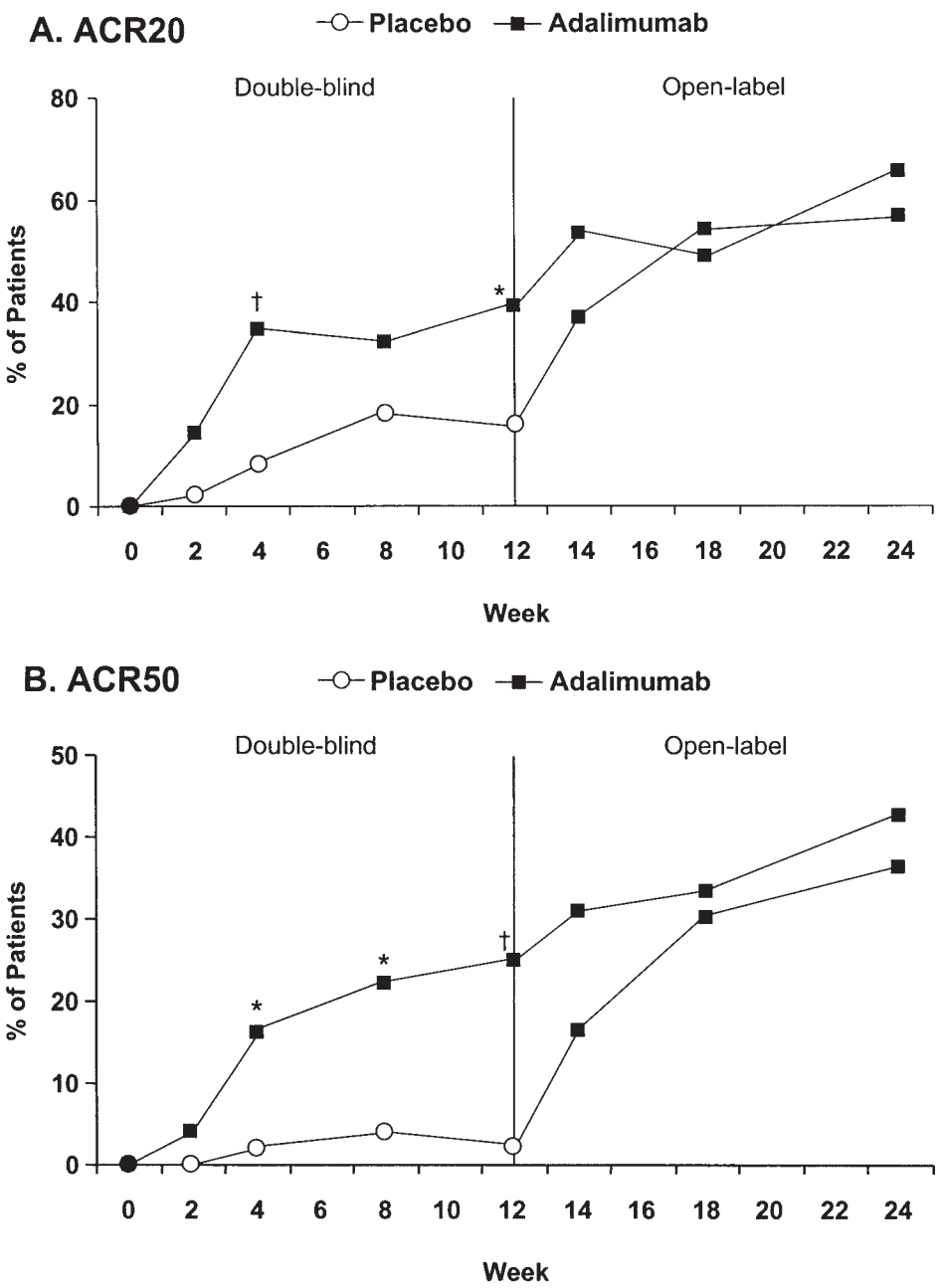

Figure 3. Percentages of patients with PsA who met ACR criteria for 20% (ACR20, panel A), 50% (ACR50, panel B), and 70% (ACR70, panel C, next page) improvements over time. *$p < 0.05$; †$p \leq 0.001$, based on Fisher's exact text combining baseline DMARD use categories. P values not calculated for results beyond Week 12. Missing responses were counted in the nonresponder category.

discontinuation of study drug. From Week 12 to Week 24, there were no cases of tuberculosis, granulomatous infection, demyelination, drug induced lupus, or congestive heart failure. During this period, cancers were reported in 3 patients from the placebo arm, with one case each of non-Hodgkin's lymphoma (NHL), squamous cell carcinoma of the skin, and adenocarcinoma of the prostate, diagnosed 3 days, 3 days, and 83 days, respectively, after administration of the first dose of adalimumab. In retrospect, the NHL was visible on a radiograph obtained before the patient had received adalimumab. No patient died during Weeks 12 to 24.

DISCUSSION

This report describes a 12-week, randomized, double-blind, placebo controlled trial with a 12-week period of open-label extension that evaluated adalimumab therapy in 100 adult

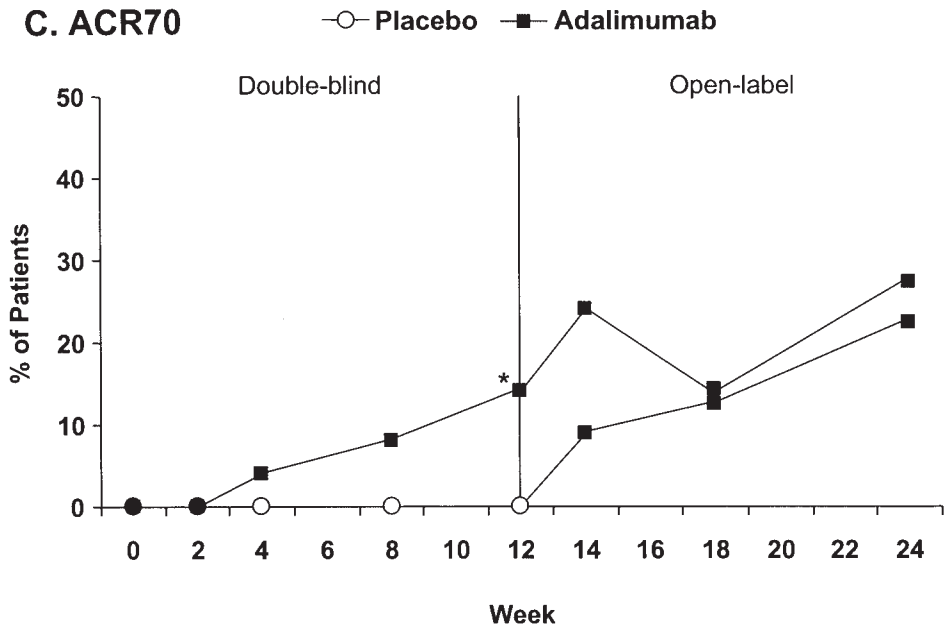

Figure 3. Continued

patients with moderate to severe PsA who had failed DMARD therapy. The results demonstrate that adalimumab was efficacious in reducing the signs, symptoms, and functional disability of PsA, as well as the severity of the associated psoriasis. Adalimumab was observed to be generally safe and well tolerated over 24 weeks of use.

Our study was the second Phase III trial to investigate the safety and efficacy of adalimumab in patients with moderately to severely active PsA. The first such trial was ADEPT, which assessed treatment in 313 patients who had failed to respond adequately to NSAID therapy[20]. Both trials studied patients with long-standing disease in a 2-arm protocol comparing adalimumab 40 mg eow with placebo. In each study, about half of patients received concomitant MTX at baseline. Concomitant use of other DMARD was permitted only in the present study. In ADEPT, the ACR20 response rates following 12 and 24 weeks of blinded treatment with adalimumab were 58% and 57%, respectively[20]. In the present study, the ACR20

Table 3. Adverse events (AE).

	Double-Blind, Weeks 0–12		Open-Label, Weeks 12–24
	Placebo, n = 49	Adalimumab 40 mg eow, n = 51	Adalimumab 40 mg eow, n = 97
Any AE	39 (79.6)*	27 (52.9)	53 (54.6)
Any serious AE	2 (4.1)	1 (2.0)	3 (3.1)
Any AE leading to discontinuation of study drug	2 (4.1)	1 (2.0)	6 (6.2)
Any infectious AE	16 (32.7)	9 (17.6)	29 (29.9)
Any serious infectious AE	1 (2.0)	0	0
AE reported by ≥ 5% of patients in either double-blind group			
Upper respiratory tract infection NOS	4 (8.2)	7 (13.7)	6 (6.2)
Injection-site pain	6 (12.2)	6 (11.8)	0
Psoriasis aggravated	8 (16.3)††	2 (3.9)	4 (4.1)
Diarrhea NOS	3 (6.1)	1 (2.0)	2 (2.1)
Back pain	3 (6.1)	1 (2.0)	2 (2.1)
Psoriatic arthropathy aggravated	7 (14.3)††	1 (2.0)	1 (1.0)
Headache NOS	3 (6.1)	0	3 (3.1)

Values indicate number of patients (%). † Includes each type of AE that occurred in ≥ 5% of placebo group or ≥ 5% of adalimumab group during blinded treatment. During the open-label period, 2 additional types of AE were reported in ≥ 5% of the 97 patients, cough (n = 6, 6.2%) and nasopharyngitis (n = 5, 5.2%). * $p < 0.01$; †† $p \leq 0.05$ vs adalimumab based on Fisher's exact test. NOS: not otherwise specified; eow: every other week.

response rates were 39% following 12 weeks of blinded adalimumab; 65% for the same patients following 12 more weeks of adalimumab, given open-label; and 57% for patients from the placebo arm following 12 weeks of open-label treatment with adalimumab. ACR50 and ACR70 rates in the present trial at 24 weeks, and in ADEPT at 12 and 24 weeks, were also similar. Both studies showed statistically significant improvements in the PsARC response with blinded adalimumab treatment. Thus, the present study and ADEPT both demonstrated the efficacy of adalimumab in treating the arthritis component of PsA.

The present study and ADEPT also both demonstrated that adalimumab was efficacious in improving psoriasis and physical function. In the present study, 12 weeks of adalimumab led to statistically significant improvements in the physician global assessment of psoriasis and in the target lesion score, with each being maintained through the open-label period to Week 24. In ADEPT, the Week 12 and Week 24 PASI50/75/90 response rates were statistically significantly greater for blinded adalimumab versus placebo, as was the improvement in the physician global assessment at Week 24[20]. In the present study, the mean changes in the HAQ-DI observed for adalimumab-arm patients at Weeks 12 and 24 (–0.3 and –0.3), and for placebo-arm patients following 12 weeks of open-label adalimumab (–0.4), were similar to the –0.4 mean change in the HAQ-DI observed in ADEPT following 12 and 24 weeks of blinded adalimumab treatment[20]. The absolute magnitude of these changes in HAQ-DI equal or exceed the minimum clinically important differences reported for PsA (0.3)[26] and RA (0.22)[27].

In both this study and ADEPT, there was evidence of a therapeutic effect following the first injection of adalimumab. However, during the first 12 weeks of this study, the response to adalimumab developed more slowly than expected, compared with (1) the greater response rates of these patients at Week 24, (2) the greater response rates observed for placebo-arm patients at Week 24, and (3) the greater response rates for ADEPT patients following 12 or 24 weeks of blinded adalimumab[20]. The reasons for the delayed response to blinded adalimumab are uncertain. Most baseline measures were similar for the adalimumab and placebo patients in this study. The 2 measures of disease activity with significant between-group differences at baseline — the percentage of RF-negative patients and the mean CRP concentration — were lower in the adalimumab arm, but subset analyses failed to reveal efficacy differences that could explain the Week 12 adalimumab results. Comparisons based on whether concomitant medications were used at baseline in this study were also uninformative. A greater ACR20 response rate with adalimumb was observed for men compared with women in this study, but the relevance of this observation is unclear because the patient numbers were small and the sexes were similarly represented in each treatment arm. Moreover, in the much larger study population of ADEPT, men and women had equal Week 12 ACR20 response rates: 58%[20,28]. Thus, the delayed response observed in the adalimumab arm of the present study was not observed elsewhere, and was probably a result of random effects unique to that small treatment group.

Adalimumab was generally safe and well tolerated during the blinded and open-label periods of the trial, as demonstrated by the incidence and severity of AE, the incidence of serious AE, the frequency of treatment discontinuations, and the results of laboratory monitoring. During the 12 weeks of blinded treatment, infections occurred in adalimumab patients about half as frequently as they did in placebo patients, but the difference was not statistically significant. Upper respiratory tract infections accounted for most of the infections reported during blinded adalimumab treatment, consistent with previous studies[29-31]. There were no cases of tuberculosis, granulomatous infection, demyelination, drug induced systemic lupus erythematosus, or congestive heart failure during the 24-week observation period reported here. No cancers were observed in adalimumab-arm patients over 24 weeks. Of the 3 cancers reported in patients from the placebo arm during the open-label period, one was retrospectively apparent prior to treatment with adalimumab, and one of the other 2 was diagnosed 3 days after the first adalimumab injection, making it unlikely that adalimumab had a causal role in at least 2 cases. The safety profile of adalimumab in this study was consistent with that reported in previous clinical studies of adalimumab in patients with PsA[20] and RA[29–32] and with that of other TNF antagonists in PsA[17,19].

Our study evaluated patients with active PsA who had had an inadequate response to DMARD therapy. It was the second Phase III trial to assess the efficacy and safety of adalimumab therapy for long-standing PsA. Despite the relatively small size of this study, adalimumab was found to have been well tolerated, to have significantly reduced the signs and symptoms of arthritis, and to have significantly improved psoriasis and disability.

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