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Radiographic, Clinical, and Functional Outcomes of Treatment With Adalimumab (a Human Anti–Tumor Necrosis Factor Monoclonal Antibody) in Patients With Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy

A Randomized, Placebo-Controlled, 52-Week Trial

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Objective. **Tumor necrosis factor (TNF) is an important proinflammatory cytokine that mediates inflammatory synovitis and articular matrix degradation in rheumatoid arthritis (RA). We investigated the ability of adalimumab, a human anti–TNF monoclonal antibody, to inhibit the progression of structural joint damage, reduce the signs and symptoms, and improve physical function in patients with active RA receiving concomitant treatment with methotrexate (MTX).**

Methods. **In this multicenter, 52-week, double-blind, placebo-controlled study, 619 patients with active RA who had an inadequate response to MTX were randomized to receive adalimumab 40 mg subcutaneously every other week (n = 207), adalimumab 20 mg subcutaneously every week (n = 212), or placebo (n = 200) plus concomitant MTX. The primary efficacy end points were radiographic progression at week 52 (total Sharp score by a modified method [TSS]), clinical response at week 24 (improvements of at least 20% in the American College of Rheumatology core criteria [ACR20]), and physical function at week 52 (disability index of the Health Assessment Questionnaire [HAQ]).**

Results. **At week 52, there was statistically significantly less radiographic progression, as measured by the change in TSS, in the patients receiving adalimumab either 40 mg every other week (mean ± SD change 0.1 ± 4.8) or 20 mg weekly (0.8 ± 4.9) as compared with that in the placebo group (2.7 ± 6.8) ($P \leq 0.001$ for each comparison). In addition, there were statistically significant changes in the components of the TSS. At week 24, ACR20 responses were achieved by 63% and 61% of patients in the adalimumab 40 mg every other week and 20 mg weekly groups, respectively, versus 30% of patients in the placebo group ($P \leq 0.001$ for each comparison). At week 52, ACR20 responses were achieved by 59% and 55% of patients taking adalimumab 40 mg every other week and 20 mg weekly, respectively, versus 24% of patients taking placebo ($P \leq 0.001$ for each comparison). At week 52, physical function as measured by the HAQ demonstrated statistically significant improvement with adalimumab 40 mg every other week and 20 mg weekly compared with placebo (mean change in HAQ score −0.59 and −0.61, respectively, versus −0.25; $P \leq 0.001$ for each comparison). A total of 467 patients (75.4%) completed 52 weeks of treatment. Adalimumab was generally well tolerated. Discontinuations occurred in 22.0% of adalimumab-treated patients and in 30.0% of placebo-treated patients. The rate of adverse events (both serious and nonserious) was comparable in the adalimumab and**

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placebo groups, although the proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8%) than in those receiving placebo (0.5%) ($P \leq 0.02$), and was highest in the patients receiving 40 mg every other week.

Conclusion. **In this 52-week trial, adalimumab was more effective than placebo at inhibiting the progression of structural joint damage, reducing the signs and symptoms, and improving physical function in patients with active RA who had demonstrated an incomplete response to MTX.**

Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by a progressive inflammatory synovitis of the joints which may result in erosion of articular cartilage and subchondral bone (1). Irreversible joint destruction frequently begins within the first year after disease onset (1), and 70% of patients exhibit radiographic disease progression after 2 years (2). Methotrexate (MTX), currently the standard traditional disease-modifying antirheumatic drug (DMARD) for RA, has been shown to improve the signs and symptoms of RA, as well as slow the progression of joint destruction in some patients (3). However, many patients fail to achieve an adequate or sustained response to MTX therapy. Consequently, MTX is often combined with other traditional DMARDs to improve outcomes.

Tumor necrosis factor (TNF) is a proinflammatory cytokine that plays a critical role in mediation of the inflammatory synovitis, articular matrix degradation, and bony erosions in RA and is an important molecular target for directed biologic intervention (4). Adalimumab (Humira; Abbott Laboratories, Parsippany, NJ), a biologic DMARD developed through phage-display biotechnology, is the first human (100% human peptide sequences) anti-TNF monoclonal antibody to be investigated for the treatment of RA (5–9). Structurally and functionally analogous to naturally occurring human IgG1, adalimumab has a terminal half-life comparable with that of human IgG1 (~14 days) and demonstrates a high specificity and affinity for TNF ($K_d = 6 \times 10^{-10}$ *M*). It does not bind other cytokines such as lymphotoxin. Adalimumab exerts its therapeutic effects by blocking the interaction of TNF with the p55 and p75 TNF cell surface receptors (5). Preliminary clinical trials have shown that adalimumab controls the signs and symptoms of RA (6–9) and has a positive effect on the long-term radiographic outcome (8).

The objective of this 52-week, double-blind, placebo-controlled study was to investigate whether the addition of adalimumab to a continuing regimen of MTX would provide additional radiographic, clinical, and functional benefits to patients who had active RA and had an incomplete response to MTX.

PATIENTS AND METHODS

Patients. Eligible patients were 18 years of age or older, had active RA diagnosed according to the 1987 revised American College of Rheumatology (ACR; formerly, American Rheumatism Association) criteria (10), and had ≥9 tender joints (of 68 evaluated), ≥6 swollen joints (of 66 evaluated), a C-reactive protein concentration >1 mg/dl, and either rheumatoid factor positivity or at least 1 joint erosion on radiographs of the hands and feet. Patients were required to have been on MTX therapy for ≥3 months at a stable dose of 12.5–25 mg/week (or ≥10 mg/week in patients intolerant to MTX) for ≥4 weeks. Major exclusion criteria consisted of prior use of anti-CD4 antibody therapy or TNF antagonists, a history of an active inflammatory arthritide other than RA, a history of active listeriosis or mycobacterial infection, a history of lymphoma or leukemia or other malignancy besides nonmelanoma skin cancer within 5 years, a major episode of infection (i.e., infections requiring hospitalization, treatment with intravenous antibiotics within 30 days prior to screening, or oral antibiotics within 14 days prior to screening), any uncontrolled medical condition, and pregnancy or breastfeeding.

Protocol. This 52-week, double-blind, parallel-group, placebo-controlled study was conducted at 89 sites in the United States and Canada. The institutional review board or research committee at each site approved the protocol, and patients gave their written informed consent. Tuberculin skin testing (using purified protein derivative [PPD]) was performed and standard chest radiographs were obtained prior to the baseline visit; patients with positivity for PPD were treated according to local recommendations.

Patients were randomly assigned to receive single self-injections (1.6 ml/injection) of adalimumab subcutaneously at 40 mg every other week (with placebo injections on alternate weeks), adalimumab subcutaneously at 20 mg every week, or placebo subcutaneously every week. The dosages used in this study were chosen to confirm the findings of an earlier phase II 3-month dose-finding study (11) that demonstrated the efficacy of weekly subcutaneous injections of adalimumab at 20 mg, 40 mg, and 80 mg doses. Results from this phase II study did not show an adalimumab dose of 80 mg to be superior to 40 mg. Furthermore, the half-life of adalimumab provided the rationale for the comparison of weekly dosing with every other week dosing. Patients who completed this study were eligible for an additional 52 weeks of open-label adalimumab treatment.

Traditional DMARDs other than MTX were discontinued at least 28 days prior to the study baseline. Doses and routes of administration of concomitant RA therapies, such as MTX, corticosteroids, and nonsteroidal antiinflammatory drugs (NSAIDs), were kept constant throughout the study. Oral corticosteroids, if used previously, were allowed at a maximum prednisone-dose equivalent of 10 mg/day. At week 16 or thereafter, patients who were not achieving an ACR20 response (improvements of at least 20% in the ACR core

criteria) were allowed to receive "rescue" treatment with a traditional DMARD at the discretion of their treating physician. Patients commencing other therapies after not achieving an ACR20 response were considered treatment failures for the purposes of clinical efficacy (determined by the ACR score for level of improvement) from that time onward. Patients who received rescue therapy and continued in the study were included in the radiographic analysis. After week 24, patients achieving an ACR20 response on 2 consecutive visits were permitted dose reductions in corticosteroids (as much as 1 mg of prednisone-dose equivalent every 2 weeks) or NSAIDs. Increases in corticosteroid doses were not permitted. One intraarticular corticosteroid injection was allowed between baseline and week 16, and 2 intraarticular corticosteroid injections were allowed between weeks 24 and 44.

Radiographic assessment. Posteroanterior radiographs of the hands/wrists and anteroposterior radiographs of the feet were performed at screening and at weeks 24 and 52, or at the last visit for patients who terminated participation in the study prior to week 52. Missing radiograph values at week 52 were imputed via linear extrapolation using data collected at baseline and week 24 or at the early-termination visit.

Radiographs were assessed using a modified version of the Sharp method (12–14). Digitized images were scored by 2 physicians who were blinded to the treatment, chronologic order, and clinical response of each patient. Erosion scores were recorded for each hand/wrist (17 joints) and each forefoot (6 joints) on a 6-point scale (0 = no erosions; 1 = 1 discrete erosion or ≤20% joint involvement; 2 = 2 separate quadrants with erosion or 21–40% joint involvement; 3 = 3 separate quadrants with erosion or 41–60% joint involvement; 4 = all 4 quadrants with erosion or 61–80% joint involvement; and 5 = extensive destruction with >80% joint involvement). Joint space narrowing scores were recorded for each hand/wrist (16 joints) and each forefoot (5 joints) on a 5-point scale (0 = no narrowing; 1 = up to 25% narrowing; 2 = 26–65% narrowing; 3 = 66–99% narrowing; and 4 = complete narrowing). To determine the modified total Sharp score for each patient, the total erosion score (scale 0–230) and the joint space narrowing score (scale 0–168) were added (total Sharp score scale 0–398).

Clinical assessment. ACR20 responses as well as responses according to the 50% and 70% improvement levels (ACR50 and ACR70, respectively) (15) were assessed at weeks 2 and 4, every 4 weeks from week 4 to week 24, every 8 weeks from week 24 to week 48, and a final time at week 52. The ACR20 response at week 24 was the primary end point, and patients who did not achieve an ACR20 response, who withdrew from the study, or who received additional traditional DMARD therapy on or after week 16 were classified as nonresponders.

Physical function and health-related quality of life assessments. Physical function was assessed at baseline and at each visit using the disability index of the Health Assessment Questionnaire (HAQ) (16). Health-related quality of life was assessed at baseline and at weeks 12, 24, and 52 using the Medical Outcomes Study 36-item Short Form health survey (SF-36) (17).

Safety assessment. Safety was assessed through recording of adverse events, physical examinations, and standard laboratory tests. At baseline and at weeks 24 and 52, serum titers of antinuclear antibodies (ANAs) (positive titer ≥1:80) and anti–double-stranded DNA (anti-dsDNA) antibodies (positive titer >3.5 IU/ml, determined only if ANAs were elevated from baseline) were established by immunofluorescence on Hep-2 cells and by Farr radioimmunoassay, respectively. At baseline and at weeks 24 and 52, serum titers of anti-adalimumab antibodies (positive titer >20 ng/ml and not suppressed by ≥50% after the addition of human serum) were determined by a double-antigen immunoassay (9).

Statistical analysis. The power calculation was based on both the predicted ACR20 response rate and radiographic findings. A sample size of 200 patients per treatment group was estimated to provide >95% power for detecting a difference of ≥20% in ACR20 response rates at week 24 between the placebo group and the adalimumab groups at a significance level of $\alpha = 0.05$, assuming a placebo response rate of 35%. Assuming that 70% of patients would have evaluable radiograph films at 12 months, a sample size of 140 patients per treatment group was estimated to provide 90% power for detecting a difference in the mean increase in the modified total Sharp scores at a significance level of $\alpha = 0.05$, assuming a mean change of 2.0 in the placebo group, 0.5 in each adalimumab group, and a pooled standard deviation of 4.0. The study, however, was not powered to distinguish differences between adalimumab groups.

Demographic and baseline clinical characteristics were analyzed by Kruskal-Wallis test for continuous variables and Pearson's chi-square test for discrete variables. An intent-to-treat population was formed for efficacy analyses and was defined as all patients who received at least 1 dose of study drug. The primary efficacy end points were the ACR20 response rate at week 24, the change in modified total Sharp scores at week 52, and the change in HAQ scores at week 52. The analysis for ACR response was nonresponder imputation (NRI), in which nonresponders were patients who did not achieve an ACR20 response, who withdrew from the study, or who received additional traditional DMARD therapy on or after week 16. The 3 primary efficacy end points were analyzed in hierarchic order, beginning with the ACR20 response rates, followed by the modified total Sharp scores, and ending with HAQ scores. A closed testing procedure was chosen to control the overall significance level at 0.05. An initial global null hypothesis was tested for the first hierarchic primary efficacy end point, the ACR20 response. If this was significant ($P \leq 0.05$), pairwise comparisons between each adalimumab group and the placebo group would be performed. If all individual hypothesis tests were significant, then a repeat of the aforementioned testing procedure for the second hierarchic primary efficacy end point, the modified total Sharp score, would be done. This was repeated a third time for the HAQ if the modified Sharp score showed a significant difference.

Tests of normality for the change from baseline in the total Sharp score and HAQ score were conducted using the Shapiro-Wilk test. If the data were normal, analysis of covariance (ANCOVA) would be performed. Otherwise, a nonparametric approach (i.e., ranked ANCOVA) would be performed, with the baseline erosion score or baseline HAQ score as the covariate. Missing Sharp score values were imputed by linear extrapolation from baseline and week 24 to week 52. Changes from baseline to the last observation carried forward in the mean erosion scores, joint space narrowing scores, HAQ

Table 1. Demographic and clinical characteristics at baseline*

Characteristic	Adalimumab 40 mg every other week plus MTX (n = 207)	Adalimumab 20 mg weekly plus MTX (n = 212)	Placebo plus MTX (n = 200)
Demographics			
Age, years	56.1 ± 13.5	57.3 ± 10.5	56.1 ± 12.0
Female, no. (%)	158 (76.3)	160 (75.5)	146 (73.0)
White, no. (%)	173 (83.6)	181 (85.4)	166 (83.0)
Disease duration, years	11.0 ± 9.2	11.0 ± 9.4	10.9 ± 8.8
ACR core set			
Tender joint count (0–68 scale)	27.3 ± 12.7	27.9 ± 13.6	28.1 ± 13.8
Swollen joint count (0–66 scale)	19.3 ± 9.8	19.6 ± 9.9	19.0 ± 9.5
Patient's assessment of pain, mm (0–100-mm VAS)†	55.9 ± 20.4	55.2 ± 23.0	56.3 ± 22.9
Patient's global assessment of disease activity, mm (0–100-mm VAS)‡	52.7 ± 21.0	51.9 ± 23.1	54.3 ± 22.9
Physician's global assessment of disease activity, mm (0–100-mm VAS)‡	62.0 ± 16.7	61.6 ± 16.8	61.3 ± 17.3
HAQ score (0–3 scale)§	1.45 ± 0.63	1.44 ± 0.64	1.48 ± 0.59
C-reactive protein, mg/dl (normal <0.8)	1.8 ± 2.3	1.4 ± 1.4	1.8 ± 2.1
Radiographic			
Modified total Sharp score (0–398 scale)¶	72.1 ± 60.7	66.4 ± 56.3	66.4 ± 47.4
Erosion score (0–230 scale)¶	41.4 ± 33.4	36.7 ± 31.4	37.2 ± 25.8
Joint space narrowing score (0–168 scale)¶	30.7 ± 29.2	29.7 ± 26.9	29.2 ± 24.5
Rheumatoid factor			
Serum concentration, IU/ml (normal <60)	272.8 ± 422.1	309.0 ± 589.4	457.0 ± 910.1
% positive at screening	81.6	81.2	89.5
SF-36 scores (0–100 scale)#			
Physical function	38.6 ± 22.6	38.0 ± 23.8	34.9 ± 21.7
Physical role	24.0 ± 35.1	23.5 ± 34.5	24.4 ± 33.8
Body pain	37.0 ± 16.2	38.6 ± 17.7	37.3 ± 17.4
General health	50.5 ± 20.0	49.4 ± 21.1	48.6 ± 20.8
Vitality	36.2 ± 20.2	37.2 ± 19.8	32.6 ± 19.9
Social function	62.9 ± 26.5	64.6 ± 25.9	61.2 ± 27.1
Emotional role	60.0 ± 42.7	58.3 ± 44.7	59.9 ± 44.2
Mental health	70.1 ± 18.1	70.0 ± 19.9	69.1 ± 19.8
DMARD therapy			
Weekly MTX dose, mg/kg			
Mean	16.7 ± 4.5	16.3 ± 4.6	16.7 ± 4.1
Median	15.0	15.0	15.0
Mean number of previous DMARDs, including MTX	2.4	2.4	2.4

* There were no statistically significant differences in any demographic or baseline characteristic between the placebo group and the 2 adalimumab dosage groups (by Kruskal-Wallis test for continuous variables and Pearson's chi-square test for discrete variables). Except where indicated otherwise, values are the mean ± SD. MTX = methotrexate; ACR = American College of Rheumatology; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; SF-36 = Medical Outcomes Study Short Form 36-item health survey; DMARDs = disease-modifying antirheumatic drugs.
† 0 = no pain and 100 = severe pain.
‡ 0 = no disease activity and 100 = extreme disease activity.
§ 0 = no difficulty and 3 = unable to perform activity.
¶ Greater scores indicate more radiographic evidence of joint damage.
# Greater scores indicate better functioning.

scores, SF-36 scores, and other ACR core criteria were evaluated using ANCOVA, with the baseline value as the covariate. Pearson's chi-square test was used to test the differences in ACR20, ACR50, and ACR70 responses (by NRI) between treatment groups. Values are reported as the mean ± SD.

RESULTS

Patient characteristics. Among the 795 patients screened, 619 were randomized to receive 1 of the 3 treatment regimens. Baseline demographic and clinical characteristics were well balanced across the 3 treatment groups (Table 1). The patient population had moderate to severe, long-standing, DMARD-resistant RA. The mean disease duration was 10.9 years, and mean tender and swollen joint counts were 27.8 (of 68) and 19.3 (of 66), respectively. The mean MTX dose was 16.6 mg/week. The mean modified total Sharp score, erosion score, and joint space narrowing score was 68.3 (scale 0–398), 38.4 (scale 0–230), and 29.9 (scale 0–168), respectively. There was no difference in the mean number of previous DMARDs,

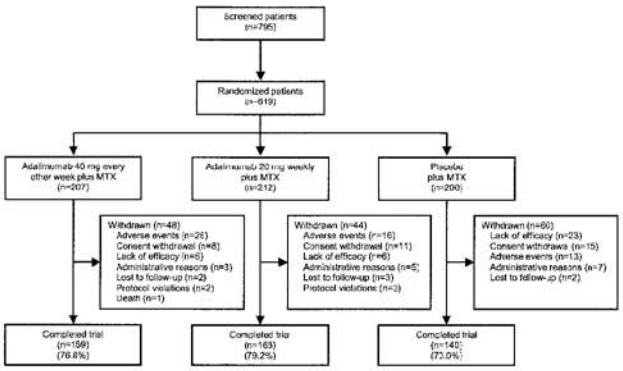

Figure 1. Profile of trial involving treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) as compared with placebo in patients with active rheumatoid arthritis receiving concomitant methotrexate (MTX) therapy.

which included MTX, between adalimumab-treated patients and placebo-treated patients (mean 2.4 for both). A total of 188 adalimumab-treated patients (44.9%) and 99 placebo-treated patients (49.5%) received oral corticosteroids at some point during the study. In addition, there were no substantial differences in terms of the types of previous DMARDs used between each adalimumab group and the placebo group.

Per protocol, the investigators were advised to follow the Centers for Disease Control and Prevention prophylaxis guidelines for the treatment of latent tuberculosis. At baseline, 2.6% of the adalimumab-treated patients (11 of 419) and 3.5% of the placebo-treated patients (7 of 200) were PPD positive. Among the PPD-positive patients, prophylaxis therapy was administered to 5 patients (1.2%) in the adalimumab group and 7 patients (3.5%) in the placebo group; not all of the PPD-positive patients received prophylaxis, for a variety of reasons, including prior prophylaxis, possible liver toxicity, or past BCG vaccination.

Disposition. A total of 467 patients (75.4%) completed 52 weeks of treatment (Figure 1). Discontinuations occurred in 92 patients (22.0%) in the adalimumab groups and 60 patients (30.0%) in the placebo group. Twelve adalimumab-treated patients (2.9%) and 23 placebo-treated patients (11.5%) withdrew because of lack of efficacy. Forty-two adalimumab-treated patients (10.0%) and 13 placebo-treated patients (6.5%) discontinued treatment because of adverse events.

Radiographic data on 88.4% of patients treated with adalimumab 40 mg every other week (183 of 207), 92.5% of patients treated with adalimumab 20 mg weekly (196 of 212), and 86.0% of patients treated with placebo (172 of 200) were analyzed. Of the radiographic findings analyzed, 52-week radiographic data were not available for 9.8% of the patients in the 40 mg adalimumab group (18 of 183), 6.6% of the patients in the 20 mg adalimumab group (13 of 196), and 6.4% of the

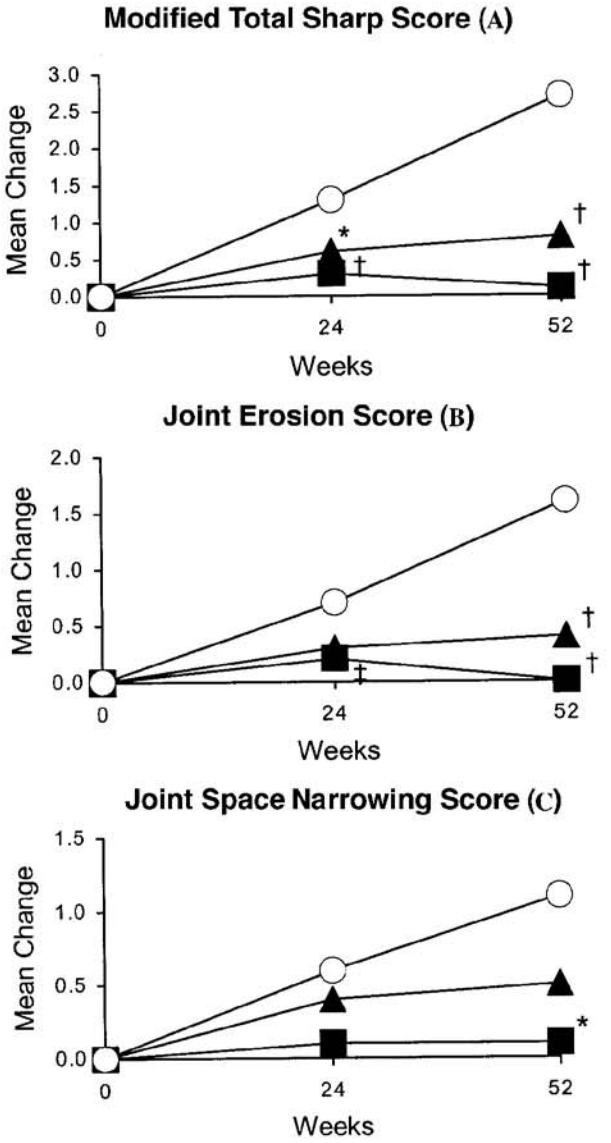

Figure 2. Changes from baseline to week 52 in the modified total Sharp radiographic progression scores (extrapolated data) **(A)**, erosion scores (last observation carried forward [LOCF] data) **(B)**, and joint space narrowing scores (LOCF data) **(C)** among the patients receiving adalimumab 40 mg every other week plus methotrexate (MTX) (■), adalimumab 20 mg weekly plus MTX (▲), and placebo plus MTX (○). * = $P \leq 0.01$, † = $P \leq 0.001$, and ‡ = $P \leq 0.05$ versus placebo (by analysis of covariance with the baseline value as the covariate).

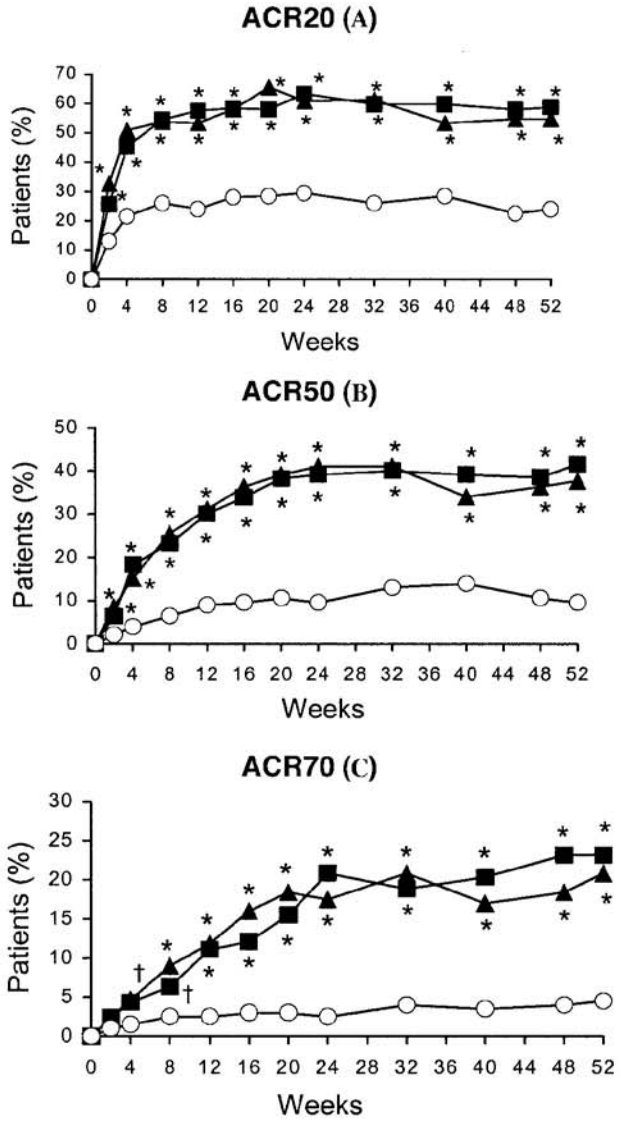

Figure 3. Distribution of patients who showed improvement in the American College of Rheumatology (ACR) criteria of at least 20%, 50%, and 70% (**A, B,** and **C,** respectively) (using nonresponder imputation), among the patients receiving adalimumab 40 mg every other week plus methotrexate (MTX) (■), adalimumab 20 mg weekly plus MTX (▲), and placebo plus MTX (○). * = $P \leq 0.001$, and † = $P \leq 0.01$ versus placebo (by Pearson's chi-square test).

patients in the placebo group (11 of 172); these radiographic data were therefore extrapolated.

Radiographic progression. The rate of radiographic progression was significantly less in the adalimumab-treated patients compared with the placebo-treated patients at both 24 weeks and 52 weeks. Changes from baseline in the mean total Sharp score among patients treated with adalimumab 40 mg every other week and those treated with adalimumab 20 mg weekly were a mean ± SD 0.1 ± 4.8 and 0.8 ± 4.9, respectively, at week 52 versus 2.7 ± 6.8 among patients receiving placebo (Figure 2A) ($P \leq 0.001$ for each comparison). The differences between the group treated with adalimumab 40 mg every other week and the group treated with adalimumab 20 mg weekly were not significant at weeks 24 or 52.

There were statistically significantly fewer joint erosions in the adalimumab-treated patients than in the placebo-treated patients (Figure 2B). The changes in the mean erosion scores at week 52 following treatment with adalimumab 40 mg every other week and 20 mg weekly were a mean ± SD 0.0 ± 2.8 and 0.4 ± 2.5, respectively, versus a change in the mean erosion score of the placebo group of 1.6 ± 4.4 ($P \leq 0.001$ for each comparison). At week 52, no new erosions were observed in significantly more patients taking adalimumab, either 40 mg every other week (61.8%) or 20 mg weekly (57.9%), as compared with patients taking placebo (46.0%) ($P \leq 0.01$ and $P \leq 0.05$, respectively). Similarly, improved erosion scores (i.e., scores <0) were observed in significantly more patients taking adalimumab, either 40 mg every other week (38.2%) or 20 mg weekly (29.5%), as compared with patients taking placebo (19.3%) ($P \leq 0.001$ and $P \leq 0.05$, respectively).

Compared with the effects of placebo, adalimumab attenuated the rate of joint space narrowing (Figure 2C). The mean change in the joint space narrowing score at week 52 was statistically significantly lower among patients treated with adalimumab 40 mg every other week (mean ± SD 0.1 ± 2.3) than among those taking placebo (1.0 ± 3.0) ($P \leq 0.01$). Significantly more patients treated with adalimumab, either 40 mg every other week (68.5%) or 20 mg weekly (67.8%), as compared with patients taking placebo (52.2%) demonstrated improvement or no change in joint space narrowing at week 52 ($P \leq 0.01$).

Signs and symptoms. Patients treated with either regimen of adalimumab demonstrated rapid, statistically significant, and sustained clinical improvements compared with those treated with placebo, as measured by the ACR response criteria. The ACR20, ACR50, and ACR70 response rates in both adalimumab groups showed a distinct separation from those in the placebo group by week 2, with this treatment effect persisting through week 52 (Figures 3A, B, and C, respectively). Adalimumab-treated patients exhibited a response quickly, with more patients achieving an ACR20 re-

Table 2. Patients with at least 20%, 50%, and 70% improvement in the ACR response criteria*

ACR response*	Adalimumab 40 mg every other week plus MTX (n = 207)	Adalimumab 20 mg weekly plus MTX (n = 212)	Placebo plus MTX (n = 200)
ACR20 response			
Week 24	131 (63.3)†	129 (60.8)†	59 (29.5)
Week 52	122 (58.9)†	116 (54.7)†	48 (24.0)
ACR50 response			
Week 24	81 (39.1)†	87 (41.0)†	19 (9.5)
Week 52	86 (41.5)†	80 (37.7)†	19 (9.5)
ACR70 response			
Week 24	43 (20.8)†	37 (17.5)†	5 (2.5)
Week 52	48 (23.2)†	44 (20.8)†	9 (4.5)

* Values are the number (%) of patients. All patients who withdrew from the study or received additional DMARD therapy were considered nonresponders. See Table 1 for definitions.
† $P \leq 0.001$ versus placebo (by Pearson's chi-square test).

sponse at week 2 (the first evaluation) than at any other time point. At week 2, an ACR20 response was achieved by 25.6% and 32.5% of patients treated with adalimumab 40 mg every other week and 20 mg weekly, respectively, versus 13.0% of patients taking placebo ($P \leq 0.001$ for each comparison) (Figure 3A). At weeks 24 and 52, ACR20, ACR50, and ACR70 response rates were statistically significantly greater with either of the adalimumab regimens than with placebo ($P \leq 0.001$) (Table 2). Furthermore, each adalimumab group was associated with statistically significant improvements in each ACR core component compared with the changes in the placebo group at weeks 24 and 52 ($P \leq 0.001$) (Table 3). In both adalimumab treatment groups, the C-reactive protein (CRP) concentrations decreased to normal or near-normal levels by week 24 and remained stable to week 52, whereas in the placebo group, CRP concentrations remained elevated at twice the normal range at week 52.

Moreover, at week 52, the number of patients requiring additional DMARD therapy was significantly lower among patients treated with adalimumab 40 mg every other week (n = 9) or adalimumab 20 mg weekly (n = 6) than among those receiving placebo (n = 33) ($P < 0.001$). The difference in the number requiring additional DMARDs between the group treated with adalimumab 40 mg every other week and the group treated with adalimumab 20 mg weekly was not statistically significant.

Physical function and health-related quality of life. At week 52, improvements (decreases from baseline) in the mean HAQ physical function scores were statistically significantly greater for those receiving adalimumab 40 mg every other week (mean ± SD −0.59 ± 0.57) or adalimumab 20 mg weekly (−0.61 ± 0.55) than for those receiving placebo (−0.25 ± 0.56) ($P \leq 0.001$ for each comparison) (Table 3). Improvements in the mean HAQ scores following treatment with either adalimumab regimen were statistically significantly greater than those seen in the placebo group at all time points, including the first scheduled study visit at week 2 (mean ± SD −0.29 ± 0.39 for adalimumab 40 mg every other week and −0.28 ± 0.41 for adalimumab 20 mg weekly compared with −0.12 ± 0.37 for placebo; $P \leq 0.001$ for each comparison) (Figure 4). A 0.22-unit decrease in HAQ scores has been associated with meaningful clinical improvements and can be considered to represent the minimum clinically important difference (MCID) (18).

At week 52, improvements (increases from baseline) in the mean SF-36 scores were statistically significantly greater for 7 of 8 domains following treatment with adalimumab 40 mg every other week and were greater for all 8 domains with adalimumab 20 mg weekly as compared with placebo (Figure 5). Increases of 5–10 points in individual SF-36 domain scores have been associated with meaningful clinical improvements and can be considered to represent MCIDs (19). At week 52, treatment with adalimumab 40 mg every other week resulted in at least a 10-point improvement in 5 of the 8 SF-36 domains (physical function, physical role, body pain, vitality, and social function). Moreover, treatment with adalimumab 20 mg weekly resulted in at least a 10-point improvement in 7 of the 8 domains (physical function, physical role, body pain, general health, vitality, social function, and emotional role). In contrast, the placebo group achieved at least a 10-point improvement in only 1 of 8 SF-36 domains (physical role).

Table 3. Changes in ACR core component criteria at week 24 and week 52*

Core set evaluation measure	Adalimumab 40 mg every other week plus MTX (n = 207)	Adalimumab 20 mg weekly plus MTX (n = 212)	Placebo plus MTX (n = 200)
Tender joint count (0–68 scale)			
Mean baseline value	27.3 ± 12.7	27.9 ± 13.6	28.1 ± 13.8
Week 24 absolute change	−15.4 ± 12.3†	−16.6 ± 12.0†	−9.3 ± 14.4
Week 24 percent change	−56.4	−59.5	−33.1
Week 52 absolute change	−16.6 ± 12.8†	−16.8 ± 13.8†	−9.6 ± 14.7
Week 52 percent change	−60.8	−60.2	−34.5
Swollen joint count (0–66 scale)			
Mean baseline value	19.3 ± 9.8	19.6 ± 9.9	19.0 ± 9.5
Week 24 absolute change	−11.1 ± 9.7†	−11.7 ± 9.8†	−5.9 ± 10.6
Week 24 percent change	−57.5	−59.7	−31.1
Week 52 absolute change	−11.9 ± 11.0†	−11.7 ± 10.9†	−5.6 ± 10.3
Week 52 percent change	−61.7	−59.7	−29.5
Patient's assessment of pain, mm (0–100-mm VAS)‡			
Mean baseline value	55.9 ± 20.4	55.2 ± 23.0	56.3 ± 22.9
Week 24 absolute change	−28.2 ± 25.8†	−27.9 ± 27.0†	−12.6 ± 26.1
Week 24 percent change	−50.4	−50.5	−22.4
Week 52 absolute change	−29.4 ± 26.4†	−27.4 ± 28.5†	−11.2 ± 27.7
Week 52 percent change	−52.6	−49.6	−19.9
Patient's global assessment of disease activity, mm (0–100-mm VAS)§			
Mean baseline value	52.7 ± 21.0	51.9 ± 23.1	54.3 ± 22.9
Week 24 absolute change	−27.2 ± 26.9†	−24.7 ± 27.2†	−11.4 ± 28.1
Week 24 percent change	−51.6	−47.6	−21.0
Week 52 absolute change	−27.5 ± 28.4†	−24.1 ± 28.4†	−10.9 ± 30.4
Week 52 percent change	−52.2	−46.4	−20.1
Physician's global assessment of disease activity, mm (0–100-mm VAS)§			
Mean baseline value	62.0 ± 16.7	61.6 ± 16.8	61.3 ± 17.3
Week 24 absolute change	−37.3 ± 21.6†	−36.3 ± 24.1†	−21.1 ± 25.3
Week 24 percent change	−60.2	−58.9	−34.4
Week 52 absolute change	−39.4 ± 22.2†	−36.2 ± 24.4†	−19.5 ± 25.8
Week 52 percent change	−63.5	−58.8	−31.8
HAQ score (0–3 scale)¶			
Mean baseline value	1.45 ± 0.63	1.44 ± 0.64	1.48 ± 0.59
Week 24 absolute change	−0.56 ± 0.52†	−0.60 ± 0.53†	−0.24 ± 0.52
Week 24 percent change	−38.6	−41.7	−16.2
Week 52 absolute change	−0.59 ± 0.57†	−0.61 ± 0.55†	−0.25 ± 0.56
Week 52 percent change	−40.7	−42.4	−16.9
C-reactive protein, mg/dl (normal <0.8)			
Mean baseline value	1.8 ± 2.3	1.4 ± 1.4	1.8 ± 2.1
Week 24 absolute change	−1.0 ± 2.9†	−0.8 ± 1.3†	−0.2 ± 1.9
Week 24 percent change	−55.6	−57.1	−11.1
Week 52 absolute change	−0.7 ± 1.4†	−0.7 ± 1.4†	−0.1 ± 1.9
Week 52 percent change	−38.9	−50.0	−5.6

* Except where indicated otherwise, values are the mean ± SD, based on the last observation carried forward to week 24 or week 52. A negative mean change indicates an improvement in that ACR criterion. See Table 1 for definitions.
† $P \leq 0.001$ versus placebo (by analysis of covariance with the baseline value as the covariate).
‡ 0 = no pain and 100 = severe pain.
§ 0 = no disease activity and 100 = extreme disease activity.
¶ 0 = no difficulty and 3 = unable to perform activity.

Adverse events. Adalimumab was generally well tolerated. Because a higher proportion of the placebo-treated patients discontinued the study compared with the adalimumab-treated patients (30% versus 22%) and the mean duration of treatment in the placebo arm was shorter than that in the adalimumab arm (268 days versus 313 days), adverse events were analyzed both by the proportion of patients experiencing an event and by the rate (expressed as number of patients per patient-year) of those events.

The overall frequencies and rates of serious adverse events were similar among the adalimumab-treated patients (n = 60: 14.3% reporting serious adverse events [0.16 patients/patient-year]). However, the proportion of patients reporting serious infections (requiring hospitalization or intravenous antibiotics) was

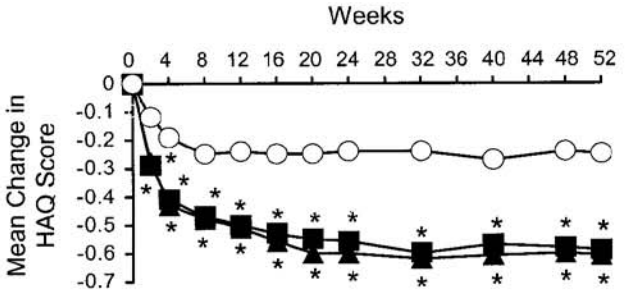

Figure 4. Changes in the Health Assessment Questionnaire (HAQ) scores (last observation carried forward data) among the patients receiving adalimumab 40 mg every other week plus methotrexate (MTX) (■), adalimumab 20 mg weekly plus MTX (▲), and placebo plus MTX (○). * = $P \leq 0.001$ versus placebo (by analysis of covariance with the baseline value as the covariate).

significantly greater with adalimumab (16 of 419, or 3.8%) than with placebo (1 of 200, or 0.5%) ($P \leq 0.02$). Serious infections were reported by significantly more patients treated with adalimumab 40 mg every other week (11 of 207, or 5.3%) than with placebo ($P \leq 0.01$), but there was no statistically significant difference between the group receiving adalimumab 20 mg weekly (5 of 212, or 2.4%) as compared with placebo. Adjusting for exposure time, serious infections occurred at a rate of 0.06 patients/patient-year with adalimumab 40 mg every other week, 0.03 patients/patient-year with adalimumab 20 mg weekly, and 0.01 patients/patient-year with placebo.

One patient treated with adalimumab 40 mg every other week was diagnosed as having primary tuberculosis of the cervical lymph nodes, and was withdrawn from the study and successfully treated. At baseline, this patient had a negative PPD test result and a normal chest radiograph. One patient treated with adalimumab 40 mg every other week plus MTX was diagnosed with histoplasmosis infection after 78 days of treatment, and was subsequently withdrawn from the study and successfully treated with antifungal therapy. This patient lived in an area that was endemic for histoplasmosis infection. One patient treated with adalimumab 40 mg every other week was diagnosed as having herpes zoster and developed encephalitis, which resolved but resulted in mild lower extremity weakness. Four adalimumab-treated patients developed non-skin cancers, including non-Hodgkin's lymphoma, adenocarcinoma, testicular seminoma, and breast cancer. One patient treated with adalimumab 20 mg weekly was diagnosed as having worsening of a central demyelinating illness. This patient had experienced an episode of paresthesia 18 years earlier and developed the latest episode 1 month after starting therapy. There were 2 deaths (1 related to multiple fractures and 1 related to urosepsis) in the group receiving adalimumab 40 mg every other week, 1 death (related to complications from chemotherapy for the treatment of lymphoma) in the group receiving adalimumab 20 mg weekly, and no deaths in the placebo group.

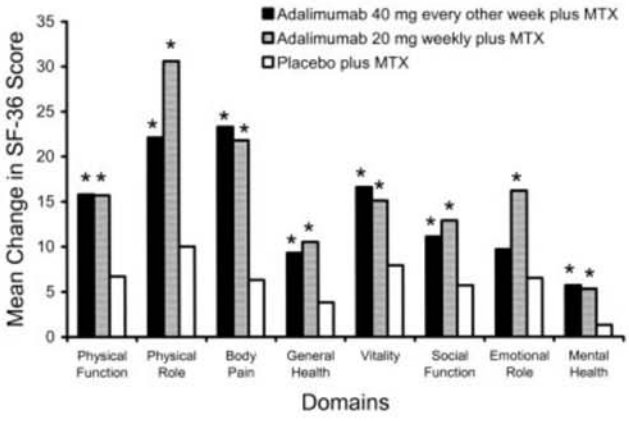

Figure 5. Changes in the Medical Outcomes Study Short Form 36-item health survey (SF-36) scores (last observation carried forward data). * = $P \leq 0.05$ versus placebo (by analysis of covariance with the baseline value as the covariate). MTX = methotrexate.

Overall, similar proportions of adalimumab-treated patients (n = 391, or 93.3%) and placebo-treated patients (n = 181, or 90.5%) reported at least 1 adverse event. Moreover, the rate of adverse events was similar between the adalimumab-treated patients (1.07 patients/patient-year) and the placebo-treated patients (1.12 patients/patient-year).

The most frequently reported adverse events (occurring in ≥10% of patients) are presented in Table 4. Injection-site reaction (defined as localized erythema, itching, hemorrhage, pain, or swelling) was the most commonly reported adverse event and was observed in similar proportions of adalimumab- and placebo-treated patients (24.1% and 24.0%, respectively). The primary injection-site reaction was injection-site pain, which was reported by 17.7% of the combined adalimumab group and 22.0% of the placebo group. Injection-site reactions consisting of localized erythema, itching, or swelling occurred in 6.2% of the adalimumab group and 3.0% of the placebo group ($P = 0.10$). Most injection-site reactions were mild or moderate in nature.

Adalimumab therapy was also associated with statistically significant decreases ($P \leq 0.05$ compared with baseline values) in the mean white blood cell count, platelet count, and neutrophil percentage, as well as

Table 4. Adverse events*

Adverse event	Adalimumab 40 mg every other week plus MTX (179.2 patient-years) (n = 207)		Adalimumab 20 mg weekly plus MTX (186.7 patient-years) (n = 212)		Placebo plus MTX (161.3 patient-years) (n = 200)	
	No. (%)	No./patient-year	No. (%)	No./patient-year	No. (%)	No./patient-year
Injection-site reaction†	54 (26.1)	0.30	47 (22.2)	0.25	48 (24.0)	0.30
Upper respiratory tract infection	41 (19.8)	0.23	41 (19.3)	0.22	27 (13.5)	0.17
Rhinitis	34 (16.4)	0.19	37 (17.5)	0.20	33 (16.5)	0.21
Sinusitis	33 (15.9)	0.18	31 (14.6)	0.17	26 (13.0)	0.16
Accidental injury	29 (14.0)	0.16	28 (13.2)	0.15	24 (12.0)	0.15
Headache	26 (12.6)	0.15	29 (13.7)	0.16	12 (6.0)	0.07
Infection	15 (7.2)	0.08	33 (15.6)	0.18	9 (4.5)	0.06
Nausea	19 (9.2)	0.11	26 (12.3)	0.14	25 (12.5)	0.16
Diarrhea	19 (9.2)	0.11	24 (11.3)	0.13	30 (15.0)	0.19
Arthralgia	14 (6.8)	0.08	29 (13.7)	0.16	24 (12.0)	0.15
Rash‡	22 (10.6)	0.12	20 (9.4)	0.11	15 (7.5)	0.09
Joint disorder	13 (6.3)	0.07	14 (6.6)	0.08	23 (11.5)	0.14
Clinical-flare reaction	12 (5.8)	0.07	8 (3.8)	0.04	29 (14.5)	0.18

* Adverse events occurring in ≥10% of patients in any treatment group. MTX = methotrexate.
† Erythema and/or itching, hemorrhage, pain, or swelling at the site of injection.
‡ At site other than injection site.

statistically significant increases ($P \leq 0.05$ compared with baseline values) in the mean hemoglobin concentration, hematocrit, and lymphocyte percentage (data not shown), with all of these indices moving toward more normal values. In the placebo group, changes in all of these parameters were of less magnitude and were not statistically significant for the platelet count and lymphocyte percentage.

At week 52, 12.1% of adalimumab-treated patients (48 of 397) and 9.1% of placebo-treated patients (17 of 186) converted from ANA negative to ANA positive (titer ≥1:80), and 5.5% of adalimumab-treated patients (22 of 397) and 5.9% of placebo-treated patients (11 of 186) converted from ANA positive to ANA negative. Among patients who had an increased ANA titer at baseline (any increase in titer), anti-dsDNA antibodies were detected in 11.7% of the adalimumab-treated patients (14 of 120) and in none of the placebo-treated patients at week 52. No patients developed symptoms of lupus-like illness. Two patients in the group receiving adalimumab 40 mg every other week, 1 patient in the group receiving adalimumab 20 mg weekly, and 1 patient in the placebo group were positive for anti-adalimumab antibodies on at least 1 occasion. The assay was performed repeatedly during the treatment period (from the first dose to up to 30 days after the last dose).

DISCUSSION

This multicenter, placebo-controlled, 52-week trial demonstrated that adding adalimumab (40 mg every other week or 20 mg weekly subcutaneously) to MTX in patients with active RA provided significant radiographic, clinical, and functional benefits compared with MTX alone. Patients in this study had moderate to severe, long-standing RA that was partially responsive to MTX and were at increased risk of radiographic disease progression. Benefits with the adalimumab plus MTX combination were achieved quickly and were sustained over 52 weeks.

Both adalimumab regimens inhibited the rate of radiographic disease progression. Modified total Sharp scores increased more with MTX alone than with adalimumab plus MTX after both 24 weeks and 52 weeks of treatment. The therapeutic effect of adalimumab was statistically significant even when erosion scores and joint space narrowing scores were analyzed independently. Such results suggest that adalimumab influences different disease manifestations, including joint erosions and joint space narrowing. These results are consistent with the recognized ability of TNF to induce bone resorption (20) and inhibit the synthesis of proteoglycans by cartilage (21). Prevention of further joint damage, as assessed by inhibition of the rate of radiographic disease progression, represents an important therapeutic goal in RA because joint damage strongly correlates with functional deterioration, particularly late in the disease course (22,23).

The rate of increase in the total modified Sharp score in the placebo group during this trial was less than the expected linear progression calculated from the baseline total Sharp score divided by disease duration.

Interventions (e.g., DMARDs, corticosteroids) used prior to the study and MTX and corticosteroids used during the study have been shown to change the rate of increase in radiographic progression. This is one explanation for this finding.

In addition to radiographic benefits, clinical and functional improvements were robust and sustained up to 52 weeks with both adalimumab regimens. The magnitude of the responses with adalimumab therapy was substantial for such a study population. ACR responses with adalimumab were rapid, with the greatest number of patients responding for the first time at week 2 (the first followup study visit). Moreover, fewer patients treated with adalimumab required the use of rescue DMARDs than did patients treated with placebo.

Improvements were observed in patient-reported evaluations (HAQ and SF-36), indicating that adalimumab therapy positively impacts patients' ability to perform physical activities necessary for daily living and health-related quality of life. Remarkably, HAQ scores demonstrated statistically and clinically significant improvement in as little as 2 weeks. During adalimumab treatment, white blood cell counts, platelet counts, and neutrophil percentages decreased, whereas hemoglobin concentrations, hematocrit, and lymphocyte percentages increased, possibly because of the antiinflammatory effect of adalimumab.

The overall incidence of adverse events was similar in the adalimumab and placebo groups, and most adverse events were mild or moderate. However, serious infections occurred significantly more often with adalimumab (3.8%) than with placebo (0.5%) ($P \leq 0.02$). Serious infection is a risk associated with TNF antagonists (24). It is recommended that administration of these agents be discontinued in patients who develop a serious infection. The rate of serious infections among adalimumab-treated patients in this 52-week study was comparable with the estimated yearly rate of serious infections among patients with RA (0.031–0.096/patient-year) (25,26) and comparable with those reported from the safety databases for the 2 currently marketed TNF antagonists, etanercept (0.048/patient-year) (27) and infliximab (6%) (28). The incidence of non-skin cancers among adalimumab-treated patients in this study was similar to that expected of the age- and sex-matched general population, based on the Surveillance, Epidemiology, End Result (SEER) database of the National Cancer Institute (29,30). As has been observed with other TNF antagonists, adalimumab treatment was associated with a higher rate of development of ANAs and anti-dsDNA antibodies, but no cases of lupus or lupus-like illness were observed in this study.

Several combination regimens have been demonstrated to be effective in RA patients who exhibit a partial response to MTX, including combinations of MTX with traditional DMARDs (cyclosporine, sulfasalazine, hydroxychloroquine, or leflunomide) or biologic DMARDs (infliximab, etanercept, or anakinra) (31). Based on the results presented here, we conclude that addition of adalimumab (40 mg every other week or 20 mg weekly administered subcutaneously) to the MTX regimen in patients partially responsive to MTX provides additional benefit, with inhibition of the progression of structural joint damage, reduction in the signs and symptoms, and improvement in physical function and health-related quality of life.

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