Adalimumab, a Fully Human Anti–Tumor Necrosis Factor-α Monoclonal Antibody, and Concomitant Standard Antirheumatic Therapy for the Treatment of Rheumatoid Arthritis: Results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis)

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ABSTRACT. ***Objective***. This study, known as STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis), evaluated the safety and efficacy of adalimumab (Humira™), a fully human monoclonal tumor necrosis factor-alpha (TNF-α) antibody, when given with standard antirheumatic therapy in patients with active rheumatoid arthritis (RA) not adequately responding to such therapies. Standard antirheumatic therapy included traditional disease modifying antirheumatic drugs (DMARD), low dose corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), and/or analgesics.

Methods. In this 24-week, double-blind, placebo-controlled study, 636 patients with RA were randomly assigned to receive adalimumab 40 mg subcutaneously (sc) every other week (n = 318) or placebo (n = 318) while continuing standard antirheumatic therapy. The frequencies of adverse events, serious adverse events, severe or life-threatening adverse events, adverse events leading to withdrawal, infection, or serious infection were the primary endpoints. Secondary endpoints were determined by American College of Rheumatology (ACR) response criteria.

Results. During the study, the majority of patients received concomitant traditional DMARD (83.5%) and/or corticosteroids, NSAID, and/or analgesics (97.3%). Overall, 56.0% of patients continued treatment with one, 23.6% with 2, and 3.9% with ≥ 3 traditional DMARD. At 24 weeks, there were no statistically significant differences between the adalimumab and placebo groups in their respective rates of adverse events (86.5% vs 82.7%), serious adverse events (5.3% vs 6.9%), severe or life-threatening adverse events (11.9% vs 15.4%), or those leading to withdrawal (2.8% vs 2.2%). There were also no statistically significant differences in the rates of infections (52.2% vs 49.4%) or serious infections (1.3% vs 1.9%) between the groups. The incidence and types of adverse events did not vary between adalimumab- and placebo-treated patients by the number of concomitant traditional DMARD (0, 1, or 2). Adalimumab-treated patients compared with placebo-treated patients achieved statistically superior ACR20 (52.8% vs 34.9%), ACR50 (28.9% vs 11.3%), and ACR70 (14.8% vs 3.5%) response rates at Week 24 ($p \leq 0.001$).

Conclusion. This study demonstrated that addition of adalimumab 40 mg given sc every other week to concomitant standard antirheumatic therapy is well tolerated and provides significant improvements in signs and symptoms of RA. The data indicate that adalimumab is a safe and effective therapeutic option in patients with active RA who have an inadequate response to standard antirheumatic therapy, including one or more traditional DMARD, corticosteroids, NSAID, and analgesics. (J Rheumatol 2003;30:2563–71)

Key Indexing Terms:
ADALIMUMAB DISEASE MODIFYING ANTIRHEUMATIC DRUGS
MONOCLONAL ANTIBODY RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR-α

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Standard antirheumatic therapy for rheumatoid arthritis (RA) typically consists of traditional disease modifying antirheumatic drugs (DMARD), low dose corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), and analgesics[1]. Because erosion of articular cartilage and marginal bone generally begins early in the disease course, early use of traditional DMARD is advocated to slow the progression of joint damage[1]. However, despite traditional DMARD therapy, many patients continue to have active disease[2]. Consequently, multiple traditional DMARD, along with other RA therapies, are often combined in clinical practice to improve outcomes[1,2].

The proinflammatory cytokine tumor necrosis factor-α (TNF-α) plays an important role in the pathogenesis of RA and, as such, is a prime target for directed biologic therapy[3]. The first 2 commercially available biologic DMARD that inactivate TNF-α are infliximab (a chimeric, anti–TNF-α monoclonal antibody, mAb) and etanercept (a synthetic, human, TNF receptor-Fc fusion protein)[1]. Adalimumab (Humira™; Abbott Laboratories, Abbott Park, IL, USA) is a novel biologic DMARD and the first fully human mAb to TNF-α to be evaluated in clinical trials for the treatment of RA[4-8].

Genetically engineered by phage display technology, adalimumab is indistinguishable in structure and function from naturally occurring human immunoglobulin G-1 (IgG1)[4]. Adalimumab has a terminal half-life comparable to that of natural human IgG1 (about 2 weeks) and a high specificity and affinity for TNF-α ($K_d = 6 \times 10^{-10}$M) but not other cytokines, such as TNF-α (lymphotoxin)[4]. Its therapeutic effects are mediated by blocking the interaction of TNF-α with the p55 and p75 TNF cell surface receptors[4]. Initial clinical trials have demonstrated the ability of adalimumab to control the signs and symptoms of RA[5-8].

This study, known as STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis), was conducted to evaluate the safety and efficacy of adalimumab 40 mg administered subcutaneously (sc) every other week for up to 24 weeks in patients with active RA receiving chronic concomitant standard antirheumatic therapy (e.g., traditional DMARD, corticosteroids, NSAID, and/or analgesics). Incorporating standard antirheumatic therapy, this study approximated clinical practice and provides insight into the administration of adalimumab treatment with other commonly used RA therapies.

MATERIALS AND METHODS

Patients. Eligible patients were 18 years of age or older, had active RA at both screening and baseline visits defined by at least 6 swollen joints and at least 9 tender joints (excluding distal interphalangeal joints), and met the 1987 revised American College of Rheumatology (ACR) criteria[9] for diagnosis of RA for at least 3 months. Exclusion criteria consisted of those used in trials of other biologic DMARD in RA. Also excluded were patients treated with anti-CD4 therapy or biologic DMARD (e.g., TNF antagonists, interleukin-1 receptor antagonists) and/or with a history of an active inflammatory arthritide other than RA, a history of active listeriosis or mycobacterial infection, 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), and any uncontrolled medical condition. Patients experienced a variety of comorbid diseases.

Protocol. This study was a 24-week, double-blind, randomized, controlled trial of adalimumab with concomitant standard antirheumatic therapy and was performed at 69 study sites throughout the United States and Canada. All patients gave written informed consent, and institutional review boards at each study site approved the study protocol. Patients were randomized to receive adalimumab 40 mg or placebo given sc every other week as a single self-administered injection (1.6 ml). Patients continued to receive their baseline doses of standard antirheumatic therapy, which could include traditional DMARD, low dose corticosteroids (prednisone equivalent dose ≤ 10 mg/day), NSAID, and/or analgesics. Treatment with traditional DMARD permitted during the study included chloroquine, hydroxychloroquine, leflunomide, methotrexate (MTX), parenteral gold, oral gold, sulfasalazine, or any combination of these. Doses of traditional DMARD, corticosteroids, NSAID, and/or analgesics must have been stable for at least 28 days before screening, with the actual length of treatment being determined by individual investigators in consultation with their patient. Patients were examined at Weeks 2, 4, 8, 12, 16, 20, and 24 of the study. Patients who failed to meet or maintain at least an ACR20 response at Week 12 or subsequent visit were allowed a single increase in dosage of their traditional DMARD and/or corticosteroid therapy (provided that the prednisone equivalent dose remained ≤ 10 mg/day) or treatment with a different traditional DMARD. To reflect current clinical practice, 3 intraarticular corticosteroid injections were permitted during the first 3 months of the study, with injected joints not assessed during joint examinations for 28 days after each injection. In case of adverse events related to concomitant therapy, the doses of background traditional DMARD, corticosteroids, NSAID, or analgesics could be decreased.

Safety was the primary endpoint of this study and was assessed by types and frequencies of adverse events, physical examination findings, and standard laboratory test results. Adverse event data were stratified for adalimumab and placebo treatment, as well as for the number of concomitant traditional DMARD (i.e., 0, 1, or 2) administered with adalimumab or placebo. Serum titers of antinuclear antibodies (ANA) (positive ≥ 1:80) and anti-dsDNA antibodies (positive > 3.5 IU/ml) (performed if ANA titers increased from baseline) were determined by immunofluorescence and the Farr radioimmunoassay, respectively, at baseline and at Week 24.

Efficacy was the secondary endpoint of this study and was assessed as ACR20, ACR50, and ACR70 responses[10]. Fulfillment of ACR20, ACR50, and ACR70 criteria was based on changes from baseline observed at Week 24 (using a nonresponder imputation technique so that all patients who withdrew from the study prior to Week 24 were counted as nonresponders). ACR20, ACR50, and ACR70 response rates were stratified for adalimumab and placebo treatment, as well as for the number of concomitant traditional DMARD (i.e., 0, 1, or 2) given with adalimumab or placebo.

Statistical analysis. A sample size of 300 patients per group was determined to demonstrate a specific adverse event rate of 1%, or less, with 95% confidence. Demographic and baseline disease characteristics were analyzed using Wilcoxon rank sum test for continuous variables and Pearson's chi-square test for discrete variables. Statistical comparisons for the frequency of adverse events were made between the adalimumab and placebo groups using Pearson's chi-square test. The efficacy analysis was performed on an intent-to-treat basis, including all patients who received at least one injection of study drug and had at least one efficacy assessment. ACR20, ACR50, and ACR70 response rates observed at Week 24 were compared between the adalimumab and placebo groups using Pearson's chi-square test with a 2-sided level of significance of $\alpha = 0.05$. No correction was made for multiple statistical comparisons.

RESULTS

Demographic and baseline disease characteristics. A total

of 636 patients were enrolled, with 318 patients randomized to receive adalimumab and 318 patients randomized to receive placebo. Demographic and baseline disease characteristics were balanced between the groups at baseline (Table 1). Mean age was 55.4 years (range 21 to 86), most patients (79.4%) were women, and mean disease duration was 10.4 years. Mean disease duration was 9.3 years in the adalimumab group and 11.5 years in the placebo group ($p \leq 0.01$). Mean baseline tender joint counts and swollen joint counts were 27.5 (out of 68) and 21.1 (out of 66), respectively, indicating significant disease activity despite the use of various antirheumatic medications. Mean C-reactive protein level was 1.5 mg/dl (normal < 0.8 mg/dl). Most patients (62.9%) were seropositive (rheumatoid factor > 40 IU/ml). In all, 92.3% of patients had previously received traditional DMARD, including 33.7% receiving one, 24.8% receiving 2, 17.1% receiving 3, and 16.7% receiving 4 or more.

Eleven patients (1.7%) (7 in the adalimumab group and 4 in the placebo group) were tuberculin skin test positive, with 7 of these patients (4 in the adalimumab group and 3 in the placebo group) receiving prophylactic treatment at screening. An additional patient in each treatment group whose tuberculin skin test results were not reported was receiving prophylactic treatment at screening. Chest radiographs revealed calcified granuloma in 51 (16.0%) adalimumab- and 55 (17.3%) placebo-treated patients, as well as pleural scarring in 34 (10.7%) adalimumab- and 44 (13.8%) placebo-treated patients.

Patient disposition. A total of 578 (90.9%) patients completed 24 weeks of treatment, with no differences between the 2 groups (Figure 1). Twenty-eight (8.8%) patients in the adalimumab group and 30 (9.4%) in the placebo group discontinued treatment. Nine (2.8%) patients in the adalimumab group and 8 (2.5%) in the placebo group discontinued treatment because of adverse events. Five (1.6%) patients in the adalimumab group and 14 (4.4%) in the placebo group withdrew because of lack of efficacy.

Concomitant standard antirheumatic therapy. Concomitant traditional DMARD treatment was statistically similar between the treatment groups (Table 2). The majority of patients (83.5%) received one or more concomitant traditional DMARD during the study. Overall, 56.0% of patients used one traditional DMARD, 23.6% used 2, and 3.9% used 3 or more. The most frequently used (≥ 5%) concomitant traditional DMARD were MTX (59.3%), antimalarial drugs (chloroquine or hydroxychloroquine, 24.7%), leflunomide (13.8%), sulfasalazine (9.8%), and parenteral gold (5.8%). Concomitant administration of corticosteroids and NSAID was statistically similar between the treatment groups (Table 2). Oral corticosteroids were received by 52.7% of patients, NSAID (including cyclooxygenase-2 inhibitors) by 63.1%, and analgesics by 28.6%. The mean oral corticosteroid dose (prednisone equivalent dose) was 5.7 mg/day (n = 119) in the adalimumab group and 5.4 mg/day (n = 119) in the placebo group.

Safety. Adalimumab plus standard antirheumatic therapy was well tolerated. The majority of adverse events were mild or moderate. Mean duration of treatment (23.2 vs 23.0 weeks) and mean number of injections of study drug (12.0 vs 12.0) were comparable between the adalimumab and placebo groups, respectively, permitting an accurate comparison of the frequency and type of adverse events.

Table 1. Demographic and baseline disease characteristics*.

Characteristic	Adalimumab Plus Standard Antirheumatic Therapy, n = 318	Placebo Plus Standard Antirheumatic Therapy, n = 318
Age, yrs	55.0 ± 12.8	55.8 ± 12.4
Women, n (%)	253 (79.6)	252 (79.2)
White, n (%)	283 (89.0)	273 (85.8)
Disease duration, yrs	9.3 ± 8.8	11.5 ± 9.7
Tender joint count [0–68]	27.3 ± 13.0	27.6 ± 13.8
Swollen joint count [0–66]	20.9 ± 11.0	21.3 ± 11.2
Patient assessment of pain, mm on VAS [0–100]†	55.1 ± 22.5	55.6 ± 22.5
Patient global assessment of disease activity, mm on VAS (0–100)‡	53.9 ± 22.3	52.9 ± 22.0
Physician global assessment of disease activity, mm on VAS (0–100)‡	59.9 ± 16.6	59.6 ± 16.3
Disability index of the HAQ (0–3)§	1.37 ± 0.62	1.43 ± 0.60
C-reactive protein, mg/dl [normal < 0.8 mg/dl]	1.5 ± 2.0	1.5 ± 1.9
Rheumatoid factor positive, n (%) [positive > 40 IU/ml]	201 (63.4)	198 (62.3)
Number of previous traditional DMARD, n (%)		
0	26 (8.2)	23 (7.2)
1	110 (34.6)	104 (32.7)
2	81 (25.5)	77 (24.2)
3	52 (16.4)	57 (17.9)
≥ 4	49 (15.4)	57 (17.9)

* Plus-minus values are mean ± standard deviation. † 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. VAS: visual analog scale; HAQ: Health Assessment Questionnaire; DMARD: disease modifying antirheumatic drug.

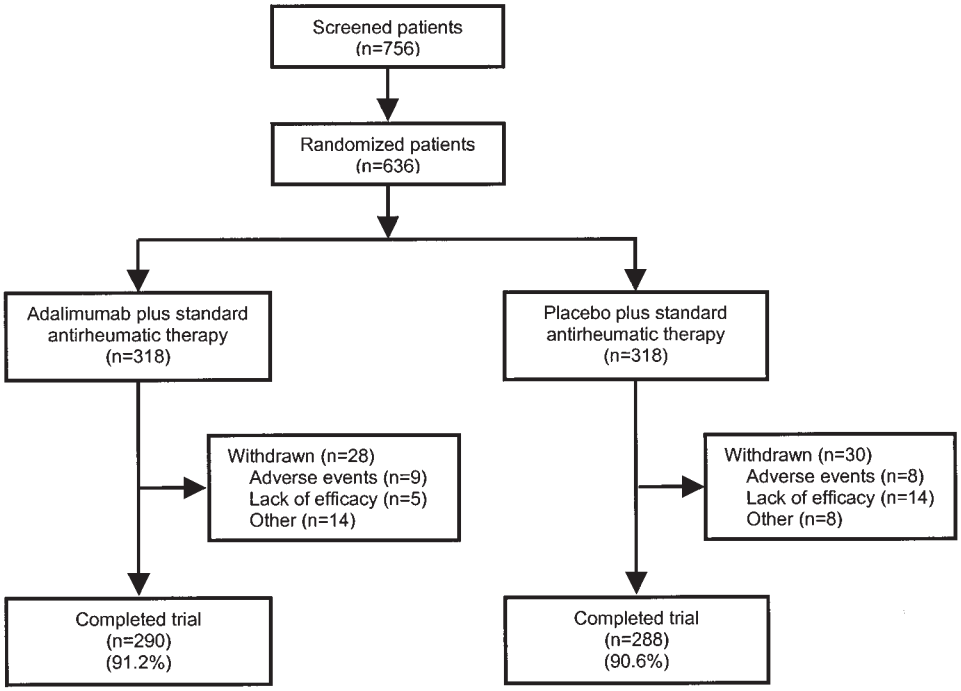

Figure 1. Patient disposition

Table 2. Concomitant standard antirheumatic therapy. Values are number (%) of patients, unless otherwise indicated.

Therapy	Adalimumab Plus Standard Antirheumatic Therapy, n = 318	Placebo Plus Standard Antirheumatic Therapy, n = 318
Number of traditional DMARD		
0	57 (17.9)	48 (15.1)
1	184 (57.9)	172 (54.1)
2	66 (20.8)	84 (26.4)
≥ 3	11 (3.5)	14 (4.4)
Mean number of DMARD	1.1	1.2
Most frequently used traditional DMARD		
At least 1 traditional DMARD	261 (82.1)	270 (84.9)
MTX	178 (56.0)	199 (62.6)
Antimalarials†	75 (23.6)	82 (25.8)
Leflunomide	42 (13.2)	46 (14.5)
Sulfasalazine	29 (9.2)	33 (10.4)
Gold	19 (6.0)	18 (5.7)
Most frequently used traditional DMARD alone		
MTX	114 (35.8)	115 (36.2)
Leflunomide	25 (7.9)	24 (7.5)
Antimalarials	23 (7.2)	17 (5.4)
Sulfasalazine	12 (3.8)	8 (2.5)
Parenteral gold	8 (2.5)	5 (1.6)
Most frequently used traditional DMARD combinations		
MTX + antimalarials	32 (10.1)	44 (13.8)
MTX + leflunomide	8 (2.5)	13 (4.1)
MTX + antimalarials + sulfasalazine	7 (2.2)	5 (1.6)
MTX + gold	6 (1.9)	4 (1.3)
MTX + sulfasalazine	5 (1.6)	11 (3.5)
Corticosteroids	162 (50.9)	173 (54.4)
NSAID	198 (62.3)	203 (63.8)

Concomitant therapy was that used at baseline and continued during the study, or that initiated during the study. † Chloroquine or hydroxychloroquine. DMARD: disease modifying antirheumatic drug; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug.

The rates of adverse events, serious adverse events, severe or life-threatening adverse events, and adverse events leading to withdrawal, as well as rates of infection and serious infection, were statistically similar between the 2 groups (Table 3). The only most frequently reported (≥ 5%) adverse events that occurred in significantly greater proportions of adalimumab-treated patients were injection-site reactions, rash at site other than injection site, and back pain ($p \leq 0.05$) (Table 3). Although injection-site reactions (defined as erythema and/or itching, hemorrhage, pain, or swelling) were the most common adverse events (occurring in 19.5% of adalimumab-treated patients and 11.6% of placebo-treated patients), all instances were mild or moderate. Most of the injection-site reactions were attributed to injection-site pain (11.3% of the adalimumab group and 10.7% of the placebo group reported injection-site pain). The incidence and types of adverse events did not differ by number of concomitant traditional DMARD received by patients (Table 4).

Occurrences of most frequent (≥ 5%) infectious adverse events were statistically similar between the groups (Table 3). Adjusting for time, serious infection occurred in 0.028 patients/patient-year in the adalimumab group and 0.043 patients/patient-year in the placebo group. Rates of infections and serious infections did not vary by number of traditional DMARD used (Table 4). No cases of reactivated tuberculosis or opportunistic infections were reported. Serious infections in adalimumab-treated patients (n = 4) included 2 cases of appendicitis, one herpes zoster with secondary streptococcal A superinfection, and one foot infection. In the placebo group (n = 6), 2 cases of pneumonia, 2 of bronchitis, one abscess, and one *Clostridium difficile* colitis were reported.

There was one death in the adalimumab group and none in the placebo group. A 70-year-old man, who was receiving concomitant MTX and prednisone and developed herpes zoster 12 days after the first injection of adalimumab, died 16 days thereafter from secondary streptococcal A superinfection (necrotizing fasciitis) at the site of the herpes lesions.

One patient, a 64-year-old man, in the adalimumab group was diagnosed with peripheral T cell lymphoma. He reported loss of appetite, weight loss, and night sweats prior to study entry and was diagnosed after 58 days of treatment and after receiving 3 doses of adalimumab. No patient in the placebo group was diagnosed with malignancies.

Mean changes in hematology values were comparable between the adalimumab and placebo groups (Table 5). Small increases in hemoglobin concentration, hematocrit, and red blood cell count were observed in both treatment groups. Changes in the white blood cell count and differential were small; mean values at each time point in both treatment groups were within the normal range. The mean white

Table 3. Overview of adverse events. Values are number (%) of patients. More than one adverse event was possible per patient.

Therapy	Adalimumab Plus Standard Antirheumatic Therapy, n = 318	Placebo Plus Standard Antirheumatic Therapy, n = 318	p†
Adverse event category			
Adverse events	275 (86.5)	263 (82.7)	NS
Serious adverse events	17 (5.3)	22 (6.9)	NS
Severe or life-threatening adverse events	38 (11.9)	49 (15.4)	NS
Adverse events leading to withdrawal	9 (2.8)	7 (2.2)¶	NS
Infection	166 (52.2)	157 (49.4)	NS
Serious infection§	4 (1.3)	6 (1.9)	NS
Most frequent (≥ 5%) noninfectious adverse events			
Injection-site reaction#	62 (19.5)	37 (11.6)	≤ 0.01
Rash*	34 (10.7)	19 (6.0)	≤ 0.05
Nausea	29 (9.1)	17 (5.3)	NS
Headache	26 (8.2)	23 (7.2)	NS
Accidental injury	22 (6.9)	25 (7.9)	NS
Abdominal pain	22 (6.9)	12 (3.8)	NS
Diarrhea	19 (6.0)	22 (6.9)	NS
Clinical flare reaction	18 (5.7)	18 (5.7)	NS
Back pain	17 (5.3)	5 (1.6)	≤ 0.01
Surgery	16 (5.0)	8 (2.5)	NS
Most frequent (≥ 5%) infectious adverse events			
Upper respiratory infection	63 (19.8)	48 (15.1)	NS
Urinary tract infection	29 (9.1)	18 (5.7)	NS
Sinusitis	24 (7.5)	28 (8.8)	NS
Flu syndrome	23 (7.2)	16 (5.0)	NS
Rhinitis	22 (6.9)	33 (10.4)	NS

† Adalimumab group vs placebo group by Pearson's chi-square test; NS: not significant. ¶ One additional patient in the placebo group withdrew because of a nontreatment-emergent adverse event, bringing the total to 8 patients (2.5%). § Requiring intravenous antibiotics or hospitalization. # Injection-site reaction was defined as erythema and/or itching, hemorrhage, pain, or swelling. * Rash at site other than injection site.

Table 4. Overview of adverse events by number of concomitant traditional disease modifying antirheumatic drugs. Values are number (%) of patients. More than one adverse event was possible per patient (DMARD)*.

	0 DMARD		1 DMARD		2 DMARD	
	Adalimumab, n = 57	Placebo, n = 48	Adalimumab, n = 184	Placebo, n 172	Adalimumab, n = 66	Placebo, n = 84
Adverse event category						
Adverse events	46 (80.7)	36 (75.0)	166 (90.2)	145 (84.3)	54 (81.8)	72 (85.7)
Serious adverse events	3 (5.3)	2 (4.2)	12 (6.5)	13 (7.6)	1 (1.5)	7 (8.3)
Severe or life-threatening adverse events	7 (12.3)	7 (14.6)	23 (12.5)	30 (17.4)	7 (10.6)	10 (11.9)
Adverse events leading to withdrawal	2 (3.5)	1 (2.1)	7 (3.8)	5 (2.9)	0	1 (1.2)
Infection	28 (49.1)	17 (35.4)	99 (53.8)	93 (54.1)	31 (47.0)	41 (48.8)
Serious infection†	0	0	3 (1.6)	3 (1.7)	0	3 (3.6)

† Requiring intravenous antibiotics or hospitalization.

Table 5. Changes in hematology variables. Values are last observation carried forward.

Therapy	Adalimumab Plus Standard Antirheumatic Therapy, n = 318, mean ± SD	Placebo Plus Standard Antirheumatic Therapy, n = 318, mean ± SD
Variable		
Hemoglobin (g/dl)		
Baseline	13.1 ± 1.4	13.0 ± 1.4
Week 24 change	0.4 ± 0.8	0.2 ± 0.8
Hematocrit (%)		
Baseline	38.8 ± 3.9	38.9 ± 3.8
Week 24 change	0.7 ± 2.6	0.1 ± 2.7
RBC (× 10^6/µl)		
Baseline	4.4 ± 0.4	4.4 ± 0.5
Week 24 change	0.1 ± 0.3	0.1 ± 0.3
WBC (× 10^3/µl)		
Baseline	8.4 ± 2.7	8.4 ± 2.6
Week 24 change	–0.7 ± 2.2	0.1 ± 2.0
Neutrophils (× 10^3/µl)		
Baseline	6.0 ± 2.5	6.0 ± 2.4
Week 24 change	–1.1 ± 2.1	0.2 ± 2.0
Lymphocytes (× 10^3/µl)		
Baseline	1.8 ± 0.8	1.8 ± 0.6
Week 24 change	0.3 ± 0.6	–0.05 ± 0.5
Monocytes (× 10^3/µl)		
Baseline	0.4 ± 0.2	0.4 ± 0.2
Week 24 change	–0.0 ± 0.2	–0.02 ± 0.1
Eosinophils (× 10^3/µl)		
Baseline	0.2 ± 0.1	0.2 ± 0.1
Week 24 change	0.04 ± 0.1	0.0 ± 0.1
Basophilis (× 10^3/µl)		
Baseline	0.1 ± 0.0	0.1 ± 0.0
Week 24 change	0.0	0.0
Platelets (× 10^3/µl)		
Baseline	297.4 ± 89.1	305.1 ± 90.8
Week 24 change	–23.9 ± 62.3	–0.5 ± 57.8

SD: standard deviation; RBC: red blood cells; WBC: white blood cells.

blood cell count and neutrophil count both decreased among adalimumab-treated patients, and the mean lymphocyte count increased. In contrast, the mean white blood cell count and neutrophil count increased, and the mean lymphocyte count decreased among placebo-treated patients. A decrease in the mean platelet count was observed in the adalimumab group but not the placebo group. Overall, the mean changes for all biochemistry variables were small and were comparable for patients treated with adalimumab and placebo. At Week 24 (last observation carried forward), both adalimumab- and placebo-treated patients demonstrated respective increases in mean values for alanine transaminase (2.4

vs 2.1 U/l), aspartate transaminase (2.9 vs 2.0), and cholesterol (7.4 vs 1.6 mg/dl). The difference in mean cholesterol levels between the adalimumab and placebo groups at Week 24 was statistically significant ($p \leq 0.01$).

By Week 24, 26.5% (66/249) of adalimumab-treated patients and 15.2% (39/256) of placebo-treated patients converted from ANA negative to positive ($p \leq 0.01$), whereas 11.1% (6/54) of adalimumab-treated patients and 12.2% (5/41) of placebo-treated patients converted from ANA positive to negative. By Week 24, conversion from anti-dsDNA negative to positive occurred in 12.5% (36/289) of the adalimumab group and 1.0% (3/299) of the placebo group, whereas conversion from anti-dsDNA positive to negative occurred in 13.0% (3/23) of the adalimumab group and 0% (0/17) of the placebo group. No patient was reported to have lupus-like illness over the course of the study.

Efficacy. Addition of adalimumab to standard antirheumatic therapy significantly improved signs and symptoms of RA. Patients receiving adalimumab plus standard antirheumatic therapy achieved statistically superior ACR20 (52.8% vs 34.9%), ACR50 (28.9% vs 11.3%), and ACR70 (14.8% vs 3.5%) response rates, compared with placebo, respectively, at Week 24 (nonresponder imputation) ($p \leq 0.001$ by Pearson's chi-square test with no corrections made for multiple comparisons). The percentage of adalimumab-treated patients achieving an ACR20 response increased from Weeks 2 through 8 and was maintained above 50% through Week 24 (Figure 2A). Similarly, the percentages of adalimumab-treated patients achieving ACR50 and ACR70 responses increased from Weeks 2 through 12 and were thereafter maintained (Figures 2B and 2C). At Week 24, adalimumab 40 mg administered sc every other week with one or 2 traditional DMARD achieved significantly greater ACR20 responses rates than did placebo ($p \leq 0.01$) (Figure 3A). ACR20 response rates among adalimumab- and placebo-treated patients receiving no concomitant traditional DMARD were 49.1% (28/57) and 33.3% (16/48), respectively. At Week 24, adalimumab 40 mg administered sc every other week with 0, 1, or 2 traditional DMARD achieved significantly greater ACR50 and ACR70 response rates than did placebo ($p \leq 0.05$) (Figures 3B and 3C).

Fewer adalimumab- than placebo-treated patients required rescue therapy (7.3% vs 13.3%), either as an increase in concomitant traditional DMARD dose (1.9% vs 4.4%) or corticosteroid dose (4.4% vs 6.3%) or addition of a new traditional DMARD therapy (0.9% vs 2.5%) because of persistently active disease.

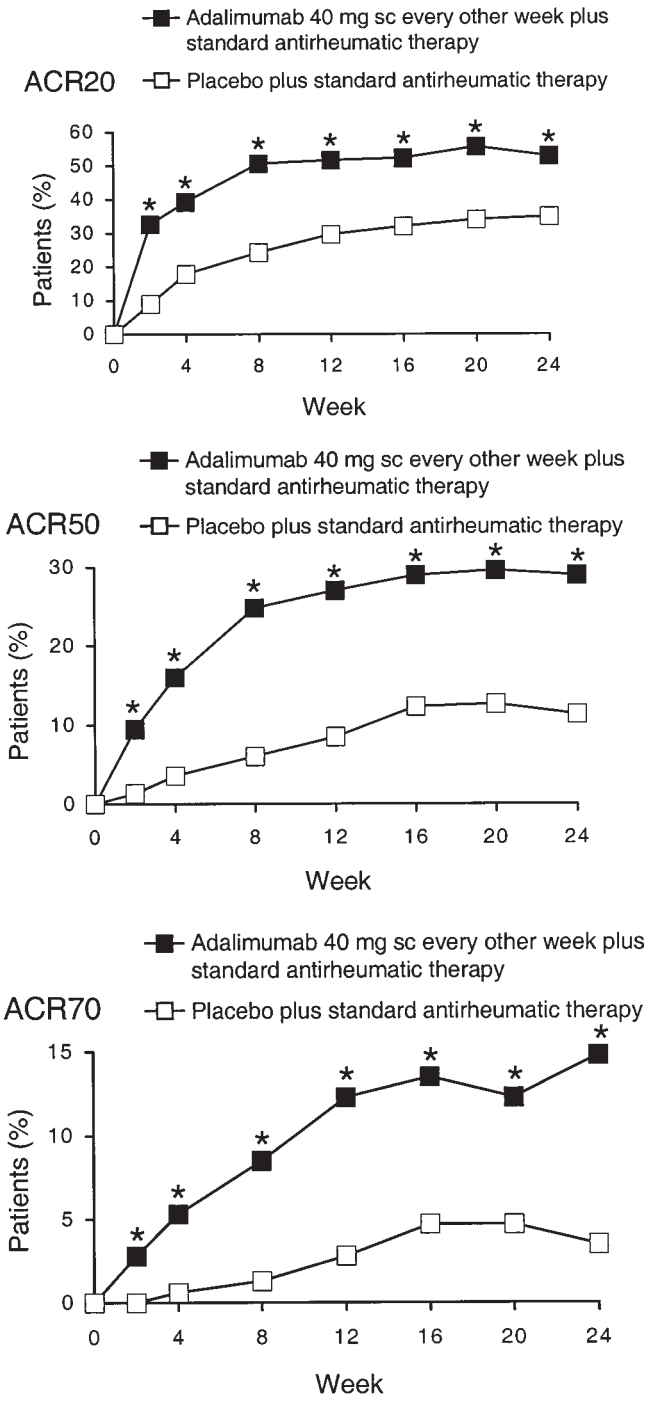

Figure 2. Percentages of patients who had improvements in ACR criteria of 20%, 50%, and 70% (ACR20, ACR50, and ACR70, respectively) with adalimumab 40 mg administered subcutaneously (sc) every other week plus standard antirheumatic therapy or with placebo plus standard antirheumatic therapy. *$p \leq 0.05$ vs placebo (based on 95% confidence intervals).

DISCUSSION

This is the first clinical study examining the use of a TNF-α antagonist in a manner that mimics regular clinical practice. This 24-week, randomized, controlled trial demonstrated that adalimumab 40 mg given sc every other week is safe and effective when used with concomitant standard antirheumatic therapy, including one or more traditional DMARD, low dose corticosteroids, NSAID, and/or analgesics. The incidence of adverse events, serious adverse events, severe or life-threatening adverse events, adverse

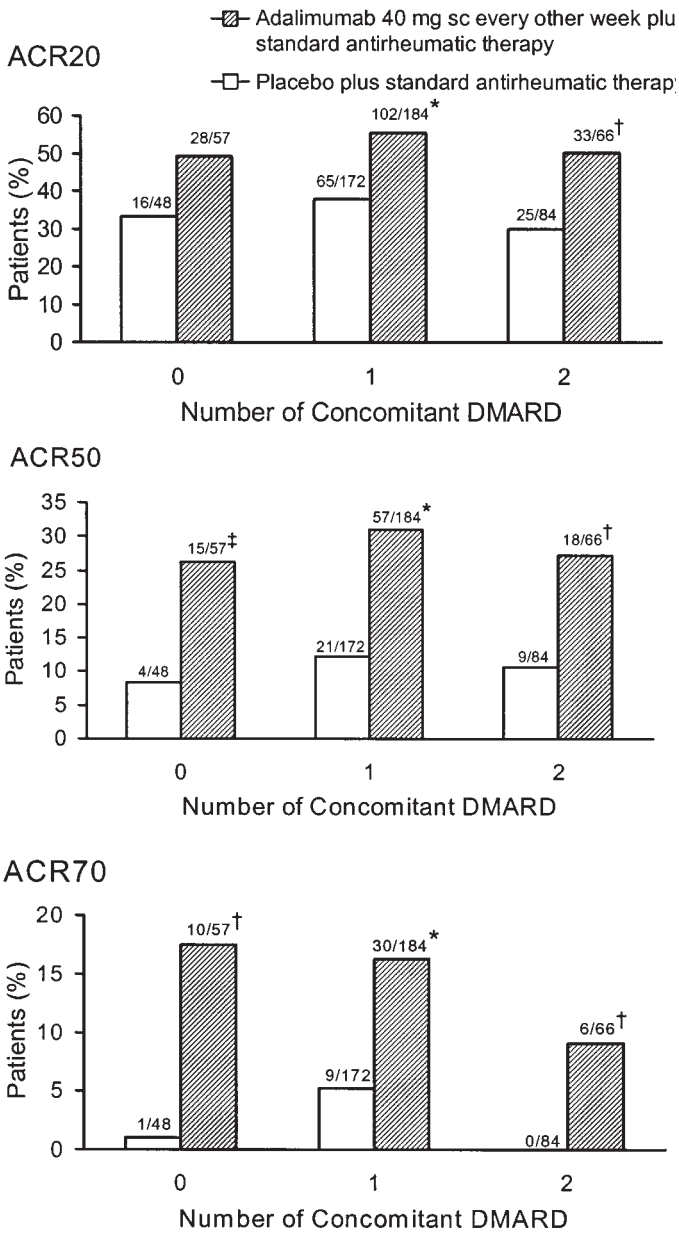

Figure 3. Percentages of patients at Week 24 who had improvements in ACR criteria of 20%, 50%, and 70% (ACR20, ACR50, and ACR70, respectively) with adalimumab 40 mg administered subcutaneously (sc) every other week plus standard antirheumatic therapy or with placebo plus standard antirheumatic therapy by number of concomitant traditional DMARD. *p ≤ 0.001; †p ≤ 0.01; and ‡p ≤ 0.05 vs placebo at Week 24 (by Pearson's chi-square test with no corrections made for multiple comparisons).

events leading to withdrawal, infection, and serious infection were statistically similar between treatment with adalimumab plus standard antirheumatic therapy and standard antirheumatic therapy alone. Adverse event profiles in adalimumab-treated patients did not appear to vary according to the number of concomitant traditional DMARD. The adverse event profile in patients receiving adalimumab as monotherapy, without background DMARD treatment, was comparable to that in patients receiving adalimumab in combination with traditional DMARD. Further, adalimumab was well tolerated when administered with commonly used, traditional DMARD, including MTX, antimalarial drugs, leflunomide, and sulfasalazine.

The incidence of the most frequently reported noninfectious and infectious adverse events was comparable between patients treated with adalimumab and placebo with or without concomitant DMARD therapy. However, one death (because of herpes zoster with secondary necrotizing fasciitis from streptococcal A superinfection) and one case of lymphoma occurred in adalimumab-treated patients, compared with none in placebo-treated patients. No patient developed reactivation of tuberculosis, although several patients in both groups were known to be positive for purified protein derivative. The rate of serious infections in patients treated with adalimumab in this 24-week study (0.028/patient-year) was comparable to the estimated yearly rate of serious infections among the general RA population (0.031 to 0.096/patient-year)[11,12]. There were no consistent treatment-related changes in standard laboratory tests. Although more adalimumab-treated patients than placebo-treated patients converted from ANA and anti-dsDNA antibody negative to positive, no patient was reported to have lupus-like illness. Such patients will have to be followed in the future to be sure that they do not develop a lupus-like illness.

Adding adalimumab to standard antirheumatic therapy significantly and rapidly improved the signs and symptoms of RA. The therapeutic effect of adalimumab was evident at Week 2, the first study visit, and was maintained through the rest of the 24-week study period. At Week 24, adalimumab-treated patients achieved superior ACR20, 50, and 70 response rates. As an additional indication of improved efficacy, fewer adalimumab-treated patients than placebo-treated patients (7.3% vs 13.3%) required increased doses of or addition of traditional DMARD therapy or increased doses of corticosteroid for persistently active disease. Significant ACR response rates were attained in the adalimumab treatment group regardless of number of concomitant traditional DMARD (0, 1, or 2), indicating that adalimumab offers additional therapeutic benefit superimposed on benefits of a wide range of traditional DMARD regimens. The increase in hemoglobin and decrease in white blood cell and platelet counts were also indicative of the superior antiinflammatory activity of adalimumab. Moreover, mean total cholesterol levels significantly increased with adalimumab therapy, possibly because of an improvement in the inflammatory state. Effective antirheumatic therapy has been shown to correct the dyslipoproteinemia associated with inflammation, leading to an increase in total cholesterol levels but not in the low density lipoprotein cholesterol to high density lipoprotein cholesterol ratio[13].

Because treatment with a single DMARD often fails to

adequately control disease activity, clinicians are increasingly prescribing multiple DMARD in combination[1,2]. In a recent survey of US rheumatologists, 97% reported using combination DMARD therapy, 47% reported that they consider it appropriate as first-line therapy, and 46% reported that they prescribe it in at least 30% of their patients[14]. Results from randomized clinical trials support the very early use of combination traditional DMARD therapy[15,16]. The advent of biologic DMARD that block the effects of TNF-α has expanded possible combination therapy options for RA, although currently available TNF-α antagonists have been systematically evaluated only in combination with MTX, and not other traditional DMARD[17-20]. Anakinra, an interleukin 1 receptor antagonist, has been evaluated with concomitant DMARD, corticosteroids, and/or NSAID in a similar safety trial[21]. Our study is the first randomized clinical trial to examine the use of a TNF-α antagonist with a variety of currently used traditional DMARD.

This investigation provides key data on the safety and efficacy of adalimumab, the first fully human anti–TNF-α mAb to be studied in RA, when given to a heterogeneous group of patients with RA in combination with multiple other RA therapies, as frequently is encountered in actual clinical practice. Addition of adalimumab 40 mg given sc every other week to standard antirheumatic therapy was safe and well tolerated and provided significant, rapid, and sustained improvements in signs and symptoms of RA. Prior to the availability of biologic DMARD, these patients would have been considered responders to standard antirheumatic therapy despite having very active disease. The results of this study suggest that what was once considered to be a good response to standard antirheumatic therapy has become inadequate. Adalimumab appears to be a safe and effective therapeutic option for patients with active RA who have an inadequate response to standard antirheumatic therapy, including one or more traditional DMARD, corticosteroids, NSAID, and analgesics.

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