Efficacy, Pharmacokinetic, and Safety Assessment of Adalimumab, a Fully Human Anti–Tumor Necrosis Factor–Alpha Monoclonal Antibody, in Adults with Rheumatoid Arthritis Receiving Concomitant Methotrexate: A Pilot Study

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ABSTRACT

Background: Because traditional therapies for rheumatoid arthritis (RA) such as methotrexate (MTX) do not produce an adequate response in many patients, newer therapies that block the proinflammatory cytokine tumor necrosis factor–alpha (TNF-alpha) are increasingly being used in combination with MTX.

Objective: This study evaluated the efficacy, pharmacokinetics, and safety profile of adalimumab, a fully human anti–TNF-alpha monoclonal antibody, when added to continuing MTX therapy.

Methods: This Phase I, randomized, dose-titration study consisted of a 4-week, double-blind, placebo-controlled treatment phase and a 26-month, open-label continuation phase. Patients with RA who had been taking stable doses of MTX (mean dose, 17 mg/wk) for ≥3 months before enrollment with an inadequate response were randomly assigned to receive 2 single doses of either adalimumab 0.25, 0.5, 1, 3, or 5 mg/kg IV or placebo in the double-blind phase. In the open-label phase, patients received treatment with 1 of the doses of adalimumab every other week or
monthly for 18 months; patients were then switched to adalimumab 40 mg IV or SC every other week or monthly. The main efficacy end point was 20% improvement in American College of Rheumatology response criteria (ACR20). Other efficacy end points included 50% (ACR50) and 70% improvements in ACR response criteria. Pharmacokinetic parameters were analyzed for adalimumab and MTX during both phases of the study. Serum adalimumab concentrations were analyzed using a validated enzyme-linked immunosorbent assay relying on the double-antigen principle. Peak and trough concentrations were determined from observed concentration-time data, and a modeling approach was used to estimate total serum clearance, mean apparent terminal half-life, apparent volume of distribution at steady state, and area under the concentration-time curve.

Results: Sixty patients entered the double-blind phase, 45 receiving adalimumab and 15 receiving placebo; 1 placebo recipient chose not to continue into the open-label phase. Overall, the study population included 47 (78.3%) women and 13 (21.7%) men. The mean age was 52.9 years (range, 24–73 years), and the mean body weight was 69.7 kg (range, 43–98 kg). ACR20 and ACR50 responses were achieved on at least 1 assessment during the 4-week double-blind phase by a respective 29 (64.4%) and 11 (24.4%) of 45 patients receiving active treatment and by 4 (26.7%) and none of the 15 patients receiving placebo. Responses to adalimumab were rapid, with 10 (22.2%) of 45 patients achieving an ACR20 response within 24 hours of dosing. Of 29 adalimumab recipients who had an ACR20 response, 18 (62.1%) had a duration of response (time from first occurrence of a response to first occurrence of a nonresponse) of 1 to 2 weeks, and 11 (37.9%) had a duration of response of 3 to 13 weeks. The pharmacokinetic properties of adalimumab appeared to be linear. The mean apparent terminal half-life after a single intravenous dose of adalimumab ranged from 15 to 19 days in the 5 dose groups. Repeated administration of adalimumab had no statistically significant effect on the pharmacokinetics of MTX, indicating that dose adjustment of MTX is not necessary. Adalimumab was well tolerated, and there were no dose-related adverse events.

Conclusions: Among patients with active RA who had not had an adequate response to MTX, addition of adalimumab to MTX achieved statistically significant, long-term improvement compared with placebo plus MTX (P ≤ 0.05), as indicated by ACR responses at 26 months. The combination was well tolerated. Adalimumab exhibited linear pharmacokinetics. In this selected patient population, adalimumab’s long half-life of 15 to 19 days supports every-other-week dosing. Coadministration of adalimumab did not alter serum levels of MTX. (Clin Ther. 2003;25:1700–1721) Copyright © 2003 Excerpta Medica, Inc.

Key words: adalimumab, disease-modifying antirheumatic drug, fully human monoclonal antibody, methotrexate, rheumatoid arthritis, tumor necrosis factor–alpha.
INTRODUCTION

Rheumatoid arthritis (RA) is a chronic idiopathic autoimmune disease characterized by symmetrical synovitis, inflammatory exudates in the joint cavity, and potential erosion of articular cartilage and marginal bone. Some 1% to 2% of the adult population worldwide are affected by RA, as indicated by epidemiologic research based on American College of Rheumatology (ACR) criteria. The long-term prognosis of RA is poor, with ~80% of patients becoming disabled after 20 years and life expectancy reduced by 3 to 18 years. Standard agents for RA, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and traditional disease-modifying antirheumatic drugs (DMARDs), are not consistently effective and do not improve long-term outcomes. Although the traditional DMARD methotrexate (MTX) is the treatment of choice for moderately to severely active RA, many patients fail to achieve an adequate or sustained response to MTX alone. Hence, MTX is often combined with other traditional DMARDs to improve efficacy. Up to 99% of US rheumatologists have reported using DMARD combinations in >25% of their patients with RA; the most widely used combination was MTX and hydroxychloroquine, prescribed by 99% of physicians surveyed.

The proinflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) plays an integral role in the progression of inflammatory synovitis and articular matrix degradation in RA and represents a potential therapeutic target. Produced mainly by monocytes and macrophages, TNF-alpha mediates a number of pathologic processes by promoting synthesis of other proinflammatory cytokines; stimulating endothelial cells to express adhesion molecules that attract leukocytes into affected joints; accelerating the production of metalloproteinases by synovial macrophages, fibroblasts, osteoclasts, and chondrocytes; and suppressing the synthesis of cartilage proteoglycans. Two biologic DMARDs that bind to and inactivate TNF-alpha are commercially available for the treatment of RA: infliximab, a chimeric (75% human and 25% mouse peptide sequences) anti-TNF-alpha monoclonal antibody, and etanercept, a recombinant human TNF receptor (p75)-Fc fusion protein. Adalimumab is a novel biologic DMARD and the first fully human (100% human peptide sequences) anti-TNF alpha monoclonal antibody to be investigated for the treatment of RA.

Genetically engineered through phage display technology, adalimumab contains neither nonhuman components nor artificially fused human peptide sequences. Indistinguishable in structure and function from naturally occurring human immunoglobulin G1 (IgG1), adalimumab has a terminal half-life (t1/2) comparable to that of human IgG1 (~2 weeks). With high specificity and affinity for TNF-alpha (dissociation constant = 6 × 10^{-10} mol/L) but not for such other cytokines as TNF-beta (lymphotoxin), adalimumab exerts its therapeutic effects...
by blocking the interaction of TNF-alpha with the p55 and p75 TNF-alpha cell surface receptors. Preliminary clinical trials have demonstrated the ability of adalimumab to control the signs and symptoms of RA.

The objective of the present 26-month study was to assess the efficacy, pharmacokinetics, and safety profile of adalimumab administered intravenously or subcutaneously in combination with stable doses of MTX in patients with active RA who had not responded adequately to MTX.

PATIENTS AND METHODS

Patients

Eligible patients were aged ≥18 years, had a confirmed diagnosis of RA based on ACR criteria, and had an inadequate response to existing MTX therapy, as evidenced by ≥6 swollen joints (out of a maximum of 66), ≥6 tender joints (out of a maximum of 68), and ≥1 of the following: erythrocyte sedimentation rate (ESR) >28 mm/h and morning stiffness lasting longer than 45 minutes. On entering the study, all patients had been receiving MTX for ≥3 months at stable weekly doses of 12.5 to 25 mg (10 mg if unable to tolerate higher doses). MTX doses remained unchanged during the study, unless patients developed toxicity that in the opinion of the investigator, necessitated a dose reduction. All other DMARDs were discontinued ≥3 weeks before the beginning of the study, although stable doses of NSAIDs and corticosteroids (equivalent to a maximum of 10 mg/d prednisone) were allowed.

Exclusion criteria consisted of administration of intra-articular or intramuscular corticosteroids within 4 weeks before screening; joint surgery within 2 months before screening; previous anti-CD4 therapy; HIV infection; history of active tuberculosis or listeriosis; a major episode of infection requiring hospitalization within 30 days before screening; any active infection at the time of screening; pregnancy or lactation; and the use of an investigational chemical or biologic drug within 2 and 6 months, respectively, before screening. Patients were also excluded if they had any clinically significant medical history that in the opinion of the investigator, placed the patient at unacceptable risk. Additional exclusions were a serum creatinine level >1.5 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥2 times the upper limit of normal, bilirubin level ≥3 mg/dL, hemoglobin value <9.5 g/dL for men or <9.0 g/dL for women, total white blood cell count (WBC) <3 × 10^9 cells/L, or platelet count <150 × 10^9 cells/L.

Study Protocol

This Phase I, randomized, dose-titration study was conducted at 6 centers in the United States and Canada. It consisted of a 4-week double-blind, placebo-controlled treatment period and a 26-month, open-label continuation phase (Figure 1).
Figure 1. Study design. MTX = methotrexate; qow = every other week. *Patients in whom the dose could be increased to 1 mg/kg qow for lack of efficacy after 6 doses at 0.25 or 0.5 mg/kg. †Patients were withdrawn if they had achieved a 20% improvement in American College of Rheumatology response criteria and later lost this response for >2 consecutive weeks.
The institutional review board at each study site approved the study protocol, and each patient gave written informed consent. An equal number of patients were to be recruited by each center.

During the double-blind period, each patient package was assigned a number from 1 to 60. Randomization occurred centrally. Dose levels were assigned randomly for the first 60 patients, and sets of 10 numbers were assigned to each of the 6 sites. For example, site 1 received patient packages 0001 to 0010, and patients were randomly assigned to receive adalimumab doses of 0.25, 0.5, 1, 3, or 5 mg/kg or placebo in a 3:1 ratio of adalimumab to placebo recipients. Study drug was administered into a peripheral vein as a single infusion over 3 to 5 minutes using standard commercial tubing. After receipt of study drug, patients were hospitalized for 24 hours for collection of blood samples for pharmacokinetic analysis. Patients were examined weekly for at least 4 weeks. They received the second dose of blinded study medication after 4 weeks or on loss of response, based on ACR 20% or 50% response criteria (ACR20 and ACR50, respectively), as described in a later section. Following the second dose of double-blind treatment, all patients, including those who had received placebo in the double-blind phase, received adalimumab in the open-label continuation phase. Allocation of patients to the 5 adalimumab dose levels in the open-label portion of the study took into account safety information gathered during the randomized phase of the double-blind study and provided comparable sample sizes for each of the 5 dose groups.

Initially, dosing occurred every other week; the dosing interval was lengthened to every month if the patient had a good response (met ACR50 criteria) after 24 weeks of treatment. In those receiving adalimumab 0.25 or 0.5 mg/kg every other week, the dose could be increased to 1 mg/kg every other week for lack of efficacy after 6 doses at the original level. Patients receiving adalimumab ≥1 mg/kg who achieved an ACR20 response but later lost this response at ≥2 consecutive assessments were withdrawn from the study. During the second year of treatment, patients were switched from a weight-based dose to an open-label 40-mg total-body dose administered intravenously or subcutaneously every other week or monthly. Patients were allowed to self-administer subcutaneous doses. Patients could be withdrawn from the study in the case of a significant adverse event or a reduction of the MTX dose to <7.5 mg/wk because of toxicity.

**Efficacy Assessment**

The main efficacy end point was ACR20. Other efficacy end points included ACR50 and ACR70 (70% improvement in ACR criteria). ACR20, ACR50, and ACR70 responses were defined as the corresponding rates of reduction in tender joint count and swollen joint count plus corresponding degrees of improvement in ≥3 of the following core components: patient’s assessment of pain, patient’s global assessment of disease activity, physician’s global assessment of disease ac-
tivity, Health Assessment Questionnaire (HAQ) Disability Index, and ESR or serum C-reactive protein (CRP) concentration.

During the double-blind phase, ACR20 and ACR50 responses were assessed at 24 hours after administration of study drug and on days 8, 15, 22, and 29. The duration of ACR20 and ACR50 responses (time from first occurrence of a response to first occurrence of a nonresponse) was determined. During the open-label continuation phase, ACR20, ACR50, and ACR70 responses were assessed on entry into the phase, monthly during the first 6 months, every other month between months 6 and 18, and at months 22 and 26.

Pharmacokinetic Assessment

Adalimumab

In the double-blind phase, serial blood samples for determination of serum adalimumab concentrations were obtained before dosing and at 0.25, 2, 6, 12, and 24 hours after dosing, as well as at weekly follow-up examinations on days 8, 15, 22, and 29. Intermittent blood sampling was performed during the 26-month open-label phase; samples were taken mainly before dosing, except during 1 dosing interval at the month-5 visit, when serial samples were taken at 0.25, 2, 6, and 24 hours after dosing.

Blood samples (~5 mL) were drawn into collection tubes with no anticoagulant. Serum was isolated by centrifugation and stored frozen until shipment to MDS Pharma Services, Inc., St. Laurent, Quebec, Canada, where they were stored frozen pending analysis. Samples were also analyzed at Abbott Laboratories in Ludwigshafen, Germany.

Serum concentrations of adalimumab were analyzed using a validated enzyme-linked immunosorbent assay that relied on the double-antigen principle (data on file, Abbott Laboratories, Abbott Park, Illinois). Briefly, plates were precoated with avidin or streptavidin. Next, recombinant human TNF-alpha coupled with biotin was bound to the microtiter plates as the capture reagent. Human serum samples (study, calibrator, or quality control sample) were then added to the plates. After a washing step to remove unbound serum components, peroxidase labeled TNF-alpha was added, which bound to the adalimumab and formed a bridge. After a second washing step, the amount of bound peroxidase was determined by the addition of hydrogen peroxide and tetramethylbenzidine. The peroxidase product produced by these reagents results in a color intensity that is proportional to the adalimumab content of the sample. The limit of quantitation was 0.72 mg/L in the original (undiluted) serum sample.

The calibration curves and quality control samples indicated that the results for adalimumab in human serum were valid and reliable. Interassay accuracy ranged from 96.7% to 101.0% of nominal values, and interassay precision was ≤10.0% at quality control sample concentrations ranging from 7.2 to 64.0 ng/mL in diluted
samples. In addition, no measurable adalimumab concentrations were observed in the predose serum samples, which led investigators to the conclusion that interference from endogenous human antibody was not a concern with this assay.

Peak ($C_{\text{max}}$) and predose ($C_{\text{pre, trough}}$) concentrations were determined from the observed concentration-time data. As the data consisted of both serial and sparse serum concentration data, individual pharmacokinetic parameters were obtained as post hoc estimates using the population pharmacokinetic analysis software NONMEM version V (University of California at San Francisco). Pharmacokinetic parameters that were estimated using a modeling approach included total serum clearance (CL), $t_{1/2}$, apparent volume of distribution at steady state ($V_{ss}$), and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).

**Methotrexate**

Blood samples (~5 mL) for the determination of MTX concentrations were obtained at 2 and 6 hours after MTX dosing during screening, and at 2, 6, and 24 hours after MTX dosing on day 1 and again during a dosing interval at the month-5 visit for assessment of acute and chronic effects of adalimumab on MTX pharmacokinetics. Serum concentrations of MTX were analyzed at Mayo Medical Laboratory, Rochester, Minnesota, using a commercial fluorescence polarization immunoassay kit. Samples were stored frozen until assayed. Six quality control samples ranging from 0.07 to 500 μmol/l were analyzed in each run. The acceptance range for quality control samples was <15% of nominal concentrations. The limit of quantification was 0.05 μmol/L. Because most concentrations at 24 hours after MTX dosing were below the limit of quantitation, exposure was evaluated using the AUC from 2 to 6 hours ($AUC_{2-6}$) calculated from the individual serum drug-concentration times. In addition, this clinical trial was designed primarily to investigate the effect of adalimumab on MTX exposure using sparse data techniques, such as single-concentration and partial-area estimates. Statistical analyses were performed to estimate the effect of adalimumab on MTX exposure within patients by comparing the $AUC_{2-6}$ obtained at screening and during the double-blind and open-label phases.

**Safety Assessment**

Assessment of the safety profile was based on adverse events reported by patients, as well as on the findings of physical examinations and clinical laboratory evaluations (eg, hematology tests [red blood cell count, hemoglobin, hematocrit, WBC] and serum chemistry tests [AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase, creatine phosphokinase, glucose, cholesterol, triglycerides, total protein, albumin, sodium, potassium, chloride, calcium, inorganic phosphorus, uric acid, urea, creatinine, IgA, IgG, IgM, CRP, rheumatoid factor, and ESR]).
During the double-blind phase, physical examinations and clinical laboratory evaluations were performed at baseline, 24 hours after administration of study drug, and on days 8, 15, 22, and 29. During the open-label continuation phase, physical examinations and clinical laboratory evaluations were performed on a monthly basis during the first 18 months and then at months 22 and 26.

Statistical Analysis
A sample size of 9 patients receiving active treatment and 3 receiving placebo in each dose group was assumed to be sufficient for this pilot trial. Continuous data were described as mean (SD), and categorical data were described in terms of number (%). Efficacy was summarized on an intent-to-treat basis, including all patients who took ≥1 dose of study medication and having ≥1 available measurement. Descriptive statistics and simple linear regression analyses were performed to indicate variability in pharmacokinetic data and to establish dose proportionality (eg, parameters such as Vss and CL were investigated graphically as a function of covariates such as sex, age, and body weight to determine whether the slopes were significantly different from zero). Differences in the AUC2–6 for MTX between screening and day 1, between day 1 and month 5, and between screening and month 5 were determined for each patient; these within-patient differences were tested for significance using a paired t test. Statistical significance was set at P ≤ 0.05 for all comparisons, without adjustment for multiple comparisons.

RESULTS
Patient Disposition
Sixty patients were enrolled in the initial double-blind, placebo-controlled phase (45 in the adalimumab group and 15 in the placebo group). One placebo recipient decided not to continue into the open-label phase because of lack of efficacy; therefore, 59 patients entered this phase. Of these 59 patients, 19 (32.2%) withdrew during the continuation phase for the following reasons: lack of efficacy (n = 10), adverse events (n = 3), withdrawal of consent (n = 3), and loss to follow-up (n = 3). By the end of the open-label continuation phase, all 40 remaining patients were receiving adalimumab 40 mg IV or SC every other week or monthly.

Demographic and Baseline Characteristics
Patients’ demographic and baseline characteristics are presented in Table I. Although there was some variability in characteristics between treatment groups, the differences were not greater than the SDs. Overall, the study population included 47 (78.3%) women and 13 (21.7%) men. The mean age was 52.9 years (range, 24–73 years), and the mean body weight was 69.7 kg (range, 43–98 kg).
<table>
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<tr>
<th>Characteristic</th>
<th>0.25 (n = 9)</th>
<th>0.5 (n = 9)</th>
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<th>3 (n = 9)</th>
<th>5 (n = 9)</th>
<th>Placebo (n = 15)</th>
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<tr>
<td>Age, y</td>
<td>50.0 (16.5)</td>
<td>55.8 (12.6)</td>
<td>51.0 (11.6)</td>
<td>56.2 (13.7)</td>
<td>53.9 (11.8)</td>
<td>51.8 (13.5)</td>
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<td>Sex, no. (%)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Female</td>
<td>8 (88.9%)</td>
<td>6 (66.7%)</td>
<td>6 (66.7%)</td>
<td>7 (77.8%)</td>
<td>8 (88.9%)</td>
<td>11 (80.0%)</td>
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<td>Male</td>
<td>1 (11.1%)</td>
<td>3 (33.3%)</td>
<td>3 (33.3%)</td>
<td>2 (22.2%)</td>
<td>1 (11.1%)</td>
<td>3 (20.0%)</td>
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<td>Body weight, kg</td>
<td>74.7 (14.5)</td>
<td>70.5 (13.5)</td>
<td>70.8 (15.4)</td>
<td>68.9 (13.3)</td>
<td>65.8 (11.4)</td>
<td>68.3 (12.6)</td>
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<td>Disease duration, y</td>
<td>16.7 (13.1)</td>
<td>13.4 (6.7)</td>
<td>16.4 (10.5)</td>
<td>15.0 (10.6)</td>
<td>18.4 (8.5)</td>
<td>15.0 (10.2)</td>
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<td>Tender joint count (maximum of 68)</td>
<td>30.6 (9.4)</td>
<td>28.3 (8.4)</td>
<td>36.6 (14.0)</td>
<td>27.9 (10.9)</td>
<td>34.1 (8.4)</td>
<td>31.5 (11.8)</td>
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<td>Swollen joint count (maximum of 66)</td>
<td>17.0 (8.1)</td>
<td>16.7 (9.8)</td>
<td>19.0 (8.0)</td>
<td>17.1 (9.9)</td>
<td>18.9 (9.2)</td>
<td>21.4 (9.1)</td>
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<td>Patient's assessment of pain, mm*</td>
<td>55.0 (24.8)</td>
<td>57.0 (20.4)</td>
<td>62.4 (24.4)</td>
<td>38.8 (20.1)</td>
<td>51.6 (25.4)</td>
<td>47.5 (26.9)</td>
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<td>Patient’s global assessment of disease activity, mm‡</td>
<td>57.2 (21.5)</td>
<td>58.0 (18.2)</td>
<td>66.4 (25.4)</td>
<td>43.2 (24.1)</td>
<td>51.7 (26.1)</td>
<td>48.6 (25.6)</td>
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<td>HAQ score‡</td>
<td>1.3 (0.8)</td>
<td>0.9 (0.6)</td>
<td>1.5 (0.8)</td>
<td>1.0 (0.7)</td>
<td>1.4 (0.4)</td>
<td>1.1 (0.8)</td>
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<td>Erythrocyte sedimentation rate, mm/h</td>
<td>38.2 (20.8)</td>
<td>27.7 (39.4)</td>
<td>40.1 (32.2)</td>
<td>42.1 (34.5)</td>
<td>48.2 (30.3)</td>
<td>37.3 (23.0)</td>
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<td>C-reactive protein, mg/dL</td>
<td>3.9 (4.0)</td>
<td>1.6 (3.3)</td>
<td>2.2 (1.9)</td>
<td>2.0 (2.3)</td>
<td>1.7 (1.7)</td>
<td>2.4 (3.1)</td>
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<tr>
<td>Total methotrexate dose, mg/wk</td>
<td>16.7 (3.1)</td>
<td>20.0 (4.1)</td>
<td>16.9 (3.5)</td>
<td>16.4 (2.8)</td>
<td>14.2 (4.7)</td>
<td>17.3 (4.6)</td>
</tr>
</tbody>
</table>

HAQ = Health Assessment Questionnaire Disability Index.

*100-mm Visual analog scale from 0 = no pain to 100 = severe pain.

‡100-mm Visual analog scale from 0 = no symptoms to 100 = severe symptoms.

‡On a scale from 0 = best to 3 = worst.
The mean duration of disease activity was 16.0 years in the combined adalimumab groups and 15.0 (10.2) years in the placebo group. The mean number of tender joints was 31.5 in the combined adalimumab groups and 31.5 (11.8) in the placebo group. The mean number of swollen joints was 17.7 in the combined adalimumab groups and 21.4 (9.1) in the placebo group. The mean HAQ score was 1.2 in the combined adalimumab groups and 1.1 (0.8) in the placebo group. The mean ESR was 39.3 mm/h in the combined adalimumab groups and 37.3 mm/h in the placebo group. The mean total weekly MTX dose at baseline for all patients was 17 mg (range, 10–25 mg). Overall, the mean number of previous RA-specific therapies discontinued before study entry was 4.0 for adalimumab recipients and 2.9 for placebo recipients. The most frequently used therapeutic class for RA was antimalarial agents (33 [55.0%]), followed by parenteral gold (31 [51.7%]) and sulfasalazine and similar agents (22 [36.7%]). The adalimumab and placebo groups were similar with respect to the proportions of patients using RA therapies (antimalarial agents: 53.3% adalimumab, 60.0% placebo; gold preparations: 51.1% and 53.3%, respectively; sulfasalazine and similar agents: 37.8% and 33.3%). In addition, 23 patients (38.3%) were receiving RA-specific steroid therapy before entering the study, either as glucocorticoids (12 [20.0%]) or local corticosteroids (11 [18.3%]), which was also discontinued before the study.

**Efficacy Results**

All 60 patients were included in the efficacy assessments for the double-blind phase. Twenty-nine (64.4%) of 45 adalimumab recipients achieved an ACR20 response on at least 1 assessment after therapy, whereas 4 (26.7%) of 15 placebo recipients achieved an ACR20 response (Table II). Overall, the greatest ACR20 response rate during the double-blind phase occurred with adalimumab 0.5 mg/kg (8/9 [88.9%]). ACR20 response rates reached a maximum on day 15, with 20 (44.4%) adalimumab recipients achieving a response. Ten (22.2%) patients responded to adalimumab within 24 hours after drug administration; no placebo recipients responded within this time. Ten (22.2%) patients receiving adalimumab maintained an ACR20 response on day 29 of the double-blind period, compared with no placebo recipients. Of 29 adalimumab recipients who achieved an ACR20 response, 18 (62.1%) had a duration of response of 1 to 2 weeks, and 11 (37.9%) had a duration of response of 3 to 13 weeks.

Eleven (24.4%) adalimumab recipients achieved an ACR50 response on at least 1 assessment after therapy, whereas no placebo recipients achieved an ACR50 response (Table II). Overall, the greatest ACR50 response rate during the double-blind period was observed with adalimumab 0.5 mg/kg (4/9 [44.4%]). ACR50 response rates reached a maximum on day 29, with 5 (11.1%) of 45 adalimumab recipients achieving a response. One patient who received adalimumab 0.25
Table II. Number (%) of patients achieving 20% and 50% improvement in American College of Rheumatology response criteria (ACR20 and ACR50, respectively) on at least 1 assessment within 4 weeks after study drug administration.

<table>
<thead>
<tr>
<th>Adalimumab Dose, mg/kg</th>
<th>0.25 (n = 9)</th>
<th>0.5 (n = 9)</th>
<th>1 (n = 9)</th>
<th>3 (n = 9)</th>
<th>5 (n = 9)</th>
<th>All Doses (n = 45)</th>
<th>Placebo (n = 15)</th>
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</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>5 (55.6)*</td>
<td>8 (88.9)*</td>
<td>4 (44.4)*</td>
<td>7 (77.8)*</td>
<td>5 (55.6)*</td>
<td>29 (64.4)*</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>ACR50</td>
<td>3 (33.3)</td>
<td>4 (44.4)</td>
<td>1 (11.1)</td>
<td>2 (22.2)</td>
<td>1 (11.1)</td>
<td>11 (24.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 versus placebo, based on 95% CI.
mg/kg achieved an ACR50 response within 24 hours after drug administration. Four (8.9%) adalimumab recipients, 2 of whom were receiving adalimumab 0.5 mg/kg, maintained an ACR50 response beyond day 29. Of the 11 patients who had an ACR50 response, 9 (81.8%) had a duration of response of 1 to 2 weeks, and 2 (18.2%) had a duration of response of 4 weeks.

For each of the ACR core components, ≥1 adalimumab group had statistically significant improvements from baseline (P ≤ 0.05) (Table III). There was no apparent dose relationship with respect to these improvements. This finding suggests that at the doses administered during the placebo-controlled portion of the study, all adalimumab doses performed equivalently or that the dose-response curve was still flat. The placebo group showed no statistically significant improvements.

At month 18, all patients were switched to a fixed dose of adalimumab 40 mg every other week or monthly. Thereafter, all patients generally maintained the same degree of disease activity and the same extent of improvement in ACR response criteria (Figure 2).

Pharmacokinetic Assessments

Adalimumab

Single-dose mean pharmacokinetic values by dose group are shown in Table IV. After single doses of adalimumab 0.25 to 5 mg/kg IV over 3 to 5 minutes, a biphasic pattern of decline was apparent in the concentration-time curves, and observed concentrations were consistent with a 2-compartment model (Figure 3). However, the number of compartments may depend on the limits of detection. The Cmax for adalimumab occurred soon after completion of the IV infusion. Mean plasma concentrations, Cmax, and AUC values increased proportionally with an increase in dose (Table IV, Figure 4), indicating that adalimumab exposure increased proportionally with increasing dose. The CL of adalimumab was considered to be low (0.009–0.012 L/h) and not dose related. The mean apparent terminal t1/2 ranged from 353.4 to 464.1 hours (15–19 days) in the 5 dose groups. The slight tendency toward lower t1/2 and higher CL at lower doses (0.25, 0.5, and 1 mg/kg) may be partly the result of concentrations that were missing or fell below quantification limits before day 29 in several patients. The mean Vss of adalimumab was dose independent and ranged from 5.10 to 5.75 L, indicating that the drug resided in both the vascular and extravascular spaces. The relationships between patient age, sex, body weight, total body dose, and CL were investigated through regression analyses. Patient age and administered dose had no apparent effect on adalimumab CL. As expected, there was a tendency toward a slight increase in CL with an increase in body weight; the predictability of this association was low, although statistically significant (r² = 0.14; P < 0.05). The mean CL across all doses of adalimumab was 0.010 L/h in women and 0.013 L/h in men (P < 0.05). The difference in CL (30%) appeared to be due mainly to differences in body weight (23%)
Table III. Absolute change in American College of Rheumatology core components from baseline to week 4. A negative value indicates a decrease from baseline to day 29 and thus an improvement.

<table>
<thead>
<tr>
<th>Adalimumab Dose, mg/kg</th>
<th>0.25 (n = 9)</th>
<th>0.5 (n = 9)</th>
<th>1 (n = 9)</th>
<th>3 (n = 9)</th>
<th>5 (n = 9)</th>
<th>Placebo (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joint count (maximum of 68)</td>
<td>-5.3</td>
<td>-12.2*</td>
<td>-4.0</td>
<td>-2.7</td>
<td>-13.0*</td>
<td>-13.0</td>
</tr>
<tr>
<td>Swollen joint count (maximum of 66)</td>
<td>-6.9*</td>
<td>-7.0</td>
<td>-4.0</td>
<td>-1.7</td>
<td>-4.2*</td>
<td>-3.1</td>
</tr>
<tr>
<td>Patient’s assessment of pain†</td>
<td>-5.7</td>
<td>-26.2*</td>
<td>-14.0</td>
<td>-12.1</td>
<td>-19.7*</td>
<td>1.2</td>
</tr>
<tr>
<td>Patient’s global assessment of disease activity‡</td>
<td>-10.7</td>
<td>-25.1*</td>
<td>-17.4</td>
<td>-16.6</td>
<td>-22.3*</td>
<td>-1.3</td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity‡</td>
<td>-15.8*</td>
<td>-14.7</td>
<td>-11.9</td>
<td>-11.6</td>
<td>-23.2*</td>
<td>-4.3</td>
</tr>
<tr>
<td>HAQ score§</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3*</td>
<td>0.7</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>-5.1</td>
<td>-16.0</td>
<td>10.9</td>
<td>-40.3*</td>
<td>11.0</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

HAQ = Health Assessment Questionnaire Disability Index.
*P ≤ 0.05, adalimumab versus baseline (based on 95% CI).
†Visual analog scale from 0 = no pain to 100 = severe pain.
‡Visual analog scale from 0 = no symptoms to 100 = severe symptoms.
§On a scale from 0 = best to 3 = worst.
Figure 2. Proportion of patients receiving adalimumab for rheumatoid arthritis who achieved improvements in American College of Rheumatology (ACR) response criteria of 20% (ACR20), 50% (ACR50), and 70% (ACR70) at months 3, 6, 9, 12, 18, 22, and 26 (last observation carried forward).

Table IV. Mean (SD) single-dose adalimumab pharmacokinetic parameters.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>0.25 mg/kg (n = 9)</th>
<th>0.5 mg/kg (n = 9)</th>
<th>1 mg/kg (n = 9)</th>
<th>3 mg/kg (n = 9)</th>
<th>5 mg/kg (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}, mg/L</td>
<td>7.38 (2.47)</td>
<td>11.97 (2.39)</td>
<td>25.37 (9.03)</td>
<td>75.61 (18.16)</td>
<td>116.78 (19.71)</td>
</tr>
<tr>
<td>Cl, L/h</td>
<td>0.010 (0.003)</td>
<td>0.011 (0.002)</td>
<td>0.012 (0.003)</td>
<td>0.009 (0.003)</td>
<td>0.009 (0.003)</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>422.8 (120.5)</td>
<td>389.0 (71.0)</td>
<td>353.4 (74.6)</td>
<td>454.8 (139.7)</td>
<td>464.4 (122.5)</td>
</tr>
<tr>
<td>V_{ss}, L</td>
<td>5.53 (0.80)</td>
<td>5.72 (0.94)</td>
<td>5.75 (1.00)</td>
<td>5.10 (0.94)</td>
<td>5.44 (0.38)</td>
</tr>
<tr>
<td>AUC_{0-\infty}, mg·h/L</td>
<td>1884 (600)</td>
<td>3169 (514)</td>
<td>5880 (1305)</td>
<td>24,775 (7295)</td>
<td>37,964 (11,585)</td>
</tr>
</tbody>
</table>

C_{max} = peak serum concentration; Cl = total serum clearance; t_{1/2} = apparent terminal half-life; V_{ss} = apparent steady-state volume of distribution; AUC_{0-\infty} = area under the concentration-time curve from time zero to infinity.
Multiple-dose mean pharmacokinetic values by dose group at month 5 are shown in Table V. Dose-related increases were observed in adalimumab $C_{\text{pre}}$ and $C_{\text{max}}$. Post hoc estimates of CL, $V_{\text{ss}}$, and $t_{1/2}$ using population pharmacokinetic analyses were obtained using all data available for the 45 patients who received active treatment (Table V). The overall mean CL (0.009 L/h) and $V_{\text{ss}}$ (5.62 L) estimated for multiple dosing using data from all dose groups were within the range of values reported after single dosing (double-blind period), indicating stable pharmacokinetics over time. The mean terminal $t_{1/2}$ for the combined data was 21.45 days, which was consistent with the $t_{1/2}$ reported for native human IgG (8–23 days).20

**Methotrexate**

Mean (SD) AUC$_{2-5}$ values for MTX at baseline, day 1, and month 5 were 996 (363), 829 (467), and 918 (429) µg·h/L, respectively. According to the
Figure 4. Relationship between systemic exposure (area under the concentration-time curve from time zero to infinity [AUC$_{0-\infty}$]) and dose after a single intravenous injection of adalimumab in patients receiving concomitant methotrexate.

Table V. Mean (SD) pharmacokinetic parameters after multiple doses of adalimumab.

<table>
<thead>
<tr>
<th>Adalimumab Dose, mg/kg</th>
<th>0.25 (n = 3)</th>
<th>0.5 (n = 7)</th>
<th>1 (n = 13)</th>
<th>3 (n = 6)</th>
<th>5 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{pre}}$, mg/L*</td>
<td>4.1 (3.7)</td>
<td>11.2 (7.9)</td>
<td>14.6 (7.0)</td>
<td>74.6 (59.7)</td>
<td>100.8 (97)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, mg/L*</td>
<td>18.6 (11.6)</td>
<td>27.5 (12.1)</td>
<td>44.8 (13.9)</td>
<td>159.5 (35.7)</td>
<td>268.5 (41.5)</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters, all doses combined (n = 45)†

- $C_{\text{pre}}$ = predose serum concentration (trough);
- $C_{\text{max}}$ = peak serum concentration;
- CL = total serum clearance;
- $V_{ss}$ = apparent steady-state volume of distribution;
- $t_{1/2}$ = apparent terminal half-life.

*Measured during a dosing interval at month 5.
†Individual post hoc estimates using combined data from the double-blind and open-label phases, excluding the placebo group.
paired t test, the AUC of MTX was not significantly affected by coadministration of adalimumab.

**Safety**

In this study, adalimumab was administered at intravenous doses up to 10-fold higher than the dose expected to be recommended for use in the clinical setting. It was reasonably well tolerated, and there were no dose-related adverse events. The most frequently reported adverse events during the double-blind phase are shown in Table VI. Overall, the proportion of patients experiencing ≥1 treatment-emergent adverse event within 4 weeks of administration of single doses of study drug was 66.7% in the adalimumab group and 60.0% in the placebo group. No relationship was found between particular adalimumab doses and the number of patients reporting adverse events immediately or within 4 weeks after administration of a single dose. In the majority of patients, hematology and biochemistry values remained within the normal reference range during the study, both before and after the switch to adalimumab 40 mg.

The most frequently reported adverse events in the 59 patients included in the open-label phase were upper respiratory tract infection (reported by 30 [50.8%] patients); rhinitis (23 [39.0%]); accidental injury (21 [35.6%]); rash (20 [33.9%]); headache (17 [28.8%]); surgical procedures involving affected joints, fractures, angina, syncope, myocardial infarction, stroke, and respiratory disorder, or other procedures common in an older population with established RA (17 [28.8%]); and increased cough (15 [25.4%]). Fifty-two (88.1%) patients experienced ≥1 nonserious infection; this adverse event did not appear to be dose related. Two adverse events that were judged serious and possibly related to adalimumab administration (septic arthritis of the hip and soft tissue infection of the heel) occurred in the same patient. Three (5.1%) patients withdrew from the study due to adverse events (1 patient with rash; 1 patient with thyroid disorder judged un-

<p>| Table VI. Most frequently reported adverse events (no. [%]) occurring in ≥10% of patients in either group within 4 weeks of study drug administration. |</p>
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Adalimumab (n = 45)</th>
<th>Placebo (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9 (20.0)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (13.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6 (13.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Increased cough</td>
<td>5 (11.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (6.7)</td>
<td>2 (13.3)</td>
</tr>
</tbody>
</table>

1717
likely to be related to treatment; 1 patient experiencing several events, including asthenia, constipation, and dizziness, the majority judged unlikely to be related to treatment and the rest possibly related. For the 5 doses of adalimumab (ie, 0.25, 0.5, 1, 3, and 5 mg/kg) administered before the switch to the 40-mg dose, there was no correlation between dose and the overall percentage of patients reporting adverse events. In patients remaining in the study at the time these data were collected, the most frequently reported adverse events after the switch to adalimumab 40 mg were clinical flare reaction (reported in 4 patients [10.0%]), headache (3 [7.5%]), upper respiratory tract infection (3 [7.5%]), and rash (3 [7.5%]). Two patients who received the 40-mg dose reported mild injection-site reactions on switching to subcutaneously administered adalimumab.

No solid organ malignancies or malignancies of the immune system (eg, lymphomas) were noted during this study. At baseline, 17 of 57 (29.8%) patients evaluated tested positive for antinuclear antibodies, and at month 18 (last observation carried forward) after the switch to adalimumab 40 mg, 7 of 21 (33.3%) patients evaluated tested positive. No patients demonstrated symptoms of lupus-like illness. Blood samples were taken at study entry and at months 6, 12, and 18 for determination of human anti-adalimumab antibody concentrations; however, only a small number of patients had concentrations adequate for quantification (≥0.5 ng/mL in diluted serum), and the results were inconclusive.

**DISCUSSION**

Over the past decade, MTX has become the treatment of choice for RA because it produces maximal clinical benefits by 6 months and potentially slows the progression of joint destruction over the long term.21–23 Because many patients do not respond adequately to MTX alone, this agent is often combined with other traditional DMARDs, such as hydroxychloroquine, sulfasalazine, cyclosporine, azathioprine, d-penicillamine, auranofin, and intramuscular gold.1,5 Most recently, biologic DMARDs that block TNF-alpha have been successfully used in conjunction with MTX.24–27 Adalimumab, a fully human biologic DMARD and TNF-alpha antagonist, may provide an additional option in patients who have an incomplete response to MTX therapy.

In this study, the addition of adalimumab to MTX achieved significant (P ≤ 0.05) and sustained responses in most patients. During the 4-week, double-blind, placebo-controlled phase, 1 dose of adalimumab plus MTX yielded ACR20 and ACR50 responses in 64.4% (29/45) and 24.4% (11/45) of patients, respectively, with the greatest response rates observed with adalimumab 0.5 mg/kg. In contrast, MTX plus placebo yielded ACR20 and ACR50 responses in 26.7% (4/15) and 0% (0/15) of patients, respectively. Responses were rapid, with 22.2% (10/45) of patients achieving an ACR20 response within 24 hours after administration of adalimumab. The response was generally maintained in all patients after the switch to a fixed dose of 40 mg every other week or monthly. These results sug-
gest that addition of adalimumab to MTX therapy may improve multiple aspects of disease activity and alter the long-term disease trajectory.

The pharmacokinetic parameters of adalimumab appeared to be similar across all dose groups, following a biphasic pattern of decline in the concentration-time curve. The mean apparent terminal $t_{1/2}$ after a single dose of intravenous adalimumab ranged from 15 to 19 days among the 5 dose groups. Regression analyses indicated that adjustment of the adalimumab dose based on body weight or sex is not warranted and that age had no effect on the CL or $V_{ss}$ of adalimumab. The estimated CL and $V_{ss}$ for MRX in this study were consistent with those reported in the literature. Repeated administration of adalimumab had no statistically significant effect on the pharmacokinetics of MTX, indicating that there are no major pharmacokinetic interactions between the 2 agents and that dose adjustment of MTX is not needed with coadministration of adalimumab.

Adalimumab given in combination with MTX was reasonably well tolerated. The overall proportions of patients experiencing adverse events within 4 weeks of study drug administration were comparable in the adalimumab groups and the placebo group, although the frequency of adverse events was relatively high. For the 5 doses of adalimumab administered before the switch to adalimumab 40 mg, there was no correlation between dose and the overall proportion of patients reporting adverse events. Although the majority (88.1%) of patients experienced a nonserious infection during treatment with adalimumab, only 1 patient experienced a serious infection.

CONCLUSIONS
The results of this study in a selected patient population suggest that addition of adalimumab to continuing MTX therapy produces clinical improvement in most patients who have had an incomplete response to standard doses of MTX. The addition of adalimumab to MTX therapy provided long-term benefit while being reasonably well tolerated. Adalimumab's long terminal $t_{1/2}$ of 15 to 19 days supports every-other-week dosing. In addition, the pharmacokinetic results indicate that clearance of adalimumab is not dose dependent. The quick onset, magnitude, and duration of the response indicate that adalimumab is a promising new therapy for the treatment of RA.

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1721