A Single Dose, Placebo Controlled Study of the Fully Human Anti-Tumor Necrosis Factor-α Antibody Adalimumab (D2E7) in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To assess the pharmacokinetics, safety profile, and efficacy of the fully human anti-tumor necrosis factor-alpha (anti-TNF-α) monoclonal antibody adalimumab (D2E7) in patients with long-standing, active rheumatoid arthritis (RA).

Methods. This was a randomized, double blind, placebo controlled study of single intravenous injections of ascending doses (0.5 to 10 mg/kg) of adalimumab in 5 cohorts of 24 patients each (18 adalimumab and 6 placebo in all cohorts except the 0.5 mg/kg cohort of 17 adalimumab, 7 placebo). A total of 120 patients participated (adalimumab 89, placebo 31). The clinical response was measured by changes in composite scores defined by the criteria of the European League Against Rheumatism (EULAR) and the American College of Rheumatology.

Results. Single doses of adalimumab showed a rapid onset of clinical effect (24 hours to 1 week), with peak efficacy at 1 to 2 weeks that was sustained for at least 4 weeks and for as long as 3 months in some patients. EULAR response was seen at least once during the 4 week period after drug injection in 29% of patients in the placebo group as well as in 41%, 78%, 72%, 89%, and 100% in the 0.5, 1, 3, 5, and 10 mg/kg groups, respectively. No dose related increases in adverse events were observed in the adalimumab patients compared with the placebo group. Adalimumab systemic drug exposure ($AUC_{0-\infty}$) increased linearly with an increase in dose. The mean total serum clearance was 0.012 to 0.017 l/h, and the steady-state volume of distribution ranged from 4.7 to 5.5 l. The estimated mean terminal half-life ranged from 10.0 to 13.6 days for the 5 cohorts, with an overall mean half-life of 12 days.

Conclusion. Treatment with the fully human Mab adalimumab was safe and well tolerated when administered as a single intravenous injection at doses up to 10 mg/kg, and was associated with a clinically significant improvement in the signs and symptoms of active RA. (J Rheumatol 2002;29:2288–98)

Key Indexing Terms:
FULLY HUMAN ANTI-TUMOR NECROSIS FACTOR-α ANTIBODY PHASE I
RHEUMATOID ARTHRITIS ADALIMUMAB D2E7 PHARMACOKINETICS

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For decades, treatment modalities for rheumatoid arthritis (RA) have included nonsteroidal antiinflammatory drugs (NSAID), disease modifying antirheumatic drugs (DMARD), and corticosteroids[1]. The DMARD methotrexate (MTX) became the treatment of choice because of its efficacy and safety in short and longterm trials[2-5]. Yet some patients do not respond to MTX treatment and others experience toxicity[6,7]. DMARD combination therapy, often with MTX, also has resulted in improved disease control compared with single agents[7-12].

Recently, the focus of novel therapies for RA has shifted to attempts to target the cellular inflammatory mechanisms involved in longterm tissue destruction in order to slow or prevent disease progression. The proinflammatory cytokines interleukin 1 and tumor necrosis factor-alpha (TNF-α) are known to play an important role in the induc-

tion and maintenance of inflammatory synovitis and articular matrix degradation; modulation of their synovial activity provides the potential for novel therapeutic interventions in RA[13,14]. Biological agents such as anticytokine antibodies and soluble receptors that bind and neutralize these mediators have been developed. These new biological treatment modalities include chimeric and humanized monoclonal antibodies (Mab)[15-17] and fusion proteins of soluble TNF-receptor proteins with human immunoglobulin Fc regions[18]. Currently, the 2 TNF-α inhibitors available for use are infliximab and etanercept. These agents show enhanced efficacy and improved tolerability compared with placebo[16,18,19]. Longterm use of biological agents with nonhuman constructs, however, may be limited by immune responses mounted against their foreign components, thereby reducing their half-life and thus efficacy[20]. In addition, there may be increased risk of adverse events due to immune complex formation[20]. Given these limitations, the development of a fully human (i.e., 100% human peptide sequences in a natural configuration) therapeutic antibody has the potential to provide improved safety and efficacy in longterm use[20].

Adalimumab (D2E7; Abbott Laboratories, Abbott Park, IL, USA) is a fully human anti-TNF-α Mab consisting of 100% human sequences developed using phage display technology[21]. The adalimumab antibody has been extensively tested in standard *in vitro* and *in vivo* toxicity assays and in animal models of disease[22,23]. We assessed the clinical pharmacology profile and evaluated the safety, tolerability, and efficacy of adalimumab over a range of doses in patients with active RA. The results have been reported in abstract form[24].

MATERIALS AND METHODS

This multicenter, double blind, randomized, placebo controlled, ascending single dose study in cohorts of patients with active RA was conducted in one center in The Netherlands and 2 in Germany. The study was administered in accord with good clinical practice guidelines and principles of the Declaration of Helsinki and followed ethics committee approval. All patients gave written informed consent to participate.

Patients. The study population included men and women ≥ 18 years of age (women of childbearing potential required a negative pregnancy test and had to use a reliable method of contraception to be included) with a diagnosis of RA and evidence of active inflammatory synovitis as defined by a Disease Activity Score (DAS) of ≥ 3.2 at study entry[25]. The body weight of patients was limited to ≤ 100 kg. Important exclusion criteria included intraarticular or intramuscular corticosteroid treatment within 4 weeks prior to study screening, joint surgery within 2 months prior to study screening (if those joints were to be included in the study assessment), and treatment with any chemical or biological investigational drugs 2 months or 12 months, respectively, prior to study screening.

Study procedures. After a 3 week washout period for DMARD, a single intravenous (IV) injection of study drug lasting 3 to 5 min was administered to qualified patients (adalimumab n = 89, placebo n = 31) hospitalized for 24 h. The study had 5 ascending cohorts with 24 patients each. Within each cohort, 18 patients received adalimumab and 6 received matching placebo, except in the 0.5 mg/kg cohort, in which 17 patients received adalimumab and 7 received placebo. Doses of adalimumab were 0.5, 1, 3, 5, and 10 mg/kg, respectively. The cohort with the next higher dose was started only if no dose-limiting adverse events were observed at the previous dose level. Concomitant treatment with antirheumatic/antiinflammatory drugs was not allowed during the study, with the exception of stable doses of NSAID and/or corticosteroids, with a maximum daily dose equivalent to 10 mg prednisolone. Analgesics, including over-the-counter preparations, propoxyphene, or codeine alone or in combinations were not allowed, with the exception of infrequent acetylsalicylic acid (ASA) (maximum daily dose 500 mg) or equivalent treatments for mild pain. Regular intake of low dose ASA for prophylaxis of myocardial infarction was allowed.

Patients were monitored with weekly examinations for at least 4 weeks. If the study drug showed efficacy in individual patients beyond this 4 week period, they continued under observation until their disease status deteriorated (i.e., a reduction of at least 1.2 in the DAS)[24] to assess the duration of efficacy of single dose administration up to Month 3. After completion of the single dose study, patients were offered the option to enter a continuation study, either at the end of the 4 week followup period (Day 29) or upon clinical deterioration. The results of the continuation study, which involved multiple injections of the study drug, will be reported separately.

Pharmacokinetic assessments. Pharmacokinetic (PK) analysis was performed using a noncompartmental approach for intravenous (IV) bolus delivery. The PK analyses were accomplished using PK software (Kinetica™ 2000, Version 3.0, InnaPhase, UK). The PK variables assessed were the model-dependent parameters for serum concentrations of drug, as follows: area under the serum concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), serum clearance, volume of distribution at steady state (Vss), and terminal log-linear phase half-life ($t_{1/2}$). Blood samples were collected predose, immediately after the end of injection, and then at 15 min and 1, 4, 8, 12 and 24 hours postdose. Additional samples were taken weekly for up to 6 weeks postdose (4 weeks minimum) and biweekly thereafter, up to a maximum of 3 months postdose. Samples were assayed for adalimumab content using a validated double antigen sandwich ELISA. The assay is sensitive (limit of quantitation 0.72 μg/ml), precise (interassay coefficient of variation < 12%), and accurate (interassay deviation from nominal < ± 20%).

Safety assessments. Safety and tolerability were evaluated based on reported adverse events, standard hematology and biochemistry measures and urinalysis, vital signs, and electrocardiogram (ECG). In addition, total immunoglobulins M, G, A, and E, and coagulation factors [activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen] and complement activity (C1q, C3, C4) were assessed using standard methods. Pulse rate, blood pressure, body weight, and temperature were measured predose and at various times through Day 29. A 12-lead ECG was recorded predose, 4 h postdose, and on Day 29.

Efficacy assessments. Efficacy analyses through Day 29 were based on the intent-to-treat population within this period. Efficacy variables were determined at each patient visit. For the Ritchie Articular Index (RAI), a variant of the tender joint count (TJC)[26], 53 joints or regions were assessed by pressure and joint manipulation upon examination. Standard pain grading was used for calculation of the RAI[26]. For swollen joint count (SJC), 44 joints were rated by examination as either swollen or not swollen. Patient's global assessment of disease activity, pain, and general health, and physician's assessment of disease activity were recorded using standard 100 mm visual analog scales (VAS). Erythrocyte sedimentation rate (ESR; mm/h) was assessed as a measure of the acute phase reactant. Standard criteria were used to determine American College of Rheumatology (ACR) response; the RAI was used to assess the number of tender joints.

From the assessments described above, DAS was calculated by the following formula[25]:

$$\text{DAS} = 0.53938 \times \sqrt{(\text{RAI})} + 0.06465 \times \text{SJC} + 0.33\ \text{Ln(ESR)} + 0.00722 \times \text{patient's general health assessment}$$

Functional capacity was assessed using either the Dutch Health Assessment Questionnaire (HAQ) or the German HAQ, depending on the location of

the center[27,28]. European League Against Rheumatism (EULAR) responses were compared with those defined by the ACR at the 20% and 50% improvement levels[29]. Responses based on EULAR criteria were defined as good response (DAS decrease from baseline > 1.20 and current DAS ≤ 2.40) or no response (DAS decrease from baseline of ≤ 0.6 or improvement of > 0.6 but ≤ 1.20 and DAS attaining > 3.7). The improvement of the remaining patients was classified as moderate response[25]. For the ACR20 and ACR50 responses, a positive response was considered to be 20% or 50%, respectively, for improvements in the TJC (RAI), SJC, and at least 3 of 5 other variables (patient's assessment of pain, patient or physician assessment of disease activity, HAQ score, and ESR).

Statistical methodology. Descriptive statistics and simple linear regression analyses were performed to determine variability in PK data and to establish dose proportionality. Analyses of efficacy data were descriptive. Accordingly, 95% confidence intervals were calculated for treatment group means or percentages, for differences between dose groups of adalimumab versus placebo, and actual or percentage differences from predose data. Safety data also were analyzed using descriptive statistics.

RESULTS

Patients. A total of 120 patients were randomized to receive study medication. No significant differences among study groups were detected in pretreatment characteristics or baseline disease activity (Table 1). The mean ages of patients in the study cohorts ranged from 53 to 59 years, and most were female (64%). Overall, the mean duration of RA was 11.5 years. All randomized patients had received therapies for RA prior to study entry. These included both drug treatment and surgery. The most frequently used drug treatments were DMARD, glucocorticoids, and NSAID. The mean number of previous DMARD per patient was 3.7 for placebo and 3.6, 3.9, 3.9, 4.4, and 3.9 for patients receiving adalimumab 0.5, 1, 3, 5, and 10 mg/kg, respectively. The most frequently given DMARD were MTX (88%), gold preparations (78%), sulfasalazine (71%), chloroquine/hydroxychloroquine (43%), azathioprine (40%), penicillamine (29%), cyclosporin A (10%), and cyclophosphamide (8%). Ninety-seven percent of patients randomized to placebo were receiving DMARD prior to study entry. In the adalimumab 0.5, 1, 3, 5, and 10 mg/kg cohorts, 94%, 100%, 94%, 94%, and 94% of patients, respectively, were receiving DMARD.

During the study period, 77.4% and 67.7% of patients receiving placebo were taking concomitant corticosteroids and NSAID, respectively. Concomitant corticosteroid use occurred in 52.9%, 77.8%, 66.7%, 77.8%, and 66.7% of patients in the adalimumab groups in order of ascending dose. Additionally, NSAID were taken concomitantly by 94.1%, 72.2%, 55.6%, 88.9%, and 72.2% of patients in the respective adalimumab groups. In all, 70.8% and 74.2% of patients were utilizing concomitant corticosteroids and NSAID, respectively. All patients received at least one concomitant medication, and the maximum number of different concomitant medications taken by a patient ranged up to 12. All concomitant medications taken were allowed by the study protocol.

All randomized patients completed the double blind study except for one patient in the 0.5 mg/kg group, who received the study drug but withdrew after 25 days because of a serious adverse event (necrotizing pancreatitis).

Pharmacokinetic results. PK variables derived using noncompartmental analyses are summarized in Table 2. Mean serum concentration-time (log-linear) profiles following single IV bolus doses of adalimumab 0.5 to 10 mg/kg are shown in Figure 1. Serum adalimumab concentrations appeared to have declined biexponentially. Mean serum adalimumab clearance ranged from 0.012 to 0.017 l/h (0.191 to 0.290 ml/min). The estimated mean steady-state volume of distribution ranged from 4.7 to 5.5 l (0.068 to 0.082 l/kg), indicating that the drug mainly resides in the vascular compartment. The mean terminal half-life ranged from 242 to 326 h (10.0 to 13.6 days). The overall mean half-life for all dose groups was 12 days. Systemic exposure ($AUC_{0-\infty}$) increased linearly with an increase in dose following single IV bolus doses of adalimumab ranging from 0.5 to 10 mg/kg (Figure 2). The clearance, terminal half-life, and steady-state volume of distribution appeared to be dose independent, indicating linear kinetics.

Safety and tolerability results. The injections of adalimumab and placebo were well tolerated. All patients in both adalimumab and placebo treated groups experienced at least one adverse event. In general, overall adverse event frequencies did not differ between the placebo and the adalimumab groups, and no increased rate of adverse events was seen with increasing doses of adalimumab (Table 3). The most frequently reported clinical adverse events were fever (body temperature ≥ 37°C), headache, and hypertension (Table 4). Pruritus and rash occurred in 6 and 5 patients, respectively, treated with adalimumab and none with placebo. No injection site reactions were reported. Two patients experienced a serious adverse event after treatment with adalimumab. One developed necrotizing pancreatitis with abdominal pain 15 days after injection of adalimumab 0.5 mg/kg. Retrospectively, it was discovered that this patient had a strongly elevated serum lipase at baseline and a hidden history of alcohol abuse. Furthermore, chronic gastritis and bronchitis due to nicotine abuse existed before the study. Nevertheless, the contributing role of administration of a single dose of adalimumab (0.5 mg/kg) to the patient's severe abdominal disease was considered to be unclear by the investigator. The second patient was from the 1 mg/kg group. He had a known long history of epilepsy and had an epileptic seizure 5 days after injection of adalimumab. The plasma concentration of the concomitant medication phenytoin was analyzed retrospectively and proved to be in a subtherapeutic range. The dosage of the antiepileptic medication was adjusted, and the patient was treated repeatedly with adalimumab in the continuation study without additional adverse events.

Changes from baseline in clinical laboratory values, vital signs, and ECG were small in all treatment groups. A few cases of clinical laboratory values meeting grades 3 or 4 of

Table 1. Demographic and baseline disease characteristics.

Demographic Characteristics	Placebo	Adalimumab, mg/kg 0.5	1	3	5	10	Total
No. patients	31	17	18	18	18	18	120
Sex, n (%)							
Male	9 (29)	7 (41)	8 (44)	10 (56)	3 (17)	6 (33)	43 (36)
Female	22 (71)	10 (59)	10 (56)	8 (44)	15 (83)	12 (67)	77 (64)
Age, yrs*	55 ± 11 (31–75)	54 ± 15 (26–72)	58 ± 8 (42–76)	54 ± 11 (24–71)	59 ± 12 (39–76)	53 ± 16 (24–80)	55 ± 12 (24–80)
Weight, kg, median							
Male	81.0	80.0	71.5	73.5	86.0	82.5	80.0
Female	62.5	72.5	58.5	57.0	63.0	67.0	64.0
RA duration, yrs†	11.9	11.0	11.2	10.8	14.5	8.9	11.5
Patients taking previous DMARD at baseline, n (%)	30 (97)	16 (94)	18 (100)	17 (94)	17 (94)	17 (94)	115 (96)
Previous DMARD, n†	3.7	3.6	3.9	3.9	4.4	3.9	3.9
Patients taking concomitant corticosteroids, n (%)	24 (77.4)	9 (52.9)	14 (77.8)	12 (66.7)	14 (77.8)	12 (66.7)	85 (70.8)
Patients taking concomitant NSAID, n (%)	21 (67.7)	16 (94.1)	13 (72.2)	10 (55.6)	16 (88.9)	13 (72.2)	89 (74.2)
Measures of arthritis activity							
DAS†	5.16	5.14	5.81	5.35	4.93	5.63	5.32
TJC (0–53, RAI), n†	23.5	23.8	27.1	21.8	20.7	27.0	23.9
SJC (0–44), n†	18.4	18.4	20.8	20.8	15.9	20.4	19.1
ESR, mm/h†	39.0	36.3	55.3	47.1	43.1	47.2	44.2
CRP, mg/l†	41.4	37.5	85.8	51.6	53.4	57.0	53.7
Physician global assessment, mm, VAS†	62.1	59.1	68.3	70.2	64.2	72.3	65.7
Patient global assessment, mm, VAS†	60.5	66.0	78.1	63.0	64.9	69.4	66.3
Patient assessment of pain, mm, VAS†	58.6	63.2	74.6	61.4	64.3	71.4	64.9
Morning stiffness, min†	132.9	106.8	143.3	130.0	111.1	143.6	128.7
HAQ score†	1.57	1.57	1.85	1.41	1.61	1.93	1.65

* Mean value ± standard deviation (range). † Mean value. DAS: Disease Activity Score; TJC: tender joint count; RAI: Ritchie Articular Index; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale; HAQ: Health Assessment Questionnaire.

Table 2. Mean (SD) pharmacokinetic measures (noncompartmental analyses) followuing single IV injection af adalimumab.

	C_{max}, μg/ml	$AUC_{0-\infty}$, μg·h/ml	$t_{1/2}$, h	Clearance, l/h	Clearance, ml/h/kg	Vss, l	Vss, l/kg
Dose, mg/kg							
0.5	25 (22)	2729 (707)	284 (119)	0.015 (0.006)	0.196 (0.068)	5.3 (1.4)	0.068 (0.013)
1	68 (76)	4363 (1807)	242 (170)	0.017 (0.006)	0.261 (0.089)	5.0 (1.3)	0.075 (0.020)
3	78 (28)	14229 (3703)	267 (90)	0.015 (0.004)	0.225 (0.061)	5.5 (1.4)	0.082 (0.022)
5	144 (46)	32963 (11556)	326 (129)	0.012 (0.004)	0.163 (0.041)	4.7 (1.0)	0.068 (0.014)
10	284 (74)	67115 (17385)	321 (117)	0.012 (0.003)	0.158 (0.038)	4.7 (1.3)	0.065 (0.018)

C_{max}: peak serum adalimumab concentration immediately after end of injection; $AUC_{0-\infty}$: total area under the serum concentration-time curve; $t_{1/2}$: half-life; Vss: volume of distribution at steady state.

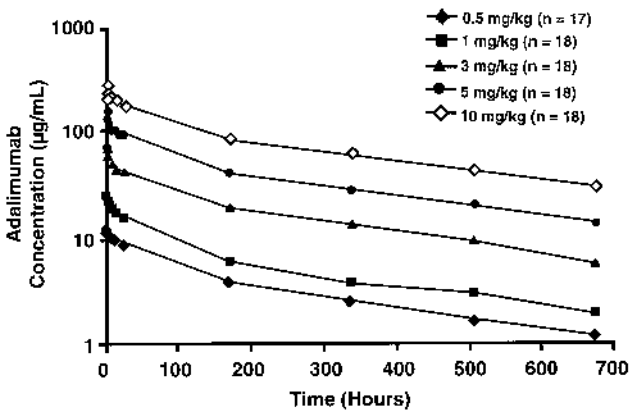

Figure 1. Mean serum profile of adalimumab following single IV injections (semilogarithmic plot).

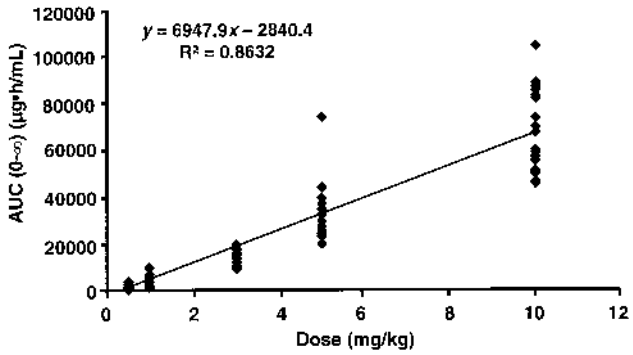

Figure 2. Relationship between area under the serum concentration-time curve and dose following single IV injections of adalimumab.

the common toxicity criteria (CTC) occurred following study drug administration, as follows: prothrombin time (grade 3) occurred in one patient in the adalimumab 0.5 mg/kg group; and low lymphocytes (grade 3 or 4), a common condition at study entry (22%), occurred in 29% of placebo patients and 28% of adalimumab patients.

Efficacy results

Primary efficacy variables (DAS, EULAR response, ACR20, ACR50). In all the adalimumab dose groups, reductions in DAS compared with baseline scores were observed. In the placebo group, by contrast, only slight mean changes in DAS from baseline were found at all evaluated time points. The improvement in DAS was smallest in the 0.5 mg/kg group. Comparatively, the improvement was much larger in the adalimumab higher dosage groups (1 to 10 mg/kg), but of similar magnitude between the groups (Table 5 and Figure 3). For the adalimumab dose groups, an initial decline in DAS was seen as early as 24 h after injection, decreasing further up to Day 8, and returning toward baseline by Days 22 and 29. For all adalimumab dose groups other than 0.5 mg/kg, DAS remained below the pretreatment level through Day 29.

Relative to placebo, treatment with adalimumab 0.5 mg/kg resulted in clinically significantly greater decreases from baseline in DAS at Days 8 and 15. For the adalimumab 1 mg/kg group, the change from baseline in DAS versus placebo was clinically significant at all evaluated time points through Day 29. Similar results were noted for the adalimumab groups receiving 3, 5, and 10 mg/kg.

Table 3. Overview of patients with treatment emergent adverse events (AE) through Day 29.

	Adalimumab Dose Cohort, mg/kg					All	All
	0.5	1	3	5	10	Adalimumab	Placebo
No. patients							
Adalimumab	17	18	18	18	18	89	—
Placebo	7	6	6	6	6	—	31
AE, n (%)							
Clinical AE							
Adalimumab	15 (88)	15 (83)	18 (100)	11 (61)	16 (89)	75 (84)	—
Placebo	7 (100)	5 (83)	5 (83)	5 (83)	5 (83)	—	27 (87)
Laboratory AE							
Adalimumab	16 (94)	16 (89)	16 (89)	18 (100)	16 (89)	82 (92)	—
Placebo	7 (100)	6 (100)	6 (100)	6 (100)	6 (100)	—	31 (100)
Possibly drug related AE							
Adalimumab	12 (71)	12 (67)	11 (61)	8 (44)	9 (50)	52 (58)	—
Placebo	6 (86)	4 (67)	3 (50)	3 (50)	2 (33)	—	18 (58)
Severe/life threatening AE							
Adalimumab	5 (29)	4 (22)	4 (22)	3 (17)	2 (11)	18 (20)	—
Placebo	1 (14)	1 (17)	1 (17)	3 (50)	1 (17)	—	7 (23)
Serious AE							
Adalimumab	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	2 (2)	—
Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	—	0 (0)
AE, leading to withdrawal							
Adalimumab	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	—
Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	—	0 (0)

Table 4. Most frequent (experienced by ≥ 2 patients) treatment emergent clinical adverse event (AE).

	Adalimumab Dose Cohort, mg/kg					All Adalimumab	All Placebo
	0.5	1	3	5	10		
No. patients							
Adalimumab	17	18	18	18	18	89	—
Placebo	7	6	6	6	6	—	31
AE, n (%)							
Fever							
Adalimumab	5 (29)	7 (39)	4 (22)	3 (17)	4 (22)	23 (26)	—
Placebo	2 (29)	1 (17)	3 (50)	2 (33)	1 (17)	—	9 (29)
Headache							
Adalimumab	2 (12)	5 (28)	5 (28)	2 (11)	3 (17)	17 (19)	—
Placebo	1 (14)	0 (0)	1 (17)	0 (0)	0 (0)	—	2 (6)
Hypertension							
Adalimumab	7 (41)	2 (11)	2 (11)	1(6)	2 (11)	14 (16)	—
Placebo	2 (29)	0 (0)	0 (0)	1 (17)	0 (0)	—	3 (10)
Asthenia							
Adalimumab	2 (12)	3 (17)	0 (0)	0 (0)	1 (6)	6 (7)	—
Placebo	1 (14)	1 (17)	0 (0)	1 (17)	0 (0)	—	3 (10)
Rhinitis							
Adalimumab	1 (6)	2 (11)	2 (11)	1 (6)	0 (0)	6 (7)	—
Placebo	1 (14)	1 (17)	0 (0)	0 (0)	0 (0)	—	2 (6)
Dizziness							
Adalimumab	0 (0)	3 (17)	1 (6)	0 (0)	1 (6)	5 (6)	—
Placebo	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	—	2 (6)
Flu syndrome							
Adalimumab	2 (12)	0 (0)	1 (6)	0 (0)	2 (11)	5 (6)	—
Placebo	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	—	1 (3)
Pruritus							
Adalimumab	1 (6)	0 (0)	2 (11)	1 (6)	2 (11)	6 (7)	—
Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	—	0 (0)
Rash							
Adalimumab	2 (12)	0 (0)	0 (0)	2 (11)	1 (6)	5 (6)	—
Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	—	0 (0)
Arthralgia							
Adalimumab	1 (6)	0 (0)	1 (6)	0 (0)	2 (11)	4 (4)	—
Placebo	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	—	1 (3)
Nausea							
Adalimub	1 (6)	0 (0)	1 (6)	1 (6)	1 (6)	4 (4)	—
Placebo	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	—	1 (3)
Joint disorder							
Adalimumab	0 (0)	1 (6)	1 (6)	2 (11)	0 (0)	4 (4)	—
Placebo	1 (14)	1 (17)	0 (0)	0 (0)	0 (0)	—	2 (6)
GI pain							
Adalimumab	0 (0)	0 (0)	2 (11)	0 (0)	1 (6)	3 (3)	—
Placebo	1 (14)	0 (0)	0 (0)	1 (17)	0 (0)	—	2 (6)

GI: gastrointestinal.

Response rates based on EULAR and ACR20 criteria (using ESR as the acute phase reactant variable) were of similar magnitude at each time point and are illustrated in Figures 4 and 5. EULAR response was seen at least once during the 4 week period after study drug injection in 29% of patients in the placebo group and in 41%, 78%, 72%, 89%, and 100% in the adalimumab 0.5, 1, 3, 5, and 10 mg/kg groups, respectively, and ACR20 response in 47%, 67%, 78%, 67%, and 83%, respectively, in the adalimumab groups and 16% in placebo. In the higher adalimumab dose groups, 60% to more than 80% of patients achieved EULAR and ACR20 response status between 24 hours and 29 days of treatment. Therapeutic effects became evident within 24 hours to 1 week after adalimumab administration and peaked after 1 to 2 weeks, with dose response seeming to reach a plateau at 1 mg/kg adalimumab. In contrast, only 29% of patients on placebo achieved EULAR response status. The ACR50 responder rates at any time through Day

Table 5. Disease activity scores (DAS) over time: mean (95% CI) baseline measurements and differences from baseline.

	Adalimumab Dose Cohort, mg/kg				
	0.5	1	3	5	10
No. Patients					
Adalimumab	17	18	18	18	18
Placebo7	6	6	6	6	
Mean DAS (95% CI) at baseline					
Adalimumab	5.14 (4.72, 5.55)	5.81 (5.32, 6.31)	5.35 (4.93, 5.77)	4.93 (4.53, 5.32)	5.63 (5.09, 6.17)
Placebo5.24 (4.59, 5.89)	4.83 (3.73, 5.92)	4.69 (3.70, 5.68)	5.79 (3.84, 7.74)	5.24 (4.05, 6.42)	
Mean difference in DAS (95% CI) from baseline					
24 hours					
Adalimumab	–0.25 (–0.49, –0.01)	–0.81 (–1.10, –0.53)	–0.49 (–0.76, –0.22)	–0.33 (–0.64, –0.02)	–0.72 (–1.00, –0.43)
Placebo	–0.02 (–0.27, 0.24)	–0.45 (–1.30, 0.39)	–0.22 (–0.66, 0.23)	–0.36 (–0.95, 0.23)	0.16 (–0.12, 0.44)
Day 8					
Adalimumab	–0.76 (–1.12, –0.39)	–1.28 (–1.58, –0.97)	–1.50 (–1.88, –1.13)	–1.21 (–1.69, –0.74)	–1.29 (–1.85, –0.73)
Placebo	–0.32 (–1.16, 0.51)	–0.04 (–0.84, 0.76)	–0.16 (–1.05, 0.72)	–0.31 (–1.21, 0.59)	0.42 (–0.10, 0.93)
Day 15					
Adalimumab	–0.82 (–1.31, –0.33)	–1.37 (–1.77, –0.97)	–1.45 (–1.87, –1.04)	–1.19 (–1.69, –0.68)	–1.50 (–1.88, –1.13)
Placebo	–0.34 (–0.88, 0.21)	0.15 (–0.52, 0.83)	0.10 (–0.94, 1.15)	–0.16 (–1.37, 1.05)	0.12 (–0.77, 1.01)
Day 22					
Adalimumab	–0.35 (–0.88, 0.18)	–1.14 (–1.58, –0.71)	–1.27 (–1.73, –0.81)	–1.56 (–2.13, –0.99)	–1.53 (–1.99, –1.08)
Placebo	0.04 (–0.48, 0.56)	0.38 (–0.06, 0.82)	0.34 (–0.21, 0.89)	0.16 (–0.68, 1.00)	0.32 (–1.44, 2.08)
Day 29					
Adalimumab	0.16 (–0.32, 0.64)	–0.81 (–1.31, –0.31)	–1.05 (–1.54, –0.55)	–1.52 (–2.08, –0.96)	–1.08 (–1.54, –0.62)
Placebo	0..22 (–0.24, 0.68)	0.38 (–0.42, 1.19)	0.30 (–0.55, 1.15)	0.04 (–0.87, 0.94)	0.37 (0.04, 0.71)

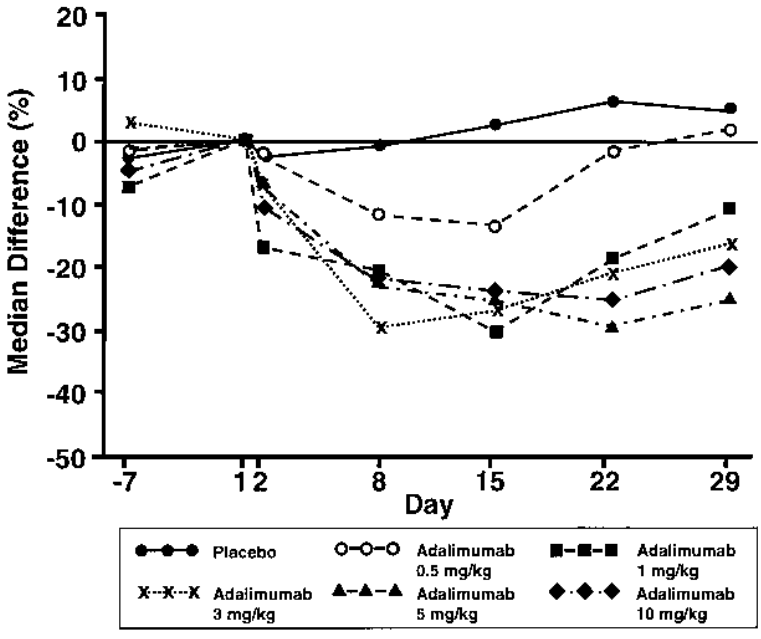

Figure 3. Disease Activity Score: Course of median percentage difference from predose values over time (all randomized patients). See Table 5 for placebo data by cohort.

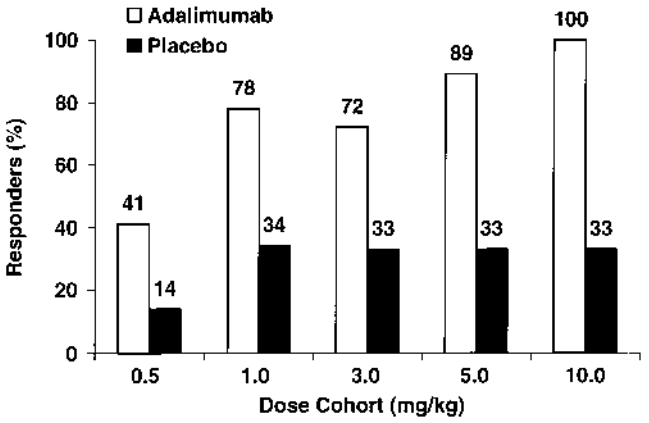

Figure 4. Percentage of patients with moderate or good EULAR response at any time. Cohort sizes were: adalimumab = 17, 18, 18, 18, and 18 patients and placebo = 7, 6, 6, 6, and 6 patients in cohorts by ascending dose of adalimumab.

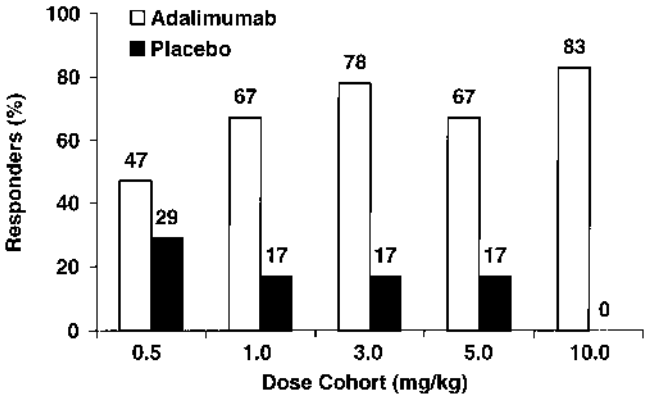

Figure 5. Percentage of patients with ACR20 response at any time. Cohort sizes were: adalimumab = 17, 18, 18, 18, and 18 patients and placebo = 7, 6, 6, 6, and 6 patients in cohorts by ascending dose of adalimumab.

29 were 18%, 17%, 28%, 28%, and 17% in the adalimumab 0.5, 1, 3, 5, and 10 mg/kg groups, respectively. No patient (0%) receiving placebo achieved an ACR50 response.

The proportion of all patients with EULAR response to a single dose of adalimumab over time is shown in Figure 6. The adalimumab dose groups had consistently longer periods of response (defined as time from injection until nonresponsiveness) compared with placebo. Duration of response was longer in the adalimumab groups receiving 1, 3, 5, or 10 mg/kg compared with the 0.5 mg/kg group and the placebo group. Of the patients receiving adalimumab 0.5 mg/kg, 6% had a EULAR response lasting until Day 29, whereas 33%, 39%, 61%, and 61% of the patients receiving adalimumab 1, 3, 5, and 10 mg/kg had responses lasting until Day 29 or longer. In some patients, the response persisted up to 3 months. No apparent differences were noted in the duration of response among the patients in the adalimumab groups receiving doses > 0.5 mg/kg. Of the patients receiving placebo, 6% achieved a EULAR response lasting until Day 29.

Other efficacy variables. Further confirmation of the beneficial effects of adalimumab treatment on inflammatory synovitis during the trial was shown by the improvement from baseline in the individual components of the EULAR and the ACR response criteria (Table 6). Following therapy with adalimumab, there were improvements in all these measures, with the least pronounced improvements in the adalimumab 0.5 mg/kg group. Improvements in the higher adalimumab dose groups (1 to 10 mg/kg) were of similar magnitude. The improvements were sustained, with values for each variable remaining below baseline at Day 29, except the Ritchie Articular Index value in the adalimumab 0.5 mg/kg group.

Patient and physician global assessments of disease activity and patient assessment of pain and general health measured using a 100 mm VAS largely paralleled the findings described above. Placebo effects were minimal, and the effects of the 0.5 mg/kg dose of adalimumab were less marked than those resulting from treatment with the higher doses. As with the other measures of efficacy, the effects with the higher adalimumab doses (1 mg/kg and higher) persisted at least up to the Day 29 observation. The acute phase reactants CRP and ESR showed an impressive drop within 1 week after injection of adalimumab for all dose groups (Figure 7).

DISCUSSION

This is the first report of a clinical study of the fully human anti-TNF Mab adalimumab in patients with active RA. Analysis of PK data indicated that systemic drug exposure (AUC) increased proportionally with an increase in dose. The drug mainly resides in the vascular compartment (Vss = 4.7 to 5.5 l) and is cleared very slowly from serum (0.012 to 0.017 l/h). The estimated mean terminal half-life ranged from 10.0 to 13.6 days for all the 5 cohorts, with an overall half-life of 12 days for all doses.

The results of this double blind, placebo controlled trial revealed that single IV doses of adalimumab from 0.5 to 10 mg/kg were safe and well tolerated. No dose related increases in adverse events were observed, and the 2 reported serious adverse events did not appear to be treatment related. The relatively high rates of abnormal clinical laboratory findings were to be expected given the patient population, and there were no differences between placebo and adalimumab groups.

Compared with placebo, treatment with adalimumab produced a statistically significant reduction in disease activity assessed by standard clinical endpoints. Adalimumab produced rapid and sustained reductions in disease activity, with the maximum clinical response seen within one to 2 weeks. The treatment effect became evident as early as 24 hours after adalimumab administration. About

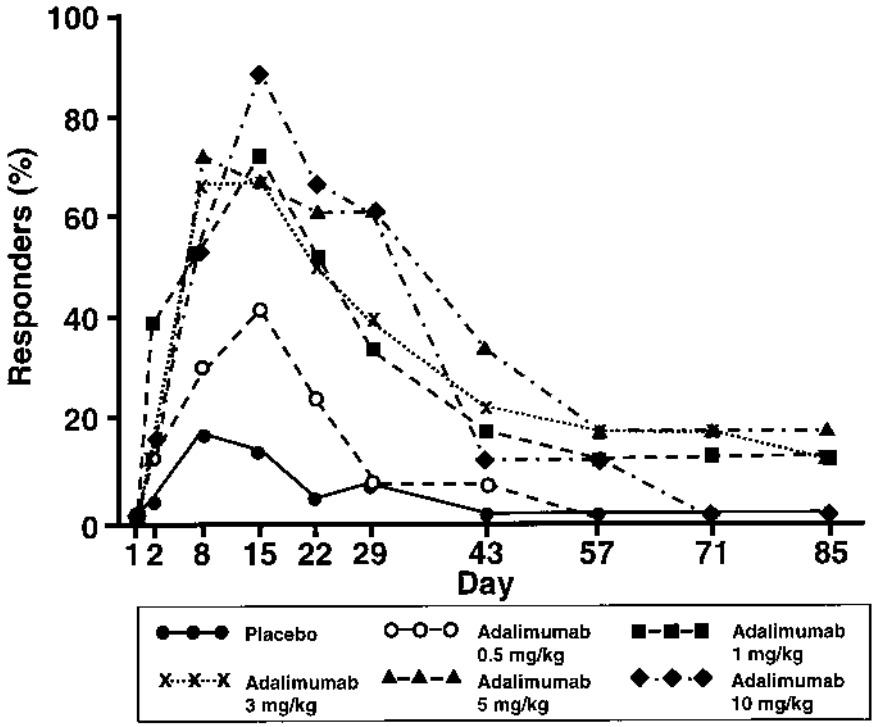

Figure 6. Responses according to EULAR response criteria over time (all randomized patients).

Table 6. Maximum median improvement (%) from baseline in key efficacy measures at any time through Day 29 following a single IV injection of adalimumab or placebo.

	Adalimumab Dose Cohort, mg/kg					
	0.5	1	3	5	10	All Placebo
No. patients						
Adalimumab	17	18	18	18	18	—
Placebo	7	6	6	6	6	31
Efficacy measure						
TJC (RAI)						
Adalimumab	29.4	49.4	54.8	51.1	51.4	—
Placebo	21.4	–23.3*	28.2	20.9	–25.0*	–11.1*
SJC						
Adalimumab	31.3	29.3	28.4	48.4	39.1	—
Placebo	17.6	10.2	–8.8*	14.3	–20.0*	–9.5*
ESR						
Adalimumab	27.5	36.2	47.4	43.8	39.1	—
Placebo	–15.4	–24.4*	–27.8*	12.7	–25.9*	–18.2*
CRP						
Adalimumab	49.5	75.7	71.3	82.2	63.2	—
Placebo	27.4	–49.0*	–35.6*	44.0	–75.8*	–19.7*
HAQ						
Adalimumab	15.7	27.9	34.7	14.3	16.8	—
Placebo	25.2	12.3	–6.8*	3.5	–10.8*	8.0

* A negative result indicates worsening. TJC: tender joint count; RAI: Ritchie Articular Index; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire.

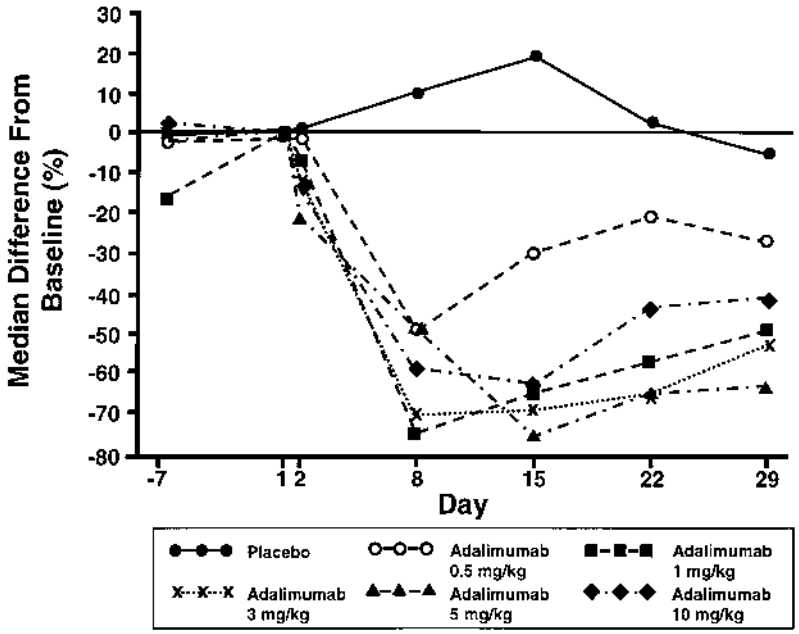

Figure 7. C-reactive protein: course of median percentage difference from baseline (Day 1) over time.

60% to 80% of patients in the higher adalimumab dose groups achieved a significant therapeutic response (EULAR and ACR20) with a single dose, which was sustained in some patients for up to 3 months. Considering the long-standing, therapeutically refractory experience of the disease in the patients studied and the relatively stringent primary efficacy measures used (EULAR, ACR20, and ACR50), it is noteworthy that such positive and sustained responses could be achieved with single doses of adalimumab. In this single dose study, efficacy initially increased at doses from 0.5 to 1.0 mg/kg, and the dose response relationship appeared flat at doses between 1 and 10 mg/kg. Therefore, doses ≤ 1 mg/kg might be adequate for future multiple dose studies. Additionally, only a small fraction of the variance of adalimumab clearance could be explained by patient body weight. Thus a fixed total body dose for all patients seems appropriate.

Single IV injections of 0.5 to 10 mg/kg of the fully human anti-TNF Mab adalimumab exhibited systemic drug exposure linearly related to dose and were well tolerated in patients with active RA. The results provide the first clinical evidence that the fully human antibody adalimumab can be used to treat RA safely and effectively. Patients from this study continue to be treated in longterm studies that will provide data on chronic safety and efficacy.

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