

# Etanercept Therapy in Rheumatoid Arthritis

## A Randomized, Controlled Trial

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**Background:** In a phase II study, etanercept (recombinant human tumor necrosis factor receptor [p75]:Fc fusion protein) safely produced rapid, dose-dependent improvement in rheumatoid arthritis over 3 months.

**Objective:** To confirm the benefit of etanercept therapy of longer duration and simplified dosing in patients with rheumatoid arthritis.

**Design:** Randomized, double-blind, placebo-controlled trial with blinded joint assessors.

**Setting:** 13 North American centers.

**Patients:** 234 patients with active rheumatoid arthritis who had an inadequate response to disease-modifying antirheumatic drugs.

**Intervention:** Twice-weekly subcutaneous injections of etanercept, 10 or 25 mg, or placebo for 6 months.

**Measurements:** The primary end points were 20% and 50% improvement in disease activity according to American College of Rheumatology (ACR) responses at 3 and 6 months. Other end points were 70% ACR responses at 3 and 6 months and other measures of disease activity at 3 and 6 months.

**Results:** Etanercept significantly reduced disease activity in a dose-related fashion. At 3 months, 62% of the patients receiving 25 mg of etanercept and 23% of the placebo recipients achieved 20% ACR response ( $P < 0.001$ ). At 6 months, 59% of the 25-mg group and 11% of the placebo group achieved a 20% ACR response ( $P < 0.001$ ); 40% and 5%, respectively, achieved a 50% ACR response ( $P < 0.01$ ). The respective mean percentage reduction in the number of tender and swollen joints at 6 months was 56% and 47% in the 25-mg group and 6% and -7% in the placebo group ( $P < 0.05$ ). Significantly more etanercept recipients achieved a 70% ACR response, minimal disease status (0 to 5 affected joints), and improved quality of life. Etanercept was well tolerated, with no dose-limiting toxic effects.

**Conclusions:** Etanercept can safely provide rapid, significant, and sustained benefit in patients with active rheumatoid arthritis.

Rheumatoid arthritis occurs in approximately 1% of the adult population and is associated with progressive joint destruction, functional disability, and decreased life expectancy (1–4). Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and hydroxychloroquine, may retard disease progression (5). However, many patients do not achieve an adequate response, and many do not maintain a response because of toxicity or lack of efficacy (6).

Although the underlying cause of rheumatoid arthritis is unknown, tumor necrosis factor (TNF)—a proinflammatory cytokine produced by macrophages and T cells—contributes to the pathogenesis of synovitis and joint destruction (7–11). There are two distinct cell-surface TNF receptors: p55 (55 kilodaltons) and p75 (75 kilodaltons), which mediate the activity of tumor necrosis factor on effector cells. Soluble TNF receptors, consisting of the extracellular portion of the receptor (12–15), serve as physiologic regulators of the inflammatory response by inhibiting TNF activity (16). Because of the involvement of TNF in the pathogenesis of rheumatoid arthritis, it was hypothesized that soluble recombinant human TNF receptors might be useful as therapy for this disease. Tumor necrosis factor exists predominantly as a trimer (17); thus, it was further hypothesized and later shown that a dimeric receptor would have greater affinity for TNF than the naturally occurring monomeric receptor and would be a more effective antagonist of the biological activity of TNF. Etanercept, a recombinant human TNF receptor Fc fusion protein (Enbrel, Immunex Corp., Seattle, Washington), is a dimer consisting of the extracellular portion of two p75 receptors fused to the Fc portion of human IgG1 (18). Previous trials in patients with active rheumatoid arthritis who had an inadequate response to DMARDs have shown etanercept to be safe, well tolerated, and able to produce significant dose-dependent improvements in disease activity (19, 20). In a phase II trial (19), responses were rapid and sustained for the full 3 months of dosing. We sought to define further the clinical activity of etanercept over a longer treat-

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ment period and to establish a simplified dosing schema.

## Methods

### Patients

Eligible patients were adults who were at least 18 years of age, met the American Rheumatism Association's diagnostic criteria for rheumatoid arthritis (21), and were in functional class I, II, or III (22). Patients were required to have had an inadequate response to one to four DMARDs (such as azathioprine, methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, or oral or injectable gold); an inadequate response was defined as discontinuation of therapy because of lack of effect. If patients were receiving DMARDs, they were required to complete a DMARD washout period that lasted at least 1 month before starting study drug treatment; no DMARDs were permitted during the study. Patients had to have active disease at enrollment (before the DMARD washout period), defined as 12 or more tender joints, 10 or more swollen joints, and at least one of the following: erythrocyte sedimentation rate of at least 28 mm/h, C-reactive protein level greater than 20 mg/L, or morning stiffness for at least 45 minutes. All patients were required to have aminotransferase levels no greater than twice the upper limit of normal, a hemoglobin level of 85 g/dL or greater, a platelet count of at least 125 000 cells/mm<sup>3</sup>, a leukocyte count of 3500 cells/mm<sup>3</sup> or higher, and a serum creatinine level of 176.8 μmol/L (2 mg/dL) or less. Concomitant therapy with stable doses of oral corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted. Corticosteroid doses could not exceed the equivalent of 10 mg of prednisone per day, and NSAID doses could not exceed the maximum dose recommended by the manufacturer. Patients could receive analgesics during the study except for the 24 hours before scheduled joint examinations. Intra-articular corticosteroids were not permitted during the study or beginning 4 weeks before enrollment. Because the inclusion criteria for this study were similar to the inclusion criteria for the previous 3-month trial in rheumatoid arthritis, 8 patients who received placebo in the 3-month trial were enrolled in the current study.

### Study Protocol

Disease status was assessed before the DMARD washout period (in patients receiving DMARDs), before the first dose of study drug (baseline), weekly through week 4, and then monthly for the remaining 6 months. Assessment of disease status

included a complete count of tender and swollen joints (71 joints were assessed; hips and cervical spine were evaluated only for tenderness). Joints were classified as tender if any amount of pain occurred with pressure or joint manipulation. Joints were classified as swollen if any amount of soft tissue swelling was present. All joint assessments, beginning with the baseline evaluation, were performed by specially trained, independent assessors who had no knowledge of the patients' treatment assignments, were not involved in patient care, and did not discuss the study with patients or investigators.

The Health Assessment Questionnaire (HAQ) was administered at each assessment to all patients (23). The HAQ (Stanford RA, January 1996, phase 30) includes the disability index, a general health assessment question, an arthritis-specific question, and the vitality and mental health domain questions from the SF-36 (24).

The other indices of disease activity evaluated at each assessment included C-reactive protein level; erythrocyte sedimentation rate; duration of morning stiffness; patient's and physician's global assessments (scale ranging from 0 [best] to 10 [worst]); and patient's assessment of pain (visual analogue scale ranging from 0 [best] to 10 [worst]). Hematology profiles, chemistry profiles, rheumatoid factor titers, antinuclear antibody titers (measured by nephelometry), anti-double-stranded DNA antibody concentrations (measured by radioimmunoassay and *Crihidia luciliae* assays), anticardiolipin antibody concentrations (measured by indirect enzyme-linked immunosorbent assay), and urinalysis results were evaluated at baseline, week 12, and week 26. Serum was evaluated for the presence of anti-etanercept antibodies at baseline, week 12, and week 26 by using a previously described assay (19).

The institutional review board at each center approved the study. All patients gave written informed consent.

### Treatment

Patients were randomly assigned to receive placebo or 10 mg or 25 mg of etanercept subcutaneously twice weekly for 26 weeks. A blocked randomization was used, with stratification according to study site and equal allocation of treatments. The randomization code was housed with the sponsor. Blinding was maintained until all patients completed 6 months of treatment and the database was locked. The study drug was supplied in vials as a sterile, lyophilized powder containing 40 mg of mannitol, 10 mg of sucrose, 1.2 mg of tromethamine, and 10 or 25 mg of etanercept per vial. Placebo was supplied in an identical format and was formulated in the same way except that it contained no etanercept.

**Table 1. Patient Demographic and Baseline Clinical Characteristics\***

Characteristic	Placebo Group (n = 80)	Etanercept Groups	
		10 mg (n = 76)	25 mg (n = 78)
<b>Demographic</b>			
Mean age, y	51	53	53
Women, %	76	84	74
White, %	89	96	94
<b>Clinical</b>			
Mean duration of disease, y	12	13	11
Mean measures of disease activity			
Tender joints, n†	35	34	33
Swollen joints, n‡	25	25	25
Duration of morning stiffness, h	4.8	4.4	5.0
Physician's global assessment§	6.9	6.9	6.9
Patient's global assessment§	6.9	6.9	7.0
Pain (visual analogue scale)	6.5	6.6	6.7
Disability index (health assessment questionnaire)			
	1.7	1.7	1.6
Vitality domain (SF-36)¶	69	68	66
Mental health domain (SF-36)¶	42	41	42
Erythrocyte sedimentation rate, mm/h	39	44	35
C-reactive protein level, mg/dL	4.1	5.3	4.7
Rheumatoid-factor positive, %	79	82	79
Hemoglobin level, g/L	130	127	133
Platelet count, × 10 <sup>3</sup> /μL	360	358	358
Albumin level, g/dL	37	36	36
Leukocyte count, × 10 <sup>3</sup> /μL	8.7	9.3	10.2
Mean previous DMARDs, n	3.0	3.4	3.3
Previous DMARDs, %			
Methotrexate	90	92	87
Hydroxychloroquine	71	70	65
Gold, injectable	46	57	58
Sulfasalazine	35	54	51
Azathioprine	28	32	32
D-Penicillamine	21	30	22
Gold, oral	21	20	22
Concomitant medications			
Corticosteroids, %			
Mean daily corticosteroid dose (prednisone equivalent), mg	6.8	7.5	7.3
Nonsteroidal anti-inflammatory drugs, %	84	67	67
Patients requiring DMARD washout, %	48	46	45

\* DMARD = disease-modifying antirheumatic drug.

† Range, 0–71.

‡ Range, 0–68.

§ 0 = best, 10 = worst.

|| 0 = best, 3 = worst.

¶ 1 = best, 100 = worst.

cept. Both placebo and the study drug were reconstituted with 1 mL of bacteriostatic water for injection.

### Study End Points

The primary efficacy end points were 20% and 50% improvement in disease activity at 3 and 6 months. The 20% American College of Rheumatology (ACR) response, defined by the ACR (25), specifies a 20% reduction in tender joint count and swollen joint count and 20% improvement in at least three of the following: patient's assessment of pain, patient's global assessment, physician's global assessment, patient's assessment of disability, and acute phase reactant measures (either erythrocyte sedimentation rate or C-reactive protein level). Other efficacy end points included 70% ACR re-

sponse at 3 and 6 months and percentage change from baseline at 3 and 6 months in the following: tender joint count, swollen joint count, duration of morning stiffness, patient's global assessment, physician's global assessment, patient's assessment of pain, quality of life, erythrocyte sedimentation rate, and C-reactive protein level. Response was also evaluated according to the Paulus index, defined as a 20% or 50% improvement in at least four of the following variables: tender joint scores, swollen joint scores, duration of morning stiffness, erythrocyte sedimentation rate, patient's global assessment, and physician's global assessment (26).

### Statistical Analyses

The ACR response rates (25) and Paulus (26) indices were compared by using the likelihood ratio chi-square test. The Fisher exact test was substituted when necessitated by low response rates (50% ACR response at 2 weeks and 70% ACR response). Patients who withdrew for any reason were counted as nonresponders subsequent to withdrawal. Individual measures of disease activity were compared by using analysis of variance in which treatment, study site, and their interaction were the factors. The last available observation was used for dropouts. If the initial comparison of the three treatments was significant at the  $P = 0.05$  level, each pair of treatments was compared (also at the 0.05 level). This procedure controls the type I error at the 0.05 level. The Stuart–Maxwell chi-square test (27) was used to test for normalization of laboratory values (within treatment groups). We conducted all analyses by using version 6.12 of SAS software (SAS Institute, Cary, North Carolina).

### Role of the Funding Source

The funding source, Immunex Corp., coordinated the design, conduct, and reporting of the study. Five of the authors are employees of Immunex Corp. Both the funding source and physicians participating in the study had a role in the decision to submit the manuscript for publication.

### Results

Baseline demographic and clinical characteristics are summarized in **Table 1**. Two hundred forty-six patients were randomly assigned. Twelve randomly assigned patients (3 in the placebo group, 6 in the 10-mg group, and 3 in the 25-mg group) did not meet eligibility criteria and therefore did not receive the study drug. An intention-to-treat analysis was performed on the 234 patients who were randomly assigned and received the study drug. The patients were primarily female (78%), with a mean age of 52

years and mean duration of disease of 12 years. Ninety percent of the patients had been treated previously with methotrexate; 22% were treated with methotrexate immediately before the DMARD washout period. Eighty patients received placebo, 76 patients received 10 mg of etanercept, and 78 patients received 25 mg of etanercept. Aside from differences in concurrent medications (more patients in the 25-mg group were receiving corticosteroids and more placebo recipients were receiving NSAIDs), no baseline imbalances were detected. Significantly more etanercept recipients than placebo recipients completed the full 6 months of therapy: 76% in the 25-mg group and 68% in the 10-mg group compared with 33% in the placebo group ( $P < 0.001$  for each etanercept group compared with the placebo group). Most withdrawals occurred because of lack of efficacy (Figure 1).

### American College of Rheumatology Response Rate

Table 2 shows the primary study end points: 20% and 50% ACR response at 3 and 6 months. At 6 months, 59% of patients in the 25-mg group, 51% in the 10-mg group, and 11% in the placebo group achieved 20% ACR response ( $P < 0.001$  for each etanercept group compared with the placebo group). At 6 months, 40% of patients in the 25-mg group, 24% of patients in the 10-mg group, and 5%

of patients in the placebo group achieved 50% ACR responses ( $P < 0.001$  for each etanercept group compared with the placebo group). Although 70% ACR response was not a prospectively defined study end point, 15% of patients in the 25-mg group and 9% of patients in the 10-mg group compared with 1% of patients in the placebo group achieved this response at 6 months ( $P < 0.031$  for each etanercept group compared with the placebo group).

In patients receiving etanercept, the clinical responses were rapid, often appearing within 2 weeks after initiation of therapy (Figure 2). Most responding patients attained substantial responses by 3 months; some patients continued to improve through 6 months. Significantly more patients in the etanercept groups achieved responses at all time points than did patients in the placebo group. The 25-mg dose was significantly more effective than the 10-mg dose in producing 20% ACR responses at 2 weeks and 3 months and in producing 50% ACR responses at 3 and 6 months.

Treatment benefit was similar in patients who used NSAIDs and those who did not. At 6 months, the 20% ACR response rates in the etanercept groups were 63% (NSAID users) and 50% (nonusers) compared with rates of 12% (NSAID users) and 8% (nonusers) in the placebo group. Similarly, corticosteroid use did not alter relative response

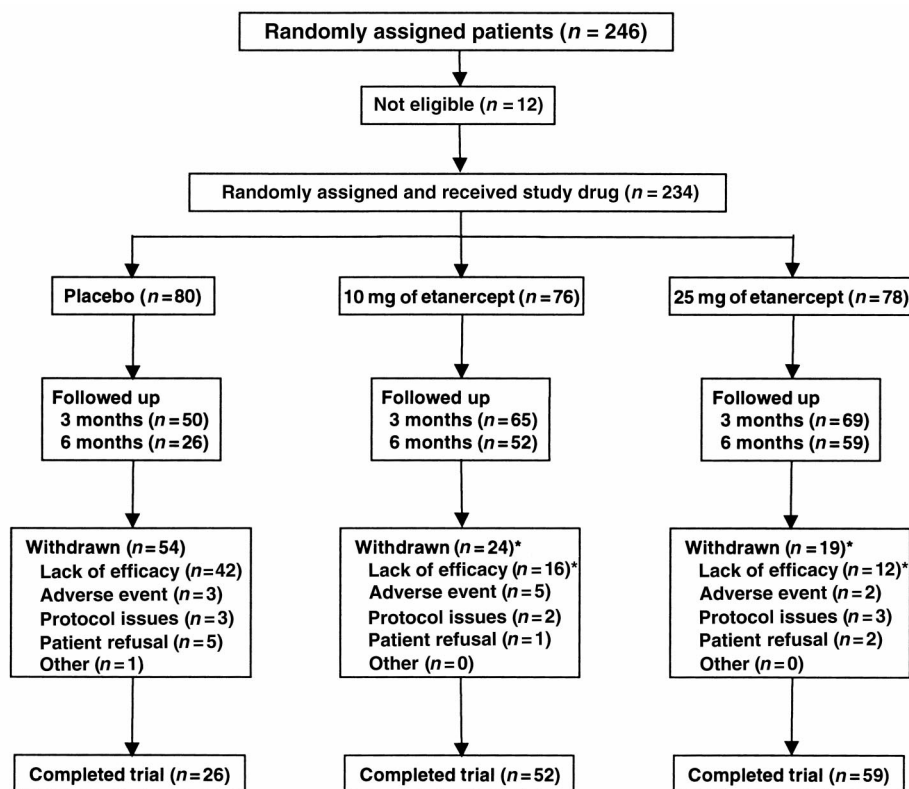


Figure 1. Study completion and withdrawal before 6 months. \* $P < 0.001$  for each etanercept group compared with the placebo group (likelihood ratio chi-square test).

**Table 2. Improvement by American College of Rheumatology Criteria\***

Criterion	Placebo Group (n = 80)	Etanercept Groups		P Value†		
		10 mg (n = 76)	25 mg (n = 78)	Placebo vs. 10 mg	Placebo vs. 25 mg	10 mg vs. 25 mg
←—————%—————→						
20% improvement						
2 weeks	1	17	32	<0.001	<0.001	0.030
3 months	23	45	62	0.003	<0.001	0.036
6 months	11	51	59	<0.001	<0.001	0.2
50% improvement						
2 weeks	0	4	6	0.113	0.027	>0.2
3 months	8	13	41	>0.2	<0.001	<0.001
6 months	5	24	40	<0.001	<0.001	0.032
70% improvement						
2 weeks	0	0	1	>0.2	>0.2	>0.2
3 months	4	8	15	>0.2	0.015	>0.2
6 months	1	9	15	0.031	0.001	>0.2

\* Group numbers reflect the starting size of each group; withdrawals were counted as treatment failures.

† Pairwise comparisons made by using a likelihood ratio chi-square test except for 50% improvement at 2 weeks and 70% improvement; these comparisons were made by using the two-tailed Fisher exact test.

(etanercept group: 60% of corticosteroid users and 53% of nonusers; placebo group: 11% of corticosteroid users and 12% of nonusers).

No significant relation between response and body weight within either etanercept group was seen. In the 25-mg group, 20% ACR responses at 6 months occurred in 69% of patients with the lowest weights and 67% of patients with the highest weights.

### Other Measures of Disease Activity

Etanercept treatment significantly decreased the number of tender and swollen joints. At 6 months, the mean tender joint count was reduced by 56% in the 25-mg group and by 44% in the 10-mg group compared with 6% in the placebo group ( $P < 0.05$  for each etanercept group compared with the placebo group). At 6 months, minimal disease, defined as 0 to 5 tender or swollen joints (28), was achieved in 17% of patients receiving 25 mg of etanercept and 14% of patients receiving 10 mg of etanercept compared with 3% of patients receiving placebo ( $P < 0.005$  for each etanercept group compared with the placebo group). Other measures of disease activity, such as C-reactive protein level, erythrocyte sedimentation rate, and duration of morning stiffness, were significantly improved with etanercept treatment (Table 3).

At 6 months, 20% Paulus responses were achieved in 68% of patients receiving 25 mg of etanercept, 64% of patients receiving 10 mg of etanercept, and 16% of patients receiving placebo ( $P < 0.001$  for each etanercept group compared with the placebo group). Paulus responses of 50% occurred in 55% of patients in the 25-mg group,

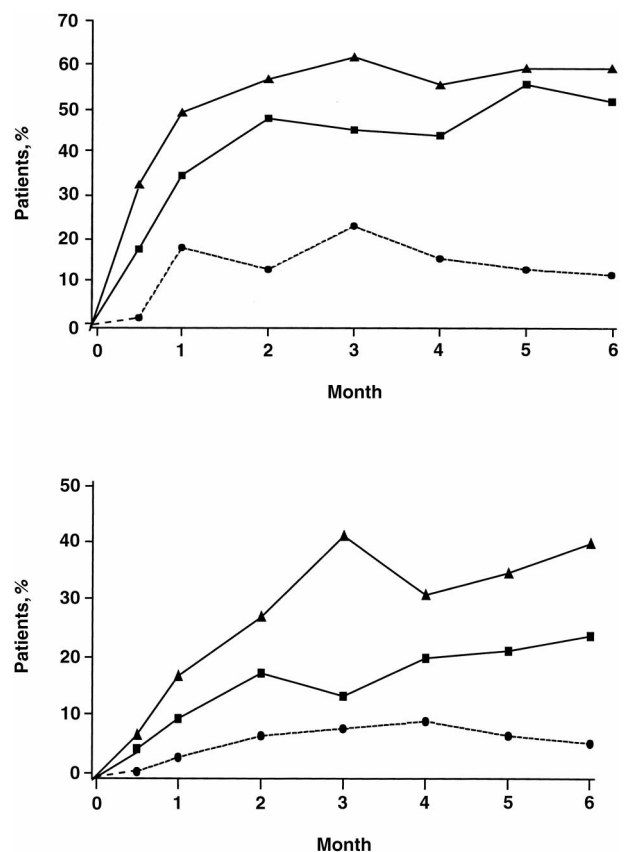
42% of those in the 10-mg group, and 8% of those in the placebo group ( $P < 0.001$  for each etanercept group compared with the placebo group).

### Quality of Life

All components of the HAQ substantially improved over baseline in both etanercept groups at 3 and 6 months compared with placebo (Table 4). Improvement was observed as early as 2 weeks after initiation of etanercept therapy.

### Safety and Tolerability

Etanercept was well tolerated. Mild injection-site reactions were the most common adverse events associated with etanercept administration (Table 5). Forty-nine percent of patients receiving 25 mg of etanercept and 43% of those receiving 10 mg of etanercept developed injection-site reactions compared with 13% of patients receiving placebo ( $P < 0.001$  for each etanercept group compared with the placebo group). Most patients who experienced injection-site reactions had reactions to 5 or fewer of the approximately 52 injections given during the study. Injection-site reactions were described as er-



**Figure 2. Percentage of patients achieving a clinical response as defined by the American College of Rheumatology. Top.** 20% American College of Rheumatology response. **Bottom.** 50% American College of Rheumatology response. Triangles represent patients receiving 25 mg of etanercept; squares represent patients receiving 10 mg of etanercept; circles represent patients receiving placebo.

**Table 3. Improvement in Disease Activity\***

Measure of Disease Activity	Mean Change from Baseline			P Value†
	Placebo Group (n = 80)	Etanercept Groups		
		10 mg (n = 76)	25 mg (n = 78)	
	←—————%—————→			
<b>3 months</b>				
Tender joint count	15	40	55	<0.001
Swollen joint count	1	30	47	<0.001
Morning stiffness	-13	32	32	<0.001
Physician's assessment	7	34	45	<0.001
Patient's assessment	3	31	46	<0.001
Pain (visual analogue scale)	-13	40	50	<0.001
Erythrocyte sedimentation rate	-14	17	20	<0.001
C-reactive protein level	-158	15	28	<0.001
<b>6 months</b>				
Tender joint count	6	44	56	<0.001
Swollen joint count	-7	45	47	<0.001
Morning stiffness	-23	34	13	<0.001
Physician's assessment	2	33	44	<0.001
Patient's assessment	-3	31	46	<0.001
Pain (visual analogue scale)	-22	39	53	<0.001
Erythrocyte sedimentation rate	-18	10	18	0.001
C-reactive protein level	-207	-18	31	<0.001

\* Group numbers reflect the starting size of each group; last-observation-carried-forward analysis was used. Positive values indicate improvement; negative values indicate worsening.

† Test for any difference among treatments; for morning stiffness and C-reactive protein level, ranks of percentage change from baseline were analyzed because of non-normality.

ythematosus, with or without itching, pain, or swelling, with a median duration of 3 days. The rate was highest in the first month of treatment, with decreasing frequency in subsequent months. Eighty-four percent of injection-site reactions were not treated; the rest were treated with topical corticosteroids or oral or topical antihistamines. One patient (in the 10-mg group) discontinued therapy with the study drug because of injection-site reactions. Efficacy was not related to the occurrence of injection-site reactions. At 6 months, 20% ACR responses occurred in 63% of patients in the 25-mg group who had an injection-site reaction and 55% of those who did not have a reaction; the corresponding rates in the placebo group were 0% and 13%.

After we adjusted for time on study attributable to the higher rate of withdrawals in the placebo group, no difference in infection was seen among the three groups. All infections resolved and were typical of those seen in outpatient populations, with the exception of bacterial tracheitis in a placebo recipient. The most common infections reported during the trial were upper respiratory tract infections.

No abnormalities in laboratory values were noted in the etanercept groups. Indeed, in patients receiving etanercept, C-reactive protein level, erythrocyte sedimentation rate, platelet count, albumin level, and leukocyte count returned to normal (Table 6); this did not occur in the placebo group. One patient in the 10-mg group had non-neutralizing etanercept antibodies at 3 months and 4 months that could not be correlated with clinical response because the pa-

tient's condition never improved while in the study. No other patients developed etanercept antibodies.

Most patients tested negative for autoantibodies during the study. Five percent of patients were positive for anti-double-stranded DNA antibody before study drug administration. By radioimmunoassay, 10 of 214 patients (5%) were newly positive for anti-double-stranded DNA antibody at the end of the trial: The percentages were 4% for the 25-mg group, 9% for the 10-mg group, and 1% for the placebo group. A majority (67%) of patient samples that tested positive for anti-double-stranded DNA antibody by radioimmunoassay were negative for antinuclear antibodies at the same time. Samples positive for anti-double-stranded DNA antibody by radioimmunoassay were further tested by using the more specific *C. luciliae* assay. The only patient positive by this assay on serial testing was a patient in the 10-mg group who had systemic lupus erythematosus/rheumatoid arthritis overlap syndrome that had been diagnosed many years before study enrollment. Of note, this patient's lupus did not worsen during the study, and her arthritis symptoms markedly improved. No evidence of new connective tissue disorders developed in any patient.

## Discussion

Etanercept was well tolerated and effective in reducing disease activity in patients with active

**Table 4. Improvement in Quality of Life\***

Variable	Mean Change from Baseline		
	Placebo Group (n = 80)	Etanercept Groups	
		10 mg (n = 76)	25 mg (n = 78)
	←—————%—————→		
<b>Disability index</b>			
2 weeks	4	16	17
3 months	8	30†	36†
6 months	2	34†	39†
<b>General health status</b>			
2 weeks	6	23	19
3 months	-6	35†	30†
6 months	-12	34†	33†
<b>Arthritis-specific health status</b>			
2 weeks	-11	11	15
3 months	-19	38†	42†
6 months	-22	31†	44†
<b>Vitality domain</b>			
2 weeks	3	8	12
3 months	5	19†	26†
6 months	2	22†	25†
<b>Mental health domain</b>			
2 weeks	-2	1	11
3 months	4	11	29†‡
6 months	3	17	35†‡

\* Positive values indicate improvement; negative values indicate worsening. Group numbers reflect the starting size of each group; last-observation-carried-forward analysis was used.

†  $P < 0.05$  for etanercept groups compared with placebo group.

‡  $P < 0.05$  for 10-mg etanercept group compared with 25-mg etanercept group.

**Table 5. Adverse Events\***

Adverse Event	Placebo Group (n = 80)†		Etanercept Groups			
			10 mg (n = 76)†		25 mg (n = 78)†	
	%	events/ patient-year	%	events/ patient-year	%	events/ patient-year
Injection-site reaction	13	0.79	43	7.39‡	49	11.76‡
Upper respiratory tract infection	16	0.93	29	0.85	33	1.11
Headache	10	0.65	20	0.81	14	0.46
Sinusitis	11	0.42	11	0.26	12	0.34
Rhinitis	11	0.51	12	0.36	10	0.37
Diarrhea	6	0.28	11	0.33	5	0.18

\*  $\geq 10\%$  of patients in any treatment group.

† Because many placebo recipients discontinued treatment before 6 months, rates were calculated per patient-year. Patient-years: placebo, 22; 10 mg of etanercept, 31; 25 mg of etanercept, 33.

‡  $P < 0.05$ .

rheumatoid arthritis who had an inadequate response to DMARD therapy. The patients studied in our trial had long-standing rheumatoid arthritis (mean duration, 12 years), and 90% had previously been treated with methotrexate (the gold standard of current rheumatoid arthritis therapy). Clinical response to etanercept was rapid, beginning as early as 2 weeks after initiation of therapy, and was maintained throughout the 6-month study. Although 20% ACR responses are useful for defining clinical utility, responses of much higher magnitude (50% and 70% ACR responses) and of greater clinical importance were also seen. Furthermore, a significant dose response was evident: Patients treated with 25 mg of etanercept achieved 20% ACR responses more quickly than those treated with 10-mg doses. At the level of 50% ACR response, the differences between etanercept groups were especially striking, with approximately twofold to threefold more patients responding in the 25-mg group than in the 10-mg group. Although the high withdrawal rate because of lack of efficacy in the placebo group (68%) makes the last-observation-carried-forward analysis of individual measures of arthritis activity problematic at later time points, etanercept treatment significantly improved these measures throughout the trial, including improvements as early as 2 weeks of treatment.

These results confirm and expand on those of a phase II, randomized, double-blind, placebo-controlled trial in which patients with active rheumatoid arthritis and inadequate responses to DMARDs were treated with etanercept (19). In that trial, patients receiving etanercept experienced rapid, dose-dependent improvements in disease activity without therapy-limiting toxicity. Stopping etanercept therapy after 3 months resulted in a return toward pretreatment symptoms, suggesting that sustained effect requires continued administration. The results of the current trial show that significant clinical

benefit can be extended over a 6-month course of treatment with no change in safety or tolerability.

The doses of etanercept used in this trial were based on those used in the phase II trial. In that study, patients receiving the highest etanercept dosage of 16 mg/m<sup>2</sup> subcutaneously twice weekly received doses ranging from 23 to 30 mg, with similar clinical responses observed throughout the range. Therefore, a simple, fixed dose of 25 mg was chosen for the phase III trial. Another group of patients in the phase II trial received 2 mg/m<sup>2</sup> (3.5 to 4 mg per dose) and had intermediate clinical responses. In the phase III trial, a dose of 10 mg (approximately 6 mg/m<sup>2</sup>) was tested to determine whether it was as effective as the 25-mg dose. The 25-mg dose is the optimal dose of etanercept tested because it results in more rapid and higher levels of response than 10 mg and is just as safe. Further analysis has confirmed that a fixed dose is effective in both small and large patients.

One limitation of conventional DMARD therapy in the treatment of rheumatoid arthritis is the compromise between effective doses and adverse events. Unacceptable toxicity is often the reason for discontinuation of DMARD therapy, and frequent monitoring is required to reduce the risk for serious or even life-threatening adverse reactions (29–32). In this 6-month trial, etanercept was well tolerated, showed no evidence of cumulative toxicity, and required no special laboratory evaluations or monitoring. Mild injection-site reactions were the most common adverse event associated with etanercept administration. These typically resolved without treatment and were a cause for withdrawal in only one patient. Although 6-month randomized, controlled trials have a limited ability to comprehensively assess drug safety, the lack of observed toxicity of etanercept is encouraging and distinguishes etanercept from currently available DMARDs. The lack of toxicity also makes etanercept therapy in combination with DMARDs feasible. A study of

**Table 6. Patients with Normal Laboratory Values**

Variable	Placebo Group (n = 80)		Etanercept Groups			
			10 mg (n = 76)		25 mg (n = 78)	
	Baseline	Last	Baseline	Last	Baseline	Last
	← % →					
C-reactive protein level	21	18	17	26	21	46*
Erythrocyte sedimentation rate	43	34	32	53*	50	67*
Hemoglobin level	78	75	73	80	84	87
Platelet count	68	69	65	80*	70	84*
Albumin level	82	83	77	89*	75	91*
Leukocyte count	75	66	68	68	60	77*

\*  $P < 0.05$  compared with baseline.

etanercept in combination with methotrexate has recently been completed (33).

In the current trial with etanercept, autoantibody titers fluctuated over the short term in patients receiving placebo as well as those receiving etanercept. Indeed, 5% of patients with rheumatoid arthritis seemed to be positive for anti-double-stranded DNA antibody by radioimmunoassay on serial testing, but no patient had sustained anti-double-stranded DNA antibodies by the more specific *C. luciliae* assay. No study patient developed clinical signs or symptoms of lupus or any other autoimmune disease.

In only one patient (in the 10-mg group) did non-neutralizing etanercept antibodies develop. This finding is especially encouraging because patients were not receiving concurrent immunosuppressive drugs to inhibit the development of antibodies to etanercept. This factor will be important because this is long-term therapy; continued dosing is necessary to control symptoms of rheumatoid arthritis. The lack of immunogenicity of etanercept in most patients may be attributed to the agent's fully human derivation.

Because rheumatoid arthritis is a chronic disease, information about the long-term safety and efficacy of etanercept is important and cannot be well addressed in 3- or 6-month trials. Preliminary results of a long-term, open-label safety and efficacy trial of etanercept in rheumatoid arthritis have been presented (34); this trial indicated that efficacy is maintained at 18 months, with no evidence of significant new toxic effects beyond those described in trials of etanercept in rheumatoid arthritis. Patients continue to be treated in long-term studies that will provide data on long-term safety and efficacy.

In summary, twice-weekly subcutaneous administration of etanercept resulted in significant improvement in disease activity and quality of life with minimal toxicity in patients with active rheumatoid arthritis. The 25-mg etanercept dose was most effective. That responses of the magnitude observed in this trial could be obtained in patients with such advanced stages of rheumatoid arthritis is encouraging. These results and those of other trials of anti-TNF biological response modifiers (35–37) suggest that TNF inhibition is a viable approach to controlling disease activity in rheumatoid arthritis. Considering the pivotal role TNF plays in the pathogenesis of rheumatoid arthritis, future studies should determine whether etanercept arrests disease progression and what degree of clinical response is possible in patients with earlier disease. These questions are being evaluated in an ongoing randomized clinical trial.

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