

Etanercept Treatment of Psoriatic Arthritis

Safety, Efficacy, and Effect on Disease Progression

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Objective. Etanercept has been shown to improve the articular and cutaneous manifestations of psoriatic arthritis (PsA). In this study, we further evaluated the safety, efficacy, and effect on radiographic progression of etanercept in patients with PsA.

Methods. Patients with PsA (n = 205) were randomized to receive placebo or 25 mg etanercept subcutaneously twice weekly for 24 weeks. Patients continued to receive blind-labeled therapy in a maintenance phase until all had completed the 24-week phase, then could receive open-label etanercept in a 48-week extension. Efficacy and safety were evaluated at 4, 12, and 24 weeks and at 12-week intervals thereafter. Radiographs of the hands and wrists were assessed at baseline and 24 weeks, at entry to the open-label phase, and after 48 weeks in the study.

Results. Etanercept significantly reduced the signs and symptoms of PsA and psoriasis. At 12 weeks, 59% of etanercept patients met the American College of Rheumatology 20% improvement criteria for joint re-

sponse, compared with 15% of placebo patients ($P < 0.0001$), and results were sustained at 24 and 48 weeks. At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the Psoriasis Area and Severity Index, compared with 3% of placebo patients ($P = 0.001$). Radiographic disease progression was inhibited in the etanercept group at 12 months; the mean annualized rate of change in the modified total Sharp score was -0.03 unit, compared with $+1.00$ unit in the placebo group ($P = 0.0001$). Etanercept was well tolerated.

Conclusion. Etanercept reduced joint symptoms, improved psoriatic lesions, inhibited radiographic progression, and was well tolerated in patients with PsA.

Psoriatic arthritis (PsA) is a chronic inflammatory disorder of the peripheral joints and axial skeleton that occurs in 7–34% of patients with psoriasis (1–4), which, in turn, has a prevalence of 1–3% of the general population (2,5). Many patients have erosive disease, physical limitations, and work-related disability. In a study by Gladman et al (6) of 220 PsA patients, >40% had deforming, erosive arthropathy and stage III or stage IV radiologic change as measured by the Steinbrocker criteria (7), and 11% had class III or class IV functional impairment. Patients with PsA may experience more pain and more role limitations due to emotional problems than do patients with rheumatoid arthritis (RA) (8), and mortality may be increased (9).

High concentrations of tumor necrosis factor (TNF) are found in the joint fluid and synovium of patients with PsA (10,11) and in psoriatic lesions (12). Etanercept, a soluble TNF receptor antagonist, binds TNF with high affinity, preventing it from interacting with its cell-surface receptor and initiating intracellular signaling. Etanercept reduces the signs and symptoms of arthritis and inhibits radiographic progression in pa-

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tients with RA (13–15). In a previous randomized controlled trial, etanercept improved the articular and cutaneous manifestations of PsA (16). Based on these observations, we evaluated the safety, efficacy, and effect on radiographic progression of etanercept in a multicenter study of PsA patients.

PATIENTS AND METHODS

Patients. The institutional review boards of the participating medical centers approved the study protocol, and all patients gave written informed consent before study entry. Eligible patients were ages 18–70 years and had active PsA, with at least 3 swollen and 3 tender joints at screening and a previous inadequate response to nonsteroidal antiinflammatory drug therapy. Patients had at least 1 of the following clinical subtypes of PsA, as described by Moll and Wright (17): distal interphalangeal (DIP) joint involvement, polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis), arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis–like arthritis. Patients had stable plaque psoriasis with a qualifying target lesion (at least 2 cm in diameter). Concomitant methotrexate therapy, which had been stable for 2 months, could be continued at a stable dosage of ≤ 25 mg/week. Other disease-modifying antirheumatic drugs were discontinued at least 4 weeks before the study start. Corticosteroids, which had been stable for 4 weeks, could be continued at the equivalent of ≤ 10 mg/day of prednisone. Phototherapy was discontinued at least 2 weeks before the study start. Oral retinoids, topical vitamin A or D analog preparations, and anthralin were not allowed. Topical therapies were permitted on the scalp, axillae, and groin only.

Study drug. Etanercept was supplied to patients in syringes, each containing the contents of 1 reconstituted vial of etanercept or otherwise identically furnished placebo. All study drug administration was done by self-administered subcutaneous injection.

Study design. This study was a placebo-controlled double-blind trial that evaluated etanercept therapy in patients with PsA at 17 sites in the US. Eligible patients were randomly assigned to receive placebo or etanercept at a dosage of 25 mg subcutaneously twice weekly in an initial 24-week blinded phase. Patients who continued receiving methotrexate were randomized separately from those not receiving methotrexate. Patients continued to receive blind-labeled therapy in a maintenance phase until all patients had completed the 24-week blinded phase and the database was locked. After the study was unblinded, all patients were eligible to receive open-label etanercept in a 48-week extension. Clinical assessments were performed at screening, baseline, and at 4, 12, and 24 weeks, and every 12 weeks thereafter. Radiographic assessments were performed at baseline and 24 weeks of the blinded phase, at entry to the open-label phase, and 1 year from baseline of the study. The study was conducted from March 2000 to August 2002.

Clinical efficacy end points. The primary measure of efficacy for arthritis was a comparison of the proportion of patients in the study groups who met the American College of Rheumatology 20% improvement criteria (ACR20) (18).

Other end points included the ACR50 and ACR70 responses and the Psoriatic Arthritis Response Criteria (PsARC), a composite measure of patient's and physician's global assessments and tender and swollen joint scores (19). The effect of etanercept on psoriasis was measured as improvement in target lesions, in the dermatologist's static global assessment of psoriasis, and in the Psoriasis Area and Severity Index (PASI 50 and PASI 75) (20). Other analyses of outcome included quality of life, as measured by the Short Form 36 (SF-36) Health Survey (21), and function, as evaluated using the Health Assessment Questionnaire (HAQ) (22).

Radiographic end points. Radiographic disease progression in the hands and wrists at 6 and 12 months was compared between the study groups using the annualized rate of change in the modified total Sharp score (TSS; joint erosion plus joint space narrowing [JSN] scores) (23). Features specific to PsA, including digital tuft resorption, juxtaarticular and shaft periostitis, gross osteolysis, pencil-in-cup deformity, joint space widening, and ankylosis, were also compared.

Safety end points. All patients who were randomized and received at least 1 dose of study drug were evaluated for safety, including adverse events, infections, and premature discontinuations from the study. Standard laboratory tests, including hematology, serum chemistry, and urinalysis, were performed at screening, 12 and 24 weeks of the blinded phase, every 12 weeks throughout the maintenance and extension periods, and at early termination or 30 days after early termination. Serum samples were obtained at baseline and week 24 to be tested for antibody to etanercept.

Statistical analysis. The sample size was chosen on the basis of results from a previous randomized double-blind trial (16). Assuming ACR20 rates of 60% in the etanercept group and 30% in the placebo group, the sample size of 100 patients per group afforded $>90\%$ power to detect a significant difference between treatment groups in the primary end point (2-sided, $\alpha = 0.05$).

Intent-to-treat analyses were performed on all patients who received at least 1 dose of blinded study drug. Binary response rates were compared by Cochran-Mantel-Haenszel test or Fisher's exact test. Patients discontinuing the study drug or receiving an oral pulse or intramuscular injections of corticosteroids were considered nonresponders for all binary end points. Continuous efficacy variables (change or percentage change from baseline) were analyzed by Wilcoxon's rank sum test, using a last observation carried forward analysis for missing data or early termination.

Arthritis activity was determined by assessing 78 joints for tenderness and 76 joints for swelling (graded 0–3; note that the ACR criteria suggest 68 joints for tenderness and 66 for swelling, to which we added the 8 DIP joints of the toes and the 2 carpometacarpal joints, which are commonly affected in PsA) (16), patient's and physician's global assessments (0–5 on a Likert scale), patient's assessment of pain (0–5 on a Likert scale), patient's assessment of disability by responses to the HAQ, and serum concentration of C-reactive protein.

A prospectively identified psoriatic lesion was evaluated for plaque elevation, scaling, and erythema. Patients with plaque psoriasis that involved at least 3% of their body surface area at baseline were evaluated using the PASI, a composite index of disease severity incorporating measures of scaling,

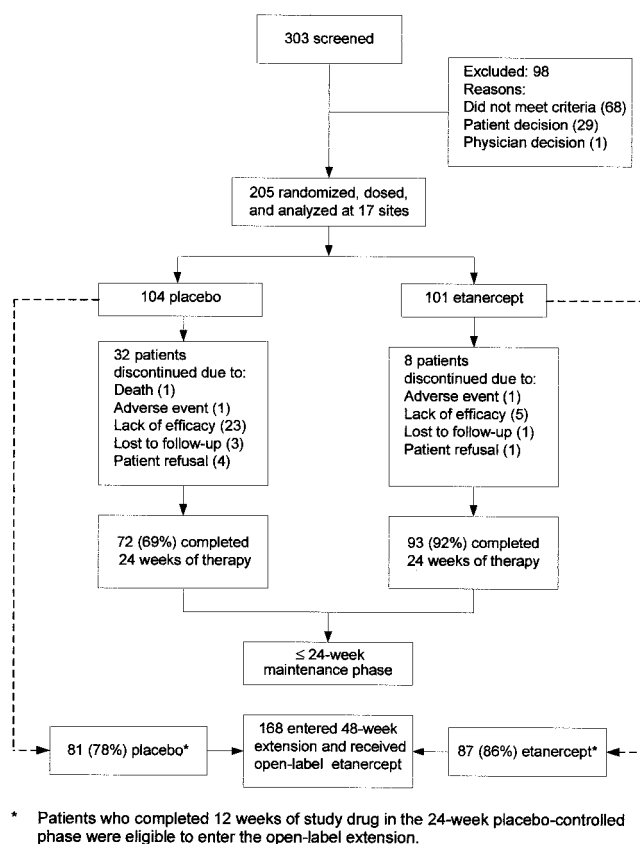


Figure 1. Study flow diagram.

erythema, and induration, weighted by severity and affected body surface area.

Radiographs of the hands and wrists were read by pairs of site-independent radiologists who were blinded to the study treatment and the chronological order of the images. For each patient at each time point (6 and 12 months), 21 joints of each hand and wrist were scored for erosions on a scale of 0–5 (0 = no damage), and 20 joints were scored for JSN on a scale of 0–4 (0 = no damage). The scores from each joint were totaled to determine erosion and JSN scores, and the erosion and JSN scores were added to determine the TSS. DIP joints were included in the analyses. Annualized rate of change was calculated by adjusting the change score to 6 or 12 months using linear interpolation/extrapolation of the observed change. For example, if the 12-month image was actually taken at 11 months, the change score was multiplied by the factor $365.25/(11\text{-month x-ray day} - \text{baseline x-ray day})$.

Readers scored digitized radiographs for erosions and JSN using a computer-assisted masked reading (CAMR) program. The CAMR presented images for scoring, recorded the radiographic scores, and electronically transmitted the scores to a central database. Images from each patient's radiographs were scored by 2 readers. The averages of the 2 readers' scores were used in these analyses.

For safety analyses, all adverse events, infections, and

abnormal laboratory results were graded on a scale derived from the common toxicity criteria of the National Cancer Institute. Treatment groups were compared with respect to the proportions of patients with adverse events and infections using Fisher's exact test. Serum samples were tested for antibody to etanercept by an enzyme-linked immunosorbent assay first described by Moreland et al (24), but revised in 1999 for optimal accuracy.

RESULTS

A total of 205 patients (104 placebo, 101 etanercept) were randomized and received at least 1 dose of blinded study drug. Clinical safety, efficacy, and radiographic progression were evaluated in all 205 patients. One hundred sixty-eight patients (81 placebo, 87 etanercept) were enrolled in the open-label study (Figure 1).

Demographic characteristics at the baseline of the blinded phase are shown in Table 1. The groups were well matched in terms of disease history, age, and race. A slight predominance of women was observed in the placebo group (55%) and of men in the etanercept group (57%). Patients in the etanercept group had more radiographic disease at baseline compared with the placebo group. The subtypes of PsA were similar in both groups.

Table 1. Demographic characteristics and disease activity measures at baseline*

Characteristic	Placebo (n = 104)	Etanercept (n = 101)
Age, mean years	47.3	47.6
Men, no. (%)	47 (45)	58 (57)
White, no. (%)	95 (91)	91 (90)
Duration of PsA, mean years	9.2	9.0
Duration of psoriasis, mean years	19.7	18.3
Psoriasis BSA, mean %	10.2	10.9
Rheumatoid factor positive, %	4	9
Radiographic scores at baseline, mean		
Total Sharp score	18.30	25.89
Erosion score	8.57	12.88
Joint space narrowing score	9.73	13.01
Concomitant therapy during study, no. (%)		
Corticosteroids	16 (15)	19 (19)
NSAIDs	86 (83)	89 (88)
Methotrexate	43 (41)	42 (42)
Weekly methotrexate dosage, mean mg	15.4	16.3
Subtypes of psoriatic arthritis, no. (%)†		
Polyarticular arthritis	86 (83)	87 (86)
DIP joints of the hands and feet	52 (50)	52 (51)
Asymmetric peripheral arthritis	40 (38)	41 (41)
Ankylosing spondylitis-like arthritis	4 (4)	3 (3)
Arthritis mutilans	2 (2)	1 (1)

* PsA = psoriatic arthritis; BSA = body surface area; NSAIDs = nonsteroidal antiinflammatory drugs; DIP = distal interphalangeal.

† Some patients were observed to have >1 subtype of arthritis.

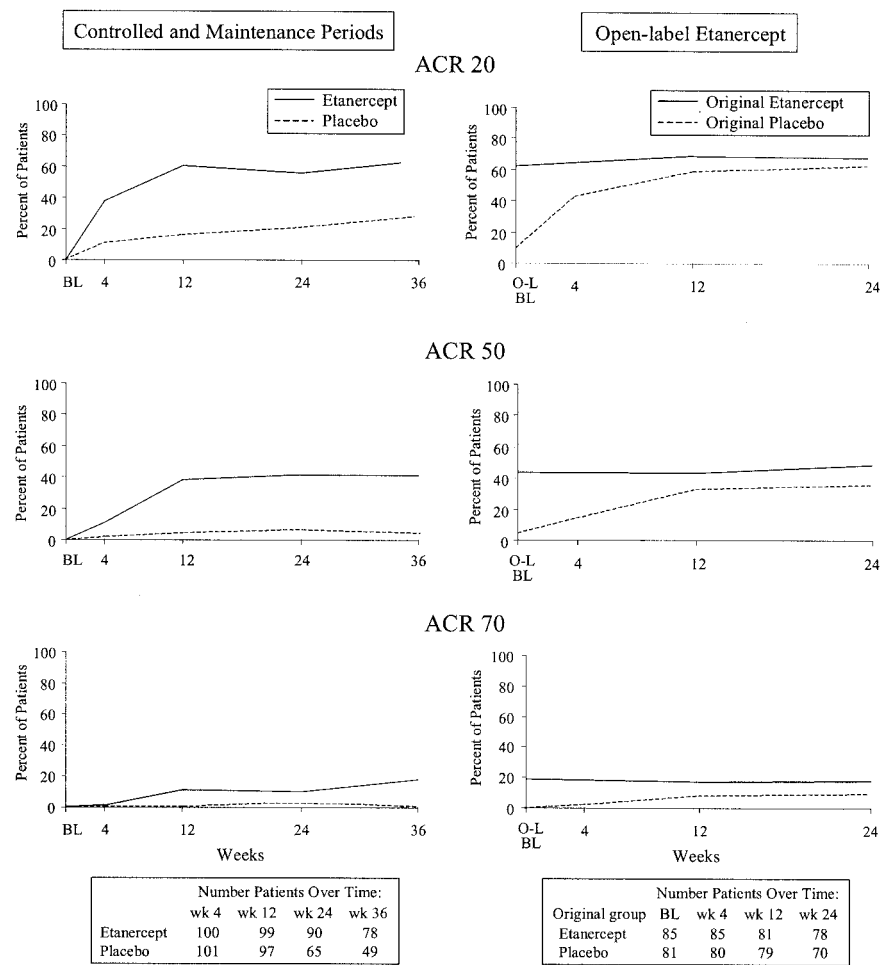


Figure 2. American College of Rheumatology (ACR) 20%, 50%, and 70% responses achieved during controlled and open-label phases of the study.

Clinical efficacy in arthritis. Clinical responses were apparent at the first visit (week 4) and were maintained for the duration of the study. At 12 weeks, ACR20, the primary end point for joint assessment, was achieved by 59% of patients in the etanercept group and by 15% of patients in the placebo group ($P < 0.0001$). Significantly greater proportions of patients in the etanercept group achieved ACR20, ACR50, and ACR70 throughout the study, compared with the patients in the placebo group (Figure 2). Responses on the composite measure, the PsARC, were also significantly different throughout the study: 72% and 70% of etanercept patients achieved the PsARC at 12 and 24 weeks, respectively, compared with 31% and 23% of placebo patients (data not shown). Etanercept effectively reduced all individual parameters of arthritis activity,

including tender and swollen joint counts (data not shown). In sensitivity analyses, no significant differences in response were observed between methotrexate strata, nor did the difference between treatment groups in percentage of women affect the primary analyses.

During the open-label extension, patients continuing with etanercept maintained or improved their clinical responses, while those in the placebo group showed similar improvements once they began receiving etanercept (Figure 2).

Quality of life. Disability, as measured by the HAQ, decreased statistically significantly in the etanercept group, compared with the placebo group. At 24 weeks, mean improvement from baseline in the etanercept group was 54%, compared with 6% in the placebo group ($P < 0.0001$) (data not shown). Function, as

Table 2. Percentage of patients achieving psoriasis end points at 24 weeks

	Placebo group (n = 104)	Etanercept group (n = 101)	P
Target lesions			
% improvement from baseline, mean $\pm$ SEM	10.8 $\pm$ 4.3	35.6 $\pm$ 4.2	<0.001
% of patients with 50% improvement from baseline	17	43	<0.001
% of patients with 75% improvement from baseline	10	22	0.017
Dermatologist's static global assessment of target lesions, % clear or almost clear	19	40	0.001
PASI response*			
% improvement from baseline, mean $\pm$ SEM	-8.1 (9.0)	42.0 (6.0)	<0.001
% of patients with 50% improvement from baseline	18	47	<0.001
% of patients with 75% improvement from baseline	3	23	0.001
Dermatologist's static global assessment of psoriasis, % clear or almost clear	11	47	<0.001

* Only patients with psoriasis involving at least 3% of body surface area were evaluated for PASI responses (n = 62 for the placebo group and n = 66 for the etanercept group).

measured by the SF-36 physical component score, also improved in more patients in the etanercept group compared with the placebo group (data not shown). The SF-36 mental component score was within the normal range in both groups at baseline and did not change significantly.

Clinical efficacy in psoriasis. The skin lesions of patients receiving etanercept improved significantly during the blinded phase of the study (Table 2). At week 24, target lesion scores improved a mean of 35.6% in the etanercept group, compared with 10.8% in the placebo group ($P < 0.001$). The proportion of patients with "clear" or "minimal" scores in the dermatologist's static global assessment of target lesions at week 24 was significantly higher in patients receiving etanercept (40%) than in those receiving placebo (19%) ($P = 0.001$).

Sixty-six patients in the etanercept group and 62 in the placebo group who had plaque psoriasis at baseline that involved at least 3% of body surface area were evaluated for PASI responses. At week 24, 47% of patients in the etanercept group met the PASI 50% improvement criteria (PASI 50) compared with 18% of patients in the placebo group ($P < 0.001$) (Table 2). Psoriasis responses continued or improved with etanercept therapy throughout the study.

Radiographic response. The study protocol stated that if the interreader correlation of DIP joints was ≥ 0.8 , the DIP joints were to be included in the primary radiographic analysis. The intraclass correlation for interreader variability of DIP joints was ≥ 0.81 (range 0.81–0.88) for the TSS at all time points; therefore, DIP joints were included in the analysis. The

primary radiographic end point was the annualized rate of change in the modified TSS. By this measure, at 12 months, radiographic disease progression was inhibited in the etanercept group (-0.03 unit) compared with worsening of $+1.00$ unit in the placebo group ($P = 0.0001$) (Figure 3). Annualized changes in the erosion score and JSN also were significantly different between groups. Features specific to PsA, including digital tuft resorption, juxtaarticular and shaft periostitis, gross osteolysis, pencil-in-cup deformity, joint space widening, and ankylosis, were observed in both treatment groups but did not change in a statistically significant way in either group during the study.

Additional analyses of the data showed no statistically significant change in radiographic outcome. Analyses were performed with and without inclusion of the DIP joints, with and without inclusion of patients receiving concomitant methotrexate therapy, with exclusion of baseline outliers (top and bottom 10% based on baseline TSS), with inclusion of only patients with radiographs obtained within 14 days of nominal 6- and 12-month visits, and by disease status at baseline (above and below median TSS), disease duration, and sex, age, and weight.

Safety. During the 24-week blinded phase of the study, adverse events and infections occurred in similar numbers and intensities in the etanercept and placebo groups (Table 3). Most events were of mild or moderate intensity. One death occurred in the placebo group, when a patient died after complications of surgery for a perforated bowel. No patients in the etanercept group developed an infection that required hospitalization or intravenous antibiotics; 1 patient in the placebo group was hospitalized for gastroenteritis.

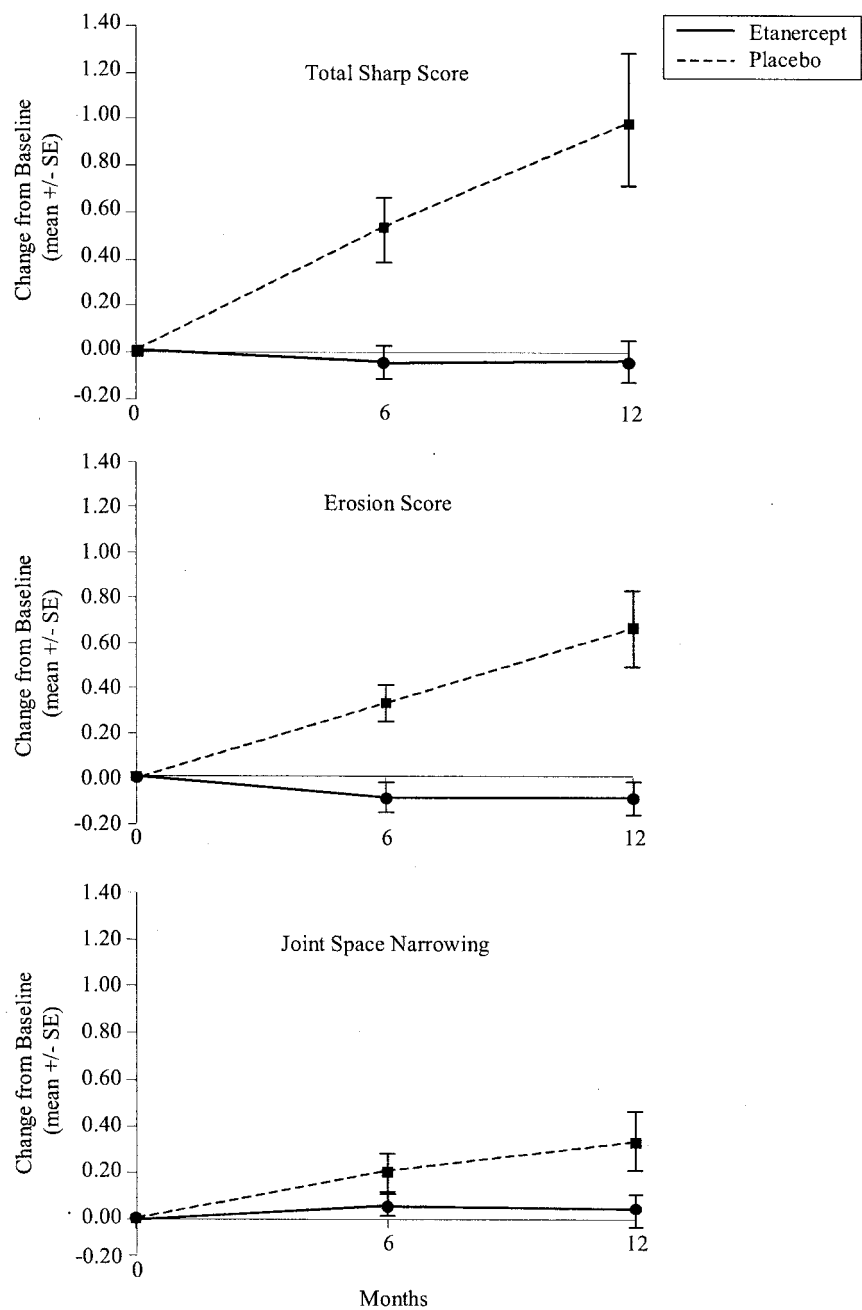


Figure 3. Mean annualized rates of radiographic progression, baseline to 12 months.

Two patients withdrew during the 24-week blinded phase of the study due to adverse events. One patient randomized to the methotrexate stratum of the etanercept group had methotrexate discontinued and was removed from the study by the investigator due to

elevated liver enzymes. One patient in the placebo group discontinued the study due to increased psoriasis. Serious adverse events occurred in 4 patients in the etanercept group and included chest pain, renal calculus, syncope, and multiple sclerosis (MS). In the

Table 3. Adverse events and infections occurring in at least 5% of patients treated with etanercept during the 24-week blinded phase of study*

Event	Placebo group (n = 104)	Etanercept group (n = 101)
Injection site reaction	9 (9)	36 (36)†
Upper respiratory tract infection	24 (23)	21 (21)
Injection site ecchymosis	11 (11)	12 (12)
Accidental injury	5 (5)	8 (8)
Headache	5 (5)	8 (8)
Sinusitis	8 (8)	6 (6)
Urinary tract infection	6 (6)	6 (6)
Rash	7 (7)	5 (5)

* Values are the no. (%).

† $P < 0.001$ versus placebo group, by Fisher's exact test.

placebo group, 4 patients experienced serious adverse events, including the previously cited patient who died after complications of surgery.

All laboratory abnormalities were of mild or moderate intensity during the study. No anti-tumor necrosis factor (TNF) antibodies were detected in any patient in the study. During the open-label extension, adverse events and infections occurred at comparable or lower rates than those observed during the 24-week blinded phase. No deaths were reported.

DISCUSSION

The central role of TNF in the pathogenesis of arthritis and psoriasis associated with PsA has been established (10,11). In this study, etanercept, the soluble TNF receptor antagonist, improved articular, cutaneous, and functionality response measures in patients with PsA, comparable to the results of an earlier trial in this patient population (16). This is the first study, however, to demonstrate inhibition of radiographic progression in PsA patients.

Controlled trials of sulfasalazine, methotrexate, and gold have shown only marginal benefit compared with placebo in treating PsA (19,20,25–27). Of these, only methotrexate had a marginal effect on the skin lesions of psoriasis (25). In contrast, this study showed that etanercept significantly improves composite and individual elements of both arthritis and skin disease activity. At 12 weeks, 72% of etanercept-treated patients achieved the PsARC, compared with 31% of placebo patients ($P < 0.0001$), and 59% of etanercept-treated patients achieved ACR20 criteria, compared with 15% of placebo patients ($P < 0.0001$). Etanercept also significantly improved the skin lesions of psoriasis, as shown by a PASI 75 response in 23% of patients in the

etanercept group at 24 weeks, compared with 3% of patients in the placebo group ($P = 0.001$). Clinical benefits persisted or improved throughout the study and open-label extension.

Radiographic disease progression and its correlation with early morbidity and mortality has been well documented in RA (28,29), and is the impetus for early, aggressive therapy to improve long-term outcomes (30,31). While radiographic progression is not as well documented in PsA, Rahman et al (32) reported measurable progression over a 2-year period using Larsen's and Steinbrocker's scoring methods (7,33). In this study, the modified Sharp method (23), which has been validated in RA patients and quantitates the progression of disease over time, was used to measure radiographic progression of disease in the hands and wrists of PsA patients. This study is the first to document radiographic progression of disease over 6- and 12-month periods.

Rahman et al (32) criticized the Sharp scoring method in PsA because it does not measure erosions outside of the joints and because it may miss important factors relevant to radiographic progression of disease, e.g., new bone formation. The original Sharp scoring method (34), however, did include erosions outside the joint space in the total score, and later modifications continued to incorporate these erosions in the score (23). In our study, we separately evaluated new bone formation, and we separately and specifically measured PsA-specific radiographic features, including joint space widening, ankylosis, pencil-and-cup deformity, gross osteolysis, shaft periostitis, and phalangeal tuft resorption.

Although Larsen's and Steinbrocker's scoring methodologies are simpler to use, there may be an additional advantage to the modified Sharp scoring method. Lassere et al (35) have determined that the amount of change that was rated as "clinically meaningful" using the Larsen scoring method was approximately one-third of the smallest detectable difference (SDD) in RA patients. The same authors determined that the "clinically meaningful change" was similar to the SDD using the TSS. The modified Sharp scoring method may therefore be more sensitive to meaningful changes than are other methods, a sensitivity that was important in this study of PsA patients in which radiographic progression over the 1-year period was inhibited in patients who received etanercept and was relatively small in placebo patients (+1.00 unit in the TSS). By comparison, radiographic progression was somewhat greater over 1 year in a study of RA patients who received methotrexate (mean 19 mg/week) or etanercept 25 mg twice weekly (+1.59 units and +1.00 unit in the TSS, respectively)

(15). This difference in progression may be because PsA is a unique disease and involves fewer joints, or it may be because we only evaluated the hands in patients with PsA versus an evaluation of both the hands and the feet in patients with RA. Additional studies are necessary to observe structural damage over longer terms.

In a study by Gladman and Farewell (36), it was noted that patients with a higher degree of baseline damage are more likely to progress. In this study, all measures of radiographic disease were more pronounced at baseline in the etanercept group than in the placebo group. Thus, patients in the etanercept group may have been at a greater risk of radiographic progression. Despite this difference in baseline structural damage, patients receiving placebo had progressive joint destruction at 6 and 12 months, whereas most patients in the etanercept group had inhibition of disease progression, comparable to results shown with etanercept in RA patients (15). No significant changes were demonstrated in new bone formation or in PsA-specific radiographic features over the 1-year period. The effect of etanercept on radiographic disease progression may have important implications for long-term disease outcome in PsA patients.

Etanercept was well tolerated in this study. The proportions of patients with adverse events and infections were similar between groups, and the safety profile was comparable to that observed in RA patients (13). As reported, 1 patient in the etanercept group developed MS at the end of the blinded phase of the study. While no clinical trials have been done to evaluate etanercept therapy in patients with MS, an increase in disease activity in patients with MS who were treated with other TNF antagonists has been reported (37,38). Overall, however, the risk-benefit profile of etanercept has been highly positive in long-term clinical studies and in post-marketing experience (39).

Etanercept therapy significantly improved the clinical symptoms and prevented radiographic disease progression of PsA. Additionally, etanercept improved the skin lesions of psoriasis in these patients. Further studies are warranted to provide longer-term observations of the safety, efficacy, and effects on disease progression of etanercept in PsA patients.

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