

Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial

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Summary

Background Etanercept, a tumour-necrosis-factor inhibitor, has shown efficacy in the treatment of rheumatoid arthritis. Psoriatic arthritis and psoriasis are disease states in which tumour necrosis factor, a proinflammatory cytokine, is present in increased concentrations in joints and in the skin. Therefore, psoriatic arthritis and psoriasis may be appropriate therapeutic targets for etanercept.

Methods This randomised, double-blind, placebo-controlled, 12 week study assessed the efficacy and safety of etanercept (25 mg twice-weekly subcutaneous injections) or placebo in 60 patients with psoriatic arthritis and psoriasis. Psoriatic arthritis endpoints included the proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC) and who met the American College of Rheumatology preliminary criteria for improvement (ACR20). Psoriasis endpoints included improvement in the psoriasis area and severity index (PASI) and improvement in prospectively-identified individual target lesions.

Findings In this 12 week study, 26 (87%) of etanercept-treated patients met the PsARC, compared with seven (23%) of placebo-controlled patients. The ACR20 was achieved by 22 (73%) of etanercept-treated patients compared with four (13%) of placebo-treated patients. Of the 19 patients in each treatment group who could be assessed for psoriasis ($\geq 3\%$ body surface area), five (26%) of etanercept-treated patients achieved a 75% improvement in the PASI, compared with none of the placebo-treated patients ($p=0.015$). The median PASI improvement was 46% in etanercept-treated patients versus 9% in placebo-treated patients; similarly, median target lesion improvements were 50% and 0, respectively. Etanercept was well tolerated.

Interpretation Etanercept offers patients with psoriatic arthritis and psoriasis a new therapeutic option for control of their disease.

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Introduction

Commonly used topical therapies for skin lesions in psoriasis include moisturisers, corticosteroids, tar, anthralin, vitamin D analogues and retinoids, and ultraviolet-light therapy. When these therapies are inadequate, systemic therapies such as psoralen-ultraviolet-light treatment, methotrexate, ciclosporin, and acitretin may be used.^{1–2} However, toxicities often limit the usefulness of these therapies.^{3–5}

Psoriatic arthritis affects from 5% to 7% of patients with psoriasis.⁶ Although psoriatic arthritis may present in a symmetric polyarticular form similar to rheumatoid arthritis, unique features include the potential for asymmetric, oligoarticular, axial and/or distal interphalangeal joint involvement, dactylitis, and enthesial inflammation.⁷ Like rheumatoid arthritis, this disorder results in joint damage, disability, and increased mortality.^{8–11}

Therapy for psoriatic arthritis has largely been derived from clinical experience in rheumatoid arthritis, without corroborating evidence from studies in patients with psoriatic arthritis.^{12–14} The response to therapy is often unsatisfactory. The few controlled trials assessing patients with psoriatic arthritis have not shown consistent efficacy.^{15–20}

Etanercept functions by inhibiting tumour necrosis factor, a proinflammatory cytokine that is involved in many inflammatory disorders, including both psoriatic arthritis and psoriasis. Tumour necrosis factor has been shown to be increased in synovial fluid and synovium in patients with psoriatic arthritis and in the skin of psoriatic lesions.^{21–24} Tumour-necrosis-factor inhibition with etanercept has previously been shown to diminish the activity of rheumatoid arthritis.²⁵ Our study was undertaken to assess the benefit of etanercept in psoriatic arthritis and psoriasis.

Methods

Patients

Eligible patients were adults between 18 and 70 years who had active psoriatic arthritis (defined as ≥ 3 swollen joints and ≥ 3 tender or painful joints) at the time of study enrolment. Patients must have had an inadequate response to non-steroidal anti-inflammatory drugs and were thought candidates for immunomodulatory therapy. Patients taking methotrexate (≤ 25 mg/week) were allowed to continue methotrexate if the dose was stable for 4 weeks before study start and remained stable throughout the study. Other disease-modifying anti-rheumatic drugs (DMARDs) were discontinued at least 2 weeks before beginning the study drug and were not allowed during the study. Corticosteroids were allowed if the dose was less than or equal to 10 mg/day of prednisone, stable for at least 2 weeks before the first dose of study drug, and maintained at a constant dose throughout the study. Patients with evidence of skin

conditions other than psoriasis (such as eczema) were not allowed to enter the study. Topical therapies and oral retinoids for psoriasis were discontinued at least 2 weeks before the baseline evaluation and phototherapy was discontinued at least 4 weeks before treatment. All patients were required to have hepatic transaminase concentrations no greater than twice the upper limit of normal, haemoglobin 85 g/L or higher, platelet count 125000 per mL or more, and serum creatinine 152.4 mmol/L or below.

Study protocol

The protocol was approved by the human research committee for the centre, and all patients gave written informed consent before entering the study. Clinical and laboratory assessments done at screening, baseline, and 12 weeks, and consisted of physical examination, vital signs, measures of disease activity (arthritis and psoriasis), concomitant medications, laboratory studies (haematology, serum chemistry, urinalysis), and monitoring of adverse events. Additionally, arthritis disease-activity measures, adverse events, and concomitant medications were monitored at 4 weeks, 8 weeks, and 30 days after the last dose of the study drug (for those patients who withdrew prematurely). The measures of arthritis disease activity included assessments of 78 joints for tenderness and 76 joints for swelling (graded 0–3), patient's and physician's global assessments (on a 0–5 Likert scale), patient's assessment of pain, patient's assessment of disability as indicated by responses on the Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate, and serum concentration of C-reactive protein. Only patients with plaque psoriasis affecting greater than or equal to 3% of body surface area were assessed for skin disease. The measures of psoriasis activity included the psoriasis area and severity index (PASI)²⁶ and assessments of prospectively identified lesions (target lesions, assessed for plaque elevation, scaling, and erythema). Adverse events and abnormal laboratory values were graded on a scale derived from the common toxicity criteria of the National Cancer Institute.

Treatment

Patients with psoriatic arthritis were randomised to receive either placebo or etanercept (Enbrel) at a dose of 25 mg twice weekly by subcutaneous administration for 12 weeks. Patients who continued on methotrexate were randomised separately. A block randomisation was used: within each group of four patients enrolled, two were assigned at random to the placebo group and two to the etanercept group. Etanercept was supplied as a sterile, lyophilised powder in vials containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine per vial. Placebo was identically supplied and formulated except that it contained no etanercept. Each vial was reconstituted with 1 mL bacteriostatic water for injection.

Study endpoints

The primary endpoint with respect to efficacy in psoriatic arthritis was the proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC, adapted from Clegg and colleagues)¹⁵ at 12 weeks. This composite measure requires improvement in two factors

Characteristic	Placebo (n=30)	Etanercept (n=30)
Median (range) age (years)	43.5 (24.0–63.0)	46.0 (30.0–70.0)
Male	18 (60%)	16 (53%)
White	25 (83%)	27 (90%)
Median (range) weight (kg)	81.4 (60.3–131.5)	90.7 (58.0–141.0)
Duration psoriatic arthritis (years, median [range])	9.5 (1.0–30.0)	9.0 (1.0–31.0)
Duration psoriasis (years, median [range])	17.5 (2.0–43.0)	19.0 (4.0–53.0)
Number previous DMARDs (median [range])	2.0 (1.0–5.0)	1.5 (0–4.0)
Concomitant therapy during study		
Corticosteroids	12 (40%)	6 (20%)
NSAIDs	23 (77%)	20 (67%)
Methotrexate	14 (47%)	14 (47%)
Patients evaluable* for psoriasis endpoints (median [range])		
Duration of psoriasis in years	2.0 (5.0–43.0)	20.0 (4.0–53.0)
Baseline PASI score	6.0 (1.5–17.7)	10.1 (2.3–30.0)
Target lesion assessment	6.0 (3.0–8.0)	6.0 (3.0–9.0)

* $\geq 3\%$ body surface area involvement.

Table 1: Demographic and clinical characteristics

(with at least one being a joint score), with worsening in none, of the following four factors: patient and physician global assessments (improvement defined as decrease by ≥ 1 unit; worsening defined as increase by ≥ 1 unit); and tender and swollen joint scores (the sums of all joints scored; improvement defined as decrease by $\geq 30\%$; worsening defined as increase by $\geq 30\%$). A secondary endpoint for the assessment of psoriatic arthritis was the proportion of patients meeting the American College of Rheumatology preliminary criteria for improvement (ACR20; designed for assessment of rheumatoid arthritis)²⁷ at 12 weeks, which requires at least 20% reductions in tender and swollen joint counts and 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 (C-reactive protein). ACR50 and ACR70 were also assessed (defined in a similar manner as ACR20, but with improvement of at least 50% and 70% in the individual measures, respectively). Individual measures of arthritis disease activity were also assessed.

The primary endpoint with respect to efficacy in psoriasis was the proportion of patients achieving a 75% improvement in psoriasis activity from baseline to 12

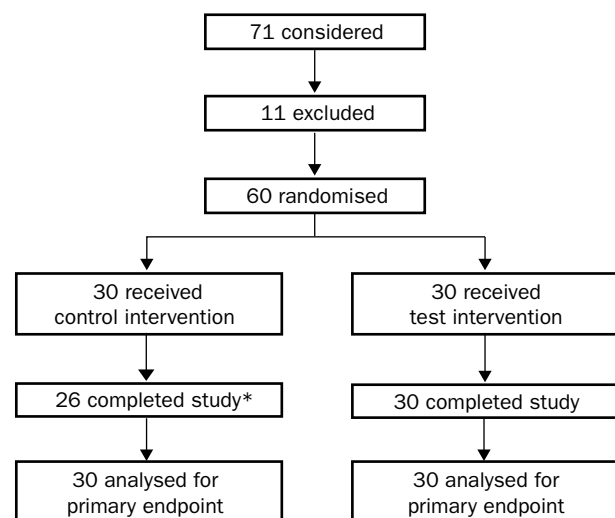


Figure 1: Trial profile

*Last observation was carried forward for efficacy analyses.

	Etanercept (n=30)	Placebo (n=30)	Difference	95% CI	p
Primary endpoint—achieved PsARC					
4 weeks	23 (77)	4 (13)	63%	44–83	<0.0001
8 weeks	25 (83)	8 (27)	57%	36–77	<0.0001
12 weeks	26 (87)	7 (23)	63%	44–83	<0.0001
Secondary endpoint—achieved at 12 weeks					
ACR20	22 (73)	4 (13)	60%	40–80	<0.0001
ACR50	15 (50)	1 (3)	47%	28–66	0.0001
ACR70	4 (13)	0	13%	1–26	0.0403

Table 2: Psoriatic arthritis endpoints—number achieving PsARC and ACR20, ACR50, and ACR70, baseline to week 12

weeks as measured by the PASI.²⁶ Additional analyses were done of the percentage change in PASI scores and improvement in the target psoriasis lesions.

Statistical analyses

On the assumption that response rates of 30% in the placebo group and 75% in the etanercept group, the sample size of 30 patients per treatment group gave over 80% power to detect a significant difference between treatments in the primary endpoint, by a two-sided $\alpha=0.05$ level test. Proportions of patients responding were compared between treatment groups with the Mantel-Haenszel χ^2 test, adjusted for the stratification variable, methotrexate use. Continuous efficacy variables (percentage change from baseline) were ranked and analysed by a general linear model with factors of treatment, methotrexate use, and their interaction. The frequency of adverse events was compared between treatment groups with Fisher's exact test. The Breslow-Day test was used to test for heterogeneity of relative response between methotrexate use strata. All tests were

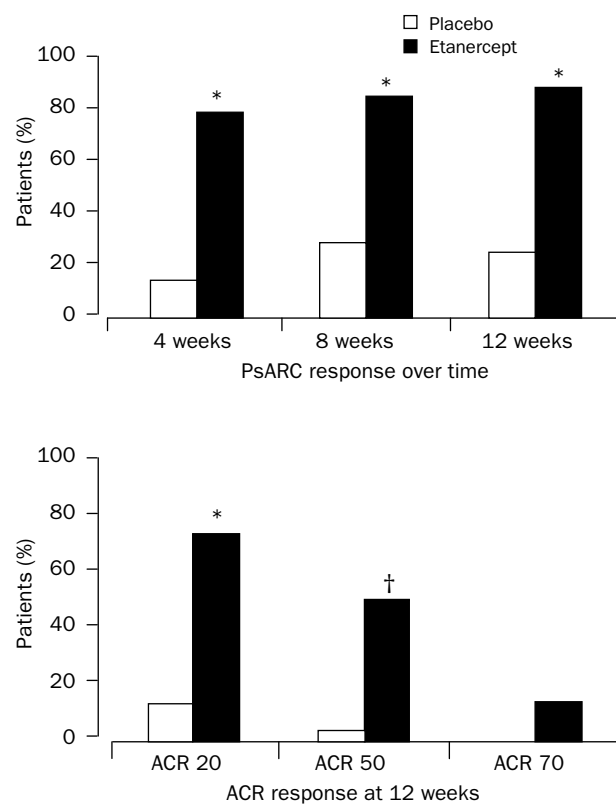


Figure 2: Percentage of patients with PsARC responses over time and with ACR20, ACR50, and ACR70 responses at 12 weeks

* $p<0.0001$. † $p=0.0001$.

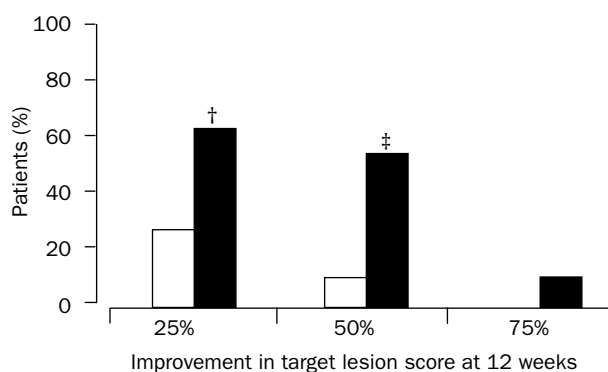
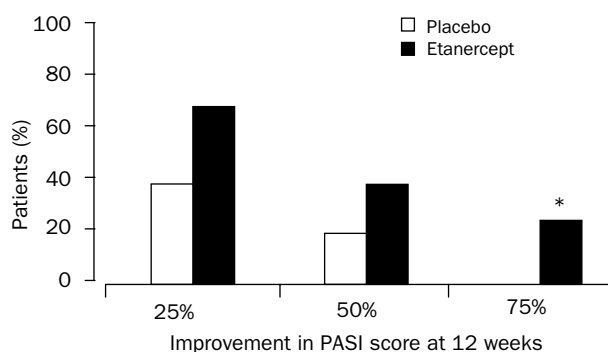


Figure 3: Percentage of patients with at least 25%, 50%, and 75% improvements in PASI and target lesion scores

* $p=0.0154$. † $p=0.0098$. ‡ $p=0.0006$.

two-sided. The last available observation was used for patients who discontinued treatment before the end of study.

Results

Table 1 shows baseline demographic and clinical characteristics. 60 patients were randomised, 30 in each treatment arm (figure 1). The median age was 45 years (range 24–70) and the median duration of psoriatic arthritis was 10 years (1–31). The median duration of psoriasis was 18 years (2–53) for all patients in the study and was 20 years (4–53) for the 38 patients with evaluable psoriasis (19 patients in each group). The median active joint counts at baseline were 20 tender and 14 swollen joints. The groups were well balanced in all characteristics except that twice as many patients in the placebo group were receiving corticosteroids than in the etanercept group, and in the groups evaluable for psoriasis, the placebo group had lower baseline PASI scores. All patients in the etanercept group completed the 12 week study; four patients in the placebo group discontinued the study prematurely, three for lack of efficacy or refusal and one was lost to follow-up.

Efficacy of etanercept in psoriatic arthritis

The etanercept group had statistically better outcomes for all clinical endpoints (table 2, figure 2). The primary endpoint for psoriatic arthritis, the number of patients who met the PsARC at 12 weeks, was achieved by 26 (87%) etanercept-treated patients compared with seven (23%) placebo-treated patients ($p<0.0001$). The response was significantly greater at all measured time points in patients who received etanercept relative to those receiving placebo. The ACR response rates were also significantly higher in the etanercept-treated group.

	Placebo (n=30)	Etanercept (n=30)
Tender joint count*		
Baseline	19.0 (10, 39)	22.5 (11, 32)
12 weeks	22.5 (11, 47)	6.0 (1, 11)
Swollen joint count†		
Baseline	14.7 (7, 24)	14.0 (8, 23)
12 weeks	11.0 (5, 28)	3.0 (1, 8)
HAQ‡		
Baseline	1.2 (0.8, 1.6)	1.3 (0.9, 1.6)
12 weeks	1.1 (0.5, 1.5)	0.1 (0, 1)
ESR§		
Baseline	16 (9, 29)	22 (9, 34)
12 weeks	18 (6, 40)	5 (3, 12)
CRP 		
Baseline	12 (8, 22)	14 (7, 28)
12 weeks	14 (4, 23)	4 (3, 11)

p<0.001 for all treatment comparisons.

*Scale 0–78; †Scale 0–76; ‡0=best, 3=worst; §Normal range: 1–13 mm/h for men; 1–30 mm/h for women; ||Normal range: 0–0.78 mg/L.

ESR=erythrocyte sedimentation rate. CRP=C-reactive protein.

Table 3: Secondary psoriatic arthritis endpoint—median (25th and 75th percentiles) values of disease activity, baseline, and 12 weeks

At 12 weeks, the ACR20 was achieved by 22 (73%) etanercept-treated patients compared with four (13%) placebo-treated patients (p<0.0001).

At 12 weeks, the etanercept group showed significant improvement in all measures of disease activity compared with the placebo group (p≤0.0002). The median percentage improvements in tender and swollen joints counts for etanercept-treated patients were 75% and 72%, respectively, compared with 5% worsening and 19% improvement in placebo-treated patients. Disability, as assessed by responses on the Health Assessment Questionnaire, was also significantly more improved in the etanercept group than in the placebo group, with improvements of 83% and 3% from baseline, respectively (p<0.0001, table 3).

Table 4 shows the results of a comparison of patients treated with etanercept and placebo who achieved 100% improvement in individual disease-activity measures at 12 weeks. Ten (34%) patients in the etanercept group achieved disability index scores of 0 (no disability) at 12 weeks, compared with only one (3%) patient in the placebo group. In addition, seven (23%) of patients in the etanercept group had no swollen joints and four (13%) had no tender joints, compared with none in both cases in the placebo group.

Characteristic	Placebo (n=30)	Etanercept (n=30)
Factor (actual value)*		
Tender joint count (none)	0	4 (13)
Swollen joint count (none)	0	7 (23)
Total tender/swollen joint count (none)	0	3 (10)
Physician global assessment (0)	0	6 (20)
Patient global assessment (0)	0	5 (17)
Morning stiffness (none)†	1 (3)	11 (39)
Pain assessment (none)	0	5 (17)
HAQ (0)‡	1 (3)	10 (34)
ESR (normal)§	12 (48)	23 (82)
CRP (≤upper limit of normal)§	8 (32)	21 (75)

Values for disease activity (especially laboratory tests) were not available for all patients at all time points.

*Except for laboratory measures, a non-zero score at baseline was required for a patient to be included in this table.

†For morning stiffness, n=29 in placebo group, n=28 in etanercept group.

‡For disability index, n=29 in etanercept group.

§For ESR and CRP tests, n=25 in placebo group, n=28 in etanercept group.

Table 4: Number (%) of patients with 100% improvement in individual disease-activity measures at 12 weeks

	Placebo (n=30)	Etanercept (n=30)	p*
Upper respiratory tract events	17 (57%)	17 (57%)	1.0000
Respiratory tract infection	4 (13%)	8 (27%)	0.3334
Pharyngitis	3 (10%)	5 (17%)	0.7065
Rhinitis	4 (13%)	5 (17%)	1.0000
Sinusitis	2 (7%)	3 (10%)	1.0000
Influenza syndrome	6 (20%)	0	0.0237
Injection-site bruise	5 (17%)	6 (20%)	1.0000
Injection-site reaction	1 (3%)	6 (20%)	0.1028
Headache	3 (10%)	4 (13%)	1.0000
Fatigue	0	4 (13%)	0.1124

*Fisher's exact test.

Table 5: Number of adverse events of all intensities

Efficacy of etanercept in psoriasis

Etanercept was also effective in improving the skin lesions of psoriasis in the trial (figure 3). Of the 19 patients in each treatment group who were evaluable for psoriasis (≥3% of body surface area involvement), five (26%) of patients in the etanercept group achieved the primary psoriasis endpoint—a 75% improvement in PASI at 12 weeks—compared with no patients in the placebo group (p=0.0154). Similar differences between treatment groups were also seen at the 25% and 50% improvements in the PASI scores; in fact, the median improvement in PASI score was 46.2% in patients receiving etanercept, compared with 8.7% in the placebo group (p=0.0032).

Additionally, the median response of a prospectively defined target lesion in the etanercept group was 50%, compared with none in the placebo group (p=0.0004).

Examination of results in patients who were or were not receiving concomitant methotrexate therapy showed that etanercept was consistently better than placebo in both strata. An imbalance in corticosteroid use and PASI scores existed between the two treatment groups at baseline that might have affected the results of the study. Additional analyses showed that these baseline imbalances did not affect the conclusions of the study (data not shown).

Safety

All 30 of the etanercept patients completed the 12 week course of therapy, and 26 of 30 (87%) placebo patients completed the study. No serious adverse events were reported in the patients receiving etanercept; one serious adverse event occurred in a placebo patient (hospitalised for surgery to correct a rectal tear). No patients developed infections that required hospitalisation or intravenous antibiotics.

The most common adverse events in the study were of the upper respiratory tract and injection-site reactions. No attempt was made to specifically distinguish infectious versus non-infectious adverse events in this study; however, event terms that could potentially refer to infections of the upper respiratory tract are grouped in table 5. Injection-site reactions were mild and well tolerated. No adverse events occurred in a significantly greater proportion in the etanercept group relative to the placebo group.

Discussion

Few double-blind, placebo-controlled trials have been done in patients with psoriatic arthritis. Most therapies used to treat psoriatic arthritis have been attempted because they showed benefit in patients with rheumatoid arthritis or were therapies that yielded apparent benefit

in open uncontrolled trials. The few controlled trials with patients with psoriatic arthritis have yielded inconsistent results.^{15–20}

Aside from non-steroidal anti-inflammatory agents, methotrexate has become the most commonly used agent in patients with psoriatic arthritis.¹⁷ Early reports described improvement in joint disorder with aminopterin (an analogue of methotrexate).^{28,29} One placebo-controlled trial with high-dose methotrexate (1–3 mg/kg) showed improvement in joint disease activity in psoriatic arthritis;¹⁸ a second trial showed only improvement in the physician's assessment of arthritis activity.¹⁹ These studies also showed some improvement in psoriasis, particularly in the percentage of body surface area involved.

Ciclosporin has been compared with methotrexate in an open trial in psoriatic arthritis.⁴ This 23-patient trial showed improvement with each therapy; responses in arthritis measures were greater with methotrexate, and psoriasis scores (PASI) improved more with ciclosporin. The study was not powered to show a difference in response between the two active agents. A randomised double-blind trial of ciclosporin in patients with psoriasis showed significant benefit in psoriasis.² However, toxicities were a limiting factor.^{2,4,5}

Other disease-modifying agents of rheumatic disease, including sulfasalazine and gold therapy, have been assessed in psoriatic arthritis. Few or no benefits were shown in either psoriatic arthritis or psoriasis.^{15–20}

There is a need for a new therapy to treat both psoriatic arthritis and psoriasis. Etanercept has been shown in previous trials to be effective against rheumatoid arthritis with no serious toxic effects. In two randomised controlled trials of etanercept (25 mg subcutaneously twice weekly) in patients with active DMARD-refractory rheumatoid arthritis, 59–71% of etanercept patients achieved the ACR20 response at 6 months, compared with 11–23% of placebo patients ($p < 0.001$); 39–40% and 3–5% of patients, respectively, achieved the ACR50 response ($p < 0.01$).^{25,30} Etanercept was well tolerated and showed no evidence of significant toxicity, with mild injection-site reactions being the only adverse event associated with etanercept administration.

This trial shows that etanercept provides clinically significant benefit to patients with active psoriatic arthritis. Contrary to studies with other antirheumatic agents where at most a small number of variables reached significance, etanercept resulted in significant clinical benefit in the composite measures (PsARC, ACR20, and ACR50) and in each individual factor of disease activity. Additionally, psoriasis improved as measured by the PASI and the target-lesion assessment. Although the study population was powered to demonstrate efficacy and was too small to clearly predict the safety of etanercept in patients with psoriatic arthritis and psoriasis, the safety profile of etanercept in these patients was similar to that previously reported in the rheumatoid arthritis population.^{25,30}

Further study in this population would be useful to further establish the safety profile of etanercept in psoriatic arthritis and psoriasis. Whether etanercept would improve articular damage measured radiographically should be examined.

The results of this study indicate that blocking tumour necrosis factor in both psoriatic arthritis and psoriasis may offer a new therapeutic option for patients with both diseases.

Contributors

P J Mease, B S Goffe, J Metz, A VanderStoep, and B Finck contributed to the protocol design. Additionally, P J Mease was principal investigator of the study and did the rheumatology assessments, B S Goffe did the dermatology assessments, and J Metz administered the study. D J Burge reviewed the progress of the study and coordinated the data management and analysis. D J Burge and P J Mease wrote the paper; B S Goffe, J Metz, A VanderStoep, and B Finck critically reviewed the paper.

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