

A Randomized Trial of Etanercept as Monotherapy for Psoriasis



Alice B. Gottlieb, MD, PhD; Robert T. Matheson, MD; Nicholas Lowe, MD; Gerald G. Krueger, MD; Sewon Kang, MD; Bernard S. Goffe, MD; Anthony A. Gaspari, MD; Mark Ling, MD, PhD; Gerald D. Weinstein, MD; Anjali Nayak, MD; Kenneth B. Gordon, MD, PhD; Ralph Zitnik, MD

Objective: To determine safety and efficacy of monotherapy with etanercept.

Design: Randomized, double-blind, placebo-controlled, multicenter study.

Setting: Outpatient, ambulatory; private practice and university dermatology research centers.

Patients: Patients aged at least 18 years, with plaque psoriasis involving 10% or more of body surface area; 148 were screened and 112 were randomly assigned to treatment groups and received study drug.

Interventions: Patients received placebo or etanercept, 25 mg, subcutaneously twice a week for 24 weeks. Other psoriasis therapies were limited during the study.

Main Outcome Measures: Safety measurements included tracking of adverse events and laboratory values. Efficacy was evaluated using the Psoriasis Area and Severity Index (PASI); the primary end point was a 75%

improvement in PASI. Other efficacy measurements included patient and physician global assessments and quality-of-life measures.

Results: After 12 weeks of treatment, 17 (30%) of the 57 etanercept-treated patients and 1 (2%) of the 55 placebo-treated patients had achieved PASI 75%, and after 24 weeks, 32 (56%) of etanercept-treated patients and 3 (5%) of placebo-treated patients had reached this level ($P < .001$ for both time points). By 24 weeks, psoriasis was clear or minimal by physician's global assessment in more than 50% of patients who received etanercept. Treatment failure (PASI response < 50) occurred in 23% of patients at week 24. All other measures confirmed the efficacy of etanercept. Adverse events were similar among etanercept and placebo groups.

Conclusion: Etanercept monotherapy provided significant benefit to patients with psoriasis and had a favorable safety profile.

Arch Dermatol. 2003;139:1627-1632

PSORIASIS IS estimated to affect 1% to 3% of the world's population¹ and current treatments reduce the symptoms of the disease but do not provide a permanent cure.^{2,3} Based on molecular and clinical evidence, T cells, especially T1 cells, and the cytokines they release appear to be critical mediators of the symptoms of plaque psoriasis.⁴ The role of the proinflammatory cytokine, tumor necrosis factor (TNF), in psoriasis has been well studied. Clinical studies using agents that block TNF activity support the hypothesis that TNF activity has an important role in psoriasis. To more conclusively demonstrate the effectiveness of blocking TNF in psoriasis, we designed a multicenter study to evaluate the efficacy of TNF blockade with etanercept monotherapy in the treatment of plaque psoriasis.

Author affiliations are listed at the end of this article.
Dr Zitnik is an employee of Amgen.

METHODS

PATIENTS

The study protocol was approved by the institutional review boards of the participating centers, and all patients gave written informed consent before study-related procedures were done. Eligible patients were required to be at least 18 years of age and to have active, stable plaque psoriasis involving 10% or more of body surface area. All patients were to have had at least 1 previous systemic psoriasis therapy or phototherapy (such as methoxsalen plus UV-A,

*CME course available
at www.archdermatol.com*

UV-B, oral retinoids, cyclosporine, or methotrexate). Psoralen-UV-A (PUVA) and systemic psoriasis therapy were not allowed within 4 weeks of study drug administration; and UV-B therapy, topical corticosteroids,

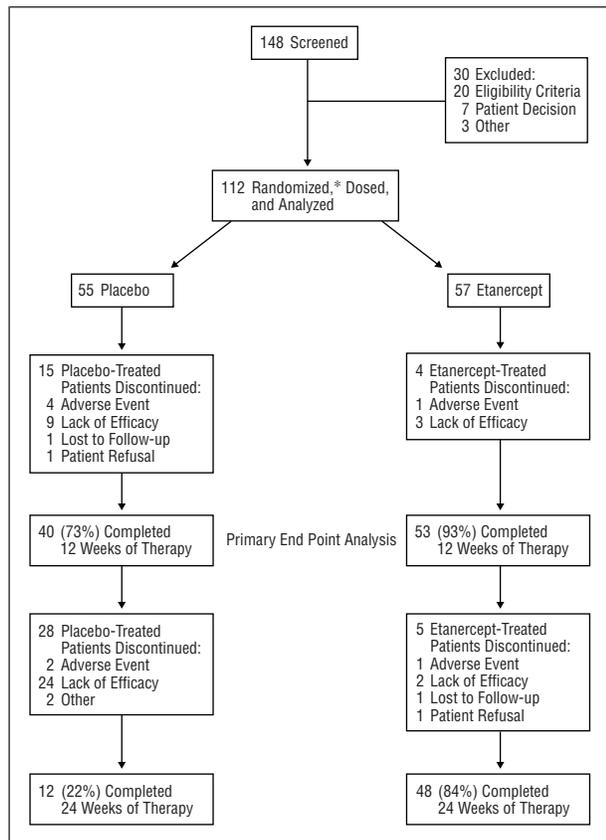


Figure 1. Disposition of patients. The asterisk indicates that 6 patients received randomization numbers but withdrew before receiving the study drug; these patients are not included in the analysis.

vitamin A or D analogues, or anthralin were not allowed within 2 weeks of baseline measurements. Some topical preparations (such as lower-potency corticosteroids and tar-based shampoo) were allowed to continue during therapy, at stable doses, on the scalp, axilla, and groin. Patients were excluded if they had guttate, erythrodermic, or pustular psoriasis; other skin conditions; or other significant medical conditions that might interfere with evaluations of the effect of study medications on psoriasis.

STUDY DRUG

Etanercept (Enbrel; Immunex Corporation, Seattle, Wash) was supplied as a sterile lyophilized powder in blind-labeled vials containing 25 mg of etanercept. The placebo was vehicle material without the active drug component. The contents of the vials were reconstituted with bacteriostatic water for injection, USP, containing 0.9% benzyl alcohol. Study drug was provided to patients in prefilled syringes.

The Immunex Biometrics Department specified that patients were to be randomized in blocks of 6 with equal allocation between the treatment groups. The randomization schedule was generated by Almedica Services, Inc (Allendale, NJ), which also performed blinded labeling and packaging of the study drug. Patients were assigned numbers based on randomization tables verified by Immunex Pharmaceutical Planning, after which the Immunex Clinical Distribution Department shipped blind-labeled vials of study drug to the pharmacies.

STUDY DESIGN

The objective of this multicenter, randomized, double-blind, placebo-controlled, phase 2 study was to evaluate the safety and efficacy of etanercept as monotherapy in patients with plaque

psoriasis. A total of 112 patients were randomly assigned to receive either 25 mg of etanercept or matching placebo, self-injected subcutaneously twice weekly for 24 weeks. Patients, investigators, and other personnel involved in the study were blinded to patient assignments until all patients completed the study and the database was locked.

EFFICACY END POINTS

The primary efficacy end point of the study was a comparison of the proportion of patients in each treatment group achieving 75% improvement in the Psoriasis Area and Severity Index (PASI 75)⁵ at 12 weeks. PASI 50 and PASI 90 (achievement of 50% and 90% improvement, respectively) also were measured. The PASI is a 72-point scale that incorporates measures of area of psoriasis involvement, and the erythema, infiltration, and desquamation of these areas. Patients were evaluated at screening, baseline, and at 2, 4, 8, 12, 16, 20, and 24 weeks. The absolute and percent changes in PASI scores at each evaluation visit were calculated.

Other disease activity assessments were completed at each visit. Both the physician and the patient were asked to rate the global severity of the psoriasis on a scale from 0 to 5 (with a higher score indicating more severe disease). A specific analysis was done on the percentage of patients who had achieved a clear-to-minimal status (ie, a score of 0 or 1) in the physician's global assessment. Photographs of lesions were taken in a subset of patients at baseline and at 12 and 24 weeks.

Quality of life was evaluated at baseline and weeks 4, 8, 12, and 24 using the Dermatology Life Quality Index (DLQI).⁶

SAFETY END POINTS

Safety was evaluated in all patients who received the study drug. Safety measurements included adverse events and serious adverse events, and premature discontinuations from study. Laboratory parameters included complete blood cell counts, serum chemistry profiles, liver function studies, and urinalysis. Safety was evaluated both as the percentage of patients experiencing a given type of event and as the rate of event occurrence in events per patient-year.

STATISTICAL ANALYSIS

The sample size of 50 patients per treatment group was chosen on the basis of results from a randomized, double-blind, phase 2 trial in psoriatic arthritis.⁷ Assuming PASI 75 response rates of 10% in the placebo group and 35% in the treatment group, the sample size of 50 patients per group afforded over 80% power to detect a significant difference in the primary end point between treatments using a 2-sided $\alpha = .05$ level (Fisher exact test). PASI response rate was analyzed using the χ^2 test. For binary end points, the χ^2 test was used to compare the 2 treatment groups with respect to the proportion who met criteria for psoriasis efficacy response. The Fisher exact test was substituted if more appropriate. For other end points, nonparametric tests were used. Patients were analyzed on an intent-to-treat basis; all patients who received at least 1 dose of study drug were evaluable for safety and efficacy of the treatment. If a patient discontinued treatment before the end of the study, the last observation was carried forward for efficacy analyses.

RESULTS

PATIENTS

A total of 148 patients were screened for eligibility in this study from August 2000 to January 2001 (**Figure 1**).

Table 1. Demographic Characteristics and Treatment History at Baseline

Characteristic	Placebo Group (n = 55)	Etanercept Group (n = 57)
Age, mean (range), y	46.5 (18-77)	48.2 (25-72)
Male, No. (%)	37 (67)	33 (58)
Race, No. (%)		
Black	1 (2)	1 (2)
White	52 (95)	51 (89)
Hispanic	1 (2)	4 (7)
Other	1 (2)	1 (2)
Weight, mean, kg	90.7	91.8
Height, mean, cm	174.5	172.3
Prior systemic therapies, No. (%)		
Methotrexate	20 (36)	22 (39)
Cyclosporine	9 (16)	4 (7)
Oral retinoids	13 (24)	14 (25)
Corticosteroids	5 (9)	8 (14)
Prior phototherapy, No. (%)		
Psoralen UV-A	23 (42)	21 (37)
UV-B	26 (47)	27 (47)

Table 2. Disease Characteristics at Baseline

Characteristic	Placebo Group (n = 55)	Etanercept Group (n = 57)
Duration of psoriasis, mean (SE), y	20 (1.7)	23 (1.6)
Patients with psoriatic arthritis, No. (%)	19 (35)	16 (28)
PASI score, mean (SE)	19.5 (1.3)	17.8 (1.1)
% Body surface area affected, mean (SE)	34 (3.0)	30 (2.3)
Physician's global score, mean (SE)	2.9 (0.1)	2.8 (0.1)
Patients's global score, mean (SE)	4.2 (0.1)	4.1 (0.1)

Abbreviation: PASI, Psoriasis Area and Severity Index.

Patients were randomized into 2 groups: 57 received etanercept, 25 mg, and 55 received placebo, subcutaneously twice weekly. These groups were well matched in terms of demographic characteristics (**Table 1**) and baseline disease activity (**Table 2**); no statistically significant differences were noted between the groups. Inclusion criteria were designed to select for patients with serious disease, and patients' disease history at baseline confirms this; patients had psoriasis for approximately 20 years, with approximately 30% body surface area involvement, and all had received previous systemic therapy or phototherapy for psoriasis. Types and numbers of previous therapies used were comparable between placebo and etanercept groups (Table 1).

Six patients withdrew from the trial after randomization but before the study drug was administered: 1 had a myocardial infarction and was hospitalized, 1 had uncontrolled hypertension, and 4 withdrew consent. A total of 112 patients received at least 1 dose of study drug and were included in all analyses. At 12 weeks (the time point for primary efficacy evaluation), 53 (93%) of the 57 etanercept-treated patients and 40 (73%) of the 55 placebo-treated patients were still receiving the study drug. At 24 weeks, 48 (84%) of the etanercept-treated patients and

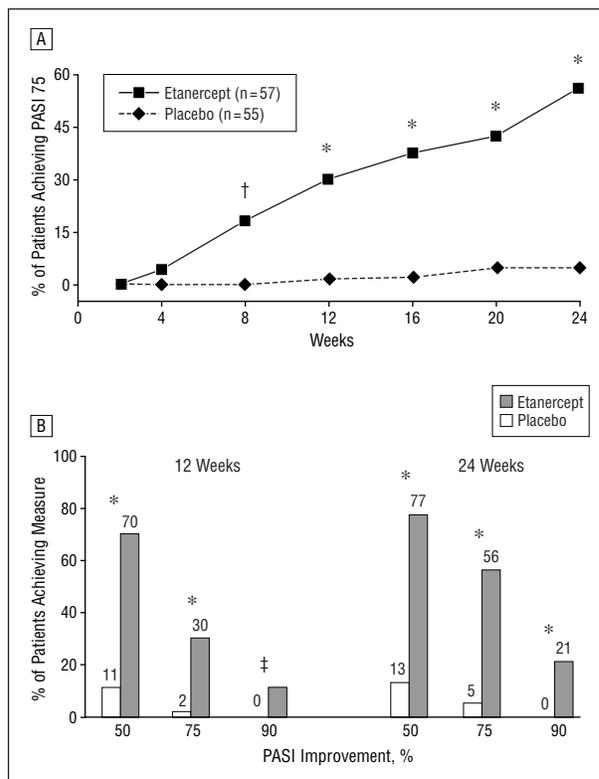


Figure 2. Percentage of patients achieving efficacy measures. A, Percentage of patients with at least 75% improvement in Psoriasis Area and Severity Index (PASI) over time. B, Percentage of patients with at least 50%, 75%, and 90% improvement in PASI at weeks 12 and 24. Asterisk indicates $P < .001$; dagger, $P = .001$; and double dagger, $P = .03$.

12 (22%) of the placebo-treated patients remained on the study drug.

EFFICACY END POINTS

Patients Achieving PASI 75

The primary end point of this study, PASI 75 at 12 weeks, was met by a significantly higher proportion of patients in the etanercept group (17/57; 30%) than in the placebo group (1/55; 2%) ($P < .001$). By 24 weeks, 32 (56%) and 3 (5%) patients in the etanercept and placebo groups, respectively, had achieved PASI 75 (**Figure 2A**; $P < .001$), for a 28% difference in response at 12 weeks (95% confidence interval, 16%-40%) and a 51% difference at 24 weeks (95% confidence interval, 36%-65%). In addition, significantly more patients in the etanercept group achieved other PASI levels (PASI 50 and PASI 90) than did those in the placebo group. At 24 weeks, 77% of patients in the etanercept group had achieved the PASI 50 and 21% had achieved the PASI 90, compared with 13% and 0% in the placebo group, respectively (**Figure 2B**). Etanercept-treated patients continued to improve as measured by PASI through week 24 of treatment.

Other Assessments

The effect of etanercept was confirmed using other measures of efficacy, including physician and patient global

Table 3. Additional Efficacy Measures: Improvement From Baseline to Week 24*

Measure	% Improvement, Mean (SE)	
	Placebo Group (n = 55)	Etanercept Group (n = 57)
PASI	1 (7)	67 (4)
Physician's global score	-2 (4)	46 (4)
Patient's global score	7 (5)	62 (5)
Body surface area affected	-12 (7)	63 (5)
Composite DLQI	7 (8)	64 (5)

Abbreviations: DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

* $P < .001$ (Wilcoxon rank sum test) between groups for all measures.

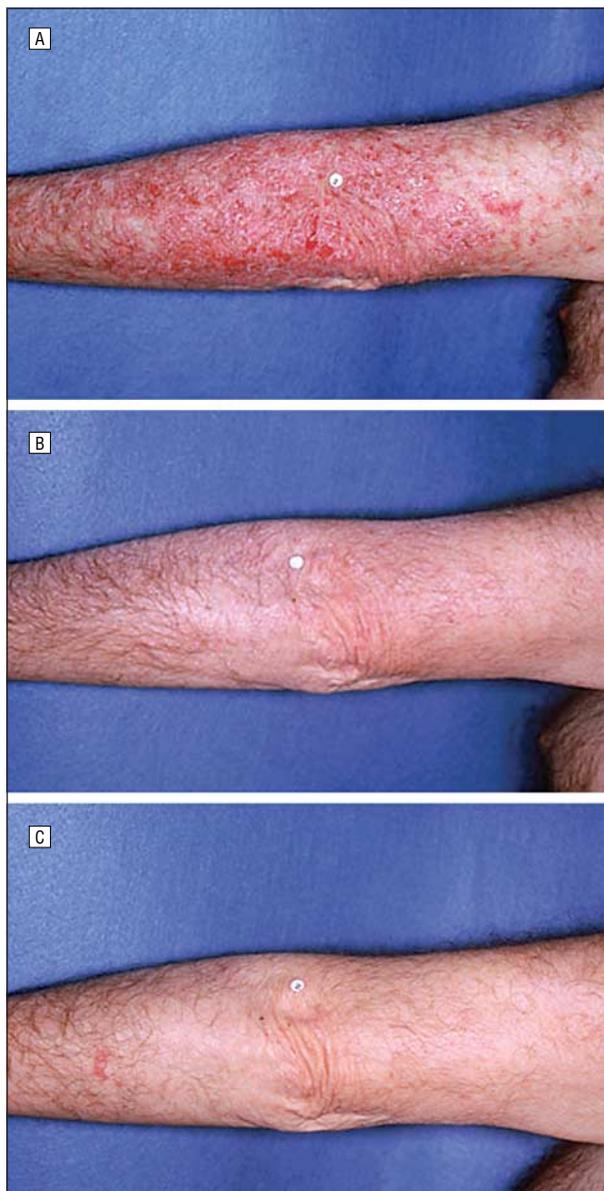


Figure 3. Psoriasis activity in an etanercept-treated patient at baseline (A, Psoriasis Area and Severity Index [PASI]=18.7), at 12 weeks (B, 59% improvement in PASI), and at 24 weeks (C, 86% improvement in PASI).

assessment of disease, and the percentage of body surface area covered by lesions (**Table 3**). Psoriasis was clear or minimal (a score of 0 or 1) in 53% of etanercept-treated patients at 24 weeks. Response was rapid; significant differences between treatment groups were first evident in the percent change in the physician global score, patient global score, and the PASI score by the first time point measured (2 weeks). A visual example of a response to treatment is shown in **Figure 3**.

Quality of Life

In addition to the clinical manifestations of the disease, patients treated with etanercept had statistically significant improvement in quality of life as measured by the DLQI starting at 4 weeks (time of first assessment) compared with patients given placebo (**Table 3**). Improvement was seen in all components of the DLQI in etanercept-treated patients (data not shown).

SAFETY END POINTS

Adverse Events and Serious Adverse Events

Safety was evaluated both as the percentage of patients experiencing a given type of event and as the rate of event occurrence (in events per patient-year). The percentage of patients who experienced adverse events, as well as the rate of occurrence of these events, was similar in patients receiving etanercept and in patients receiving placebo (**Table 4**). Patients in the placebo group reported peripheral edema more frequently than did patients in the etanercept group, which may have been related to poorly controlled psoriasis in the lower extremities. Injection site reactions occurred more frequently in etanercept group than in the placebo group (9% vs 0%, respectively). The injection site reactions were mild (grade 1 or 2), and no patient discontinued because of injection site reactions. Five serious adverse events occurred during the study: 2 in etanercept-treated patients (appendicitis, which occurred 16 days after the last dose of study drug, and a motor vehicle crash) and 3 events in 2 placebo-treated patients (pharyngitis and stroke in the same patient, and pustular psoriasis). None of these events was considered by the investigators to be related to etanercept treatment.

In 2 patients, nonplaque psoriasis was reported after initiation of drug treatment. One patient receiving placebo was reported to have pustular psoriasis (mentioned above), and guttate psoriasis (considered by the investigator to be possibly related to study drug) was observed in one patient receiving etanercept. No opportunistic infections, tuberculosis, or skin cancers were observed.

No grade 3 or 4 abnormal laboratory results were noted during the 24-week study, and no patient discontinued the study because of an abnormal laboratory value.

Rate of Premature Discontinuations From Study

Eight patients discontinued the study drug because of adverse events: 2 patients in the etanercept group (the aforementioned patient with guttate psoriasis and another with

Table 4. Adverse Events Occurring in 10% or More of Groups Combined

Event	Placebo Group		Etanercept Group	
	% of Patients (n = 55 Total)	Rate (n = 14.5 Patient-Years)	% of Patients (n = 57 Total)	Rate (n = 23.6 Patient-Years)
Upper respiratory tract infection	20	1.10	35	1.19
Headache	13	0.55	16	0.72
Bruise at injection site	9	0.48	11	0.25
Sinusitis	4	0.14	14	0.38
Pain	7	0.28	7	0.21
Peripheral edema	9	0.41	2	0.04*
Hypertension	4	0.14	7	0.17
Accidental injury	4	0.14	7	0.17

* $P < .05$ (Fisher exact test).

a grade 2 worsening of psoriasis after 4 days on study drug) and 6 patients in the placebo group (1 each upper respiratory tract infection, cerebrovascular accident, abdominal pain, and the aforementioned pustular psoriasis; and 2 for allergic reactions).

COMMENT

Results from this study indicate that etanercept as monotherapy provided significant benefit to patients with psoriasis, with 56% of patients achieving PASI 75 and 77% of patients achieving PASI 50 by week 24, and few patients reporting adverse events. Treatment failure (defined as PASI < 50) occurred in 23% of patients. Treatment failure in these patients may be the result of the need for higher levels of TNF antagonism or, alternatively, psoriatic inflammation driven by mediators other than TNF. The patients in this trial had moderate to severe psoriasis and had tried at least one systemic therapy, making them candidates for treatment with stronger immunomodulating drugs, such as methotrexate and cyclosporine. The favorable efficacy and safety profile of etanercept distinguishes it from these current therapies, which are associated with significant toxic effects. The results of this study are similar to the results of a trial of etanercept for the treatment of psoriatic arthritis, wherein 26% of etanercept-treated patients and no placebo-treated patients had reached PASI 75 at 12 weeks,⁷ although patients in the psoriatic arthritis trial were allowed to use stable doses of concomitant methotrexate.

Adverse effects observed in this trial were unremarkable, and were similar in patients receiving either etanercept or placebo. In addition to the short-term data on psoriasis presented herein, long-term safety data are available for large numbers of patients who have received etanercept for rheumatoid arthritis. In data from more than 2000 patients with rheumatoid arthritis who received etanercept for up to 5 years in clinical trials, etanercept has been generally well tolerated.⁸ These data from patients with rheumatoid arthritis suggest that long-term treatment of psoriasis with etanercept may be a viable option, an important consideration for management of this chronic disease.

The efficacy of etanercept, which blocks the effect of TNF, in the treatment of psoriasis is particularly in-

teresting in light of increasing clinical evidence that disruption of specific interactions within the immune system can improve psoriasis. Drugs that interfere with T-cell function, such as efalizumab (a monoclonal antibody directed against CD11a),^{9,10} alefacept (which reduces the number of peripheral blood memory T cells),¹¹ and CTLA4Ig (which interferes with the activation of cytotoxic T cells) have been shown to be efficacious in the treatment of psoriasis. Infliximab, an antibody directed against TNF, also has provided benefit.¹² Our study shows the benefit of TNF blockade by etanercept. Improvement was rapid in onset and consistent across different end points including the PASI 75, physician global score, patient global score, and DLQI. Patients receiving etanercept experienced significant improvement in quality of life. Most important, more than 50% of patients treated with etanercept achieved clear or minimal status by the physician global assessment at 24 weeks. Etanercept may prove to be an effective and safe long-term monotherapy for this chronic disease.

Accepted for publication June 10, 2003.

From the University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School, New Brunswick (Dr Gottlieb); Oregon Medical Research Center, Portland (Dr Matheson); Southern California Dermatology, Santa Monica (Dr Lowe); Department of Dermatology, University of Utah Medical Center, Salt Lake City (Dr Krueger); University of Michigan Medical Center, Taubman Center, Ann Arbor (Dr Kang); Minor and James Medical, Seattle, Wash (Dr Goffe); University of Maryland, Baltimore (Dr Gaspari); MedaPhase Inc, Newnan, Ga (Dr Ling); University of California, Irvine, UCI Gottschalk Medical Plaza, Medical Science I, Irvine (Dr Weinstein); Innovative Clinical Solutions, Bloomington, Ill (Dr Nayak); Division of Dermatology, Loyola University Medical Center, Maywood, Ill (Dr Gordon); and Amgen, Inc, Thousand Oaks, Calif (Dr Zitnik).

This study was sponsored by Immunex Corp, a subsidiary of Amgen, Inc.

This study was presented in abstract form at American Academy of Dermatology; March 2002; New Orleans, La.

Linda Melvin, BA, and MaryAnn Foote, PhD, assisted with the writing of the manuscript.

Corresponding author and reprints: Alice B. Gottlieb, MD, PhD, Clinical Research Center, UMDNJ–Robert Wood Johnson Medical School, 51 French St, New Brunswick, NJ 08901-0019 (e-mail gottliab@umdnj.edu).

REFERENCES

1. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. *Dermatol Clin*. 1996;14:485-496.
2. Greaves MW, Weinstein GD. Treatment of psoriasis. *N Engl J Med*. 1995;332:581-588.
3. Linden KG, Weinstein GD. Psoriasis: current perspectives with an emphasis on treatment. *Am J Med*. 1999;107:595-605.
4. Gottlieb AB. Psoriasis: immunopathology and immunomodulation. *Dermatol Clin*. 2001;19:649-657.
5. Fredrickson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. *Dermatologica*. 1978;157:238-244.
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210-216.
7. Mease P, Goffe B, Metz J, Vanderstoep A. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet*. 2000;356:385-390.
8. Klareskog L, Moreland LM, Cohen SJ, Sanda M, Burge DJ. Global safety and efficacy of up to five years of etanercept (ENBREL) therapy [abstract]. *Arthritis Rheum*. 2001;44:S77.
9. Gottlieb A, Krueger JG, Bright R, et al. Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. *J Am Acad Dermatol*. 2000;42:428-435.
10. Papp K, Bissonnette R, Krueger JG, et al. The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. *J Am Acad Dermatol*. 2001;45:665-674.
11. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med*. 2001;345:248-255.
12. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet*. 2001;357:1842-1847.

Editorial Comment

Obtaining satisfactory control of disease activity and minimizing drug toxicity are challenges in managing patients with psoriasis. This randomized clinical trial of the TNF antagonist etanercept was designed with the expectation of a reduction of PASI score by 75% (PASI 75) at 12 weeks in 35% of patients actively treated and in 10% of patients receiving placebo (relative risk reduction, 27%). This rate of improvement is lower than the rate of improvement observed short term with cyclosporine or PUVA. About 17 (30%) of 57 patients receiving active treatment and only 1 (2%) of 55 in the placebo arm achieved PASI 75 at 12 weeks. However, at 24 weeks, about 56% of etanercept-treated patients and 5% placebo-treated patients achieved PASI 75. It means treating about 2 patients over 24 weeks to clear 1 (number needed to treat = 2). Treatment failure (defined as not achieving PASI 50) occurred in 23% of patients.

Before defining a place for etanercept in the management of psoriasis, we need additional information, including estimates of the rate of relapse on withdrawal, a better understanding of predictive factors for treatment failure, and more reliable and extensive data on drug safety with special emphasis on adverse events with an incidence lower than 1% (which implies collecting data on drug exposure from more than 10000 people). Comparative effectiveness is also an issue. An increasing number of active treatments are already available and it is increasingly difficult to understand why placebo is still heavily used in the context of randomized clinical trials.

Luigi Naldi, MD