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# THE FUTURE OF TREATING PSORIASIS AND PSORIATIC ARTHRITIS

## Introduction: TNF Inhibition

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## Safety and Efficacy of TNF Inhibition

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## TNF Inhibition for the Treatment of Psoriatic Arthritis

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## The Role of TNF Inhibition in the Treatment of Psoriasis

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# THE FUTURE OF TREATING PSORIASIS AND PSORIATIC ARTHRITIS

- 3 INTRODUCTION: TNF INHIBITION
- 5 SAFETY AND EFFICACY OF TNF INHIBITION
- 8 TNF INHIBITION FOR THE TREATMENT OF PSORIATIC ARTHRITIS
- 10 THE ROLE OF TNF INHIBITION IN THE TREATMENT OF PSORIASIS
- 11 CME POST-TEST AND EVALUATION

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## Target Audience

This activity has been developed for dermatologists and other health care professionals involved in the treatment of psoriasis and psoriatic arthritis.

## Educational Needs

It is now known that tumor necrosis factor (TNF) plays a role in the development of psoriasis and psoriatic arthritis. Clinical studies have demonstrated that inhibition of TNF is a safe and effective strategy for treating selected patients. The TNF inhibitor, etanercept, previously approved for the treatment of adult and juvenile rheumatoid arthritis, recently was approved by the Food and Drug Administration for the treatment of psoriatic arthritis. In addition, the results of recent clinical trials have shown that anti-TNF therapy also has promise as a treatment for the skin lesions of psoriasis. This activity provides dermatologists with up-to-date information on the efficacy and safety of etanercept in the treatment of psoriatic arthritis and psoriasis.

## Learning Objectives

Upon completion of this program, participants should be able to:

- Explain the rationale for the use of TNF inhibitors in the treatment of immune-mediated inflammatory diseases such as rheumatoid arthritis and psoriatic arthritis.
- Discuss the accumulated safety data concerning etanercept from clinical trials and from postmarketing surveillance.
- Describe the efficacy and safety of etanercept in patients with psoriatic arthritis.
- Describe the efficacy and safety in patients with cutaneous psoriasis.

## Accreditation

The American Academy of Dermatology certifies that this educational activity has been recognized for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

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Dr. Genovese has received clinical grants from Immunex Corp., and is a consultant to Wyeth Pharmaceuticals. Dr. Gottlieb has received clinical grants from and is a consultant to Wyeth and Immunex. She discusses the unlabeled use of etanercept for the treatment of psoriasis. Dr. Lebwohl has been an investigator for and on the speakers' bureau of Wyeth and Immunex. He discusses the unlabeled use of etanercept for the treatment of psoriasis.

# INTRODUCTION: TNF Inhibition

MARK G. LEBWOHL, MD

In January 2002, the Food and Drug Administration approved for the first time a tumor necrosis factor (TNF) inhibitor for the treatment of psoriatic arthritis (PsA). The TNF-inhibiting agent, etanercept, has previously been approved for the treatment of rheumatoid arthritis (RA) in children and adults. Although a number of medications have been used for many years for the treatment of patients with PsA (see **Table**), none of these agents was approved specifically for this condition.

## CHARACTERISTICS OF PsA

According to the results of a recent National Psoriasis Foundation survey,<sup>1</sup> approximately 15% of patients with psoriasis—about one in seven—have PsA, equally distributed among men and women. In most cases, the age of onset is between 30 and 50 years of age, but onset may be at any age, including childhood. In the majority of patients, cutaneous psoriasis lesions precede joint involvement by months or years.

Several patterns of involvement are seen in patients with PsA. Oligoarthritis is the most common form. Distal interphalangeal joint involvement is characteristic of PsA, and spondylitis is not uncommon. Symmetric polyarthritis also may occur, with deformities similar to those seen in RA. Arthritis mutilans, a rapidly destructive form of PsA, is rare, affecting only about 4% of patients with PsA.<sup>2</sup>

Torre Alonso and colleagues<sup>2</sup> report that between 40% and 57% of patients with PsA have deforming erosive joint disease and 17% have at least five deformed joints. From 11% to 19% of patients with PsA report disability. Further, these investigators<sup>2</sup> as well as other authors<sup>3,4</sup> report an increased incidence of premature death in patients with PsA.

## RATIONALE FOR TNF INHIBITION

The rationale for inhibition of the cytokine TNF as a treatment strategy emerged with the growing recognition of TNF's role in the development of immune-mediated inflammatory diseases such as RA. The experience with

etanercept and other TNF-blocking medications in RA—both FDA-approved and investigational—has demonstrated the blockade of TNF is a safe and effective intervention, a therapeutic benefit that may apply to other diseases in which this cytokine is central.

It is known that TNF is synthesized and released by injured keratinocytes and that TNF induces in keratinocytes the production of TNF- $\alpha$  and other cytokines.<sup>5</sup> Studies have demonstrated that TNF levels are increased in the epidermis of lesional skin in patients with psoriasis compared with nonlesional skin in these patients and the skin of healthy subjects.<sup>6-8</sup>

It has further been shown that patients with severe psoriasis established by high Psoriasis Area Severity Index

(PASI) scores have higher TNF concentrations both in lesional skin and in serum, and that levels of TNF and interleukin-1 are higher in the synovial tissue and fluid of patients with PsA and RA compared with patients with osteoarthritis.<sup>9-12</sup> It has also been demonstrated that successful anti-TNF treatment is associated with reductions in TNF levels in skin and serum.<sup>13,14</sup>

Etanercept, a fully human molecule, is a fusion protein of the human p75 receptor and the Fc portion of human immunoglobulin G. Etanercept competitively binds soluble and cell-bound TNF- $\alpha$ , preventing circulating TNF- $\alpha$  from binding to the TNF receptors on cell surfaces.

## CONCLUSION

Etanercept is the first of what will likely become a list of new biologic agents that will be available for the treatment of PsA and psoriasis. Many of these drugs will be given subcutaneously, as is etanercept; others will require intravenous administration. In dermatology, the administration of drugs via these routes currently is not routine but will become so. It is important for dermatology clinicians to anticipate the changes in practice that the use of these new drugs will require.

## Plantar and Palmar Psoriatic Lesions



The recently published results of the National Psoriasis Foundation's Benchmark Survey for Psoriatic Arthritis showed that about 85% of patients with psoriatic arthritis also have psoriatic skin lesions. The results also suggest that approximately 1 million adults in the United States have psoriatic arthritis.<sup>1</sup>

**TABLE** Treatments Used in PsA

DRUG	COMMENTS
<b>Corticosteroids, IM</b>	Rebound on discontinuation is a concern with use of corticosteroids
<b>Cyclosporine<sup>a</sup></b>	Effective as monotherapy and in combination with azathioprine; nephrotoxicity is a concern with long-term use
<b>Gold, IM<sup>b</sup></b>	Effective in a small number of patients with PsA; nephrotoxicity is a concern with long-term use
<b>NSAIDs</b>	Standard therapy for mild PsA
<b>Methotrexate<sup>c</sup></b>	One of the most effective and most commonly used treatments for severe PsA; bone marrow toxicity and hepatotoxicity are concerns with long-term use
<b>Sulfasalazine<sup>d</sup></b>	Effective in a small number of patients with PsA
<b>Etanercept<sup>e</sup></b>	Recently approved by the FDA for the effective treatment of PsA, this TNF inhibitor is the only drug approved for this indication; no major organ toxicity reported to date

FDA = Food and Drug Administration; IM = intramuscular; NSAIDs = nonsteroidal anti-inflammatory drugs; PsA = psoriatic arthritis; TNF = tumor necrosis factor

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# Safety and Efficacy of TNF Inhibition

MARK C. GENOVESE, MD

The tumor necrosis factor (TNF) inhibiting agent recently approved by the Food and Drug Administration for the treatment of psoriatic arthritis (PsA) has a demonstrated track record of clinical use in rheumatoid arthritis (RA) in both clinical trials and medical practice. Long-term safety data from studies in patients with RA have shown that this drug, etanercept, is effective and well tolerated in this population. It is important to focus on the safety and efficacy data from patients with rheumatic diseases and to reflect on how these data may be germane to the treatment of patients with dermatologic diseases.

## EFFICACY IN RHEUMATOID ARTHRITIS

In rheumatology, the efficacy of an intervention often is measured on the basis of a composite score known as the American College of Rheumatology (ACR) response index, which entails assessment of improvement in seven parameters:

1. joint swelling
2. joint tenderness
3. patient's global assessment
4. physician's global assessment
5. pain (as measured on a visual analog scale)
6. erythrocyte sedimentation rate or C-reactive protein
7. a health assessment questionnaire.

In clinical trials in rheumatology, efficacy is established by a minimum improvement of 20% in the first two parameters plus three out of the other five, and a subsequent result is reported as ACR 20. (Similarly, ACR 50 and ACR 70 indicate, respectively, 50% and 70% improvements in these parameters.)

Several clinical studies comparing etanercept with placebo and comprising 2,054 patients with RA—and accounting for just over 4,700 patient-years of experience—were reported in composite form at the American College of Rheumatology annual scientific meeting in 2001.

The results were sustained and consistent<sup>1</sup> (Figure). It is notable that the

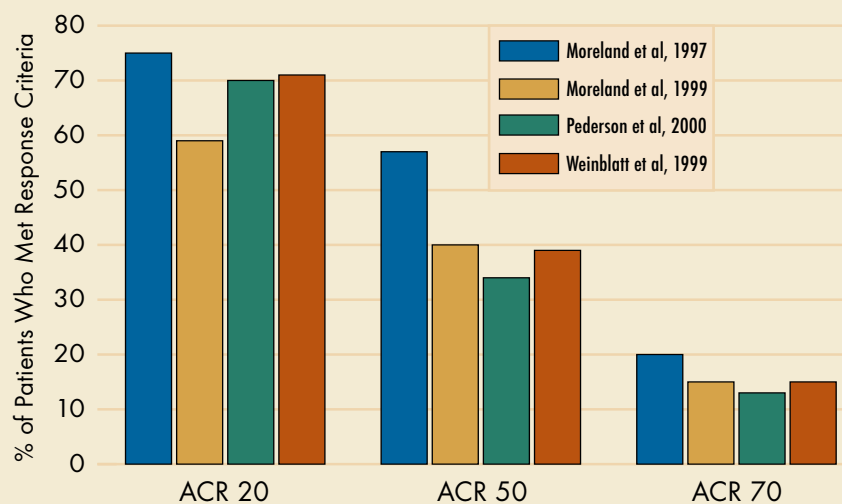
reported efficacy has been achieved across studies, across patient populations, and across different study sites, both within the United States and in Europe.

## REDUCTION IN CONCOMITANT MEDICATIONS

In a previously published trial,<sup>2</sup> 89 patients treated with methotrexate (MTX) for at least 6 months but with an inadequate response were enrolled in a 6-month, double-blind, placebo-controlled trial of etanercept given in combination with MTX. At the start of the study, patients were on a stable dosage of MTX of 15 to 25 mg/wk (some who were unable to tolerate this regimen received a lower dosage, as low as 10 mg/wk). The patients were randomly assigned to receive twice-weekly subcutaneous injections of either etanercept (25 mg) or placebo; MTX was continued in both groups. The results are shown in the Figure (see the bars in red).

At the end of the study period, 79

FIGURE Etanercept Clinical Responses in RA



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Source: Klareskog L, Moreland LM, Cohen SB, Sanda M, Burge DJ. Global safety and efficacy of up to five years of etanercept (Enbrel) therapy. Abstract #150. Presented at the American College of Rheumatology 65th Annual Scientific Meeting, San Francisco, November 2001.

patients entered an open-label extension study, and long-term data have been reported on a median of 26 months (34 months maximum) of additional treatment with etanercept.<sup>3</sup> At baseline the mean dose of MTX was approximately 17.6 mg. At the time the data were analyzed, the mean dose of MTX had been reduced to 9.3 mg/wk. Sixty-eight percent of patients had reduced or discontinued their use of MTX, with 29% having discontinued MTX entirely.

The mean baseline dosage for a subgroup of patients on prednisone was 6.4 mg/day. During the period of the open-label extension study, the mean dosage of prednisone was reduced to approximately 2.3 mg/day; 85% of patients reduced or discontinued their prednisone dose, with 50% discontinuing its use entirely.<sup>3</sup> These results suggest that etanercept use allows a decrease in concomitant medications as well as providing improvement in RA signs and symptoms.

## SAFETY

Safety with initial and long-term use of biologic agents is an issue that may be even more pressing than that of efficacy. In studies comparing etanercept with placebo, a number of issues have been addressed.

- **No Significant Increase in Infection Rates**

Complaints of upper respiratory tract symptoms have been reported occasionally in patients treated with etanercept. However, the accumulated data from 1,960 patients treated for up to 5 years in controlled clinical trials<sup>4</sup> have demonstrated no statistically significant difference between etanercept and placebo groups in the incidence of upper respiratory tract infections. Further, no statistically significant differences were seen between treated and control groups in the incidence of other types of infections. No cases of tuberculosis or opportunistic infections were seen in any of the clinical trials.

In previous controlled clinical trials of etanercept use in patients with RA, the rates of infection for significant or severe infections and hospitalizations

## Moderate to Severe Psoriasis



**An estimated 20% to 25% of patients with psoriasis have moderate to severe involvement; approximately 1 million patients in the United States have severe involvement of more than 20% of their body surface area. Psoriatic arthritis develops in about 50% of patients with severe psoriatic skin lesions.**

Source: Benchmark Survey for Psoriatic Arthritis. Portland, Ore.; National Psoriasis Foundation; 2002.

requiring the administration of intravenous antibiotics were comparable in the etanercept-treated and control-group patients. In addition, all patients enrolled in those trials were offered the opportunity to enroll in open-label extension studies. The composite data from those extension studies show that the discontinuation rates are low.

- **No Significant Increased Risk for Malignancy**

Because inhibitors of TNF work by altering immune system function, the possibility of an increased risk for malignancy is an issue that must be addressed in any review of safety of TNF inhibitors. To date, no evidence suggests that the use of etanercept is associated with an increased risk for malignancy. Data on patients in the etanercept clinical trials were compared with data from age-, gender-, or sex-matched controls from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program database. The number of expected malignancies out of this cohort is similar to those reported in clinical trials thus far, with no type of cancer predominating. Five cases of lymphoproliferative disorders have been seen, which is comparable with what would be expected in the population of patients with RA not on etanercept.<sup>1</sup>

## POSTMARKETING SURVEILLANCE SAFETY DATA

As of September 2001, data had been collected on 2,054 patients in clinical trials (representing 4,794 patient-years) and on more than 114,000 patients (representing more than 133,000 patient-years) who have used etanercept since it was introduced on the market.

Based on the literature, an incidence of 0.03 to 0.09 serious infections per patient-year is expected.<sup>5,6</sup> In the clinical trials, the reported rate was 0.04 per patient-year (4,343 patient-years),<sup>1</sup> and the reporting rate in the postmarketing period, through June 2001, was 0.007 per patient-year.<sup>4</sup> Postmarketing experience often does not reflect a true picture of adverse events because the reporting rate is usually much smaller than ideal. However, nothing in the postmarketing experience to date suggests that the incidence of serious infections increases with etanercept use in the RA population.

Nevertheless, some risk factors for serious adverse events with etanercept use have been identified in patients with RA.<sup>5,6</sup> These probably also would apply to patients with psoriatic arthritis (PsA) or cutaneous psoriasis who use this drug. Serious infections are more likely to occur in patients with profound disability, diabetes mellitus, long-term cardiovascular disease, pulmonary dis-

ease, a long-term history of corticosteroid use, or concomitant use of other immunosuppressant agents.

Although no cases of opportunistic infection were seen in the clinical trials, rare reports have been received of patients acquiring candidiasis (seven cases), aspergillosis (five cases), cytomegalovirus (five cases), *Pneumocystis carinii* pneumonia (four cases), and, rarely, infections involving Cryptococci (three cases), Listeria (two cases), Histoplasma (one case), and Sporothrix (one case).<sup>7</sup> In an assessment of the significance of the occurrence of these infections, it is important to consider the overall picture, including the number of patients treated and the potentially confounding issue of concomitant therapies.

Worldwide, 13 cases of tuberculosis—10 localized, 3 miliary; 8 in the United States, 5 in Europe—have been confirmed in etanercept users as of September 2001.<sup>8</sup> Seven patients were culture-positive; in the other six, the diagnosis was presumptive, based on clinical parameters. In the clinical trials, 29 patients were known to be either TB-positive or to have a positive result on a purified protein derivative (PPD) of tuberculin test. Despite the evidence of exposure to tuberculosis prior to initiation of etanercept treatment, none of these 29 patients developed recrudescence of TB, and none had any evi-

dence of active TB after an average of 34 months of therapy. It is not yet clear whether etanercept treatment may be associated with an increased incidence of TB infection. Nevertheless, patients who may be at high risk for TB or who have had prior exposure to the disease should be screened, with chest x-rays and PPD, before etanercept treatment is started.

Rare cases of demyelinating disease have been reported with the use of TNF inhibitors. Infliximab has been used as treatment in a small case series of patients with active multiple sclerosis (MS); magnetic resonance imaging demonstrated a worsening of MS lesions.<sup>9</sup> A p55 fusion molecule known as lenercept also was used in clinical trials in patients with MS; results suggested a worsening of the disease.<sup>10</sup>

Etanercept has not been used to treat MS in any clinical trials. However, demyelinating disease has been reported rarely—three observed and five probable cases—in patients taking etanercept for inflammatory arthritis. Eleven cases of MS relapse also have been observed in patients who were taking etanercept for RA or PsA. Based on epidemiologic data on MS, out of 133,000+ patient-years of experience, between three and eight new cases of MS might be expected as a background incidence. Four cases of optic neuritis have

been observed as of September 2001.

Rare hematologic complications have been reported, with five cases of aplastic anemia observed in patients treated with etanercept. The baseline relative risk for aplastic anemia is increased in patients with RA not on etanercept therapy, and all five patients on etanercept also were undergoing concomitant treatment with immunosuppressive or cytotoxic therapies.

## CONCLUSION

The long-term safety and efficacy data with the use of etanercept in patients with RA have demonstrated that the use of this drug results in substantial and sustained improvement in patients with articular disease. Specifically, studies have shown that in patients with RA, treatment with etanercept reduces disease progression as demonstrated on radiographs and may decrease the concomitant use of corticosteroids and MTX. In postmarketing experience to date, the types and the rates of adverse events reported are consistent with those seen in the clinical trials. Nevertheless, long-term safety surveillance and pharmacovigilance are exceptionally important at the outset as this drug is used for the treatment of patients with other diseases, including psoriatic arthritis and the possibility in the future for psoriasis.

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# TNF Inhibition for the Treatment of Psoriatic Arthritis

ALICE B. GOTTLIEB, MD, PHD

**P**сориаз and psoriatic arthritis (PsA) are chronic illnesses that have a major adverse impact on quality of life. Safe and effective treatments for long-term management have heretofore been unavailable. During the past several years, mounting evidence has shown that biologic agents that inhibit tumor necrosis factor (TNF) have a role in the treatment of immune-mediated inflammatory diseases, including psoriasis and PsA.<sup>1</sup> Because of this finding, the recent approval of etanercept for the treatment of PsA (for use with or without methotrexate) is significant. This anti-TNF agent, which is self-administered by subcutaneous injection twice weekly, was previously approved for the treatment of both adult and juvenile rheumatoid arthritis (RA).

## RATIONALE FOR ETANERCEPT USE IN PsA

Research in the pathogenesis of cutaneous psoriasis and PsA has shown that inflammation of both skin and synovium in patients with these diseases occurs with elevations in interleukin-1 (IL-1) and TNF- $\alpha$ .<sup>2</sup> Production of these cytokines causes stimulation of other events that result in a chronic T-lymphocyte response, an ongoing circular feedback loop that eventually results in expression of disease.

From studies in RA, it is now also understood that, along with IL-1 and TNF- $\alpha$ , nuclear factor kappa B (NF kappa B ligand) is activated in synovial cells.<sup>3,4</sup> In the synovium, this leads to cellular hypertrophy and hyperplasia,<sup>5,6</sup> with leukocyte infiltration, collagenase release, fibroblast proliferation, and endothelial activation of E selectin, intercellular adhesion molecule, and vascular cell adhesion molecule. This process leads to cartilage destruction and to increased bone resorption, destruction of bone at the margin with articular cartilage, and, ultimately, joint destruction.<sup>7</sup>

The results of a phase II clinical efficacy and safety trial of etanercept in PsA showed that this drug improved signs and symptoms of PsA as well as of psoriasis and was generally well tol-

erated in both psoriasis and associated PsA.<sup>8</sup> The balance of this discussion focuses on the phase III, multicenter, double-blind, placebo-controlled trial conducted to establish the statistical significance of efficacy and safety data.<sup>9</sup>

## PHASE III STUDY OF ETANERCEPT IN PsA: DESIGN AND METHODS

In the 24-week phase III trial of etanercept in patients with PsA, 205 patients were enrolled and randomized to receive

twice-weekly subcutaneous injections of either 25 mg of etanercept (101 patients) or placebo (104 patients). Qualifying criteria for entry into the study were the presence of a cutaneous psoriasis plaque, at least three swollen and tender joints, and a diagnosis of PsA.

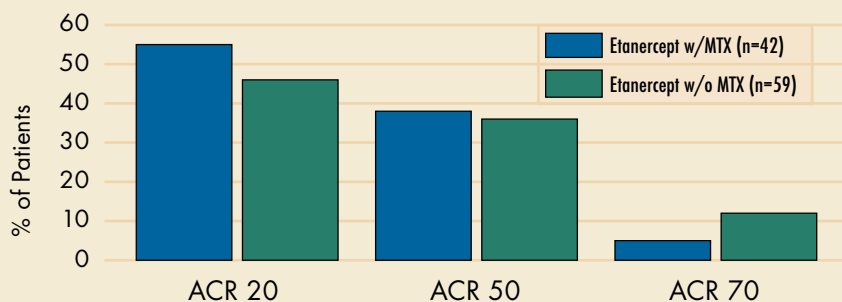
During the study, patients on stable dosages of 25 mg/wk or less of methotrexate (MTX), 10 mg/day of systemic corticosteroids, and/or nonsteroidal anti-inflammatory drugs (NSAIDs) were permitted to continue using these medications. Use of other systemic drugs for the treatment of PsA or psoriasis was not permitted. At the start of the study, about 50% in both the etanercept and placebo group were taking concurrent MTX, 20% in each group were using systemic corticosteroids, and 80% were on NSAIDs.

## SIGNIFICANT EFFICACY ACHIEVED

In the placebo group, 72 patients (69%) completed the study, with most of the other 32 dropping out because of lack of efficacy, despite concomitant use of MTX, systemic corticosteroids, and NSAIDs. In the active treatment group, 93 patients (92%) completed the study.

The primary efficacy end point was

**FIGURE 1** Concomitant Methotrexate Does Not Affect Response at 24 Weeks



MTX = methotrexate; ACR = American College of Rheumatology

Source: Mease P, Kivitz A, Burch F, Siegel E, Cohen S, Burge D. Improvement in disease activity in patients with psoriatic arthritis receiving etanercept (Enbrel): results of a phase 3 multicenter clinical trial. Abstract #226. Presented at the American College of Rheumatology 65th Annual Scientific Meeting, San Francisco, November 2001.

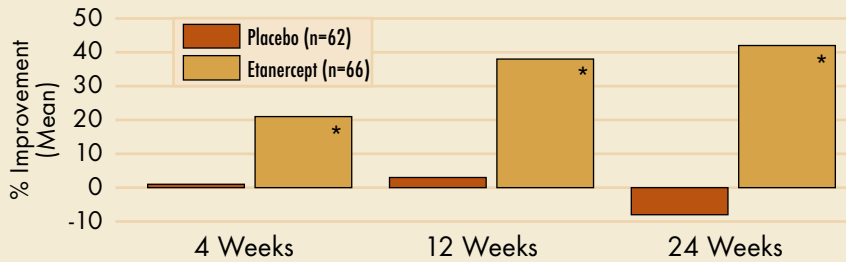
a minimum of 20% improvement on the American College of Rheumatology index (ACR 20) at the midpoint, 12 weeks (for more detailed discussion of ACR index criteria, see page 5). Arthritis severity was also measured by the psoriatic arthritis response criteria (PsARC). Improvement in target lesion score was used to track psoriasis activity. Both PsARC and the Psoriasis Area and Severity Index (PASI) were used in a subset of patients with at least 3% body surface area (BSA) involvement with psoriasis (66 of those on etanercept, 62 of those in the placebo group).

At week 12, 60 (59%) of the patients receiving etanercept versus 16 (15%) of those in the placebo group met the ACR 20 criteria ( $P < 0.001$ ). At week 24, 50% of patients in the etanercept group met the ACR 20 criteria, versus 13% of those in the control group ( $P < 0.0001$ ). ACR 50 (50% response based on ACR criteria) was achieved in 37% of those on etanercept and in 4% of patients in the control group ( $P < 0.0001$ ) at week 24. The most stringent criteria, ACR 70 (70% response on ACR criteria), was achieved in 9% of those on etanercept and 1% of patients in the placebo group ( $P = 0.009$ ) at the end of the study period.

When the subsets of patients who used and did not use MTX concurrently were compared, the investigators found that MTX use made no significant difference in response according to ACR 20, ACR 50, or ACR 70 (Figure 1).

In terms of psoriasis response, PASI showed significant improvement at weeks 4, 12, and 24 (Figure 2) in the 66 patients in the etanercept group and 62 patients on placebo who had at least 3% BSA involvement ( $P < 0.001$ ).

**FIGURE 2 PASI Percent Improvement from Baseline**



\* $P < 0.001$

PASI = Psoriasis Area and Severity Index

Source: Mease P, Kivitz A, Burch F, Siegel E, Cohen S, Burge D. Improvement in disease activity in patients with psoriatic arthritis receiving etanercept (Enbrel): results of a phase 3 multicenter clinical trial. Abstract #226. Presented at the American College of Rheumatology 65th Annual Scientific Meeting, San Francisco, November 2001.

### DATA SHOW GOOD SAFETY PROFILE

The only adverse event that occurred significantly more often in the treatment group compared with the placebo group was injection site reactions—36% versus 9%, respectively—which were mild. There was no increased incidence of upper respiratory infections (there was approximately a 20% incidence in both groups), urinary tract infections (6% incidence in both groups), or other infectious complications.

No significant clinical laboratory abnormalities were noted in either group. Further, no antibodies to etanercept were seen. Unlike the RA trials, no aplastic diseases were observed in this study.

### CONCLUSION

In clinical trials, patients with PsA treated with etanercept derived signif-

icant symptomatic benefit, and levels of disability were decreased. Further, etanercept has been shown to be well tolerated in patients with psoriasis and PsA. As a result of the safety data accumulated to date, no recommendations are made for monitoring patients on etanercept for liver or renal toxicity.

Nevertheless, it may be prudent to obtain a baseline complete blood count, liver function tests to rule out hepatitis, renal function tests, and purified protein derivative of tuberculin test before starting patients on etanercept or other anti-TNF agents.

Further, the coexistence of multiple sclerosis (MS) and psoriasis is very rare, but administering TNF inhibitors to patients with MS should be avoided. As a precaution, a neurologic history should be taken before prescribing these drugs.

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# The Role of TNF Inhibition in the Treatment of Psoriasis

MARK G. LEBWOHL, MD

Because tumor necrosis factor (TNF) plays an important role in the pathogenesis of psoriatic skin lesions, TNF inhibitors offer a promising new treatment option for dermatologists. The anti-TNF agent etanercept recently was approved by the Food and Drug Administration for the treatment of psoriatic arthritis (PsA). The data from the PsA clinical trials also demonstrated the benefit of anti-TNF therapy in skin lesions. A phase II trial of the anti-TNF agent etanercept showed that this agent is safe and effective in patients with psoriasis.

## STUDY DESIGN AND DEMOGRAPHICS

In this double-blind, placebo-controlled trial, patients underwent a 4-week washout of other psoriasis therapies and then were randomized to receive either etanercept or placebo. The study medications were administered subcutaneously twice weekly for 24 weeks. Patients were evaluated at the end of the 24-week treatment period and again 30 days later; they were then followed monthly for an additional 24 weeks.

The mean duration of psoriasis in the 57 patients assigned to the etanercept group was 23 years; the 55 patients in the placebo group had a mean psoriasis duration of 20 years. The mean baseline Psoriasis Area Severity Index (PASI) for the active treatment and control group was 17.8 and 19.5, respectively, and mean baseline body surface area (BSA) involvement was 30% and 34%, respectively.

## PRELIMINARY RESULTS

Onset of clearing of psoriasis occurred within 4 weeks, and patients in the active-treatment group achieved clinically significant improvement in all parameters of psoriasis that were used in the evaluation, including erythema, induration, scaling, and global assessments.

PASI scores at 12 and 24 weeks are summarized in the **Table**. At 12 weeks,

30% of patients in the etanercept group had 75% improvement in PASI compared with only 2% of patients in the placebo group. PASI 75 was achieved by 56% of etanercept patients at 24 weeks, compared with 5% of those in the control group. Also at 24 weeks, 20% of patients in the active treatment group had achieved 90% improvement in PASI—that is, PASI 90, defined as clear or almost clear; none of the placebo-treated patients achieved PASI 90.

Thus, improvement began within 1 month and gradually increased through 24 weeks of treatment in this study. Efficacy of etanercept was statistically significant, clinically meaningful, and consistent across all measures.

## GOOD SAFETY PROFILE

Etanercept was well tolerated. The infections reported in the treatment group were not serious, with the majority being low-grade upper respiratory

infections resembling the common cold. No opportunistic infections occurred in any of the study subjects.

The only adverse effects of note were injection site reactions, which occurred in 9% of patients in the etanercept group. These were mild to moderate reactions characterized by erythema, itching, pain, and swelling, usually occurring only in the first month of treatment. Of interest, some patients who did have such a reaction had signs and symptoms both at the current and a previous injection site, suggesting an immunologic reaction. Injection site reactions resolve spontaneously within a few days; no intervention is necessary.

No laboratory tests are required for monitoring patients on etanercept. However, a chest x-ray and/or purified protein derivative of tuberculin test should be considered before initiating therapy in patients who may have been exposed to *Mycobacterium tuberculosis*. Etanercept should be discontinued if any serious infection develops.

## CONCLUSION

TNF plays an important role in the pathogenesis of both joint and skin lesions of psoriasis. Antagonism of TNF is an attractive treatment modality, and etanercept provides significant efficacy and good safety for patients with psoriasis. Further studies of etanercept for the treatment of psoriasis are ongoing.

**TABLE PASI 75 and 90 Scores at 12 and 24 Weeks**

PASI 75, 12 Weeks	PASI 75, 24 Weeks	PASI 90, 24 Weeks
30% etanercept	56% etanercept	20% etanercept
2% placebo	5% placebo	0% placebo

PASI = Psoriasis Area Severity Index; PASI 75 = 75% improvement in Psoriasis Area Severity Index; PASI 90 = 90% improvement in Psoriasis Area Severity Index

Source: Data on file, Immunex Corp., Seattle, Wash.

## The Future of Treating Psoriasis and Psoriatic Arthritis CME Post-Test and Evaluation

The American Academy of Dermatology certifies that this educational activity has been recognized for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

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**INSTRUCTIONS:** For each question or incomplete statement, one answer is correct. Circle the most appropriate response. Six correct responses are required for credit.

- Effective January 16, 2002, etanercept is the only TNF agent indicated for the treatment of all of the following except
  - adult rheumatoid arthritis
  - Crohn's disease
  - juvenile rheumatoid arthritis
  - psoriatic arthritis
- Which one of the following statements is false concerning patients with severe psoriasis established by high Psoriasis Area Severity Index (PASI) scores?
  - these patients have higher tumor necrosis factor concentrations in lesional skin and serum
  - these patients have higher tumor necrosis factor concentrations in synovial tissue and fluid
  - these patients have higher tumor necrosis factor concentrations in lesional skin and synovial tissue, but not in serum or synovial fluid
  - successful anti-tumor necrosis factor treatment is associated with reductions in tumor necrosis factor levels in both skin and serum
- Etanercept works in psoriatic arthritis by
  - causing the production and release of TNF-inhibiting cytokines
  - inhibiting the release of TNF into the circulation
  - inducing keratinocyte TNF- $\alpha$  production
  - binding to circulating TNF
- In a trial published by Weinblatt and colleagues comparing etanercept plus methotrexate with placebo plus methotrexate, what percentage of patients in the etanercept/methotrexate group achieved a 20% improvement in American College of Rheumatology criteria (ACR 20)?
  - 31%
  - 51%
  - 71%
  - 91%
- The accumulated data from 1,960 patients with RA treated for up to 5 years in controlled clinical trials show that
  - no differences were seen in the rate of infections between the active-treatment and placebo groups in any of the studies
  - only upper respiratory tract infections occurred significantly more often in the etanercept versus the placebo cohorts
  - the rate of severe infections was significantly higher in the etanercept cohort
  - the risk for malignancy, particularly lymphoproliferative disorders, was higher in the etanercept cohort
- The number of expected malignancies from age-, gender-, and sex-matched controls from the National Cancer Institute's SEER database
  - far exceeds that which has been seen in patients treated to date with etanercept
  - is similar to that which has been seen in patients treated to date with etanercept
  - is far below that which has been seen in patients treated to date with etanercept
  - shows that lymphoproliferative disorders may be a problem with drugs that alter immune system function, including TNF inhibitors
- In the 24-week phase III trial of etanercept versus placebo in patients with psoriatic arthritis, which of the following statements concerning concomitant methotrexate use is not true?
  - concomitant use of methotrexate was not permitted during the study
  - methotrexate use made no significant difference in the primary response criteria
  - use of methotrexate made a significant difference only after 12 weeks of concomitant use with etanercept
  - use of methotrexate made a significant difference only at week 24
- In the phase II study of etanercept in patients with psoriasis, at 24 weeks, 75% improvement in Psoriasis Area Severity Index was seen in 5% of patients in the placebo group and in what percentage of patients in the active treatment group?
  - 16%
  - 36%
  - 56%
  - 76%

**EVALUATION FORM:** We would appreciate your answering the following questions in order to help us plan for other activities of this type.

Name \_\_\_\_\_

Degree \_\_\_\_\_ Specialty \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_

Phone \_\_\_\_\_ Fax \_\_\_\_\_

Signature \_\_\_\_\_

1. How would you rate the clarity of the presentation of the material? (Please check.)

**Excellent    Good    Fair    Poor**

Text \_\_\_\_\_  
Photographic Images \_\_\_\_\_  
Post-Test \_\_\_\_\_

2. How would you rate the clinical relevance of the material?  
\_\_\_\_\_

3. How would you rate this material compared with similar independent study presentations in print format?  
\_\_\_\_\_

4. Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.  
\_\_\_\_\_  
\_\_\_\_\_

5. Do you believe such materials, supported by education grants from industry, are appropriate and useful? Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful). \_\_\_\_\_

6. What topics would you find useful for future programs?  
\_\_\_\_\_  
\_\_\_\_\_

7. Other comments:  
\_\_\_\_\_  
\_\_\_\_\_

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