

A SUPPLEMENT TO

*Skin & Allergy News*<sup>®</sup>

# The Emerging Role of TNF Blockade in the Treatment of Psoriatic Arthritis and Psoriasis



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## **The Role of TNF in Autoimmune Disorders**

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## **New Concepts in the Management of Psoriatic Arthritis**

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## **TNF Blockade for Psoriasis and Psoriatic Arthritis: Clinical Experiences**

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## **New Developments in the Treatment of Moderate-to-Severe Psoriasis**

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### TARGET AUDIENCE

This activity has been developed for dermatologists and other clinicians involved in the treatment of patients with psoriasis and psoriatic arthritis.

### EDUCATIONAL NEEDS

Tumor necrosis factor (TNF) blockade has been used successfully for a number of years to treat patients with rheumatoid arthritis. Recently, data have emerged indicating the potential benefits of anti-TNF therapy in the treatment of psoriasis, psoriatic arthritis, and other immune-mediated inflammatory diseases. Clinicians must understand the underlying rationale for the use of TNF inhibition in these diseases, and need to be kept up-to-date on the results of clinical trials involving the use of anti-TNF agents such as etanercept and infliximab.

### LEARNING OBJECTIVES

By reading and studying this supplement, participants should be able to:

- Discuss the clinical experience to date with TNF blockade in the treatment of psoriatic arthritis, including the results of phase III clinical trials that led to the recent U.S. Food and Drug Administration approval of etanercept for the treatment of patients with this disease.
- Describe and explain the clinical studies involving the use of anti-TNF therapy in patients with psoriasis.
- Explain the rationale for the use of TNF blockade in the treatment of immune-mediated inflammatory diseases such as rheumatoid arthritis, psoriasis, and psoriatic arthritis.
- Discuss the data accumulated to date regarding the safety and efficacy of anti-TNF therapy, including the experience in clinical trials as well as postmarketing surveillance data.

### FACULTY DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

**Dr. Breedveld** is a consultant to Centocor, Inc., Schering-Plough Corporation, Wyeth, Amgen Inc., and Abbott Laboratories. **Dr. Gottlieb** has received clinical grants from and is a consultant to Wyeth and Amgen. 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 Amgen. He discusses the unlabeled use of etanercept for the treatment of psoriasis. **Dr. Lowe** has received clinical grants from Immunex Corporation. He discusses the unlabeled use of etanercept, methotrexate, hydroxyurea, and acitretin in the treatment of psoriasis and the investigational use of etanercept for the treatment of psoriasis.

# THE ROLE OF TNF IN AUTOIMMUNE DISORDERS

Ferdinand C. Breedveld, MD, PhD

**T**he current information available about tumor necrosis factor (TNF) inhibition is based on solid, basic preclinical research and clinical studies conducted with the strictest scientific discipline. The breakthrough in therapy of autoimmune disorders is one that was desperately needed, both in terms of patient care and, in a broader sense, in immunology research.

The purpose of this presentation is to review the discovery and identification of the role of the TNF molecule in the pathophysiology of autoimmune disease and the anti-TNF compounds that have been developed and used clinically in immune-mediated inflammatory diseases.

## CHARACTERIZING TNF: A HISTORICAL PERSPECTIVE

In the 1970s, investigators working with macrophages discovered that in vitro exposure of these cells to lipopolysaccharide caused an expression of a biologically significant substance that caused hemorrhagic necrosis of tumor cells.<sup>1</sup> Almost a decade later, the substance, called tumor necrosis factor, was cloned and further characterized,<sup>2</sup> but the significance of this work was still unknown. In 1987, Cerami and colleagues<sup>3</sup> independently identified this macrophage-derived factor, which they called cachectin because it was determined to be responsible for cachexia associated with chronic parasitic infections. Later, it was found that this molecule also mediated fever and shock.

About a decade ago, the molecule TNF was found to be a key member of a large family of proteins that have roles in immunology. TNF is a natural human, proinflammatory cytokine—or cellular messenger—with a trimeric structure. It cross-links receptors on the cell surfaces (primarily macrophages and T lymphocytes), launches signaling processes, and causes gene ac-

tivation. The surface receptors that are involved in this activity are the p55 and p75 molecules, which have been cloned and used as the basis of drug development.

A number of key inflammatory actions have been attributed to TNF.<sup>4-7</sup> In macrophages, TNF induces the production of other proinflammatory cytokines and chemokines, particularly interleukin (IL)-1, IL-6, and granulocyte colony-stimulating factor. In the endothelium, TNF increases the production of adhesion molecules and vascular endothelial growth factor. Increased keratinocyte proliferation (in keratinocytes), upregulated metalloproteinase synthesis (in synoviocytes), and increased osteoclastogenesis (in osteoclast progenitors) are other TNF-associated actions.

One avenue of clinical research that has led to the approval and marketing of TNF-inhibiting agents is the role of TNF in rheumatoid arthritis (RA). It was discovered that TNF is a major proinflammatory cytokine in RA, and that TNF is a driving force of RA synovitis and bone destruction.

## TNF-INHIBITING AGENTS

Two products have been developed and marketed to date: etanercept and infliximab. Etanercept, a fully human molecule, is composed of the extracellular parts of the p75 TNF receptor linked to the Fc region of an immunoglobulin (IgG)-1 molecule. Infliximab is a chimeric monoclonal antibody.

Etanercept binds both soluble and

membrane-bound TNF. Because it is a soluble receptor, etanercept does not fix, complement, or lyse TNF-producing cells in vitro. It has a median half-life of 4.8 days, so it is administered twice a week, subcutaneously. In clinical trials, etanercept has been shown to have a favorable efficacy-toxicity spectrum in RA, both as monotherapy and in combination with methotrexate (MTX). Currently, etanercept is approved for the treatment of adult and juvenile RA and psoriatic arthritis (PsA).

Infliximab binds to soluble and cell-bound TNF, and as an IgG-1 molecule it can bind, complement, and lyse TNF-expressing cells. It is administered via intravenous infusion every 4 to 8 weeks and has a half-life of 9.5 days. Because of the mouse sequences in this molecule, an immunogenic response is possible. Therefore, most investigators have tested infliximab in combination with MTX. Infliximab is approved in the United States for the treatment of adult RA and Crohn's disease.

## EXPERIENCE WITH ANTI-TNF AGENTS IN RHEUMATOID ARTHRITIS

The anti-TNF inhibitors were first approved for clinical use in patients with RA. Although the exact etiology and pathogenesis of RA are still unknown, it has been demonstrated that it is an autoimmune inflammatory disease. Immunohistochemistry studies of synovial tissue affected by RA show a broad range of structures that play a role in the inflammatory process, including CD4 cells, the helper T cells, cytotoxic cells, B cells, plasma cells, mast cells, and macrophages, as well as their products, including TNF, and IL-1, IL-6, and matrix metalloproteinases.

The foundations for the clinical use of anti-TNF therapy in RA were laid in laboratory experiments with a mouse

model. It was demonstrated that injections into the knee joint of type 2 collagen would result in destruction of cartilage, with extension of inflammation into the bone tissue—findings consistent with what occurs in RA. However, animals injected with anti-TNF agents—either the monoclonal antibody or the soluble receptor compound—did not develop damage or inflammation in the joints.

Williams and colleagues<sup>8</sup> conducted a clinical study of infliximab in RA in 1992, in an open-label trial involving 10 patients who were chosen on the basis of multiple treatment failures with the traditional therapies for RA, including MTX, cyclosporine, sulfasalazine, and antimalarials. The investigators noted a direct clinical response, and although complete remission did not occur, all patients experienced substantial reductions in the number of swollen and painful joints, a decrease of fatigue, and, over time, cessation of progression of the disease documented radiographically.

In a later study, Tak and coworkers<sup>9</sup> obtained synovial biopsies before and 4 weeks after a single treatment with a TNF-inhibiting agent and showed ei-

### Table: Diseases in Which TNF May Play a Role

In addition to rheumatoid arthritis, psoriatic arthritis, and psoriasis, TNF—and, therefore, possibly anti-TNF therapy—is thought to play a role in the following:

- ▶ Acute myeloid leukemia
- ▶ Ankylosing spondylitis
- ▶ Asthma (severe)
- ▶ Cachexia
- ▶ Chronic obstructive pulmonary disease
- ▶ Endometriosis
- ▶ Graft-versus-host disease
- ▶ Interstitial pulmonary fibrosis
- ▶ Polymyositis
- ▶ Scleroderma
- ▶ Wegener's granulomatosis

ther the marked reduction or disappearance of T cells, activated macrophages, adhesion molecules on endothelial cells, and matrix metalloproteinases. The literature is replete with reports of many other well-controlled studies using both infliximab and etanercept in patients with RA, and, more recently, in PsA and psoriasis.

### SAFETY OF TNF INHIBITION

The literature involves a substantial database of patients with RA treated with etanercept. The proven safety

record of any anti-TNF agent is an important consideration for its use in new indications. In addition to approval for the initial indication of RA, etanercept is the first agent approved by the U.S. Food and Drug Administration for the treatment of PsA and currently is in phase III clinical trials for psoriasis.

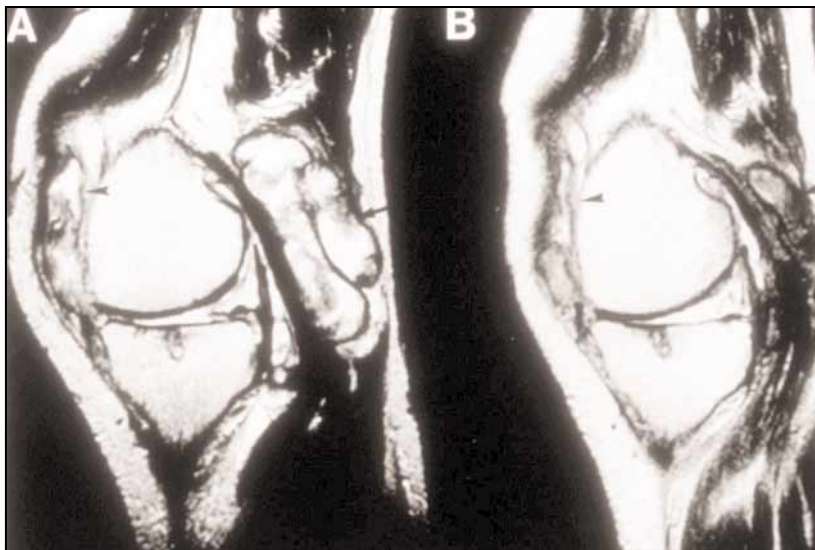
The patient database consists of information from two areas: the clinical trials, involving 2,054 patients and 4,794 patient-years,<sup>10</sup> and the postmarketing surveillance data on more than 114,000 patients and more than 133,000 patient-years.<sup>11</sup>

The patients in the clinical trials were all adults with RA from North America and Europe who were treated with etanercept and evaluated every 3 to 4 months. The safety analyses include data on all patients (including those who discontinued treatment), and the efficacy analyses include data from trials allowing continuous treatment into an open-label protocol.

The rate of drug continuation—71%—among patients on etanercept is unprecedented in RA studies. The continuation rate for MTX, previously the most popular and effective treatment for RA, is approximately 50%. Of the 29% of patients who discontinued etanercept treatment, 9% dropped out because of adverse events. The most common, injection site reaction, was the only adverse event that occurred significantly more often in the treatment groups compared with the placebo groups in the clinical trials.

Respiratory disease, cough, and pharyngitis occurred more often in the

### FIGURE: MRI Before and After TNF Blockade



An MRI image (A) shows swelling both in front of and behind this patient's knee (note arrows). A repeat MRI (B) 1 week after administration of anti-TNF therapy shows marked reduction of swelling.

Source: Courtesy of Ferdinand C. Breedveld, MD, PhD

etanercept-treated patients, and although the differences between the treatment and control groups were not significant, the theoretical concern about an increased risk for infection exists with anti-TNF agents. However, it is important to note that there was no difference between the active-treatment and placebo groups in the rate of serious infections—that is, infections requiring hospitalization or intravenous antibiotics.

The rate of malignancies also was no higher in patients treated with etanercept. In fact, according to the National Cancer Institute (United States) Surveillance, Epidemiology, and End Results (SEER) database, the expected number of malignancies in the treat-

“In addition to demonstrated efficacy in RA, Crohn’s disease, PsA, and psoriasis, TNF may play a role in a variety of other diseases.”

ment population was 42, but only 41 cancers occurred. Five of these were lymphomas, which are particularly common cancers in patients with RA; this is a number that is similar to what is expected in a population of RA patients.

All-cause mortality among etanercept-treated patients in the clinical trials in the United States was 22 (5 deaths in patients with early RA and 17 among those with advanced disease). The expected mortality was 32.<sup>12</sup> (Eight deaths occurred among the patients with advanced RA in the European trials, but no expected mortality statistics are available.)

The postmarketing surveillance statistics have been gathered as part of an extensive program involving sponta-

neous reports of adverse events and reports directly from consumers via patient support and enrollment telephone contact. The accumulated long-term data indicate that etanercept is generally well tolerated. No cumulative toxicity has been seen with extended use, and the incidence of malignancy and serious infection is consistent with what is predicted in the literature.

## CONCLUSION

In addition to demonstrated efficacy in RA, Crohn’s disease, PsA, and psoriasis, TNF may play a role in a variety of other diseases, including those listed in the **Table**. With such a broad base of current and potential applications, it is essential that the safety as well as the efficacy of anti-TNF therapies continue to be carefully documented and reported. ■

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# NEW CONCEPTS IN THE MANAGEMENT OF PSORIATIC ARTHRITIS

Mark G. Lebwohl, MD

**P** soriatric arthritis (PsA) is an inflammatory, frequently seronegative, asymmetrical arthritis that often affects the spine, sacroiliac, and distal interphalangeal joints. The cause is not specifically known. Erosive disease can develop in up to 70%, and 24% of patients with PsA will develop joint deformities.

The treatments used traditionally for PsA are those typically used for rheumatoid arthritis, including non-steroidal antiinflammatory drugs, methotrexate (MTX), and cyclosporine. Many of these drugs are associated with toxicity if used long term. Corticosteroids and antimalarials also have been used to treat PsA, but both agents have been reported to exacerbate psoriasis and have been associated with the development of pustular and erythrodermic psoriasis in many patients.

Currently, the only agent approved by the U.S. Food and Drug Administration for the treatment of PsA is a tumor necrosis factor (TNF) inhibitor, the soluble fusion protein, etanercept. Two other biologic response modifying drugs, infliximab and anakinra, are currently being studied for use in patients with PsA. Both the chimeric monoclonal anti-TNF agent infliximab and the interleukin (IL)-1 inhibitor anakinra are currently approved for the treatment of rheumatoid arthritis.

TNF has been reported to be present in high concentrations in the synovial fluid and skin of patients with PsA, and the role of IL-1 in the inflammatory cascade continues to be studied (see "TNF Blockade for Psoriasis and Psoriatic Arthritis: Clinical Experiences," page 8).

## PHASE II STUDY

In a double-blind, placebo-controlled phase II clinical trial by Mease and col-

leagues,<sup>1</sup> 60 patients were randomly assigned to receive either etanercept, 25 mg twice weekly via subcutaneous injection (n = 30), or placebo (n = 30). After a 3-month double-blind phase, all patients were included in a 6-month open-label study.

The primary end points were improvement at 3 months on Psoriatic Arthritis Response Criteria (PsARC) and the American College of Rheumatology (ACR) response index. The PsARC consists of (1) improvement in at least two of four parameters (physician global assessment, patient global assessment, tender joint score, and swollen joint score); (2) improvement in at least one of two joint scores; and (3) no worsening in any criteria. The parameters assessed according to the ACR include joint swelling and tenderness, physician global assessment, patient global assessment, pain, erythrocyte sedimentation rate or C-reactive protein and a health assessment questionnaire. Efficacy according to ACR criteria is established by a 20% improvement in joint swelling and tenderness plus a 20% improvement in three of the other five items.

In the etanercept group, 26 patients (87%) achieved PsARC improvement versus 7 (23%) of those in the placebo group ( $P < 0.001$ ). Improvement of at least 20% in ACR (ACR 20) was achieved in 73% of etanercept-treated patients versus 13% of those in the placebo group ( $P < 0.001$ ). A 50% im-

provement in ACR (ACR 50) occurred in 50% of the active treatment group and in 3% of those in the control group ( $P < 0.001$ ). Thirteen percent of patients receiving etanercept achieved a 70% improvement in ACR (ACR 70); none of the patients in the placebo group achieved an ACR 70 response.

Improvements also were seen in skin disease among the subgroup of patients who had  $> 3\%$  body surface area (BSA) psoriatic involvement (the minimum BSA required for a valid assessment on the Psoriasis Area and Severity Index [PASI]). There were 19 patients in each group who qualified for PASI scoring. In 26% of those on etanercept, PASI improved by 75%; none of the patients in the placebo group achieved PASI 75 ( $P = 0.037$ ). The median improvement in PASI score was 46% in the etanercept-treated patients and 9% in the control group ( $P = 0.003$ ). The researchers reported a 50% median improvement in target lesions in the etanercept group and no target lesion improvement in the placebo group ( $P = 0.001$ ).

## PHASE II EXTENSION STUDY

Fifty-six of the original 60 patients continued after 3 months of treatment into the 6-month, open-label extension phase.<sup>2</sup> During this part of the trial, patients were permitted to reduce the dosages of any concomitant arthritis medications they were using. Among the patients who had originally been treated with etanercept, the added 6 months of treatment resulted in an additional 14% of patients who achieved ACR 20, for a total of 87% reaching this benchmark. In the blinded phase of this study, 13% of the placebo group achieved ACR 20; 61% achieved ACR 20 on 6 months of etanercept treatment.

Improvements in psoriasis were reflected in both PASI scores and target lesions. The median improvement in PASI scores was 62% in both groups (that is, those previously treated with etanercept and those who had been in the control group in the blinded phase of the study). Target lesions showed a median improvement of approximately 50% in both groups.

The mean dosage of MTX at baseline was 17.9 mg, and this was reduced to 12.0 mg ( $P = 0.001$ ) by the end of the open-label study. In addition, approximately 25% of patients were able to discontinue using MTX. The prednisone dosages also were significantly decreased, from a mean of 7.6 mg at baseline to a mean of 3.5 mg ( $P < 0.001$ ); 44% of patients were able to withdraw from systemic corticosteroids.

### PHASE III STUDY

The phase III trial of etanercept was a multicenter version of the phase II trial.<sup>3</sup> The phase III study was a 6-month, double-blind, randomized, placebo-controlled trial involving 17 sites and 205 patients. As in the previous study, etanercept (25 mg) or placebo was given subcutaneously twice weekly.

To qualify for enrollment, patients had to have active PsA with at least three swollen and tender joints, the presence of psoriasis, and no other inflammatory rheumatic diseases. The concomitant use of prednisone (up to 10 mg) and/or MTX (up to 25 mg) was permitted, if the drug dosages had been stable for 2 months prior to the beginning of the study. The primary end point was ACR 20 at 12 weeks. The other measures of arthritis activity, skin disease, and quality of life included ACR 20 at 6 months, ACR 50, ACR 70, target lesion response, PASI (in the 128 patients with at least 3% BSA skin involvement), and Health Assessment Questionnaire (HAQ) scores.

At 12 weeks, 59% of etanercept-treated patients achieved ACR 20, compared with 15% of the placebo group ( $P < 0.001$ ). The differences in ACR 50 and ACR 70 scores also were statistically significant ( $P < 0.001$ ), with 38% of the etanercept group achieving ACR 50 versus 4% of the placebo group, and 11% of the active-treatment group achieving ACR 70 versus 0% in the placebo group. At week 24, the ACR responses were comparable with what was seen at week 12.

In the patients using MTX, 62% in the etanercept group achieved ACR 20 at 12 weeks versus 19% in the control group ( $P = 0.001$ ). Among those who did not use MTX, 58% in the etanercept group achieved ACR 20 at 12 weeks versus 13% of patients in the placebo group ( $P = 0.001$ ).

The PsARC responses in the etanercept group were 56% (versus 24% in the placebo group) at 4 weeks, 72% (versus 31%) at 12 weeks, and 70% (versus 23%) at 24 weeks—all statistically significant differences ( $P = 0.001$ ). In addition, there were consistent and statistically significant improvements in measures of arthritis activity over the period from baseline to 12 weeks, including physician assessment, patient assessment, pain score, morning stiffness, and C-reactive protein. Marked improvement was seen on HAQ at week 12, with a 63% median change from baseline in the etanercept group versus no change in the placebo group ( $P = 0.001$ ). This improvement was maintained through week 24, with a 58% median change in HAQ at the end of the study in the active-treatment group versus no change in the placebo group ( $P = 0.001$ ).

The median improvement in PASI score was 47% in the etanercept group compared with 0% for placebo ( $P < 0.001$ ). The percentage of patients whose PASI score improved by 50% was 47% in the etanercept group (ver-

“...patients who received etanercept experienced a significant improvement in arthritis and psoriatic target lesions [compared with those who received placebo].”

sus 18% in the placebo group), and 23% of the etanercept-treated patients achieved a 75% reduction in PASI score (versus 3% of those in the placebo group,  $P = 0.001$ ).

In the etanercept group, the median percent improvement in target lesions was 33% in the treatment group, with 43% of these patients experiencing an improvement of 50% and 22% of patients achieving a 75% improvement.

### SAFETY

The adverse events that occurred in the etanercept group were virtually identical to those that occurred in the placebo group, except for injection site reactions. In the etanercept group, 36 patients reported injection site reactions versus 9 of those in the placebo group, a statistically significant difference ( $P < 0.001$ ).

### CONCLUSION

The results from phase III clinical studies examining the use of etanercept for the treatment of PsA demonstrate that patients with PsA who received etanercept experienced significant improvement in the signs and symptoms of their disease compared with placebo. Specifically, compared with patients who received placebo, patients who received etanercept experienced a significant improvement in arthritis and psoriatic target lesions. These studies show that etanercept represents a promising treatment for PsA, and demonstrate that TNF inhibitors may fill a considerable treatment gap for this group of patients. ■

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# TNF BLOCKADE FOR PSORIASIS AND PSORIATIC ARTHRITIS: CLINICAL EXPERIENCES

Nicholas J. Lowe, MD

Clinicians who manage patients with psoriasis and psoriatic arthritis (PsA) face a variety of challenges. It has been estimated that only 33% of patients with psoriasis are actively treated for their disease, despite the continued presence of symptoms.<sup>1</sup> Even patients who are receiving therapy may be undertreated because physicians are reluctant to prescribe more aggressive therapies to avoid what they perceive as an excess risk for side effects.<sup>2,3</sup> Further, limited experience with the use of some systemic treatments for psoriasis leads many dermatologists to refer such patients to regional centers specializing in this disease, meaning that many patients must travel, sometimes great distances, to receive treatment for their psoriasis.

The latest statistics on psoriasis indicate that up to 23% of patients with psoriasis develop PsA.<sup>4</sup> Although PsA usually develops within 10 years of the onset of psoriasis, PsA develops before the onset or diagnosis of skin disease in about 15% of patients.<sup>5</sup> Early diagnosis and treatment of PsA are critical, as irreversible damage and deformity can occur before either the physician or the patient is aware that the disease is progressing. Complicating the clinical picture is the fact that agents such as systemic corticosteroids and antimalarials used for the treatment of PsA may exacerbate skin disease.<sup>6</sup>

## RATIONALE FOR A NEW APPROACH TO THERAPY

The exact mechanisms involved in the pathogenesis of psoriasis and PsA are not yet clearly established but certainly are multifactorial. It is known that proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and other cytokines play an important role in both psoriasis and PsA.<sup>7</sup> Skin and synovial inflammation in pa-

tients with these conditions is characterized by elevated levels of TNF and IL-1.<sup>8,9</sup> Other key pathogenic aspects include activation of nuclear factor kappa B (leading to the release of cytokines and chemokines, recruitment of inflammatory cells, and collagen release and fibroblast proliferation),<sup>8-11</sup> as well as hyperplasia of the synovium in PsA<sup>12,13</sup> and of epidermal keratinocytes.<sup>14</sup> Recognition of these mechanisms has led to research into antagonists of what are the likely initial activators of the pathogenic processes, namely anti-TNF and anti-IL-1 compounds.

Patients with psoriasis and PsA report that the burden of disease is great, including significant reduction in work days, discrimination, depression, financial distress, and even decisions about the clothing they wear.<sup>2,3,15</sup> About 20% of the population of patients with psoriasis have disease that is categorized as moderate-to-severe or extremely severe—the same group that is most likely to also develop PsA.<sup>5</sup>

The traditional treatments for psoriasis, including topical therapy, systemic,

and phototherapy modalities, clearly do not meet patients' needs. These treatments often are inconvenient, may have limited efficacy, can have unacceptable toxicity, and, in all cases, treat only the symptoms of disease, not its cause. The first-line agents usually used for PsA are nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, and analgesics. The typical second-line agents are sulfasalazine and methotrexate, with corticosteroids used in a pulsed fashion to manage flare-ups. However, as noted above, many of these agents can exacerbate psoriatic skin lesions, and none is approved by the U.S. Food and Drug Administration for the treatment of PsA.

Because psoriasis and PsA appear to share a number of etiologic factors, principally involving proinflammatory cytokines such as TNF, the targeted therapies that have been developed as antagonists of TNF and IL-1 offer the possibility for safer and more effective management of patients with these diseases. Indeed, one TNF-inhibiting agent, etanercept, has been approved by the FDA for the treatment of PsA, the only drug approved for this indication to date. Etanercept shows promise in clinical trials for the management of psoriatic skin lesions as well.

## REPORT OF SIX CASES

In our practice, my colleagues and I used the TNF-inhibiting agent etanercept in six patients with severe psoriasis refractory to treatment with the usual modalities (in five cases, systemic therapy).<sup>16</sup> The patients ranged in age from 33 to 57 and included four men and two women. Three patients had PsA in addition to skin lesions. Prior to the addition of etanercept to their current treatment regimens, Psoriasis Area

Severity Index (PASI) scores were documented and routine blood chemistries were performed.

Improvements in skin lesions and arthritis were graded as major, moderate, mild, or none. Patients continued on their previous therapy until improvement was seen.

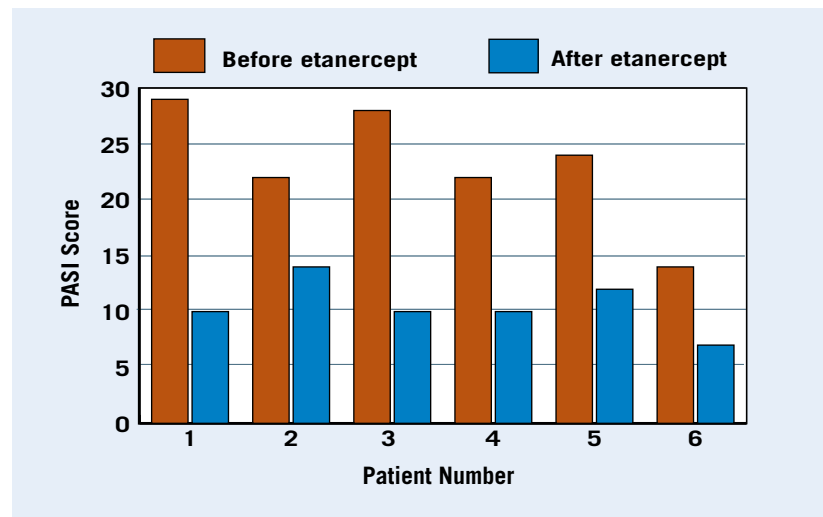
The PASI scores at baseline and at the time of maximum improvement (in most cases, at 8 weeks after the start of combination therapy with etanercept) are shown in the **Figure**. In addition, all three patients with PsA had a marked improvement in their arthritis following the introduction of etanercept, with two showing a major and one showing a moderate improvement.

The addition of etanercept to other therapies caused resistant disease to be more responsive to treatment. Further, once maximum improvement was achieved, inclusion of etanercept in the treatment regimen allowed patients to lower the dosages of the other drugs. As important, no added toxicity was found during etanercept treatment.

## CONCLUSION

There is a growing need for the development of newer medications for the

**FIGURE: PASI Scores Before and After Anti-TNF Therapy**



In a case series, the Psoriasis Area Severity Index (PASI) score in all six patients with severe, recalcitrant psoriasis improved when etanercept was added to their previous therapy. No increased toxicity was observed.

Source: Iyer S, et al.<sup>16</sup>

treatment of psoriasis. The anti-TNF medications are emerging as a potential class of therapy. In our experience with six cases, etanercept can be safely added to other systemic and topical agents to augment their efficacy in se-

vere, recalcitrant psoriasis and can play a role in reducing the short- and long-term toxicities of traditionally used treatments. ■

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# NEW DEVELOPMENTS IN THE TREATMENT OF MODERATE-TO-SEVERE PSORIASIS

Alice B. Gottlieb, MD, PhD

**P**сориаз is a disease that results in disability equal to that of other major diseases, including cancer, heart disease, and major depression.<sup>1</sup> Approximately 2 million patients in the United States have psoriasis that is classified as moderate to severe. According to a National Psoriasis Foundation survey, between 7% and 10% of patients between 18 and 54 years old say they have contemplated suicide.<sup>2</sup>

The economic burden also is great, with an estimated \$1.6 to \$3.2 billion spent each year on therapy in the United States. Despite such large expenditures, the currently available treatments are far from adequate, with shortcomings ranging from inconvenience to toxicity, and not least of all including the fact that none is curative. Although clearing of skin lesions can be accomplished with any of a variety of drugs, such as cyclosporine, toxicity limits long-term use of these medications. Therefore, for patients with moderate-to-severe psoriasis, specifically, the therapeutic challenge is to provide safe and effective long-term management of this life-impacting disorder.

Fortunately, research over the past decade has yielded the development of a new class of agents known collectively as biological response modifiers, which hold great promise for safe and effective long-term treatment of patients with psoriasis, as well as a range of other immune-mediated inflammatory diseases. Two of these are anti-tumor necrosis factor (TNF) agents, the fusion protein etanercept and the chimeric monoclonal antibody infliximab. The most recent addition to the list, anakinra, inhibits interleukin-1.

Etanercept, previously approved by the U.S. Food and Drug Administration for the treatment of patients with rheumatoid arthritis (RA) and juvenile RA, recently was approved for the ad-

ditional indication of psoriatic arthritis (PsA). It is the only drug approved for PsA at this time. Infliximab and anakinra, now approved for the treatment of rheumatoid arthritis, are being studied in PsA as well. (Infliximab is also approved for the treatment of Crohn's disease.) Meanwhile, a phase II trial of etanercept in psoriasis has been completed, and phase III studies are now under way.

## NEW UNDERSTANDING OF PSORIASIS PATHOGENESIS

Traditionally, psoriasis was considered to be a disease caused by abnormal keratinocytes; the infiltrate of lymphocytes observed in biopsies of psoriatic skin lesions was thought to be a secondary response. However, advances in immunology, together with the development of new systemic immunosuppressants, suggest that psoriasis is primarily an inflammatory disease.

TNF plays a prominent role in the cytokine cascade that contributes to the inflammatory response throughout the body. Notably, TNF is found in increased concentration in the areas affected by psoriasis, including the skin and synovium. TNF is produced by macrophages and other antigen-presenting cells, some synoviocytes, keratinocytes, and activated T cells. TNF potentially could contribute to the pathogenesis of psoriasis by increasing the synthesis of inflammatory cy-

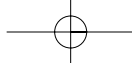
tokines, T-cell infiltration into the skin, angiogenesis, keratinocyte proliferation, and synthesis of acute-phase reactants by the liver.

This new understanding of the pathogenesis of psoriasis and of the role of the T cell in the disease process has led to the concept of TNF blockade as a treatment. The TNF-inhibitor etanercept is a fully human soluble fusion molecule that binds both free and cell-bound TNF. It is administered twice weekly as a subcutaneous injection. Etanercept has been approved for use as monotherapy, but also may be used with methotrexate. The remainder of this presentation will focus on the clinical trials of etanercept therapy in patients with psoriasis.

## EXPERIENCE WITH TNF BLOCKADE IN PSORIASIS

The requirements for enrollment in the 24-week phase II double-blind, placebo-controlled study<sup>3</sup> included stable plaque psoriasis with at least 10% body surface area involvement and previous use of at least one systemic therapy for psoriasis. Excluded from the study were patients with guttate, erythrodermic, or pustular psoriasis and those who had previously used etanercept or anti-TNF antibody therapy. Patients currently being treated with systemic therapy or psoralen plus ultraviolet A phototherapy were required to undergo a 4-week washout period prior to initiation of etanercept treatment. A 2-week washout period was required for those using topical medications.

Of the 112 patients eligible for the study, 57 were randomly assigned to receive etanercept, 25 mg subcutaneously twice weekly, and 55 were assigned to the placebo group. The primary end point was the proportion of patients achieving a 75% improvement in the



Psoriasis Area Severity Index (PASI) score at 12 weeks (**Table**, The PASI Score: A Review). Secondary end points included PASI scores at other time points; target lesion clearing; physician and patient global assessments; Dermatology Life Quality Index (DLQI), SF-36; and photographs and biopsies of selected sites.

### PASI SCORES

In the etanercept group, 70% of patients at week 12 achieved a 50% improvement in PASI (PASI 50), compared with 11% in the placebo group ( $P < 0.0001$ ). By the end of the study at week 24, 77% of those in the etanercept group had achieved PASI 50, compared with 13% in the placebo group ( $P < 0.0001$ ).

The primary end point, PASI 75 at week 12, was reached by 30% of etanercept-treated patients versus 2% of those in the placebo group ( $P < 0.0001$ ). At week 24, 56% of patients in the active treatment group had achieved PASI 75 versus 5% of those in the control group ( $P < 0.0001$ ).

A PASI 90 response was seen in 11% of the etanercept group at week 12 and in 21% at week 24; none of the patients in the placebo group had 90% improvement in PASI at week 12 or week 24 ( $P < 0.05$  and  $P = 0.0003$ , respectively).

### PHYSICIAN AND PATIENT GLOBAL EVALUATIONS

The differences between the active treatment and the control group also were significant when the secondary end point of lesion clearing was measured. In the etanercept group, 46% of patients were rated as clear or almost clear at week 12 versus 3% of those in the control group ( $P < 0.0001$ ). At week 24, 53% of etanercept-treated patients were clear or almost clear versus 5% of placebo-treated patients ( $P < 0.0001$ ). Interestingly, the patient global scores were comparable, with reported mean improvements of 58%

### Table: The PASI Score: A Review

The Psoriasis Area and Severity Index (PASI) is a standardized, well-accepted scoring method developed as an objective tool for use in clinical research. Efficacy of interventions typically are expressed as percent improvement in PASI score.

- ▶ Evaluations are performed by investigators.
- ▶ Anatomic regions are evaluated separately for erythema, induration, and scaling (EIS).
- ▶ EIS scores are weighted by fraction of region involved and contribution of that region to total body surface area involvement.
- ▶ Weighted region scores are added to give the total PASI.

and 62% in the etanercept group at weeks 12 and 24, respectively, versus 5% at week 12 and 4% at week 24 in the control group ( $P = 0.0002$  for both time points).

Improvement in the DLQI showed a statistically significant difference between the treatment and placebo groups as early as week 4, with 30% mean improvement from baseline versus 2% ( $P = 0.0011$ ). At week 8, the mean improvement over baseline was 60% in the active treatment group versus 5% in the placebo group ( $P < 0.0001$ ), and these

rates remained virtually unchanged throughout the remaining 16 weeks of the study.

### SAFETY

The incidence of side effects in the phase II study of etanercept in psoriasis was similar to what has been seen in other etanercept trials. The only statistically significant differences in adverse events between the etanercept and placebo groups occurred in the categories of infection (any) ( $P = 0.049$ ) and injection site reaction ( $P < 0.0001$ ). It is not possible to determine the importance of the slight increase seen in the rate of infections—for example, whether this represented a higher incidence of common colds. A formal database and analysis from a larger study will clarify this issue. Injection site re-

actions occurred in 9% of patients treated with etanercept and none of the patients in the placebo group. In all cases, the reactions were low grade, typically occurring about 2 weeks after the first treatment. No intervention was necessary, and in no case was an injection site reaction a cause for discontinuation of therapy.

### CONCLUSION

The clinical response to targeted TNF inhibition demonstrated in clinical trials of etanercept provides compelling evidence that TNF plays a role in the pathogenesis of psoriasis. Etanercept monotherapy achieved significant clinical improvement in clearing psoriasis, and the adverse event profile has been unremarkable. Patients continue to improve while on therapy. Two pivotal phase III trials are now in progress. ■

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"...new understanding of the pathogenesis of psoriasis and of the role of the T cell in the disease process has led to the concept of TNF blockade as a treatment."

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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.

- According to the latest statistics from the National Psoriasis Foundation, up to \_\_\_% of patients with psoriasis develop psoriatic arthritis.
  - 13%
  - 23%
  - 33%
  - 43%
- The group of patients with psoriasis who are most likely to develop psoriatic arthritis are those with:
  - a family history of psoriatic arthritis
  - long-standing disease
  - moderate-to-severe disease
  - skin lesions refractory to therapy
- The proinflammatory molecules that have been cloned and used as the basis for drug development for anti-tumor necrosis factor therapy are:
  - granulocyte colony-stimulating factor
  - matrix metalloproteinases
  - p55 and p75 receptors
  - vascular endothelial growth factor
- Three of the four items apply to the chimeric monoclonal antibody infliximab. Which one does not apply?
  - approved in the United States for treatment of Crohn's disease
  - median half-life of 9.5 days
  - lysis of tumor necrosis factor-expressing cells
  - subcutaneous administration
- Which one of the following does not produce tumor necrosis factor?
  - activated T cells
  - intracellular adhesion molecules
  - keratinocytes
  - synoviocytes
- In the phase II study of etanercept in psoriasis by Gottlieb and colleagues, \_\_\_% of patients in the active-treatment group achieved the primary end point, a 75% reduction in Psoriasis Area Severity Index (PASI) at week 12, versus 2% of patients in the control group.
  - 20%
  - 30%
  - 40%
  - 50%
- Which of the following statements concerning concomitant use of etanercept and methotrexate in patients with psoriasis and psoriatic arthritis is true?
  - concomitant use has made a dramatic difference in target lesion response in clinical trials
  - concomitant use has resulted in increased risk for toxicity in clinical trials
  - the drugs are approved by the U.S. Food and Drug Administration for concomitant use
  - the drugs should not be used concomitantly
- Compared with a 31% response according to Psoriatic Arthritis Response Criteria (PsARC) in the control group, \_\_\_% of patients who received etanercept in the phase III clinical trial reported by Mease and colleagues showed PsARC responses by week 4.
  - 42%
  - 52%
  - 62%
  - 72%

**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 \_\_\_\_\_ Email \_\_\_\_\_

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

	Excellent	Good	Fair	Poor
Text	_____	_____	_____	_____
Photographic Images	_____	_____	_____	_____
Post-Test	_____	_____	_____	_____
- How would you rate the clinical relevance of the material?  
 \_\_\_\_\_
- How would you rate this material compared with similar independent study presentations in print format?  
 \_\_\_\_\_

- Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.  
 \_\_\_\_\_  
 \_\_\_\_\_
- 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).  
 \_\_\_\_\_
- What topics would you find useful for future programs?  
 \_\_\_\_\_  
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- Other comments:  
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