



A Supplement to

Skin & Allergy News®

THE EMERGING ROLE OF TNF INHIBITION IN PSORIASIS AND PSORIATIC ARTHRITIS

TNF INHIBITORS IN THE TREATMENT OF PSORIATIC ARTHRITIS: RESULTS FROM CLINICAL TRIALS

Alice B. Gottlieb, MD, PhD

University of Medicine and Dentistry
of New Jersey
Robert Wood Johnson Medical School
New Brunswick

THE ROLE OF TNF INHIBITION IN THE TREATMENT OF PSORIASIS

Mark G. Lebwohl, MD

Mount Sinai School of Medicine, New York

EXPERIENCE WITH TNF INHIBITORS: FIVE YEARS OF USE IN RHEUMATIC DISEASE

Marc D. Cohen, MD

Mayo Medical School, Jacksonville, Fla.

IMMUNOBIOLOGY OF PSORIASIS AND PATHOGENIC ROLES FOR TNF

James G. Krueger, MD, PhD

Rockefeller University School of Medicine
New York



Accredited for Dermatologists

Skin & Allergy News®

GENERAL MANAGER

Alan J. Imhoff

VICE PRESIDENT, MARKETING & BUSINESS DEVELOPMENT

Sylvia H. Reitman

MANAGER, MEDICAL EDUCATION

Jenny R. McMahon

CLINICAL EDITOR

Joanne M. Still

NATIONAL ACCOUNT MANAGER

Cheryl J. Gromann

COPY EDITOR

Megan Henley Kinney

GRAPHIC DESIGN

Louise A. Lynch

PRODUCTION SPECIALIST

Rebecca Slebodnik

The articles in this supplement were developed through physician interviews and from a continuing medical education satellite symposium held on August 1, 2002, in New York.

This supplement to SKIN & ALLERGY NEWS, designated by the American Academy of Dermatology (AAD) for AAD CME credit, was supported by an unrestricted educational grant from

Wyeth®

AMGEN®

It was produced by the medical education and business development department of International Medical News Group. Neither the Editor of SKIN & ALLERGY NEWS nor the reporting staff contributed to its contents.

Copyright 2002 International Medical News Group, an Elsevier Science company. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without prior written permission of the Publisher. The opinions expressed in this supplement are those of the presenters and do not necessarily reflect the views of the supporter or the Publisher. International Medical News Group will not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to the products, drugs, or services mentioned herein.

Cover photo, lower right, © Arthritis Foundation, upper left, courtesy of Mark G. Lebwohl, MD.

THE EMERGING ROLE OF TNF INHIBITION IN PSORIASIS AND PSORIATIC ARTHRITIS

3 TNF INHIBITORS IN THE TREATMENT OF PSORIATIC ARTHRITIS: RESULTS FROM CLINICAL TRIALS

Alice B. Gottlieb, MD, PhD

5 THE ROLE OF TNF INHIBITION IN THE TREATMENT OF PSORIASIS

Mark G. Lebwohl, MD

7 EXPERIENCE WITH TNF INHIBITORS: FIVE YEARS OF USE IN RHEUMATIC DISEASE

Marc D. Cohen, MD

9 IMMUNOBIOLOGY OF PSORIASIS AND PATHOGENIC ROLES FOR TNF

James G. Krueger, MD, PhD

12 CME POST-TEST AND EVALUATION

FACULTY

MARC D. COHEN, MD

Professor of Medicine
Mayo Medical School
Chairman, Division of Rheumatology
Department of Internal Medicine
Mayo Clinic, Jacksonville, Fla.

ALICE B. GOTTLIEB, MD, PHD

W.H. Conzen Chair in Clinical Pharmacology
Professor of Medicine
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick

JAMES G. KRUEGER, MD, PHD

Associate Professor
Medical Director
Laboratory for Investigative Dermatology
Rockefeller University
New York

MARK G. LEBWOHL, MD

Professor and Chairman
Department of Dermatology
Mount Sinai School of Medicine
New York

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.

Term of approval: August 2002-August 2003.

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

This activity is designed to fulfill the growing need among dermatologists to understand the potential role of TNF inhibitors in the treatment of psoriatic arthritis and psoriasis. The activity focuses on a variety of issues relative to this topic, including the role of TNF in the pathophysiology of psoriasis and psoriatic arthritis, experience with TNF inhibitors in rheumatic diseases, and findings of phase II and phase III studies of etanercept for psoriatic arthritis and psoriasis.

LEARNING OBJECTIVES

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

- Understand how experience with TNF inhibitors in the rheumatology setting influences the use of etanercept in dermatology.
- Explain the rationale for TNF inhibition in the treatment of patients with immune-mediated inflammatory diseases such as psoriatic arthritis and psoriasis.
- Discuss the 5-year experience with efficacy and safety of TNF inhibitors in patients with rheumatic disease.
- Describe current concepts on the role of TNF in the pathophysiology of psoriasis and psoriatic arthritis.

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. Cohen has received research grants from Amgen Inc., Centocor Inc., and Wyeth, and is a consultant to Centocor, Amgen, Merck & Co., Pharmacia Corp., Pfizer Inc., and Wyeth. **Dr. Gottlieb** has received clinical grants and is a consultant to Wyeth and Amgen. She discusses the unlabeled and investigational use of etanercept for psoriasis. **Dr. Krueger** has nothing to disclose.

Dr. Lebwohl has received clinical grants and is a consultant to Wyeth. He discusses the unlabeled and investigational use of etanercept for psoriasis.

TNF INHIBITORS IN THE TREATMENT OF PSORIATIC ARTHRITIS: RESULTS FROM CLINICAL TRIALS

ALICE B. GOTTLIEB, MD, PHD

Psoriatic arthritis (PsA) has a significant impact on the lives of patients. According to the results of the recent Benchmark Survey for Psoriatic Arthritis, conducted under the auspices of the National Psoriasis Foundation,¹ 84% of patients with PsA say their day-to-day activities are severely affected, 75% lose sleep or do not have restful sleep, and 69% say that their PsA is severe enough to interfere with their educational, vocational, and social activities.

ROLE OF THE DERMATOLOGIST IN TREATING PSA

Most patients with PsA can be diagnosed and treated by dermatologists. Indeed, all dermatologists should be aware of, and vigilant for, arthritic signs and symptoms in patients who have been diagnosed with or who may have PsA.

On taking a history, the dermatologist should ask patients about morning stiffness, persistent joint pain or other arthritic symptoms, fluctuation of joint pain with exacerbations of psoriasis, and a family history of PsA. On physical examination, clinicians should evaluate such patients for asymmetric inflammatory arthritis, the presence of dactylitis (the so-called sausage digits), enthesitis, involvement of both proximal and distal interphalangeal joints, and joint swelling and/or tenderness.

The traditional therapies for psoriatic arthritis include, in addition to non-steroidal antiinflammatory drugs (NSAIDs), medications with which many dermatologists are familiar, such as methotrexate, cyclosporine, and oral corticosteroids. Many of these medications are associated with serious toxicity involving major organs.

TNF-INHIBITION OFFERS NEW ALTERNATIVE

The inhibition of tumor necrosis factor (TNF) represents an innovative biologic approach to the treatment of a variety of immune-mediated inflammatory diseases, including rheumatoid arthritis (RA), Crohn's disease, and psoriatic

arthritis (PsA). Recently, the TNF inhibitor etanercept, previously approved by the U.S. Food and Drug Administration for the treatment of RA and juvenile RA, became the first agent approved for the treatment of PsA.

Etanercept is approved for use with or without methotrexate (MTX), and is administered subcutaneously twice weekly.

Etanercept is a fusion protein that consists of a dimer of a TNF receptor chain, specifically, the human p75 chain, fused by biotechnologic techniques with the Fc genome of human immuno-

globulin G:1. Etanercept, like the chimeric antibody TNF inhibitor infliximab, removes circulating TNF with a spongelike activity and binds to TNF on the cells that produce this protein.

DOCUMENTATION OF EFFICACY IN PSA

The phase III trial of etanercept was a 24-week randomized, double-blind placebo-controlled study, in which either etanercept (25 mg) or placebo was given subcutaneously twice a week.² A total of 205 patients were enrolled, with 101 assigned to the etanercept group and 104 to the placebo group. The design and methods were similar to those in the clinical studies for etanercept in patients with rheumatoid arthritis.

Enrollment criteria for the PsA study included the presence of a cutaneous psoriasis plaque, at least three swollen and tender joints, and a clinical diagnosis of PsA. The primary end point was the achievement of a 20% improvement in the American College of Rheu-

FIGURE: Hand with Psoriatic Arthritis



Onset of psoriatic arthritis (PsA) usually occurs in patients between 30 and 55 years of age. In 70% of cases, skin psoriasis precedes articular involvement, usually by at least 10 years. In 20% of cases, PsA precedes psoriasis, and in 10% - 15% of cases, skin lesions and PsA appear simultaneously. These photos demonstrate the classic deformities seen in PsA.

© American College of Rheumatology

matology Index (Table) at 12 weeks.

Patients were permitted to use up to 25 mg/week of MTX, low-dose corticosteroids (up to 10 mg/day), and/or nonsteroidal antiinflammatory drugs (NSAIDs). No other concomitant therapy was permitted. At the time of enrollment, about 50% of patients in both the active treatment and placebo groups were taking MTX, about 20% were on systemic corticosteroids, and about 80% were using NSAIDs.

EFFICACY ACHIEVED

Although ACR 20 was the primary end point and its achievement was sufficient to qualify etanercept for approval by the FDA, the drug exceeded these expectations. At week 12, 59% of the patients ($n = 60$) who were receiving etanercept achieved ACR 20, compared with 15% of those ($n = 16$) in the placebo group ($P < 0.001$). By week 24, 50% of patients in the etanercept group met the ACR 20 criteria, compared with 13% of the control group ($P < 0.0001$).

The results of the assessments at 12 and 24 weeks provide an indication concerning duration of a trial of therapy. In the phase III study, the therapeutic response to etanercept at 24 weeks was not significantly better than the response at 12 weeks. Thus, for an individual patient with PsA, if the response is clinically acceptable and the patient is satisfied with the results at 12 weeks, it is reasonable to continue for a full course of treatment. If the response is not satisfactory at 12 weeks, an additional 3 months of treatment may not make a significant clinical difference.

When more stringent criteria of efficacy were applied, the results in the etanercept group were still significantly better. At week 24, 38% of patients in the etanercept group met the criteria for ACR 50, versus 4% of patients in the control group ($P < 0.0001$). Nine percent of patients in the etanercept group achieved 70% improvement on the ACR index, versus 1% of patients in the placebo group at week 24 ($P = 0.009$).

The use of MTX made no difference in response. A comparison of the subset of MTX users showed 38% of patients who used MTX achieved ACR 50

TABLE: Understanding the ACR Response Index

To provide a consistent method of documenting the efficacy of interventions for rheumatologic diseases, the American College of Rheumatology developed a composite response index, most commonly known as the ACR.

The parameters that are assessed in the ACR index are:

- Joint swelling
- Joint tenderness
- Patient's global assessment
- Physician's global assessment
- Pain (as measured on a visual analog scale)
- Erythrocyte sedimentation rate or C-reactive protein
- Health assessment questionnaire

In rheumatology clinical studies, efficacy is established by achievement of at least 20% improvement in the first two parameters (joint swelling and tenderness) plus at least a 20% improvement in three of the other five items. Such a result is referred to as ACR 20.

Greater improvement—50% or 70% improvement in these parameters—is referred to as ACR 50 or ACR 70, respectively.

at week 24 versus 36% of patients who did not use MTX.

The quality-of-life improvement as documented on the Health Assessment Questionnaire (HAQ) was significantly better in the etanercept group. At 24 weeks, compared with baseline scores, 50% of patients in the etanercept group had an improvement in HAQ score of ≥ 0.5 versus 14% of placebo-treated patients ($P < 0.001$). HAQ improvements of ≥ 1.0 were seen in 23% of etanercept-treated patients versus 5% of those in the placebo group ($P < 0.001$).

IMPROVEMENT IN PSORIATIC SKIN DISEASE

In the subset of patients with psoriatic skin involvement of at least 3% of body surface area, improvements in the Psoriasis Area Severity Index (PASI) were assessed. The improvements from baseline were significantly better in the etanercept group. At week 24, the improvement in PASI 75 (that is, an improvement of 75% or better in psoriatic lesions) in the etanercept group was 23% versus 3% in the control group ($P = 0.001$). At that same point, the

PASI 50 (or 50% improvement in PASI) was 47% in the etanercept group versus 18% in the control group ($P < 0.001$).

SAFETY CONFIRMED IN PHASE III TRIAL

In the etanercept group, injection site reactions were the only adverse event reported more frequently than in the placebo group (36% versus 9%, respectively). No deaths were reported, no infections occurred that required hospitalization or administration of intravenous antibiotics, and there was no increase in the rate of malignancy. Finally, no significant laboratory abnormalities were associated with the use of etanercept, and no antibodies to etanercept were detected. ■

REFERENCES

1. Benchmark Survey for Psoriatic Arthritis. Portland, Ore.: National Psoriasis Foundation; 2002.
2. Mease PJ, 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. *Arthritis Rheum.* 2001;44(suppl):S90.

THE ROLE OF TNF INHIBITION IN THE TREATMENT OF PSORIASIS

MARK G. LEBWOHL, MD

Approximately 7 million individuals in the United States are affected by psoriasis. Although some develop the disease at birth and others have an onset of psoriasis as late as the ninth decade of life, most patients experience onset of psoriasis in the third decade, with an average age of onset of 28 years.¹

An estimated 150,000 to 260,000 new cases of psoriasis are diagnosed each year in the U.S.¹ Despite annual costs to treat outpatients of between \$1.6 and \$3.2 billion,¹ and despite the fact that psoriasis is every bit as disabling as other major diseases (including hypertension, heart disease, diabetes, and depression),² about half of all patients with psoriasis are not adequately treated.¹

The systemic treatments, phototherapies, and topical drugs used to treat psoriasis have limitations that are well known to dermatologists and patients alike, including the most serious, toxicity to major organs. The advent of tumor necrosis factor (TNF) inhibitors offers these patients a new way of treating psoriasis and the associated complication psoriatic arthritis (PsA). The anti-TNF agent etanercept is the first treatment approved by the U.S. Food and Drug Administration for therapy in patients with PsA. The clinical trials in PsA indicated that etanercept was also beneficial in reducing psoriatic skin lesions.

Etanercept and other TNF-inhibiting agents offer a promising new treatment option for difficult-to-treat patients with generalized psoriasis, an option that has safety advantages over many of the other treatments that are available.

PHASE II TRIAL IN PSORIASIS

A double-blind, placebo-controlled phase II trial³ of etanercept as monotherapy for psoriasis was conducted involving a total of 112 patients with a mean duration of psoriasis in excess of 20 years. Fifty-seven patients were randomly assigned to receive etanercept, 25 mg twice weekly for 24 weeks; 55 patients received placebo injections. Prior to randomization to

their treatment groups, all patients underwent a 4-week washout of other system and phototherapy treatments for psoriasis, and a 2-week washout of topical medications. Involvement of at least 10% of body surface area was a requirement for enrollment. (Interestingly, the incidence of PsA was 28% in the etanercept group and 35% in the placebo group, confirming data from Gladman⁴ and others that the incidence of PsA in

patients with moderate to severe skin disease is quite high.)

The primary end point was a 75% reduction in Psoriasis Area Severity Index (PASI 75) at 12 weeks. Secondary end points included PASI determinations at other time points; clearing of the target lesion; physician and patient global assessments; scores on a health assessment questionnaire, the Dermatology Life Quality Index (DLQI), as well as scores on the Short Form SF-36 General Health Questionnaire; and photographs and biopsies from selected sites.

OVERVIEW OF EFFICACY RESULTS

Thirty percent of patients in the etanercept group achieved PASI 75 at week 12 versus 2% of those in the placebo group. At 24 weeks, 56% of those taking etanercept had achieved PASI 75 versus 5% of patients taking placebo. Of note is the fact that the PASI 75 is a standard equal to a 70% improvement on the American College of Rheumatology response index (ACR 70), and the demonstrated efficacy for approval of rheumatology drugs is the modest

FIGURE 1: Improvement in Psoriasis



In the phase II trial of etanercept in psoriasis, 56% of patients on etanercept achieved at least a 75% improvement in Psoriasis Area Severity Index at week 24. To illustrate the clinical implications of such an improvement, the photos above show one patient's arm lesions at baseline (left) and after 24 weeks of treatment (right). This patient's PASI improvement was 87%.

Gottlieb AB, et al. Poster presented at: AAD, 2002.

ACR 20 (for an explanation of the ACR response index, see the table on page 4).

Seventy-percent of patients in the etanercept group achieved PASI 50 (that is, a 50% improvement in the PASI score) at week 12 versus 11% of those in the placebo group. At week 24, 77% of etanercept-treated patients achieved PASI 50 compared with 13% of those in the placebo group.

According to the physicians' global evaluation of psoriasis—that is, the percentage of patients whose psoriasis was judged to be clear or almost clear—45% of patients who received etanercept were clear or almost clear at week 12 versus less than 5% of those in the placebo group. At week 24, the results were similar. More than 50% of patients in the etanercept group were clear or almost clear by the end of the study, versus < 5% of placebo-treated patients.

The mean improvement in the DLQI was 60% in the etanercept group versus 10% in the placebo group.

GOOD SAFETY PROFILE

A small increase in the number of infections occurred in the etanercept group versus the placebo-treated patients, although the source of these infections has not yet been established. It may be that these represent upper respiratory infections.

Low-grade injection site reactions occurred in 9% of patients in the etanercept group; there were no such reactions in the placebo group. These reactions resolved spontaneously within a few days and in no case required treatment or drug discontinuation.

No laboratory test abnormalities were noted, and no opportunistic infections occurred in any of the study subjects.

TNF INHIBITION: POTENTIAL FUTURE APPLICATIONS

Although the phase II study of etanercept

FIGURE 2: Self-Administration of Subcutaneous Drugs

Experience from clinical trials with a self-administered subcutaneous injection of an anti-TNF agent showed that most patients learn the technique in one teaching session. Audiovisual, print, and other training materials are available to support hands-on teaching so that patients quickly acquire the necessary skill.



in psoriasis was a monotherapy trial, etanercept can be used with methotrexate if clinical indications warrant combination therapy. Etanercept can be added to a methotrexate regimen very safely, and the methotrexate dosage adjusted downward based on clinical response.

Dermatologists should also be aware that etanercept has applications in other dermatologic conditions. To date it has been studied in Behçet's disease, cicatricial pemphigoid, graft-versus-host disease, and Sjögren's syndrome. Etanercept is likely to become an important part of our armamentarium for a wide range of diseases and conditions.

SUBCUTANEOUS DRUG ADMINISTRATION

With the introduction into dermatology of subcutaneously administered drugs such as etanercept comes the challenge to our specialty to incorporate education about self-administration of these injections into our practices.

Our experience with etanercept clinical trials shows that teaching this skill is far easier than one might imagine. In fact, most patients required only one demonstration session to acquire the ability to self-inject the drug. Furthermore, industry-supported audiovisual, print, and other training materials and assistance are available to physicians and patients (Figure 2).

CONCLUSION

It is clear from clinical experience that new therapies for psoriasis are needed to improve the quality of life for millions of patients. In the past decade, it has become apparent that TNF plays a significant role in the immunopathology of psoriasis. The phase II trials involving TNF-inhibiting biologic agents demonstrate that use of such drugs results in marked improvements in both primary and secondary measures of disease.

In the 5-year experience of the use of TNF inhibitors in patients with rheumatoid arthritis, these drugs have been shown to be safe and well tolerated. To date, they appear to be well tolerated in patients with psoriasis. Nevertheless, TNF inhibitors have distinct differences and similarities, and further studies are needed in patients with psoriasis to confirm the efficacy and safety of these drugs in this patient population. ■

REFERENCES

1. National Psoriasis Foundation Statistics, 2002.
2. Rapp SR, Feldman Sr, Exum ML, Fleischer AB Jr, Reboussin DM. *J Am Acad Dermatol.* 1999;41:401-407.
3. Gottlieb AB, Lowe N, Matheson R, Lebsack ME. Poster presented at American Academy of Dermatology annual meeting, August 2002.
4. Gladman DD. Psoriatic arthritis. *Rheum Dis Clin North Am.* 1998;24:829-844.

EXPERIENCE WITH TNF INHIBITORS: FIVE YEARS OF USE IN RHEUMATIC DISEASE

MARC D. COHEN, MD

The impetus for the development of a new approach to the treatment of rheumatoid arthritis (RA) was the need for a modality that would yield long-term efficacy, not only in the control of symptoms, but also in the inhibition of other markers of disease progression, including radiographic progression. The novel biologic agents that inhibit the inflammatory cytokine tumor necrosis factor (TNF) have radically altered the expectations of both rheumatologists and patients with RA.

Long-term safety and efficacy data from clinical trials in patients with RA have demonstrated that these agents, etanercept and infliximab, are both effective and well tolerated, presenting patients with RA an alternative to agents such as corticosteroids and methotrexate (MTX). Unlike the experience with these and other traditional disease-modifying antirheumatic drugs (DMARDs), no major organ toxicity has been reported to date with the use of TNF inhibitors.

Recently, one of these agents, etaner-

cept, was approved by the U.S. Food and Drug Administration for the treatment of psoriatic arthritis (PsA). It is currently the only approved treatment for PsA. Dermatologists who will be using etanercept and other TNF-inhibiting agents in their patients with PsA should be familiar with the long-term safety data accumulated to date.

DEMONSTRATED EFFICACY

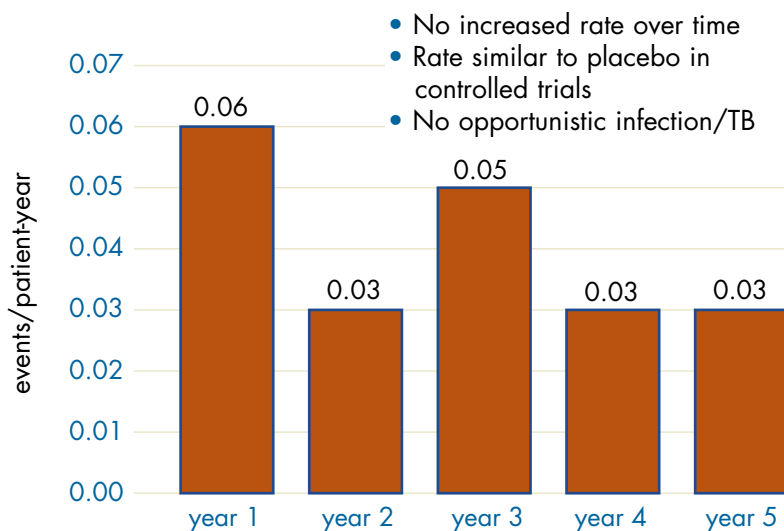
Moreland et al¹ published the findings from one of the first clinical trials con-

ducted on etanercept. In this double-blind, placebo-controlled study, etanercept was given to 234 patients with active RA who were refractory to traditional DMARDs (such as non-steroidal antiinflammatory drugs, corticosteroids, MTX, cyclosporine, intramuscular gold, and sulfasalazine). The mean duration of disease was 11-13 years. The primary end points were 20% and 50% improvement in disease activity, according to American College of Rheumatology responses (ACR 20 and ACR 50, respectively), at 3 and 6 months. Particularly given the longstanding and refractory nature of the disease in the subjects in this trial, the results of this study were impressive: At 6 months, 59% of the patients who received 25 mg of etanercept twice weekly achieved an ACR 20 response, 40% achieved an ACR 50, and 15% achieved an ACR 70.

This group of patients, pooled with others who have been receiving etanercept for RA, continues to be studied over time in an ongoing, open-label study of safety and efficacy. Data from 1,960 patients, representing 4,343 patient-years of experience over a period of up to 5 years, have been published so far.² The results show that the response seen at 6 months has been sustained.

In a double-blind study of 89 patients who still had active RA despite using MTX for at least 6 months, Weinblatt and colleagues³ further demonstrated the efficacy of etanercept and also showed that the use of etanercept reduced the use of both MTX and corticosteroids. In this study, patients were randomly selected (in a 2:1 randomization scheme) to receive either etanercept plus MTX (59 patients) or placebo plus MTX (30 patients). At 6 months, 71% of patients in the combination-therapy group achieved ACR 20, versus 27% of those who received placebo plus MTX ($P < 0.001$). In the combination-therapy group, 39% achieved ACR 50 (ver-

**FIGURE: Etanercept Monotherapy Extended Observation:
No Change in Serious Infection Rate**



Source: Klareskog L et al²

sus 3% of the placebo/MTX group, $P < 0.001$), and 15% achieved ACR 70 (versus 0% of the placebo/MTX group, $P = 0.03$).

At the end of 6 months, 79% of these patients continued in an open-label extension study,⁴ and subjects were permitted to reduce their use of MTX and corticosteroids. The data on a median of 26 months (maximum of 34 months) show that 54 patients (68%) were able to decrease their use of MTX by a mean of 62% and 23 (29%) discontinued taking MTX. Thirty-one (69%) of the 45 patients who had been using corticosteroids were able to reduce their use of these agents by a mean of 77%, and 19 (42%) discontinued taking corticosteroids.

SAFETY: NO INCREASED RISK FOR SIDE EFFECTS SHOWN

The accumulated evidence from the controlled trials reported to date—up to 60 months of experience—shows that there is no statistically significant difference between etanercept- and placebo-treated patients in the incidence of infections, including upper respiratory infections.² Further, no cases of either tuberculosis or opportunistic infections were seen in any patients in any of the clinical trials of etanercept (Figure on page 7).² In ongoing surveillance data, a few cases of tuberculosis have been reported.⁵

The accumulated data show that etanercept has not yet been associated with any statistical increased risk for malignancy.

In the Early Rheumatoid Arthritis (ERA) trial,⁶ a double-blind study comparing etanercept with MTX in patients with the early stages of RA, 632 MTX-naive patients were randomized to receive either weekly oral MTX alone or subcutaneous injections of 10 or 25 mg of etanercept twice weekly for 12 months. In the blinded phase of this study (which also had an open-label extension phase to further assess efficacy), the patients taking 25 mg of etanercept had significantly fewer adverse events ($P = 0.02$) and infections ($P = 0.006$) than did those using MTX. Safety data from the end of the third year of the ERA trial, which included 2 years of open-label phase data, were similar to those reported at the end of the blinded phase of the study. There were no increases in the rates of malignancies or significant infections associated with parenteral antibiotics or hospitalization.

INFLIXIMAB IN RA

The efficacy and safety of infliximab, the chimeric antibody TNF inhibitor, were established in the 54-week phase III study known as the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT).^{7,8} In this study, 428 patients who had active, long-standing RA despite treatment with an average of three DMARDs were randomized to one of five groups: infliximab/MTX, 3 mg/kg every 4 weeks ($n = 86$); infliximab/MTX, 3 mg/kg every 8 weeks ($n = 86$); infliximab/MTX, 10 mg/kg every 4 weeks ($n = 81$); infliximab/MTX,

10 mg/kg every 8 weeks ($n = 87$); or placebo infusion plus MTX ($n = 88$).

Patients who received infliximab plus MTX (with all regimens and at all doses) did significantly better in achieving ACR 20 than did those on MTX alone ($P < 0.001$ for all infliximab groups). Further, in the treated groups, impressive reductions were seen in joint swelling and tenderness, and radiographic progression of disease was significantly reduced compared with MTX monotherapy ($P < 0.001$).

To date, the accumulated evidence indicates that infliximab is generally safe and well tolerated. However, it is important to note that some patients using infliximab have developed tuberculosis (TB), invasive fungal infections, and other opportunistic infections. The package insert for infliximab states that a purified protein derivative (PPD) tuberculin test should be performed to evaluate all patients for latent TB infections before starting treatment.

CONCLUSION

Sufficient experience has not yet accrued to allow a determination of whether the efficacy results seen to date with TNF inhibitors are sustainable; the data thus far are promising. Further, the biologic agents have a rapid onset of action and are well tolerated, with a favorable side effect profile. Here, again, long-term data are not yet available, but the clinical studies completed to date have demonstrated good tolerance and no evidence of major organ toxicity. ■

REFERENCES

1. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med.* 1999;130:478-486.
2. 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.
3. Weinblatt ME, Kremer KM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med.* 1999;340:253-259.
4. Kremer JM, Weinblatt ME, Fleischmann RM, Bankhurst AD, Burge DJ. Etanercept (Enbrel) in addition to methotrexate (MTX) in rheumatoid arthritis (RA): Long-term observations. Abstract #152. Presented at the American College of Rheumatology 65th Annual Scientific Meeting, San Francisco, November 2001.
5. Wallis WJ, Burge DJ, Sabath D, Gardiner M. Tuberculosis reports with etanercept (Enbrel) therapy. Abstract #153. Presented at the American College of Rheumatology 65th Annual Scientific Meeting, San Francisco, November 2001.
6. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586-1593.
7. Lipsky PE, van der Heijde DM, St. Clair EM, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med.* 2000;343:1594-1602.
8. Data on file, Centocor, Inc., Malvern, Pa.

IMMUNOBIOLOGY OF PSORIASIS AND PATHOGENIC ROLES FOR TNF

JAMES G. KRUEGER, MD, PHD

The discovery of tumor necrosis factor (TNF) and the development of the current knowledge about this protein began with the observation that a factor circulating in the blood of mice infected with a mycobacteria species could be induced to cause cell death. This factor was called TNF because its administration caused in vivo hemorrhagic necrosis of tumor cells. TNF is the founding cytokine for a superfamily of proteins that includes approximately 18 ligands and 26 receptors, all related by structure.

In general, the roles of these proteins include three functions: the regulation of acute inflammation, the regulation of cell-mediated immunity, or the induction of cell death in various settings. It is important to note that these functions are not always separable, and one protein may have biologic activity in all three areas, depending on the context.

Studies were performed on cytokine cascades in sepsis, in which the response to a lipopolysaccharide (LPS) challenge was explored.¹ It was determined that circulating levels of three so-called acute phase proteins—TNF, interleukin-1 (IL-1), and IL-6—increase dramatically beginning within 15 minutes after LPS administration. This cytokine cascade begins with TNF, with circulating levels of TNF peaking at about 30 minutes, while IL-6 peaks between 3.5 and 4 hours. Induction of these acute phase proteins may be followed by local inflammation, fever, shock, vascular collapse, and death.

An acute inflammatory reaction also includes neutrophil trafficking into sites where TNF is expressed as a result of induction of adhesion molecules (Figure 1). TNF is considered to be the master regulator of the sepsis cascade, as administration of TNF will produce all “downstream” inflammatory events as described for LPS (Figure 2 on page 10).

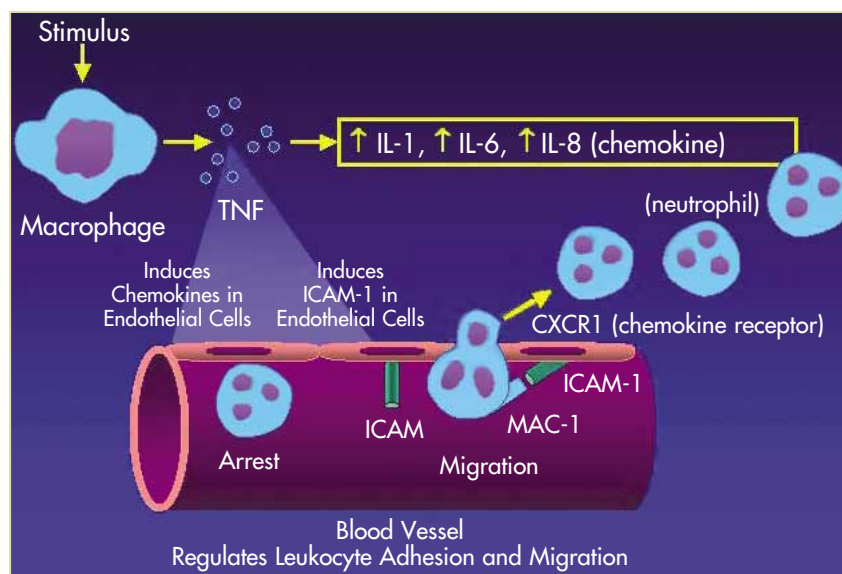
ROLE OF TNF IN JOINT DESTRUCTION AND PLAQUE FORMATION

The hypothesis that this innate immune response also might play a role in chronic inflammation was based on the un-

derstanding of cytokine activation in response to sepsis and the role of TNF in acute injury. In RA, type 1 T cells or circulating immune complexes trigger macrophages to release TNF, which then induces other cytokines such as IL-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor, all of which are known to be increased in joint fluid in patients with RA. Elaboration of these proinflammatory cytokines causes further proliferation and inflammation in the synovium.

In both RA and PsA, degradation of joints, development of pain and other signs and symptoms, and loss of articular function result when cartilage is eroded. Destruction of collagen in joints in patients with these diseases is largely the result of the activity of matrix metalloproteinases (MMPs) which, in turn,

FIGURE 1: TNF in Innate Immunity

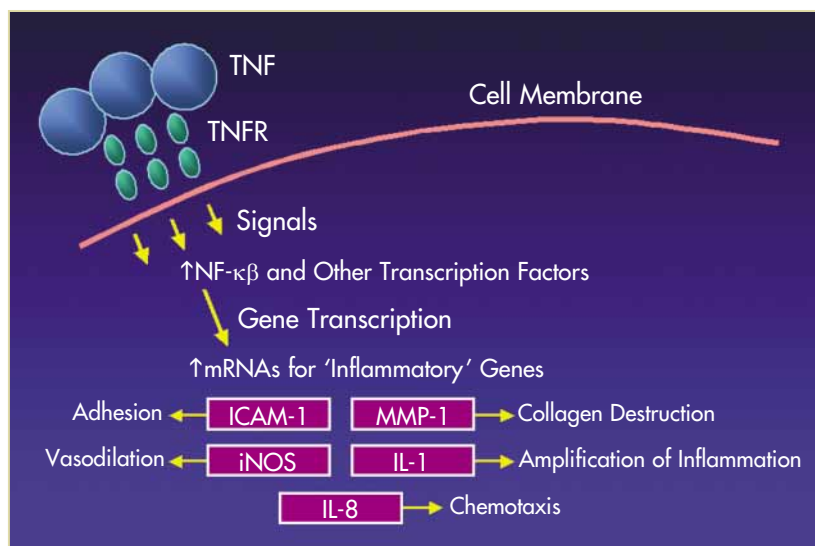


TNF stimulates endothelial cells to express ICAM-1 and other adhesion molecules for leukocytes. In addition, the chemokine IL-8 is induced by TNF, and this chemokine attracts leukocytes (such as neutrophils) that express the IL-8 receptor, CXCR1. Hence, translocation of leukocytes into peripheral tissues is indirectly regulated by TNF.

CXCR1 = chemokine receptor for IL-8; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; MAC = macrophage; TNF = tumor necrosis factor.

Courtesy James G. Krueger, MD, PhD

FIGURE 2: Immediate Response to TNF



Administration of TNF triggers messenger RNA for inflammatory genes, including those that are associated with adhesion, vasodilation, collagen destruction, amplification of inflammation, and chemotaxis.

ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; iNOS = inducible nitric oxide synthase; MMP-1 = matrix metalloproteinase-1; mRNA = messenger ribonucleic acid; NF-κβ = nuclear factor kappa beta; TNF = tumor necrosis factor; TNFR = TNF receptor.

Courtesy James G. Krueger, MD, PhD

seem to be under the direct transcriptional control of TNF (Figure 3 on page 11).

In addition, in these diseases, neutrophils adhere to intercellular adhesion molecule 1 (ICAM-1)-positive blood vessels, and migration into the joint space occurs. Elastase and other toxic substances are subsequently released, further increasing inflammation.

In psoriatic skin plaques, certain key activities are parallel. Psoriasis, once thought to be caused primarily by keratinocyte hyperproliferation associated with abnormal epidermal differentiation, is now recognized as a T-cell-mediated inflammatory disease in which epidermal hyperplasia is a reaction to the activation of the immune system at certain skin sites. TNF has been shown to be present in increased levels in psoriatic lesions, as are several genes regulated by nuclear factor κβ, a transducer of TNF signals. TNF induces the release of IL-8, which is a chemokine that enhances inflammation by attracting neutrophils to the lesion site. As in joint inflammation, the recruitment and

migration of neutrophils into the epidermis result in the release of elastase and other inflammatory products.

WHY TNF INHIBITION WORKS

The recognition that TNF and other cytokines are elevated in RA and PsA, as in the sepsis cascade described above,² formed the basis for the clinical testing of TNF inhibitors. In fact, a body of evidence from clinical studies (discussed in the other articles in this supplement) continues to accumulate, demonstrating that administration of TNF-inhibiting agents is effective in improving signs and symptoms of inflammatory arthritis, both RA and PsA.

As ongoing clinical research further

demonstrates the efficacy and safety of anti-TNF therapy, investigation also continues to explore, explain, and clarify the mechanisms by which TNF inhibition works in these diseases. For example, Catrina and colleagues³ have demonstrated that anti-TNF therapy with etanercept downregulates MMP-3 and MMP-1 in RA.

UNDERSTANDING TNF INHIBITION IN PSORIASIS: TODAY'S QUESTIONS

While clinical studies with etanercept have demonstrated that more than 50% of patients with psoriasis experience improvement after 6 months of continuous TNF blockade, it has been noted that the clinical response to TNF blockade is rapid in RA⁴ but is relatively slow in psoriasis. What is the relevant therapeutic mechanism in psoriasis?

One possibility is that etanercept is cytolytic for some TNF-positive leukocytes, although the data to support such an explanation are weak.⁵ Another possibility is that TNF inhibition in psoriasis alters different immune pathways compared with RA. TNF may regulate activation and migration of Langerhans' cells and, along with γ-interferon, induce the trafficking of T cells and other leukocytes into skin lesions. It seems likely, from what is known to date, that TNF regulates the immune response at that point by influencing the synthesis of chemokines in lesions. Nevertheless, TNF is not likely to be the sole regulator of these activities—many γ-interferon-regulated genes and chemokines also are upregulated in psoriasis. A plausible scenario is that TNF and γ-interferon work synergistically to produce these chemokines. Thus, blocking TNF may result in a decrease rather than in a

TNF has been shown to be present in increased levels in psoriatic lesions, ... [and clinical studies have demonstrated] that administration of TNF-inhibiting agents is effective in improving signs and symptoms of inflammatory arthritis, both RA and PsA.

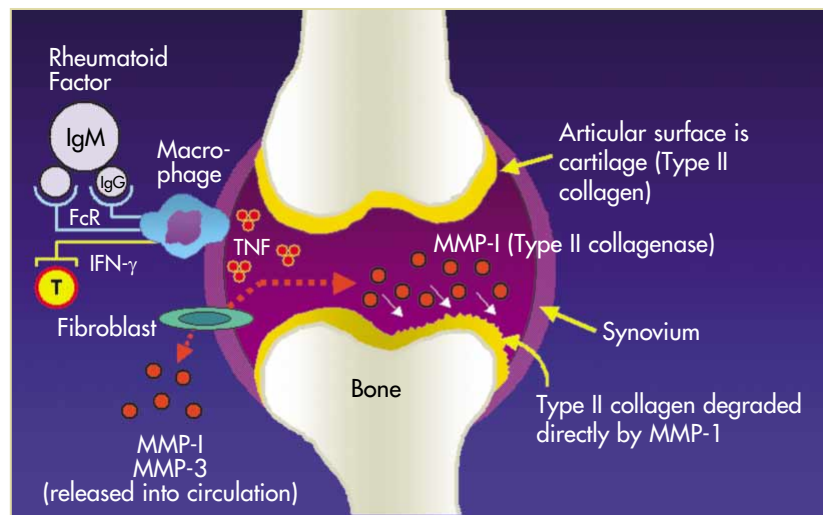
complete cessation of the inflammatory reaction.⁶⁻⁹

CONCLUSION

Clinical studies have established an important role for TNF or TNF-positive leukocytes in psoriasis. The difference in time course of therapeutic improvement in psoriasis compared with RA suggests that a different set of pathogenic functions for TNF is operating in these two diseases. It is known that TNF plays different roles in regulating cell activation in acquired versus innate immunity, and its role in psoriasis may be more analogous to functions in acquired immunity.

Many complex cellular immune functions are regulated by TNF, and further studies are required in psoriasis to better understand the mechanisms through which TNF improves disease symptoms. ■

FIGURE 3: MMP-1 Induced by TNF Degrades Cartilage in Inflammatory Arthritis



As indicated in this figure, circulating immune complexes (rheumatoid factor) or cytokines produced by activated T cells trigger macrophages to synthesize and release TNF. TNF, in turn, directly induces other cell types to produce MMP-1, which is a type II collagenase and can directly degrade articular cartilage.

FcR = fractional catabolic rate; IgG = immunoglobulin G; IgM = immunoglobulin M; IFN = interferon; MMP = matrix metalloproteinase; TNF = tumor necrosis factor.

© James G. Krueger, MD, PhD

REFERENCES

1. Abbas AK, Lichtman AH, Pober JS, eds. *Cellular and Molecular Immunology*, 2nd ed. Philadelphia: WB Saunders; 1994:247.
2. Partsch G, Steiner G, Leeb BF, Dunky A, Broll H, Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol*. 1997;24:518-523.
3. Catrina AI, Lampa J, Ernestam S, et al. Anti-tumour necrosis factor (TNF)-alpha therapy (etanercept) down-regulates serum matrix metalloproteinase (MMP)-3 and MMP-1 in rheumatoid arthritis. *Rheumatology*. 2002;41:484-489.
4. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet*. 1994;344:1105-1110.
5. Luger A, Schmidt M, Luger N, Pauels HG, Domschke W, Kucharzik T. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. *Gastroenterology*. 2001;121:1145-1157.
6. Ohmori Y, Hamilton TA. Cooperative interaction between interferon (IFN) stimulus response element and kappa beta sequence motifs controls IFN gamma- and lipopolysaccharide-stimulated transcription from the murine IP-10 promoter. *J Biol Chem*. 1993;268:6677-6688.
7. Ohmori Y, Schreiber RD, Hamilton TA. Synergy between interferon-gamma and tumor necrosis factor-alpha in transcriptional activation is mediated by cooperation between signal transducer and activator of transcription 1 and nuclear factor kappa beta. *J Biol Chem*. 1997;272:14899-14907.
8. Ganster RW, Taylor BS, Shao L, Geller DA. Complex regulation of human inducible nitric oxide synthase gene transcription by Stat 1 and NF-kappa beta. *Proc Natl Acad Sci U S A*. 2001;98:8638-8643.
9. Pine R. Convergence of TNFalpha and IFN-gamma signalling pathways through synergistic induction of IRF-1/ISGF-2 is mediated by a composite GAS/kappa beta promoter element. *Nucleic Acids Res*. 1997;25:4346-4354.

SUGGESTED READING

- Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol*. 1996;14:397-440.
- Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol*. 2001;19:163-196.
- Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol*. 2002;46:1-23.
- Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell*. 2001;104:487-501.
- Sedgwick JD, Riminton DS, Cyster JG, Korner H. Tumor necrosis factor: a master-regulator of leukocyte movement. *Immunol Today*. 2000;21:110-113.

The Emerging Role of TNF Inhibition in 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.

There is no fee to participate in this activity. CME credit will be sent to the AAD for addition to your CME record. If you wish to receive CME credit, please mail or fax a photocopy of this completed form before August 2003 to:

Course No. 514-100 Dermatology, SKIN & ALLERGY NEWS
60 Columbia Road, Bldg. B, Morristown, NJ 07960-4526 • (973) 290-8200 • (973) 290-8245 Fax

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

- In both rheumatoid arthritis and psoriatic arthritis, destruction of collagen in joints is largely the result of the activity of enzymes known as _____, which seem to be under the direct transcriptional control of TNF.
 - elastase
 - metalloproteinase
 - protease
 - transcriptase
- Which one of the following statements concerning the activity of TNF is false?
 - the cytokine cascade in sepsis begins with interleukin-1 and TNF levels rise beginning about 2 hours later
 - TNF plays a role in cytokine activation in response to sepsis
 - the response to TNF blockade is rapid in rheumatoid arthritis but is relatively slow in psoriatic arthritis
 - the superfamily that includes TNF can induce cell death in various settings
- In the study by Moreland and colleagues of etanercept in patients with active rheumatoid arthritis, what percentage of patients achieved a 20% improvement in the American College of Rheumatology response index?
 - 19%
 - 39%
 - 59%
 - 79%
- The Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) was designed to study the effects of:
 - etanercept plus infliximab
 - etanercept plus methotrexate
 - infliximab plus methotrexate
 - infliximab plus systemic corticosteroids
- Which one of the following statements is true concerning the phase III trial of etanercept in patients with psoriatic arthritis?
 - patients were permitted concomitant use of only one of the standard treatments for psoriatic arthritis (that is, etanercept plus methotrexate or etanercept plus cyclosporine)
 - patients were permitted concomitant use of only methotrexate
 - patients were permitted concomitant use of methotrexate, systemic corticosteroids, and nonsteroidal antiinflammatory drugs
 - this was a monotherapy trial
- Which one of the following statements is true concerning the phase II trial of etanercept in patients with psoriasis?
 - patients were permitted concomitant use of only one of the standard treatments for psoriasis
 - patients were permitted concomitant use of only methotrexate
 - patients were permitted concomitant use of methotrexate, systemic corticosteroids, and nonsteroidal antiinflammatory drugs
 - this was a monotherapy trial
- In the phase III clinical trial of etanercept in patients with psoriatic arthritis, which one of the following adverse events was reported more frequently in the active treatment group compared to the placebo group?
 - deaths
 - injection site reactions
 - malignancies
 - serious infections
- In the phase II trial of etanercept in patients with psoriasis, 2% of patients in the placebo group achieved the primary end point, a 75% improvement in the Psoriasis Area Severity Index. What percentage of those in the active treatment group achieved a PASI 75 at 12 weeks?
 - 10%
 - 20%
 - 30%
 - 40%

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 _____

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:

