



A SUPPLEMENT TO
Skin & Allergy News®



TNF Inhibition for Psoriatic Disease:

Long-Term Efficacy and Safety Data Provide the Basis for Clinical Decisions



The Role of TNF in Treating Psoriatic Disease

Richard G.B. Langley, MD, FRCPC, Chair
Dalhousie University
Halifax, Nova Scotia, Canada

Clinical Experience Shows Efficacy of TNF Inhibition in Patients With Psoriatic Disease

Alice B. Gottlieb, MD, PhD
UMDNJ-Robert Wood Johnson Medical School
New Brunswick, N.J.

Safety Data for the TNF Inhibitors: Considerations for the Treatment of Psoriasis and Psoriatic Arthritis

Bruce E. Strober, MD, PhD
New York University School of Medicine
New York, N.Y.

Produced in affiliation with the
10th International Psoriasis Symposium

Accredited for Dermatologists

Group Publisher/General Manager

Alan J. Imhoff

Vice President, Medical Education & Business Development

Sylvia H. Reitman

Clinical Editor

Joanne M. Still

Program Manager, Medical Education

Sara M. Hagan

National Account Manager

Cheryl J. Gromann

Graphic Design

Emily Brannan

Production Manager

Judi Sheffer

The presentations from which this supplement was developed took place at the Skin Disease Education Foundation's 10th International Psoriasis Symposium, a continuing medical education conference, held June 10-13, 2004, in Toronto, Ontario, Canada.

The supplement was produced by the medical education department of International Medical News Group. Neither the Editor of SKIN & ALLERGY NEWS, the Editorial Advisory Board, nor the reporting staff contributed to its content. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or of the Publisher.

This supplement was supported by an educational grant from:



Copyright 2004 Elsevier Inc. 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. Elsevier Inc. 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 photos courtesy of ©2004 National Psoriasis Foundation

TNF Inhibition for Psoriatic Disease: Long-Term Efficacy and Safety Data Provide the Basis for Clinical Decisions

3 The Role of TNF in Treating Psoriatic Disease

Richard G.B. Langley, MD, FRCPC, Chair

4 Clinical Experience Shows Efficacy of TNF Inhibition in Patients With Psoriatic Disease

Alice B. Gottlieb, MD, PhD

7 Safety Data for the TNF Inhibitors: Considerations for the Treatment of Psoriasis and Psoriatic Arthritis

Bruce E. Strober, MD, PhD

12 CME Post-Test and Evaluation

Faculty

Richard G.B. Langley, MD, FRCPC, Chair

Assistant Professor
Department of Dermatology
Dalhousie University
Director of Research
Department of Dermatology
Queen Elizabeth II
Health Sciences Centre
Halifax
Nova Scotia, Canada

Alice B. Gottlieb, MD, PhD

Professor of Medicine
Department of Medicine
UMDNJ-Robert Wood Johnson Medical School
Director, Clinical Research Center
W.H. Conzen Chair in Clinical Pharmacology
UMDNJ-Robert Wood Johnson
Medical Center
New Brunswick, N.J.

Bruce E. Strober, MD, PhD

Assistant Professor
Ronald O. Perelman Department of
Dermatology
New York University School of Medicine
Associate Director,
Dermatopharmacology Unit
New York University Medical Center
New York, N.Y.

CME Recognition

SKIN & ALLERGY NEWS 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. This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.

Term of Approval:

October 2004 – September 30, 2005

Target Audience

This activity has been developed for dermatologists and other health care professionals involved in the identification and treatment of patients with psoriatic disease (skin psoriasis and psoriatic arthritis).

Educational Needs

Tumor necrosis factor (TNF) has been definitively established as a major factor in the development of plaque psoriasis and psoriatic arthritis (PsA). The recognition of this mechanism in psoriatic disease led to the development of TNF-inhibiting biologic drugs. Because dermatologists are in the position to identify patients with plaque psoriasis early in the course of the disease, knowledge about the efficacy and safety of these biologic drugs is essential so that dermatologists can include these agents in their roster of potential therapies.

Learning Objectives

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

- Discuss the rationale for incorporating biologic therapy for psoriatic disease into the practice of dermatology.
- Explain the immunologic effect of targeting tumor necrosis factor (TNF) in psoriatic disease.
- Describe the long-term efficacy and safety data regarding TNF-inhibiting drugs in patients with both rheumatoid and psoriatic disease.

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 Gottlieb has received funding for clinical grants from and is a consultant to Abbott Laboratories, Amgen Inc., Biogen Idec, Centocor, Inc., and Genentech, Inc. She discusses the unlabeled use of the investigational drugs adalimumab and infliximab for the treatment of psoriasis and psoriatic arthritis. **Dr Langley** has received funding for clinical grants from Amgen, Biogen, Centocor, and Serono S.A. He is also a consultant to Biogen and Novartis AG. **Dr Strober** is a consultant to Amgen, Biogen, Fujisawa Healthcare, Inc., and Genentech. He discusses the unlabeled use of the investigational drugs adalimumab and infliximab for the treatment of psoriasis and psoriatic arthritis.



The Role of TNF in Treating Psoriatic Disease

Richard G.B. Langley, MD, FRCPC, Chair

Over the past several years, it has become increasingly clear that tumor necrosis factor (TNF) is an important regulator of immune and inflammatory responses.¹ Further, it has been shown in healthy individuals that TNF is important to the host defense system by initiating antitumor activity and modulating cell growth and differentiation.¹ In patients with immune-mediated disease, it has been demonstrated that overexpression of TNF plays a role in disease pathogenesis.¹

Some of the earliest evidence that TNF inhibition was clinically important occurred when patients with psoriatic plaques who were being treated with infliximab for rheumatoid arthritis (RA) were seen to have improvements in their skin disease. A randomized trial of infliximab monotherapy suggested that TNF inhibition seemed to be effective and safe in patients with psoriasis,² and subsequent clinical trials with infliximab as well as the other two anti-TNF agents available in the United States—etanercept and adalimumab—were launched. Overall, these clinical trials have supported, in fact, what had been theoretically proposed—that inhibition of TNF would result in an improvement in immune-mediated inflammatory diseases such as psoriasis. In fact, studies to date have shown that patients on anti-TNF therapy typically have a rapid and significant improvement in their disease.

TNF in Pathophysiology

One of the first discoveries about TNF was that the molecule lyses tumor cells. Later laboratory studies showed that TNF modulates cell growth and differentiation in a number of important ways. Among these are increased inflammation through the induction of proinflammatory cytokines, the increase of cell infiltration via adhesion molecules, increased angiogenesis as a result of an increase in vascular endothelial growth factor, and an increased acute-

phase response, leading to increased C-reactive protein levels in serum.

Of greatest interest to dermatologists is the action of TNF on keratinocytes. It has been demonstrated that TNF plays a critical role in increasing keratinocyte hyperproliferation, resulting in the formation of skin plaques. In the laboratory, it has been shown that TNF production is increased in psoriasis: TNF levels are elevated in serum³ and in psoriatic plaques.^{4,5} Further, TNF levels correlate strongly with disease severity, as indicated by the Psoriasis Area and Severity Index,^{3,4} and decrease with effective

“Overall, these clinical trials have supported, in fact, what had been theoretically proposed—that inhibition of TNF would result in an improvement in immune-mediated inflammatory diseases such as psoriasis.”

treatment, the extent of reduction correlating with clinical response.^{3,5}

TNF-alpha likely plays a central role in both the initiating and perpetuating steps of psoriatic inflammation. Psoriasis results from an unchecked cascade of steps, initiated when an unknown antigen within the skin encounters an antigen-presenting cell (APC), such as a Langerhans cell or a dermal dendritic cell. Such an encounter induces a “maturation” of the APC, which subsequently migrates to a local lymph node via the afferent lymphatics. In the lymph node, the APC presents the antigen to a naive or “resting” T cell.⁶⁻¹⁰

This process certainly relies on a multitude of protein-protein interactions between the cells and also on the release of proinflammatory cytokines such as TNF-alpha. The result is the conversion of naive T cells to memory-effector (or activated) T cells. The memory-effector T cells clonally expand, subsequently re-enter the vasculature, and circulate

freely throughout the body. Occasionally, memory-effector T cells may traffic back into the skin, reencounter the antigen, and then profusely release many different types of cytokines—such as TNF-alpha—that elicit more inflammatory cell infiltration and keratinocyte proliferation. In this light, an unchecked positive feedback between cytokines and inflammatory cells perpetuates and augments cutaneous inflammation, resulting macroscopically in a plaque of psoriasis.⁶⁻¹⁰

Conclusion

Investigations in both basic science and clinical arenas have yielded important results that have elucidated the crucial role that TNF plays in the inflammatory process. Specifically, TNF has been shown to be associated with the development of immune-mediated inflammatory diseases, such as RA and Crohn's disease. More recently, studies have demonstrated the role of TNF in plaque psoriasis and psoriatic arthritis. ■

References

1. Aggarwal BB. Signalling pathways of the TNF superfamily: A double-edged sword. *Nat Rev Immunol.* 2003;3:745-756.
2. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomised trial. *Lancet.* 2001;357:1842-1847.
3. Mussi A, Bonifati C, Carducci M, et al. Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. *J Biol Regul Homeost Agents.* 1997;11:115-118.
4. Bonifati C, Carducci M, Cordiali Fei P, et al. Correlated increases of tumour necrosis factor- alpha, interleukin-6 and granulocyte monocyte-colony stimulating factor levels in suction blister fluids and sera of psoriatic patients—relationships with disease severity. *Clin Exp Dermatol.* 1994;19:383-387.
5. Ameglio F, Bonifati C, Pietravalle M, Fazio M. Interleukin-6 and tumour necrosis factor levels decrease in the suction blister fluids of psoriatic patients during effective therapy. *Dermatology.* 1994;189:359-363.
6. Nickoloff BJ. The immunologic and genetic basis of psoriasis. *Arch Dermatol.* 1999;135:1104-1110.

Continued on page 11

Clinical Experience Shows Efficacy of TNF Inhibition in Patients With Psoriatic Disease

Alice B. Gottlieb, MD, PhD

Patients with moderate to severe psoriasis and their physicians have anticipated the results of clinical trials with therapies that offer new avenues for managing their disease. One of the most important of these is the availability of biologic therapies. Recent results of trials using these treatments—in particular, the inhibitors of tumor necrosis factor (TNF)—demonstrate that the hope invested in these new approaches is being realized.

In this article, the available data regarding efficacy of TNF inhibition in patients with psoriatic disease—plaque psoriasis and psoriatic arthritis (PsA)—will be reviewed. Because anti-TNF therapy provides the potential for reduced morbidity for patients with skin disease, joint disease, or both, dermatologists need to become familiar with the capabilities of these agents, as well as with their appropriate use.

Pivotal Trial Results in Psoriasis and PsA

Etanercept is a fully human receptor fusion protein composed of a human TNF type II receptor and the human immunoglobulin G1 (IgG1):Fc region. It is approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA), juvenile RA down to 4 years of age, ankylosing spondylitis, PsA, and moderate to severe plaque psoriasis. In patients with PsA, this drug has been shown to reduce the clinical signs and symptoms of the disease and to inhibit the progression of structural damage to joints, as demonstrated on x-rays.

Recently, the results of a global phase III study of etanercept in psoriasis and PsA were published.¹ This was a double-blind, 24-week study in which 672 patients were randomized and 652 received for 12 weeks either placebo or etanercept in one of three dosage regimens (low-dosage, 25 mg once weekly; medium-dosage,

25 mg twice weekly; or high-dosage, 50 mg twice weekly). For the second 12-week period, all patients already on etanercept continued their original regimen, but the patients on placebo received etanercept, 25 mg twice weekly.

The primary end point was the proportion of patients achieving a 75% or greater improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12. The investigators reported that only 4% of patients in the placebo group had achieved PASI 75 at week 12, compared with 14% of those in the low-dosage

“Because anti-TNF therapy provides the potential for reduced morbidity for patients with skin disease, joint disease, or both, dermatologists must become familiar with the capabilities of these agents, as well as with their appropriate use.”

etanercept group, 34% of patients in the medium-dosage group, and 49% of those in the high-dosage group (see **Figure** on page 5 for a summary of these results).

Ninety percent improvement in PASI (PASI 90) was seen at week 12 in 3% of those in the low-dosage group, 12% of patients in the medium-dosage group, and 22% of subjects in the high-dosage group compared with 1% of placebo-treated patients.

At the end of 24 weeks, further clinical improvements were seen in the treated groups. PASI 75 was achieved by 59% of patients in the high-dosage group, 44% of those in the medium-dosage group, and 25% of those in the low-dosage group. Thirty-three percent of patients who had received placebo during the first 12 weeks achieved PASI 75.

In sum, the higher-dosage group had a higher response rate and achieved responses more quickly than the lower-dosage etanercept group.

Infliximab in Psoriasis: SPIRIT Trial

Infliximab is a chimeric monoclonal antibody to TNF that is composed of murine regions and the human IgG1:Fc region. Infliximab is approved by the FDA for the treatment of Crohn's disease and RA; pivotal trials using this drug in patients with psoriasis and PsA are nearing completion.

Full results from the recently completed trial of infliximab in psoriasis—formally known as the Study of Psoriasis With Infliximab (Remicade) Induction Therapy (SPIRIT)—are expected to appear soon in peer-reviewed journals. Meanwhile, preliminary results are available.²

This phase II study was a multicenter, randomized, double-blind, placebo-controlled trial involving 249 patients with plaque psoriasis. Patients were randomized to receive infusions of infliximab, 3 mg/kg (n=99) or 5 mg/kg (n=99), or placebo (n=59) at weeks 0, 2, and 6. Eighty-eight percent of patients in the 5-mg/kg group achieved an improvement of PASI 75 or better at week 10 compared with only 4% of those in the placebo group. These differences held regardless of gender, age, patient weight, baseline PASI score, body surface area involved at baseline, and history of previous systemic antipsoriasis therapy.

Dermatology Quality of Life Index (DLQI) and Global Assessment Improvements

Differences in the DLQI were noted between groups in the etanercept phase III study. As with clinical improvement, patients receiving the higher dosages had earlier and more substantial improvements. The SPIRIT trial of infliximab also included assessment of quality-of-life

Table. Criteria for American College of Rheumatology 20% (ACR 20) Response

■ 20% improvement in BOTH of the following:

- Swollen joints
- Tender joints

Plus

■ 20% improvement in three of the following:

- Patient's pain assessment
- Patient's assessment of disability
- Physician's global assessment
- Patient's global assessment
- C-reactive protein or erythrocyte sedimentation rate

Source: Felson DT, et al. *Arthritis Rheum.* 1995;38:727-735.

improvement using the DLQI as a rating instrument. Those results have not yet been published.

The improvements noted—both in the clinical trials and in clinical practice—in patients' overall sense of well-being and wellness are, of course, attributable to the alleviation of a host of problems caused by psoriatic disease. These problems range from inconvenience to pain and various levels of physical and social disability. However, it is the observation of many clinicians who have treated psoriasis patients with TNF inhibitors that their quality-of-life improvements tend to occur soon after initiation of therapy, leading to the hypothesis that inhibiting TNF actually may have some central nervous system effects in addition to the effects on the skin and joints.

The PASI 75 results in the etanercept phase III study were echoed by the data from the physician's static global assessment of clear or almost-clear status. By week 12, 49% of patients in the high-dosage group were judged as clear or almost clear; this status was achieved by 34% of patients in the medium-dosage group and 23% of the low-dosage group. In comparison, only 5% of patients in the placebo group were clear or almost clear on physician's static global assessment at week 12 ($P < 0.001$ for comparison with all

active-treatment groups). The results of the patient's static global assessments were similar to those of the physician's global assessments.

TNF Efficacy in PsA

Dermatologists must recognize that psoriasis is a multisystem disease and patients with both plaque psoriasis and PsA must be identified and treated for both aspects of this disorder. Anti-TNF therapy has been shown to be effective in managing the signs and symptoms of PsA. In a double-blind, randomized trial of etanercept involving 205 patients,³ 101 received etanercept and 104 were randomized to the placebo group. Patients who were already on stable doses of up to 25 mg weekly of methotrexate and/or up to 10 mg daily of prednisone were permitted to continue this therapy; almost all of the patients were taking nonsteroidal antiinflammatory drugs (NSAIDs).

For 6 months, the active-treatment group received etanercept, 25 mg twice weekly. An open-label extension of the controlled study followed, lasting for an additional 6 months. Patients were evaluated clinically for signs and symptoms of PsA, as well as for x-ray progression of the disease.

Response was evaluated according to achievement of a 20% improvement in the American College of Rheumatology

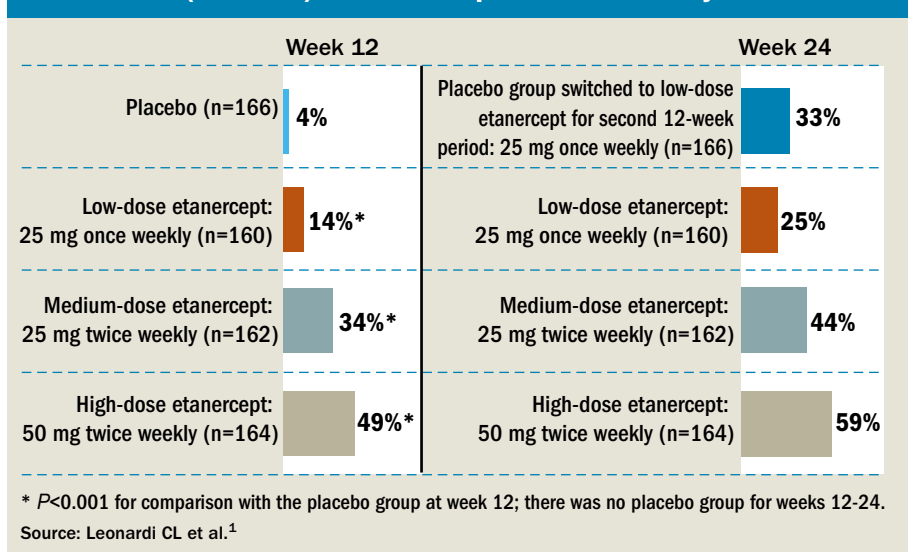
score (ACR 20) (Table). In the etanercept-treated group, 59% of patients achieved ACR 20 at the 3-month evaluation compared with 15% of those who received placebo ($P < 0.001$).³

X-ray progression was evaluated according to a qualitative assessment known as the modified Sharp score, in which 21 joints in the hands and wrists are examined for erosions and 20 are examined for joint-space narrowing and the examiner assigns a composite score according to the number and severity of affected joints. At 12 months, the placebo group—despite the continued use of methotrexate, prednisone, and NSAIDs—experienced progression of disease, whereas the etanercept group had no x-ray progression ($P < 0.0001$).

Conclusion

Dermatologists are increasingly aware that psoriasis is a multisystem disease and that about one third of patients with moderate to severe skin disease have psoriatic joint disease as well. However, dermatologists must be vigilant, because it is unlikely that patients with psoriasis will complain of signs and symptoms at the dermatology office. First, the onset of PsA typically is gradual, so patients may become accustomed to creeping pain and disability, accepting these as normal. Second, patients are not likely to realize that joint symptoms are associated with

Figure: Patients Who Achieved at Least a 75% Improvement in the Psoriasis Area and Severity Index (PASI 75) in Etanercept Psoriasis Study



their skin disease. Third, if they do notice joint symptoms, they probably would not associate the dermatologist with help for these problems.

Etanercept has been shown to inhibit joint destruction, bone erosion, and joint-space narrowing, in addition to controlling both signs and symptoms. Two other available TNF inhibitors, infliximab and adalimumab, are being evaluated for their value in psoriatic disease. (Adalimumab, a recombinant human IgG1 monoclonal antibody to TNF, is indicated at this time only for the treatment of RA; it was not discussed

in this article because studies with this drug in psoriatic disease are in their early stages.)

The former paradigm in the treatment of PsA was to treat to alleviate joint symptoms, particularly pain, a function most commonly associated with the rheumatologist. With the newer therapies, it is possible to take therapy a significant step further, and that is to treat early to avoid disability. Drugs that inhibit x-ray progression clearly must be introduced earlier rather than later in the disease to prevent deformity and functional loss and to preserve quality of

life. Dermatologists can and should be involved in that process. ■

References

1. Leonardi CL, Powers JL, Matheson RT, et al, for the Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349:2014-2022.
2. Gottlieb AB, Evans R, Li S, Leonardi C. The efficacy of infliximab across a variety of subgroups with plaque psoriasis [abstract]. *J Am Acad Dermatol.* 2004;50:P158.
3. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: Safety, efficacy, and effect on disease progression. *Arthritis Rheum.* 2004;50:2264-2272.

Safety Data for the TNF Inhibitors: Considerations for the Treatment of Psoriasis and Psoriatic Arthritis

Bruce E. Strober, MD, PhD

In both clinical trials and in post-marketing use, tumor necrosis factor (TNF) inhibitors have been shown to be generally safe. Most of the data regarding the safety of TNF inhibitors have been established from investigations of patients receiving these drugs for the treatment of rheumatoid arthritis (RA). However, the current body of evidence regarding TNF-inhibitor safety in patients with psoriasis and psoriatic arthritis (PsA), is growing. This article emphasizes the safety data collected to date in patients with RA and psoriasis.

Three TNF inhibitors currently are approved for use in the United States by the US Food and Drug Administration (FDA). Etanercept is approved for RA, juvenile RA in patients down to 4 years of age, ankylosing spondylitis, PsA, and moderate to severe plaque psoriasis. Infliximab is approved for Crohn's disease and RA, and pivotal trials using this agent in patients with psoriasis and PsA are nearing completion. Adalimumab is indicated at this time only for the treatment of RA, but currently is being studied in patients with psoriasis and PsA.

In the following sections, the data on clinical trials involving etanercept and infliximab in patients with psoriatic disease will be reviewed. Adalimumab is a newer drug, and, thus, its postmarketing experience is brief. Further, the detailed safety data from clinical trials of adalimumab in psoriasis are limited.¹

Results of Major Clinical Trials to Date*

A large body of evidence has been accumulated on etanercept. Because etanercept was first approved and used for patients with RA, most of the safety data are derived from the RA population. As of December 2003, clinical trial data had been collected on more than 5,100 patients, for

a total of approximately 10,500 patient-years of evidence. In post-marketing use, more than 230,000 patients have received etanercept, equivalent to more than 423,000 patient-years. More than 1,000 patients are now in their fifth year of treatment, and some 425 patients have continued treatment into their sixth year.

Clinical studies of etanercept in psoriatic disease, specifically, have included approximately 2,500 patients enrolled in a variety of trials. Those have involved studies of psoriasis and/or PsA, including a recently published 24-week, double-blind study involving 672 patients receiving various dosage regimens of etanercept.² Another study completed in Europe, Canada, and the United States adds approximately 580 more psoriasis patients. A new trial with etanercept, the EASE study, is under way and will add another 2,500 patients. Yet another study evaluating the long-term use of the higher dose of etanercept, 50 mg twice weekly, will add approximately 600 patients to the database. Ultimately, controlled and open-label data will be available on more than 5,500 patients with psoriatic disease. Of course, post-

marketing safety data will also grow rapidly for the psoriasis population as the drug currently is being used extensively in clinical practice in the United States for both psoriasis and PsA.

Similarly, a large amount of safety data has been gleaned from studies involving infliximab. Most of these safety data are derived from populations of patients with RA and Crohn's disease. As of March 2003, more than 1,650 patients, representing approximately 3,500 patient-years of exposure, have been enrolled in clinical trials for infliximab. Furthermore, in postmarketing use across all indications, more than 430,000 patients have received infliximab, representing more than 750,000 patient-years of use. Infliximab use for psoriasis and PsA currently is off-label, and, thus, post-marketing surveillance for patients with psoriatic disease is limited.

The results of the Study of Psoriasis With Infliximab (Remicade) Induction Therapy (SPIRIT), are not available as of the publication of this supplement. The safety evidence on infliximab discussed in this supplement is from the 54-week phase III, Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis With Concomitant Therapy (ATTRACT) study.³

Reported Adverse Events

The combined data from the clinical trials with etanercept completed to date show that adverse events occurred less frequently in the psoriasis clinical trials than had been observed in the RA clinical trials.

In the psoriasis trials, the rates of infection were low—approximately 1%. These rates were similar among all active-treatment groups as well as in each active-treatment group compared to placebo groups.

No treatment-related laboratory abnormalities were observed and no subjects withdrew from these studies because of an

Patient Exposure to Etanercept

- More than 5,100 patients have participated in clinical trials for etanercept, totalling approximately 10,500 patient-years of evidence.
- More than 5,500 patients with psoriatic disease will be available for controlled and open-label trials using etanercept.
- More than 1,650 patients have been enrolled in clinical trials for infliximab, for a total of about 3,500 patient-years of exposure.

The figures in this summary are taken from the accumulated clinical trial and postmarketing surveillance data.

* Unless other references are cited, the information contained in this section is supported by data published in the package inserts for etanercept and infliximab.

abnormal laboratory result. Further, there were no new or unanticipated patterns of adverse events observed in psoriasis trials when compared to other etanercept trials for other indications. There were no differences in frequency of adverse events based on age, race, gender, or weight.

In addition, no dose-related toxicities were reported with etanercept. Specifically, when compared to the lower dosages (25 mg twice weekly and 25 mg once weekly), use of the 50-mg twice-weekly dose did not represent an increase in risk with regard to adverse events and serious adverse events (including serious infections) over the 24 weeks of formal study.

An injection-site reaction (ISR) is one of the most common adverse events that

etanercept.⁴ Clinical studies on etanercept for psoriasis also focused on the effect of abrupt discontinuation of the drug after 24 weeks of continuous therapy. When etanercept was withdrawn abruptly, a gradual return of psoriasis was seen over an average of 3 months.⁵ No morphologic conversion to other forms of psoriasis (pustular or erythrodermic) was observed, and in no cases did discontinuation result in hospitalization due to psoriasis-related serious adverse events.⁴ Initiation of retreatment at the same dose of etanercept yielded efficacy rates comparable to those seen prior to withdrawal of the drug, with no increase in antigenicity.⁶ In fact, at this time, no clinical studies of etanercept have shown the formation of neutralizing antibodies to this medication.

In patients with RA treated with infliximab in the ATTRACT trial³ and other published clinical studies, the most commonly reported adverse events included upper respiratory infections, nausea, sinusitis, and diarrhea. In all cases, these were mild and did not interfere with therapy or prevent administration of the next dose of infliximab.

Infusion reactions are a well documented feature of infliximab administration in some patients. Generally, an infusion reaction is defined as any adverse event occurring during infusion and up to 1 to 2 hours postinfusion. The most common symptoms and signs associated with infusion reactions are fever, chills, chest pain, hypotension, hypertension, dyspnea, urticaria, and pruritus. In clinical studies, approximately 20% of patients receiving infliximab experience an infusion reaction, compared to 10% of control patients receiving a placebo. Most infusion reactions are mild, with less than 1% defined as serious, resulting in anaphylaxis, convulsion, erythematous rash, or hypotension. In clinical trials, approximately 3% of subjects discontinued infliximab because of infusion reactions. Patients who develop antibodies to infliximab have a two- to threefold increased risk of developing an infusion reaction. Concomitant use of another immunomodulatory medication (such as methotrexate) reduces the risk of both developing antibodies to infliximab and the infusion reaction.

TNF Inhibition And Infection Risk

When TNF-inhibiting treatment was introduced, there was great concern over a theoretical risk for serious infections such as pneumonia, severe urinary tract infections, tuberculosis (TB), and sepsis. When considering data on infections in any study, it is important to examine the results from two perspectives. First, if a patient has an infection and treatment with a particular agent is initiated, does a risk exist that the infection will be exacerbated or more difficult to treat? Second, if a patient does not have an infection and therapy is started, will there be a greater likelihood of infection developing? Importantly, does there exist the potential for an increased risk for opportunistic infections including TB?

The rates of serious infections observed in the clinical trials of etanercept were comparable across all treatment arms and in the placebo groups. Of note is the fact that no increase in serious infections was seen in the high-dosage treatment groups through 24 weeks of treatment with etanercept. During weeks 1 through 12, three patients receiving etanercept experienced cellulitis and one had gastroenteritis. During this same period, infections occurred in four patients in the placebo group: one case each of cellulitis, furunculosis, pharyngitis, and pneumonia.

With regard to long-term tolerability in patients receiving etanercept for RA in clinical trials, there does not seem to be an increased risk of serious infection, regardless of whether they have early RA or advanced RA, when compared to their control populations. The lack of increased infection risk persists as patients receive this drug chronically.

It should be noted that in postmarketing use of etanercept, infliximab, and adalimumab, serious infections and sepsis have been reported. Most of these cases involved patients also receiving concomitant immunosuppressive therapy that, in addition to their underlying medical condition (such as RA), could predispose them to infection.

Patients who received infliximab in published RA clinical trials did have higher rates of serious infections than did those in placebo groups, but the differences

Figure: Injection-Site Reaction



A mild skin reaction is the most predictable and consistent adverse event that occurs in patients who receive etanercept.

occurs in patients who receive etanercept, and it has been seen in approximately 15% of those who receive this agent for psoriasis. Further, the incidence of ISR is the same regardless of the dose of etanercept used. The reaction appears as an erythematous patch, macule, or plaque that may be tender and/or pruritic. The histology of ISR resembles that of a delayed-type hypersensitivity reaction. In the majority of cases, ISR is mild and usually is not noticed by the patient. If it occurs and treatment is desired, a midpotency topical cortico-steroid and an antihistamine may be used. In general, patients “become desensitized” to the reaction over the first 2 months of use, and so the ISR tends to wane in intensity and frequency with long-term use of

were not statistically significant. Further, sepsis is not an uncommon problem among patients with RA who are taking methotrexate, and subjects in many of the infliximab trials were given methotrexate with infliximab.

From the accumulated long-term tolerability data, it does not appear that TNF-inhibiting therapy greatly increases the risk of infection. However, given the theoretical risk of infection after TNF blockade, vigilance on this issue is warranted, and patients who do develop infections during a course of therapy with any of these agents should be monitored closely. Use of a TNF-inhibiting agent should be discontinued in the context of a febrile illness—especially bacterial or fungal—or if sepsis develops. The patient should be observed and the infection treated appropriately. Treatment with the TNF inhibitor may be restarted when the infection clears, especially if the clinical situation dictates the use of a TNF inhibitor as the best or only reasonable therapy.

Local infection—such as a herpes simplex virus or a human papillomavirus infection—does not require cessation of anti-TNF therapy. Patients should not be started on anti-TNF therapy if they have an active infection or a history of recurrent bacterial or fungal infections requiring frequent antimicrobial treatment.

TB reactivation has occurred subsequent to the initiation of anti-TNF therapy, often presenting as extrapulmonary or disseminated TB. Infliximab and adalimumab carry a boxed warning regarding TB in their labeling, and a purified protein derivative (PPD) test is required prior to initiation of therapy with these drugs. Owing to a lower postmarketing rate of TB reactivation associated with etanercept, a PPD test is not required for patients to begin therapy with etanercept, but it may be advisable depending on geographic location. For example, in New York City, the incidence of latent TB is much higher than the national average, so performance of a PPD test may be a reasonable precaution for patients living in metropolitan areas with large populations of people who come from countries with high endemic rates of TB. The author's personal preference

is to perform a PPD on any patient receiving a TNF-inhibiting therapy. In all instances of detected latent TB, effective anti-TB therapy should be initiated prior to starting anti-TNF therapy.

Low Risk For Malignancy With TNF Inhibition

For all three anti-TNF agents, both clinical trial data and postmarketing surveillance do not support early concerns

Infection and Anti-TNF Therapy: Strategies for Managing Risk

- Patients who develop a new infection while on anti-TNF therapy should be monitored closely.
- Treatment should be discontinued in patients with serious infections or sepsis.
- Treatment should not be initiated in patients with active infection.

that TNF blockade might increase the risk for malignancy. In fact, as of March 2003, open-label extension clinical trials of etanercept (involving more than 8,300 patient-years of exposure), infliximab (more than 2,400 patient-years of exposure), and adalimumab (involving more than 4,800 patient-years of exposure) do not reveal an occurrence of malignancies (including lymphoreticular malignancy) exceeding that which would be expected in a matched population not receiving these drugs.⁷

Malignancy rates in the etanercept clinical trials for psoriasis and PsA are comparable to those that would be expected in patients with severe psoriasis on systemic therapies.⁸ Nevertheless, not enough data are available to state definitively that anti-TNF agents such as etanercept are safe to use in patients with a history of a solid tumor (excluding nonmelanoma skin cancer) or lymphoreticular malignancy.

Patients with RA or psoriasis are believed to carry a two- to threefold increased lifetime risk for lymphoma.⁹ Therefore, any analysis of the effect of medication on these populations must consider the risk

of lymphoma specific to the disease entity. At this time, the consensus is that patients receiving anti-TNF therapy for RA are not believed to have an increased risk of de novo lymphoma development that exceeds the underlying risk for the entire RA population (regardless of previous or ongoing therapy).^{10,11}

TNF And Demyelination

Early investigators hypothesized that blocking TNF might be an effective means of treating multiple sclerosis (MS). The TNF inhibitor lenercept (not marketed in the United States), a soluble p55 TNF-receptor fusion molecule, was used in a double-blind, placebo-controlled phase II study involving 168 patients with active MS.¹² There were no significant disease differences between the lenercept- and placebo-treated groups evaluated using magnetic resonance imaging, but the number of lenercept-treated patients experiencing MS exacerbations was significantly increased compared with patients receiving placebo. Furthermore, the lenercept-treated patients had MS exacerbations that occurred earlier. Finally, neurologic deficits were more severe in the lenercept treatment groups.

Cases of new-onset MS or demyelinating neurologic syndromes (such as optic neuritis, transverse myelitis, or seizure disorder) or exacerbations of previously existing conditions have been reported in patients receiving anti-TNF therapy, including etanercept, infliximab, and adalimumab. In most cases, symptoms resolved partially or fully on discontinuation of therapy, and, in a few of these patients, rechallenge with the TNF inhibitor resulted in reappearance of symptoms.¹³

As a result of the association between TNF inhibition and demyelination suggested by these reports, anti-TNF agents should not be initiated in patients with a history of demyelinating neurologic disease. At baseline, the practitioner should question patients for any current neurologic symptoms or history of neurologic disease. This will assist in determining if a symptom or sign that occurs during treatment is preexisting or is truly new-onset.

Cardiac Safety

Both infliximab and etanercept were evaluated for their possible beneficial effects in patients with congestive heart failure (CHF). In multiple clinical trials, neither agent showed benefit when given to patients with CHF. One study suggested higher mortality in patients with CHF who received etanercept, but another study did not corroborate this phenomenon.¹⁴ In one study of infliximab, patients receiving a higher dose of the drug (three doses at 10 mg/kg) had worse outcomes (hospitalization or death).¹⁶ Furthermore, case reports have identified a small group of people with new-onset CHF while receiving either etanercept or infliximab. Some of these patients had neither precipitating factors nor preexisting heart disease, and some were under the age of 50.¹⁶ Currently, there are no published data regarding the risk of using adalimumab in the setting of CHF. But the data regarding etanercept and infliximab support caution

Patient Selection For Anti-TNF Therapy

Anti-TNF therapy is effective and safe in most patients with psoriasis and PsA. In general, TNF inhibitors should be avoided in patients with:

- Active bacterial infections or chronic bacterial infections
- Multiple sclerosis or demyelinating neurologic disease
- Solid tumors (except for nonmelanoma skin cancers) or lymphoproliferative malignancies
- Congestive heart failure

A careful risk:benefit assessment should be performed to determine whether patients with these conditions should start anti-TNF therapy. If treatment is initiated, careful monitoring is warranted, and ongoing consultation with another specialist (ie cardiologist, neurologist, etc.) should be considered.

when considering an anti-TNF therapy for patients with concomitant CHF, and patients should be followed for new-onset cardiac signs and symptoms while on anti-TNF therapy.

Lupuslike Syndromes

All three anti-TNF therapies are associated with the development of auto-antibodies. Specifically, antinuclear antibodies (ANAs) have been seen in some patients receiving these therapies. This laboratory abnormality usually has no clinical significance, but a few reports and postmarketing surveillance have revealed isolated cases of lupuslike syndromes (systemic and cutaneous lupus erythematosus) arising during anti-TNF therapy. In nearly all cases, the syndromes resolved after discontinuation of anti-TNF therapy.¹⁷⁻²³

Other Safety Considerations

In the clinical trials of etanercept, infliximab, and adalimumab, no new-onset, clinically significant laboratory abnormalities developed during the use of these agents. Indeed, the package inserts for these medications do not specifically recommend laboratory monitoring. There are rare postmarketing reports of pancytopenia arising in patients receiving etanercept. The relationship of these events to the use of the drug is unclear, but an alternative therapy should be considered in patients with a prior history of hematologic abnormalities. Additionally, patients receiving etanercept (or any drug) who develop signs or symptoms of bleeding abnormalities or infections should be thoroughly evaluated and discontinuation of treatment should be considered.

Clinical common sense suggests obtaining baseline laboratory studies, including a complete blood count, liver function tests, and a comprehensive metabolic panel. Some clinicians advocate a baseline ANA titer and hepatitis B and C serologies. The baseline laboratory values can be compared to subsequent laboratory tests performed during therapy, and the drug may be ruled out or implicated as the source of any possible new-onset clinical sign or symptom. Regardless, in a patient tolerating anti-TNF therapy, laboratory

monitoring for these agents need not be frequent.

None of the anti-TNF therapies should be given concomitantly with anakinra, another agent approved for the treatment of RA. Further, it should be noted that concomitant use of methotrexate reduces the clearance of adalimumab.

At this time, although specific studies have not been conducted, dosage adjustments do not appear to be necessary for patients with hepatic or renal insufficiency who are on anti-TNF therapy.

Patients on anti-TNF therapy who require immunization may receive any vaccine except a live virus vaccine (eg, vaccinia for smallpox). If such live virus vaccination is necessary, consider interrupting anti-TNF therapy. For example, etanercept therapy can be discontinued 10 days prior to and restarted approximately 10 days after the vaccination. Reassure patients that rebound of their disease will not occur on discontinuation of therapy and that worsening of psoriasis on discontinuation of treatment occurs very slowly.

All three anti-TNF therapies are pregnancy category B drugs. It is not known whether these agents are excreted in human milk or whether they are absorbed systemically after ingestion. Until more experience is reported in pregnant and lactating women and unless therapy with the drug is deemed medically essential to the mother, it is prudent to have women discontinue these therapies during pregnancy and resume treatment after babies have been weaned from breastfeeding.

Conclusion

To summarize, anti-TNF therapy should be avoided in patients who have:

- Active or chronic bacterial infections
- MS or demyelinating neurologic disease
- Solid tumors (except for nonmelanoma skin cancers) or lymphoproliferative malignancies
- CHF

However, in the overwhelming majority of patients with psoriasis, with or without PsA, anti-TNF therapy is not contraindicated and serious adverse events are rare. Clinical trials have demonstrated that the benefit-to-risk ratio of using

these medications is quite good. Dermatologists who use care in patient selection and provide regular follow-up can confidently offer anti-TNF therapy to patients with psoriatic disease. (At this time, etanercept is the only one of the three TNF-inhibiting agents approved by the FDA for use in patients with psoriatic disease.) ■

References

- Gordon KB, et al. Results of a double-blind placebo-controlled, phase II trial of adalimumab in psoriasis and psoriatic arthritis. Presented at: 62nd Annual Meeting of the American Academy of Dermatology; February 6-11, 2004; Washington, DC. Abstract P2.
- Leonardi CL, Powers JL, Matheson RT, et al, for the Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349:2014-2022.
- Lipsky PE, van der Heijde DM, St. Clair EW, 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.
- Zeltser R, Valle L, Tanck C, Holyst MM, Ritchlin C, Gaspari AA. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: A recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol.* 2001;137:893-899.
- Gottlieb AB, et al. Poster presented at: 62nd Annual Meeting of the American Academy of Dermatology; February 6-11, 2004; Washington, DC. Poster 566.
- Leonardi CL, et al. Poster presented at: 62nd Annual Meeting of the American Academy of Dermatology; February 6-11, 2004; Washington, DC. Poster 568.
- US Food and Drug Administration Arthritis Advisory Committee. Briefing Information, March 4, 2003. Available at: <http://www.fda.gov/ohrtms/dockets/ac/03/briefing/3930b1.htm>. Accessed July 20, 2004.
- Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. *Arch Dermatol.* 2001;137:778-783.
- Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: Results from a population-based cohort study in the United Kingdom. *Arch Dermatol.* 2003;139:1425-1429.
- Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: The effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum.* 2004;50:1740-1751.
- Symmons DP, Silman AJ. Anti-tumor necrosis factor alpha therapy and the risk of lymphoma in rheumatoid arthritis: No clear answer [editorial]. *Arthritis Rheum.* 2004;50:1703-1706.
- The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. TNF neutralization in MS: Results of a randomized, placebo-controlled multicenter study. *Neurology.* 1999;53:457-465.
- Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum.* 2001;44:2862-2869.
- Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol.* 2002;86:123-130.
- Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: Results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation.* 2003;107:3133-3140.
- Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med.* 2003;138:807-811.
- Stratigos AJ, Antoniou C, Stamathioudaki S, Avgerinou G, Tsega A, Katsambas AD. Discoid lupus erythematosus-like eruption induced by infliximab. *Clin Exp Dermatol.* 2004;29:150-153.
- Sarzi-Puttini P, Ardizzone S, Manzionna G, et al. Infliximab-induced lupus in Crohn's disease: A case report. *Dig Liver Dis.* 2003;35:814-817.
- Swale VJ, Perrett CM, Denton CP, Black CM, Rustin MH. Etanercept-induced systemic lupus erythematosus. *Clin Exp Dermatol.* 2003;28:604-607.
- Klapman JB, Ene-Stroescu D, Becker MA, Hanauer SB. A lupuslike syndrome associated with infliximab therapy. *Inflamm Bowel Dis.* 2003;9:176-178.
- De Rycke L, Kruihof E, Van Damme N, et al. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. *Arthritis Rheum.* 2003;48:1015-1023.
- Garcia-Planella E, Domenech E, Esteve-Comas M, et al. Development of antinuclear antibodies and its clinical impact in patients with Crohn's disease treated with chimeric monoclonal anti-TNF alpha antibodies (infliximab). *Eur J Gastroenterol Hepatol.* 2003;15:351-354.
- Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet.* 2002;359:579-580.

The Role of TNF in Treating Psoriatic Disease

Continued from page 3

- Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol.* 2002;46:1-23.
- Giolomoni G, Pastore S, Albanesi C, Cavani A. Targeting tumor necrosis factor-alpha as a potential therapy in inflammatory skin diseases. *Curr Opin Investig Drugs.* 2002;3:1590-1595.
- Bonifati C, Ameglio F. Cytokines in psoriasis. *Int J Dermatol.* 1999;38:241-251.
- Peters BP, Weissman FG, Gill MA. Pathophysiology and treatment of psoriasis. *Am J Health Syst Pharm.* 2000;57:645-659.

SKIN & ALLERGY NEWS 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. If you wish to receive CME credit, please mail or fax a photocopy of this completed form before September 30, 2005 to:

Course No. 356-100 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 or completion is correct. Circle the most appropriate response. Five of six correct responses are required for credit.

1. The most rapid onset of and best results in the phase III etanercept trial in patients with psoriasis were seen in the group that received:
 - a. 25 mg once weekly
 - b. 25 mg twice weekly
 - c. 50 mg once weekly
 - d. 50 mg twice weekly
2. Which one of the following statements is true concerning the Study of Psoriasis With Infliximab (Remicade) Induction Therapy (SPIRIT) trial?
 - a. No differences in response were seen between the active-treatment groups and the placebo group.
 - b. No differences in response were seen between men and women.
 - c. Patients with no history of antipsoriasis therapy did better than those who had received prior treatment.
 - d. Patients with greater body surface area involvement at baseline showed a greater response to treatment.
3. Which one of the following is a measure of x-ray progression of psoriatic arthritis?
 - a. American College of Rheumatology 20 score
 - b. Dermatology Quality of Life Index
 - c. Psoriasis Area and Severity Index
 - d. Sharp score
4. One of the first discoveries about tumor necrosis factor (TNF) was that:
 - a. It causes increased C-reactive protein in serum.
 - b. It is an activator of naive T cells.
 - c. It lyses tumor cells.
 - d. It modulates cell growth and differentiation.
5. Studies have shown that TNF levels correlate strongly with disease severity as indicated by the:
 - a. ACR 20 score
 - b. DLQI
 - c. PASI score
 - d. Sharp score
6. When activated by TNF, antigen-presenting cells migrate through afferent lymphatics to lymph nodes, where they:
 - a. Activate naive T cells and other immune cells.
 - b. Form nuclear factor of activated T cells.
 - c. Inhibit the clonal expansion of effector cells.
 - d. Up-regulate selectins.
7. Patients with Crohn's disease and rheumatoid arthritis are at increased risk for developing non-Hodgkin's lymphoma:
 - a. As a result of an immune dysregulation inherent in their diseases.
 - b. As a result of long-term treatment with disease-modifying antirheumatic drugs.
 - c. When they receive anti-TNF therapy.
 - d. When they stop anti-TNF therapy.

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 _____ E-mail _____

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 educational 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:

