A Supplement to
Skin & Allergy News®

WHEN TO TREAT, HOW TO USE:
THE EXPANDING ROLE OF
TNF-α ANTAGONISTS IN DERMATOLOGY

Getting to the Cause: TNF-α
Antagonists in the Treatment of
Psoriatic Disorders
Executive Editor
Craig Leonardi, MD
Associate Clinical Professor of Dermatology
Saint Louis University
Central Dermatology
St Louis, Mo.

Improving Outcomes With the Use of
TNF-α Antagonists: Assessment of
Treatment Safety
Alexa Boer Kimball, MD, MPH
Assistant Professor
Director, Clinical Unit for Research Trials in Skin
Harvard Medical School
Massachusetts General Hospital and
Brigham and Women’s Hospital
Boston, Mass.

Optimizing Care: Applying Outcome
Data to Clinical Practice
Alan Menter, MD
Chief, Division of Dermatology
Baylor University Medical Center
Dallas, Tex.

Jointly sponsored by the Office of Continuing Education at the State University of New York (SUNY)
Upstate Medical University and Precept Educational Sciences.

SUNY Upstate Medical University and Precept Educational Sciences gratefully acknowledge an
educational grant from Abbott Immunology in support of this CME activity.
WHEN TO TREAT, HOW TO USE: THE EXPANDING ROLE OF TNF-α ANTAGONISTS IN DERMATOLOGY

3 Getting to the Cause: TNF-α Antagonists in the Treatment of Psoriatic Disorders
Craig Leonardi, MD

5 Improving Outcomes With the Use of TNF-α Antagonists: Assessment of Treatment Safety
Alexa Boer Kimball, MD, MPH

8 Optimizing Care: Applying Outcome Data to Clinical Practice
Alan Menter, MD

Accreditation and Credit Designation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the SUNY Upstate Medical University and Precept Educational Sciences. SUNY Upstate Medical University is accredited by the ACCME to provide continuing medical education (CME) for physicians.

SUNY Upstate Medical University designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in this activity.

Target Audience
When to Treat, How to Use: The Expanding Role of TNF-α Antagonists in Dermatology is designed for dermatologists and other health care professionals who treat patients with psoriatic disease.

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

- Examine the clinical features of psoriatic diseases and the role of tumor necrosis factor (TNF-α) in the treatment of these diseases.
- Discuss the most recent psoriasis and psoriatic arthritis (PsA) clinical trial data demonstrating the efficacy and safety of TNF-α antagonists, as well as improvements these therapies bring about in quality of life.
- Focus on important issues critical to the safe use of TNF-α antagonists, such as vaccination during treatment, history of malignancy, pregnancy, combination therapy, a demyelinating disorder, or congestive heart failure.
- Illustrate the evolving role of dermatology health care professionals in the diagnosis, monitoring, and long-term treatment of psoriasis and PsA with TNF-α antagonists.

Faculty Disclosure
As a provider accredited by the ACCME, the Office of Continuing Medical Education at SUNY Upstate Medical University must ensure balance, independence, objectivity, and scientific rigor in its educational activities. All faculty are required to disclose relationships with commercial grantors or products. Faculty are also required to identify trade names, investigational products, and unlabeled uses that are discussed in their presentations. Disclosure is published in this supplement so readers may formulate their own judgment regarding the articles. Unlabeled product use is discussed in each article.

Executive Editor's Disclosure
Dr Leonardi has received grant/research support from Abbott Laboratories, Amgen Inc., Genentech, Inc., and Centocor, Inc. He is a consultant for and is on the speakers’ bureau for Abbott, Amgen, and Genentech.

Faculty Disclosure

Dr Menter has received research support from and/or is a consultant and/or lecturer for Abbott, Amgen, Biogen Idec, Centocor, Genentech, and Serono, Inc.
Getting to the Cause: TNF-α Antagonists in the Treatment of Psoriatic Disorders

Craig Leonardi, MD

Psoriasis is a chronic, inflammatory dermatologic disorder that currently affects more than 7 million Americans, and the National Psoriasis Foundation (NPF) estimates that 200,000 new cases of psoriasis are recorded in the United States each year. The median age at onset of psoriasis is 28 years; however, the development of the disease in pediatric patients is not uncommon. In fact, 10% to 15% of all individuals with psoriasis experience the clinical onset of this condition before their 10th birthday.1

Historically, psoriasis has been perceived as a relatively mild condition. However, the potentially serious negative consequences of the disease have been increasingly recognized in recent years. Over the past decade, studies have demonstrated that psoriasis is associated with considerable morbidity in both the physical and the psychosocial domains.2-4 Furthermore, although psoriasis typically is not a fatal disease, it has been estimated that approximately 400 psoriasis-related deaths occur annually, with most resulting from treatment-related complications or from systemic complications associated with more serious forms of psoriasis (eg, erythrodermic psoriasis, generalized pustular psoriasis).1

Psoriasis Traditional Treatment Model

Until recently, psoriasis had traditionally been managed using an initial approach in which all patients, regardless of disease severity, received the mildest form of treatment possible. From there, patients would progress to increasingly aggressive therapies only after less aggressive ones had been tried and proven to be ineffective. As a result, the most effective therapeutic options—phototherapy, for example, and systemic agents such as methotrexate, cyclosporine, and acitretin—would be administered to a given patient only after it had been shown that milder options, including over-the-counter and prescription topical agents, could not produce the desired therapeutic effect.

This traditional psoriasis treatment paradigm showed substantial limitations, particularly from the perspective of patients with severe psoriasis. In a 1998 telephone survey of 502 randomly selected patients with severe psoriasis who had previously responded to an NPF mail survey,2 nearly one third (32%) of all interviewees felt they were not being treated aggressively enough. In addition, an even larger percentage (78%) of interviewees reported feelings of frustration due to the ineffectiveness of the therapy that they were receiving. Patients were dissatisfied not only with the conservative approach that was being used to treat their psoriasis but also with the actual treatment options that were available.

This sentiment regarding the utility of traditional treatment options extended to clinicians. In a review published in 2000, Al-Suwaidan and Feldman3 commented that it was important for patients with psoriasis to recognize the limitations of the therapeutic modalities that were available at that time. They concluded that complete clearing of cutaneous lesions was not a realistic expectation of psoriasis treatment. Thus, in light of patient dissatisfaction with traditional approaches to the treatment of psoriasis and how patients and clinicians perceived the effectiveness of traditional psoriasis therapies, an overall change in the management of psoriasis was perhaps imminent.

Pathogenesis of Psoriasis

The evolution of our understanding of the pathogenesis of psoriasis has helped set the stage for large-scale changes in disease management. Over the last 20 years, the classic picture of psoriasis as a primary skin disorder has given way to a new model, in which psoriasis is viewed as an immunologic dysfunction with cutaneous manifestations. In short, this new model5-7,10 which is supported by numerous experimental findings from the last two decades, suggests that psoriasis is initiated by the binding of antigen-presenting cells (APCs) to an unknown antigen in the epidermis. From there, the bound antigen is internalized, processed, and subsequently expressed on the cell surface by these APCs, which then travel to the lymph nodes. In the lymph nodes, interaction of the APCs with naïve T cells results in conversion of the naïve T cells to activated memory T cells. Following clonal expansion, these newly activated T cells migrate from the lymph system to the dermis and epidermis. There, upon encountering their target antigen (ie, the antigen originally bound by the APCs), these T cells induce epidermal and dermal macrophages to release a variety of inflammatory cytokines (eg, tumor necrosis factor [TNF]-α, interleukin [IL]-1), which ultimately mediate the processes responsible for the psoriatic skin phenotype.

Of the cytokines that are putatively involved in the pathogenesis of psoriasis, TNF-α is one that has received particular attention. It has been shown that TNF-α is overproduced in psoriatic skin8,9 and, in conjunction with this finding, the known biologic functions of TNF-α have suggested a central role in the pathogenesis of psoriasis. In addition to mediating inflammation and inducing the production of other inflammatory cytokines, TNF-α is capable of promoting epidermal hyperplasia (a feature evident in psoriatic plaques) by altering the keratinocyte cell cycle, and possibly also by inhibiting keratinocyte apoptosis.10 Furthermore, TNF-α upregulates various adhesion molecules and chemokines that are critical for the trafficking of activated T cells from the lymph system to the skin.11 Thus, TNF-α expression may play a direct role in the inflammatory and hyperplastic processes that
are features of psoriasis. It may also contribute to the chronicity of the disease by stimulating T-cell trafficking, thereby promoting further operation of the psoriatic immune cascade.

Psoriatic Arthritis
In concordance with the modern view that psoriasis is not a primary skin disease but rather the cutaneous manifestation of a systemic immunologic disorder, it has been found that, in addition to the skin, the joints may be affected by the psoriatic disease process. The impact of psoriatic disease on the joints can be seen in an inflammatory joint condition known as psoriatic arthritis (PsA), which occurs in 6% to 39% of all patients with psoriasis.11,12

Articular and enthesal inflammation are the core features of PsA, leading to pain, swelling, and/or tenderness at affected joints and tendons. Psoriatic arthritis can have various other potentially serious consequences. For example, PsA is capable of taking an aggressive natural course, causing progressive damage to bone and joints. In fact, prospective observational studies have found that 43% of patients with PsA have at least one joint deformity13 and that 57% have radiographically detectable peripheral joint erosions.14 Furthermore, 11% to 19% of patients with PsA have been found to exhibit significant disability,13,14 highlighting the point that PsA-related structural damage can lead to functional impairment. Aside from joint damage and functional disability, there is also evidence to suggest that patients with PsA may experience increased mortality relative to the general population.15

Pathogenesis of PsA
As would be expected, PsA, like psoriasis, is thought to be an immune-mediated condition. Furthermore, as in the pathogenesis of psoriasis, TNF-α is believed to play an important role in the pathogenesis of PsA.17 TNF-α is known to mediate inflammatory processes and to upregulate other proinflammatory cytokines (eg, IL-1, IL-6, IL-8) that increase the production of matrix metalloproteases (enzymes that catalyze bone and cartilage erosion) by synovial chondrocytes, fibroblasts, and osteoblasts. Thus, the finding of elevated synovial TNF-α concentrations in patients with active psoriatic joint disease16 suggests that TNF-α is centrally involved in PsA-related joint inflammation. It also suggests that TNF-α promotes the destruction of bone and joints seen in more advanced cases of PsA.

Changes in the Prevailing Treatment Model of PsA
With improved understanding of the pathogenesis of psoriatic disease, dramatic changes have been made in the way that psoriasis and PsA are treated. Perhaps most significant is the emergence of novel systemic biologic treatments that specifically target key steps in the inflammatory process. Among these novel treatments, biologic agents designed to suppress pathologic TNF-α overactivity have been well characterized in the setting of psoriatic disease (as well as in other inflammatory disease states).

Currently, three such agents—the TNF-α antagonists etanercept, infliximab, and adalimumab—are known, on the basis of clinical trial findings, to be highly effective in reducing disease activity in patients with PsA. Furthermore, all three agents have been shown to have the unique ability to inhibit the progression of PsA—related damage to bone and joints.17 Likewise, more recent clinical testing has confirmed that etanercept, infliximab, and adalimumab all provide significant therapeutic benefit when used in the treatment of moderate to severe plaque psoriasis.18

By broadening the palette of effective treatment options available for patients with psoriatic disease, systemic biologic agents have facilitated the implementation of treatment strategies that are both more individualized and more comprehensive than the traditional treatment approach. This change is reflected in contemporary psoriasis treatment guidelines, such as those developed at an international consensus conference of dermatology experts in 2004. The consensus guidelines set forth at that conference state that treatment approaches should be individually tailored on the basis of disease severity and other patient-specific characteristics. These guidelines further advocate that more potent treatment modalities (eg, phototherapy, systemic therapy [either traditional or biologic]) rather than less potent ones be used in the first-line treatment of patients judged to have moderate to severe psoriasis.19

Summary
Because psoriatic disease can be associated with a variety of undesirable outcomes, appropriate and timely management is a critical goal. In the past, the management of psoriatic disease was widely considered to be suboptimal. Many patients reported dissatisfaction with the conservative treatment strategy that was traditionally followed, and patients and physicians alike voiced concerns regarding the effectiveness of traditional therapeutic options.

More recently, however, advances in the understanding of psoriatic disease as an immune-mediated phenomenon have led to the introduction of novel biologic agents that directly target the immune mechanisms thought to cause psoriasis and PsA. For example, one such class of agents, the TNF-α antagonists, has already been shown to possess efficacy in treating the spectrum of psoriatic diseases, including the unique ability to inhibit progression of PsA-related structural damage. Furthermore, in a departure from the traditional treatment paradigm, newly emerging psoriasis treatment guidelines have advocated for the use of more effective systemic treatments as first-line options for patients with moderate to severe disease. With these recent developments in disease management, there is renewed hope that favorable treatment outcomes can become the norm, even for those patients who are most severely affected by psoriatic disease.
Improving Outcomes With the Use of TNF-α Antagonists: Assessment of Treatment Safety

Alexa Boer Kimball, MD, MPH

Throughout the clinical testing programs for etanercept, infliximab, and adalimumab, the aggregate exposure of patients to each of these agents has amounted to thousands of patient-years. Based on this experience, the majority of which has been accumulated in rheumatoid arthritis (RA), it has been concluded that the tumor necrosis factor (TNF-α) antagonists as a class have a good risk-benefit profile, and that the safety risks associated with TNF-α antagonist use are typically manageable. Still, despite having a favorable overall safety profile, anti–TNF-α therapy may, in some cases, disrupt normal TNF-α-mediated physiologic processes to such an extent that the likelihood of experiencing a serious adverse event is increased. Thus, an understanding of the serious adverse event risks associated with TNF-α antagonist use and of the steps that can be taken to address these risks is critical for clinicians seeking to administer TNF-α antagonist therapy.

Tuberculosis and Other Serious Infections

Because of the role of TNF-α in normal immune function, anti–TNF-α therapy may confer an increased risk of serious infection, particularly tuberculosis (TB). Available data suggest that TNF-α is involved in processes that are necessary for preventing the initial proliferation of Mycobacterium tuberculosis (MTB) in infected individuals and for subsequently maintaining the MTB infection in a controlled, latent state. Therefore, patients receiving anti–TNF-α therapy may have an increased likelihood of developing disseminated, active TB disease, either through inadequate containment of a primary MTB infection or through activation of a previously latent MTB infection.

In clinical experience, cases of active TB have been documented in TNF-α antagonist-treated patients in the clinical trial setting as well as in postmarketing surveillance. However, the true TB risk for patients receiving anti–TNF-α therapy is unknown, since background TB rates in RA, psoriatic arthritis (PsA), and psoriasis populations have not been determined. Nonetheless, based on existing evidence, it is reasonable to believe that in general, TNF-α antagonist therapy does confer some amount of increased TB risk, although the degree to which TB risk is elevated appears to vary somewhat depending on the TNF-α antagonist used.

In addition to TB risk, the risk of developing other serious infections has been cited as a potential hazard of TNF-α inhibition. In a recent meta-analysis of safety data from 3- to 12-month placebo-controlled clinical trials of infliximab or adalimumab therapy for RA, Bongartz and colleagues found that the likelihood of serious infection was significantly greater for patients who received active treatment than for placebo-treated patients (odds ratio [OR], 2.0). In addition, based on the calculated rates of serious infection, the authors determined that the number needed to harm (NNH) was 59, meaning that treatment of 59 patients with infliximab or adalimumab for 3 to 12 months would be projected to result in one more serious infection than could be expected if 59 patients received placebo for the same length of time.

Interpretation of the findings presented by Bongartz and colleagues is complicated by certain methodologic limitations. Perhaps most notably, serious infection rates for actively treated and placebo-treated patients were calculated on a “per-patient” basis, rather than on a “per-patient-year” basis. Consequently, the reported serious infection OR for actively treated patients relative to placebo-treated patients was not controlled for the apparent difference between the two groups in terms of the average length of study participation per patient. The average placebo-treated patient in the meta-analysis appeared to have logged a shorter duration of study participation than did the average actively treated patient. Thus, having spent less time as a study participant, the average placebo-treated patient presumably would have had less opportunity to have had a serious infection detected by a study investigator, as well as less exposure to methotrexate and other immunosuppressive agents that were often administered concomitantly with randomized treatment during the studies analyzed. For these reasons, the decision to calculate infection rates on a per-patient basis may have resulted in an artificially elevated OR estimate for actively treated patients. Consistent with this hypothesis, previous analyses of safety findings from RA clinical programs for etanercept and adalimumab have indicated that the incidence of serious infection per patient-year of TNF-α antagonist exposure does not exceed the background incidence of serious infection in patients with RA.

Malignancy

Rare cases of treatment-emergent malignancy (lymphoma, typically) have been documented in TNF-α antagonist-treated patients. However, assessment of whether TNF-α inhibition is causally linked to an increased risk of malignancy has been complicated by the finding that the normal recipients of TNF-α antagonist therapy—patients with severe RA or severe psoriatic disease—already have an inherently elevated malignancy risk. In this regard, striking findings were made in a case-control study involving patients retrospectively identified from a population-based Swedish RA database covering the period from 1964 to 1995. After grouping patients into deciles according to cumulative RA activity, the investigators in that study found that lymphoma risk remained relatively constant across the lowest six disease-activity deciles. However, in higher deciles, a dramatic risk...
increase was observed, with lymphoma ORs as high as 9.4 and 61.6, respectively, recorded in the second highest and highest disease-activity deciles (relative to the lowest decile).

Despite the confounding link between inflammatory disease activity and malignancy, efforts have been made to characterize the association between TNF-α antagonist use and malignancy risk. Most recently, in the previously described safety meta-analysis by Bongartz and colleagues,4 the investigators concluded, based on data from nine placebo-controlled RA trials, that patients exposed to infliximab or adalimumab had a significantly elevated malignancy risk relative to placebo-treated patients (OR, 3.3; NNH, 154). However, once again, certain methodologic issues must be considered in interpreting this result. For instance, for reasons analogous to those discussed previously, the reported malignancy OR may have been falsely elevated because of the decision to calculate malignancy rates on a per-patient basis as opposed to a per-patient-year basis. Also problematic is that all treatment-emergent malignancies, regardless of timing, were considered in calculating malignancy risk. It is generally thought that the typical time from initiation of the carcinogenic process to clinical emergence of malignancy is on the order of months to years, or even longer in the case of nonmelanoma skin malignancy.

Thus, in the trials analyzed, malignancies arising shortly after baseline, as well as nonmelanoma skin malignancies arising at any postbaseline time point, may not have been attributable to study treatment. Two sensitivity analyses—one that excluded malignancies detected within 6 weeks postbaseline and another that excluded all nonmelanoma skin malignancies—yielded malignancy ORs similar to the OR yielded by the primary meta-analysis. (In other words, the relative likelihood of malignancy for TNF-α antagonist-treated patients compared with placebo-treated patients did not change.) Nonetheless, despite the absence of a substantial change in malignancy OR in either sensitivity analysis relative to the primary meta-analysis, NNH values would be expected to increase considerably with the exclusion of nonmelanoma skin malignancies and malignancies detected within 6 weeks of baseline, since approximately one third of all malignancies occurring in TNF-α antagonist-treated patients in the meta-analysis fell into one of these two categories. The exact increase in NNH upon exclusion of such malignancies is unknown, however, as Bongartz et al4 did not calculate NNH values using the data obtained in their sensitivity analyses of malignancy risk.

**Other Serious Adverse Events**

In a randomized pilot trial of infliximab therapy for moderate to severe congestive heart failure (CHF), patients receiving high-dose infliximab (10-mg/kg doses) were significantly more likely than were placebo-treated patients to achieve an unfavorable clinical end point (death due to any cause or hospitalization for worsening CHF) during the 28-week study period (hazard ratio, 2.84).9 This finding, along with anecdotal reports of CHF exacerbation in patients receiving TNF-α antagonist therapy for other conditions,10,12 has led to the hypothesis that TNF-α inhibition may be associated with the worsening of existing cases of CHF, particularly cases that are of moderate or high severity.

Aside from CHF, demyelinating disease has also been putatively linked to TNF-α antagonist use, primarily based on results from a randomized, placebo-controlled trial examining the use of the anti–TNF-α fusion protein lenepact to treat multiple sclerosis (MS).13 That trial found that lenepact, when compared with placebo, was associated with a significant, dose-dependent increase in the annualized incidence of MS exacerbations. Nonetheless, data from postmarketing surveillance of the three commercially available TNF-α antagonists suggest that treatment-emergent demyelination is relatively rare, with analyses of voluntary adverse event-reporting databases yielding incidence rates of 0.01 to 0.03 demyelinating events per 100 patient-years exposure in patients receiving etanercept, infliximab, or adalimumab.14,15

Hepatotoxicity has emerged as another safety issue that may warrant attention in TNF-α antagonist-treated patients. Recent concerns regarding hepatotoxicity have centered around infliximab, because of findings made in a combined analysis of four randomized, controlled clinical trials (duration, 24 to 52 weeks) of infliximab therapy for psoriatic disease.16 In that analysis, 3.4% of patients randomized to receive 3-mg/kg infliximab doses and 6.4% of patients randomized to receive 5-mg/kg infliximab doses showed marked treatment-emergent increases in serum alanine aminotransferase (ALT) levels. Moreover, marked serum ALT elevations were documented in 4.7% of all placebo-randomized patients who crossed over to receive infliximab therapy during the course of a trial. In con-
When to Treat, How to Use: The Expanding Role of TNF-α Antagonists in Dermatology

Managing TNF-α Antagonist-Related Safety Risks

Pretreatment Interventions

Thorough pretreatment screening of candidates for TNF-α antagonist therapy is critical for minimizing the likelihood of serious adverse events. Pretreatment screening efforts should include the acquisition of a medical history, with emphasis on historical features (eg, personal history of lymphoma, CHF, or hepatic disease; personal/family history of demyelination) that may put the candidate at increased risk for a serious adverse event. Furthermore, it is generally useful to evaluate the overall health of the candidate by performing a physical examination and laboratory workup as part of pretreatment screening. Equipped with the information obtained through screening, clinicians can perform individualized risk-benefit assessments and thereby determine which patients are well suited for anti-TNF-α therapy.

For patients who are judged to be suitable candidates for TNF-α antagonist use, TB testing and, if necessary, TB treatment are additional important steps that must be considered prior to the initialization of TNF-α antagonist therapy. Current guidelines state that patients about to begin TNF-α antagonist therapy should undergo purified protein derivative (PPD) testing to ascertain whether an MTB infection is present. Patients found to be PPD negative may immediately start receiving anti-TNF-α therapy, whereas it is advised that patients with positive PPD findings undergo chest radiography to determine the appropriate course of action before initiating TNF-α antagonist use (Figure).

Interventions While Treatment Is Ongoing

Regular follow-up is essential for maximizing treatment safety once TNF-α antagonist therapy is underway. Although there is no standard schedule of follow-up for patients receiving TNF-α antagonist therapy, it is not uncommon for patients to undergo follow-up assessment once every 2 to 3 months during the course of treatment. Furthermore, follow-up may need to be performed more frequently for TNF-α antagonist therapy recipients who have risk factors (eg, history of CHF) that increase their susceptibility to serious adverse events.

At follow-up visits, clinicians should be watchful for signs that are suggestive of a serious treatment-related adverse event (Table), and they should be prepared to halt treatment if it is suspected that such an event has occurred. Oral questioning and physical examination are typically sufficient for follow-up of patients receiving anti-TNF-α therapy. However, standard laboratory testing is often performed twice yearly as part of routine follow-up for TNF-α antagonist therapy recipients, and, aside from twice-yearly laboratory evaluation, a more frequent schedule of liver function testing may benefit patients in whom hepatic adverse events are of more concern (eg, patients with known hepatic risk factors, patients receiving infliximab therapy).

Summary

Although there is substantial evidence indicating that TNF-α antagonists are generally safe and well tolerated in the treatment of inflammatory diseases (including psoriasis and PsA), patients receiving anti-TNF-α therapy may have an increased susceptibility to certain serious adverse events. However, serious adverse events arising in association with TNF-α antagonist use appear to be uncommon, and, overall, TNF-α antagonists are thought to have a favorable risk/benefit profile. Moreover, by taking appropriate steps both before the initiation of treatment and once treatment is underway, clinicians can further reduce the risk of causing harm with a TNF-α antagonist, thereby making the achievement of favorable treatment-related outcomes an even more readily attainable goal.

References


TABLE. Possible Clinical Features of Rare But Serious Adverse Events That May Occur in Association With TNF-α Antagonist Use

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Possible Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB or other serious infection</td>
<td>Unexplained night sweats, chills, fever with body temperature exceeding 100°F, cough, chronic diarrhea, weight loss</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Painless swelling of the lymph nodes; itchy, reddish-purple subcutaneous lumps; swelling of the chest or abdomen</td>
</tr>
<tr>
<td>CHF</td>
<td>Shortness of breath (typically orthopnea), edema of the lower extremities, weight gain, fatigue, confusion/cognitive impairment</td>
</tr>
<tr>
<td>Demyelination</td>
<td>Tingling, numbness, or weakness (particularly if unilateral); visual disturbances; incoordination</td>
</tr>
<tr>
<td>Severe hepatotoxicity</td>
<td>Abnormal LFT results, jaundice, abdominal pain, discoloration of stools, darkening of urine</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; LFT = liver function test; TB = tuberculosis; TNF = tumor necrosis factor.

Continued on page 11
Optimizing Care: Applying Outcome Data to Clinical Practice

Alan Menter, MD

The first large-scale trials of tumor necrosis factor (TNF-α) antagonist therapy for psoriatic disease showed that etanercept, a dimeric construct comprising two monomeric units in which the human immunoglobulin G1 Fc region is fused to the extracellular ligand-binding domain of the human p75 TNF receptor, was superior to placebo in treating psoriasis and psoriatic arthritis (PsA).\(^2,3,6\) Since then, however, two other TNF-α antagonists, the murine/human monoclonal anti-TNF-α antibody infliximab and the human monoclonal anti-TNF-α antibody adalimumab, have also been identified through clinical testing as effective options for treating psoriatic disease.\(^3,7\)

Here, an overview of outcome data from clinical trials of etanercept, infliximab, and adalimumab in the setting of psoriatic disease is provided.

Psoriatic Arthritis

The efficacy profiles of etanercept, infliximab, and adalimumab in PsA are well established—in fact, all three agents are approved by the US Food and Drug Administration (FDA) for the treatment of PsA. Separate placebo-controlled trials have shown that each agent, when administered using a standard regimen (etanercept: 25 mg twice weekly [biw]; infliximab: 5 mg/kg at baseline, weeks 2 and 6, and then once every 8 weeks; adalimumab: 40 mg every other week [eow]), is effective in reducing disease activity in patients with PsA. In these trials, between baseline and 10 to 12 weeks (nonresponder imputation [NRI] analyses), approximately 60% of actively treated patients experienced a reduction of at least 20% in overall arthritic disease activity, approximately 35% to 40% experienced a reduction of at least 50%, and approximately 10% to 20% experienced a reduction of at least 70%.\(^2,3,6\) Notably, these same trials have also demonstrated the efficacy of etanercept, infliximab, and adalimumab in inhibiting the advancement of PsA-related bone and joint damage.\(^2,3,6\) This proven ability to slow structural deterioration is a key feature of anti–TNF-α therapy, given the potentially debilitating effects of progressive bone and joint damage associated with PsA.

Psoriasis

Etanercept

In addition to being approved for the treatment of PsA, etanercept is indicated by the FDA for use in moderate to severe plaque psoriasis. Various clinical trials have yielded similar findings regarding the efficacy of etanercept in treating the cutaneous symptoms of psoriasis.\(^1,8,9\) In the most recent trial,\(^9\) patients with moderate to severe plaque psoriasis were randomized to receive 12 weeks of double-blind treatment with either etanercept 50 mg biw or placebo administered via subcutaneous (SC) injection. By the end of the 12-week, double-blind treatment period (last-observation-carried-forward [LOCF] analysis), etanercept therapy (n=311) was found to be associated with a significantly higher rate of PASI 75 response (47% vs 5%, respectively; \(P=0.0001\)) when compared with placebo (n=307). (PASI 75 response, defined as a decrease in Psoriasis Area and Severity Index [PASI] score of at least 75% relative to baseline, is considered indicative of a clinically significant improvement in cutaneous symptoms\(^10\) and is therefore commonly reported as a primary end point in contemporary trials.) Furthermore, looking beyond 12 weeks of double-blind treatment with either etanercept 50 mg biw, relative to their placebo-treated counterparts, experienced significantly larger mean improvements in scores on three secondary efficacy measures—the Beck Depression Inventory (\(P=0.0001\)), the Hamilton Depression Rating Scale (\(P=0.0012\)), and the Functional Assessment of Chronic Illness Therapy Fatigue scale (\(P=0.0001\))—between baseline and 12 weeks (LOCF), suggesting that TNF-α antagonist therapy may also confer benefit in relieving symptoms of depression and fatigue in patients with psoriatic disease.

The aforementioned 12-week trial was immediately followed by an 84-week extension study,\(^11\) in which all participants, regardless of their randomization in the 12-week trial, received open-label treatment with etanercept 50 mg biw. At the end of the extension study period, 96 weeks from baseline (ie, from the start of double-blind treatment), the PASI 75 response rate for patients originally randomized to etanercept therapy was 51% (LOCF), similar to the response rate seen at 12 weeks from baseline. From a practical perspective, this finding is significant in that it demonstrates that clinical responses can be maintained effectively for up to 2 years with continued TNF-α antagonist therapy. Nonetheless, an important point to note is that the 50-mg biw dosing regimen shown to be effective in maintaining PASI 75 responses over a 2-year period differs from the FDA-approved regimen for etanercept dosing in patients with moderate to severe plaque psoriasis. The FDA-approved dosing regimen—etanercept 50 mg biw for the first 12 weeks of treatment followed by etanercept 50 mg once weekly (qw) thereafter—has been found to yield PASI 75 responses that are robust for up to 12 weeks after the switch is made from biw to qw dosing.\(^3\) However, there is evidence to suggest that, at subsequent time points, rates of PASI 75 response achieved using this step-down regimen are slightly reduced.\(^3\)
Infliximab

Infliximab is indicated in the European Union for treatment of moderate to severe plaque psoriasis, and the FDA is currently reviewing an application requesting the same indication for infliximab in the United States. The efficacy of infliximab therapy for psoriatic skin disease was characterized in a 50-week trial involving patients with moderate to severe plaque psoriasis. In that trial, patients were randomized at baseline to one of two treatment arms—an infliximab arm, in which patients received double-blind, intravenous infusions of infliximab 5 mg/kg at baseline, weeks 2 and 6, and then once every 8 weeks for the remainder of the study; or a placebo arm, in which patients received double-blind placebo intravenous infusions at weeks 0, 2, 6, 14, and 22 before crossing over, still in a double-blind manner, to receive infusions of infliximab 5 mg/kg at weeks 24, 26, and 30 and then every 8 weeks thereafter.

Prior to the crossover portion of the trial, the rate of PASI 75 response was found to be significantly higher in the infliximab arm (n=501) than in the placebo arm (n=77). This was the case at the study's primary end point, 10 weeks from baseline (PASI 75 response rates, 80% vs 3% [NRI], respectively; P<0.0001), and PASI 75 responses in the infliximab arm were subsequently well maintained through study week 24. After week 24, however, responses were lost to some extent among infliximab-randomized patients, such that at week 50 (modified NRI; n=281), these patients exhibited a PASI 75 response rate of 61%.

Long-term efficacy outcomes for infliximab-randomized trial participants showed some association with serologic parameters. In an analysis of infliximab-randomized patients who (1) achieved a PASI 75 response at week 10 and (2) were subsequently tested for anti-infliximab antibodies at selected time points through week 66 postbaseline (ie, 16 weeks after study end), it was found that only 39% of those who tested positive for anti-infliximab antibodies, compared with 81% of antibody-negative patients and 96% of patients with inconclusive antibody assay results, had their PASI 75 responses maintained through week 50. Taken together, these findings suggest that sustained responses to infliximab are dependent on the maintenance of stable, elevated serum infliximab concentrations, and they also suggest that patients who develop anti-infliximab antibodies may have a reduced likelihood of experiencing a prolonged response to infliximab therapy. In general, however, more comprehensive characterization of the variables that influence the long-term efficacy of infliximab is warranted.

Adalimumab

Clinical trial findings made in patients with psoriasis suggest that adalimumab is also an effective option for treating the cutaneous manifestations of psoriatic disease. In one trial designed to assess the therapeutic utility of adalimumab in the setting of psoriasis, 7 patients who had moderate to severe plaque psoriasis for at least 1 year leading up to study entry were randomized to receive 12 weeks of double-blind treatment with adalimumab 40 mg qw, adalimumab 40 mg eow, or placebo via SC injection. At the conclusion of the 12-week study period, both adalimumab regimens were found to be superior to placebo with regard to PASI 75 response rates (adalimumab 40 mg qw [n=52], 80%; adalimumab 40 mg eow [n=45], 53%; placebo [n=50], 4%; P<0.001 for each adalimumab arm vs placebo [NRI]). Furthermore, an additional noteworthy finding made after 12 weeks of treatment was that 26% of all patients receiving adalimumab 40 mg qw and 11% of all patients receiving adalimumab 40 mg eow, compared with 0% of placebo-treated patients (P<0.001 for each adalimumab arm vs placebo [NRI]), exhibited a PASI 100 response—that is, a 100% reduction in PASI score, corresponding to complete lesional clearing.

The long-term efficacy of adalimumab was explored in a 48-week extension study conducted immediately following the previously described 12-week trial. In this extension study, patients originally randomized to either adalimumab treatment arm continued to receive treatment as dictated by their randomization, whereas placebo-randomized patients were switched from placebo to adalimumab 40 mg eow. Analysis of long-term efficacy data from the extension study for patients who had initially been randomized to receive adalimumab therapy revealed that there was some loss of response among those originally assigned to adalimumab 40 mg qw during the placebo-controlled period. At the close of the extension study, after 48 additional weeks of treatment, patients in the adalimumab 40-mg qw arm (n=50) registered a PASI 75 response rate of 64% (NRI), as compared with 80% at the end of the placebo-controlled treatment period. Nonetheless, it was found that the cutaneous responses elicited by adalimumab 40 mg eow, the dosing schedule approved for use in PsA, were highly robust over the long term. In particular, among patients initially randomized to receive 12 weeks of placebo-controlled treatment with adalimumab 40 mg eow (n=45), continued eow dosing throughout the 48-week extension study resulted in a final...
PASI 75 response rate of 56% (NRI), slightly higher than the 53% response rate recorded at the end of placebo-controlled treatment.

Another important finding yielded by the analysis of long-term efficacy results was that it was not uncommon for PASI 100 responses to be maintained over the course of prolonged treatment with adalimumab. Among patients who received up to 60 weeks of treatment (12 weeks of treatment in the placebo-controlled period and 48 weeks of treatment in the extension study period) with adalimumab 40 mg qw (n=50), 26% were classified as PASI 100 responders at week 60 (NRI). Furthermore, of the 45 patients who received up to 60 weeks of treatment with adalimumab 40 mg eow, 16% had documented PASI 100 responses at week 60 (NRI).

In practical terms, these findings indicate that a nontrivial percentage of patients treated with adalimumab experienced sustained, complete clearance of their psoriatic skin lesions. Thus, in addition to providing clinically meaningful relief of cutaneous symptoms, TNF-α antagonist therapy may offer hope for the total eradication of psoriatic lesions, a highly favorable outcome that has long been considered unattainable.

Summary

In recent years, the TNF-α antagonists etanercept, infliximab, and adalimumab have emerged as effective options for reducing arthritic activity and inhibiting disease progression in patients with PsA, and, as a result, all three agents are approved by the FDA for the treatment of PsA. Nonetheless, the efficacy of TNF-α antagonist therapy does not appear to be limited to the joint manifestations of psoriatic disease, as clinical trials have demonstrated that all three TNF-α antagonists, when administered under appropriate conditions, are also capable of producing prolonged, clinically relevant cutaneous responses in patients with moderate to severe plaque psoriasis. These findings (along with preliminary findings indicating that TNF-α inhibition may alleviate symptoms of depression and fatigue in patients with psoriatic disease) suggest that TNF-α antagonist therapy can serve as a highly effective intervention for treating either psoriatic disease entity alone, and also as an option for comanaging PsA and psoriasis in patients requiring therapy for both conditions.

References

Getting to the Cause: TNF-α Antagonists in the Treatment of Psoriatic Disorders

Continued from page 4

References

15. Kent JD, Pangan AL, Fitzpatrick SB. Analysis of the US postmarketing safety of adalimumab (Humira®) in patients with rheumatoid arthritis during the first 2 years after approval. Presented at: European League Against Rheumatism Annual Meeting; June 8-11, 2005; Vienna, Austria.

Improving Outcomes With the Use of TNF-α Antagonists: Assessment of Treatment Safety

Continued from page 7

15. Kent JD, Pangan AL, Fitzpatrick SB. Analysis of the US postmarketing safety of adalimumab (Humira®) in patients with rheumatoid arthritis during the first 2 years after approval. Presented at: European League Against Rheumatism Annual Meeting; June 8-11, 2005; Vienna, Austria.
Skin & Allergy News®
When to Treat, How to Use: The Expanding Role of TNF-α Antagonists in Dermatology

CME Post-Test and Evaluation

Release Date: November 1, 2006
Expiration Date: November 1, 2007
Estimated Time to Complete This Activity: 1.0 hour

CONTINUING EDUCATION INSTRUCTIONS: In order to obtain 1 AMA PRA Category 1 Credit™, participants are required to: (1) Read the activity objectives, review the publication, and complete the following Activity Registration and Activity Evaluation Forms and Post-Test Answer Form (must score a minimum grade of 80%) and (2) Send the completed forms to: Precept Educational Sciences, Attn: Registrar, by mail: 400 Connell Drive, Suite 602, Berkeley Heights, NJ 07922-2705; by FAX: (908) 288-0150.

INSTRUCTIONS: Circle the most appropriate response. Eight of 10 correct responses are required for credit.

1. According to the National Psoriasis Foundation, approximately how many new cases of psoriasis are documented in the United States annually?
   a. 100,000  
   b. 150,000  
   c. 200,000  
   d. 250,000

2. In the traditional approach to treatment of psoriasis, which of the following therapeutic modalities would be the first to be used to treat a patient with severe psoriasis?
   a. Topical therapy  
   b. Phototherapy  
   c. Systemic therapy  
   d. Systemic biologic therapy

3. Available data indicate that psoriatic arthritis is present in up to what percentage of patients with psoriasis?
   a. 7%  
   b. 18%  
   c. 26%  
   d. 39%

4. The dimeric fusion protein construct etanercept consists of monomers in which a __________ component is linked to a human p75 tumor necrosis factor (TNF-α) receptor component.
   a. Human immunoglobulin A1  
   b. Human immunoglobulin E  
   c. Human immunoglobulin G1  
   d. Human immunoglobulin M

5. In clinical testing, approximately what percentage of patients with psoriatic arthritis experienced a reduction of at least 50% in overall disease activity after 10 to 12 weeks of standard treatment with a TNF-α antagonist?
   a. 15% to 20%  
   b. 25% to 30%  
   c. 35% to 40%  
   d. 45% to 50%

6. Which of the following is commonly reported as a primary efficacy measure in contemporary psoriasis clinical trials?
   a. Psoriasis Area and Severity Index (PASI) 50 response rate  
   b. PASI 75 response rate  
   c. PASI 90 response rate  
   d. PASI 100 response rate

7. Which of the following agents is not a TNF-α antagonist?
   a. Adalimumab  
   b. Alefacept  
   c. Infliximab  
   d. Lenercept

8. In voluntary adverse event-reporting databases, the incidence of treatment-emergent demyelination in patients receiving TNF-α antagonist therapy has ranged from ___ to ___ cases per 100 patient-years exposure.
   a. 0.01; 0.03  
   b. 0.05; 0.08  
   c. 0.1; 0.3  
   d. 0.5; 0.8

9. In a pooled analysis of controlled trials of infliximab therapy for psoriatic disease, it was found that 6.4% of patients randomized to receive infliximab 5 mg/kg had marked treatment-emergent increases in levels of what hepatic enzyme?
   a. Aspartate aminotransferase  
   b. Alanine aminotransferase  
   c. γ-Glutamyltransferase  
   d. Alkaline phosphatase

10. Which of the following statements is concordant with current guidelines for tuberculosis (TB) screening and treatment in patients about to receive TNF-α antagonist therapy?
    a. A patient who has active TB disease should have the disease treated to resolution before starting TNF-α antagonist therapy.  
    b. A patient who has latent TB infection should complete a full course of TB prophylaxis before starting TNF-α antagonist therapy.  
    c. A patient who has negative purified protein derivative test results should have TB prophylaxis initiated before starting TNF-α antagonist therapy.  
    d. None of the above

EVALUATION FORM: To assist in evaluating the effectiveness of this activity and to make recommendations for future activities, please take a moment to complete this evaluation form. (Note: CME credit letters will be issued only on receipt of a completed evaluation form.)

Please Print
Full Name________________________  Degree__________ Speciality______________________
Address__________________________  City________________________ State________ ZIP______
Phone__________________________ FAX________________________
E-mail__________________________ Signature________________

Please indicate amount of time spent on this activity:
AMA PRA Category 1 Credit™ (maximum 1.0 hours):

___ hrs ___ min spent on activity
If you have any questions regarding this CME activity, please contact:
Continuing Medical Education, SUNY Upstate Medical University,
750 East Adams Street, WH 217, Syracuse, NY 13210, (800) 283-4606, (315) 464-4422 (FAX), cme@upstate.edu, www.upstate.edu/cme

Activity Evaluation Form:
1. This enduring material met the stated objectives.
   YES NO (circle one)
2. The information increased my awareness/understanding of the subject matter.
   YES NO (circle one)
3. The information will help me improve patient care.
   YES NO (circle one)
4. The information presented will influence how I practice.
   YES NO (circle one)
5. This enduring material was free from commercial bias.
   YES NO (circle one)
6. I would recommend this program to my colleagues.
   YES NO (circle one)

Please list any topics that you would like to see addressed in future activities: __________________________

Copyright © 2006 Elsevier Inc. www.skinandallergynews.com