



A SUPPLEMENT TO

Skin & Allergy News®



Two Years of Clinical Experience With Biologic Agents for Psoriasis

Latest Study Findings and Individual Physician Experience

**Biologic Agents for Psoriasis:
Latest Study Findings**

**New Biologic Agents
on the Horizon**

**Individual Physician
Experience and Insights**

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Target Audience

- Dermatologists
- Dermatology physician assistants and nurse practitioners
- Dermatology nurses

Educational Needs

The past several years have seen a major change in the treatment options available for patients with psoriasis and their physicians. The emerging clinical data indicate that biologic agents may offer safer therapeutic options for long-term continuous control of moderate to severe psoriasis than has been possible in the past with traditional systemic agents. This will translate into a major improvement in quality of life for the patient. Three biologic agents have been approved for the treatment of psoriasis, with an additional two that are likely to be approved in the near future. This educational activity provides physicians with an overview of the established information regarding each of these biologic agents and a summary of the latest information about the use of biologic agents in psoriasis.

Learning Objectives

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

- Describe the established clinical profiles of the biologic agents that are currently approved for the treatment of psoriasis.

- Describe the evolving clinical profiles of the biologic agents that are likely to be approved for psoriasis in the near future, and list some of the new agents in the early stages of clinical development.
- Evaluate the latest findings on the long-term use of biologic agents in the treatment of psoriasis.
- List the key safety concerns associated with each of the biologic agents.

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Dr Hamilton has received grants/research support from Abbott Laboratories, Amgen Inc., Biogen Idec Inc., Centocor, Inc., Genentech, Inc., Immunex Corp., Synta Pharmaceuticals Corp., and Vertex Pharmaceuticals Incorporated. She is a consultant to Amgen, Dermik Laboratories, and Genentech. **Dr Hamilton** is also on the Speaker's Bureau at Amgen, Biogen, Centocor, Dermik, and Genentech. **Dr Yamauchi** has received grant/research support from Abbott, Amgen, Biogen, Genentech, and Serono S.A. He is a consultant to and on the Speaker's Bureau at Amgen, Biogen, and Genentech. **Dr Hamilton** and **Dr Yamauchi** both discuss the unlabeled use of adalimumab, alefacept, efalizumab, etanercept, and infliximab for the treatment of psoriasis.

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Two Years of Clinical Experience With Biologic Agents for Psoriasis

Latest Study Findings and Individual Physician Experience

Introduction

Since the introduction of biologic agents for the treatment of moderate to severe psoriasis 2 years ago, every dermatology meeting has featured an increasing number of sessions and poster presentations on this expanding therapeutic category. Most of the material presented prior to this year focused on the findings of short-term, controlled clinical studies designed to support Food and Drug Administration (FDA) approval. Poster and podium presentations from a recent dermatology meeting held in February 2005 in New Orleans, La., have featured a larger number of long-term clinical studies as well as explorations of alternative dosing regimens. In addition, several physicians reported on their own clinical experience with biologic agents. Indeed, as more physicians begin to incorporate biologic agents into their clinical practices, they will be better able to determine how well the results of controlled clinical trials reflect what can be expected with expanded use of these agents and how best to optimize treatment outcomes in different patient types.

This review will focus on the latest findings on the three biologic agents that are currently approved for the treatment of psoriasis (efalizumab, etanercept, and alefacept) and the two that are likely to be approved in the near future (infliximab and adalimumab). This review will also cover preliminary findings for two agents in the early stages of development (onercept and an interleukin [IL]-12 antibody). For each of the biologic agents, the new data will be preceded by an overview of the established efficacy and safety profile so that the new findings can be placed in their appropriate context.

Biologic Agents for Psoriasis: Latest Study Findings

Efalizumab

Clinical Profile

Efalizumab is a humanized monoclonal antibody that blocks T-cell activation, reactivation, and trafficking into the skin by binding to CD11a (a leukocyte function-associated antigen type 1 subunit) on T cells.¹ It is approved for the treatment of moderate to severe psoriasis and is administered by the patient as weekly subcutaneous (SC) injections involving an initial conditioning dose of 0.7 mg/kg SC followed by 1 mg/kg SC each week thereafter.¹

Efalizumab has shown a consistent safety and efficacy profile in short-term clinical trials. When the efficacy results of three 3-month, double-blind, placebo-controlled trials (1651 total patients; 1172 treated with efalizumab) were pooled, Psoriasis Area and Severity Index (PASI) 75 was achieved by 27% of efalizumab-treated patients and 4% of placebo-treated patients after 3 months of treatment. Also at the 3-month time

- There is no one best biologic therapy, but rather agents are suitable for different types of patients
- The variety of available biologic agents increases the possibility that individual patients can find a therapy that works for them
- Biologic therapies may offer safer treatment options for the long-term continuous control of moderate to severe psoriasis than has been possible in the past

point, PASI 50 was achieved by 59% of efalizumab patients and 14% of placebo patients.² When data from the individual studies were analyzed separately, the percentage of patients achieving PASI 75 after 3 months of treatment ranged from 27%³ to 39%.⁴ The short-term safety database for efalizumab includes the results from these three trials together with those of a fourth 3-month safety study (2335 patients total; 1620 treated with efalizumab). The most common adverse events were mild to moderate flu-like symptoms (including headache, chills, fever, and nausea) that occurred after the first one or two doses

of efalizumab. By the third dose, the rates of these acute adverse events among efalizumab-treated and placebo-treated patients were similar. The incidence of serious adverse events, infection, and malignancy was low and was also similar for efalizumab and placebo.²

In a 6-month clinical trial,⁵ patients were treated with either efalizumab 1 mg/kg for 3 months (double-blind phase) or placebo, followed by an additional 3 months of efalizumab 1 mg/kg (open-label phase). In this study, 27% and 44% of efalizumab-treated patients achieved PASI 75 after 3 and 6 months, respectively. Efalizumab was well tolerated through 6 months of therapy, with a decline in overall adverse events with continued treatment because of the lack of the acute adverse reaction associated with the first one or two injections.⁵ In short-term clinical studies (through 3 months), psoriasis adverse events were reported in 3% of efalizumab-treated patients and 1% of placebo-treated patients.¹ Such psoriasis adverse events can manifest in one of two ways: transient neutrophilic dermatosis (formerly referred to as “papular eruption”),

which can generally be managed by adding a topical therapy until the problem resolves, or generalized inflammatory exacerbation (formerly referred to as “generalized inflammatory flare”), which is much less frequently seen and which may require adding another systemic therapy.⁶ In placebo-controlled portions of the clinical trials, only five cases of serious psoriasis worsening (among 2859 patients; <0.2%) occurred during efalizumab treatment.¹

Latest Findings

Recent presentations on efalizumab included information on its safety and efficacy during 3 years of continuous use in patients with psoriasis and a prospective analysis of its safety and efficacy in a cohort of “high-need” patients (those unable to use at least two other currently available systemic psoriasis therapies).

Long-term Therapy. A 3-year open-label study of efalizumab in patients with psoriasis demonstrated that both efficacy and safety were maintained over 3 years of continuous treatment.⁷ In this study, patients were treated for the first 3 months with efalizumab 2 mg/kg/wk. This dosage was used because the study was initiated before it was determined that 1 mg/kg was the most appropriate dose.¹ Those patients who had achieved PASI 50 or a Physician’s Global Assessment (PGA) of mild, minimal, or clear were eligible to enroll in the maintenance treatment phase and receive 1 mg/kg/wk for an

EFALIZUMAB

- ▶ **A humanized monoclonal antibody that blocks T-cell activation, reactivation, and trafficking into the skin**
- ▶ **Approved for the treatment of moderate to severe psoriasis**
- ▶ **Administered by the patient as weekly subcutaneous (SC) injections of 1 mg/kg following a single 0.7-mg/kg conditioning dose**
- ▶ **Evaluated in long-term use during 3 years of continuous use in psoriasis patients**

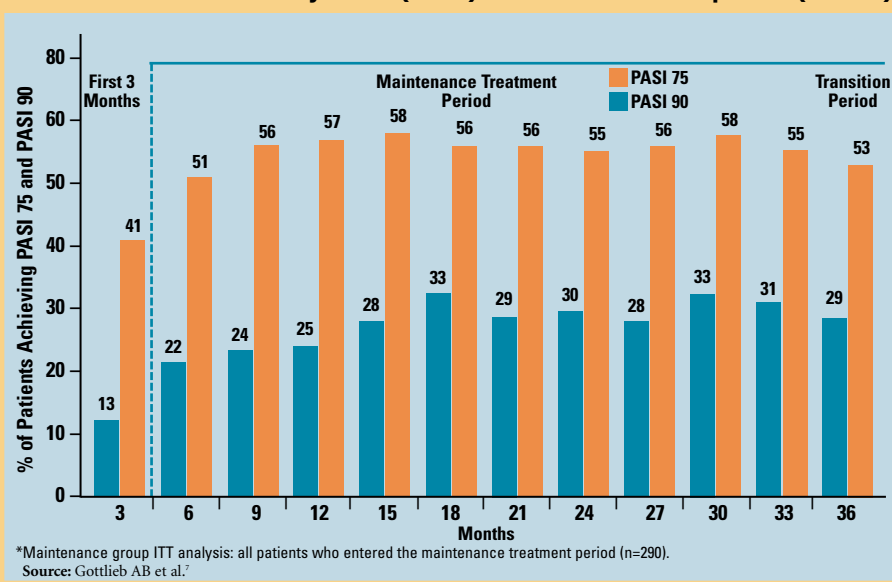
additional 33 months (a total treatment duration of 3 years). During the maintenance period, patients who were treated for psoriasis with a systemic agent were counted as nonresponders. Patients who discontinued from the study for any other reason had their last observation carried forward for the rest of the study visits. In the intent-to-treat (ITT) analysis (which included all patients who entered the study even if they did not continue into the maintenance period; N=339), 41% of patients had a PASI 75 at 3 months and 45% had a PASI 75 at 36 months. In the maintenance group ITT (MITT) analysis (which included only those patients who entered the maintenance treatment period; n=290), 53% had a PASI 75 at 36 months (Figure 1).⁷ In the ITT analysis, 13% of patients had a PASI 90

at 3 months and 25% had a PASI 90 at 36 months. In the MITT analysis, 29% had a PASI 90 at 36 months (Figure 1).⁷ Importantly, there was no increase in the overall incidence of adverse events over time, no emergence of new common adverse events, no evidence of cumulative or end-organ toxicity, and no trend toward an increasing incidence of infection or malignancy throughout the 3-year study period (Figure 2 on page 5).⁷

The safety findings of the 3-year study were supported by the results of a 60-week safety and tolerability study.⁸ In this study, all patients who completed a 3-month double-blind comparison of efalizumab 1 mg/kg/wk versus placebo (placebo-controlled phase) were eligible to enter a 48-week extended treatment period in which all patients were treated with efalizumab 1 mg/kg/wk. Upon completion of the extended treatment period, patients entered a 12-week follow-up phase in which they had the option of discontinuing treatment or continuing to receive efalizumab at their current dose. Consequently, patients who had been on efalizumab throughout the first two periods received a total of 60 weeks of continuous treatment and some patients received 72 weeks of continuous therapy. In this study, there was no increase in the incidence of adverse events over time, no evidence of new common adverse events, and no evidence of cumulative or end-organ toxicity.⁸

Efficacy in High-Need Patients With Psoriasis. A 3-month, placebo-controlled study demonstrated that efalizumab 1 mg/kg/wk was also effective and well tolerated in high-need patients (defined as those for whom at least two other currently available systemic psoriasis therapies were either contraindicated or unsuitable because of lack of efficacy or tolerability).⁹ This study enrolled all patients who either had received systemic therapy for psoriasis in the past or were considered eligible for such therapy (a total of 794 patients); a large cohort comprised high-need patients (526/794). At 3 months, PASI 75 was achieved by 31% of all patients and 30% of the high-need patients. The results for the high-need patients were also similar to those of the overall population in terms of all secondary efficacy measures (including

Figure 1. Efficacy of Efalizumab Over 3 Years of Continuous Use: Psoriasis Area and Severity Index (PASI) 75 and PASI 90 Responses (MITT*)



PASI 50, PGA, and percentage of PASI improvement) and safety findings.⁹

Etanercept

Clinical Profile

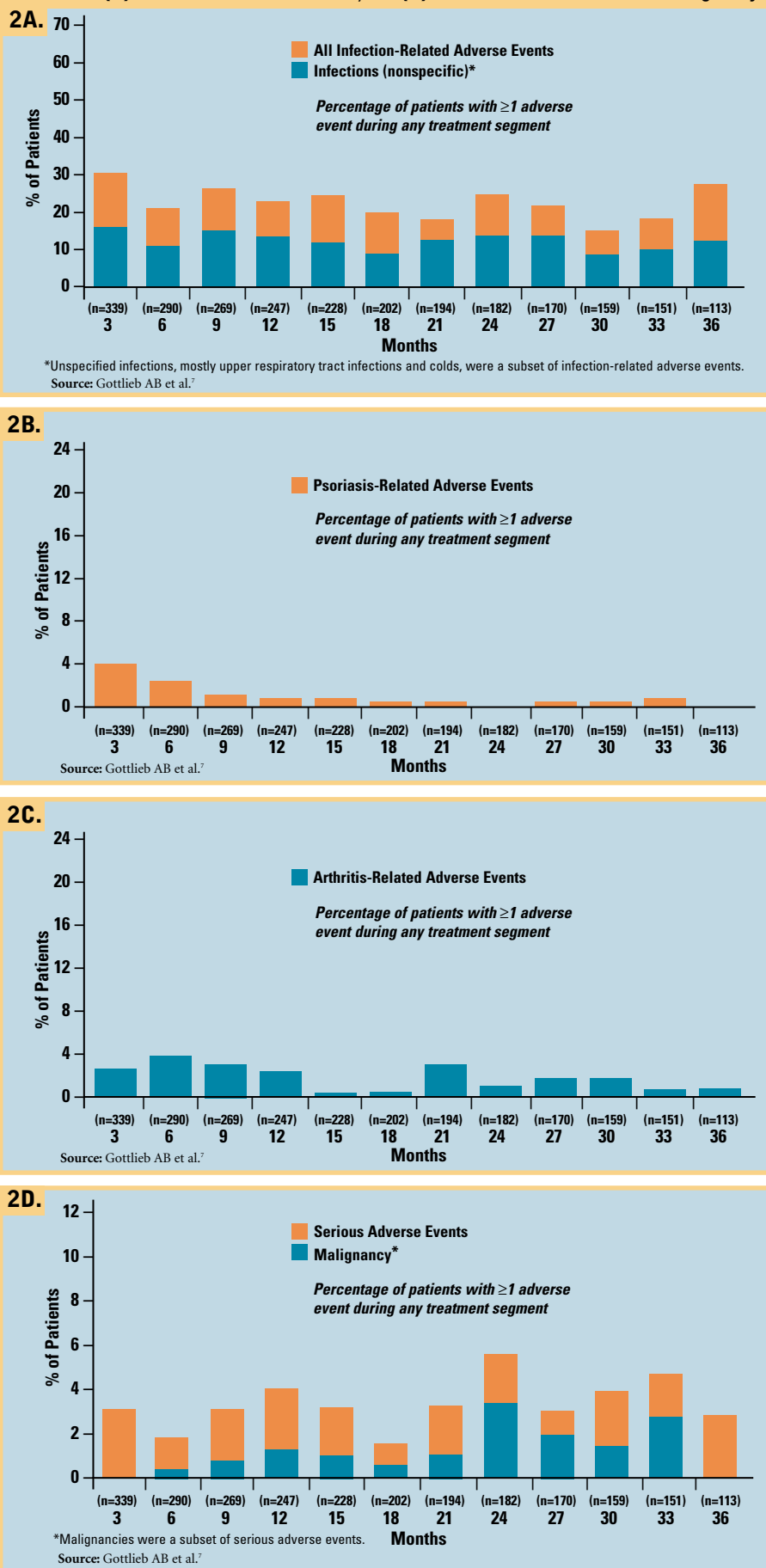
Etanercept is a fusion protein that blocks tumor necrosis factor (TNF)- α . It is approved for the treatment of moderate to severe psoriasis and psoriatic arthritis. The recommended dosing for etanercept in the treatment of psoriasis is 50 mg SC twice weekly (BIW) for 3 months, followed by 25 mg SC BIW (or 50 mg once weekly) thereafter (a stepped-dosing regimen).¹⁰

When etanercept was used in a 6-month, double-blind, placebo-controlled clinical study with the recommended stepped-dosing regimen, 49% of patients achieved PASI 75 at week 12 and 54% achieved PASI 75 at week 24.¹¹ Among patients in this clinical trial who were treated with 25 mg SC BIW throughout the study, PASI 75 was achieved by 34% at week 12 and 45% at week 24. Etanercept was well tolerated, with adverse events similar in patients treated with etanercept or placebo, with the exception of injection-site reactions. During the placebo-controlled phase, injection-site reactions occurred in 18% of patients treated with etanercept 50 mg BIW and 13% of patients treated with etanercept 25 mg BIW.¹¹

In a 6-month, double-blind, placebo-controlled, stable-dosing clinical trial,¹² PASI 75 was achieved by 34% of patients treated with etanercept 25 mg BIW after 3 months and 44% of these patients after 6 months. Among patients treated with etanercept 50 mg BIW, 49% achieved PASI 75 after 3 months and 59% achieved PASI 75 after 6 months. In a separate analysis, the median time to relapse when therapy was stopped after 6 months was 70 days among patients treated with etanercept 25 mg/wk, 85 days for patients treated with 25 mg BIW, and 91 days for patients treated with 50 mg BIW.¹³ One patient treated with 25 mg/wk experienced rebound.

Two integrated analyses of safety data from multiple studies confirmed that the rates of adverse events and infections were similar between patients treated with placebo or etanercept, with no reports of opportunistic infections or tuberculosis.^{14,15} In an analysis that

Figure 2. Safety of Efalizumab Over 3 Years of Continuous Use:
(A) Adverse Events of Infection, (B) Adverse Events of Psoriasis,
(C) Adverse Events of Arthritis, and (D) Serious Adverse Events and Malignancy



included 364 patients treated for at least 12 months and 52 patients treated for at least 15 months, no new or unanticipated pattern of adverse events emerged with extended use.¹⁵

The product labeling for etanercept indicates a risk of serious infection and that patients should be evaluated for infection or any predisposition for infection prior to treatment.¹⁰ There is also a warning about an increased risk of central nervous system (CNS) demyelinating disorders and lymphoma. Consequently, patients who develop a new infection or any signs of neurologic problems or lymphoma during treatment should be monitored closely and etanercept discontinued if a serious condition is confirmed. Etanercept should also be used with caution in patients with heart failure. It is important to note that cases of lupus-like syndrome, albeit rare, have been reported in association with etanercept treatment.¹⁰

Latest Findings

The recent presentations on etanercept provided new information on long-term efficacy and safety in patients with psoriatic arthritis, and some new insights into its mechanism of action.

Efficacy Against Psoriasis in Patients With Psoriatic Arthritis. The long-term effects of up to 2 years of continuous etanercept treatment have been reported in a study of patients with psoriatic arthritis.¹⁶ In this study, patients were treated with either etanercept 25 mg BIW or placebo for 3 months (double-blind portion), followed by a variable maintenance period in which all patients continued on blinded therapy until 6 months of treatment had been completed. This was then followed by an open-label extension to 24 months in which all patients received etanercept 25 mg BIW.¹⁶ Of the 85 etanercept-treated patients evaluated for PASI, 38% achieved PASI 75 after 24 months of treatment (**Figure 3**). Etanercept continued to be well tolerated throughout the study, with no deaths or new cases of demyelinating disorders and no increase in the rate of adverse events or infections (**Table 1** on page 7).¹⁶

In addition to the long-term study described above, a separate open-label assessment demonstrated that psoriasis improved in a large cohort of patients

ETANERCEPT

- ▶ **A fusion protein that blocks TNF- α**
- ▶ **Approved for psoriatic arthritis and moderate to severe psoriasis**
- ▶ **Administered by the patient: 50 mg SC twice weekly (BIW) for 3 months, followed by 25 mg SC BIW (psoriasis dose)**
- ▶ **Efficacy evaluated during up to 2 years in patients with psoriatic arthritis**

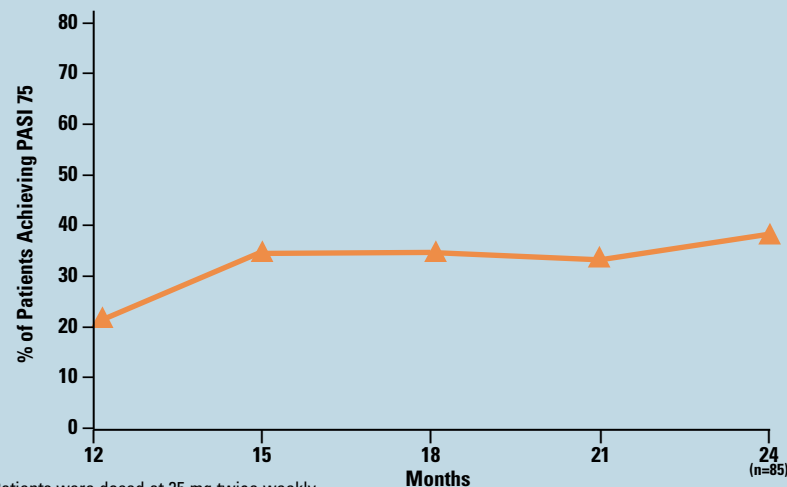
with both psoriasis and psoriatic arthritis.¹⁷ This study was notable because it included 1122 patients from 140 dermatology clinics (85% of which were community based) with long-standing psoriasis (mean duration: 19 years). However, the mean duration of psoriatic arthritis was 7.21 years, once again reinforcing the need for dermatologists to be vigilant for the onset of psoriatic arthritis in their patients with psoriasis. Patients were treated with etanercept 50 mg/wk (administered as two 25-mg SC injections given within 1 hour of each other) for 24 weeks. At 24 weeks, approximately 55% of patients had a PGA of clear or almost clear, and no tuberculosis or opportunistic, granulomatous, or atypical infections were reported.¹⁷

Psoriasis Worsening Associated With Etanercept Therapy. A small case series reported three cases of disease rebound

(defined as PASI 125) after discontinuation of etanercept therapy and one case of psoriasis worsening during etanercept therapy.¹⁸ In all three cases of rebound, disease worsening occurred within 3 months of the discontinuation of etanercept and involved more than 60% of body surface area (BSA). In all cases, disease control was reestablished by either placing the patient on cyclosporine or reinitiating etanercept. The one case of disease worsening on etanercept began 6 months after etanercept was started and reached PASI 144 within a few months. Disease control was reestablished by adding methotrexate 25 mg/wk for 3 months without discontinuing etanercept.¹⁸

Mechanism of Action. A laboratory study demonstrated that etanercept interacted with the TNF- α molecule differently than did the TNF- α antagonists infliximab and adalimumab.¹⁹ Infliximab and adalimumab (both anti-TNF monoclonal antibodies) form large precipitable protein complexes with TNF, whereas etanercept (a soluble receptor for TNF) forms much smaller protein complexes. Also, both infliximab and adalimumab bind significantly to Fc receptors (which appears to activate complement- or antibody-dependent cytotoxicity) as well as to C1q (a component of the complement system) in the presence of TNF, whereas etanercept does not. This may account for the different clinical profiles of these three biologic agents and may explain why etanercept is effective over a somewhat smaller

Figure 3. Etanercept: PASI 75 Improvement in Skin Lesions in Patients With Psoriatic Arthritis*†



*Patients were dosed at 25 mg twice weekly.

†Psoriasis involving $\geq 3\%$ body surface area was included.

Source: Lebowitz M et al.¹⁶

Table 1. Safety of Etanercept After 2 Years of Continuous Use

Event*	Frequency (%)	Exposure (Event per Patient-Year)
Any adverse events	70	2.14
Injury accident	11	0.15
Hematoma injection site	9	0.10
Hypertension	8	0.08
Back pain	8	0.07
Headache	6	0.08
Any infectious events	62	1.31
Upper respiratory infection	30	0.39
Flu syndrome	13	0.13
Sinusitis	9	0.13
Bronchitis	7	0.11
Pharyngitis	5	0.07

*Adverse events and infectious events occurring in 5% of patients treated with etanercept during open-label extension.
Source: Lebwohl M et al.¹⁶

range of disease states than are the other two agents and also why etanercept seems to be associated with lower rates of opportunistic infections.

NF-κB is a member of a family of transcription factors that play a role in numerous cellular processes, including both the immune and stress response as well as keratinocyte proliferation and differentiation. A clinical study in normal and psoriatic patients demonstrated that NF-κB is upregulated in psoriatic skin and is reduced in response to treatment with etanercept.²⁰

Alefacept

Clinical Profile

Alefacept is a fusion protein that blocks the interaction between T cells and antigen-presenting cells, thereby preventing T-cell activation.²¹ It also causes apoptosis of memory T cells by forming bridges between T cells and natural killer cells. Alefacept is approved for the treatment of moderate to severe psoriasis. A course of alefacept therapy consists of 12 weeks of 15-mg weekly intramuscular (IM) injections, followed by 12 weeks of follow-up. Weekly monitoring of CD4⁺ and CD8⁺ T-lymphocyte counts is required during treatment. A study has shown, however, that a reduced CD4⁺ testing schedule (to every other week) in patients with stable CD4⁺ cell counts did not increase the risks associated with alefacept treatment.²¹ Alefacept should be withheld if CD4⁺ cell counts fall below 250 cells/μL and discontinued if they remain below 250 cells/μL for a month or more.²¹

In a double-blind, randomized, placebo-controlled clinical trial, 21% of alefacept-treated patients achieved PASI 75 2 weeks after the last dose (at week 14)²² and 33% achieved PASI 75 at any time during either 12 weeks of treatment or 12 weeks of posttreatment observation.²³ Among these patients, a PASI 50 response was maintained for a median duration of 209 days from the time PASI 75 was first achieved.²⁴ The package insert reports that, during a single course of treatment, the adverse events that occurred with at least a 5% higher incidence with alefacept than with placebo were headache, pruritus, infection, rhinitis, injection-site pain, and injection-site inflammation.²¹

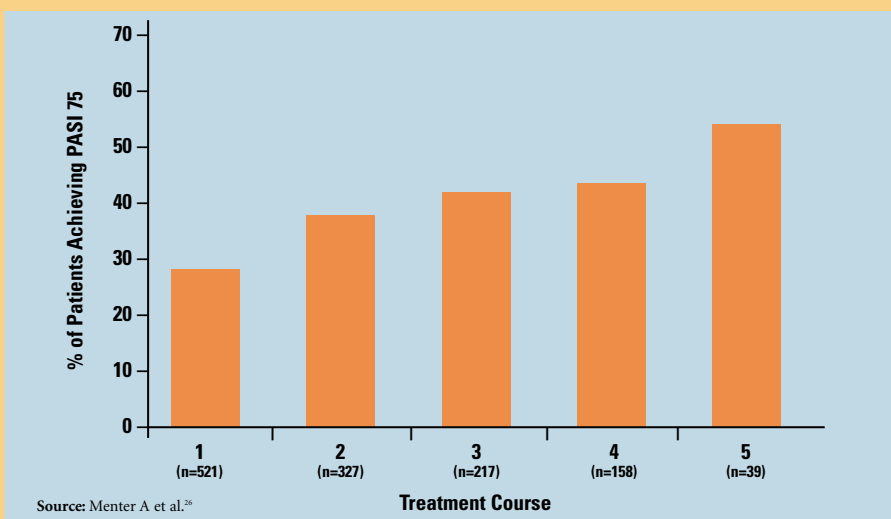
Treatment efficacy can be improved by extending the treatment period to 16 weeks. Patients treated with alefacept for 16 weeks continued to show

improvements from their baseline PASI through week 24, whereas PASI scores in patients switched to placebo after week 12 gradually declined.²⁵

Latest Findings

Recent presentations on alefacept included interim reports from ongoing multiple-course studies and investigations of alternative dosing regimens.

Efficacy and Safety Over Multiple Courses of Therapy. An analysis of the long-term extension studies associated with several phase III clinical trials demonstrated that, in the subset of patients who responded, the efficacy of alefacept gradually increased with each successive course of treatment (up to five courses).²⁶ This analysis included patients who had received alefacept 10 or 15 mg IM and those who had received alefacept 7.5 mg intravenously (IV). It is important to note that the IV formulation is no longer available for clinical use in the United States. Among patients treated with alefacept IM, the percentage of patients achieving a PGA of clear or almost clear at any time during a course of therapy increased from approximately 21% during the first course of therapy (n=457) to approximately 41% during the fourth course of therapy (n=100), before declining to approximately 28% during the fifth course (n=50). Among patients treated with alefacept IV, approximately 29% achieved PASI 75 at any time during the first course of therapy (n=521), and, by the fifth course of therapy, approximately 54% achieved PASI 75 (n=39) (Figure 4).²⁶

Figure 4. Efficacy of Alefacept IV Over Five Courses of Therapy

An integrated analysis of safety and tolerability data from phase I, II, and III clinical trials and their open-label extensions demonstrated that safety was maintained over as many as nine courses of alefacept therapy.²⁷ It should be noted, however, that this analysis included relatively few patients who had been treated with more than five courses of therapy (decreasing from 171 patients for course 5 to eight patients for course 9). This analysis pooled data from patients who had been treated with either IM or IV formulations of alefacept, and the safety findings were similar to those seen in short-term clinical trials. There were no opportunistic infections and no increase in the incidence of adverse events, discontinuations due to adverse events, serious adverse events, infections, or malignancies with multiple courses of therapy (Table 2). This analysis also showed that the incidence of infections was not related to CD4⁺ cell counts.²⁷

A study is currently under way to evaluate the safety and efficacy of multiple courses of alefacept therapy in combination with other psoriasis treatments.²⁸ The results from the first course of treatment showed that 76% of patients treated with alefacept alone or in combination with low-potency topical steroids (n=128) achieved some improvement in their PGA. This percentage stayed the same or increased when alefacept was used in combination with mid- to high-potency topical steroids (n=147; 75%), systemic retinoids (n=14; 79%), or ultraviolet B light (n=17; 88%). In contrast, efficacy seemed to be reduced in patients treated with methotrexate (n=38; 39%) or cyclosporine (n=27; 56%) in addition to alefacept.²⁸

Alternative Dosing Regimens. A study of weight-based and extended dosing in patients with psoriasis who weighed between 100 and 150 kg suggested that a 16-week course of treatment may be more effective than a 12-week course but that weight-based dosing may be no more effective than fixed dosing.²⁹ In this double-blind study, patients were randomized to receive weekly injections of either alefacept 7.5 mg IV for 16 weeks (extended dosing) or 0.075 mg/kg IV for 12 weeks (weight-based dosing). In the extended-dosing group, 21% of patients achieved PASI

ALEFACEPT

- ▶ **Fusion protein that prevents T-cell activation and depletes activated T cells**
- ▶ **Approved for the treatment of moderate to severe psoriasis**
- ▶ **Administered via intramuscular injection by a healthcare professional**
- ▶ **A course of alefacept therapy consists of 12 weeks of 15-mg weekly intramuscular (IM) injections, followed by 12 weeks of follow-up**
- ▶ **Weekly monitoring of CD4⁺ and CD8⁺ T-lymphocyte counts is required during treatment**
- ▶ **Efficacy in psoriasis evaluated in a small number of patients receiving up to 9 courses of therapy**

75 at any time during alefacept dosing or 12 weeks of follow-up. In the weight-based dosing group, only 10% of patients achieved PASI 75 at any time during treatment or follow-up. Regardless of patient weight, patients in the extended-dosing group achieved greater reductions in PASI than did those receiving weight-based dosing. The incidence of adverse events, including infections, was similar in the two treatment groups.²⁹

Preliminary data from an open-label, community-based study suggest that an extended course of up to 24 weeks of alefacept is safe.³⁰ In this study, patients who completed a standard 12-week course of therapy were eligible to

receive up to 12 additional weeks of alefacept. To date, 109 patients have received a total of 16 weeks of continuous therapy, 77 have completed 20 weeks, and 49 have completed 24 weeks. No serious adverse events have been reported, and seven patients (6%) experienced temporary decreases in CD4⁺ lymphocyte counts to below 250 cells/ μ L. Efficacy results from this trial have not yet been reported.³⁰

Preliminary data from a small dose-escalation study of 16 patients suggest that alefacept 15 mg IM for 6 weeks followed by alefacept 30 mg IM for 6 weeks is a safe treatment regimen.³¹ All patients tolerated the treatment well, and no serious adverse events were reported. The rate of infection was similar during 15-mg and 30-mg dosing, and no doses were withheld because of low CD4⁺ lymphocyte counts. The preliminary efficacy results did not allow any conclusions to be drawn.³¹

Infliximab

Emerging Clinical Profile

Infliximab is a chimeric (approximately 30% murine, 70% human) monoclonal antibody to soluble and membrane-bound TNF- α .³² Infliximab may also cause apoptosis of cells expressing transmembrane TNF- α .^{33,34} Infliximab is not yet approved for the treatment of psoriasis, but in the clinical studies conducted in patients with psoriasis, infliximab 3 or 5 mg/kg was administered as a 2-hour IV infusion at weeks 0, 2, and 6, and every 8 weeks thereafter.^{34,35}

Table 2. Safety of Alefacept Over Nine Courses of Therapy

Adverse Event (AE), n (%)	Alefacept Course								
	1 (n=1869)	2 (n=1152)	3 (n=554)	4 (n=362)	5 (n=171)	6 (n=56)	7 (n=39)	8 (n=21)	9 (n=8)
Discontinuations for AEs	33 (1.8)	13 (1.1)	5 (0.9)	5 (1.4)	0	1 (1.8)	0	1 (4.8)	0
Serious AEs	86 (4.6)	46 (4.0)	21 (3.8)	11 (3.0)	2 (1.2)	2 (3.6)	1 (2.6)	1 (4.8)	0
All infections	878 (47)	524 (45)	206 (37)	156 (43)	68 (40)	26 (46)	17 (44)	5 (24)	3 (38)
Serious infections	12 (0.6)	6 (0.5)	5 (0.9)	3 (0.8)	0	0	0	0	0
Malignancies	24 (1.3)	12 (1.0)	9 (1.6)	4 (1.1)	1 (0.6)	0	0	1 (4.8)	0

Source: Goffe B et al.²⁷

In a double-blind, placebo-controlled phase II study, 72% of patients treated with infliximab 3 mg/kg at weeks 0, 2, and 6 and 88% of patients treated with infliximab 5 mg/kg at weeks 0, 2, and 6 achieved PASI 75 at week 10.³⁴ The percentage of patients maintaining PASI 75 in both groups gradually declined over the following 16 weeks. The most common adverse events were infusion reactions, headache, pruritus, fatigue, and myalgia, but these events occurred with similar frequency in the placebo group. Infusion reactions were reported in 16% of patients treated with infliximab and 2% of patients treated with placebo.³⁴

The package insert for the use of infliximab in rheumatoid arthritis and Crohn's disease states that infusion reactions occur in 22% of patients and that serious reactions such as anaphylactic shock (although infrequent) have occurred.³² Neutralizing antibodies to infliximab can develop as a result of treatment, requiring larger or more frequent doses in the future or rendering the patient completely unresponsive to future infliximab therapy. The package insert also states that methotrexate should be administered along with infliximab to prevent the development of neutralizing antibodies.³² Serious infection is also a risk with infliximab, and testing for tuberculosis is required prior to use.³² Infliximab should be used with caution in patients with heart failure and discontinued if patients develop

INFLIXIMAB

- ▶ Chimeric monoclonal antibody to soluble and membrane-bound TNF- α
- ▶ Not yet approved for the treatment of psoriasis
- ▶ In clinical studies conducted in patients with psoriasis, infliximab 3 or 5 mg/kg was administered as a 2-hour IV infusion at weeks 0, 2, and 6, and every 8 weeks thereafter
- ▶ Evaluated during up to 50 weeks of therapy in patients with both psoriasis and psoriatic arthritis

new or worsening symptoms. It should also be used with caution in patients with preexisting or recent onset of CNS demyelinating disorders and discontinued if symptoms worsen or new symptoms appear. The labeling also carries a warning about an increased risk of lymphoma and lupus-like syndrome. Any signs of these conditions should be evaluated thoroughly and treatment discontinued if a serious condition is confirmed.³²

Latest Findings

Long-term Efficacy in Patients With Psoriasis and Psoriatic Arthritis. Two separate, long-term studies demonstrated that the efficacy of infliximab was maintained for most patients through 24 and 50 weeks of treatment in patients with both psoriasis and psoriatic arthritis.³⁵ In a 24-week, dou-

ble-blind clinical trial (IMPACT II study; N=200), patients with both psoriasis and psoriatic arthritis were treated with either placebo or infliximab 5 mg/kg at weeks 0, 2, 6, 14, and 22 (study included 170 patients with psoriasis BSA $\geq 3\%$). Among patients in the infliximab treatment group who had psoriasis BSA $\geq 3\%$, 64% achieved PASI 75 at week 14 and 60% at week 24 (Figure 5).³⁵ In a 50-week, double-blind clinical trial (IMPACT study; N=104), patients with psoriatic arthritis (82 patients also had psoriasis) were treated with either placebo or infliximab 5 mg/kg at weeks 0, 2, 6, and 14, followed by evaluation at week 16. After week 16, patients in both treatment groups could continue to receive infliximab every 8 weeks for a total of 50 weeks. Among patients in the infliximab treatment group who also had psoriasis, 68% achieved PASI 75 at week 16 and 59% at week 50 (Figure 5).³⁵ Infliximab was generally well tolerated in both of these trials, with adverse events similar between the infliximab and placebo treatment groups and no reports of opportunistic infections, tuberculosis, demyelinating disorders, congestive heart failure, or autoimmune events.³⁵

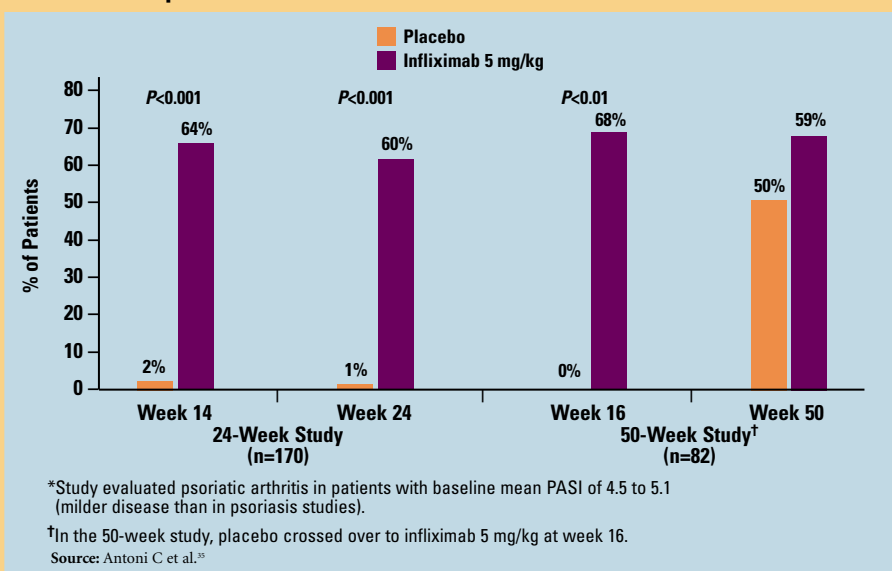
Adalimumab

Emerging Clinical Profile

Adalimumab is a fully human monoclonal antibody with a high affinity for both soluble and membrane-bound TNF- α .³⁶ In the presence of complement, adalimumab can cause the lysis of cells expressing TNF- α on their surface. Although adalimumab is not yet approved for use in psoriasis, in investigations of its use in psoriasis it is administered at a dose of 40 mg SC either weekly or every other week (EOW).³⁷ Patients treated EOW receive a single loading dose of 80 mg at week 0. Patients treated weekly receive a loading dose of 80 mg at weeks 0 and 1 before starting their 40-mg dosing at week 2.³⁷

In a 12-week, double-blind, placebo-controlled phase II trial, PASI 75 was achieved by 80% of patients in the adalimumab weekly group, 53% of patients in the adalimumab EOW group, and 4% of patients in the placebo group ($P < 0.001$ for adalimumab versus pla-

Figure 5. Efficacy of Infliximab in 24- and 50-Week Studies: PASI 75 Response in Patients With Psoriatic Arthritis*



cebo).³⁸ The rates of adverse events were similar in the adalimumab and placebo groups, and there were very few discontinuations due to adverse events.³⁸

The package insert for the use of adalimumab in nonpsoriasis indications states that there is a risk of serious infection with adalimumab and that testing for tuberculosis is required prior to treatment.³⁶ The labeling also carries a warning about an increased risk of CNS demyelinating disorders and lymphoma and rare cases of lupus-like syndrome in association with adalimumab treatment. Patients who develop a new infection or any signs of neurologic problems or lymphoma during treatment should be monitored closely and adalimumab discontinued if a serious condition is confirmed.³⁶

Latest Findings

Recent presentations on adalimumab included information about long-term use in patients with psoriasis or rheumatoid arthritis, the durability of effect in patients with psoriasis, and the clinical effects in patients with both psoriasis and psoriatic arthritis.

Long-term Safety and Efficacy in Psoriasis. A long-term, open-label extension study demonstrated that the safety and efficacy of adalimumab in patients with psoriasis was maintained over 48 weeks of continuous treatment.³⁹ This extension study enrolled patients who had completed a 12-week, double-blind, dose-ranging clinical trial

ADALIMUMAB

- ▶ Fully human monoclonal antibody to soluble and membrane-bound TNF- α
- ▶ Not yet approved for the treatment of psoriasis
- ▶ In studies of its use in the treatment of psoriasis, adalimumab is administered by the patient: 40 mg SC weekly with one 80-mg loading dose at week 0, or 40 mg SC every other week (EOW) with 80-mg loading doses at weeks 0 and 1
- ▶ Efficacy in psoriasis evaluated during up to 1 year of continuous use in psoriasis patients

and offered them up to 48 weeks of additional therapy at their original dose of adalimumab (11 patients were escalated to the higher-dose regimen; the impact of this on the overall response rates is unknown⁴⁰). Patients who had been treated with placebo during the double-blind phase were treated with one 80-mg loading dose followed by adalimumab 40 mg EOW. In the adalimumab weekly group, PASI 75 was achieved by 80% of patients at the end of the 3-month double-blind study and 73% at the end of the 48-week extension. In the adalimumab EOW group, PASI 75 was achieved by 53% of patients at the end of the 3-month double-blind study and 67% at the end of

the 48-week extension (Figure 6).³⁹ The most common adverse events were nasopharyngitis and upper respiratory infections occurring at similar rates in the adalimumab and placebo groups. Serious adverse events occurred in 11% of patients treated with adalimumab weekly but in no patients in either of the other treatment groups. The nature of the serious adverse events was not reported (Table 3 on page 11).³⁹ A sub-analysis of those patients in the study who also had psoriatic arthritis demonstrated that adalimumab was slightly less effective against psoriasis in patients with both conditions.⁴¹ In the adalimumab weekly group, PASI 75 was achieved by 76% of patients with psoriasis alone and 58% of patients who also had psoriatic arthritis. In the adalimumab EOW group, PASI 75 was achieved by 70% of patients with psoriasis alone and by 53% of patients who also had psoriatic arthritis.⁴¹

Durability of Effect in Patients With Psoriasis. Durability of treatment response was evaluated following withdrawal from a dose reduction of adalimumab therapy.⁴² During the first phase of this study, all patients were treated with adalimumab 40 mg weekly (following 80-mg loading doses at weeks 0 and 1) for 12 weeks (open-label phase). After completion of the open-label phase, patients who achieved PASI 50 were randomized to receive placebo (discontinuation group) or adalimumab 40 mg EOW (dose-reduction group) for an additional 12 weeks (to week 24 of the study). At the end of this period, all treatments were discontinued, and the patients were observed every 90 days until relapse or until they reached 76 weeks from the beginning of the study. No cases of rebound were observed in either treatment group. In the discontinuation group, 66% of patients maintained a PASI 50 through 12 weeks after the switch to placebo. In the dose-reduction group, 78% of patients maintained PASI 50 throughout 12 weeks of treatment with EOW dosing, and 68% of patients in this group had a PASI 75 at week 24 despite the dose reduction.⁴²

Efficacy and Safety in Patients With Both Psoriasis and Psoriatic Arthritis. In a placebo-controlled, double-blind, 6-month clinical trial, adalimumab treatment was shown to improve psori-

Figure 6. Efficacy of Adalimumab After 48 Weeks of Therapy: PASI 75 Response in 48-Week Extension Trial

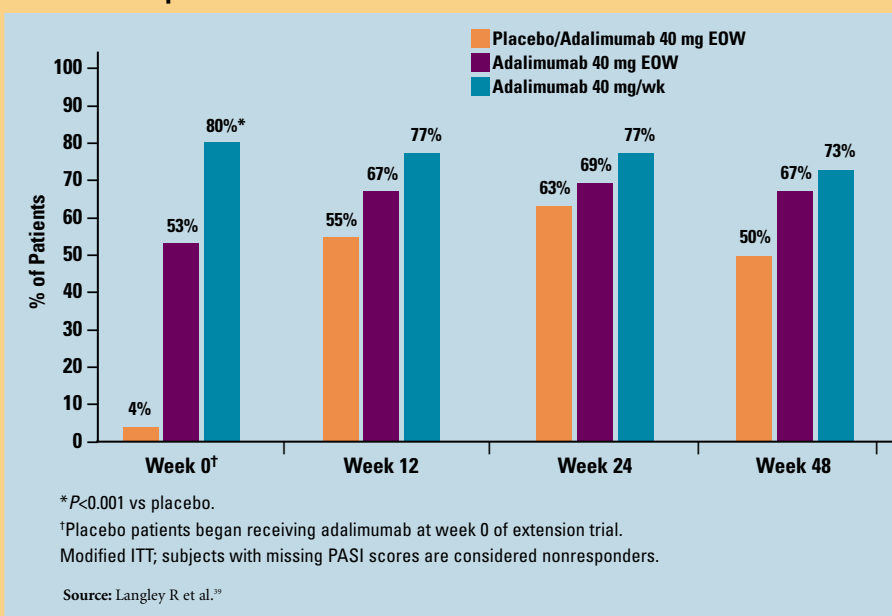


Table 3. Safety of Adalimumab After 48 Weeks of Therapy

Adverse Event (AE), n (%)	Blinded Period Weeks 0-12 (n=137)			Open-Label Period Weeks 12-48 (n=132)		
	Placebo/Adalimumab 40 mg EOW (n=47)	Adalimumab 40 mg EOW (n=43)	Adalimumab 40 mg Weekly (n=47)	Placebo/Adalimumab 40 mg EOW (n=46)	Adalimumab 40 mg EOW (n=42)	Adalimumab 40 mg Weekly (n=44)
Any AE	28 (60)	30 (70)	29 (62)	27 (59)	31 (74)	35 (80)
Any serious AE	0 (0)	2 (5)	2 (4)	0 (0)	0 (0)	5 (11)
Any infectious serious AE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any AEs leading to discontinuation	0 (0)	1 (2)	1 (2)	1 (2)	1 (2)	4 (9)

MedDRA coding.

Source: Langley R et al.³⁹

asis in patients with both psoriasis and psoriatic arthritis.⁴³ In this study, patients with psoriatic arthritis and a history of psoriasis were randomized to receive either adalimumab 40 mg EOW or placebo for 24 weeks. Among patients who had active psoriasis at study entry, PASI 75 was achieved by 49% of adalimumab-treated patients at week 12 and 59% at week 24. In the placebo group, PASI 75 was achieved by only 4% at week 12 and 1% at week 24. Adalimumab was well tolerated during the 24-week trial, with an incidence of adverse events similar to that of placebo. There were no cases of tuberculosis, granulomatous infection, malignancy, demyelination, drug-induced lupus, or congestive heart failure.⁴³

New Biologic Agents on the Horizon

Two new biologic agents in early development for the treatment of moderate to severe psoriasis are oncept and an anti-IL-12 drug.

Onercept

Onercept is an unmodified, soluble type 1 TNF receptor (p55). Data from three phase III clinical trials of this agent in moderate to severe psoriasis were recently presented. However, since then, it has been noted that two patients were diagnosed with sepsis and one died. After analyzing the available blinded efficacy data at 12 weeks for the two placebo-controlled trials and the data from the first 12 weeks of the open-label trial, it was determined that the efficacy response observed was less than that observed both in the earlier

phase II trial and with other available treatments. Thus, the development of oncept for moderate to severe psoriasis has been discontinued.⁴⁴

IL-12 Antibody

A human monoclonal antibody to IL-12 p40 is in the very early stages of clinical development.⁴⁵ In a small (n=5 per group), multicenter, double-blind, placebo-controlled, dose-ranging phase I trial, patients received single SC injections of placebo or anti-IL-12 p40 at 0.3, 0.75, 1.5, or 3.0 mg/kg. Most adverse events were mild in severity, and no serious adverse events were reported. Across all anti-IL-12 p40 doses, PASI 75 was achieved by 77% of patients 24 weeks after the single dose was administered. The degree of improvement in PASI was dose dependent.⁴⁵

Individual Physician Experience and Insights

At this meeting, several physicians presented their assessments of the overall safety or relative merits of the different biologic agents.

Safety was discussed in symposia presentations by Drs Gordon, Wolverton, and Lebwohl.⁴⁶⁻⁴⁸ Dr Gordon pointed out that the most reliable safety data come from placebo-controlled clinical trials, but the relatively small number of patients evaluated means that infrequent adverse events may not be detected.⁴⁶ Open-label trials often enroll more patients, but the lack of a control group means that the relevance of some adverse events may not be clear. Voluntary reporting to MedWatch (at the FDA) of adverse events that occur

during the widespread use of a drug is valuable and may be the only way to detect extremely rare adverse events. However, such reports generally tend to underestimate the incidence of a particular adverse event because of poor compliance by physicians. In addition, Dr Gordon pointed out that a drug's true effect on the risk of certain problems, such as malignancies or infections, can be assessed only by comparing the incidence during treatment to the background incidence in the relevant patient population. He also pointed out that safety data from one patient population may not be relevant to a different patient population. For example, the safety profile of anti-TNF agents in patients with rheumatoid arthritis may not be reproduced in patients with psoriasis, who may be prone to different comorbidities and on different types of concurrent medications. Dr Gordon also pointed out that the risk of tuberculosis with anti-TNF agents can almost be eliminated with good pre-screening, and he recommends purified protein derivative (PPD) tests for all patients being considered for immunosuppressive therapy, with chest x-rays if PPDs are positive.

Dr Wolverton presented a detailed analysis of the risk of lymphoma during biologic therapy.⁴⁷ Although lymphoma does occur at a two- to threefold higher rate in patients with psoriasis than in the general population, the data available at this time suggest that biologic therapy does not increase this rate. Dr Lebwohl also reviewed the adverse event profiles of the biologic agents.⁴⁸ He stated that the T-cell agents efa-

lizumab and alefacept do not seem to increase the risk of infection but that it was not yet clear if there was a causal relationship between anti-TNF agents and increased rates of infection or lymphoma. He stated that he considers the link between reactivation of tuberculosis and the anti-TNF agents, especially infliximab, to be genuine, but, like Dr Gordon, he believes this risk can be minimized by prescreening for tuberculosis. He also believes that there is a clear link between high doses of infliximab (10 mg/kg) and an increased risk of congestive heart failure but that the evidence of a link between heart failure and the other anti-TNF agents is far less clear. In contrast, he believes there is a very clear link between anti-TNF agents and an increased risk of CNS demyelinating disorders. He stated that the strongest evidence for this comes from reports of demyelinating disorders occurring during either etanercept or infliximab therapy, then resolving when the drug was withdrawn and recurring when the drug was readministered (rechallenge).

Dr Abramovits as well as Dr Nelson and his colleagues presented separate posters in which they assessed the relative advantages and disadvantages of all of the different biologic agents.^{49,50} Both physicians concluded that there is no one best biologic therapy but rather that each agent has its own unique set of strengths and weaknesses that make them suitable for different types of patients. A third poster by Myers et al described a retrospective chart review that found that patients with psoriasis who did not respond well to one biologic or immunomodulatory therapy usually did respond well to a different biologic or immunomodulatory thera-

PHYSICIAN INSIGHTS

- ▶ **Placebo-controlled trials supply the most reliable safety data**
- ▶ **Safety data from a drug used for one indication should be extrapolated with care to other patient populations**
- ▶ **Biologic agents do not appear to increase the rate of lymphoma**
- ▶ **The risk of tuberculosis reactivation with anti-TNF agents can be minimized by prescreening**
- ▶ **Although the incidence is very low, there is strong evidence for a link between anti-TNF agents and an increased risk of CNS demyelinating disorders**
- ▶ **Each biologic agent has its own set of strengths and weaknesses**
- ▶ **Patients with psoriasis who do not respond to one biologic agent may respond to a different agent**

py.⁵¹ This suggests that the variety of available biologic agents increases the chance that individual patients will be able to find a therapy that will work well for them.⁵¹

Summary

Presentations at recent dermatology meetings provided important new information on a wide range of issues related to biologic therapy. These included the long-term use of biologic agents in the treatment of psoriasis, the efficacy of biologic therapies against psoriasis in patients who also have psoriatic arthritis, and the use of alternative

dosing regimens. Additional long-term studies are needed, but evidence was presented of the long-term safety and efficacy of efalizumab (3 years of continuous use), etanercept (up to 2 years of continuous use), alefacept (over multiple courses), infliximab (periodic use in 24-week and 50-week studies), and adalimumab (up to 48 weeks of continuous therapy). More must also be learned about how best to optimize treatment outcomes during biologic therapy, but the studies of alternative dosing regimens suggest that it is safe to vary the doses of some of the biologic agents in an attempt to improve efficacy in some patients.

Overall, it appears that biologic agents are an effective alternative for patients with psoriasis. Based on data to date, it seems that the biologic agents will be safe for long-term use. It also appears that worsening of psoriasis during therapy or upon termination of therapy can occur with any of the agents used to treat psoriasis. It is important to note, however, that all of the biologic agents work differently from each other and have different safety profiles. If a patient is not responding optimally to one biologic agent, it may be that the patient would respond if given a different biologic agent. Since the safety profiles of the biologic agents differ from one another, it is important to obtain an accurate patient history before selecting a particular agent for an individual patient.

On balance, the latest findings suggest that biologic therapies may live up to their potential to offer safer treatment options than have been possible in the past for long-term continuous control of moderate to severe psoriasis.

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Continuing Education Instructions: There is no fee to participate in this activity. Please forward the Posttest Answer Sheet and Evaluation Form to: **Elsevier, Office of Continuing Medical Education, Department 290033, 685 Rt. 202/206, Bridgewater, NJ 08807**
FAX: (800) 201-7217. Responses for AMA/Physician's Recognition Award credit must be submitted by **May 31, 2006.**

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

1. What is the longest period of time that efalizumab has been evaluated in patients with psoriasis?
a. 72 weeks
b. 2 years
c. 3 years
d. 50 weeks
e. Five treatment courses
2. Which statement most accurately describes the overall long-term performance of the currently approved biologic agents in patients with psoriasis?
a. Increased incidence of adverse effects
b. Safety generally maintained over the time period studied
c. Efficacy generally maintained over the time period studied
d. b and c
e. a and c
3. Which of the following best describes how the long-term effects of etanercept on psoriasis have been evaluated in clinical trials?
a. Over nine treatment courses
b. Over the course of 3 years of continuous use in patients with psoriasis
c. Over the course of 50 weeks of use in patients with psoriatic arthritis who also had psoriasis
d. Over the course of 2 years of continuous use in patients with psoriatic arthritis who also had psoriasis
4. What are some of the alternative dosing regimens that are being evaluated for alefacept?
a. Step-down dosing
b. Dose escalation
c. Extended dosing
d. Weight-based dosing
e. a, b, and c
f. b, c, and d
5. What are some of the factors that should be considered when determining if a particular adverse event is associated with a biologic therapy?
a. Incidence during treatment compared to background incidence in the patient population
b. Data from placebo-controlled clinical trials
c. Data from voluntary reporting to MedWatch (FDA)
d. All of the above
e. None of the above
6. Of the two biologic agents that are likely to be approved for the treatment of psoriasis in the near future, which one is administered via a subcutaneous injection?
a. Adalimumab
b. Alefacept
c. Etanercept
d. Infliximab
e. Efalizumab
7. Which of the following best describes how the long-term effects of infliximab on psoriasis have been evaluated in clinical trials?
a. Over nine treatment courses
b. Over the course of 3 years of continuous use in patients with psoriasis
c. Over the course of 50 weeks of use in patients with psoriatic arthritis who also had psoriasis
d. Over the course of 2 years of continuous use in patients with psoriatic arthritis who also had psoriasis
8. True or false: One of the new biologic agents in the early stages of development for the treatment of psoriasis is an antibody to IL-12.
a. True
b. False

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