

Biologic Therapy for Psoriasis: The Tumor Necrosis Factor Inhibitors— Infliximab and Etanercept

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GOAL

To understand the biologic agents infliximab and etanercept

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the mechanisms of action for infliximab and etanercept.
2. Explain the clinical data behind infliximab and etanercept.
3. Discuss the side effect profiles of infliximab and etanercept.

CME Test on page 46.

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During the past several years, one of the major focuses in psoriasis research has been the development of novel biologic therapies for this

disease. The aim of these therapies is to provide selective, immunologically directed intervention, with the hope that such specificity will result in fewer side effects than traditional therapies. In this 2-part review, we present an update on the progress of the 4 biologic agents that most likely will be the first available for clinical use: infliximab, etanercept, efalizumab, and alefacept. The structure and mechanism of each drug will be reviewed, as well as the most recent clinical experience and safety data. The first article of this review will focus on the therapies that inhibit tumor necrosis factor α (TNF- α).

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The recent implication of immunologic phenomena in the pathogenesis of psoriasis has led to new research for possible treatment options over the past few years.¹ The result has been the birth of biologic therapies, ie, those drugs that target the activity of T lymphocytes and cytokines responsible for the inflammatory nature of this disease. Singri et al² recently outlined a conceptual model for immunomodulation in psoriasis. They defined 4 strategies within this model that clarify the mechanism of action for the various biologic agents: (1) reduction of pathogenic T cells, (2) inhibition of T-cell activation, (3) immune deviation (“deviation” of a helper T cell subtype 1 [T_H1] immune response toward a greater T_H2-type response through the involvement of these T_H2-type cytokines), and (4) blocking the activity of inflammatory cytokines.²

In this issue, we present a 2-part update on the progress of biologic agents in the forefront, those either under review at the US Food and Drug Administration (FDA) or close to FDA submission. These agents include infliximab (strategy 4), etanercept (strategy 4), efalizumab (strategy 2), and alefacept (strategy 1)(Table). In the first article, we will focus on the tumor necrosis factor (TNF) inhibitors infliximab and etanercept, and in the second article, we will review efalizumab and alefacept.

Infliximab

Structure and Mechanism—Infliximab (Figure 1) is a chimeric (mouse-human) immunoglobulin G subclass 1 monoclonal antibody that binds to TNF- α . It also inhibits production of other proinflammatory cytokines, reducing cell infiltration and eventually the proliferation of keratinocytes. Currently, the drug is approved for Crohn disease and rheumatoid arthritis as an intravenous infusion.

Clinical Experience—Chaudhari et al³ reported the results of a double-blind randomized trial to assess the clinical benefit and safety of infliximab in psoriasis. Thirty-three patients with moderate to severe plaque psoriasis were randomly assigned intravenous placebo (n=11), infliximab 5 mg/kg (n=11), or infliximab 10 mg/kg (n=11) at weeks 0, 2, and 6. Patients were assessed at week 10 for the primary end point (score on the Physician Global Assessment [PGA]).

Nine of 11 (82%) subjects in the infliximab 5-mg/kg group were responders (good, excellent, or clear rating on PGA) compared with 2 of 11 (18%) in the placebo group and 10 of 11 (91%) in the infliximab 10-mg/kg group. When evaluating improvement in the psoriasis area and severity index (PASI) score, the investigators found that infliximab 5 mg/kg resulted in 82% of patients showing at least a 75% improvement in PASI, while infliximab 10 mg/kg resulted in 73% of patients with at least a 75% improvement in PASI. The placebo group only had an average 15% improvement in PASI. The median time to response was 4 weeks for patients in both infliximab groups. There were no serious adverse events, and infliximab was well tolerated.³

Schopf et al⁴ treated 8 patients with severe psoriasis in an open-label clinical trial in which patients received infliximab 5 mg/kg intravenously at weeks 0, 2, and 6. The PASI score was used to monitor disease activity at weeks 0, 2, 4, 6, 8, 10, and 14. Between weeks 0 and 10, the researchers documented a nearly 85% reduction in mean PASI score. At week 14, 2 months after the patient had received the last infliximab dose, the mean PASI score was reduced dramatically by 67% from baseline. Pruritus decreased from 2.5 (± 0.26) at week 0 to 0.43 (± 0.2) at week 10 to 0.83 (± 11.3) at week 14.

Biologic Therapies for Psoriasis*

Agent	Mechanism of Action	Administration	Status
Infliximab	TNF- α inhibitor	IV infusion (>120 min)	Phase 2 trials
Etanercept	TNF- α inhibitor	SC twice weekly	Phase 3 trials
Efalizumab	Inhibits T-cell activation, migration	SC once weekly	Phase 3 trials
Alefacept	Reduces memory-effector T cells	IV/IM push once weekly	Filed with FDA

*TNF- α indicates tumor necrosis factor α ; IV, intravenous; SC, subcutaneous; IM, intramuscular; FDA, US Food and Drug Administration.

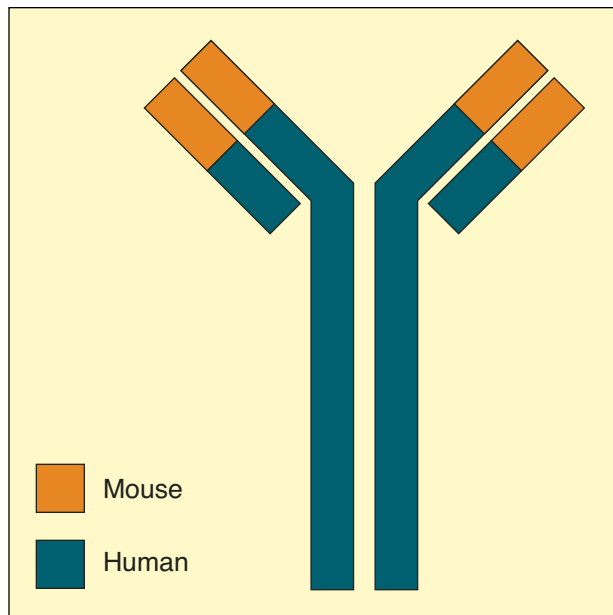


Figure 1. Structure of infliximab.

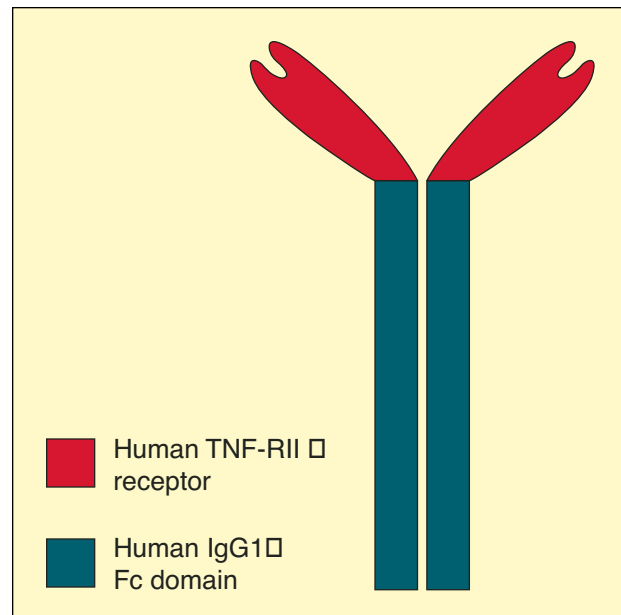


Figure 2. Structure of etanercept.

No adverse effects other than occasional fatigue during infusion were reported.⁴

Ogilvie et al⁵ described treatment with infliximab in 6 patients with both psoriasis and psoriatic arthritis. All patients had long-standing disease that was refractory to several treatments with methotrexate, and all received infusions of infliximab 5 mg/kg at weeks 0, 2, and 6. In addition, patients continued to receive the same doses of methotrexate or sulfasalazine during the study period. Ten weeks after the start of therapy, all patients experienced dramatic improvement in their arthritis, as well as dramatic and rapid improvement of their skin lesions, with a decrease in their PASI score by as much as 80%.⁵

Infliximab also has been shown to be effective in pustular psoriasis. Newland et al⁶ reported a rapid response to infliximab in a 44-year-old white woman with a 26-year history of severe, generalized, pustular psoriasis of the von Zumbusch type. The patient had failed to respond completely to various antipsoriatic medications and treatments, including topical steroids, UVB, acitretin, psoralen-UVA, cyclosporine, and dapsone. She was started on infliximab 5 mg/kg infused over 3 hours and experienced rapid improvement.⁶

O'Quinn and Miller⁷ recently reported the effectiveness of infliximab for the treatment of recalcitrant psoriasis. Two patients with psoriasis unresponsive to multiple topical and systemic therapies were treated with a single infusion of infliximab over 3 hours. The first patient, a 52-year-old white man with a 17-year history of psoriasis, noted

a decrease in pruritus and erythema of the skin within 2 days. Results of a follow-up examination at 4-weeks showed complete resolution of all psoriatic plaques, erythema, and scaling. The second patient, a 33-year-old white woman with an 8-year history of psoriasis and psoriatic arthritis, along with concomitant inflammatory bowel disease, reported decreased erythema in the psoriatic plaques within 24 hours of infusion. Results of a follow-up examination after 2 weeks were significant for complete clearing of all psoriatic plaques with residual macules and patches of hyperpigmentation and minimal overlying scale.⁷

Safety—Infliximab has been associated with a number of adverse events.⁸ Infusion reactions have been reported in 19% of patients in clinical trials and consist of fever or chills or, rarely, chest pain, hypotension, hypertension, and dyspnea. Neutralizing antibodies are formed, and patients can develop a serum sickness reaction days after administration of the drug. Infection is an issue of major concern, and there have been multiple reports of reactivation of latent tuberculosis.⁹ Infections are common in patients treated with infliximab, most likely because many are receiving other immunosuppressive therapy. In controlled trials, however, there does not appear to be an increased risk of serious infection in patients treated with infliximab.⁸

Etanercept

Structure and Mechanism—Etanercept is a 100% human TNF receptor, made from the fusion of 2 naturally occurring TNF receptors (Figure 2). It binds to

TNF with greater affinity than natural receptors, which are monomeric. The binding of etanercept to TNF renders the bound TNF biologically inactive, resulting in significant reduction in inflammatory activity. Etanercept currently is approved for the treatment of rheumatoid arthritis and psoriatic arthritis. Etanercept is administered subcutaneously by patients at home.

Clinical Experience—Mease et al¹⁰ reported the results of a randomized, double-blind, placebo-controlled, 12-week study to evaluate the safety and efficacy of etanercept (25 mg subcutaneous injections twice weekly) compared with placebo in a study population of 60 patients with psoriatic arthritis and psoriasis. Psoriatic arthritis end points included the proportion of patients who met both the Psoriatic Arthritis Response Criteria (PsARC) and the American College of Rheumatology preliminary criteria for improvement (ACR20). Psoriasis end points included improvement in the PASI score and improvement in prospectively identified individual target lesions. In this study, 26 (87%) patients treated with etanercept met the PsARC compared with 7 (23%) in the placebo-treated patients. The ACR20 was achieved in 22 (73%) patients treated with etanercept compared with 4 (13%) in the placebo-treated patients. Of the 19 patients in each treatment group who could be assessed for psoriasis ($\geq 3\%$ body surface area), 5 (26%) patients treated with etanercept achieved a 75% improvement in PASI compared with none in the placebo-treated patients ($P=.015$). The median PASI improvement was 46% in patients treated with etanercept versus 9% in placebo-treated patients; similarly, median target lesion improvements were 50% and 0, respectively. Etanercept was well tolerated.¹⁰

In a phase 2 clinical study assessing the safety and efficacy of this biologic therapy, 112 patients with moderate to severe plaque psoriasis were randomized evenly to receive 25 mg of etanercept or placebo subcutaneously twice a week for 6 months.¹¹ The primary end point of the study was the proportion of patients achieving a PASI reduction of at least 75% after 12 weeks. At 3 months, 30% of 57 patients receiving etanercept achieved a 75% reduction in PASI score compared with 2% of 55 patients receiving placebo ($P<.0001$). Fifty-six percent of patients treated with etanercept achieved a 75% reduction in PASI score at 6 months compared with 5% receiving placebo. Furthermore, at 6 months, 21% of patients receiving etanercept achieved a 90% reduction in PASI compared with none receiving placebo, while 77% of patients receiving etanercept achieved a 50% reduction in PASI compared with 13% receiving placebo. Side

effects included mild upper respiratory tract infections and sinusitis and reactions at the injection site.¹¹

Similar findings were seen in a report of 6 patients, ranging in age from 33 to 57 years, with severe residual psoriasis (3 also with psoriatic arthritis) who had been unresponsive to systemic treatments and phototherapy.¹² The PASI scores of these patients before receiving etanercept and, in some cases, combination therapy, averaged 24, with the highest being 29, while the scores following treatment with etanercept had a mean of 9, with the highest being 14. In addition, no toxicity secondary to treatment was noted. In patients where etanercept was added in combination with other systemic and topical medications, resistant disease became more responsive to treatment and permitted the usage of lower doses of systemic agents.¹²

Like infliximab, etanercept also has been shown to be useful for the treatment of pustular psoriasis. Kamarashev et al¹³ reported the case of a 50-year-old male patient with a 15-year history of psoriasis, including mutilating psoriatic arthritis, in whom the withdrawal of cyclosporin A induced a generalized pustular exacerbation and aggravation of the joint condition. Two weekly injections of 25 mg of etanercept led to a rapid improvement of his psoriatic arthritis, as well as regression of the pustular eruption, although residual erythema was still present.¹³

Safety—Etanercept has been used safely over the past few years. The main adverse events noted are reactions at the injection site. There have been rare observations of demyelinating disorders, such as multiple sclerosis, allergic reactions, and aplastic anemia.⁸ Because etanercept has been available for rheumatoid arthritis for several years, it possesses a good safety profile as to the risk of malignancy and infection. Results from 1272 patients (3706 patient years) in North America demonstrate continued safety of etanercept after more than 5 years of therapy.¹⁴ Overall, the rate of adverse events remains low. The frequency of infections requiring hospitalization or intravenous antibiotics was 0.04 per patient year in the total population, which is the same as the rate in the control group in controlled trials. The incidence of malignancies was not increased in the etanercept group compared with the expected number from the National Cancer Institute, Surveillance, Epidemiology, and End Results database (35 observed vs 35 expected).¹⁴ In addition, from 1993 to 2001, reports of tuberculosis in patients receiving etanercept were rare (20), and reporting rates were comparable to background incidence.¹⁵ More important, there was no apparent temporal association of onset of clinical tuberculosis with the introduction of etanercept therapy.

Conclusion

Infliximab and etanercept are 2 new promising therapies for psoriasis. Inhibition of TNF appears to have favorable efficacy in the treatment of this disease. Because these agents are used in other inflammatory disorders, we have more long-term data on safety and side effect profiles for these drugs compared with others in development. Data from ongoing trials will help elucidate further the proper roles for these drugs in the psoriasis treatment algorithm. The second part of this update will review those drugs, efalizumab and alefacept, that target, respectively, pathogenic T cells and their activation.

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