

# Biologic Therapy for Psoriasis: The T-Cell–Targeted Therapies— Efalizumab and Alefacept

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## GOAL

To understand the biologic agents efalizumab and alefacept

## OBJECTIVES

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

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

**CME** Test on page 46.

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*During the past several years, a new generation of therapies for psoriasis has been in development.*

*These biologic therapies target the activity of T lymphocytes and cytokines responsible for the inflammatory nature of this disease. The first article of this 2-part update reviewed the tumor necrosis factor (TNF) inhibitors, infliximab and etanercept. In this article, we will review 2 therapies that target the T cell, efalizumab and alefacept.*

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**T**he recent implication of immunologic phenomena in the pathogenesis of psoriasis has led to new research for possible treatment options over the past few years.<sup>1</sup> 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. 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. The first article focused on the tumor necrosis factor (TNF) inhibitors infliximab and etanercept, and this article will review efalizumab and alefacept. The mechanism of action for each drug will be reviewed, as well as the most recent efficacy and safety data.

### Efalizumab

*Structure and Mechanism*—Efalizumab is a humanized monoclonal antibody against the CD11a molecule. CD11a and CD18 comprise subunits of leukocyte function-associated antigen-1 (LFA-1), a T-cell surface molecule important in T-cell activation, T-cell migration into the skin, and cytotoxic T-cell function. The binding of this drug to CD11a on T cells blocks the interaction between LFA-1 and intercellular adhesion molecule-1 (ICAM-1), its partner molecule for adhesion. The blockade is reversible and does not deplete T cells. Efalizumab has been studied in both intravenous and subcutaneous forms but will be developed for weekly subcutaneous injections.

*Clinical Experience*—Gottlieb et al<sup>2</sup> explored the immunobiologic and clinical effects of treating moderate to severe psoriasis vulgaris with a single intravenous dose of humanized monoclonal antibody against CD11a (hu1124). This was an open-label study with a single 0.03- to 10-mg/kg dose of hu1124. Clinical psoriasis area and severity index (PASI) scores and immunohistologic parameters (epidermal thickness, epidermal and dermal T-cell numbers, and keratinocyte ICAM-1 expression) were followed.

It was found that treatment with hu1124 at doses higher than 1.0 mg/kg (group 3) completely blocks CD11a staining in both blood and psoriatic plaques for at least 14 days. At doses between 0.3 mg/kg and 1.0 mg/kg, T-cell CD11a staining was blocked completely; however, blockade lasted less than 2 weeks (group 2). Only partial saturation of either blood or plaque cellular CD11a was observed at doses between 0.01 mg/kg and 0.1 mg/kg (group 1). This pharmacodynamic response was accompanied by decreased numbers of epidermal and dermal CD3<sup>+</sup> T cells, decreased keratinocyte and blood vessel expression of ICAM-1, and epidermal thinning. Statistically significant decreases in PASI scores compared with baseline were observed at weeks 3 and

4 in group-2 patients and at weeks 2 through 10 in group-3 patients. No significant decrease in PASI score was observed in group-1 patients.<sup>2</sup>

Adverse events were mild at doses of 0.3 mg/kg or lower and included mild chills, abdominal discomfort, headache, and fever. At a single dose of 0.6 mg/kg or higher, headache was the most common dose-limiting toxicity observed. The investigators concluded that targeting CD11a may improve psoriasis by inhibiting T-cell activation, T-cell migration into the skin, and cytotoxic T-cell function.<sup>2</sup>

Papp et al<sup>3</sup> reported the results of a double-blind, placebo-controlled, phase 2, multicenter study with anti-CD11a, in which 145 patients with minimum PASI scores of 12 and an affected body surface area (BSA) of 10% or greater were enrolled sequentially into low-dose (0.1 mg/kg, n=22) or high-dose (0.3 mg/kg, n=75) groups. Patients then were randomized to treatment or placebo (n=48) in a 2:1 ratio. Intravenous infusions were administered at weekly intervals for 8 weeks. Seven (15%) placebo patients and 36 (48%) of those receiving high-dose efalizumab achieved a greater than 50% improvement on the physician's global assessment (PGA) one week after receiving the final dose. The percentage of patients with a PGA of excellent (>75% improvement) was higher in the 0.3-mg/kg group (25%, n=19) compared with the placebo group (2%, n=1). PASI scores were also lower in the group receiving efalizumab (10.9±8.4) versus those in the placebo group (13.9±7.5). The overall treatment was well tolerated, and the most common adverse events were mild to moderate flu-like symptoms.<sup>3</sup>

Gottlieb et al<sup>4</sup> examined the immunobiologic and clinical effects of treatment with multiple doses of efalizumab. In an open-label, multiple-dose, dose-escalation study, 39 patients with stable, moderate to severe plaque psoriasis (>15% BSA involvement and a PASI score >15) were treated with efalizumab.<sup>4</sup> The subjects received infusions of the following dose levels for 7 weeks in an ascending dose-escalation paradigm: 0.1 mg/kg every other week or 0.1 mg/kg weekly (category 1; n=10); 0.3 mg/kg weekly (category 2; n=17); or 0.3 mg/kg increasing to 0.6 mg/kg or 1.0 mg/kg for the remaining weeks (category 3; n=12). The median baseline PASI score was 23, ranging from 15 to 42. Because of early discontinuations or damage to some biopsy samples during transit, histologic analyses were conducted for only 32 subjects. Biopsies of the skin were performed on days 0, 28, and 56.<sup>4</sup>

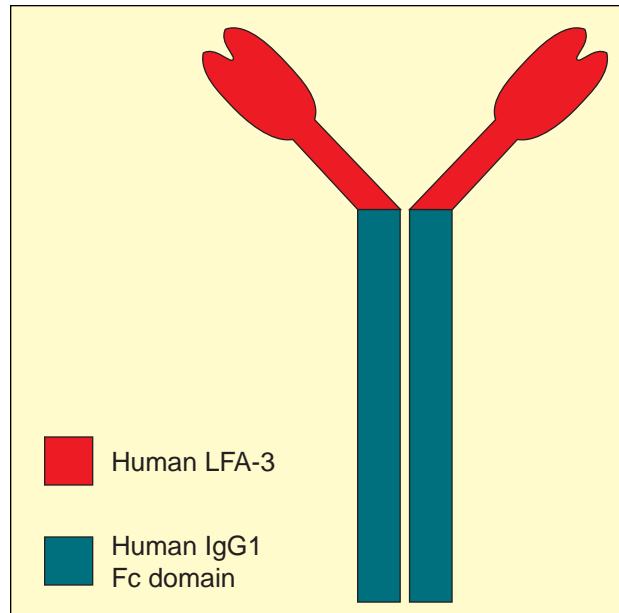
The main outcome measures included serum efalizumab levels, levels of total and unoccupied T-cell CD11a, T-cell counts, epidermal thickness,

cutaneous ICAM-1, and keratin 16 (K16) expression, as well as PASI scores. Results showed that category 1 failed to maintain detectable serum efalizumab or T-cell CD11a down-modulation between doses. Category 2 achieved both, as did category 3, which also maintained sustained T-cell CD11a saturation between doses. Clinically, the mean decrease in the PASI score was 47% in category 3, 45% in category 2, and 10% in category 1 ( $P < .001$ ). Epidermal and dermal T-cell counts, epidermal thickness, ICAM-1, and K16 expression decreased in categories 2 and 3 but not in category 1. In addition, circulating lymphocyte counts increased in categories 2 and 3. Therefore, intravenous efalizumab at a dose of 0.3 mg/kg or higher per week produced significant clinical and histologic improvement in psoriasis, correlating with sustained serum efalizumab levels and T-cell CD11a saturation and down-modulation.<sup>4</sup>

Recently, 2 phase 3 trials with subcutaneous efalizumab administered to nearly 1100 patients showed promising results for the treatment of moderate to severe plaque psoriasis.<sup>5</sup> The major end point was achievement of 75% improvement in PASI score (PASI 75); other efficacy end points were achievement of an overall lesion severity score of minimal or clear, and a PGA score of excellent or clear. Included subjects had moderate to severe plaque psoriasis (BSA 10%; PASI 12) and were candidates for systemic therapy. Treatment regimens were identical in both trials. Subjects were randomized to treatment consisting of an initial conditioning dose of 0.7 mg/kg at week 1, followed by 11 weekly doses of either 1.0 mg/kg or 2.0 mg/kg of efalizumab or placebo.<sup>5</sup>

In comparison to patients on placebo, those receiving efalizumab showed a marked improvement on all efficacy measures. More subjects treated with efalizumab achieved PASI 75 than those on placebo.<sup>5</sup> In the 1.0-mg/kg per week group, 29.2% achieved PASI 75, and 55.6% achieved PASI 50; in the 2.0-mg/kg per week group, 27.6% achieved PASI 75, and 54.5% achieved PASI 50. Of the patients in the placebo group, 3.4% achieved PASI 75, and 15.1% achieved PASI 50.<sup>5</sup> Combined results from both trials show that the PASI for both efalizumab groups was improved in comparison with the placebo group after only 2 to 4 doses ( $P < .005$ ).<sup>5</sup>

**Safety**—Efalizumab has been used safely in nearly 2000 patients. Most have been treated from 12 to 24 weeks, with a small number treated for up to 1 year.<sup>6</sup> More important, there have been no opportunistic infections, no clinical signs of immunosuppression, and no hepatotoxicity or nephrotoxicity associated with the use of efalizumab.<sup>6</sup>



Structure of alefacept.

In initial trials, patients were treated for 12 weeks, but on discontinuation of the medication, many patients experienced flares of their psoriasis.<sup>6</sup>

### Alefacept

**Structure and Mechanism**—Psoriatic plaques are characterized by infiltration with CD4<sup>+</sup>, CD45RO<sup>+</sup>, CD8<sup>+</sup>, and CD45RO<sup>+</sup> memory-effector T lymphocytes. The recombinant protein alefacept binds to CD2 on memory-effector T lymphocytes, inhibiting their activation and reducing their number. It is a fusion protein composed of LFA-3 protein and human IgG1 Fc domains (Figure). The drug is administered by either intramuscular or intravenous injection.

**Clinical Experience**—In a multicenter, randomized, placebo-controlled, double-blind study, Ellis et al<sup>7</sup> evaluated alefacept as a treatment for psoriasis. Two hundred twenty-nine patients with chronic psoriasis received intravenous alefacept (0.025 [n=57], 0.075 [n=55], or 0.150 mg/kg [n=58] of body weight) or placebo (n=59) weekly for 12 weeks, with follow-up for 12 additional weeks. Before treatment, the median PASI scores were between 14 and 20 in all groups (0 denotes no psoriasis and 72 the most severe disease possible). In the study, alefacept was well tolerated and nonimmunogenic. The mean reduction in PASI score 2 weeks after treatment was greater in the alefacept groups (38%, 53%, and 53% in the groups receiving 0.025, 0.075, and 0.150 mg/kg, respectively) than in the placebo group (21%) ( $P < .001$ ). Twelve

weeks after treatment, 28 patients who had received alefacept alone were clear or almost clear of psoriasis. Three patients in the placebo group were clear or almost clear; all 3 patients had received additional systemic therapy for psoriasis. Alefacept reduced peripheral blood memory-effector T-lymphocyte (CD45RO<sup>+</sup>) counts, which correlated with improvement in psoriasis.<sup>7</sup>

An international multicenter trial randomized more than 500 patients to 1 of 3 arms: intramuscular alefacept 15 mg once a week for 12 weeks, intramuscular alefacept 10 mg once a week for 12 weeks, or placebo.<sup>8</sup> Two weeks after the last dose, 21% of patients treated with the 15-mg dose achieved at least PASI 75 compared with 5% of patients receiving placebo ( $P<.001$ ).<sup>8</sup> Such results are contributing to an anticipated FDA approval of this drug in early 2003.

Another multicenter phase 3 study evaluated the efficacy and safety of once-weekly alefacept 7.5 mg administered by 30-second intravenous bolus in patients with moderate to severe chronic plaque psoriasis.<sup>9</sup> This study consisted of 2 treatment courses, each with a 12-week treatment and 12-week follow-up phase. Patients (N=553) were randomized to 1 of 3 cohort studies: cohort 1 received alefacept during both courses, cohort 2 received alefacept followed by placebo, and cohort 3 received placebo followed by alefacept. Clinical response was measured by change in the PASI

score from baseline and on the PGA. During the first course of treatment, 14% and 4% of patients receiving alefacept and placebo, respectively, achieved PASI 75 at week 14 (primary end point;  $P<.001$ ). PASI 50 was achieved by 38% of patients treated with alefacept and 10% of those treated with placebo at week 14 after the first course ( $P<.001$ ). At any time after the first dose of alefacept during the first course of treatment, 28% and 56% of patients achieved PASI 75 and PASI 50, respectively ( $P<.001$  vs placebo). Patients in the cohort 1 study who were randomized to receive 2 courses of alefacept showed additional improvement at the end of the second course of therapy, with 40% and 71% of subjects achieving PASI 75 and PASI 50 at any time point. The percentage of these patients who achieved clear or almost clear on the PGA at any time after the first dose was 23% after the first course of alefacept and 32% after the second course. There was no increased risk of infection (placebo, 11%; alefacept, 10%) and no complicated or opportunistic infections associated with alefacept therapy.<sup>9</sup>

**Safety**—As to adverse events, patients treated with alefacept had a reduction in CD45RO<sup>+</sup> memory T cells, which correlated with improvement in psoriasis. The drug has been studied in more than 1500 patients, with some receiving as many as 6 courses of treatment. To date, no clinically significant signs of immunosuppression or opportunistic

### Clinical Efficacy of Biologic Therapies for Psoriasis\*

Agent	Dose (Duration)	PASI 50	PASI 75	PASI 90	Reference
Infliximab	5 mg/kg (0, 2, 6 wk)	...	10 wk: 73%–82%	...	Chaudhari et al, 2001 <sup>10</sup>
Etanercept	25 mg SC 2×/wk (12–24 wk)	12 wk: 70% 24 wk: 77%	12 wk: 30% 24 wk: 56%	12 wk: 11% 24 wk: 21%	Gottlieb et al, 2002 <sup>11</sup>
Efalizumab	1 mg/kg per wk (12 wk) 2 mg/kg per wk (12 wk)	12 wk: 55.6% 12 wk: 54.5%	12 wk: 29.2% 12 wk: 27.6%	...	Gottlieb et al, 2002 <sup>5</sup>
Alefacept	15 mg IM/wk (12 wk)	14 wk: 42%	14 wk: 21%	...	Christophers et al, 2001 <sup>8</sup>
	10 mg IM/wk (12 wk)	14 wk: 36%	14 wk: 12%		
	7.5 mg IV/wk (12 wk)	14 wk: 38%	14 wk: 14%	...	Lebwohl et al, 2002 <sup>9</sup>

\*PASI indicates psoriasis area and severity index; PASI 50, 50% improvement in PASI; SC, subcutaneously; IM, intramuscularly; IV, intravenously.

infections and no increase in malignancy have been observed.<sup>6</sup> The FDA most likely will require monitoring of T cells in patients treated with alefacept.

## Conclusion

Biologic therapy research continues to make great strides in the treatment of psoriasis. With continued progress at this rate, it is possible that one or more of these pharmacologic agents will become major therapeutic options for psoriasis. Data from this work are very encouraging; the Table summarizes the efficacy of all 4 of the new agents from clinical trials. However, we await further data from ongoing trials for several of these medications, as well as for those treatments that are in the early stages of development. Hopefully, the next year will continue to bring us favorable reports regarding the safety and efficacy of these new therapies.

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