

# Alefacept for Psoriasis

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Alefacept was the first biological agent approved by the Food and Drug Administration for the treatment of psoriasis. Alefacept was initially approved as an intravenous and intramuscular medication. It is available only as an intramuscular medication. Alefacept is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 linked to the Fc (hinge, CH2, CH3 domains) portion of human immunoglobulin G.<sup>1</sup> Alefacept selectively blocks the leukocyte function antigen-3:CD2 costimulatory pathway, which is important in the reactivation of memory effector T cells. Alefacept also reduces the number of memory effector T cells in the blood and in the skin.<sup>2</sup>

Alefacept is indicated for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose of alefacept is 15 mg given once weekly as an intramuscular (IM) injection. The approved regimen is a course of 12 weekly injections. Retreatment with an additional 12-week course may be initiated if CD4<sup>+</sup> T lymphocyte counts are within the normal range and a minimum of a 12-week interval has passed since the previous course of treatment. Alefacept is Pregnancy category B. It should only be used when clinically indicated in pregnant women and nursing mothers.

## Variations in Administration

In 2005, Gribetz et al<sup>3</sup> reported a randomized, single-center study comparing the safety and efficacy of a standard 12-week versus extended 16-week alefacept dosing period in 20 patients with chronic plaque psoriasis. Both dose groups

showed improvement in mean Psoriasis Area and Severity Index (PASI) score from baseline through week 24 (between-group difference: not significant). In each group, 60% of patients achieved PASI 50 ( $\geq 50\%$  reduction from baseline PASI score) at any time between weeks 12 and 24. For patients who received 16 weeks of alefacept, the mean percentage change from week-12 PASI score was greater and continued to increase through week 24 compared with that for patients who received 12 weeks of alefacept ( $P < 0.05$ ). Adverse events were similar between the 2 groups and comparable with those observed in phase 2 and 3 clinical studies of alefacept.<sup>3</sup> There are also reports of subcutaneous alefacept administration and it is approved for home administration in Canada.<sup>4,5</sup>

## Combination Therapy

Alefacept has also been reported in combination with phototherapy,<sup>6,7</sup> methotrexate, and cyclosporine.<sup>8</sup> Combination regimens are covered in a separate article in this volume.

## Efficacy

Two randomized, double-blind, placebo-controlled studies were conducted<sup>9,10</sup> in adults with chronic ( $\geq 1$  year) plaque psoriasis and  $>10\%$  body surface area who were candidates for or had previously received systemic therapy or phototherapy. Each course consisted of once-weekly administration for 12 weeks (intravenous [IV], IM) of placebo or alefacept. Patients could receive concomitant low-potency topical steroids. Phototherapy or systemic therapy was not allowed.

In the IV study, patients were randomized to receive 1 or 2 courses of alefacept, 7.5 mg administered by IV bolus. The first and second courses in the 2-course cohort were separated by at least a 12-week postdosing interval. A total of 553 patients were randomized into 3 cohorts. The IM study compared patients treated with either 10 or 15 mg of alefacept IM and placebo. One hundred seventy-three patients were randomized to receive 10 mg of alefacept IM, 166 to receive 15 mg of alefacept IM, and 168 to receive placebo.

Response to treatment in both studies was defined as the proportion of patients with at least a 75% reduction in the PASI (PASI-75) from baseline at 2 weeks after the 12-week treatment period. Other treatment responses included the

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proportion of patients who achieved a scoring of “almost clear” or “clear” by Physician Global Assessment and the proportion of patients with a reduction in PASI of at least 50% from baseline 2 weeks after the 12-week treatment period.

The PASI-75 at the primary endpoint for the IV study was 14% versus 4% for placebo. The PASI-75 at the primary endpoint for the 15 mg IM dose was 21% versus 5% for placebo. In the IM study, the proportion of responders to the 10 mg IM dose was greater than placebo, but the difference was not statistically significant. In both studies, onset of response to alefacept treatment (at least a 50% reduction of baseline PASI) began 60 days after the start of therapy. In the studies, an additional 11% (42/367) and 7% (12/166) of patients treated with alefacept, respectively, achieved a 75% reduction from baseline PASI score at one or more visits after the first 2 weeks of the follow-up period.

With 1 course of therapy in the IV study, the median duration of response (defined as maintenance of a 75% or greater reduction in PASI) was 3.5 months for alefacept-treated patients and 1 month for placebo-treated patients. In the IM study, the median duration of response was approximately 2 months for both alefacept-treated patients and placebo-treated patients. Most patients who had responded to either alefacept or placebo maintained a 50% or greater reduction in PASI through the 3-month observation period. Among responders who received alefacept 7.5 mg IV or alefacept 15 mg IM and were followed off active treatment before alefacept retreatment, a 50% or greater reduction in PASI was maintained for a median of 7 months.

As part of the application for approval in Canada, an additional 195 patient trial for whom 3 or more therapies had failed or were inappropriate was conducted with the 15-mg IM formulation. The results showed a PASI-50 of 24% for the alefacept treated versus 11% for placebo arm. There was no statistically significant difference for PASI-75 and quality of life.<sup>11</sup>

## Retreatment

In 2006, Menter et al<sup>12</sup> reported on the safety and efficacy of up to 5 courses of alefacept. Although this article considered only those patients who remained in this study, it is clear that some patients experienced benefit from multiple courses of therapy.

## Malignancy

Among 1869 patients who received alefacept at any dose in clinical trials, 43 patients were diagnosed with 63 treatment-emergent malignancies. Most of the malignancies were non-melanoma skin cancers: 46 cases (20 basal cell, 26 squamous cell carcinomas) occurring in 27 patients. Other malignancies observed in alefacept-treated patients included melanoma ( $n = 3$ ), solid organ malignancies ( $n = 12$  in 11 patients), and lymphomas ( $n = 5$ ); the latter consisted of 2 Hodgkin's and 2 non-Hodgkin's lymphomas, and 1 cutaneous T-cell lymphoma (mycosis fungoides).<sup>13</sup>

## Infection

Serious infections (infections requiring hospitalization) were seen at a rate of 0.9% (8/876) in alefacept-treated patients and 0.2% (1/413) in the placebo group. In patients receiving repeated courses of alefacept, the rates of serious infections remained similar across multiple cycles of therapy. Serious infections among 1869 alefacept-treated patients included cellulitis, abscesses, wound infections, toxic shock, pneumonia, appendicitis, cholecystitis, gastroenteritis, and herpes infections.

## Hypersensitivity Reactions

In clinical studies, 4 of 1869 (0.2%) patients were reported to experience angioedema: 2 of these patients were hospitalized. In the placebo-controlled studies, urticaria was reported in 6 (<1%) alefacept-treated patients versus 1 patient in the control group. Urticaria resulted in discontinuation of therapy in one of the alefacept-treated patients.

## Lymphocyte Monitoring

The package insert states that CD4<sup>+</sup> T lymphocyte counts of patients receiving alefacept should be monitored before initiating dosing and every 2 weeks throughout the course of the 12-week dosing regimen. If CD4<sup>+</sup> T lymphocyte counts are less than 250 cells/ $\mu$ L, alefacept dosing should be withheld and weekly monitoring instituted. Alefacept should be discontinued if the counts remain less than 250 cells/ $\mu$ L for 1 month.<sup>1</sup>

In the IM study,<sup>9</sup> 4% of patients temporarily discontinued treatment and no patients permanently discontinued treatment due to CD4<sup>+</sup> T lymphocyte counts below the specified threshold of 250 cells/ $\mu$ L. Ten percent, 28%, and 42% of patients had total lymphocyte, CD4<sup>+</sup>, and CD8<sup>+</sup> T lymphocyte counts below normal, respectively. Twelve weeks after a course of therapy, 2%, 8%, and 21% of patients had total lymphocyte, CD4<sup>+</sup>, and CD8<sup>+</sup> T cell counts less than normal.

In the first course of the intravenous study,<sup>10</sup> 10% of patients temporarily discontinued treatment and 2% permanently discontinued treatment as the result of CD4<sup>+</sup> T lymphocyte counts below the threshold of 250 cells/ $\mu$ L, 22% of patients had total lymphocyte counts less than normal, 48% had CD4<sup>+</sup> T lymphocyte counts less than normal, and 59% had CD8<sup>+</sup> T lymphocyte counts less than normal. The maximal effect on lymphocytes was observed within 6 to 8 weeks of initiation of treatment. Twelve weeks after therapy, 4% of patients had total lymphocyte counts less than normal, 19% had CD4<sup>+</sup> T lymphocyte counts less than normal, and 36% had CD8<sup>+</sup> T lymphocyte counts less than normal.

For patients receiving a second course of IV alefacept, 17% of patients had total lymphocyte counts less than normal, 44% had CD4<sup>+</sup> T lymphocyte counts less than normal, and 56% had CD8<sup>+</sup> T lymphocyte counts less than normal. Twelve weeks later, 3% of patients had total lymphocyte counts less than normal, 17% had CD4<sup>+</sup> T lymphocyte counts less than

normal, and 35% had CD8<sup>+</sup> T lymphocyte counts less than normal.

## Hepatic Injury

There have been reports of asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis, and severe liver failure. In the studies, 1.7% (15/876) of alefacept-treated patients and 1.2% (5/413) of the placebo group experienced ALT and/or AST elevations of at least 3 times the upper limit of normal.

## Injection-Site Reactions

In the IM study, 16% of alefacept-treated patients and 8% of placebo-treated patients reported injection-site reactions. In patients receiving repeated courses of alefacept IM therapy, the incidence of injection site reactions remained similar across courses of therapy. Reactions at the site of injection were generally mild, typically occurred on single occasions, and included either pain (7%), inflammation (4%), bleeding (4%), edema (2%), nonspecific reaction (2%), mass (1%), or skin hypersensitivity (<1%). In the clinical trials, a single case of injection site reaction led to the discontinuation of alefacept.

## Immunogenicity

Approximately 3% (40/1357) of patients receiving alefacept developed low-titer antibodies to alefacept. No apparent correlation of antibody development and clinical response or adverse events was observed. The long-term immunogenicity of alefacept is unknown.

## Uses Beyond Psoriasis

The authors are unaware of any future development efforts planned by the manufacturers. There are several scattered reports of the use of alefacept for diseases other than psoriasis. These include alopecia areata,<sup>14,15</sup> lichen planus, and graft-versus-host disease.<sup>16</sup>

## Conclusions

Alefcept has been limited by its lack of clinical clearance. It remains one of the most difficult drugs to use primarily because of inconsistent effects on psoriasis, slow time to onset, and poor response. For most psoriasis experts, it has been relegated to a treatment for patients who have failed most of the other available treatments. "The utility of alefacept will likely be enhanced when: (1) subpopulations of psoriatics who will respond to therapy before treatment with alefacept is initiated can be identified; (2) the optimal duration of a course of treatment is determined; (3) the role of CD4 testing

in patients taking alefacept is defined and if it is found that there is no role for such testing the recommendation for testing is eliminated; and (4) whether the combination of alefacept and phototherapy is truly synergistic and provides a therapeutic combination that can improve the PASI score more than existing treatments."<sup>17</sup>

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