Alefacept: A New Therapy for Psoriasis
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INTRODUCTION
Psoriasis is an autoimmune, chronic, inflammatory skin disorder characterized by the presence of scaly, thickened, erythematous plaques. The disease primarily affects the skin but can involve the joints, tendons, and ligaments.

Psoriasis affects approximately 2% of the population in the U.S. It often manifests between the ages 15 and 35, but it can develop in people of any age. The disease appears to be slightly more prevalent in women than in men.

About 30% of patients have moderate-to-severe psoriasis, which affects more than 3% of the body. Severe forms of psoriasis can compromise the skin’s ability to control body temperature and to fight off infections. Psoriasis affects quality of life; approximately 75% of patients with moderate-to-severe psoriasis report that their disease has a significant impact on their everyday lives, and approximately 26% mention the need for alterations in normal daily activities. An additional 40% of patients say that having psoriasis affects their clothing choices; 36% say that it affects their sleeping patterns; and 36% report feeling the need to bathe more often than normal.

Although the exact etiologic mechanism of psoriasis remains unknown, its pathogenesis is immune-mediated and is characterized by activation of skin-directed T cells. After these T cells are activated, they proliferate and infiltrate the skin, releasing inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ). The psoriatic plaques are thus characterized by a predominance of T lymphocytes, including CD4/CD45RO+ and CD8/CD45RO+ memory-effector cells. T lymphocytes have also been implicated in the proliferation of keratinocytes in patients with psoriasis.

There is no known cure for chronic plaque psoriasis. Current therapies include topical treatments, chemophototherapy (psoralen and ultraviolet A light [PUVA]), and systemic immunosuppressive agents (methotrexate, cyclosporine, and azathioprine). These treatments are less than optimal because they do not eliminate the disease, are associated with serious adverse effects, and are inconvenient to administer. These shortcomings demonstrate the need for safe and effective treatment alternatives to provide sustained remissions from the disease and to improve quality of life for patients.

Immunomodulating therapies that target T-cell activity are specific modalities that have been developed for the treatment of psoriasis. One of these agents is an injectable, fully human recombinant fusion protein, alefacept (Amevive®, Biogen, Inc.). The Food and Drug Administration (FDA) has recently approved this agent for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

PHARMACOLOGY
An immunosuppressive dimeric fusion protein, alefacept consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) and the body portion of the alefacept molecule that binds to the natural killer (NK) cells, causing apoptosis of memory-effector T cells, and reduces T-cell counts in the psoriatic plaques.

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signed to receive one of the IV dosing regimens of alefacept (0.025, 0.075, or 0.150 mg/kg of body weight) or placebo (normal saline) once weekly for 12 weeks. The patients were followed for 12 additional weeks after the completion of therapy. The patients received alefacept if their total lymphocyte count was at least 67% of the lower limit of the normal range within 24 hours of injection and if an absolute CD4 T-lymphocyte count was at least 300 cells/mm² in the previous week of therapy.

Systemic treatments, phototherapy, and potent topical medications were not permitted for four weeks before treatment and for two weeks after the completion of alefacept therapy. The limited use of moderate-potency topical corticosteroids, keratolytic agents, coal tar, or calcipotriene was allowed only in the groin, scalp, and palm areas and in the soles of the feet.

The Psoriasis Area and Severity Index (PASI) and Physician Global Assessments (PGAs) were used to evaluate the severity and extent of the condition. The PASI scoring system ranges from 0 (no psoriasis) to 72 (the most severe disease possible). This system combines scores for (1) the degree of erythema, (2) induration, (3) desquamation, and (4) the percentage of body surface area that is affected by psoriasis plaques.

The overall PGA of the extent of psoriasis was reported on the seven-point PGA review. It is apparent that 12 weeks of alefacept treatment resulted in improvement of chronic plaque psoriasis and in sustained clinical responses after completion of therapy.

Krugger et al.18

In another randomized, double-blind phase III clinical study, Krugger and colleagues recruited 553 patients with chronic plaque psoriasis involving a minimum of 10% of body surface area who were candidates for, or had previously received, systemic therapy or phototherapy. Patients received two 12-week courses of once-weekly IV doses of alefacept 7.5 mg or a placebo. For patients weighing less than 50 kg, the dose of alefacept was reduced by 33%. Patients were observed for 12 weeks after each course of therapy.

Phototherapy or other agents, including systemic steroids, systemic fumarates, methotrexate, cyclosporine, azathioprine, thioguanine, and high-potency topical steroids, were prohibited for four weeks prior to entry into the study. The use of moderate-potency topical corticosteroids, vitamin D analogues, keratolytic agents, and coal tar was not allowed during the two weeks before enrollment. For patients with sustained absolute CD4 T-lymphocyte counts below 250 cells/mm² after four or more consecutive visits, placebo was substituted for the dose of alefacept.

Patients were considered to have achieved a clinical response to treatment if they demonstrated a reduction in PASI scores from baseline values of at least 75% after two weeks of completing the first 12-week course of treatment. Patients were graded according to the PGA scale, and the number of patients who showed improvements of “almost clear” or “clear” during or after the 12-week course of therapy was recorded.

At the baseline evaluation, most patients had moderate or moderate-to-severe psoriasis and had received previous therapy with ultraviolet B, methotrexate, PUVA, and retinoids. Overall, in both courses of therapy, mean PASI scores of patients taking alefacept decreased more than the scores of those taking placebo:

- Patients who received two courses of alefacept experienced a maximum mean reduction from baseline PASI scores of 54% six weeks after treatment. After the two-week follow-up of the first course, a 75% or greater reduction in PASI scores was achieved by 14% of alefacept-treated patients and by 4% of placebo-treated patients (P < .001).
- Patients who received a single course of alefacept and achieved a 75% or greater reduction in PASI scores after treatment (without phototherapy or systemic therapies) maintained a 50% or greater reduction in PASI scores for a median duration of greater than seven months.
- Of the patients who received two courses of alefacept, 40% achieved a 75% or greater reduction in PASI scores, whereas 71% of patients reached a 50% or greater reduction in PASI scores, and 32% of patients had “clear” or “almost clear” scores on the PGA review.

In this study, alefacept significantly improved PASI scores from baseline val-

After two weeks of treatment, the mean reduction in PASI scores was significantly greater in the alefacept groups: 38%, 53%, and 53% for those receiving 0.025, 0.075, and 0.150 mg/kg, respectively, than in the placebo group (21%) (P < .001).

Two weeks after treatment, 21%, 33%, and 31% of patients receiving 0.025, 0.075, and 0.150 mg/kg of alefacept, respectively, achieved at least a 75% reduction in PASI scores from baseline evaluation, compared with 10% of patients who received placebo (P = .02).

After 12 weeks of treatment, 33%, 31%, and 19% of patients in the respective alefacept groups experienced at least a 75% reduction in PASI scores, compared with 11% of patients taking placebo (P = .02).

Overall, 118 patients treated with alefacept completed the 12-week regimen and required no supplementary therapy for psoriasis during the next 12 weeks of monitoring. After a 12-week post-treatment evaluation, 28 patients (24%) who had received alefacept were clear or almost clear of psoriasis. The median time for the initiation of additional treatment with alefacept was 306 days (range, 185–533 days) in 26 patients. Three patients in the placebo group were clear or almost clear of psoriasis plaques 12 weeks after their last dose, and all of these patients received other systemic therapy for psoriasis. The alefacept patients showed significantly greater improvement in the dermatology-specific quality-of-life scales than did patients taking placebo (P < .05).17

On the basis of these results of this phase II clinical trial, it is apparent that 12 weeks of alefacept treatment resulted in improvement of chronic plaque psoriasis and in sustained clinical responses after completion of therapy.
ues in patients with chronic plaque psoriasis and produced durable clinical responses.

Lowe et al.\textsuperscript{15}

The effects of IM administration of alefacept in 507 patients with chronic plaque psoriasis were analyzed in an international, randomized, double-blind trial.\textsuperscript{10} Patients were assigned to receive two courses of once-weekly IM administration of alefacept (10 or 15 mg) or placebo for 12 weeks. Patients were allowed to use low-potency topical steroid treatments, but concomitant phototherapy or systemic therapy was not permitted.

Although the proportion of responders to the 10-mg dose was higher than the number of patients taking placebo, a statistically significant difference was not achieved. The patients who had been randomly selected to take the 15-mg dose achieved a 21% reduction of 75% or more in PASI scores, compared with a 5% reduction observed in the placebo group two weeks after the first course of therapy (\(P < .001\)).\textsuperscript{10} The PGAs of “almost clear” or “clear” responses were exhibited by 14% of patients taking 15 mg of alefacept but by only 5% of patients taking placebo two weeks after completion of the first course (\(P = .006\)).\textsuperscript{10} The median duration of response was approximately two months for both the alefacept and the placebo groups.

Loew et al\textsuperscript{19}

In an extension of an IM alefacept study, Lowe and associates evaluated the efficacy of a second 12-week course in patients with chronic plaque psoriasis. Patients who received at least eight doses and completed the 12-week follow-up assessment in the previous IM alefacept study were eligible to participate. In this ongoing study, patients received an additional course of IM alefacept or placebo. So far, 367 patients have completed the study.

Of the patients who received two courses of alefacept (15-mg IM doses), 20% demonstrated at least a 75% reduction in PASI scores relative to baseline scores; 50% of patients had at least a 50% reduction in PASI scores, and 15% had “clear” or “almost clear” PGA scores two weeks after the last dose of the courses. The overall response rates for the first and the second cycles of therapy showed that a second course of alefacept enhanced the benefits of a single course of therapy.

Goedkoop et al\textsuperscript{20}

The clinical efficacy of alefacept and the assessment of immunological markers were investigated in patients with psoriatic arthritis in a prospective, single-center, open-label trial. Patients received 7.5 mg of IV alefacept weekly for 12 weeks and were monitored for an additional four weeks at the end of treatment. Overall, 11 patients with psoriatic arthritis entered the study.

Compared with baseline values, alefacept significantly reduced the number of tender and swollen joints at 4, 12, and 16 weeks’ follow-up (\(P \leq .05\)); decreased levels of C-reactive protein at 16 weeks’ follow-up (\(P < .05\)); and reduced pain, as measured by the Visual Analogue Scale (VAS) at 12 and at 16 weeks’ follow-up (\(P \leq .05\)). CD4 and CD8 T-cell counts in synovial tissues were significantly lower at the 16-week assessment (\(P < .05\)). The reduced CD4 and CD8 T-cell counts in the skin also correlated with a lessening of epidermal thickness (\(P < .05\)).

SAFETY PROFILE

Ellis and Krueger\textsuperscript{14}

In a dose-ranging study of IV alefacept therapy, treatment was generally well tolerated. The incidence of adverse effects was higher in the alefacept groups than in the placebo group in terms of:

- accidental injury unrelated to the study protocol (13% vs. 5%, respectively).
- dizziness (9% vs. 2%, respectively).
- nausea (6% vs. 0%, respectively).
- chills (5% vs. 0%).
- cough (5% vs. 0%).

Overall, infection or infection-associated events were reported in 108 of 229 patients (47%) studied. Infectious complications were reported by 31 of 59 patients (53%) and by 77 of 170 patients (45%) in the alefacept groups (\(P = .34\)). The most commonly reported infections were pharyngitis, influenza-like syndrome, nonspecific infection, bronchitis, and herpes simplex virus infection.

Following a 12-week treatment period, total lymphocyte counts were evaluated in 155 patients who received alefacept; of these patients, nine had counts below the normal range. In addition, 12 of 156 patients had CD4 T-cell counts that were below 300 cells/mm\(^3\). Subsequently, the counts returned to the normal range.

Delayed-type hypersensitivity skin testing revealed that the immune response to recall antigens was similar in the alefacept and placebo groups. One patient had a low titer of antibodies to alefacept but had no signs or symptoms of an allergic reaction.

Krueger et al\textsuperscript{18}

In the IV study, therapy with 7.5 mg of alefacept was well tolerated in both courses of the treatment. Adverse side effects following two courses of alefacept included accidental injury, such as sprains (18%); headache (12%); pharyngitis (13%); rhinitis (8%); pruritus (3%); flu syndrome (4%); and infections, such as common colds (10%). The most common adverse effect following the first cycle of therapy was chills, reported by 10% of the alefacept patients and by 1% of the placebo patients. Chills tended to occur soon after administration, and most cases were thus manifested within 24 hours of therapy.

During the first cycle of alefacept treatment, 10% of patients had to be switched to placebo because their CD4 T-lymphocyte counts were below 250 cells/mm\(^3\). No opportunistic infections were noted during the study. Further analysis of laboratory parameters revealed that a greater proportion of alefacept patients (17%) had elevated alanine aminotransferase levels than did the placebo group (8%). Anti-alefacept antibodies were detected in fewer than 1% of patients, and no immune reactions were observed.

Lowe et al\textsuperscript{19}

In the extension of an IM study, the most common adverse effects included injection-site reactions, headache, pruritus, infection (mostly colds), accidental injuries, pharyngitis, asthenia, flu syndrome, and rhinitis. The incidence of adverse events leading to discontinuation of therapy with alefacept was 2% in both courses.
Malignancies

In the clinical trials, 13 malignancies, most of them basal or squamous cell skin cancers, were diagnosed in 11 alefacept-treated patients. The overall incidence of malignancies was 1.3% in the patients receiving alefacept and 0.5% in the patients receiving placebo.10 Three cases of lymphoma were observed; one was classified as non-Hodgkin’s follicle center cell lymphoma, and two were classified as Hodgkin’s disease.10

CONCLUSION

Psoriasis is a chronic inflammatory skin condition characterized by exacerbations and remissions. Alefacept is a novel, biological, injectable fusion protein with activity directed toward T lymphocytes in psoriatic plaques. In clinical trials, alefacept patients have shown greater improvement in PASI and PGA scores, compared with baseline values and with the scores of patients taking placebo.

Although alefacept therapy appears to be well tolerated, all patients should be assessed for the possibility of lymphopenia, infections, and malignancy. The manufacturer recommends close monitoring of CD4 T-lymphocyte counts before initiation of therapy, and CD4 T-lymphocyte counts should also be monitored weekly for the duration of therapy. If the counts fall below 250 cells/mm³, alefacept therapy should be withheld.

Alefacept is a promising new medication for patients with chronic plaque psoriasis. After long-term and comparative studies of other immunomodulating therapies become available, these data should help health care professionals clarify the role of this medication in treatment.

REFERENCES