Clinical Update on Alefacept: Consideration for Use in Patients With Psoriasis

JAY N. GADE, MD, PhD

ABSTRACT

OBJECTIVE: Alefacept was the first of the biologic agents to be approved for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis, who are candidates for systemic therapy or phototherapy. This fully human fusion protein inhibits the activation of and reduces levels of memory (CD45RO+) T cells, a subpopulation of lymphocytes that plays a critical role in the pathogenesis of psoriasis. The purpose of this article is to provide a clinical update on the use of this agent in patients with psoriasis.

SUMMARY: A single course of alefacept, defined as 12 weekly injections followed by 12 treatment-free weeks, provides clinically meaningful improvements in the symptoms of psoriasis for a majority of patients. Patients who achieved a response have been shown to maintain the benefit for a median duration of about 7 months, without the need for systemic therapy or phototherapy. With each additional course of alefacept, the percentage of patients responding increases, confirming the incremental benefit of repeated administration. More than 1,300 patients have received alefacept in controlled clinical trials. Over multiple courses of therapy, alefacept-induced reductions in circulating lymphocyte counts were consistent and not cumulative.

The incidences of serious adverse events, discontinuations, malignancies, and antialefacept antibodies were low and did not increase with subsequent courses. No relationship was observed between decreases in lymphocyte counts and incidences of infections or malignancies. No cases of opportunistic infections, including tuberculosis, have been reported. The favorable safety profile of alefacept was maintained in patients who received concomitant or prior immunosuppressants. Alefacept did not cause reactivation of tuberculosis in case studies of patients who showed a purified protein derivative reaction prior to the initiation of therapy. Immune responses to a neoglycan and recall antigen remained intact in alefacept-treated patients, suggesting that vaccinations may be possible during therapy.

CONCLUSION: Alefacept is an effective intermittent therapy for psoriasis that can provide extended treatment-free and disease-free periods, which may lessen the need for treatment over time. The incremental efficacy seen with each subsequent course of alefacept suggests that physicians should administer 2 courses to determine efficacy before altering therapeutic interventions. The selective mechanism of action of alefacept affords multiple safety advantages and no apparent increased risk of infections or malignancies.

KEYWORDS: Alefacept, Psoriasis, Biologic therapy, Lymphocyte/T cell

J Manag Care Pharm. 2004;10(3)(suppl S-b):S33-S37

Psoriasis is a chronic, immune-mediated dermatologic disease in which memory T cells play a central role. Approximately 80% of individuals afflicted with this disease have chronic plaque psoriasis, which is characterized by the presence of well-defined, erythematous, scaling plaques. These lesions typically affect the elbows, knees, scalp, and intergluteal cleft, but can occur anywhere on the body. According to the National Psoriasis Foundation, an estimated 4.5 million adults in the United States have psoriasis and, of these, about one third (1.5 million) have moderate-to-severe psoriasis. The worldwide prevalence of psoriasis may be as high as 2.5%.

The significant negative impact of psoriasis on health-related quality of life is well recognized. In fact, the burden of psoriasis on both physical and mental functioning has been found to be comparable to that of other major medical diseases such as cancer, depression, diabetes, heart disease, and hypertension. The lesions of psoriasis are often itchy and painful, and individuals may suffer from a variety of psychological effects, including embarrassment, depression, difficulties at work, and, in social situations, fear of worsening disease, sexual problems, and sleep disturbances. The financial burden of psoriasis is also considerable, with estimates of up to $4.3 billion per year in the United States alone.

Patients with psoriasis seek safe, effective, and aggressive therapies and are searching for new therapeutic options. The conventional treatments for moderate-to-severe disease comprise systemic agents (e.g., cyclosporine, methotrexate, and acitretin) and phototherapy (i.e., ultraviolet B and psoralen plus ultraviolet A light). Although these treatments demonstrate varying degrees of efficacy, the vast majority do not provide long-lasting improvement of symptoms. In addition, serious adverse effects, including major organ system toxicities, may limit or contraindicate their use.

An increased understanding of the role of T cells in the pathogenesis of psoriasis has led to the development of biologic agents that more specifically interfere with various aspects of the immunologic cascade of psoriasis. Alefacept, the first of the biologics to be approved in the United States for the treatment of moderate-to-severe chronic plaque psoriasis, has now been available for more than 1 year. Alefacept selectively targets the T cells implicated in the pathogenesis of psoriasis (i.e., skin-homing memory T cells) by inhibiting their activation and reducing their numbers. The objective of this article is to provide a clinical update on the use of this fully human fusion protein in patients with psoriasis.

Efficacy of Alefacept

As summarized in the following sections, alefacept is a remittive therapy for chronic plaque psoriasis, which means that it provides sustained disease improvement in the absence of continuous treatment. Thus, alefacept is administered on an intermittent basis,
and, with each subsequent treatment course, incremental benefits in efficacy have been achieved. Importantly, patients who respond to a given course of alefacept are highly likely to respond to subsequent treatment courses.

### Efficacy Following 1 and 2 Courses of Alefacept

The clinical program of alefacept included 2 phase III, randomized, placebo-controlled, double-blind studies in which 1,060 patients with moderate-to-severe chronic plaque psoriasis were treated for up to 2 courses. Each course was defined as 12 weeks of once-weekly injections (intramuscular [IM] in 1 trial, intravenous [IV] in the other) followed by ≥12 weeks of observation.

The Psoriasis Area and Severity Index (PASI) is considered by regulatory authorities to be the standard for evaluating anti-psoriatic efficacy in clinical trials and thus was used in these trials. PASI is a composite measurement of body surface area affected, erythema, induration, and desquamation. The U.S. Food and Drug Administration has established PASI 75 (i.e., the percentage of patients who achieved a ≥75% reduction from baseline PASI) as the rigorous end point for clinical trials of drugs to treat psoriasis.

A PASI 50 is regarded by patients and physicians to be a clinically meaningful end point. Although the primary end point was initially set at 2 weeks after the last dose of alefacept, results of the phase II clinical trial showed that patients responded to alefacept at any time during the treatment and follow-up periods. In the 2 phase III trials, a key efficacy outcome was the overall response rate, defined as the percentage of patients who achieved a PASI 75 or PASI 50 at any time during the treatment and follow-up periods.

In course 1 of the trial with IM alefacept, PASI 75 and PASI 50 were achieved by 33% and 57%, respectively, of patients who received alefacept 15 mg (P<0.001 versus placebo). A postdosing effect with alefacept was clearly apparent. The mean reduction from baseline PASI reached a maximum of 46% in the alefacept 15-mg group at 6 weeks after the last dose of the first course. The clinical response to a single course of alefacept was durable. Patients who achieved a PASI 75 at any time after the first dose of alefacept 15 mg in course 1 maintained a PASI 50 response for a median of 209 days (−7 months), without the need for systemic therapy or phototherapy.

A second course of alefacept 15 mg resulted in incremental benefit, with 43% and 69% of patients achieving a PASI 75 and PASI 50, respectively. Among patients who did not achieve a PASI 50 in the first course, 35% did achieve this level of efficacy with a second course. The duration of response following a second course of alefacept was longer. The estimated median duration of response following the second course could not be determined because ≥50% of patients had maintained a PASI 50 response at the final study end point, which was nearly 1 year after the start of the study. Over the course of the study, no alefacept-treated patient experienced rebound or flare of disease activity after the cessation of treatment.

The other phase III study evaluated the clinical effects of up to 2 courses of alefacept 7.5 mg when administered by weekly IV injection. The efficacy results obtained with this regimen were comparable to those described for alefacept 15 mg IM.

### Multiple-Course Use

Given the chronic and relapsing nature of psoriasis, repeated courses of treatment are often necessary to maintain adequate control of the disease. New long-term data on the efficacy of a multiple course of alefacept were recently presented at the 62nd Annual Meeting of the American Academy of Dermatology in Washington, DC.

Patients who completed phase II studies of alefacept were eligible to participate in an ongoing, multicenter, open-label extension provided they had received ≥28 doses of study medication and had completed the final 12-week postdosing assessment in the previous trial, were in need of systemic therapy for psoriasis, and had CD4+ T-cell counts at or above the lower limit of normal. Patients were either naive to alefacept (i.e., received placebo in phase II) or had received up to 2 courses of alefacept in previous studies.

The initial treatment course in the open-label extension is referred to as course A; subsequent courses are labeled course B, C, and so on. In each course, patients received alefacept 7.5 mg IV once weekly for 12 weeks followed by 12 weeks of treatment-free follow-up. Retreatment courses were administered provided patients met the same criteria mentioned previously. For course C and subsequent courses, lymphocyte counts were required to be ≥75% of the count recorded at the screening visit of the open-label extension. In course A, PASI was evaluated at weeks 1, 3, 5, 7, 9, 11, and 12 during treatment and at 2, 4, 6, 8, and 12 weeks after treatment. For subsequent courses, PASI assessments were performed at weeks 1 and 7 during treatment and at 2 and 12 weeks after treatment.

At the time of the analysis, 175 patients had received ≥1 course of alefacept, 126 received ≥2 courses, 96 received ≥3 courses, and 71 received ≥4 courses. As shown in Figure 1, the percentages of patients who achieved a PASI 50 at 2 or 12 weeks after the last dose of alefacept increased with each subsequent course (range, 61% in course A to 79% in course D). For courses A through D, the incremental benefit and repeat response of additional courses of alefacept are shown in Figure 2. For patients who achieved a PASI 50 in course A and who received additional courses of alefacept, the percentages of patients who achieved a PASI 50 increased with each subsequent course (incremental benefit). In general, patients continued to respond to repeat treatment with alefacept, with no evidence of tachyphylaxis. Of those who achieved a PASI 50 in a given course, 75% to 90% of patients achieved a PASI 50 in subsequent alefacept courses (repeat response).

### Safety of Alefacept

In phase II and III clinical studies, alefacept has demonstrated excellent safety and tolerability. As described subsequently, this safety profile is maintained over multiple courses of therapy.
and is not altered by concomitant or prior use of immunosuppressants. Opportunistic infections, including tuberculosis, have not been observed among alefacept-treated patients. In case studies, alefacept did not cause reactivation of tuberculosis in patients who showed a purified protein derivative (PPD) reaction prior to treatment initiation. In addition, the results of an immune function study suggest that vaccinations may be possible while undergoing treatment with alefacept.

### Pooled Safety Analysis Over Multiple Courses

Data from all studies in the alefacept clinical program were pooled to better evaluate safety and tolerability. As shown in Table 1, the incidences of serious adverse events, discontinuations because of adverse events, malignancies, and antialefacept antibodies were low and did not increase over up to 4 courses of treatment. Accidental injury and cholelithiasis were the most frequent serious adverse events; headache, nausea, and herpes zoster were the most common events that led to withdrawal. Each of these events occurred in <1% of patients in any course. No relationship was observed between the incidence of infections and CD4+ or CD8+ T-cell counts (Table 2). Most infections were common colds. Serious infections were rare (0.7%, 0.6%, 0.7%, and 0% during the first through fourth courses, respectively). There were no cases of opportunistic or unusual infections, tuberculosis, or deaths related to infections. The incidence of malignancies also was not related to CD4+ and CD8+ T-cell counts. Skin carcinoma (basal and squamous cell carcinomas) was the most frequently diagnosed malignancy. The overall malignancy rate among patients who received alefacept was 25.6 per 1,000 person-years of exposure, which is less than that in the general psoriasis population (29.0 per 1,000 person-years).

### Effects on T Lymphocytes

In the phase III studies, alefacept reduced circulating CD4+ and CD8+ T-cell counts, the magnitude of which was similar after 1 or 2 courses. In the open-label extension described previously (see “Multiple-Course Use”), alefacept-induced reductions in CD4+ T-cell counts were consistent and not cumulative over up to 4 courses of therapy (Figure 3). Mean CD4+ T-cell counts remained above the lower limit of normal (404 cells/mm<sup>3</sup>) for all courses and did not decrease with multiple-course exposure to alefacept. Consistent with the phase III clinical trial protocols, the prescribing information for alefacept recommends weekly monitoring of CD4+ T-cell counts during treatment. Based on the safety of alefacept, the consistency of the T-cell response in the phase III studies, and the lack of adverse events reported that could be associated with a reduction in T cells, a biweekly monitoring schedule for T-cell counts was evaluated in subsequent open-label extension trials. Patients were eligible to receive up to 3 additional courses of alefacept (IM or IV), consistent with what they had received in the phase III studies. During the first open-label course (course A), lymphocyte and lymphocyte subset counts were obtained weekly during treatment and at 2, 6, and 12 weeks after treatment. In courses B and C, counts were obtained biweekly during treatment and at 2 and 12 weeks after treatment. Mean CD4+ T-cell counts remained above the lower limit of normal (approximately 400

---

**FIGURE 1** Percentages of Patients in Courses A Through D Achieving a ≥50% Reduction From Baseline Psoriasis Area and Severity Index (PASI 50) at 2 or 12 Weeks After Alefacept Treatment

**FIGURE 2** Percentages of Patients Achieving a ≥50% Reduction From Baseline Psoriasis Area and Severity Index (PASI 50) in Courses B Through D Relative to Course A (Incremental Benefit) and Prior Course (Repeat Response)
Clinical Update on Alefacept: Consideration for Use in Patients With Psoriasis

**TABLE 1** Pooled Analysis of Safety and Tolerability Over Multiple Courses of Alefacept Therapy

<table>
<thead>
<tr>
<th>T-Cell Counts</th>
<th>Course A (n = 1,395)</th>
<th>Course B (n = 826)</th>
<th>Course C (n = 415)</th>
<th>Course D (n = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=250 cells/mm³</td>
<td>4.9% (n = 1,223)</td>
<td>4.1% (n = 420)</td>
<td>3.1% (n = 208)</td>
<td>0.8% (n = 11)</td>
</tr>
<tr>
<td>Discontinuations for adverse events</td>
<td>1.8% (n = 61)</td>
<td>0.8% (n = 32)</td>
<td>0.9% (n = 37)</td>
<td>0.8% (n = 1)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1.2% (n = 16)</td>
<td>1.1% (n = 21)</td>
<td>1.2% (n = 20)</td>
<td>0.8% (n = 1)</td>
</tr>
<tr>
<td>Antialefacept antibodies*</td>
<td>2.4% (n = 2,168)</td>
<td>1.5% (n = 2,168)</td>
<td>1.3% (n = 2,168)</td>
<td>0% (n = 2,168)</td>
</tr>
</tbody>
</table>
| * All patients with available data were included in the analysis.

Values presented represent percentages of patients.

**TABLE 2** Pooled Analysis of Infections by T-Cell Counts Over Multiple Courses of Alefacept Therapy

<table>
<thead>
<tr>
<th>T-Cell Counts</th>
<th>Course A</th>
<th>Course B</th>
<th>Course C</th>
<th>Course D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4⁺</td>
<td>26% (n = 121)</td>
<td>38% (n = 85)</td>
<td>39% (n = 28)</td>
<td>63% (n = 8)</td>
</tr>
<tr>
<td>CD8⁺</td>
<td>33% (n = 178)</td>
<td>31% (n = 155)</td>
<td>36% (n = 78)</td>
<td>40% (n = 35)</td>
</tr>
</tbody>
</table>

**FIGURE 3** Mean CD4⁺ T-Cell Counts by Course of Alefacept

Use of Alefacept in Special Populations

Concomitant and Prior Use of Immunosuppressants

The incidence and nature of adverse events reported in the phase III studies were examined in patients who received alefacept and any of the following immunosuppressants: methotrexate, cyclosporine, prednisone, etanercept, leflunomide, infliximab, and mycophenolate mofetil. Use of these therapies during the study resulted in disqualification from the efficacy analysis. One or more of these drugs were used concomitantly by 21 (6%) patients in the alefacept 7.5 mg IV group, 4 (2%) in the alefacept 15 mg IM group, and 22 (6%) in the placebo group. The frequency and spectrum of adverse events, including infections, were not altered by concomitant use of immunosuppressants in patients treated with alefacept. Similar results were found for patients who had used an immunosuppressant within 60 days before alefacept.

Positive Tuberculin Reaction

The latest guidelines for targeted tuberculin testing for latent tuberculosis infection have been published. Tuberculin testing is not a prerequisite for alefacept therapy. However, some investigators chose to test for tuberculosis before initiating any of the biologic therapies. Menter et al. reported that none of the 4 patients who showed a PPD reaction before beginning alefacept therapy experienced a reactivation of tuberculosis after receiving a 12-week course of alefacept 15 mg IM.

Immunizations

Gottlieb et al. evaluated the effect of alefacept on immune responses to a neoantigen (X174) and recall antigen (tetanus toxoid) in patients with psoriasis randomized to alefacept (7.5 mg IV weekly x 12) or control groups. Mean anti-X174 titers were similar in both groups at all time points after the first and second immunizations (P = NS) and comparable to those reported for healthy volunteers. Two weeks after the second immunization, the percentage of patients with anti-X174 immunoglobulin G (IgG) of ≥30% of the total anti-X174 response was similar in the alefacept (86%) and control (82%) groups (P = NS). IgG titers after the third and fourth exposures in the alefacept group showed durability of memory responses. Response to tetanus also was similar between the 2 groups, with 89% of alefacept recipients and 91% of controls having antitetanus toxoid titer increases ≥2 times baseline at 3 weeks after immunization. These data demonstrate that alefacept-treated patients maintain their ability to mount an immune response to new or previously encountered antigens.

Pregnancy

Alefacept has a pregnancy category B rating. The results of preclinical studies have not demonstrated a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women.
During pregnancy, alefacept should be used only if clearly needed. If pregnancy occurs while receiving alefacept, its continued use should be assessed.

Conclusions

Alefacept offers patients with psoriasis an effective intermittent therapy that can provide extended treatment-free and disease-free periods. Given the incremental benefits of alefacept, additional courses of alefacept therapy increase the likelihood for patients to achieve a clinically meaningful response. Thus, it seems reasonable to attempt 2 courses of therapy before concluding that treatment is ineffective. Because of prolonged remissions, the potential exists that a lesser amount of drug will be needed over time and that the use of alefacept may reduce overall drug and health care utilization.

The once-weekly dosing schedule of alefacept is convenient, and because it is administered in a doctor’s office, physicians can easily monitor compliance. The selective mechanism of action of alefacept affords multiple safety advantages in terms of no apparent increased risk of infections or malignancies, the potential to use it concomitantly with other drugs and vaccines, and safe use in special patient populations. The excellent safety profile of alefacept may reduce the overall use of health care services to manage untoward effects in patients who have chronic plaque psoriasis.

DISCLOSURES

Funding for this paper was provided by Biogen Idec Inc. Author Jay N. Gade is a consultant to Biogen.

REFERENCES