Treatment of Psoriasis With Alefacept

Correlation of Clinical Improvement With Reductions of Memory T-Cell Counts

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Objective: To examine the relationship between the pharmacodynamic and antipsoriatic effects of alefacept, a biological agent that targets CD4+ and CD8+ memory T cells.

Design: Randomized, double-blind, placebo-controlled study of 3 parallel groups.

Setting: Fifty-one study centers.

Patients: Five hundred fifty-three patients with chronic plaque psoriasis.

Interventions: Patients were randomized (1:1:1) to 1 of the following 3 cohorts: alefacept, 7.5 mg, in both courses (cohort 1); alefacept, 7.5 mg, in the first course and placebo in the second course (cohort 2); or placebo in the first course and alefacept, 7.5 mg, in the second course (cohort 3). In each course, alefacept or placebo was administered by intravenous bolus once weekly for 12 weeks, followed by 12 weeks of observation.

Main Outcome Measures: Circulating lymphocyte levels and the Psoriasis Area Severity Index.

Results: One or 2 courses of alefacept reduced CD4+ and CD8+ memory T-cell counts, while sparing the naive population. At 12 weeks after the last dose of alefacept in courses 1 and 2, 88% and 83% of patients, respectively, had CD4+ cell counts greater than the lower limit of normal. In course 1, alefacept-treated patients with the largest decreases in memory T-cell counts experienced the greatest reductions in disease activity (P<.001). The duration of clinical benefit seemed to be longer among patients who had the greatest reduction in CD4+ and CD8+ memory T-cell counts.

Conclusions: One or 2 courses of intravenous alefacept reduced circulating memory T-cell counts while sparing the naive T-cell population. The reductions in memory T-cell counts were related to all measures of disease activity evaluated and the duration of response to therapy, suggesting that prolonged remissions of psoriasis can be attained with reduction of the pathogenic T-cell count.

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Scientific and clinical evidence now points to the pivotal role of the T cell in the pathogenesis of psoriasis. Experiments using the severe combined immunodeficiency disorder (SCID) mouse model strongly suggested a central role for T cells. Elimination of T cells using the selective lymphocyte toxin, DAB389IL-2, improved disease severity and reversed the epidermal alterations that define this chronic disease. The lesional skin of patients with psoriasis contains an abundance of CD4+ and CD8+ T cells that belong to the memory subset (CD4+CD45RO+ and CD8+CD45RO+) and express an activated phenotype (CD25+ and CD69+), therefore rendering these cells as attractive targets for therapeutic intervention. In the blood, a correlation has been found between the numbers of circulating CD4+ and CD8+ activated T cells and the severity of psoriasis. The CD4+ and CD8+ T cells are capable of producing type I inflammatory cytokines (eg, interferon-γ, interleukin 2) that are purported to be important for keratinocyte hyperproliferation and disease. Recent clinical research in psoriasis has therefore focused on biologic therapies that interfere with 1 or more of the key steps necessary for perpetuating T-cell immune responses. More selective targeting of the immune system may improve tolerability compared with currently available treatment options.

Alefacept (Amevive; Biogen Inc, Cambridge, Mass) is a fully human fusion protein consisting of the first extracellular domain of leukocyte function–associated antigen 3 fused to the hinge, Cα2, and Cα3 domains of IgG1. The interaction be-
between leukocyte function–associated antigen 3 on antigen-presenting cells and CD2 on T cells represents a key co-stimulatory pathway for T-cell activation. The leukocyte function–associated antigen 3 domain of alefacept blocks this interaction by binding CD2 on T cells, whereas engagement of FcγRIIa receptors on accessory cells by the IgG1 domain of alefacept induces T-cell apoptosis in vitro. Furthermore, it has been shown that T cells belonging to the memory subset, which express the highest levels of CD2 cells on their surface, are preferentially targeted by alefacept. In a phase 2 study, treatment of patients with psoriasis with a once-weekly regimen of intravenous alefacept for 12 weeks had no significant effect on naive (CD45RA+CD2+) T cells, but significantly decreased the level of circulating memory T cells. Patients with clear or almost clear results after treatment cessation did not require retreatment with antipsoriatic therapy for a median of 10 months. It has been theorized that reductions in levels of circulating memory T cells would correlate with clinical efficacy and the prolonged responses seen with alefacept. The present study examined the relationship between the pharmacodynamic and antipsoriatic effects of intravenous alefacept in a large phase 3 trial involving patients with chronic plaque psoriasis.

Methods

Institutional review boards approved the study protocol. Standard written consent was obtained from all patients, and the study was conducted in accordance with the ethics principles outlined in the Declaration of Helsinki.

Patients

Patients eligible for enrollment were 16 years or older with moderate to severe stable plaque psoriasis for at least 12 months that involved at least 10% of body surface area and normal CD4+ lymphocyte counts. Patients with erythrodermic, guttate, or generalized pustular forms of psoriasis, serious local or systemic infection within the previous 3 months, or a history of malignancy other than basal cell carcinoma or fewer than 3 squamous cell carcinomas were excluded. Patients who were receiving systemic corticosteroids, vitamin D analogues, keratolytics, and coal tar were prohibited within 4 weeks before study drug administration and throughout the study: phototherapy, systemic retinoids, systemic steroids, systemic fumarates, methotrexate, cyclosporine, azathioprine, thioguanine, or high-potency topical corticosteroids. Use of moderate-potency topical corticosteroids, vitamin D analogues, keratolytics, and coal tar was prohibited within 2 weeks before study drug administration and throughout the study, except on the scalp, palms, groin, anal fold, and soles. Sparing use of low-potency topical corticosteroids and emollients was permitted, except within 12 hours of efficacy assessments.

Study Design

This was a multicenter (51 sites in the United States and Canada), double-blind, parallel-group study consisting of 2 treatment courses. Patients were randomized (1:1:1) to 1 of the following 3 cohorts: alefacept, 7.5 mg, in both courses (cohort 1), alefacept, 7.5 mg, in the first course and placebo in the second course (cohort 2), or placebo in the first course and alefacept, 7.5 mg, in the second course (cohort 3). Patients were randomized to treatment based on initial Psoriasis Area Severity Index (PASI) (≤20 or >20) and previous treatment history (received or did not receive systemic therapy/phototherapy). The study drug inven-
efficacy of alefacept in course 1. Assuming that 50% of patients would have a PGA of clear, withdraw from treatment, or fail to achieve CD4+ T-cell counts above 250 cells/µL between the 2 dosing periods, an additional 185 patients were required to determine the efficacy of alefacept in course 2, for a total accrual of 559 patients.

STATISTICAL METHODS

A Cochran-Armitage trend test evaluated the relationship between the magnitude of reduction in memory T-cell levels and the prospectively defined end point of the percentage of patients who achieved at least a 75% reduction in PASI at any time during treatment or follow-up. This analysis was performed for alefacept-treated patients in course 1 (cohorts 1 and 2 combined). A log-rank test was used to compare Q4 with Q1 through Q3 (pooled) with respect to the prospectively defined end point of median duration of at least a 50% reduction in PASI among cohort 2 patients who achieved at least a 75% reduction in PASI at any time during treatment or follow-up in course 1. This analysis was performed for cohort 2 because these patients were followed for up to 36 months after the last alefacept dose (ie, 12 months of follow-up, 12 months of placebo, and another 12 months of follow-up).

RESULTS

BASELINE CHARACTERISTICS

Study enrollment began on November 21, 1999; the last date of follow-up was March 22, 2001. A total of 553 patients were randomized and received at least 1 injection (cohort 1, n = 183; cohort 2, n = 184; cohort 3, n = 186). In course 1, 490 patients (89%) completed the 12-week treatment period, and 482 (87%) completed the 12-week follow-up period. A total of 449 patients (cohort 1, n = 154; cohort 2, n = 142; cohort 3, n = 153) received treatment in both courses. All of the 449 patients who received treatment in both courses underwent 1 or more assessments of levels of total lymphocytes or lymphocyte subsets after dosing and were included in the analysis of pharmacodynamic effects in course 1. All of the 449 patients who received treatment in both courses underwent 1 or more assessments of levels of total lymphocytes or lymphocyte subsets after dosing and were included in the analysis of pharmacodynamic effects in both courses.

PHARMACODYNAMICS

Course 1

Consistent with its mechanism of action, alefacept reduced circulating total lymphocyte counts and CD4+ and CD8+ lymphocyte subset counts (Table 2). Reductions were selective for memory T cells with relative sparing of naive T cells (Figure 2 and Table 2). The median time of most marked reduction of CD4+CD45RO+ and CD8+CD45RO+ T-cell levels during the dosing period was 71 days for cohorts 1 and 2 (alefacept), and 36 and 43 days, respectively, for cohort 3 (placebo). Thus, reductions in lymphocyte counts were evident in both active treatment groups, as expected based on the mechanism of action of alefacept. In the placebo group, 6% and 1% of patients had at least 1 CD4+ T-cell count below 400

Table 1. Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohorts†</th>
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<tr>
<td></td>
<td>1 (n = 183)</td>
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<tr>
<td>Male</td>
<td>72</td>
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<td>Psoralen–UV-A</td>
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<td>Retinoids</td>
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*Unless otherwise indicated, data are expressed as percentage of patients. †Described in the “Study Design” subsection of the “Methods” section.
and 300 cells/µL, respectively, demonstrating the normal variation in T-cell counts in patients with psoriasis.

In contrast to memory T-cell subsets, changes in naïve T-cell counts were negligible. The mean percentage of changes in CD4+CD45RA+ T-cell counts from baseline to 12 weeks after the last dose in course 1 for cohorts 1 and 2 were 3% and 0%, respectively. Similar results were observed for CD8+CD45RA+ T-cell counts.

Alefacept had no notable effect on CD19+ B cells or CD16+/CD56+ natural killer cells.

In cohort 1, 98% of patients had total lymphocyte counts, 87% had CD4+ T-cell counts, and 70% had CD8+ T-cell counts above the lower limit of normal at 12 weeks after the last alefacept dose in course 1. Corresponding results for cohort 2 patients were similar: 98% for total lymphocyte counts, 89% for CD4+ T-cell counts, and 64% for CD8+ T-cell counts. At the end of the 12-week follow-up interval of course 1, mean total lymphocyte counts relative to baseline were −12% for cohort 1, −17% for cohort 2, and 5% for cohort 3. Corresponding percentages were −23%, −29%, and 3%, respectively, for CD4+ T-cell counts and −24%, −35%, and 2%, respectively, for CD8+ T-cell counts.

During course 1, placebo was substituted for alefacept treatment at least once in 10% of patients in cohort 1 and 11% of patients in cohort 2. There were 7 (1.9%) permanent placebo substitutions in course 1 (2 patients in cohort 1 and 5 patients in cohort 2). One placebo-treated patient in cohort 3 (0.5%) had a CD4+ T-cell count below 300 cells/µL.

### Course 2

We found no evidence of a cumulative effect of alefacept on total lymphocyte count or CD4+, CD8+, and CD45RO+ lymphocyte subset counts. Similar maximum reductions of blood lymphocyte counts were reached during courses 1 and 2 (Table 2 and Figure 2). The nadirs (mean count at the time of the most marked reduction during the dosing period) for cohort 1 were not significantly lower for course 2 vs course 1 with respect to total lymphocyte (1303 vs 1284 cells/µL) or CD4+ (467 vs 479 cells/µL), CD8+ (234 vs 250 cells/µL), CD4+CD45RO+ (212 vs 232 cells/µL), or CD8+CD45RO+ cell counts (52 vs 63 cells/µL). Thus, a nadir was reached during course 1 and did not change during course 2. As observed during the first alefacept course, changes in CD19+ B and CD16+/CD56+ natural killer cell counts were negligible during the second alefacept course.

Rates of recovery in course 2 were similar to those in course 1. In cohort 1, 97% of patients had total lymphocyte counts, 83% had CD4+ T-cell counts, and 63% had CD8+ T-cell counts above the lower limit of normal at 12 weeks after the last dose in the second alefacept course. In the same cohort, the mean total lymphocyte count relative to the course 1 baseline was −13% at the

<table>
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<tr>
<th>Lymphocytes, Cells/µL</th>
<th>Cohort 1 (n = 154)</th>
<th>Course 1</th>
<th>Cohort 2 (n = 154)</th>
<th>Course 2</th>
<th>Cohort 3 (n = 153)</th>
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<tr>
<td>Total</td>
<td>38 ± 17</td>
<td>37 ± 16</td>
<td>41 ± 14</td>
<td>33 ± 15</td>
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<td>54 ± 22</td>
<td>56 ± 16</td>
<td>47 ± 17</td>
<td>22 ± 19</td>
<td>51 ± 19</td>
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<tr>
<td>CD4+CD45RO+</td>
<td>57 ± 17</td>
<td>61 ± 18</td>
<td>60 ± 18</td>
<td>51 ± 17</td>
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<tr>
<td>CD8+CD45RO+</td>
<td>70 ± 17</td>
<td>75 ± 17</td>
<td>73 ± 17</td>
<td>61 ± 18</td>
<td>23 ± 22</td>
<td>69 ± 20</td>
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*Values are expressed as mean ± SD. Cohorts are described in the “Study Design” subsection of the “Methods” section.

Table 2. Mean Maximum Percentage Reductions During the Dosing Period*
end of the 12-week follow-up interval of course 2. Corresponding percentages were −23% for CD4+ and −31% for CD8+ T-cell counts.

In course 2, placebo was substituted for alefacept treatment at least once in 9% of patients in cohort 1 and 5% of patients in cohort 3. There was 1 permanent placebo substitution (0.3%) in course 2 (cohort 3). No patient who received 2 courses of alefacept required permanent placebo substitution during the second course.

RELATIONSHIP BETWEEN PHARMACODYNAMICS AND EFFICACY

In courses 1 and 2, the relationship between the magnitude of change in CD4+CD45RO+ T-cell counts and probability of response was consistent, regardless of the definition of response (Figure 3). Patients with the most profound and sustained reductions in this T-cell subset showed the greatest reduction in disease activity. For example, in course 1, the percentages of alefacept-treated patients in the lowest quartile (Q1, 0–2209, cumulative reduction in T cells [CRT]) who achieved at least a 75% reduction from baseline PASI at any time during treatment or follow-up were 13% (6/46) (cohort 1) and 20% (9/46) (cohort 2). These percentages increased to 41% (18/44) and 47% (22/47), respectively, in the highest quartile (Q4, 4723–7660 CRT). In course 1, among alefacept-treated patients (cohorts 1 and 2 combined), there was a significant trend for increasing response rates (≥75% reduction in Psoriasis Area Severity Index [PASI]) with increasing CD4+CD45RO+ EAUC quartile (Cochran-Armitage trend test, P < .001). Analysis of changes in CD8+CD45RO+ T-cell counts and response rates showed a similar trend (P < .001). A similar association was observed between quartiles of memory T-cell effects and the percentages of alefacept-treated patients (cohorts 1 and 2 combined) who achieved at least a 50% reduction from baseline PASI at any time during treatment or follow-up: 33% in Q1 (30/92), 51% in Q2 (47+92), 62% in Q3 (57/92), and 75% in Q4 (68/91) for CD4+CD45RO+ T cells and 36% in Q1 (33/92), 51% in Q2 (47+92), 59% in Q3 (55/93), and 77% in Q4 (69/90) for CD8+CD45RO+ T cells.

In course 2, despite receiving placebo, cohort 2 patients continued to benefit from the first course of alefacept, which is indicative of the remittive effects of the study drug (Figure 3). For example, in the highest CD4+CD45RO+ EAUC quartile (Q4, 4723–7660 CRT), 47% (22/47) of cohort 2 patients achieved at least a 75% reduction from baseline PASI at any time after the first alefacept dose in course 1, whereas 36% (10/28) of cohort 2 patients met this criterion at any time after the initiation of placebo treatment in course 2. Cohort 1 patients had additional clinical improvement during the second alefacept course relative to the first alefacept course, particularly among patients in the highest CD4+CD45RO+ EAUC quartile (Figure 3).
The mechanism of action of alefacept would be expected to result in prolonged remissions of psoriasis symptoms after treatment cessation. Kaplan-Meier analysis demonstrated that the duration of response to alefacept was indicative of a remittive therapy and suggested a relationship between the duration of therapeutic effect and the magnitude of the reduction in CD4+ and CD8+ memory T-cell counts. Figure 5 shows the median duration of at least a 50% reduction in PASI by CD4+CD45RO+ (Figure 5A) and CD8+CD45RO+ (Figure 5B) E_{AUC} quartiles in cohort 2 patients who achieved at least a 75% reduction from baseline PASI at any time during treatment or follow-up in course 1. In this subset of 52 patients, those who experienced the greatest reductions in memory T-cell count (ie, Q4) had a longer median duration of response to alefacept (271.1 days for CD4+ memory T cells; 240.6 days for CD8+ memory T cells) relative to patients who experienced a smaller reduction in memory T-cell count (173.2, 194.5, and 193.9 days for Q1, Q2, and Q3, respectively, for CD4+ memory T cells; 173.2, 228.0, and 221.4 days, for Q1, Q2, and Q3, respectively, for CD8+ memory T cells). Due to the limited sample size in this analysis, a statistically significant result was not achieved.

One or 2 courses of alefacept induced a decrease in circulating absolute counts of the CD4+ and CD8+ memory T-cell subsets from baseline while sparing the naive population. These results are consistent with the preferential binding of alefacept to memory T cells, which have a higher level of expression of CD2 compared with that observed in the naive compartment. A cumulative effect on lymphocyte subsets was not observed in this trial or in an earlier multiple-course study in patients with psoriasis. In this study, similar maximum reductions in memory T-cell counts and comparable rates of recovery were observed during both alefacept courses for cohort 1 patients. There was also a consistent lack of effect on naive T cells during 2 courses of alefacept therapy.

Previous studies have demonstrated that most lymphocytes in psoriatic lesions are memory T cells and...
that these T cells are distinct from naive T cells in that they have been previously activated by an antigen or primed. If memory T cells are the effector cells that drive psoriatic activity, then a relationship would be expected between the extent of reduction in this population and clinical outcome of alefacept therapy. The results of this trial strongly support a critical role for memory T cells in the pathogenesis of psoriasis. First, reductions in the memory T-cell subset counts were related to improvements in clinical symptoms, as measured by the PASI. Most patients who experienced the greatest reductions in memory T-cell counts (≥75%) achieved a clinically meaningful response (≥50% PASI reduction) to therapy. These results suggest that alefacept-induced T-cell changes in the blood are a surrogate for changes in the skin. Second, most of the alefacept-induced reductions in T-cell count preceded the peak improvement in PASI, which was not unexpected considering that alefacept interferes with memory T-cell levels and activity, but not further downstream in the T-cell–mediated inflammatory pathway (eg, inhibition of cytokines).

The remittive effects of alefacept also are consistent with a key role of memory T cells in psoriasis pathogenesis. Once memory T-cell levels are reduced by alefacept, it likely takes a prolonged period of time to build them up again to provoke symptom reappearance. Although it was previously speculated that the mechanism of action of alefacept would result in lasting remissions, no definitive data have been available until now. However, several observations of the present study results confirm the prolonged benefit of alefacept on the symptoms of psoriasis. For example, cohort 2 patients who were followed up for approximately 36 months after a single 12-week dosing period continued to benefit from the initial alefacept course during the second placebo course. Moreover, the clinical response to alefacept peaked and was sustained during the observation period well after the last dose of study drug. In cohort 2, the median duration during both courses of at least a 50% reduction from baseline PASI was 7 to 8 months in responders, defined as patients who achieved at least a 75% reduction from baseline PASI or a PGA of clear or almost clear at any time during the study. The present analysis suggested that the duration of clinical benefit was longer among patients who had the greatest reduction in memory T-cell levels. Although this will need further investigation, it is an expected result if memory T cells drive the psoriatic process.

The results of the present trial parallel those of previous studies investigating the effect of alefacept on T-cell subsets in the skin of patients with psoriasis. A administration of intravenous alefacept, 7.5 mg once weekly for 12 weeks, reduced activated T-cell subset counts (CD3+CD69+ and CD3+CD25+) in lesional skin, and these changes correlated significantly with PASI improvement (r=0.93 and r=0.79, respectively). Moreover, a decrease in the number of interferon-γ–producing T cells in lesional skin correlated with PASI improvement (r=0.80). Interferon-γ T-cell production was similarly inhibited in the blood (serum) of patients treated with alefacept. Further study of the relationship between T-cell changes in blood and skin and clinical outcome is under investigation.

In the present study, T-cells began to return toward baseline levels during the treatment-free follow period after alefacept administration, although recovery was not complete for all patients. Despite the alefacept-induced reductions in T-cell counts, no related safety concerns were identified during this 2-course study. As described elsewhere, no opportunistic infections were reported, and there was no association between infections and CD4+ T-cell counts. In a separate study, a single course of alefacept therapy did not produce detectable alterations in antibody responses to an experimental neoantigen or recall antigen challenge. Further longer-term, multiple-course studies are needed to provide a more complete assessment of the safety of alefacept as it relates to reduction of T-cell counts.

This phase 3 trial indicates that the reduction in levels of circulating memory T-cell subsets with alefacept treatment correlates to improvement in psoriasis and suggests a relationship between the length of response to alefacept and alterations in the memory T-cell population. These data strongly support the central role of memory T cells in psoriasis and the potential efficacy advantages...
of targeting the effector cells in this disease. Although this study does not evaluate individual clinical responses in relation to the pharmacodynamic effects of alefacept, it clearly suggests that further study of the T-cell effects of alefacept with particular emphasis on treatment protocols is warranted.

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