Alefacept for Severe Alopecia Areata

A Randomized, Double-blind, Placebo-Controlled Study

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Objective: To assess the efficacy of alefacept for the treatment of severe alopecia areata (AA).

Design: Multicenter, double-blind, randomized, placebo-controlled clinical trial.

Setting: Academic departments of dermatology in the United States.

Participants: Forty-five individuals with chronic and severe AA affecting 50% to 95% of the scalp hair and resistant to previous therapies.


Main Outcome Measure: Improved Severity of Alopecia Tool (SALT) score over 24 weeks.

Results: Participants receiving alefacept for 12 consecutive weeks demonstrated no statistically significant improvement in AA when compared with a well-matched placebo-receiving group ($P = .70$).

Conclusion: Alefacept is ineffective for the treatment of severe AA.

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Alopecia areata (AA) is a chronic, potentially reversible autoimmune skin disease characterized by non-scarring patchy hair loss involving any hair-bearing surface. Alopecia areata often causes considerable emotional distress and has limited treatment options. The presentation and course of AA differ from patient to patient and are unpredictable. Most often involving the scalp, AA typically presents as well-demarcated patches of hair loss that may be either isolated or numerous. Patients may develop total loss of scalp hair (alopecia totalis) or loss of all body hair (alopecia universalis). Alopecia areata has an incidence rate of 0.1% to 0.2%, with a lifetime risk of roughly 1.7%. Most often it is those with AA of the scalp who present for evaluation.

T lymphocytes seem to play a central role in AA through a targeted immunologic attack on the hair follicle leading to anagen arrest. Histologically, lesions of active AA reveal dense peribulbar lymphocytic infiltration, consisting of activated T lymphocytes and antigen-presenting Langerhans cells. When lesions of AA are transplanted into mice with severe combined immunodeficiency that lack T lymphocytes, hair growth may resurface, further confirming the potential pathogenic role of T lymphocytes.

Treatment options for more severe presentations of AA are limited, and neither a cure nor preventive treatment is available. Most of the effective therapies for AA are either immunosuppressive or immunomodulatory. Of the therapeutic options, corticosteroids (topical and intraleisional) remain the most popular, although other therapies, including anthralin, minoxidil, systemic corticosteroids, topical immunotherapy, psoralen–UV-A (PUVA), and cyclosporine are also commonly used with varying success. Interestingly, the biologic agents etanercept and efalizumab—both effective in treating psoriasis, a T-cell–mediated disease—demonstrate no efficacy in treating AA.

Despite these failures, other biologic agents with different mechanisms of action may be effective. Alefacept (Amevive; Astellas Pharma US Inc, Deerfield, Illinois) is a bioengineered lymphocyte function–associated antigen-3/immuno-
globulin fusion protein that interrupts T-lymphocyte activation by binding to CD2 on T lymphocytes and consequently interrupting the costimulation between antigen-presenting cells and T lymphocytes. Perhaps more important, alefacept specifically induces the apoptosis of both CD4+ and CD8+ memory effector T lymphocytes, cells that comprise the peribulbar lymphocytic infiltrate and have been implicated in the pathogenesis of AA. Case reports have shown that alefacept may be effective in the treatment of AA. Herein, we report the results of a double-blind, randomized, placebo-controlled study of alefacept in patients with severe AA.

**METHODS**

The primary objective of this study was to assess the safety and therapeutic efficacy of a weekly regimen of intramuscular (IM) alefacept compared with placebo over a course of 12 weeks in patients with chronic, severe scalp AA. This was a double-blind, randomized, placebo-controlled, multicenter, investigator-initiated study in a voluntary population of patients with chronic, severe scalp AA. There were 5 participating study sites. The study was approved by the institutional review boards at each of the study sites and was conducted in accordance with Good Clinical Practice guidelines, the US Food and Drug Administration (FDA) guidelines for clinical trials, and the principles set forth by the Declaration of Helsinki. All participants provided written informed consent prior to the initiation of any study procedures.

Eligible individuals were randomized to receive either weekly IM administration of placebo or alefacept, 15 mg, for 12 weeks, followed by a 12-week, posttreatment observation period. Safety and efficacy were assessed throughout the 24-week study period. Randomization lists detailing the person's identification (ID) number and medication allocation were provided by a coordinating monitor. An unblinded study coordinator or pharmacist maintained the randomization lists responsible for participant ID number assignment and drug shipment and coordination. An unblinded study coordinator or pharmacist was responsible for tracking patient enrollment throughout the study and for data entry. The study coordinator or pharmacist assigned the participant an ID number and dispensed study medication as listed in the randomization list. Participants were monitored for safety and efficacy throughout the entire study by a blinded investigator. Efforts were made to ensure that the same investigator monitored any specific participant for the entire study period.

**PATIENT ELIGIBILITY**

Eligible individuals were 18 to 65 years of age, with a diagnosis of chronic, severe, scalp AA defined as at least a 50% to 95% patchy scalp hair loss of at least 6 months' duration. Patients with alopecia totalis, alopecia universalis, or coexisting significant androgenetic alopecia (Norwood-Hamilton stage IV or greater in males, Ludwig stage III in females) were excluded. Individuals with CD4+ T-lymphocyte counts below the lower limit of the reference range at screening (as determined by the local laboratory) were not included, nor were those with either abnormal hepatic function or hematologic test results. In addition, individuals were not enrolled if they had a known history of unstable cardiovascular or pulmonary disease, or poorly controlled diabetes mellitus; were seropositive for human immunodeficiency, hepatitis C, or hepatitis B viruses; had a history of recurrent bacterial, fungal, atypical mycobacterial, viral or opportunistic infections; a history of lymphoproliferative or malignant disease (other than treated basal cell carcinoma or ≤3 squamous cell carcinomas); a history of active tuberculosis (TB) or were currently undergoing treatment for active TB; or were pregnant or breastfeeding. Individuals with a history of treatment with alefacept or treatment with another investigational medication also were not allowed to participate in the study. Systemic therapies (eg, corticosteroids, fumaric acid derivatives, cyclosporine A, methotrexate, biologic medications, retinoids, azathioprine) and phototherapy (UV-B, PUVA) were discontinued for 1 month prior and during the entire study treatment period. Topical therapies (corticosteroids, contact sensitizing agents, tacrolimus, or pimecrolimus) were discontinued for 2 weeks prior to and during the entire study treatment period. The use of prescription medications for conditions unrelated to AA was permitted.

Serum samples, measuring hepatic, renal and hematologic function, and CD4+ T-lymphocyte count, were drawn throughout the study, and participants were assessed for signs and symptoms of infection. Study medication was withheld if the CD4+ T-lymphocyte count fell below 250 cells/mm³.

The severity of AA and clinical response were measured with the Severity of Alopecia Tool (SALT) as detailed in the Aloppecia Areata Investigational Guidelines. The SALT score is computed by measuring the percentage of hair loss in each of 4 areas of the scalp—vertex (40%), right profile (18%), left profile (18%), and posterior (24%)—and adding the total to achieve a composite score. Hair regrowth is reflected by a decrease in the SALT score (eg, complete hair regrowth would confer a SALT score of 0). The primary efficacy end point was the percentage of participants with at least a 50% improvement from the baseline in their SALT score at week 24. Treatment response was also measured at week 12. The SALT score was measured visually by the study physician and corroborated by photographic analysis. The participant's perception of the extent of scalp disease on completion of the treatment phase and at the end of the post-treatment, observational phase was also assessed.

**STATISTICAL ANALYSIS**

Efficacy and safety analyses were based on the modified intent-to-treat population, which included all randomized patients who received at least 1 dose of the study medication. For the population and safety analyses, patients were separated based on the treatment groups to which they were randomized. The proportion of patients who achieved a 50% or greater reduction in their SALT scores in the alefacept and placebo groups was analyzed using the χ² test. Participants' assessment of disease was analyzed by the Wilcoxon rank-sum test. All statistical tests were 2-sided, and all tests for efficacy were performed at the α = 0.05 level. The planned sample size was 76, with 38 patients expected in each treatment arm in order to detect a 30% difference between treatment and placebo groups with 80% power and a 2-sided test at a significance level of P = 0.05. Difficulty with participant enrollment necessitated reducing the study population to a total of 45 individuals. We were unable to perform statistical tests for those persons who achieved greater than 50% improvement in SALT scores owing to the low sample size.

Fifteen participants were enrolled, of whom 23 (51%) were randomized to receive alefacept and 22 (49%) to receive placebo (Figure 1). All participants received at least 1 treatment with study medication. In the placebo-treated group, 3 patients withdrew after day 29, and 2 patients withdrew after day 92. No patients from the alefacept treatment group withdrew from the study. The alef-
The alefacept treatment group and the placebo group had comparable baseline demographics and disease characteristics (Table 1). Most of the participants were female (71%). Of the participants, 56% were white, 27% black, 16% Hispanic, and 2% Asian. The mean age of the participants was 36 years, with a mean age at onset of AA of 21 years. All 45 individuals had received prior treatment for AA, including systemic and topical immunosuppressant therapies and phototherapy.

At baseline, the mean SALT scores were comparable: 71.1 in the alefacept treatment group and 67.0 in the placebo treatment group. The mean percentage of hair regrowth as measured by the SALT score was not significantly different (P > .05) in either treatment group (Table 2). Neither group achieved the primary efficacy end point of at least a 50% improvement in SALT scores at the end of the treatment and observation periods. By the end of the treatment period at week 12, the alefacept-treated group, when compared with the placebo group, did not demonstrate a statistically relevant treatment response (P > .05). Specifically, only 2 patients in the alefacept treatment group and 2 patients in the placebo group achieved at least 50% improvement in their SALT scores at week 12. Of the 2 alefacept-treated patients who had at least 50% improvement in their SALT scores at week 12, only 1 patient maintained this improvement at week 24. We were unable to perform statistical tests for those patients who achieved greater than 50% improvement in SALT scores owing to the low sample size.

Participant assessment of disease (Table 3) was analyzed by grading patient perception of the extent of hair loss on a 7-point qualitative scale (none, trace, mild, mild to moderate, moderate, moderate to severe, severe). Participants graded both scalp and nonscalp hair loss. The mean participant assessment of disease scores was unchanged throughout the study duration, from screening to study completion, for both the placebo and alefacept treatment groups. In both treatment groups, the mean patient rating of scalp hair loss remained moderate to severe from screening to week 24.

Adverse events (AEs) occurring in the group receiving alefacept were similar to those occurring in the placebo group and to those noted in clinical trials of alefacept for moderate to severe psoriasis (Table 4). Most AEs were rated as mild and considered unrelated to study medication. The most frequently reported AEs in both treatment groups were infections (upper respiratory infections, influenza), headaches, and nasal congestion.

Three serious adverse events (SAEs) occurred during the course of the study. None of the SAEs had an in-
fectious etiology or were thought to be related to the study medication. Of the 3 SAEs, 2 occurred in participants receiving placebo—an episode of asthma exacerbation and an episode of vomiting and dehydration. The alefacept-receiving individual was hospitalized for right elbow arthropathy without evidence of bacterial or viral infection. The patient’s symptoms were not considered by the investigator to be related to the study medication.

Laboratory tests revealed no clinically significant changes in findings for serum chemical analysis. CD4+ T-lymphocyte counts were monitored throughout the study, and the mean CD4 counts remained higher than 250 cells/mm^3 (Figure 2). Only 1 person in the alefacept treatment group developed a CD4 count lower than 250 cells/mm^3 (239 cells/mm^3). Alefacept was held for 1 dose, after which the patient’s CD4 count returned to normal (658 cells/mm^3). This individual experienced no further declines in CD4 count.

Anecdotal experience and case reports have noted an improvement of AA following alefacept treatment. With this randomized, double-blind, placebo-controlled trial, we demonstrate that a 12-week course of IM alefacept, 15 mg, does not effectively treat severe AA. In the enrolled population of patients, treatment with alefacept was well tolerated. Most AEs were rated as mild, and the AE profile was comparable with those from previous clinical studies of alefacept. Serious infections in persons receiving alefacept were not observed. Alefacept may reduce CD4+ T-lymphocyte counts, but most participants who received alefacept demonstrated a CD4+ count that remained higher than 250 cells/mm^3. In the 1 patient whose CD4+ count transiently fell below 250 cells/mm^3, no infections or other adverse events were observed.

This study was limited by the number of patients randomized to receive treatment. The planned sample size was 76 participants, with 38 patients in each group to detect at least a 30% difference at the primary end point between the treatment and placebo groups. Owing to slow enrollment, only 45 participants were enrolled. Consequently, the study may be underpowered to detect a statistically significant treatment effect of alefacept. However, given the negligible response rate in either group of this study, a larger sample size likely would not significantly change the nature of the results.

It is unclear why alefacept failed to treat AA. Alefacept is an FDA-approved therapy for psoriasis, which also is a T-lymphocyte–mediated disease. The failure of alefacept to treat AA in this setting suggests that AA has a more complex pathophysiologic mechanism that may not be driven by memory-effector T lymphocytes. Studies from animal models indicate that the inhibition of T-lymphocyte activation may not completely treat AA. Blocking costimulatory signals and thereby inhibiting T-lymphocyte activation in mice with chronic AA had little effect on the course of AA. However, inhibiting costimulation did prevent the development of AA in the skin-grafted mouse model, suggesting that the maintenance of chronic AA requires multiple mechanisms. Indeed, single-agent therapies, including efalizumab, also an inhibitor of T-lymphocyte function, are ineffective in treating AA.

Because AA may have multiple effectors, successful treatment for AA may require combination therapy with mechanistically different agents; perhaps alefacept in combination with other modalities would be effective. Because active AA is characterized by a type-1 immune response, future use of therapies that inhibit this response may prove successful. Also, successful therapy may involve the shifting from a type 1 to a type 2 immune response. Clearly, AA is a complex disease, and further research into both understanding its pathophysiologic mechanism and the development of effective therapies is needed.

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Author Contributions: Drs Strober and Menon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Strober, McMichael, Krueger, and Shapiro. Acquisition of data: Strober, Menon, McMichael, Hordinsky, Krueger, Panko, and Lustgarten. Analysis and interpretation of data: Strober, Menon, Hordinsky, Siu, and Ross. Drafting of the manuscript: Strober, Menon, and Hordinsky. Critical revision of the manuscript for important intellectual content:

Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Alefacept Treatment Group</th>
<th>Placebo Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Congestion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cold</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Headaches</td>
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<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

a Data are given as number of patients.

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REFERENCES