An International, Randomized, Double-blind, Placebo-Controlled Phase 3 Trial of Intramuscular Alefacept in Patients With Chronic Plaque Psoriasis

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Background: Alefacept, human lymphocyte function-associated antigen 3/immunoglobulin 1 fusion protein, binds to CD2 molecules on the surface of activated T cells, selectively targeting memory-effector (CD45RO+) T cells, which comprise more than 75% of T cells in psoriatic plaques.

Objective: To examine the efficacy and tolerability of intramuscular alefacept.


Patients: A total of 507 patients with chronic plaque psoriasis.

Intervention: Placebo, 10 mg of alefacept, or 15 mg of alefacept administered once weekly for 12 weeks followed by 12 weeks of observation.

Main Outcome Measure: Psoriasis Area Severity Index (PASI).

Results: Alefacept treatment was associated with dose-related significant improvements in PASI from baseline. Throughout the study, a greater percentage of patients in the 15-mg group than in the placebo group achieved a significant reduction in PASI. Of patients in the 15-mg group who achieved at least 75% PASI reduction 2 weeks after the last dose, 71% maintained at least 50% improvement in PASI throughout the 12-week follow-up. There were no opportunistic infections and no cases of disease rebound.

Conclusion: Intramuscular administration of alefacept was a well-tolerated and effective therapy for chronic plaque psoriasis and thus represents a convenient alternative to intravenous dosing.

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Psoriasis is a chronic, inflammatory, hyperproliferative skin disorder estimated to affect up to 2.5% of the world’s population. Patients with psoriasis have a range of psychosocial difficulties and stresses commensurate with their physically disfiguring condition. This psychosocial aspect of the disease is consistently underestimated and often results in suboptimal care and reduced quality of life.

Treatment options for moderate to severe psoriasis include phototherapy and a variety of systemic therapies, which are often used in combination to adequately manage the disease. Unfortunately, few current therapies are able to produce remissions, and most patients do not achieve prolonged, disease-free periods without continued maintenance therapy. Most agents also have poor safety profiles and limited long-term tolerability with substantial organ toxic effects, which limits their use in terms of cumulative exposure. The nonselective or generalized immunosuppressive effects of some of these agents have the potential to increase the risk of developing infections and malignancies. There is an unmet need for less toxic and more effective psoriasis treatments that produce long-lasting remissions.

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While the predisposition to psoriasis is genetically determined, its precise cause remains unknown. Nevertheless, it is now becoming clear that psoriasis is probably an autoimmune disease, with activation of skin-directed T cells playing a major role. After initial contact with an unidentified antigen, a subset of T cells are activated to form memory T cells (CD4+CD45RO⁺ and CD8⁺CD45RO⁺). On secondary activation, possibly by a self-antigen, these cells proliferate and transit from lymph nodes to the skin where they...
secretes cytokines, which initiate cutaneous inflammation and drive the disease process.\textsuperscript{11,13} This hypothesis is supported by the fact that generalized immunosuppressants that affect T-cell function (eg, cyclosporine) are effective in the treatment of psoriasis.\textsuperscript{14}

To avoid the tolerability issues associated with generalized immunosuppression, newer strategies for the treatment of psoriasis have focused on selectively targeting the T cells implicated in the pathogenesis of the disease.\textsuperscript{11,15,16} Alefacept (Amevive; Biogen Inc, Cambridge, Mass) is a fully human lymphocyte function–associated antigen 3/immunoglobulin 1 (LFA-3/IgG1) fusion protein.\textsuperscript{17-19} This novel and selective biologic recombinant protein consists of the first extracellular domain of LFA-3 fused to the hinge, C\textsubscript{H}2 and C\textsubscript{H}3, domains of human IgG1. The LFA-3 domain of alefacept binds CD2 on T cells to block T-cell activation and proliferation,\textsuperscript{7} while the IgG1 domain interacts with Fc\gammaRIII receptors on accessory cells to produce selective T-cell apoptosis.\textsuperscript{10} The interaction between the LFA-3 of alefacept and CD2 on T cells reproduces the naturally occurring interaction and is of an affinity such that cells expressing high levels of CD2 molecules will be preferentially targeted by alefacept. CD2 is up-regulated on memory T cells.\textsuperscript{20,21} Thus, treatment with alefacept results in selective reductions in memory cells,\textsuperscript{22,23} which contain a clonal population implicated in the pathogenesis of psoriasis.\textsuperscript{24-28}

Alefacept has now been tested clinically for the treatment of chronic plaque psoriasis. In a pivotal phase 2 study, patients given intravenous (IV) bolus alefacept once weekly for 12 weeks showed significant improvements in the Psoriasis Area Severity Index (PASI) at 2 and 12 weeks after treatment relative to placebo-treated patients.\textsuperscript{23} Patients assessed as “clear” or “almost clear” by Physician Global Assessment (PGA) after completion of alefacept therapy required no retreatment for a median of 10 months. As expected and predicted from the mechanism of action of alefacept, these clinical improvements were related to selective reductions in memory T cells.\textsuperscript{23}

Previous phase 2 data demonstrated the feasibility and comparable pharmacokinetic profile of intramuscular (IM) administration of alefacept.\textsuperscript{29} The present international phase 3 study was conducted to confirm and extend the efficacy and tolerability profile for IM treatment with alefacept in patients with moderate to severe chronic plaque psoriasis.

**METHODS**

**PATIENTS**

Men and women aged at least 18 years were enrolled if they had chronic plaque psoriasis for more than 1 year before dosing, had a body surface area involvement of 10% or more, and had a normal CD4\(^+\) lymphocyte count. Patients were excluded for erythrodermic, guttate, or pustular psoriasis; abnormal hematologic, blood chemistry, or urinalysis; serious local (eg, cellulitis or abscess) or systemic infection (eg, pneumonia) within 3 months of the study; positive human immunodeficiency virus antibody; or positive hepatitis C antibody/hepatitis B surface antigen. Pregnant or nursing women also were excluded, as were patients with a history of malignancy (other than basal cell carcinomas or \(\leq 3\) cutaneous squamous cell carcinomas) or other skin disease potentially interfering with assessment of psoriasis. The following treatments were prohibited within 4 weeks of study drug administration and throughout the study: phototherapy, other investigational drugs or approved therapy for investigational use, systemic steroids, systemic retinoids, systemic immunomodulators, immunosuppressants (methotrexate, cyclosporine, azathioprine, and thioguanine), and high-potency topical corticosteroids. Use of moderate-potency topical corticosteroids, topical retinoids, coal tar, keratolytics, and vitamin D analogues was prohibited within 2 weeks of study drug administration and throughout the study, except on the scalp, palms, groin, anal fold, and soles. Low-potency topical corticosteroids and emollients were permitted but were not to be used within 12 hours of efficacy assessments.

**STUDY DESIGN**

The present multicenter, randomized, double-blind, placebo-controlled, parallel-group study was designed to evaluate the efficacy and tolerability of IM alefacept in patients with chronic plaque psoriasis. Patients were randomized in a 1:1:1 ratio to receive placebo, 10 mg of alefacept, or 15 mg of alefacept once weekly for a total of 12 weeks followed by a 12-week postdosing observation period. Randomization was stratified into 4 categories based on screening PASI assessment (PASI \(\geq 20\) or PASI \(\leq 20\)) and prior systemic therapy (patients who had never received systemic or phototherapy or those who had prior exposure to these treatments). ICT Inc (Lambertville, NJ), a contract research organization, was responsible for patient randomization and tracking and study drug inventory. Treatments were administered by a 1-mL IM injection to the anterolateral thigh, alternating legs each week. Injection volume was kept constant in all groups, and 0.9% isotonic sodium chloride (normal saline) served as the placebo control.

Approval of the study protocol was obtained at each study site from the independent ethics committee and institutional review board, and all aspects of the study were conducted according to the ethical principles outlined in the Declaration of Helsinki. Before study participation, each patient signed written informed consent in accordance with good clinical practice guidelines.

Patients were evaluated at baseline, at weekly intervals for 12 weeks during treatment (weeks 1 to 12), then at 2, 4, 6, 8, and 12 weeks after the last dose (weeks 14 to 24). Each scheduled dose was administered to patients only if they had no clinical evidence of significant viral, bacterial, or fungal infection; otherwise, dosing was withheld for 2 weeks if infection was present or if patients had a fever (temperature \(> 38^\circ\text{C}\)). Circulating lymphocyte and lymphocyte subset counts were determined at all study visits. If a patient’s CD4\(^+\) cell count from the prior week was lower than 250/µL, the scheduled dose was substituted with placebo. Four consecutive weeks with a CD4\(^+\) cell count below 250/µL resulted in permanent substitution of active drug with placebo.

An independent physician who had no contact with patients or with the assessing physician unless an adverse event occurred maintained blinding at each site. This physician received and evaluated laboratory data from a central laboratory (Covance Central Laboratories, Indianapolis, Ind, and Geneva, Switzerland), reviewed adverse events to determine if intervention was necessary, and recommended modification of the treatment schedule to the examining physician. An unblinded pharmacist prepared, coded, and dispensed the treatments and maintained drug accountability at each study site.

**EFFICACY MEASURES**

All efficacy measures were assessed at each study center by a dermatologist blinded to treatment. Severity of disease was mea-
TOLERABILITY

The incidence and severity of treatment-emergent adverse events were monitored throughout the study and included infections and signs or symptoms of infections as well as the incidence of malignancies. The incidence of infections over the course of the study was compared with placebo and was examined in patients stratified by CD4+ cell count (<250/µL or ≥250/µL). In those patients with CD4+ cell counts lower than 250/µL, infections were counted after the CD4+ count had dropped below 250/µL. Physical examination was performed at screening and at weeks 7, 14, 18, and 24. In addition, vital signs, urinalysis, and blood chemistry (creatinine, albumin, total bilirubin, alanine transaminase, aspartate transaminase [AST]) were assessed at screening and at weeks 1 and 24. Hematology analysis (complete blood count with differential and platelets) was performed at all study visits. The posttreatment incidence of decreases from baseline to below the lower limit of normal was determined for hematology and blood chemistry, and the posttreatment incidence of increases from baseline to above the upper limit of normal was determined for all laboratory parameters. A blood pregnancy test was administered to women at screening and repeated at weeks 14 and 24. Pharmacokinetic and pharmacodynamic parameters were determined for all laboratory parameters. A blood pregnancy test was administered to women at screening and repeated at weeks 14 and 24. Hematology analysis (complete blood count with differential and platelets) was performed at all study visits. The posttreatment incidence of decreases from baseline to below the lower limit of normal was determined for hematology and blood chemistry, and the posttreatment incidence of increases from baseline to above the upper limit of normal was determined for all laboratory parameters. A blood pregnancy test was administered to women at screening and repeated at weeks 14 and 24. Measurement of antialefacept antibodies was performed using an enzyme-linked immunosorbent assay (Biogen Inc) from blood samples collected prior to the first dose and at weeks 14, 18, and 24. The number of patients testing positive in each treatment group was noted at each time point.

STATISTICAL ANALYSIS

Frequency distributions or basic summary statistics were used to describe baseline demographic data, disease characteristics, prior therapy, and concomitant medications for each treatment group. Statistical analyses for efficacy measures were based on the intent-to-treat population composed of those patients who were randomized, had at least 1 injection, and had a baseline assessment. Logistic regression was used to compare the treatment groups, and comparisons of 10- or 15-mg alefacept group and placebo were partitioned to ensure an overall 1 error of .05 using the Bonferroni adjustment. Therefore, treatment effects for comparison of each alefacept dose with placebo were considered significant at P≤.025. To achieve this error rate and 80% power, assuming a 15% difference between alefacept and placebo for the primary end point and a 20% dropout rate, the sample size estimate was 304 patients.

RESULTS

A total of 507 patients were randomized to receive IM placebo (n = 168), 10 mg of alefacept (n = 173), or 15 mg of alefacept (n = 166) at 64 centers in Europe, the United States, and Canada (Figure 1). Study enrollment began on March 23, 2000; the last date of follow-up was January 5, 2001. A higher percentage of patients withdrew from the study in the placebo group than in the active treatment groups; reasons for withdrawal included worsening psoriasis and patient request. Treatment arms were well balanced with respect to all demographic characteristics (Table 1).
The mean percentage change in PASI showed dose-dependent decreases from baseline during the treatment period, with patients continuing to improve after the 12-week treatment period had been completed (Figure 2). Mean reductions in PASI in the 15-mg alefacept, 10-mg alefacept, and placebo groups reached a maximum of 46%, 41%, and 25%, respectively, at 6 weeks postdosing. Improvement was long-lasting, and 12 weeks after treatment end, mean PASI in both alefacept groups had not returned to baseline values. Moreover, no patient experienced rebound of disease, defined as a significant improvement on therapy followed by a marked worsening after cessation of treatment.

The finding that the peak effect of alefacept occurred after cessation of treatment underscores the importance of evaluating the benefit of alefacept over the entire course of the study rather than at a single time point. Phase 2 data also have demonstrated that alefacept has its greatest effects during the postdosing period,23 which provided the rationale for assessing overall response rates as key efficacy end points in the present trial. Patients receiving 15 mg of alefacept by IM injection showed consistent and significant improvements in all clinical measures of psoriasis activity compared with placebo. Throughout the study period, the percentage of patients responding with at least 75% PASI reduction from baseline was significantly higher (P<.001) in patients receiving 15 mg of alefacept (33%) or 10 mg of alefacept.
(28%) than in the placebo group (13%). The percentage of patients achieving at least 50% PASI reduction from baseline increased steadily throughout the 12-week treatment period, and patients continued to respond to alefacept treatment even after dosing had been completed (Figure 3). The percentage of patients achieving at least 50% reduction in PASI throughout the study period was 57% in the 15-mg alefacept group compared with 35% in the placebo group \((P<.001\)). The same end point was attained by 53% of patients in the 10-mg alefacept group \((P=.002\) vs placebo). The overall response rates for PGA of clear or almost clear were 24%, 22%, and 8% of patients in the 15-mg alefacept, 10-mg alefacept, and placebo groups, respectively \((P<.001\) for both comparisons of alefacept vs placebo).

Figure 4 illustrates the visibly apparent clinical improvement in a patient in the 15-mg group who achieved a 54% reduction in PASI. The clinical relevance of this level of PASI reduction is further supported by the finding that substantial enhancement in patient quality of life is seen when the PASI is reduced by at least 50% to less than 75%, similar to that observed in patients achieving a 75% or greater PASI reduction or a PGA of clear or almost clear. \(^{31}\)

The clinical response to alefacept was durable. Of the patients in the 15-mg group who achieved at least 75% PASI reduction from baseline 2 weeks after the last dose, 74% maintained at least a 50% reduction in PASI during the 12-week follow-up period. Of the patients in the 15-mg group who achieved at least 50% to less than 75% PASI reduction from baseline 2 weeks after the last dose, 79% maintained at least a 25% reduction in PASI during their participation in the 12-week follow-up period. Figure 4 illustrates the prolonged duration of response to 15-mg alefacept. This patient achieved a 54% reduction in PASI at 2 weeks after the last dose, with further improvement (77% PASI reduction) at 12 weeks after the last dose.

When clinical response to alefacept was analyzed by severity of disease at baseline (see Table 2 for stratification), PASI response rates increased with dose in all 4 severity strata. Response rates were slightly lower for patients who had received prior systemic therapy for psoriasis than for those who had not in all 3 treatment groups. Alefacept therapy was superior to placebo regardless of baseline disease severity, as assessed by PASI \((\leq 20\) vs \(>20\)), PGA (mild to moderate or mild disease vs more severe disease), and body surface area (\(\leq 30\%\) vs \(>30\%\) involvement). In the alefacept groups, patients with more severe disease on study entry tended to have higher response rates than patients with less severe disease. For example, in the 15-mg alefacept group, 66% of patients with a screening PASI higher than 20 achieved at least 50% PASI reduction from baseline throughout the study period, and 33% of patients with a screening PASI of 20 or lower achieved this same level of improvement. Corresponding percentages were 33% and 36% in the placebo group and 56% and 52% in the 10-mg alefacept group.

TOLERABILITY

Intramuscular administration of alefacept was well tolerated throughout the study, with similar adverse event rates in the placebo and active treatment groups. The most commonly reported adverse events with an incidence of at least 10% in either alefacept group are listed in Table 3. Adverse events that occurred at an incidence of at least 5% higher in either alefacept group than in the placebo included headache, pruritus, infection, rhinitis, injection site pain, and injection site inflammation. Most of the headache and pruritus episodes were single events during the course of the study. Injection site reactions were typically classified as mild, were often restricted to single episodes per patient, and did not lead to discontinuation of therapy in any patient.

Patients were examined each week for infections. Overall, events coded as infection, viral infection, and flu syndrome were most common in this category, with a slightly higher incidence in the alefacept groups than in the placebo group. The most frequent event coded to the COSTART term infection were common colds, contributing to approximately 50% to 70% of all infections across treatment groups. The incidence of infections was examined by CD4+ cell count lower than 250 and at least 250/µL. No relationship was evident between the over-

Figure 2. Mean percentage change from baseline in the Psoriasis Area Severity Index. The solid bar indicates the dosing interval; arrow, 2 weeks after the last treatment dose.

Figure 3. Percentage of patients achieving at least 50% Psoriasis Area Severity Index reduction from baseline at each study visit over the treatment and follow-up periods. The solid bar indicates the dosing interval; arrow, 2 weeks after the last treatment dose.
all incidence of infections and decreased CD4+ cell counts. Two infections occurred after patients had a CD4+ cell count lower than 250/µL, 1 in each alefacept group. Both infections (a sore throat in the 10-mg group and a cold in 15-mg group) were mild and study drug treatment was continued. No evidence was found for predisposition to viral reactivation syndromes (herpetic lesions) or opportunistic infections in the few patients with CD4+ cell counts lower than 250/µL.

The numbers of patients with a serious adverse event during the course of the study were 10 (6%), 8 (5%), and 7 (4%) in the placebo, 10-mg alefacept, and 15-mg alefacept groups, respectively. No evidence for any drug-related serious adverse events. No increase in malignancies was noted in patients receiving alefacept. Overall, 3 patients had malignancies diagnosed during the study, 1 in the placebo group (prostatic carcinoma) and 2 receiving 15-mg alefacept (both with basal cell carcinoma). Of the 2 cases of basal cell carcinoma, 1 patient was a 36-year-old woman with a 15-year history of psoriasis and a treatment history of psoralen plus UV-A and UV-B, and the other patient was a 66-year-old man with a 38-year history of psoriasis but no prior therapy recorded; both patients underwent routine surgical excision.

Elevation in serum transaminase levels (typically up to a 3-fold increase above the normal range in AST) was observed in patients from all 3 treatment groups. At baseline, 8%, 16%, and 14% of patients in the placebo, 10-mg alefacept, and 15-mg alefacept groups, respectively, had elevations in AST. During the study, elevations in AST were observed in 9%, 8%, and 13% of patients, respectively. Most patients with these transaminase elevations also had a history of exposure to therapy with hepatotoxic drugs or had prior hepatic illness. No elevations were noted in other blood chemistry parameters (eg, total bilirubin or albumin levels) for any of the 3 study groups. Alefacept-treated patients did not differ from those receiving placebo in other laboratory parameters, physical examination findings, or vital signs.

Fourteen patients (4%) tested positive for antialefacept antibodies after the last dose of alefacept (10/171, or 6%, in the 10-mg group and 4/161, or 2%, in the 15-mg group). The assay for antialefacept antibodies can yield false-positive results, as demonstrated by 1 patient in the placebo group testing positive at baseline. Titers were not clinically important because they were low (<1:40), were not associated with hypersensitivity reactions, were not neutralizing, and did not show amplification over sequential samples in those patients who tested positive more than once.

**COMMENT**

The benefits of targeted therapy with alefacept are evident in the results of the present phase 3 clinical trial, the first randomized, controlled trial of weekly IM doses of alefacept in patients with psoriasis. Once-weekly administration of IM alefacept for 12 weeks in patients with chronic plaque psoriasis significantly and dose-dependently improved symptoms and was well tolerated. These data agree with results from an earlier phase 2 and a recent phase 3 study in which alefacept was administered by IV bolus23,33 and support IM use as a convenient alternative form for administration of this bio-

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Table 3. Adverse Events Reported in at Least 10% of Patients in Either Alefacept Group

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 168)</th>
<th>10 mg of Alefacept (n = 173)</th>
<th>15 mg of Alefacept (n = 166)</th>
<th>Total Alefacept (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>26 (15)</td>
<td>34 (20)</td>
<td>30 (18)</td>
<td>64 (19)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16 (10)</td>
<td>24 (14)</td>
<td>30 (18)</td>
<td>54 (16)</td>
</tr>
<tr>
<td>Infection†</td>
<td>19 (11)</td>
<td>25 (14)</td>
<td>26 (16)</td>
<td>51 (15)</td>
</tr>
<tr>
<td>CD4+ cell count &lt;250/µL‡</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>15 (9)</td>
<td>20 (12)</td>
<td>20 (12)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>19 (11)</td>
<td>22 (13)</td>
<td>16 (10)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>11 (7)</td>
<td>24 (14)</td>
<td>9 (6)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18 (11)</td>
<td>19 (11)</td>
<td>18 (11)</td>
<td>28 (8)</td>
</tr>
</tbody>
</table>

*Data are number (percentage) of patients.
†Includes events coded to the COSTART (COSTART, Coding Symbols for Thesaurus of Adverse Reaction Terms) term infection; common cold was the most commonly used description in this category.
‡Includes infections that occurred after the onset of CD4+ cell count <250/µL.

logical agent. Following IM administration of 15-mg alefacept, significant improvements were observed in all of the prespecified PASI and PGA end points.

Notably, PASI and PGA in both dose groups showed continued improvement during the postdosing period after alefacept treatment was stopped. This profile of sustained activity suggests that alefacept is a remittive therapy for patients with chronic plaque psoriasis, which is consistent with previous findings. It also highlights the fact that assessing the benefit of alefacept at a single time point is not an accurate measure of the efficacy potential with this treatment. A more meaningful analysis is to determine the effectiveness of alefacept over the entire course of treatment and follow-up, as was done with the prespecified overall response rate end points in the present study. Another interesting observation was that PASI reductions between 50% and 74% were associated not only with clinical improvement that was visibly evident but also with substantial enhancement in patient quality of life. Patients did not require complete or near clear lesions to experience better quality of life. Throughout the 24-week study, nearly 60% of patients treated with a 15-mg dose of alefacept achieved at least 50% PASI reduction.

No patient had rebound or flare of disease activity associated with withdrawal of therapy after the 12-week treatment phase. This finding contrasts with other currently available systemic therapies. Withdrawal of cyclosporine, for example, has been associated with relapse of disease within 6 to 12 weeks and may be associated with disease flares following cessation of therapy. Overall, IM alefacept was well tolerated by patients throughout the study, with no evidence of broad-based immunosuppression or organ toxic effects. Adverse events were generally mild and did not lead to study discontinuation. Consistent with its fully human structure, alefacept showed a low potential for immunogenicity and no tendency for development of antibodies that affect the treatment regimen. The safety profile of IM alefacept in the present study is comparable with that reported for IV alefacept. Alefacept selectively reduced the memory T-cell subset, reductions which were related to clinical efficacy. These results are consistent with those of previous studies and will be the subject of a separate report. These findings provide further support for the key role of activated-memory T cells in the pathogenesis of psoriasis and the ability of alefacept to selectively target these cells. With this mechanism of action, alefacept might be expected to affect normal immune function. In the present study, however, several lines of evidence indicated lack of significant immunosuppression. First, placebo substitutions on the basis of low T-cell counts occurred in few patients, and there were no permanent placebo substitutions, indicating no sustained T-cell depletion during alefacept therapy. Second, infections were reported in fewer than 20% of patients in any treatment group, and there was no evidence of any increased risk of opportunistic infections or malignancies. The infections that were reported were generally mild and responded to typical treatments. Additionally, there was no association between infection and decreased CD4+ lymphocyte count.

In a separate phase 3 study, the incidence of infection was no different between alefacept and placebo.

Finally, these clinical observations are supported by results from a study specifically designed to investigate whether alefacept had any negative impact on novel or acquired immune responses. Patients with psoriasis who were treated with alefacept were challenged with foreign or recall antigens. Neither primary nor subsequent antibody responses to these challenges in patients treated with alefacept were found to differ significantly from control patients. Alefacept has minimal effects on naive T cells, leaving them intact to mount an appropriate immune response to a novel antigen. Additionally, because most memory T cells migrate to peripheral tissues and lymphoid organs in response to antigen challenge, the reductions in circulating memory cells may not reflect changes in the noncirculating population. In one study, for example, a significant accumulation of CD4+ memory T cells in response to antigen challenge was visually detected in lymphoid and nonlymphoid tissues, including the spleen, lymph nodes, liver, lungs, salivary glands, and lamina propria of the gut. Not all T-cell memory function resides in the CD4+CD45RO+ and CD8+CD45RO+ subsets; some aspects of T-cell memory function reside in a lymphocyte subset with an apparently naive phenotype, CD8+CD45RA+. Furthermore, numerous studies suggest that redundant physiological mechanisms may exist to replenish memory T-cell clones. Alefacept is able to target cells implicated in the pathogenesis of psoriasis without affecting other critical immune responses, despite reductions in memory T cells.

The clinical data presented herein confirm that IM alefacept effectively improves psoriasis and produces durable remissions without appearing to compromise normal immune function. Its targeted mechanism of action was associated with a favorable safety profile, with no evidence of opportunistic infections or an increased incidence of malignancy. Patients receiving alefacept may experience prolonged, disease-free intervals with less need for maintenance therapy and potentially fewer retreatment periods. Intramuscular alefacept provides a safe, effective, and convenient alternative to IV administration for delivery of this novel treatment for patients with psoriasis.

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