

TREATMENT OF CHRONIC PLAQUE PSORIASIS BY SELECTIVE TARGETING OF MEMORY EFFECTOR T LYMPHOCYTES

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ABSTRACT

Background Psoriatic plaques are characterized by infiltration with CD45RO+ memory effector T lymphocytes. The recombinant protein alefacept binds to CD2 on memory effector T lymphocytes, inhibiting their activation.

Methods In a multicenter, randomized, placebo-controlled, double-blind study, we evaluated alefacept as a treatment for psoriasis. Two hundred twenty-nine patients with chronic psoriasis received intravenous alefacept (0.025, 0.075, or 0.150 mg per kilogram of body weight) or placebo weekly for 12 weeks, with follow-up for 12 additional weeks. Before treatment, the median scores on the psoriasis area-and-severity index were between 14 and 20 in all groups (0 denotes no psoriasis and 72 the most severe disease possible).

Results Alefacept was well tolerated and nonimmunogenic. The mean reduction in the score on the psoriasis area-and-severity index two weeks after treatment was greater in the alefacept groups (38, 53, and 53 percent in the groups receiving 0.025, 0.075, and 0.150 mg per kilogram, respectively) than in the placebo group (21 percent, $P < 0.001$). Twelve weeks after treatment, 28 patients who had received alefacept alone were clear or almost clear of psoriasis. Three patients in the placebo group were clear or almost clear; all three had received additional systemic therapy for psoriasis. Alefacept reduced peripheral-blood memory effector T-lymphocyte (CD45RO+) counts, and the reduction in the number of memory effector T lymphocytes was correlated with the improvement in psoriasis.

Conclusions Treatment with alefacept for 12 weeks is associated with improvement in chronic plaque psoriasis; some patients have a sustained clinical response after the cessation of treatment. Alefacept selectively targets CD45RO+ memory effector T lymphocytes, suggesting that they have a role in the pathogenesis of psoriasis. (N Engl J Med 2001;345:248-55.)

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PSORIASIS is a skin disorder that affects approximately 2 percent of the world's population.^{1,2} Although persons with mild psoriasis can often control the disease with topical agents, more than 1 million patients in the United States require ultraviolet or systemic immunosuppressive therapy.^{1,2} Unfortunately, the inconvenience and risks of ultraviolet irradiation and the toxic effects of methotrexate and cyclosporine limit their long-term use.¹⁻³ Moreover, psoriasis usually recurs shortly after the cessation of immunosuppressive therapy.⁴

The recognition that T lymphocytes are involved in many chronic autoimmune diseases, including psoriasis, has led to the development of new strategies to inhibit lymphocyte activation. One approach is to block the interaction between CD2 and its ligand, leukocyte-function-associated antigen type 3 (LFA-3). The LFA-3-CD2 signal plays an important part in the activation of T lymphocytes. When CD2, which is expressed on all T-lymphocyte subgroups,⁵ interacts with LFA-3 on antigen-presenting cells, there is an increased proliferation of T lymphocytes, and cytotoxic T-lymphocyte effector functions are enhanced.^{6,7}

The recombinant protein alefacept (human LFA-3-IgG1 fusion protein, Amevive, Biogen, Cambridge, Mass.) was designed to prevent the interaction between LFA-3 and CD2. The LFA-3 portion of alefacept binds to the CD2 receptor on T lymphocytes, blocking the interaction between LFA-3 and CD2 both in vitro and in vivo, interfering with the activation of T lymphocytes, and modifying the inflammatory process (Fig. 1).⁸⁻¹²

In psoriatic lesions, most lymphocytes are memory effector (CD4+CD45RO+ and CD8+CD45RO+) T cells.^{13,14} CD2 is up-regulated on the surface of these cells; therefore, alefacept binds preferentially to them. T-cell apoptosis (programmed cell death) occurs in vitro when the LFA-3 portion of alefacept binds CD2 on T cells and the IgG1 portion binds CD16 (Fcγ receptor III) on natural killer cells (Fig. 1).¹⁰ Because alefacept inhibits the activation of T cells and induces apoptosis in critical subgroups of T cells, we evaluated the use of alefacept as immunomodulatory therapy for psoriasis.

METHODS

Subjects

Eligible subjects were men and women (age range, 18 to 70 years) with chronic plaque psoriasis that had been diagnosed at least 12 months before the screening for enrollment in the study and that involved 10 percent or more of body-surface area. Only patients who had previously received systemic treatment or phototherapy or who were candidates for such treatment were enrolled. We excluded subjects with serious hepatic or renal disease or a history of cancer (except basal-cell carcinoma or less than three squamous-cell carcinomas of the skin), those whose weight was 75 percent or more above their ideal weight, and those who had had a

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*The centers and investigators participating in the Alefacept Clinical Study are listed in the Appendix.

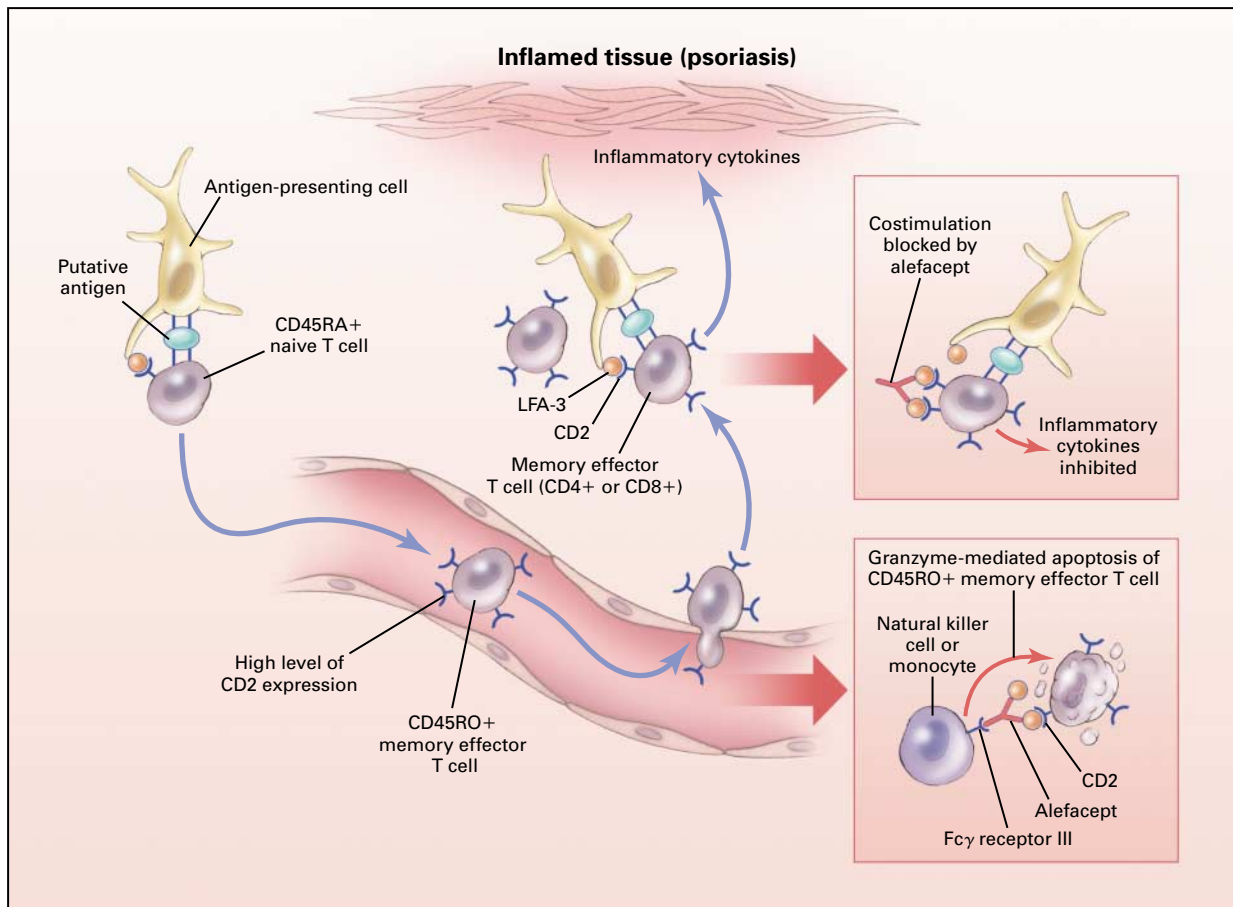


Figure 1. Proposed Mechanism of Action of Alefacept.

Antigen-presenting cells in the skin (e.g., Langerhans' or dermal dendritic cells) process antigen, migrate to regional lymph nodes, and interact with naive CD45RA+ T cells. The antigen in psoriasis is not known, and the interaction between antigen-presenting cells and T cells in psoriasis may be nonspecific. This interaction induces skin-specific memory effector T cells expressing CD45RO to proliferate in lymph nodes, enter the circulation, and eventually home to the skin. When such memory effector T cells interact with antigen-presenting cells in psoriatic lesions, they release inflammatory cytokines, prolonging and intensifying the inflammatory response. For this to occur, costimulatory molecules on the T cell and the antigen-presenting cells (including CD2 and leukocyte-function-associated antigen [LFA-3], respectively) must interact. Psoriasis-mediating T cells are subject to the action of alefacept, a fusion protein of the first extracellular domains of human LFA-3 and the Fc portion of IgG1. Alefacept inhibits T-cell activation by blocking CD2-LFA-3 costimulation. When alefacept binds CD2 on memory effector T cells and interacts with CD16 (Fc γ receptor III) receptors on natural killer cells and monocytes (probably in the bloodstream), granzyme-mediated apoptosis (programmed cell death) of T cells is facilitated. Because CD45RO+ memory effector T cells express more CD2 than do CD45RA+ naive T cells, alefacept binds preferentially to the memory effector T cells.

serious infection within the previous three months. Women of child-bearing potential were excluded unless they agreed to use contraception. The institutional review board at each participating center approved the protocol, and all subjects provided written informed consent.

Study Design

The trial was a double-blind, placebo-controlled, parallel-group study conducted at 22 centers in the United States. The authors designed the protocol for the sponsor (Biogen), which submitted it to the Food and Drug Administration under an investigational-new-drug application. The randomization scheme was generated before the study, with a block size of four at each center and with an equal number of subjects assigned to each treatment group. Subjects were randomly assigned to receive alefacept, at a dose of

0.025 mg per kilogram of body weight, 0.075 mg per kilogram, or 0.150 mg per kilogram, or placebo (normal saline) administered as an intravenous 30-second injection once a week for 12 weeks.

A pharmacist who had no contact with the patients or the physicians evaluating them prepared the study drugs; all preparations were identical in appearance. The treatment assignments were not released until all aspects of the study, including data collection, had been completed.

An independent investigator at each center reviewed safety and laboratory data. Interaction between the independent investigator and the treating physician was permitted only if laboratory values were markedly abnormal or if the treating physician needed laboratory data in order to manage adverse events. None of the investigators had access to data on serum levels of alefacept.

Patients were evaluated every 2 weeks during the treatment

phase of the study and at weeks 1, 2, 4, 8, and 12 during follow-up. The criteria for administering each dose of alefacept were a total lymphocyte count that was at least 67 percent of the lower limit of the normal range within 24 hours before injection and an absolute CD4+ T-lymphocyte count of at least 300 per cubic millimeter in the previous week. If these criteria were not met, the independent investigator contacted the pharmacist and placebo was given until the laboratory values met the criteria for the administration of alefacept.

Patients were not allowed to receive systemic treatments, phototherapy, or potent topical medications from four weeks before treatment was started until two weeks after the completion of treatment. The restricted use of moderate-potency topical corticosteroids, keratolytics, coal tar, or calcipotriene was permitted in the groin and on the scalp, palms, and soles. Emollients were permitted, but not within 12 hours before each assessment of efficacy.

Efficacy Assessments

The extent and severity of psoriasis were evaluated with the use of the psoriasis area-and-severity index and global assessments by the treating physicians. The psoriasis area-and-severity index ranges from 0 (no psoriasis) to 72 (the most severe disease possible); it combines scores for the degree of erythema, induration, desquamation, and the percentage of body-surface area affected.¹⁵ We also used the treating physician's overall assessment of the extent of psoriatic involvement, as reported on a seven-point scale: 0, clear (no psoriasis); 1, almost clear; 2, mild; 3, mild to moderate; 4, moderate; 5, moderate to severe; and 6, severe.

The efficacy end points, determined two weeks after the completion of treatment, were the change from base line (just before the initial administration of the study drug) in the mean overall score on the psoriasis area-and-severity index and the proportion of patients who were clear or almost clear of psoriasis according to the physician's global assessment. Patients were also classified according to whether they had a 50 percent or greater reduction in the score on the psoriasis area-and-severity index and whether they had a 75 percent or greater reduction in the score.

Safety Assessments

Safety was monitored on the basis of physical examination, vital signs, laboratory tests, and assessment for infections. Before the 1st, 6th, and 12th doses of the study drug were administered, blood was obtained for measurements of antibodies to alefacept with the use of an enzyme-linked immunosorbent assay. Delayed hypersensitivity for recall antigens was determined with the use of the Multitest CMI device (Mérieux Institute, Miami) before the 1st dose of the study drug was administered, after the 12th (last) dose was administered, and 12 weeks after the completion of treatment.

Pharmacokinetic and Pharmacodynamic Analysis

Before the 7th and 12th doses of the study drug were administered, serum alefacept levels were quantified by a two-step enzyme-linked immunosorbent assay that incorporated murine monoclonal antibodies against LFA-3 and a peroxide colorimetric method. Samples were diluted to the working range of the assay (80 to 900 ng per milliliter; coefficients of variation, <9 percent [intraplate] and <16 percent [interplate]). To correlate serum levels with the efficacy end points, alefacept levels (the mean of the values obtained before the 7th and 12th doses) were divided into four categories, each representing the values in approximately 25 percent of the patients: 0 (below the limit of detection), 0.10 to 0.79, 0.80 to 2.19, and 2.20 to 6.60 μg per milliliter. These categories were assessed for changes in the psoriasis area-and-severity index and the physician's global assessment as a function of time.

Flow-cytometric analyses were performed at each study visit to quantify populations of CD4+, CD8+, CD45RO+, and CD45RA+ T lymphocytes; CD19+ B cells; and CD16+ or CD56+ natural killer cells. The cumulative reduction in the base-line counts over the 12-week treatment period was reported as the area under the curve.

Statistical Analysis

All analyses, controlled for geographic region, were conducted according to the intention-to-treat principle with the use of two-tailed tests and an alpha value of 0.05. Dichotomous data were analyzed by logistic regression, and continuous data by correlation or analysis of variance.¹⁶ Linear trends in the association between the serum alefacept level and the response to treatment were tested with a logistic-regression model.¹⁶ The sponsor of the study collected the data and performed the statistical analysis; the authors interpreted the data, prepared its presentation, and wrote this report.

RESULTS

A total of 426 patients were screened for participation in the study, of whom 229 were randomly assigned to a treatment group. Among the patients who were not enrolled, the most common reasons were reluctance to risk receiving placebo, disease of insufficient severity, and a history of cancer. Base-line demographic and clinical characteristics were similar among the treatment groups (Table 1). The first patient began treatment on May 14, 1998; the last dose of study medication was given on November 30, 1998. The last follow-up visit was on February 22, 1999. A total of 197 patients (86 percent) received all 12 injections (Table 1). Five of the 59 patients assigned to receive placebo (8 percent) discontinued treatment because of worsening psoriasis, as compared with 3 of the 170 patients assigned to receive alefacept (2 percent). The use of topical treatments during the study was similar in all four groups.

Efficacy of Treatment

During the 12-week treatment phase, patients receiving alefacept had a greater decrease in the psoriasis area-and-severity index than those receiving placebo (Fig. 2A). Two weeks after the completion of treatment, the mean scores on the index were 38, 53, and 53 percent lower than the base-line scores in the groups that received 0.025, 0.075, and 0.150 mg of alefacept per kilogram, respectively, as compared with a score that was 21 percent lower than the base-line value in the placebo group ($P < 0.001$ for the comparison between the alefacept groups and the placebo group).

Two and 12 weeks after treatment, the proportion of patients who had a 50 percent or greater reduction in their base-line scores on the psoriasis area-and-severity index and the proportion who had a 75 percent or greater reduction were significantly higher in the three alefacept groups than in the placebo group. Two weeks after treatment, 36 percent of the patients who received 0.025 mg of alefacept per kilogram, 60 percent of those who received 0.075 mg per kilogram, and 56 percent of those who received 0.150 mg per kilogram had at least a 50 percent reduction in the score on the psoriasis area-and-severity index, as compared with 27 percent of the patients who received placebo ($P = 0.001$), and 21, 33, and 31 percent of the patients in the three alefacept

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 229 PATIENTS, RATES OF TREATMENT COMPLETION, AND REASONS FOR NOT COMPLETING TREATMENT.*

CHARACTERISTIC	PLACEBO (N=59)	ALEFACEPT		
		0.025 mg/kg (N=57)	0.075 mg/kg (N=55)	0.150 mg/kg (N=58)
Age — yr				
Median	42	50	44	44
Range	18–67	19–70	23–70	21–67
Sex — no. of patients				
Female	24	12	14	16
Male	35	45	41	42
Race or ethnic group — no. of patients				
Black	1	0	1	1
White	56	50	45	48
Asian	2	1	1	0
Hispanic	0	6	8	8
Other	0	0	0	1
Weight — kg				
Median	98	94	98	97
Range	58–132	61–158	56–137	47–156
Duration of psoriasis — yr				
Median	18	15	19	18
Range	1–40	3–48	1–59	2–62
Affected body-surface area — %				
Median	20	20	18	25
Range	10–80	10–90	10–85	10–85
Score on psoriasis area-and-severity index				
Median	15	14	15	20
Range	3–72	4–45	4–45	7–53
Physician's global assessment — % of patients				
Moderate, moderate-to-severe, or severe disease	81	89	91	91
Mild or mild-to-moderate disease	19	11	9	9
Clear or almost clear of disease	0	0	0	0
Completion of treatment — no. of patients (%)	49 (83)	51 (89)	48 (87)	49 (84)
Reasons for not completing treatment — no. of patients (%)	10 (17)	6 (11)	7 (13)	9 (16)
Loss to follow-up	1 (2)	2 (4)	0	2 (3)
Voluntary withdrawal	3 (5)	0	1 (2)	5 (9)
Adverse event	0	1 (2)	3 (5)	0
Laboratory abnormality	0	0	1 (2)	1 (2)
Worsening of disease	5 (8)	2 (4)	1 (2)	0
Other	1 (2)	1 (2)	1 (2)	1 (2)

*There were no statistically significant differences among the groups.

groups, respectively, had at least a 75 percent reduction, as compared with 10 percent of the patients in the placebo group ($P=0.02$). Twelve weeks after treatment, 47, 63, and 42 percent of the patients in the three alefacept groups, respectively, had at least a 50 percent reduction in the base-line score, as compared with 32 percent of the patients in the placebo group ($P=0.02$), and 33, 31, and 19 percent of the patients in the three alefacept groups had at least a 75 percent reduction in the score, as compared with 11 percent of the patients in the placebo group ($P=0.02$).

Duration of Clinical Response

A total of 118 patients completed the alefacept regimen and required no additional therapy during the post-treatment phase. Two weeks after treatment

had been completed, 19 of these patients (16 percent) were considered to be clear or almost clear of psoriasis. None of the patients in the placebo group had this degree of disease resolution two weeks after treatment (Fig. 2B).

Of the 19 patients who were clear or almost clear of psoriasis 2 weeks after the last dose of alefacept had been administered, 16 were clear or almost clear after 12 weeks without therapy, and an additional 12 patients became clear or almost clear without further treatment, for a total of 28 patients (24 percent). Twenty-six of these patients participated in subsequent studies of alefacept (data not shown); the median time from the administration of the last dose of alefacept in this study to the initiation of further treatment with alefacept was 306 days (range, 185 to 533).

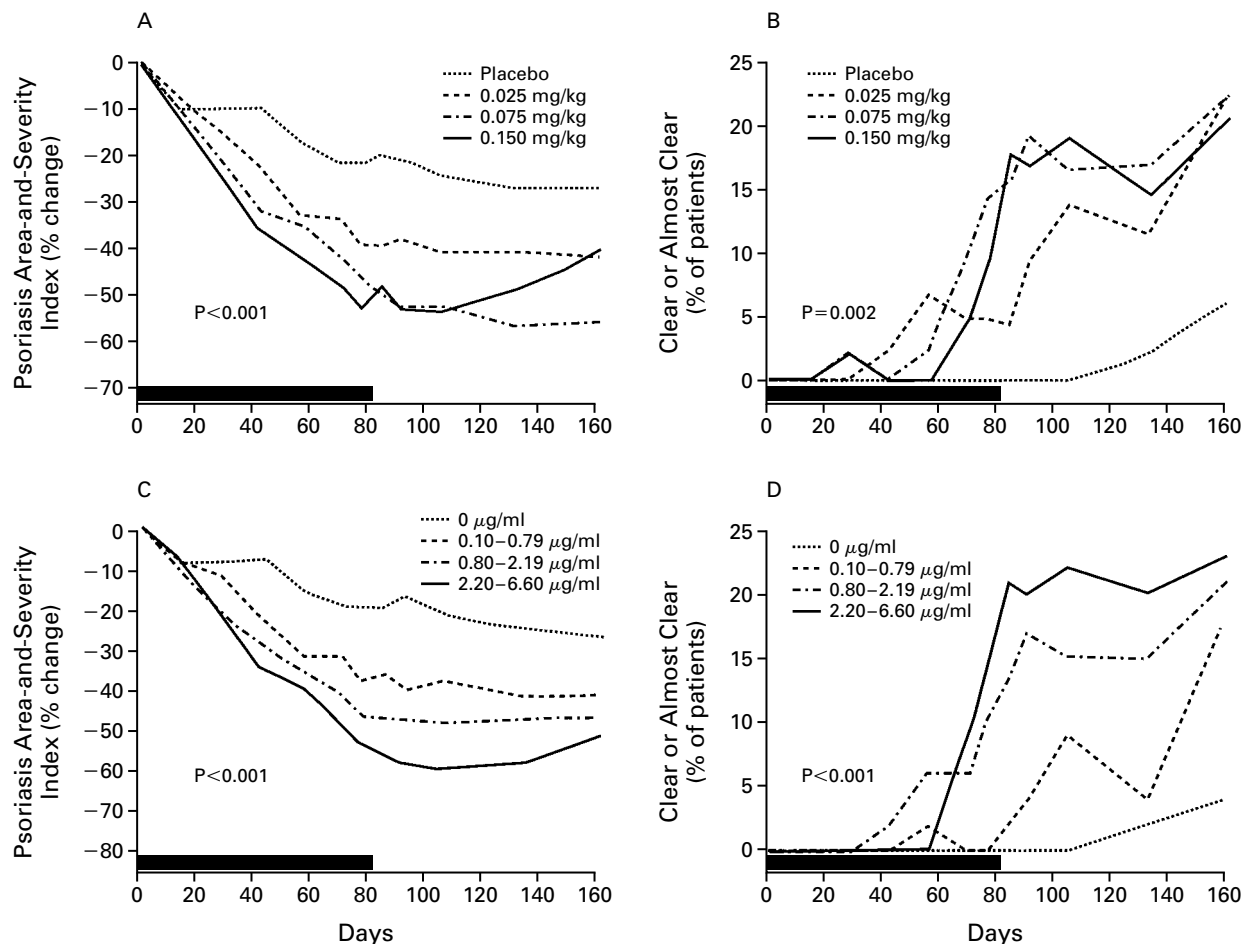


Figure 2. Response to Treatment as Measured by the Psoriasis Area-and-Severity Index and the Physician's Global Assessment. The bars represent the treatment period. Mean data for all patients who could be evaluated in the intention-to-treat analysis, including those who received concomitant medications in the follow-up period, are shown. Panels A and B show the results according to study group; the P values are for differences among the study groups (by analysis of variance). Panels C and D show the results according to the serum alefacept level; the P values are for linear trend (by logistic regression). Panels A and C show the percentage change from base line in the score on the psoriasis area-and-severity index; Panels B and D show the percentage of patients who were considered to be clear or almost clear of psoriasis, according to the physician's global assessment.

There were no reports of a flare or rebound of psoriasis after the cessation of alefacept therapy. During the 12-week post-treatment phase of the study, 11 patients who had received placebo, 4 who had received 0.025 mg of alefacept per kilogram, 4 who had received 0.075 mg per kilogram, and 3 who had received 0.150 mg per kilogram were treated with ultraviolet irradiation or systemic medications other than alefacept because of worsening psoriasis. The use of additional therapy accounted for most of the improvement in the placebo group during the post-treatment phase (Fig. 2B). Twelve weeks after the treatment phase had ended, three patients in the placebo group (5 percent) were considered to be clear or almost clear of psoriasis; all three had received additional systemic therapy.

Pharmacokinetic and Pharmacodynamic Findings

Figures 2C and 2D show the clinical response to treatment according to the serum alefacept level. Two weeks after treatment, the improvement in psoriasis, as determined by the psoriasis area-and-severity index (Fig. 2C) and the physician's global assessment (Fig. 2D), was linearly related to the serum alefacept level ($P < 0.001$ in both analyses).

During treatment, there was a dose-dependent reduction in peripheral-blood CD4+ memory effector cells (CD45RO+) but not in CD4+ naive cells (CD45RA+) (Fig. 3). The results were similar for CD8+ cells (data not shown). The reductions in the CD4+CD45RO+ cells in the alefacept-treated patients were significantly correlated with the improvement in psoriasis (Fig. 4).

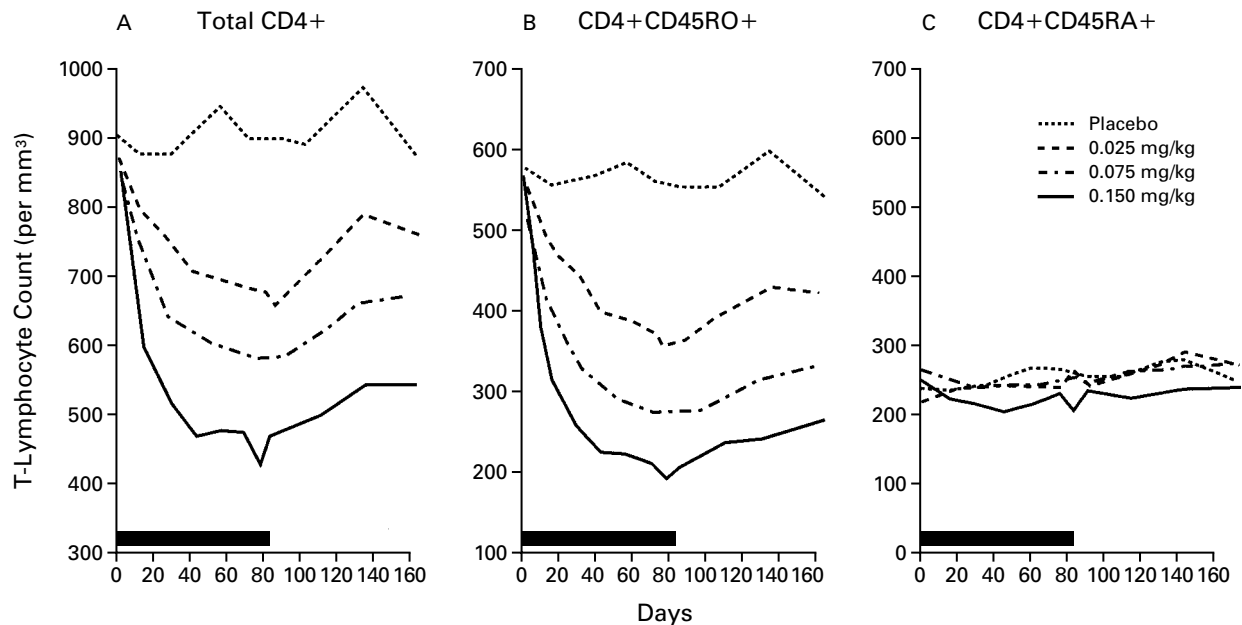


Figure 3. Peripheral-Blood T-Lymphocyte Counts.

Mean counts of CD4+ T lymphocytes (Panel A), CD4+CD45RO+ memory effector T lymphocytes (Panel B), and CD4+CD45RA+ naive T lymphocytes (Panel C) are shown according to treatment group. The bars represent the treatment period. Data for all patients who could be evaluated in the intention-to-treat analysis, including those who received concomitant medications in the follow-up period, are shown. The results for CD8+ memory effector and naive T lymphocytes in the four groups of patients were nearly identical to the results for CD4+ cells.

Safety

Alefacept therapy was well tolerated. No patient had signs or symptoms suggestive of cytokine release or capillary leak syndromes (e.g., rapid weight gain, peripheral edema, shortness of breath, abdominal cramps, or fever). Adverse events were generally mild, and no serious adverse events related to the study drug were noted. For the following adverse events, the incidence in alefacept-treated patients exceeded that in placebo-treated patients by 5 percentage points or more: accidental injury unrelated to the study protocol (13 percent vs. 5 percent), dizziness (9 percent vs. 2 percent), nausea (6 percent vs. 0 percent), chills (5 percent vs. 0 percent), and cough (5 percent vs. 0 percent). In no case did the incidence of an adverse event in the placebo group exceed that in the alefacept groups by more than 5 percentage points.

Infection or events associated with infection were reported in 108 of the 229 patients (47 percent) — in 31 of the 59 patients in the placebo group (53 percent) and in 77 of the 170 patients in the alefacept groups (45 percent, $P=0.34$ by the chi-square test). There was no association between the dose of alefacept and adverse events coded as infection. The most commonly reported infections were pharyngitis (in 25 percent of the patients who received placebo and 21 percent of those who received alefacept), an in-

fluenza-like syndrome (5 percent and 8 percent), non-specific infection (8 percent and 6 percent), bronchitis (3 percent and 4 percent), and a clinical diagnosis of herpes simplex virus infection (3 percent and 3 percent).

Twelve weeks after treatment, total lymphocyte counts were obtained in 155 patients who had received alefacept; 9 patients had counts below the normal range. On subsequent testing, three of the nine patients had normal counts, and one patient had a count that approached the lower limit of the normal range; the other five patients were lost to follow-up. Twelve of 156 patients had CD4+ T-cell counts that were less than 300 per cubic millimeter. In 11 patients, the count subsequently returned to the normal range; 1 patient was lost to follow-up. There were no significant changes in the numbers of peripheral-blood CD16+ or CD56+ natural killer cells (those known to express CD2) or B cells during the study.

Delayed-type hypersensitivity skin testing showed that the immune response to recall antigens was similar in the alefacept groups and the placebo group. Laboratory tests showed no significant changes in serum chemical or hematologic values in any of the study groups during or after treatment. One patient had a low titer of antibodies to alefacept, without signs or symptoms of an allergic reaction.

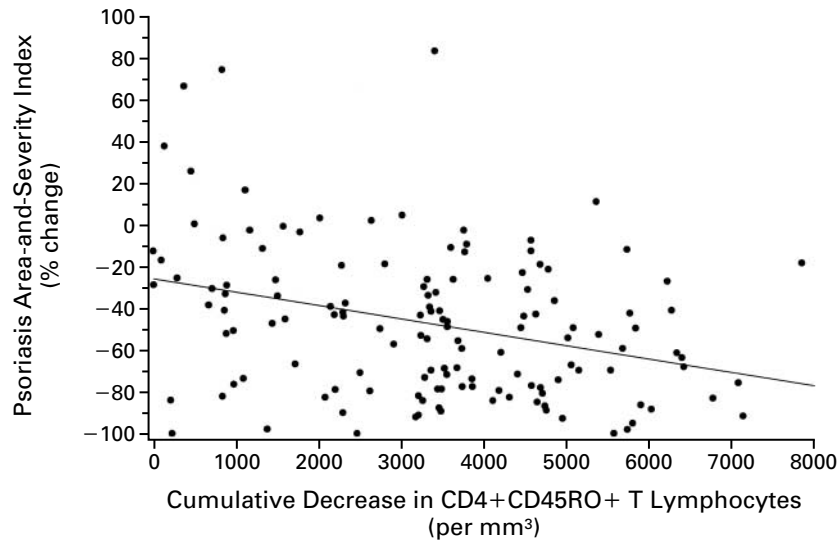


Figure 4. Relation between the Cumulative Decrease in the Number of CD4+CD45RO+ Memory Effector T Cells during the Treatment Period (the Area under the Curve) and the Change in the Score on the Psoriasis Area-and-Severity Index.

Higher numbers indicate greater decreases in counts. Two patients had an increase in the area under the curve, which is plotted as 0. Each dot represents one patient who received 11 or 12 doses of alefacept and no additional therapy for psoriasis. The area under the curve was correlated with the percent change in the score on the psoriasis area-and-severity index from base line to week 2 after treatment ($r = -0.33$, $P < 0.001$). The results for CD8+CD45RO+ cells were nearly identical to those shown here.

DISCUSSION

We found that alefacept, administered once a week for 12 consecutive weeks, was an effective and well-tolerated treatment for chronic plaque psoriasis. The clinical response rates, as defined by reductions in the scores on the psoriasis area-and-severity index and the treating physicians' global assessments, were higher in all three alefacept groups than in the placebo group.

Clinical improvement with alefacept therapy was sustained after the 12-week treatment period. On the basis of the treating physicians' global assessments, 28 patients were clear or almost clear of psoriasis at the end of the 12-week post-treatment phase of the study; among the 26 patients who received subsequent alefacept therapy, the median interval between the completion of the study and retreatment was 306 days (range, 185 to 533). This period of remission was substantially longer than that which would be expected if systemic therapy with methotrexate or cyclosporine were administered.^{4,17}

The T-cell infiltrate in psoriatic lesions is derived from circulating memory effector (CD45RO+) T cells, which express high levels of CD2 and cutaneous lymphocyte antigen (CLA), a skin-homing antigen.¹⁸⁻²³ The higher density of surface CD2 molecules on CD45RO+ memory effector T lymphocytes is consistent with the selectivity of alefacept therapy in reducing these cell populations without

substantially reducing CD45RA+ naive T cells, which have lower levels of CD2. The reduction in circulating CD45RO+ memory effector T cells during alefacept therapy in our patients was correlated with the improvement in psoriasis.

Therapies for psoriasis have been described as disease-remitting (e.g., phototherapy, denileukin diftotox, and methotrexate) or disease-suppressing (e.g., cyclosporine).¹⁸ Remitting therapies are characterized histologically by marked apoptosis of intralesional and circulating activated T cells.^{19,20} On the basis of the specific reduction in circulating CD45RO+ memory effector T cells, alefacept is a disease-remitting therapy. The pronounced effects of alefacept on CD45RO+ T-lymphocyte subgroups, which contain the clonal precursors driving the pathogenic process, may account for the sustained response to the drug.

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A patent on the use of alefacept (LEA3TIP) for the treatment of psoriasis has been assigned to Biogen and the University of Michigan; neither Dr. Ellis nor Dr. Krueger has a financial interest in the patent. Dr. Ellis and Dr. Krueger are consultants to Biogen, as well as to other companies that manufacture treatments for psoriasis.

APPENDIX

The following investigators participated in the Alefacept Clinical Study: Biogen, Cambridge, Mass. — D. Bennett, J. Haney, D. Magilavy, A. McAllister, D. Shrager, A. Vaishnav, and G. Vighiani; site investigators: Tucson,

Ariz. — M. Epstein and F. Dunlap; Scottsdale, Ariz. — J. Powers and G. Wolfley; Palo Alto, Calif. — R.D. Bright and E. Farber; Irvine, Calif. — R. Cotliar and S. Rosenblatt; Santa Monica, Calif. — N. Lowe and A. Shamban; New Haven, Conn. — R.C. Savin and L. Donofrio; West Palm Beach, Fla. — D. Zeide and S. Lederman; Peoria, Ill. — R. Swaminathan and N. Nayak; Boston — R. Langley and A. Sober; Papillon, Nebr. — T.B. Casale and H. Stoller; Lawrenceville, N.J. — W.T. Garland; East Windsor, N.J. — J. Bagel; New York — M.-H. Tan, M. Lebwohl, J. Shupack, and K. Washenik; Winston-Salem, N.C. — D. Liu and R. Holmes; Philadelphia — H. Farber, A. Mangione, L.C. Parish, and J. Witkowski; Nashville — M. Gold and M. Bell; New Braunfels, Tex. — W.C. Anderson III and E.C. Hampel, Jr.; San Antonio, Tex. — J. Gonzalez and P. Ratner; Dallas — A. Menter, N. Abdelmalek, and F. Niroomand; Salt Lake City — P. Tristani, K. Meadows, and M. Weidner; Norfolk, Va. — R.J. Pariser and M. Scott.

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