

Letter to the Editor

Alefacept (lymphocyte function-associated molecule 3/IgG fusion protein) treatment for atopic eczema*To the Editor:*

Atopic eczema (AE) is a chronic inflammatory skin disease characterized by a predominantly T_H2 cell-mediated immune response. T-cell activation is mediated by the interaction between T-cell receptor and peptide-MHC on antigen-presenting cells but also requires costimulation through accessory molecules, such as CD2/lymphocyte function-associated molecule (LFA) 3.¹ Alefacept (Amevive; Biogen Dompé, Zug, Switzerland) is a fusion protein composed of the first extracellular domain of LFA-3 (CD58) and the human IgG1 fragment crystallizable (Fc) domain.² Binding of the LFA-3 fragment to CD2 blocks costimulation and the subsequent activation of T cells.² Furthermore, by binding to CD2 and Fcγ receptor III (CD16), alefacept mediates cognate interaction between T cells and natural killer cells, resulting in T-cell apoptosis.³

Because T cell/antigen-presenting cell interactions, as well as T-cell activation and proliferation, are key pathomechanisms in AE, we aimed to investigate the effects of alefacept in AE. In this investigator-initiated, open-label pilot study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT00376129) identifier: NCT 00376129), 10 patients with moderate-to-severe AE not adequately responding to topical corticosteroid therapy, calcineurin inhibitor therapy, or both (6 female patients; age, 19-51 years) were enrolled. The study was approved by the local ethics committee. Written informed consent was obtained from all patients before participation in the study. There was a 2-week washout period for topical and a 4-week washout period for systemic AE therapy. Two weeks before and during the study, patients were allowed to exclusively take moderately potent topical corticosteroids and antihistamines. Low CD4⁺ cell numbers and severe infections had been ruled out before alefacept treatment. Patients received 12 weekly intramuscular injections of 15 mg of alefacept.

Clinical parameters (eczema area and severity index [EASI], pruritus score, and concomitant medication), differential white blood cell analysis (including immunophenotyping), skin histology, immunofluorescence analysis, and cytokine expression analysis of PBMCs and skin-infiltrating cells on mRNA and protein levels, were monitored (for methods, see Simon et al⁴). Data are presented as means ± SEMs. For statistical analyses, the paired *t* test and 1-way repeated-measures analysis, followed by the Tukey test or the corresponding nonparametric tests, were applied. A *P* value of less than .05 was considered statistically significant.

All patients experienced a significant improvement on alefacept therapy. The EASI levels continuously decreased over the treatment period, starting after the fourth injection, except in one patient who had an acute exacerbation at week 8. After treatment, EASI levels remained low or decreased further during the observation period until week 22, suggesting a sustained effect of alefacept (Fig 1, A and B). Mean percentage EASI improvement was 78% at week 12 and 86% at week 22. In parallel, the pruritus (patient assessment: 0, no; 1, mild; 2, moderate; and 3, severe) significantly decreased (2.5 ± 0.17 before therapy, 0.85 ± 0.18 at week 12, and 1.05 ± 0.19 at week 22; *P* < .001). Moreover, with the improvement of the skin lesions, all patients could

drastically reduce the application of concomitant medication. Before therapy, topical corticosteroids were applied on 5.6 ± 0.6 days per week, and after therapy, they were applied on 1.1 ± 0.3 days per week (*P* < .001). In parallel with the reduction of the EASI, the area of affected skin requiring corticosteroid therapy decreased. Three patients were able to stop the use of any concomitant AE medication. The therapy with alefacept was well tolerated, and no severe adverse events were observed.

Total and differential white blood cell counts, including CD4⁺ and CD8⁺ T-cell counts, were monitored before and every second week during the treatment period. We observed nonsignificant reductions in the numbers of leukocytes, lymphocytes, CD4⁺ and CD8⁺ T cells, neutrophils, and eosinophils. Immunophenotyping revealed decreases in the numbers of CD4⁺ and CD8⁺ cells expressing CD25, HLA-DR, and CD95 after therapy, suggesting reduced activation of T cells. Statistically significant differences were determined for CD4⁺CD95⁺ (*P* < .001), CD8⁺CD95⁺ (*P* < .001), and CD8⁺CD25⁺ (*P* = .018) cells.

Alefacept therapy had no effect on the spontaneous cytokine production of PBMCs, but on stimulation with anti-CD3 mAb, we observed a significant decrease in the production of IL-4 (*P* = .009), IL-5 (*P* = .012), and IL-13 (*P* = .043), indicating reduced numbers of T_H2 effector memory cells in the blood. Moreover, the production of IFN-γ after LPS stimulation decreased with alefacept therapy (*P* = .027).

The histopathologic alterations, such as hyperkeratosis, acanthosis, spongiosis, and dermal inflammatory cell infiltrate, that were observed in lesional skin markedly decreased on alefacept therapy toward findings usually seen in nonlesional skin. Before therapy, the dermal infiltrate was composed mainly of CD4⁺ and CD8⁺ T cells. With alefacept therapy, the numbers of T cells, but also B cells (CD21⁺) and eosinophils (eosinophil cationic protein positive), were significantly reduced (Fig 1, C).

Measuring mRNA expression of cytokines in the skin of patients with AE revealed a 75% decrease of *IL5* and a 50% decrease of *IL13* expression with alefacept therapy. The mRNA expression of *IFNG* and *IL10* decreased by approximately 25% (data not shown). The decrease of cytokine expression was confirmed by means of double-immunofluorescence staining and confocal microscopy. In parallel with the decrease of inflammatory cell numbers, the numbers of CD4⁺ and CD8⁺ T cells expressing the cytokines IL-5, IL-10, IL-13, or IFN-γ were significantly reduced (Fig 1, D and E).

This study demonstrated that alefacept is effective in the treatment of moderate-to-severe AE, revealing an improvement of symptoms during the treatment period and a sustained effect over the following 10 weeks. The time course of clinical response to alefacept in patients with AE and the safety profile were similar to those observed in patients with psoriasis.^{5,6}

In agreement with the dual function of alefacept, we observed decreased numbers of skin T cells and reduced T-cell activation with therapy. Alefacept preferentially targets activated CD45RO⁺ T cells expressing relatively high levels of CD2.³ Although T-cell numbers were reduced, a critical decrease of blood CD4⁺ cells, which would have compelled us to stop therapy, was not observed.

In patients with AE, alefacept therapy had anti-inflammatory effects by reducing the numbers of CD4⁺ and CD8⁺ T cells, as

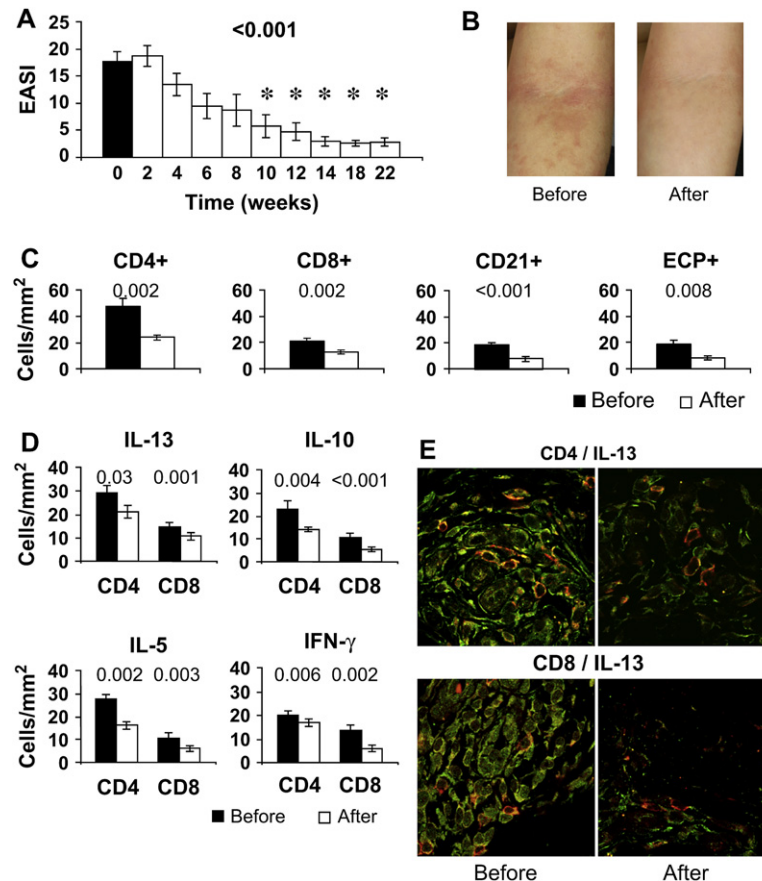


FIG 1. Reduced skin inflammation with alefacept therapy. **A**, Reduction of the EASI. Asterisks indicate *P* values of less than .05. **B**, Clinical response. **C**, Number of skin inflammatory cells. *P* values of significant differences are indicated. *ECP*, Eosinophil cationic protein. **D**, Quantification of cytokine-expressing CD4⁺ and CD8⁺ cells in lesional skin. **E**, Representative original images of data presented in Fig 1, D (original magnification ×1000).

well as IL-5 and IL-13 cytokine expression, in the skin. The reduction of B cells and eosinophils is probably a secondary effect caused by decreased numbers and activation of T cells.⁷ Although the number of patients has been small, our results are promising. Further placebo-controlled studies are required to define the efficacy and safety of alefacept in patients with AE.

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