

## Alefacept for treatment of moderate to severe adult atopic dermatitis

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### ABSTRACT

**BACKGROUND:** Atopic dermatitis is a common inflammatory skin disease presenting with a dominance of memory T cells. Alefacept is a fully human LFA-3/IgG1 fusion protein that inhibits T-cell activation and selectively reduces memory T cells.

**OBJECTIVE:** To evaluate clinical response of alefacept intramuscular (IM) injection given for 12 weeks in adults with severe atopic dermatitis not responding to conventional drugs.

**METHOD:** Seven adult patients with moderate-to-severe AD were enrolled in this study. All patients had not responded adequately to topical therapy and/or systemic treatment. Patients received 12 weekly intramuscular injections of 15 mg of alefacept. EASI score, a pruritus score were used to evaluate the clinical efficacy of alefacept therapy. The differential white blood cell counts were monitored at 2 weeks interval during the entire treatment period.

**RESULT:** All patients experienced a significant clinical improvement on alefacept therapy. All patients showed a decrease in EASI score of more than 50%, minimal or no pruritus was reported by all the patients. The 12-week course of alefacept was well tolerated.

**CONCLUSION:** The treatment regimen of alefacept for 12 weeks was well tolerated by our patients. All the 7 patients with atopic dermatitis responded to treatment with alefacept. Additional studies with a larger sample size, may be warranted to evaluate the possibility of alefacept as a therapy for patients with atopic dermatitis.

### INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, relapsing cutaneous disease with typical cellular and humoral immunologic abnormalities that can result in significant physical and psychological morbidity to the patient. Atopic dermatitis typically begins in childhood and can often persist through adolescence into adulthood. Atopic dermatitis affects 10% to 20% of children and 1% to 3% of adults.

Severe AD cannot be adequately controlled with topical agents. Consequently, many patients are treated with phototherapy, systemic corticosteroids, cyclosporine, azathioprine, methotrexate, and other immunosuppressant medications that carry the risk of severe adverse effects. Although of these variety of treatments for atopic dermatitis, many patients' symptoms do not improve or they

have adverse reactions to medications, requiring the search for other, effective therapeutic agents.

T cells play a key role in the pathogenesis of AD as evidenced by immunohistochemical studies revealing an inflammatory infiltrate of primarily CD45RO+ memory T cells.<sup>1,2</sup> In addition, T cell-specific inhibitors, such as cyclosporine and tacrolimus, improve disease outcomes.<sup>3,4</sup>

Alefacept (Amevive, Astellas Pharma US Inc, Deerfield, Ill) was the first biologic agent approved in the United States for the treatment of chronic plaque psoriasis (January 2003). The dual mechanism of action involves both the inhibition of T-cell activation and the selective induction of apoptosis of memory T cells.<sup>5</sup>

The aim of the study is to evaluate the potential safety and efficacy of alefacept, an inhibitor of T cell activation, in adults with severe AD.

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## PATIENTS AND METHODS

Seven patients with moderate-to-severe AD according to the criteria of Hanifin and Rajka<sup>6</sup> (4 women, 3 men; age, 19-54 years; average,  $35 \pm 6$  years) were enrolled between January 2008 and January 2010. All patients had not adequately responded to topical corticosteroid and/or calcineurin inhibitor therapy or both and had previously received systemic treatment. Written informed consent was obtained from all patients before participation in the study. All patients had a 2-week washout of all topical therapy except corticosteroids and a 4-week washout of systemic treatment. Two weeks before and during the study, patients were allowed to exclusively take moderately potent topical corticosteroids and antihistamines as needed. Low CD4<sup>+</sup> cell numbers and severe infections had been ruled out before alefacept treatment. Patients received 12 weekly intramuscular injections of 15 mg of alefacept.

Punch biopsies were taken from lesional skin before and from the same or symmetrical areas 6 weeks after therapy.

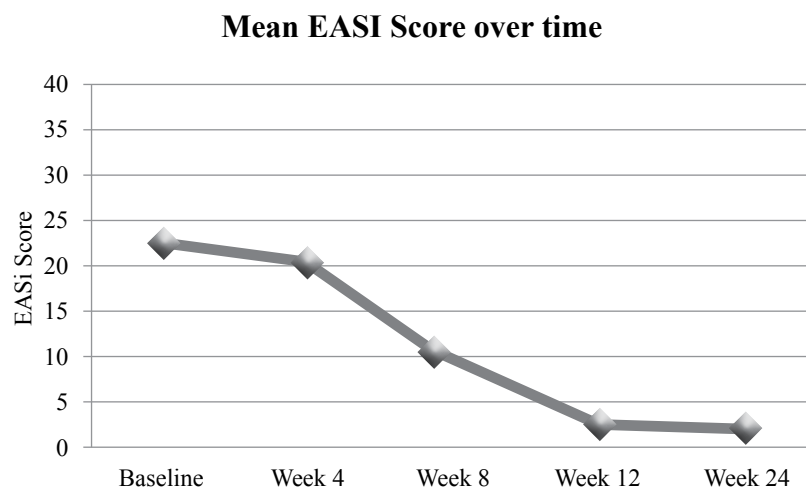
To evaluate the clinical efficacy of alefacept therapy, the eczema area and severity index (EASI score, which ranges from 0 to 72), a pruritus score (patient assessment: 0, no; 1, mild; 2, moderate; and 3, severe), the use of concomitant therapy for AD such as topical corticosteroids and antihista-

mines, differential white blood cell analysis (including immunophenotyping, CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts), were monitored at each second week during the treatment period.

## RESULT

All 7 patients completed the study including the follow up till 24-week. All patients experienced a significant improvement on alefacept therapy. The EASI levels continuously decreased over the treatment period, starting after the fourth injection, in all the patients. After treatment, EASI levels remained low or decreased further during the observation period until week 24, suggesting a sustained effect of alefacept (Fig. 1). Mean EASI scores decreased from 22.5 (week 0) to 10.6 (week 8) following alefacept therapy, indicating improvement of at least 53%. Mean percentage EASI improvement was 81% at week 12 and 92% at week 24. Equivalent to the reduction of the EASI, the area of affected skin requiring corticosteroid therapy decreased.

Pruritus significantly improved (Fig. 2) in all patients with AD ( $2.8 \pm 0.21$  before therapy,  $0.79 \pm 0.15$  at week 12, and  $0.94 \pm 0.17$  at week 24;  $P < .001$ ). Moreover, with the improvement of the skin lesions, all patients could significantly diminish the application of related medication. All patients reduced the application of topical corticosteroids.



**Fig. 1** Mean improvement in EASI score of 52.3% ( $P < .0001$ ).

The average frequency of application was 6 times per week before therapy and declined to 3 times at week 8. Moreover, with the decrease of affected skin areas, the amount of applied corticosteroids markedly decreased.

Five patients were able to stop the use of any related AD medication. The therapy with alefacept at the 15-mg dose was well tolerated, and no severe adverse events (AE) were observed.

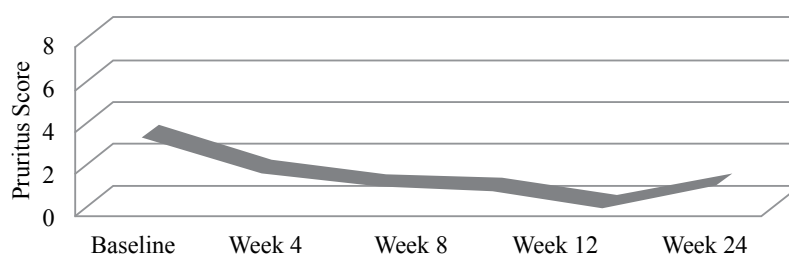
The biopsy specimen from all patients taken from lesional AD skin before therapy revealed the typical features of eczematous skin. After treatment, the skin histology showed an impressive improvement as hyperkeratosis, acanthosis, spongiosis, and the infiltration by dermal inflammatory cells decreased significantly toward findings usually seen in nonlesional skin of AD.

of patients with atopic dermatitis produce reduced levels of interferon-gamma spontaneously and in response to stimuli. Due to this constellation of features, atopic dermatitis was initially viewed as a prototypical type 2 helper T lymphocyte (Th2) disease.<sup>7</sup>

Alefacept is an LFA-3 (lymphocyte function-associated antigen-3) / Immunoglobulin fusion protein that induces memory-effector T-lymphocyte apoptosis and interrupts T-lymphocyte activation.<sup>8</sup>

This study demonstrated that alefacept is effective in the treatment of moderate-to-severe AD, revealing an improvement of symptoms during the treatment period and a sustained effect over the following 12 weeks. The time course of clinical response to alefacept in patients with AD and the safety profile were similar to those observed in

### Mean Pruritus Score over time



**Fig. 2** Mean pruritus scores improvement over time after Alefacept treatment.

There were 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.

### DISCUSSION

Patients with atopic dermatitis often have an elevation of serum immunoglobulin IgE levels, depressed cellular immunity, elevated blood eosinophilia, and increased interleukin IL-4 production. In addition, peripheral blood mononuclear cells

patients with psoriasis.<sup>5,9</sup>

The safety profile of alefacept treatment was evaluated based on the incidence of adverse events. Alefacept was well tolerated by our patients. There were no serious AEs. During this study, 2 patients reported fatigue and one patient reported headache which did not require medical intervention and were classified as mild adverse events.

Clinical experience with alefacept indicates that response continues after treatment is completed in our patients, because alefacept has a peak effect after treatment completion, and produces prolonged remissions which may last more than 6 months.

## CONCLUSION

The results of this study demonstrate that the adverse effects of alefacept therapy are acceptable, with no serious adverse effects occurring in any patients. In addition to being a highly effective drug in the treatment of moderate-severe AD, alefacept is also characterized by a low toxicity profile, causing only moderate adverse effects. For those patients with moderate to severe psoriasis showing response to their treatment of alefacept, the potential exists for disease-free intervals ( $\geq 6$  months) between subsequent courses of treatment. Additional studies with a larger sample size are warranted to further investigate the potential role of alefacept as a treatment for adults with moderate to severe atopic dermatitis.

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