

REPORT

Efalizumab for severe atopic dermatitis: A pilot study in adults

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Background: Severe atopic dermatitis (AD) often cannot be adequately controlled with topical agents. The continuous use of current systemic therapies for AD is limited by end-organ toxicities. A safe and effective systemic therapy for patients with recalcitrant AD is greatly needed.

Objective: To evaluate the potential safety and efficacy of efalizumab, an inhibitor of T cell activation and migration, in adults with severe AD.

Methods: An investigator-initiated, prospective, open-label, pilot study was conducted involving ten subjects with severe AD. Subjects received an initial conditioning subcutaneous dose of efalizumab of 0.7 mg/kg followed by 1.0 mg/kg weekly for another 11 weeks for a total of 12 doses. The primary efficacy outcome was the change in the mean Eczema Area and Severity Index (EASI) score from baseline as measured at week 12. Monitoring of adverse events continued for 8 weeks after discontinuation of therapy.

Results: EASI scores improved from a mean baseline score of 37.1 ± 13.5 to 17.6 ± 14.5 at week 12 (52.3% improvement; $P < .0001$). Six out of ten subjects reached at least a 50% improvement in EASI score by week 12. Pruritus levels decreased from $6.9 \text{ cm} \pm 1.8 \text{ cm}$ to $4.9 \text{ cm} \pm 2.5 \text{ cm}$ utilizing a visual analogue score ($P < .015$). Overall, efalizumab was well tolerated. There were three significant adverse events during the course of this study, including thrombocytopenia, viral gastroenteritis, and a subject with worsening of disease beyond baseline levels after drug discontinuation.

Limitations: It is difficult to apply these findings to larger populations of patients with AD because this study lacked a control group and involved a small number of subjects with very severe disease. Long-term efficacy and safety of efalizumab in this population is not known.

Conclusions: Efalizumab therapy resulted in significant clinical improvements in six of ten subjects with severe AD. Efalizumab may serve as a good alternative to current systemic immunosuppressants used for AD; however, double-blind placebo-controlled studies are needed to test its efficacy and safety. (J Am Acad Dermatol 10.1016/j.jaad.2006.08.031.)

Most cases of childhood atopic dermatitis (AD) improve or resolve after childhood. A subset of patients, however, retain features

of AD as adults, and some continue to have severe disease. 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. The chronic use of current immunosuppressive agents is limited by cumulative end-organ toxicities. A targeted systemic agent that has long-term efficacy and safety has not been discovered for this chronic disease.

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.^{1,2} In addition, T cell-specific inhibitors, such as cyclosporine and tacrolimus, improve disease outcomes.^{3,4} Efalizumab, approved for the

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treatment of chronic, moderate to severe plaque psoriasis in adults (aged ≥ 18 years), is a humanized monoclonal antibody that blocks T cell–dependent functions mediated by leukocyte function antigen–1 (LFA-1). Efalizumab specifically binds to the LFA-1 subunit, CD11a. LFA-1 is a T cell adhesion molecule that interacts with intracellular adhesion molecule 1 (ICAM-1) found on vascular endothelium to facilitate T cell adhesion to the endothelium and egress into tissues, including the skin. LFA-1 on the surface of T cells also interacts with ICAM-1 on the surface of antigen-presenting cells to facilitate full T cell activation. Thus, by blocking LFA-1 functions, efalizumab prevents migration of T cells out of the peripheral blood vessels and into the skin and prevents full T cell stimulation.^{5,6} The blockade of one or both of these steps by efalizumab explains the clinical improvement seen in psoriasis patients.⁷ Interestingly, the blockade of LFA-1 suppressed the ability to induce inflammation in the NC/Nga mouse, a mouse model that has some features resembling AD.⁸ For these reasons, we hypothesized that inhibition of LFA-1 may have beneficial clinical effects in patients with AD.

METHODS

Patients

Ten patients with severe AD were recruited from the outpatient dermatology clinics at Oregon Health & Science University. Entry criteria included age ≥ 18 years, diagnosis of AD using standard criteria,⁹ moderate to severe AD as determined by a Rajka–Langeland severity score ≥ 6 ,¹⁰ an Eczema Area and Severity Index (EASI) score ≥ 18 ,¹¹ and a candidate for, or having previously received, systemic therapy, including cyclosporine, methotrexate, ultraviolet light, or other immunosuppressant. Candidates for systemic therapy were defined as subjects whose disease was not adequately controlled using topical therapies or where side effects prevented the further safe use of topical therapies. Exclusion criteria included a known hypersensitivity to efalizumab or any of its components, current treatment with systemic immunosuppressive agents, history of an immunocompromised state (eg, lymphoma, HIV disease, Wiskott–Aldrich syndrome), corticosteroid-dependent asthma, active infection of any type at the time of enrollment, pregnancy or lactation, and any other condition that the investigator believed would pose a significant hazard to the subject if the investigational therapy were initiated. All subjects had a 2-week washout of all topical therapies prior to receiving the study drug excluding a stable dose (2 weeks or longer) of triamcinolone ointment 0.1%. Systemic therapies, including

phototherapy, were discontinued 4 weeks before the study. Topical and systemic antibiotic and antiviral treatments were allowed if an infection developed during the course of the study.

Study design

This was an investigator-initiated, open-label, pilot study conducted at Oregon Health & Science University from July through December 2005 with the approval of our institutional review board. The study consisted of 12 weeks of open-label efalizumab at the recommended dose approved by the US Food and Drug Administration for psoriasis (initial conditioning dose of 0.7 mg/kg followed by weekly doses of 1 mg/kg) administered by subcutaneous injection. At the end of the treatment phase, subjects had 8 weeks of follow-up adverse event monitoring for a total study duration of 20 weeks.

Efficacy and safety

The primary efficacy outcome was the change in mean EASI score from baseline as measured at 12 weeks. The range of the EASI is 0 to 72, with scores above 18 representing a patient with severe disease.¹² Secondary outcomes included subjects' assessment of pruritus (using a 10-cm visual analog scale), the proportion of subjects reaching 50% improvement in EASI score (EASI 50), the proportion of subjects reaching 75% improvement in EASI score (EASI 75), the investigator's global assessment (IGA), and change in the serum IgE level. The IGA is a subjective assessment of overall disease severity with the following categories: clear or almost clear, mild, moderate, severe, and very severe. Safety evaluations included a complete physical exam, elicitation of adverse events, and laboratory monitoring including a complete blood count and total serum IgE levels. Outcome measures and safety evaluations were performed at baseline, week 2, week 4, and at 4-week intervals throughout the study.

Statistical analysis

Repeated measures analysis of variance was performed using SAS software (SAS, Inc, Cary, NC).

RESULTS

Baseline characteristics

Twelve subjects were screened and ten subjects were enrolled in this study; all were considered severe by Rajka–Langeland scoring. Two subjects failed screening because of a baseline EASI score <18 .

Protocol variations

Compliance throughout the study was excellent. All ten subjects completed the full 20 weeks of the

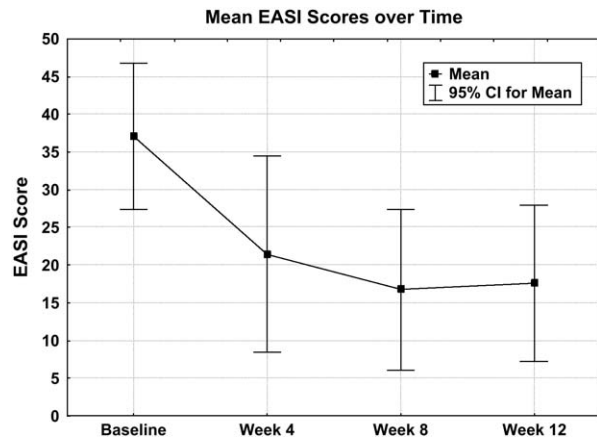


Fig 1. Mean improvement in EASI score of 52.3% ($P < .0001$).

study. Minor variations to the study protocol occurred on four instances. Four subjects held doses of efalizumab for 1 to 2 weeks at some point in the study for the following reasons: a change in eczema phenotype noticed by subject 10, a case of suspected herpes simplex in subject 2, the development of diarrhea in subject 8; subject 7 was instructed to hold one dose of efalizumab during a 1-week course of prednisone (40 mg/day) for a mild flare prior to his wedding between weeks 4 and 8. This subject's EASI score improved briefly, but within 2 weeks returned to the EASI score he had before the course of prednisone. Therefore, the week of prednisone therapy did not significantly affect the final EASI score mean. Time off of treatment was not included in the statistical evaluation. More detailed descriptions are found in the adverse events section below.

Efficacy

The mean EASI score at baseline was 37.1 ± 13.5 with a median of 35.9 and range of 23.0 to 66.1. At week 12, the EASI score significantly improved to a mean of 17.6 ± 14.5 at week 12 for a mean improvement of 52.3% ($P < .0001$; Fig 1). Some improvement was noted in all ten subjects enrolled in this study (Figs 2 and 3). Six out of 10 subjects achieved EASI 50 and two of ten subjects achieved EASI 75 at week 12.

At baseline, five subjects had an IGA of severe and five were rated as very severe. At week 12, only two subjects achieved an IGA of mild and no subjects achieved an IGA of clear or almost clear. Four subjects reached an IGA of moderate, two improved to severe, and two remained very severe at week 12. At week 12, pruritus scores (0-10 cm on the visual analog scale) decreased by a mean of 2 cm ($P < .015$; 6.85 cm to 4.9 cm) compared to baseline (Fig 4).



Fig 2. Arm of subject 4 showing erythema and excoriation.

Laboratory data

Mean serum IgE levels decreased minimally from baseline at 12 weeks from 23218.71 at baseline to 19288.14 at week 12 ($P < .2976$). When comparing the response of subjects with high-serum IgE to those with normal to near normal serum IgE, there were no significant differences in clinical response (data not shown). Percent lymphocyte counts increased from a mean baseline of 20.3 ± 6.4 to 37.4 ± 9.2 ($P < .0001$). Percent eosinophil counts decreased from a mean baseline of 10.5 ± 4.3 to 7.8 ± 5.1 at week 12 ($P < .05$). Mean platelet count at baseline was 247 K/cu mm and 228 K/cu mm at week 12 ($P < .47$). There were no other significant hematologic changes during the study except one case of thrombocytopenia described below.

Adverse events

Overall, efalizumab was well-tolerated. One hundred and twenty doses were administered to ten subjects with one serious adverse event (thrombocytopenia which is discussed below). Secondary bacterial infection was the most common adverse event noted during the course of this study. Five of the ten subjects in the study were diagnosed with a superficial bacterial infection clinically consistent with *Staphylococcus aureus*, which responded quickly to short courses of either oral dicloxacillin or cephalexin. These subjects all had long histories of recurring



Fig 3. Arm of subject 4 showing improvement of erythema and excoriation after 12 weeks of efalizumab therapy.

S aureus infection. Three subjects were diagnosed with herpes simplex virus, two confirmed by viral culture, which cleared following a course of acyclovir. These three subjects had a history of similar herpes simplex virus infections prior to the study. All infections were noted to be mild in nature. Two of the ten subjects described flu-like symptoms (fever, headache, and chills) for approximately 24 hours after the initial doses of efalizumab. These symptoms resolved by week 4 and were noted to be mild.

Two subjects developed a change in eczema morphology with the appearance of scattered nummular eczematous plaques that had not been experienced by the subjects prior to the study. These lesions lasted for approximately 1 month and resolved spontaneously during therapy. No biopsies were performed.

One subject reported a 2-week history of loose stools during week 3 of therapy. Efalizumab was held for 2 weeks during a full gastroenterology work-up. Stool cultures, stool ova and parasite examination, and colonoscopy revealed no underlying infection or inflammatory bowel disease and a diagnosis of viral gastroenteritis was suspected. The loose stools resolved spontaneously after 4 weeks while receiving efalizumab therapy.

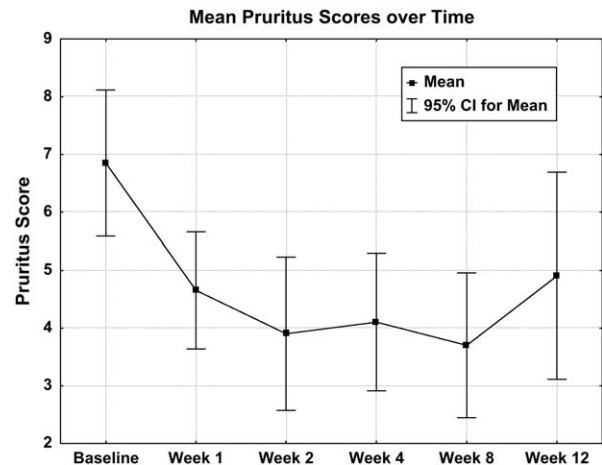


Fig 4. Efalizumab improves mean pruritus scores over time.

One subject developed thrombocytopenia with platelets decreasing from 240 K/cu mm at baseline to 81 K/cu mm at week 12. Four weeks after drug discontinuation, the platelet count decreased to 39 K/cu mm. The subject did not note any abnormal bruising or bleeding. The platelet count recovered after treatment with oral prednisone for 1 month, but the thrombocytopenia reappeared 2 months off therapy. Six months after discontinuing efalizumab, a platelet count confirmed recovery of his platelets to a normal value of 173 K/cu mm with no additional treatment.

Subjects were monitored for adverse events for 8 weeks following drug discontinuation. Nine subjects experienced gradual return of disease activity to baseline levels by 4 to 8 weeks following drug discontinuation and were transitioned to additional topical therapy or systemic agents. One subject experienced an increase in EASI score of 152% over baseline at 2 weeks and a 204% increase over baseline at 4 weeks following drug discontinuation despite the use of high potency topical steroids. He required 1 week of systemic prednisone 60 mg per day to control his flare.

DISCUSSION

Efalizumab, a monoclonal antibody that inhibits T cell migration and activation, provided significant clinical improvement for subjects with severe AD and may serve as a new therapeutic option for this disease. Of note, an improvement of 53% in disease activity with efalizumab is better than improvements reported for interferon- γ ¹³ and azathioprine¹⁴ and is comparable to previous open-label studies of cyclosporine and mycophenolate mofetil.^{15,16} Six out of ten subjects achieved a clinically significant

improvement (EASI 50), which is almost three times the expected placebo response seen in a previous study of injectable interferon- γ .¹⁷ These comparisons serve only to confirm that efalizumab has clinical activity in AD. Drawing firm conclusions as to how efalizumab may compare to these other agents cannot be justly done without randomized comparison studies. No subjects achieved clear or almost clear disease as measured by the IGA scale but many of the subjects were pleased to experience significant improvement in the disease. At the end of the study, five of ten subjects requested further treatment with efalizumab despite the experimental nature of the therapy. Overall, these results are encouraging and warrant the further study of efalizumab for the treatment of AD. New systemic therapies that can allow safe, long-term, and continuous control of severe AD are greatly needed.

This study was based on the hypothesis that efalizumab, by inhibiting certain T cell functions, may serve as a novel therapeutic approach in severe AD. Peripheral blood total lymphocyte counts increased in all subjects shortly after starting therapy as has been reported in previous studies with efalizumab.^{6,7} An increase in peripheral blood lymphocyte counts is expected and reflects inhibition of T cell migration from the peripheral blood vessels into the skin.

Overall, efalizumab was well-tolerated, with two subjects developing flu-like symptoms within 24 hours of the first dose. These symptoms were mild in severity and resolved after the first 1 to 4 doses. Similar mild first and second dose reactions have been previously reported with efalizumab therapy in psoriasis clinical studies.⁷ Bacterial infection was the most common adverse event noted during the course of this study (5 subjects), and 3 subjects were also diagnosed with herpes simplex virus. All infections were mild in severity and responded promptly to the appropriate antimicrobial therapy. Although no increases in infection have been observed in previous studies of patients with psoriasis treated with efalizumab, patients with AD are uniquely susceptible to cutaneous infections. It is unclear whether efalizumab contributed to the development of these secondary infections, because patients with AD have a known susceptibility to cutaneous bacterial and viral infections. Controlled studies will help elucidate how efalizumab alters the risk of infection in this patient population.

Thrombocytopenia developed in one patient at the 12-week time point and required prednisone therapy. Thrombocytopenia has been reported in 0.3% of subjects with psoriasis treated with efalizumab in the pooled psoriasis clinical studies (efalizumab package insert). The mechanism by which

efalizumab induces thrombocytopenia is unknown, but is believed to be immune-mediated, and anti-platelet antibodies have been detected in one patient (efalizumab package insert). It is unclear whether patients with AD have a greater susceptibility to thrombocytopenia than do patients with psoriasis when treated with efalizumab. Careful monitoring of platelets will be needed in future studies of efalizumab for the treatment of AD.

One concern with the use of efalizumab in AD was disease worsening upon discontinuation of therapy. Worsening of disease above 125% of baseline levels (rebound) upon drug withdrawal has been seen in up to 13.8% of patients with psoriasis treated with efalizumab.¹⁸ Applying this definition to our current study, one subject experienced rebound within 2 weeks of discontinuation of efalizumab. Rebound is not uncommon upon discontinuation of therapy in AD and can also be seen with cyclosporine and prednisone. Transitioning to another systemic agent or potent topical steroid upon discontinuation of efalizumab will likely blunt the development of disease worsening in this patient population.

In conclusion, efalizumab holds promise for the treatment of patients with moderate-to-severe AD requiring systemic therapy. Its level of safety and efficacy rates compare favorably to other systemic therapies currently in use for AD. A small open-label study such as this suffers from a lack of a control group and the sample size may not be large enough to capture all-important adverse events. Randomized, double-blind, placebo-controlled studies are needed to test the safety and efficacy of efalizumab in the treatment of AD before it can be recommended for routine use in this patient population.

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