

Successful Treatment of Severe Atopic Dermatitis in a Child and an Adult With the T-Cell Modulator Efalizumab

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

An 8-year-old white boy presented in January 2003 with a long-standing history of atopic dermatitis, with onset between ages 1 and 2 years, in addition to insulin-dependent diabetes mellitus diagnosed at age 7 years. During the prior 6 years, he had undergone treatment with a variety of topical corticosteroids, 1% pimecrolimus cream, emollients, and courses of prednisone. Both diseases were poorly controlled.

The patient was initially treated with 0.05% diflurasone diacetate ointment, petroleum jelly, and oral cetirizine. In February 2003, 4 mg/kg per day of oral cyclosporine was added to his regimen. This was subsequently increased to 5.6 mg/kg per day in late March and to 6.2 mg/kg per day in late April. In March and May 2003, he received 2 courses of oral cephalexin for flares.

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In June 2003, UV-B therapy was added 3 times weekly. The patient showed improvement over the next 2 months, but UV light treatment was discontinued in late August after he purposefully removed his protective eyewear, looked at the light source, and suffered a retinal burn. During this period, the patient received another course of oral cephalexin and a course of nasal mupirocin ointment. He continued to use a variety of topical corticosteroids on an intermittent basis. By November 2003, the patient's disease was flaring; at this point, medical non-compliance was a concern.

In January 2004, twice-weekly treatment was begun with 25 mg of subcutaneous etanercept. The cyclosporine therapy was discontinued approximately 1 month later. In March 2004, the patient experienced a flare of atopic dermatitis necessitating hospitalization (**Figure 1 A** and **Figure 2 A**). He was treated with a 10-day course of oral cephalexin, topical medications, and oral montelukast sodium. Therapy was also begun with inter-



Figure 1. Patient 1. A, Flare of atopic dermatitis on legs in March 2004. B, Improvement 7 months after institution of efalizumab therapy.

feron gamma at 25 $\mu\text{g}/\text{m}^2$ 3 times weekly. One month later, there was no improvement. The etanercept treatment was discontinued, and the interferon gamma dose was increased to 50 $\mu\text{g}/\text{m}^2$ per day with no subsequent improvement. In addition, the patient developed alopecia areata.

CASE 2

A 48-year-old woman presented in the spring of 2003 with a history of atopic dermatitis since childhood associated with extreme pruritus, impaired sleep, and a poor quality of life. On physical examination, she had diffuse lichenification and excoriations over her arms, legs, and trunk associated with hypopigmentary and hyperpigmentary changes. Given the clinical appearance and chronic course of the condition, 2 skin biopsies were performed to rule out cutaneous T-cell lymphoma. On histologic examination, both specimens demonstrated

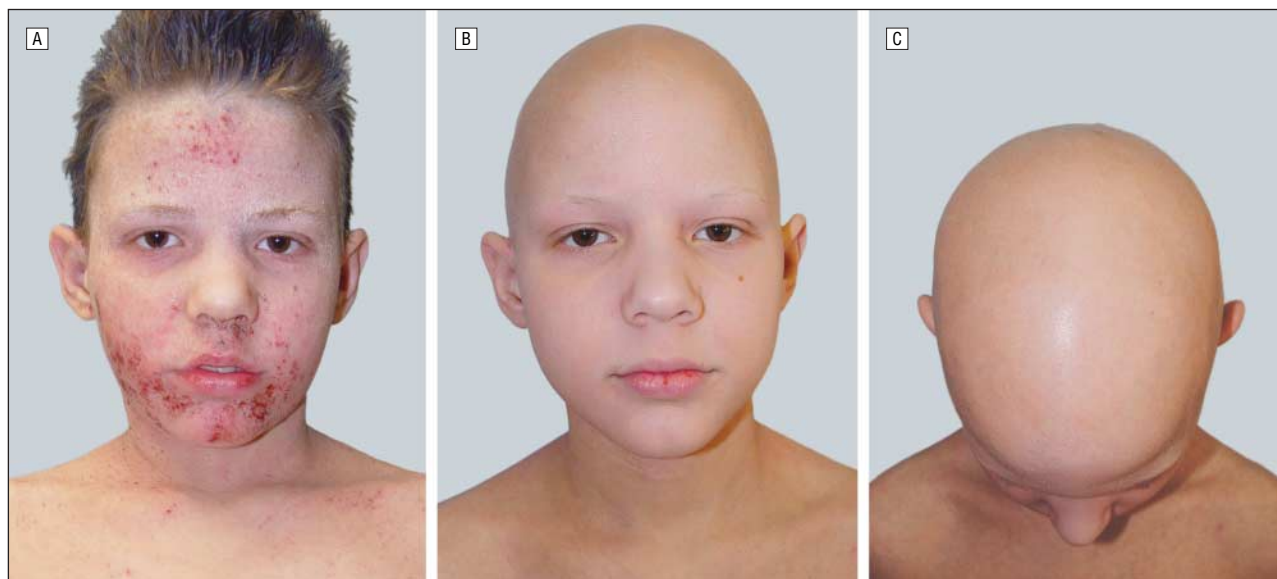


Figure 2. Patient 1. A, Flare of atopic dermatitis on face in March 2004. B and C, Clearance 7 months after institution of efalizumab therapy.

chronic spongiotic dermatitis. Over the first year, the patient was treated with a number of topical corticosteroids and 0.1% tacrolimus ointment, with little improvement in her condition. She declined UV-B therapy.

THERAPEUTIC CHALLENGE

Treatment of severe atopic dermatitis is challenging and often unsuccessful. Therapeutic options include a variety of topical and systemic immunosuppressants (corticosteroids, UV light, azathioprine, mycophenolate, and cyclosporine) or immunomodulators (interferon gamma and intravenous immunoglobulins). Limitations of these therapies include varying efficacy, limited accessibility, and potential for systemic toxic effects.

SOLUTION

Both of these patients were offered a trial of subcutaneous efalizumab treatment. By July 2004, patient 1 had experienced a flare of his atopic dermatitis, and his alopecia areata had progressed to totalis involvement. Weekly treatment with subcutaneous efalizumab was initiated with a 0.7-mg/kg loading dose followed by 1 mg/kg weekly doses. One month later, interferon gamma therapy was discontinued. During the next 3 months his eczema gradually improved.

On follow-up in December 2004, his atopic dermatitis was well controlled with infrequent use of topical medications. At his follow-up in February 2005, he reported complete discontinuation of topical therapy, and his skin was nearly clear of disease (Figure 1B and Figure 2B). His school performance and family and social relationships had also dramatically improved. Cetirizine treatment was discontinued, and plans were made to discontinue montelukast therapy if his disease remained controlled. After 19 months of efalizumab monotherapy, he had regrowth of eyebrows, eyelashes, and most scalp hair (**Figure 3**).

For patient 2, efalizumab treatment was initiated in May 2004, with a 0.7-mg/kg loading dose followed by weekly doses of 1 mg/kg. Over the next few months, she continued therapy with slow improvement. She received intermittent concomitant treatment with 0.1% tacrolimus ointment, 1% pimecrolimus cream, 0.025% desoximetasone ointment, and 25 mg of hydroxyzine hydrochloride at bedtime. By January 2005, the patient reported a substantial improvement in her condition over the last 2 months. On physical examination, she had no visible excoriations and a significant decrease in lichenification and pigmentary changes. She noted that this was the best control of her disease in almost 10 years. In fact, she noted that she had been on her first date in 7 years, now that the appearance of her skin was not an impediment to her social life.

COMMENT

Efalizumab is a humanized monoclonal antibody against the CD11a molecule. CD11a and CD18 are subunits of leukocyte function-associated antigen 1 (LFA-1), a T-cell surface molecule important in T-cell activation, T-cell migration into skin, and cytotoxic T-cell function. The interaction between LFA-1 on T cells and ICAM-1 (intercellular adhesion molecule 1) on antigen-presenting cells is an important costimulatory signal resulting in T-cell activation.¹ Located on endothelial cells, ICAM-1 also interacts with LFA-1 on circulating T cells, a necessary interaction for migration of T cells into inflamed skin. Efalizumab can therefore treat psoriasis by blocking T-cell migration into the skin and by preventing T-cell activation.² The blockade is reversible and does not deplete T cells.

Phase 3 trials with subcutaneous efalizumab have shown promising results in treatment of moderate to severe plaque psoriasis.³ The drug was granted US Food and Drug Administration approval in October 2003 with an indication for the treatment of chronic moderate to severe plaque psoriasis.



Figure 3. Patient 1. A, After 19 months of treatment with efalizumab monotherapy, he noted regrowth of eyebrows and eyelashes. B, Most of the scalp hair also regrew after 19 months of treatment.

Several immune effector cells have been investigated for their potential role in the pathogenesis of atopic dermatitis. Skin lesions in atopic dermatitis evolve as the result of complex interactions between IgE-bearing antigen presenting cells, T-cell activation, mast-cell degranulation, keratinocytes, eosinophils, and a combination of immediate and cellular immune responses. T-cell-mediated processes play an essential role in the pathogenesis of this condition.⁴

The role of T cells in atopic dermatitis has been demonstrated by the successful use of cyclosporine to treat this condition. Van Joost et al⁵ examined the modulation in the expression of immunologic markers in lesional skin. In this study 7 patients with severe and therapy-resistant atopic dermatitis underwent therapy with 5 mg/kg per day of cyclosporine for 6 weeks. After 2 weeks of therapy, a reduction of 60% in the disease severity and extent was observed. This reduction increased to 89% after 4 weeks and 90% after 6 weeks of therapy. The authors found that a statistically significant reduction in the number of activated T cells and in the number of cells expressing the interleukin 2 receptor (CD25) paralleled a marked improvement in the disease. These findings supported the view that the pathogenesis of atopic dermatitis is based on a T-cell-mediated immune inflammation.⁵

The role of T-cell-mediated inflammation in atopic dermatitis and efalizumab's mechanism of action supports the choice of this treatment for our patients. The product labeling for efalizumab includes cautions about a potential increased risk of infection and malignancy, but an increase in the risk of either of these conditions has not been clearly demonstrated in the phase 3 trials.^{3,6-8} There have been no opportunistic infections, no clinical signs of immunosuppression, and no hepatotoxic effects or nephrotoxic effects associated with the use of efalizumab in study subjects treated for

up to 3 years (unpublished data, Genentech Inc, South San Francisco, Calif, February 2005).¹ This lack of end-organ toxic effect and lack of demonstrated risk of immunosuppression differentiates efalizumab from cyclosporine and makes it an appealing long-term option for patients with severe atopic dermatitis.

In clinical trials, 14% of efalizumab-treated subjects abruptly withdrawn from treatment experienced an increase in the severity of their psoriasis to worse than it had been at baseline (rebound).⁶ The risk of this adverse event in atopic dermatitis is unclear. A further minor safety concern during efalizumab therapy is thrombocytopenia. During clinical trials for efalizumab, a small number of patients with psoriasis (8/2762; 0.3%) experienced reversible thrombocytopenia.⁶ The causal relationship between efalizumab therapy and thrombocytopenia is unknown, but the product labeling recommends that platelet counts be obtained monthly for the first 3 months of efalizumab treatment, and every 3 months thereafter.⁶

Our pediatric patient developed alopecia areata while undergoing interferon gamma treatment. Following efalizumab therapy, he had initial regrowth of a small hair tuft on the vertex of the scalp. He regrew his eyebrows and eyelashes and most of his scalp hair after 19 months of treatment. It is possible that this was a result of the T-cell modulation provided by efalizumab; alternatively, it may have been the result of spontaneous regrowth.

A pertinent clinical observation is that both patients experienced gradual rather than abrupt improvement over 3 to 6 months of efalizumab treatment. Our pediatric patient began to experience improvement after 2 months of therapy, with almost complete clearing by 6 months. The adult patient did not begin to show significant improvement until after 6 months of therapy. This gradual response may be attributable to the severity of their dis-

ease or to the time required for efalizumab to correct the pathophysiologic conditions. Further investigations of this drug in patients with atopic dermatitis will help to clarify the role of efalizumab in this condition.

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Submissions

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see Instructions for Authors). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (<http://manuscripts.archdermatol.com>).

Correction

Error in Byline. In the the Study by Menzies et al titled "The Performance of SolarScan: An Automated Dermoscopy Image Analysis Instrument for the Diagnosis of Primary Melanoma," published in the November 2005 issue of the ARCHIVES (2005;141:1388-1396), the name of the one of the authors was misspelled. The author's name is Alexandra Varol, B Med.