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Oral tacrolimus for severe recalcitrant atopic eczema

To the Editor:

The patient is a 19-year-old man who has had eczema his entire life, with generalized eczema, including his scalp, hands, and feet, developing within 1 month of birth. To date, he has not had asthma, rhinitis, or conjunctivitis. Exacerbations are not related to specific foods or allergen exposure, except for cat allergen, which causes severe pruritus and worsening eczema. Symptoms are also exacerbated by "weather changes" and sweating associated with physical activities. Swimming in a chlorinated pool relieves symptoms to some extent.

Before age 7 years, various treatment programs, such as coal tar, oatmeal baths, antibiotic therapy, and topical triamcinolone cream, resulted in no long-term relief. Various dust mite prevention programs, including the use of a special vacuum, hot-water clothes washing, covering mattresses and pillows, and removing carpets, did not result in improvement. About age 7 years, he began taking systemic glucocorticosteroids intermittently throughout each year for more than half of the year. His symp-

toms resulted in poor attendance during middle school, eventually necessitating home schooling during the last 3 years of high school.

He was first seen by Dr Lockey in May 1998. At that time, he had intractable pruritus and severe eczema covering his entire body. Laboratory studies revealed an IgE level of 4962 IU/mL (normal, 0-149 IU/mL), a RAST score to peanut of +4 and mite of +5 (class +1-+5), and positive prick-puncture test responses to a variety of different aeroallergens, including pollen (+4), dog (+3), dust mite (+4), cat (+2), and molds (+4) (+2 is defined as a wheal <3 mm with erythema of >20 mm, +3 as a wheal >3 mm with surrounding erythema, and +4 as a wheal with pseudopods and surrounding erythema). He was treated with prevention, topical glucocorticosteroids, hydroxyzine hydrochloride and then doxepin hydrochloride, lubricants, and eventually immunotherapy. The immunotherapy was discontinued after 1 year because it caused his atopic dermatitis to flare. By December 1998, he began taking prednisone every other day continuously, with periodic bursts and intermittent oral antibiotics for worsening eczema. Attempts to decrease the glucocorticosteroids resulted in exacerbations. He was given a diagnosis of osteopenia (total T score of 1.72) in 1999, for which he is being treated with alendronate.

In March 2000, he was consulted at National Jewish Medical and Research Center, Denver, Colorado, and started on a treatment regimen of high-dose prednisone, topical tacrolimus, 10 mg of montelukast daily, and hot-water baths, followed by full-body triamcinolone cream topped with wet wraps and a lubricant. This resulted in substantial improvement of his symptoms. He was tapered from prednisone and discharged taking 2 mg of prednisone daily with continuation of the same treatment program. Within 1 month of return to Florida, on the same regimen, the eczema symptoms returned to pretreatment levels. He once again began to have flares of eczema necessitating short bursts of prednisone (45-60 mg in divided doses daily), with maintenance at about 15 mg every other day. The increase in symptoms on return to Florida could be due to an increased allergen burden in the patient's home because of its tropical locale.

In May 2002, he began oral tacrolimus therapy. The dose was increased from 1 mg twice daily to 5 mg twice daily to achieve therapeutic levels, with resultant improvement in his pruritus and eczema and discontinuation of his oral prednisone by September 2002. The severe rash and lichenified skin has shown great improvement. His symptoms improved, and the systemic glucocorticosteroids were discontinued by September 2002. As of September 2002, he began to attend junior college and now rides his dirt bike outdoors, both activities that used to severely exacerbate his disease. He continues to do well as of mid-February 2003. He is more affable, has a higher energy level, and has lost approximately 14 pounds, which is attributed to a decrease in appetite. He has not required systemic glucocorticosteroids since they were discontinued.

Atopic dermatitis or eczema is a disease of the skin that results in significant physical and emotional morbidity. Chronic atopic dermatitis is characterized by means of lichenification of the skin with a hyperplastic epidermis, prominent hyperkeratosis, and minimal spongiosis. An increased number of IgE-bearing Langerhans cells, T_H1 cells, T_H2 cells, eosinophils, and mast cells with higher levels of the cytokines IL-4, IL-5, GM-CSF, IL-12, IL-13, and IFN- γ are present in the chronic disease.¹ GM-CSF is important in sustaining the function and survival of Langerhans cells, monocytes-macrophages, and eosinophils. There are increased numbers of IgE-bearing Langerhans cells that seem to be important in antigen presentation to T_H2 memory cells, as well as in causing differentiation of naive T_H0 cells to T_H2 cells. IgE binds to the high-affinity Fc ϵ RI receptors on Langerhans cells, facilitating antigen presentation. The level of binding has been correlated with serum IgE levels. Low levels of Fc ϵ RI expression on Langerhans cells are found in normal individuals and individuals with respiratory allergy, whereas high levels are present in atopic dermatitis.¹ Therefore the treatment modality must affect these different immunologic parameters to successfully treat atopic dermatitis.

Although various treatment modalities are used to treat atopic eczema, until recently, the only successful treatment for severe atopic dermatitis has been the use of systemic glucocorticosteroids or oral cyclosporin A, both of which can lead to considerable side effects. Topical tacrolimus is at least as effective as topical glucocorticosteroids, without the concomitant side effects.² Tacrolimus (FK506) interferes with intracellular signaling of T cells by binding to FK506-binding protein and thereby inhibiting the phosphatase activity of calcineurin. This prevents dephosphorylation of nuclear factor of activated T-cell protein, blocking migration of this protein into the T-cell nucleus and preventing the transcription of IL-2, IL-3, IL-4, TNF- α , IFN- γ , and GM-CSF.³ Panhans-Gros et al⁴ have also shown that tacrolimus decreases Fc ϵ RI expression on Langerhans cells. Hauk and Leung⁵ demonstrated that tacrolimus blocks *Staphylococcus aureus* superantigen-induced T-cell activation, which glucocorticosteroids do not affect. Thus tacrolimus has been shown to target multiple links in the pathogenesis of atopic dermatitis.

Systemic tacrolimus has been successfully used for patients undergoing both kidney and liver transplantation. The principal side effects include tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction. Hyperkalemia, hypomagnesemia, hypophosphatemia, and diabetes mellitus have been reported. There is also an increased risk of non-Hodgkin lymphoma and skin malignancies. Routine tests and laboratory studies should include measurements of the following: blood pressure, serum blood urea nitrogen, creatinine, potassium, and glucose. Klein et al,⁶ in a study on healthy subjects, showed that tacrolimus had no effect on renal function and blood pressure over a 2-week period, whereas cyclosporine, another treatment for severe refractory der-

matitis, caused a statistically significant decrease in renal function and increase in blood pressure.

There are numerous reports showing the efficacy of topical tacrolimus for treatment of atopic dermatitis; however, there are no reports demonstrating the efficacy of systemic tacrolimus. Treatment with topical tacrolimus failed in our patient, and therefore he was started on systemic tacrolimus treatment because of the debilitating effects of the continued use of glucocorticosteroids. The patient greatly prefers tacrolimus therapy over glucocorticosteroid therapy. While taking systemic tacrolimus, his eczema has improved at least 80%, he has stopped taking systemic glucocorticosteroids, and he is now able to attend college and participate in many activities appropriate for his age. Double-blind, randomized controlled trials are necessary to show that tacrolimus is an effective and safe treatment for severe, refractory, steroid-dependent atopic dermatitis and that the risk/benefit ratio is better than that with long-term use of oral glucocorticosteroids and cyclosporine. Such therapy should be the last option for individuals who have exhausted all other forms of therapy.

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Anaphylaxis caused by skin prick testing with aeroallergens: Case report and evaluation of the risk in Italian allergy services

To the Editor:

Skin prick testing (SPT) is the first-line diagnostic method of demonstrating an IgE-mediated hypersensitivity, especially for inhalant allergens. The number of allergenic products for diagnosis has increased in the last years, and their quality has improved as well. Now we have commercial extracts derived from many sources, including mites, pollens, stinging insects, domestic animals, foods, antibiotics, latex, and other less common allergens.

SPT is generally considered a safe procedure. The frequency of systemic reactions caused by extracts of