The Safety and Efficacy of Tacrolimus Therapy in Patients Younger Than 2 Years With Atopic Dermatitis

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Background: Atopic dermatitis (AD) is a common inflammatory skin disease that affects adults and children. Tacrolimus (FK 506) ointment is a recently developed topical immunomodulator that has been approved for use in patients with AD who are older than 2 years. Concern regarding potential systemic toxic effects has limited treatment options for children younger than 2 years. We wanted to determine whether topical tacrolimus therapy is safe and effective in patients with AD who are younger than 2 years.

Observations: Twelve patients fitting our criteria who were treated with tacrolimus ointment were identified by retrospective chart review. Data collected included severity of AD, response to therapy, concentration and blood levels of tacrolimus, any adverse effects, and results of laboratory tests, including complete blood cell count, liver function tests, and serum chemistry profiles. As the review was retrospective, baseline laboratory studies were not performed. All the patients experienced improvement in their symptoms, and no significant adverse effects were noted. Nine patients used 0.03% tacrolimus ointment; 3 used 0.1%. All patients had blood levels of tacrolimus that were less than 1.5 ng/mL. There was no apparent difference in tacrolimus levels in patients whether they were treated with 0.03% or 0.1% ointment. Four patients had elevated platelet counts.

Conclusion: Tacrolimus ointment appears to be effective and safe in the treatment of AD in children younger than 2 years.

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A TOPIC DERMATITIS (AD) is a chronic relapsing dermatitis characterized by intense pruritus that occurs in patients with a personal or family history of atopy. It affects up to 20% of the population, and its incidence is on the rise. More than 80% of patients experience disease onset when they are younger than 5 years. First-line therapy for AD is preventive, ie, avoidance of precipitating agents. Topical steroids have been the mainstay of therapy, but their adverse effects are numerous, and sufficient absorption can occur such that the risks of systemic steroids may be incurred. Patients with the worst disease may be treated with UV-light therapy (broadband or narrow band UV-B or psoralen plus UV-A), interferon gamma, or immunosuppressive agents such as azathioprine, mycophenolate mofetil, cyclosporine, and systemic corticosteroids.

Compared with older children, infants have an increased body surface area–weight ratio, increasing the risk of systemic absorption with the use of topical agents as well as creating concern about the extrapolation of data obtained in children for use in infants. Because of the limitations of topical steroid therapy and the difficulties inherent in treating children and infants, there has been a need for the development of new topical nonsteroidal therapies to treat patients with AD. Tacrolimus and pimecrolimus are 2 new topical immunomodulating agents that have been developed for the treatment of AD.2,3

Clinical trials using topical tacrolimus therapy in children aged 2 to 15 years with moderate to severe AD have demonstrated significant improvement with both 0.1% and 0.03% ointments with minimal adverse effects.2,3 As the use of topical tacrolimus has not previously been reported in children younger than 2 years, we report our retrospective results with tacrolimus therapy in 12 patients with AD who were younger than 2 years.
In this retrospective study, we describe 12 patients with AD who were younger than 2 years and who were treated with topical tacrolimus. These patients all experienced significant improvement in their AD, and none experienced any adverse outcomes. Furthermore, all patients had tacrolimus levels that were below the limits of quantification, suggesting that there is no increased risk of systemic tacrolimus absorption in children younger than 2 years. We recognize that the condition of most of the patients was much improved by the time blood levels were drawn, thereby decreasing their tendency to absorb the tacrolimus and likely reflecting lower levels than might have been measured, eg, 1 week after treatment initiation. The finding of an elevated platelet count in 4 of the 12 patients in this small study is consistent with a previous report of thrombocytosis in patients with AD and suggests that an elevated platelet count may be present in patients with chronic inflammatory diseases.  

It is noted, however, that baseline platelet levels were not determined in any of our patients. Future prospective studies are necessary to elucidate any definitive relationship between AD and thrombocytosis. The lack of measurable tacrolimus levels as well as any toxic effects in these infants suggests that tacrolimus may be an appropriate therapy for children who are younger than 2 years. Given our small sample size and the limitations of a retrospective study, a placebo-controlled, randomized study would be necessary to confirm the safety and efficacy of tacrolimus therapy in children who are younger than 2 years. An open-label trial would allow a more formal pharmacokinetic analysis of topical tacrolimus therapy, enabling a measurement of body surface area, quantification of the amount of tacrolimus used, and correlation of the timing of blood draws with the application of tacrolimus.

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A retrospective chart review at the Dermatology Department of the University Hospitals of Cleveland, Cleveland, Ohio, was performed to find patients younger than 2 years with AD who had been seen within the past year. It included patients with moderate to severe AD who had been treated with tacrolimus ointment. Data collected include disease severity before and after treatment, patient age, age at treatment initiation, length of treatment, measurement of tacrolimus levels, results of liver function tests, serum chemistry profiles, complete blood cell counts, and adverse effects (reported by patients, parents, or physicians). Disease severity (either mild, moderate, or severe) was determined by means of the particular clinician’s documentation before and after therapy. In most cases, the severity of disease after treatment was determined at the patient’s follow-up visit, while the patient was still receiving therapy. The tacrolimus blood levels determined at the follow-up visit were trough levels. The patients were instructed to discontinue use of the drug 1 day before undergoing phlebotomy or to avoid using the medication in the antecubital spaces for that period to avoid contamination. Again, as the review was retrospective, baseline laboratory studies were not performed. The institutional review board of the University Hospitals of Cleveland approved the protocol.

All 12 patients experienced improvement in their AD, and no significant adverse effects were reported (Table). The tacrolimus blood levels, which were measured at a minimum of 1 month after the initiation of tacrolimus treatment, were less than 1.5 ng/mL (the lower limit of quantification for the laboratory used) in all patients, regardless of tacrolimus concentration (Table). Trough levels of tacrolimus responsible for immunosuppression are 5 to 20 ng/mL. The results of liver function tests and the serum chemistry profiles were unremarkable. Four patients had elevated platelet counts, ranging from 460 to 702 × 10^9/L (reference range, 150-400 × 10^9/L). Two infants had possible burning (as noted by crying upon application), which subsided after 2 days.

**METHODS**

**RESULTS**

**COMMENT**

The tacrolimus level was less than 1.5 ng/mL in all patients.
This study was presented as a poster at the annual meeting of the Society for Pediatric Dermatology; July 17-20, 2002; Annapolis, Md.

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REFERENCES


ARCHIVES Web Quiz Winner

Congratulations to the winner of our June quiz, Prachaya Nitichaikulvatana, International Trainee, Boston University Medical Center, Boston, Mass. The correct answer to our June challenge was eosinophilic cellulitis. For a complete discussion of this case, see the Off-Center Fold section in the July ARCHIVES (Segal JM, Rao C, Shea CR, Prose NS. Recurrent vesicles, papules, and plaques in a teenager. Arch Dermatol. 2003;139:933-938).

Be sure to visit the Archives of Dermatology World Wide Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the The Art of JAMA II.