

Tacrolimus Ointment in the Treatment of Eyelid Dermatitis

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The safety and efficacy of tacrolimus ointment 0.1% (Protopic®) in the treatment of atopic dermatitis of the eyelids were assessed in an open-label clinical trial of 21 patients with moderate to severe eyelid dermatitis. Of those 21 patients, 20 received study drug and were followed. Patients applied tacrolimus ointment 0.1% twice daily for 8 weeks and were followed for 2 additional weeks after the last day of treatment. Complete eye examinations were conducted throughout the study. Efficacy was assessed through the investigator's evaluation of the patients' individual signs and symptoms of eyelid dermatitis and the physician global assessment (PGA) of eyelid clinical response.

Improvement in the investigator's evaluation of the signs and symptoms of eyelid dermatitis was observed during the study. A total of 80% of patients (16/20) experienced marked improvement or better in PGA at 8 weeks. Adverse events were limited to local burning and itching after the first few applications of study medication. Of the 20 patients, 12 reported burning (60%), and 5 reported itching (25%). There was no statistically significant increase in intraocular pressure (IOP) during the study compared with baseline. In addition, none of the

patients developed cataracts or glaucoma during the study. In summary, tacrolimus ointment 0.1% may be a safe and effective treatment option for patients with moderate to severe eyelid dermatitis.

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Localization of atopic dermatitis on the eyelids is common, with an incidence ranging from 8% to 23%.¹⁻³ Until now, the main treatment for eyelid dermatitis has been topical application of corticosteroids. However, use of corticosteroids around the eyes has been associated with the development of glaucoma and cataracts, as well as local cutaneous side effects, such as atrophy and formation of telangiectasia.⁴⁻¹⁴

Tacrolimus ointment, a nonsteroidal topical agent, represents a new therapeutic option for patients with eyelid dermatitis. Tacrolimus is a macrolide immunosuppressant that targets calcineurin and plays an essential role in the intracellular signal transduction pathway leading to the activation of genes encoding cytokines, which have been implicated in the pathogenesis of atopic dermatitis.¹⁵ The present study was designed to assess the safety and efficacy of tacrolimus ointment 0.1% in the treatment of moderate to severe eyelid dermatitis in adult patients.

Methods

The study was a phase 2, open-label, single-arm, single-center clinical trial of tacrolimus ointment in 21 patients with moderate to severe atopic dermatitis of the eyelids. Subjects with glaucoma, cataracts, or elevated intraocular pressure (IOP) were excluded. All patients gave informed consent to participate in the study, and the protocol was approved by the appropriate institutional review board. Patients were not allowed to use topical therapies or systemic corticosteroids during the study. Patients applied tacrolimus ointment 0.1% twice daily to the eyelids for 8 weeks and were followed for 2 additional

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weeks after the last day of treatment. Clinical evaluations were conducted at baseline, days 8, 15, 29, 43, 57 (end of treatment [EOT]), and 71 (end of study).

The primary efficacy parameter was the investigator's evaluation of the patients' individual signs and symptoms of eyelid dermatitis. The clinical signs of erythema, lichenification, pruritus, scaling/dryness, and oozing/crusting were rated using the following scale: 0=absent, 1=mild, 2=moderate, and 3=severe, with allowable half values. Patients had to have a total score of at least 10 out of 15 to meet inclusion criteria. The change in score from baseline to EOT for each of the signs and symptoms was calculated and statistically compared using the Wilcoxon signed rank test. Secondary efficacy assessments were the physician global assessment (PGA) of the clinical response and the patient's evaluation of the eyelid dermatitis. The PGA was based on the following scale: clearance of signs and symptoms (100%), excellent improvement (90%–99%), marked improvement (75%–89%), moderate improvement (50%–74%), slight improvement (30%–49%), no appreciable improvement (0%–29%), and worsening of signs and symptoms. At baseline and EOT, patients also completed self-administered questionnaires evaluating the treatment effects and cosmetic acceptability.

For safety, eye examinations, including slitlamp, fundus, and IOP measurements, were performed at baseline and EOT. For each patient, IOP at EOT was then compared with the value at baseline to assess whether there was any significant increase; the mean change from baseline at EOT, as reported in the Results section, is the upward change in value from baseline to EOT (IOP at day 57 minus IOP at baseline). Statistical significance was based on a *P* value of less than 0.05. Additional IOP measurements were conducted at days 8 and 29. Patients were followed for signs of skin atrophy, striae, and telangiectasia on the eyelids, as well as for other adverse events at all study visits.

Results

A total of 21 patients were enrolled in the study. One patient was excluded after enrollment based on an abnormal baseline eye examination that revealed cataract disease. Although the patient received study medication, he was not followed in the study. Of the 20 patients who received the study drug and were followed, 12 (60%) were female. Fourteen (70%) of the patients were white, 3 (15%) were black, and 3 (15%) were Asian. The median age was 45 years (range, 21–68 years). All patients had atopic dermatitis of the eyelids. Two patients had a family history of glaucoma.

A total of 4 patients withdrew from the study prematurely, including 3 patients who discontinued

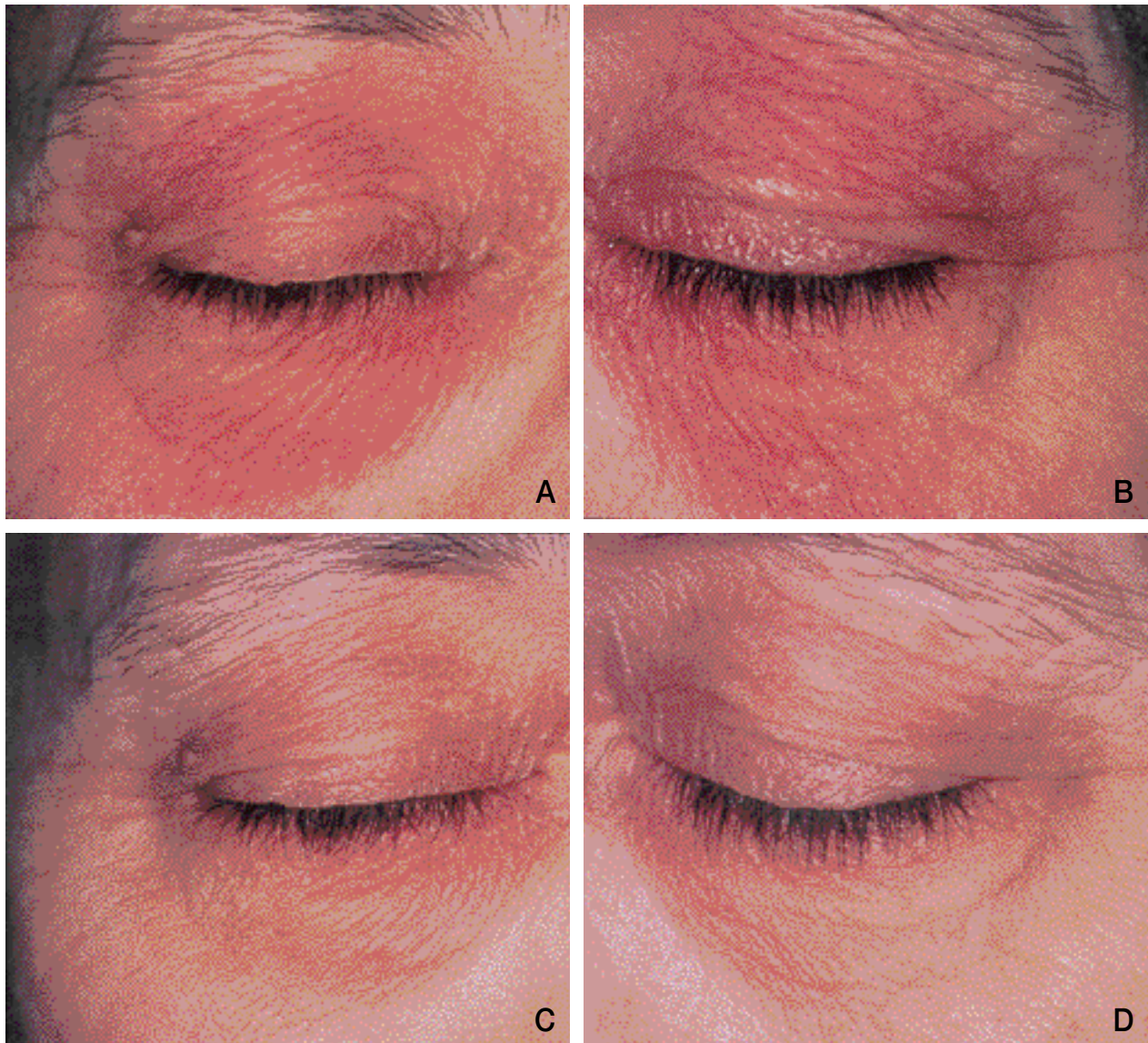
because of the adverse events of itching and burning and 1 patient who was withdrawn from the study because of noncompliance. Sixteen patients completed the study according to the protocol.

In all, 15 patients experienced at least one adverse event on the eyelid. The most common application site adverse events were burning (60%; 12/20) and itching (25%; 5/20) on the eyelid, which occurred during the first few days of application. Most episodes were mild in severity, lasted about 15 minutes, and resolved on their own without treatment. There were no reports of change in vision. Other application site adverse events included tearing (10%; 2/20), pain (10%; 2/20), swelling (5%; 1/20), and lower lid retraction (5%; 1/20). A non-application site adverse event, flu-like symptoms, was reported in one patient (5%) and was considered to be unrelated to tacrolimus ointment. None of the patients developed atrophy, telangiectasia, or striae during the study.

There was no statistically significant increase in IOP measurements in either the right eye or the left eye during the study based on the paired *t* test. At day 57 (EOT), the mean change from baseline was 0.75 mm Hg (standard, 1.77; *P*=.11; 95% CI, –1.14–2.63). The mean difference in the left eye of 0.125 mm Hg (standard, 2.68; *P*=.85; 95% CI, –2.74–2.99). The sample size in our study had approximately 80% power to detect a mean difference in IOP of 1.5 mm Hg from baseline. No abnormalities on eye examination developed in any patient during the course of the study.

Patients continued to improve in primary efficacy variables as the study progressed (Figure). In the PGA of the individual signs of erythema, lichenification, pruritus, and scaling/dryness, the average pretreatment scores for each of these were between 2 (moderate) and 3 (severe)(Table). By day 57 (EOT), mean scores were between 0 (absent) and 1 (mild), with each of these signs showing statistically significant improvements from baseline (*P*<.001). For the sign of oozing/crusting, mean baseline scores were about 0.40, and improvements by EOT were close to 0 (*P*<.15).

Improvement based on the PGA was seen at the first follow-up visit, which occurred 8 days after the start of treatment. Twelve patients experienced at least a slight improvement, and 5 had no appreciable improvement at this visit. At day 29, 3 patients were evaluated as completely clear, 9 as excellent improvement, 2 as marked improvement, 1 as moderate improvement, and 1 as slight improvement. All patients were evaluated as showing some degree of improvement at day 29. At day 43, 7 patients were evaluated as cleared of their eyelid dermatitis,



Patient with eyelid dermatitis at baseline (A and B) and at day 15 of treatment with tacrolimus (C and D).

and 9 were evaluated as having excellent improvement. By EOT, 12 patients were noted as being completely cleared, and 4 as having excellent improvement. A follow-up visit was scheduled 2 weeks after stopping tacrolimus ointment. At this visit on day 71, 9 patients still had complete clearance, while 6 continued to report excellent improvement. One patient was evaluated as having marked improvement. In summary, by day 57/EOT, the percentage of patients with excellent improvement or better was 100%, and including the 4 patients who prematurely withdrew but still had EOT evaluations, the percentage was 80% (95% CI, 62%–98%).

At EOT, all patients were asked whether they would continue to use the ointment if they had the

choice. Fourteen patients (70%) indicated a positive response, and 6 (30%) indicated a negative response.

Comment

The treatment of atopic dermatitis throughout the years has been frustrating, with few safe and effective long-term options. Topical corticosteroids have been the mainstay of treatment; however, the use of corticosteroids is associated with multiple side effects, including atrophy, telangiectasia, striae, acne, folliculitis, infections, glaucoma, and cataracts, among others.¹⁶⁻¹⁹ Such concerns underscore the long-term use of topical corticosteroids. Presently, there are other options that appear to be just as effective, yet safer. While it is possible that

Physician Global Assessment of Individual Signs of Eyelid Dermatitis*

Signs	Right Eyelid (n=20)			Left Eyelid (n=20)		
	Mean	Standard	Change in Mean From Baseline	Mean	Standard	Change in Mean From Baseline
Erythema						
Day 1	2.40	0.42		2.40	0.42	
Day 57	0.43	0.91	-1.97 [†]	0.43	0.91	-1.97 [†]
Lichenification						
Day 1	1.83	0.57		1.83	0.57	
Day 57	0.43	0.80	-1.40 [†]	0.43	0.80	-1.40 [†]
Pruritus						
Day 1	2.75	0.38		2.75	0.38	
Day 57	0.53	0.95	-2.22 [†]	0.53	0.95	-2.22 [†]
Scaling/dryness						
Day 1	2.83	0.34		2.78	0.38	
Day 57	0.50	1.01	-2.33 [†]	0.50	1.01	-2.28 [†]
Oozing/crusting						
Day 1	0.40	0.68		0.33	0.80	
Day 57	0.05	0.22	-0.35 [‡]	0.00	0.00	-0.33 [§]

*0=absent, 1=mild, 2=moderate, 3=severe.
[†]P<.001
[‡]P=.0625
[§]P=.1250

topical corticosteroids could be applied to most patients for 8 weeks without causing elevated IOP, we have supported the safety of applying topical tacrolimus to the eyelids for that period.

Tacrolimus ointment 0.1% also was shown to be effective based on the PGA at EOT. Twelve of the 16 patients who completed the study had complete clearance of their eyelid dermatitis. Most patients maintained their improvement at the 2-week follow-up visit. Most adverse events associated with tacrolimus ointment were mild in intensity, occurred during the first few days of application, and then subsequently resolved without discontinuation of treatment. These included burning and itching. Notably, there were no reports of skin atrophy, telangiectasia, and striae during the course of the study. None of the patients developed cataracts, glaucoma, or increased IOP during the course of the study.

There were several limitations to our study (eg, the small, open-label, uncontrolled nature of the study) that should be considered when examining

our positive conclusions. Perhaps future research should readdress these issues in larger controlled studies. It may be worthwhile to compare tacrolimus ointment with topical corticosteroids in the treatment of eyelid dermatitis. In addition, it is difficult to control intraobserver reproducibility of qualitative assessments in the study.

In other clinical trials, tacrolimus has had promising results in patients with atopic dermatitis. Early phase-1 and phase-2 clinical studies revealed that topical tacrolimus is minimally absorbed into the systemic circulation, even after repeated application.²⁰⁻²² The safety and efficacy of tacrolimus have been supported by this study and other clinical studies.^{20,23-30} A significant reduction of atopic dermatitis was seen in most patients treated with tacrolimus ointment. The most common adverse events were transient burning and pruritus at the site of application, which tended to occur during the first few days of treatment; however, few subjects discontinued use because of these events. Long-term safety and efficacy studies also

have been conducted with positive results. Tacrolimus ointment 0.1% can be used daily up to one year without increasing the risk for various adverse events and without losing effectiveness in pediatric and adult patients with atopic dermatitis.²⁹⁻³⁰ Tacrolimus also has been shown to have a beneficial effect on quality of life in pediatric and adult patients with atopic dermatitis.³¹ This included both mental health and physical parameters, such as feelings, sleep, daily activities, and working or studying.

In conclusion, these results demonstrate that tacrolimus ointment 0.1% may be a safe and effective nonsteroidal alternative in the treatment of moderate to severe eyelid dermatitis. Further large-scale controlled studies are needed to support these conclusions.

REFERENCES

- Bos JD, Smitt JHS. Atopic dermatitis. *J Eur Acad Dermatol Venereol.* 1996;7:101-114.
- Boguniewicz M, Leung DY. New concepts in atopic dermatitis. *Compr Ther.* 1996;22:144-151.
- Beltrani V. The clinical manifestation of atopic dermatitis. In: Leung DYM, ed. *Atopic Dermatitis: From Pathogenesis to Treatment.* Austin, Tx: RG Landes Co; 1996;1:14-15, 26-27.
- Brodell RT, O'Brien MJ Jr. Topical corticosteroid-induced acne. three treatment strategies to break the 'addiction' cycle. *Postgrad Med.* 1999;106:225-226, 229.
- Chaffman MO. Topical corticosteroids: a review of properties and principles in therapeutic use. *Nurse Pract Forum.* 1999;10:95-105.
- Fukaya M. Why do patients with atopic dermatitis refuse to apply topical corticosteroids? *Dermatology.* 2000;201:242-245.
- Hanifin JM, Chan S. Biochemical and immunologic mechanisms in atopic dermatitis: new targets for emerging therapies. *J Am Acad Dermatol.* 1999;41:72-77.
- Hanifin JM. Atopic dermatitis in infants and pediatric patients. *Pediatr Clin North Am.* 1991;38:763-789.
- Hoffmann K, Auer T, Stucker M, et al. Comparison of skin atrophy and vasoconstriction due to mometasone furoate, methylprednisolone and hydrocortisone. *J Eur Acad Dermatol Venereol.* 1998;10:137-142.
- McLean CJ, Lobo RF, Brazier DJ. Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment [letter]. *Lancet.* 1995;345:330.
- Morales J, Good D. Permanent glaucomatous visual loss after photorefractive keratectomy. *J Cataract Refract Surg.* 1998;24:715-718.
- Piacquadio DJ. Topical corticosteroids in clinical practice: focus on fluticasone propionate. *Cutis.* 1996;57(suppl 2):4-9.
- Rapaport MJ, Rapaport V. Prolonged erythema after facial laser resurfacing or phenol peel secondary to corticosteroid addiction. *Dermatol Surg.* 1999;25:781-785.
- Trozak DJ. Topical corticosteroid therapy in psoriasis vulgaris: update and new strategies. *Cutis.* 1999;64:315-318.
- Bekersky I, Fitzsimmons W, Tanase A, et al. Nonclinical and early clinical development of tacrolimus ointment for the treatment of atopic dermatitis. *J Am Acad Dermatol.* 2001;44:S17-S27.
- Mills CM, Marks R. Side effects of topical glucocorticoids. *Curr Probl Dermatol.* 1993;21:122-131.
- Takeda K, Arase S, Takahashi S. Side effects of topical corticosteroids and their prevention. *Drugs.* 1988;36(suppl 5):15-23.
- Coskey RJ. Adverse effects of corticosteroids, I: topical and intralesional. *Clin Dermatol.* 1986;4:155-160.
- Cooper TW, Eisen AZ. The cutaneous effects of glucocorticoids. *Adv Exp Med Biol.* 1984;171:73-80.
- Alaiti S, Kang S, Fiedler VC, et al. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. *J Am Acad Dermatol.* 1998;38:69-76.
- Kawashima M, Harada S, Tamaki K, et al. A safety study of FK 506 ointment in patients with atopic dermatitis. *J Clin Ther Med.* 1997;13:1483-1492.
- Kawashima M, Nakagawa H, Ohtsuki M, et al. Tacrolimus concentrations in blood during topical treatment of atopic dermatitis [letter]. *Lancet.* 1996;348:1240-1241.
- Boguniewicz M, Fiedler VC, Raimer S, et al. A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. *J Allergy Clin Immunol.* 1998;102:637-644.
- Ruzicka T, Bieber T, Schopf E, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. *N Engl J Med.* 1997;337:816-821.
- Nakagawa H, Etoh T, Ishibashi Y, et al. Tacrolimus ointment for atopic dermatitis [letter]. *Lancet.* 1994;344:883.
- Hanifin JM, Ling MR, Langley R, et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol.* 2001;44:S28-S38.
- Soter NA, Fleischer AB, Webster GF, et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. *J Am Acad Dermatol.* 2001;44:S39-S46.
- Paller A, Eichenfield LF, Leung DYM, et al, and the Tacrolimus Ointment Study Group. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol.* 2001;44:S47-S57.
- Reitamo S, Wollenberg A, Schopf E, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol.* 2000;136:999-1006.
- Kang S, Lucky AW, Pariser D, et al. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *J Am Acad Dermatol.* 2001;44:S58-S64.
- Drake L, Prendergast M, Maher R, et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *J Am Acad Dermatol.* 2001;44:S65-S72.