

Long-term Follow-up of Tacrolimus Ointment for Treatment of Atopic Keratoconjunctivitis

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- **PURPOSE:** To evaluate the long-term clinical outcomes of 0.1% tacrolimus dermatologic ointment (Protopic) in cases of refractory atopic keratoconjunctivitis (AKC).

- **DESIGN:** Prospective, nonrandomized, noncontrolled case series.

- **METHODS:** Twenty-two eyes from 11 patients with severe AKC who were treated with 0.1% tacrolimus ointment were followed prospectively. The mean age of the patients was 32.27 ± 12.7 years (range, 19–61 years). Each patient completed a follow-up period of at least 48 months, during which the signs and symptoms of AKC were assessed. Changes in the total scores of signs and symptoms from baseline were recorded at each visit, and the main outcome measure was the clinical response to topical tacrolimus treatment.

- **RESULTS:** Dramatic improvements in clinical signs and symptoms were achieved 1 week after starting topical tacrolimus treatment, and complete clinical resolution was observed in almost all patients 6 weeks after starting treatment. Treatment was gradually reduced, with increasing intervals between applications. Eight patients remained asymptomatic for up to 3 years, although recurrence occurred in 3 patients who attempted to discontinue treatment. All patients complained of a mild burning sensation upon application of the ointment. No additional medications were required to provide relief, and no patient discontinued treatment because of adverse drug effects. No drug-related ocular complications were encountered, and no significant changes in visual acuity or refraction were documented.

- **CONCLUSIONS:** Tacrolimus dermatologic ointment is a potentially safe and effective treatment for AKC cases refractory to standard treatment and may substitute for steroid treatments aimed at controlling disease activity. (*Am J Ophthalmol* 2014;157:280–286. © 2014 by Elsevier Inc. All rights reserved.)

ATOPIC KERATOCONJUNCTIVITIS (AKC) IS A CHRONIC atopic disease of the conjunctiva. It is the most serious type of allergic conjunctival disease because of the associated corneal and lenticular complications. In

severe cases, subepithelial fibrosis of the conjunctiva, fornix shortening, symblepharon, corneal ulceration and neovascularization, and cataracts may occur.¹ Atopic dermatitis is considered the most common systemic association. Symptoms of AKC include itching, burning, photophobia, and foreign body sensation, and the clinical signs include eczematous lid changes, conjunctival injection, edema, papillae on the upper tarsal conjunctiva, and corneal punctate erosions. Antihistamines or mast cell stabilizers are often insufficient to control AKC; therefore, the addition of steroids may be required to give patients symptomatic relief. However, the side effects of these steroids include cataracts, glaucoma, herpetic keratitis, eyelid skin atrophy, and depigmentation.² In addition, immunosuppressive medications, such as steroid-sparing agents, have been introduced to relieve patient symptoms, reduce disease morbidity, and avoid the serious side effects of steroids. Topical cyclosporine is effective but can result in an intense stinging sensation with topical application, leading to poor compliance.³ Therefore, although 0.05% cyclosporine emulsion has been shown to be effective for use in AKC patients, its clinical efficacy was not sufficient in some steroid-dependent cases.^{4,5}

Tacrolimus (formerly FK-506) is a nonsteroidal, strong immunosuppressant isolated from *Streptomyces tsukubaensis*⁶ and demonstrates a much higher potency than cyclosporine (up to 100 times).^{7–10} Tacrolimus suppresses T-cell activation, T helper cell-mediated responses, B-cell proliferation, and cytokine release, especially that of interleukin 2. This drug acts by forming a complex with its cytosol partner FK506-binding protein 12, which also binds calcineurin. As a result, both calcineurin inhibitors (CIs) inhibit the phosphatase-controlled translocation of nuclear factor of activated T cells (NFAT) into the nucleus and prevent the induction of cytokines and expression of their receptors, which helps to prevent the activation and proliferation of lymphocytes and other immune cells.¹¹ Eosinophil cationic protein (ECP), which is released from the secretory granules of eosinophils upon activation, has been shown to play an important role in the pathogenesis of allergic conjunctivitis; for example, tear ECP levels in allergic patients were found to be linked to the severity of clinical disease.^{12,13} Although systemic tacrolimus has been used to treat allergic eye disease,¹⁴ there is no commercially available ophthalmic preparation for tacrolimus. Therefore, dermatologic tacrolimus ointment has been used instead. Previous studies have reported improvements in the symptoms of conjunctivitis, without significant side effects, following treatment with tacrolimus

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ointment in atopic blepharoconjunctivitis.^{15–18} Topical tacrolimus ointment (0.02%-0.1%) has also been used to treat giant papillary conjunctivitis, AKC, and vernal keratoconjunctivitis (VKC),^{19–26} with good results. Furthermore, a 0.1% tacrolimus ophthalmic suspension has been used for the treatment of AKC and VKC with only 4 weeks of follow-up.²⁴ The purpose of this study was to evaluate the long-term clinical outcomes with the use of tacrolimus ointment for refractory AKC.

METHODS

THIS PROSPECTIVE, NONRANDOMIZED, NONCONTROLLED case series included 22 eyes from 11 patients with active AKC who were refractory to conventional treatments. The Institutional Review Board of King Khalid University in Abha, Saudi Arabia, approved the study protocol. Patients were recruited from Abha Private Hospital and Aseer Central Hospital after written informed consent was obtained to participate in this study.

Atopic keratoconjunctivitis was diagnosed with a typical history including chronic, bilateral itching, redness, and signs of thickened scaly lid conjunctival hyperemia; papillae on the upper tarsal conjunctiva; and corneal erosions. All of the included patients were steroid dependent, and their diseases were active despite treatment with cyclosporine as well as conventional treatments, such as antihistamines, mast cell stabilizers, and topical nonsteroidal anti-inflammatory medications. The patients were asked to discontinue all other medications, including topical or systemic immunosuppressive medications, 1 week before beginning treatment with tacrolimus ointment. The exclusion criteria consisted of coexisting conjunctival disorders, chemical injury, Stevens-Johnson syndrome, corneal diseases, uveitis, ocular infections, contact lens use, a history of using systemic nonsteroidal anti-inflammatory medications or immunosuppressive drugs, and ocular surgery within the previous 3 months.

Complete ophthalmic examinations, including the assessment of best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy, fluorescein staining, funduscopy, and applanation tonometry, were conducted. Prior to the initiation of the study, the advantages and disadvantages of the treatment were explained to the patients. All patients with severe AKC were instructed to apply tacrolimus 0.1% dermatologic ointment (Protopic; Astellas Pharma Inc., Northbrook, Illinois, USA) into the inferior conjunctival fornix of each eye once daily for 1 week followed by weekly tapering (ie, every other day for 1 week, twice a week for 1 week, and once a week afterwards). The patients with moderate AKC were advised to use the tacrolimus ointment once every other day for 1 week, tapering to twice a week in the following week and once a week thereafter. The dosing for patients with mild AKC was twice a week for the first week and then

TABLE 1. Clinical Grading Scale for Atopic Keratoconjunctivitis

Sign	Score	Definition
Conjunctival hyperemia	3	Diffuse dilated blood vessels over the entire bulbar conjunctiva
	2	Dilation of many vessels
	1	Dilation of few vessels
	0	None
Lid thickening and/or scales	3	Severe
	2	Moderate
	1	Mild
	0	None
Papillae	3	Papillae size: more than 0.3 mm
	2	Papillae size: 0.2-0.3 mm
	1	Papillae size: less than 0.2 mm
	0	None
Superficial punctate keratopathy	3	Total corneal surface
	2	More than half corneal surface
	1	Less than half corneal surface
	0	None

once a week thereafter. During treatment, patients returned for evaluation after 1 week, 4 weeks, and 6 weeks, and every 6 months thereafter. The main outcome measures were graded according to the clinical severity of disease at each visit and included symptoms of itching or redness, foreign body sensation, signs of lid thickening, conjunctival hyperemia, the presence of papillary hypertrophy of the superior tarsal conjunctiva, and superficial punctate keratopathy. The patients' signs and symptoms were graded on a 4-point scale, and the severity of each sign or symptom was graded using the following scale: 0 (no symptoms); 1 or mild (occasional symptoms); 2 or moderate (frequent symptoms); and 3 or severe (constant symptoms) (Table 1). The change in the total scores of signs and symptoms from baseline at each visit was recorded.

All data were analyzed using a statistical software package (SPSS Inc, Chicago, Illinois, USA). An analysis of variance (ANOVA) and the paired *t* test were used to statistically analyze changes in the mean scores of signs and symptoms following treatment with topical 0.1% tacrolimus ointment; *P* values of .05 or less were considered statistically significant.

RESULTS

TWENTY-TWO EYES FROM 11 PATIENTS (10 MALE AND 1 female) with refractory AKC were included in this study.

TABLE 2. Characteristics of Patients With Atopic Keratoconjunctivitis

Patient No.	Sex/Age (y)	AKC Duration (y)	Treatment Duration (mo)	Follow-up (mo)
1	M/20	10	9	60
2	M/36	7	63	63
3	M/27	6	10	58
4	M/61	20	11	56
5	M/23	11	63	63
6	F/19	3	11	49
7	M/29	9	8	52
8	M/30	4	12	55
9	M/51	6	6	54
10	M/34	5	12	51
11	M/25	3	63	63

AKC = atopic keratoconjunctivitis.

These patients had a mean age of 32.27 ± 12.7 years (range, 19-61 years), and all had experienced bilateral involvement of AKC for a mean duration of 7.63 ± 4.90 years (range, 3-20 years) (Table 2).

All patients had active perennial symptomatic disease despite previous use of various medications, including antihistamines, mast cell stabilizers, topical cyclosporine, and steroids. Itching was the most prominent symptom, with other complaints including redness and foreign body sensation. All patients had a history of atopic dermatitis, and all eyes examined had lid thickening, conjunctival hyperemia, and papillary conjunctivitis.

After starting treatment with 0.1% tacrolimus dermatologic ointment (Protopic), the patients were followed for a mean duration of 54.18 ± 4.75 months (range, 49-63 months). The changes in their mean scores of symptoms following tacrolimus treatment are shown in Figure 1.

All symptoms significantly improved after treatment, and itching was the first symptom to show improvement. Previously, 3 of the patients had suffered from severe itching and the other 8 patients had suffered from moderate itching; but 1 week after starting treatment with tacrolimus ointment, all of the patients showed a dramatic improvement in itching. After 1 month, all patients achieved complete resolution of their symptoms (Figure 1).

At the end of the follow-up period, the patients remained asymptomatic but continued to apply topical tacrolimus ointment. No additional medications, such as mast cell stabilizers, topical cyclosporine, or steroids, were required to provide additional relief to patients. We observed a dramatic improvement in the patients' clinical signs of disease after starting tacrolimus treatment (Figure 2).

Conjunctival hyperemia improved as early as 3 days after treatment and showed continuous improvement, with complete resolution in 19 of 22 eyes by 4 weeks after the initiation of treatment. Prior to treatment, conjunctival

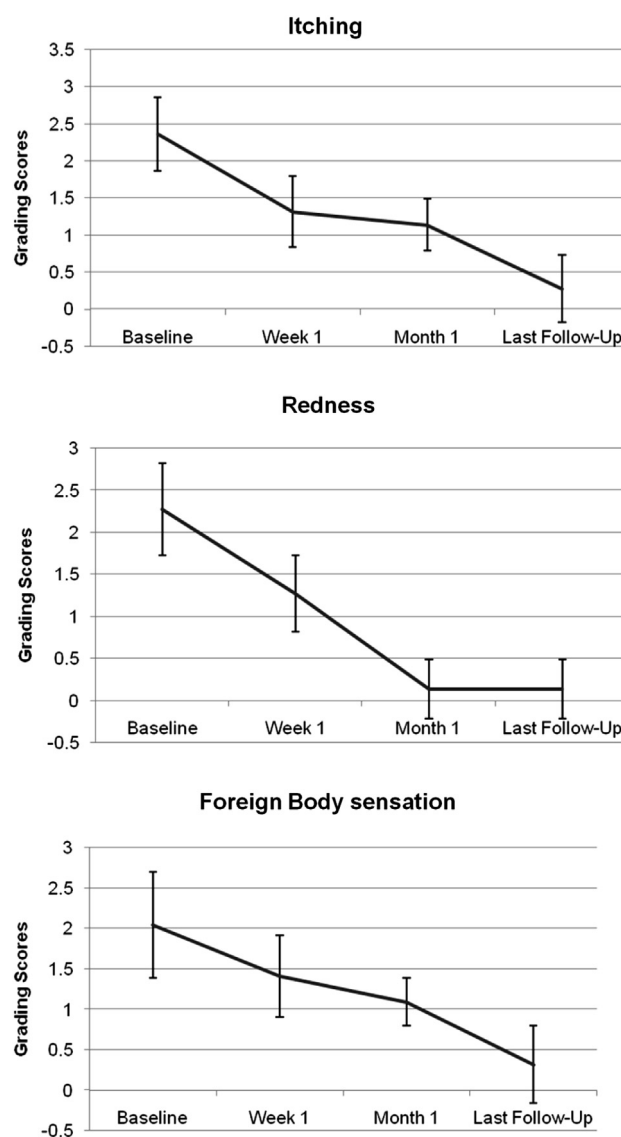


FIGURE 1. Mean scores of symptoms: (Top) itching, (Middle) redness, and (Bottom) foreign body sensation in patients with atopic keratoconjunctivitis before and after treatment with 0.1% tacrolimus ointment.

hyperemia was severe in 7 eyes and moderate in 14 eyes; after 4 weeks, 19 eyes showed no sign of hyperemia and 2 eyes showed mild hyperemia. No worsening of conjunctival hyperemia was noted during treatment. In addition, improvements in conjunctival papillary hypertrophy were observed for all eyes; 7 out of 11 patients showed improvement as early as 3 days, and all patients with moderate or severe papillary formation (10/11) showed improvement 1 week after starting treatment (Figure 2). After 1 month, all of the patients had only mild papillary hypertrophy, and complete resolution of papillary hypertrophy was achieved in all patients by the final follow-up visit. Twenty-one eyes with moderate or severe lid thickening showed improvements in clinical signs 1 week after starting treatment,

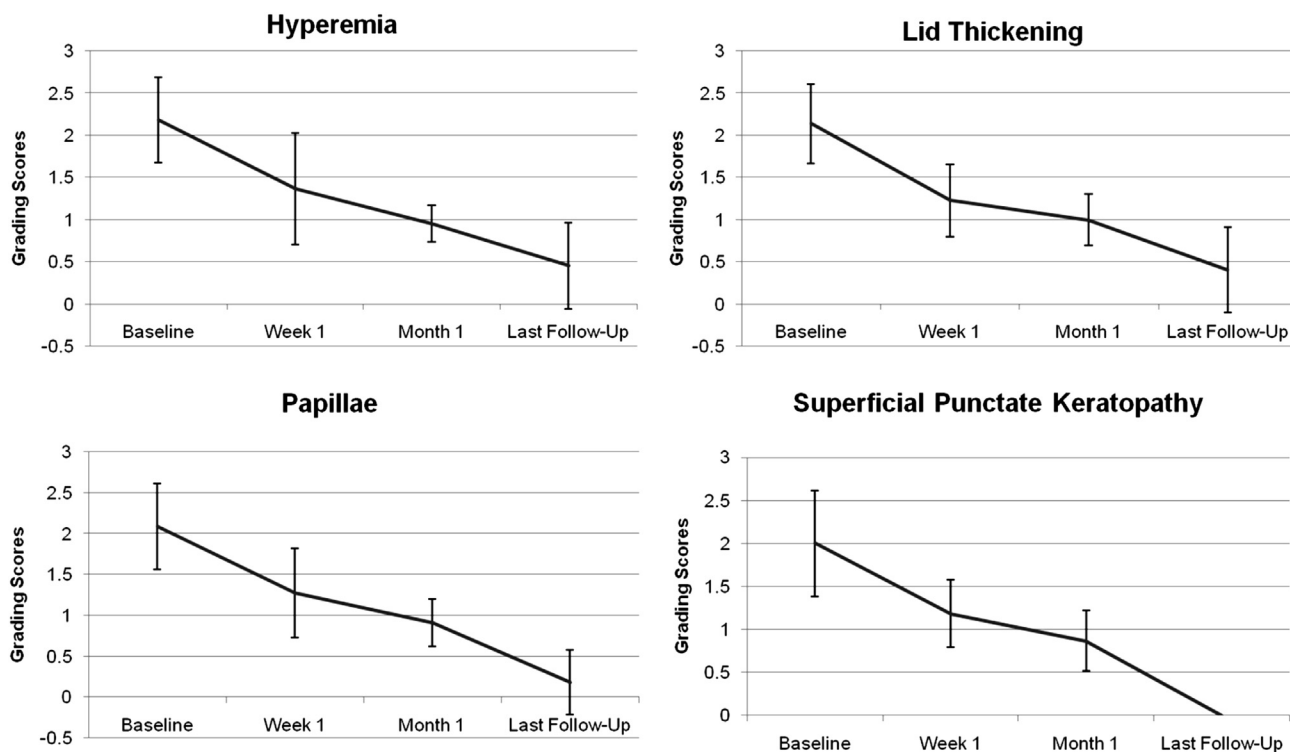


FIGURE 2. Mean scores of signs: (Top left) hyperemia, (Top right) lid thickening, (Bottom left) papillae, and (Bottom right) superficial punctate keratopathy in patients with atopic keratoconjunctivitis before and after treatment with 0.1% tacrolimus ointment.

and after 1 month of treatment all of these eyes showed a dramatic improvement in eczematous lid signs. Furthermore, 1 patient with recalcitrant AKC who developed absolute glaucoma secondary to the chronic use of steroids, which resulted in a total loss of vision (no light perception) in both eyes, achieved complete resolution of his severe AKC after using tacrolimus ointment. All patients with moderate or severe corneal punctate epithelial erosions (10/11) showed improvement 1 week after starting treatment (Figure 2), and all of these patients displayed mild corneal punctate epithelial erosions after 1 month of treatment and had achieved complete resolution of the corneal punctate epithelial erosions at the last follow-up visit (Figure 2).

At the end of the study, 3 patients (3/11) with AKC were still using tacrolimus ointment because of recurrence while attempting to discontinue treatment. However, these patients experienced dramatic clinical improvement in their signs and symptoms upon recommencing treatment and were therefore prescribed to continue a once-weekly tacrolimus treatment regimen. Of the patients studied, 8 remained asymptomatic for up to 3 years. All patients complained of a mild burning sensation upon application of the tacrolimus ointment, although no patient had to discontinue the medication owing to adverse drug effects. No major drug-related ocular complications were encountered in any patient, and the patients' BSCVA and refraction

measurements remained unchanged throughout the follow-up period.

DISCUSSION

TOPICAL TACROLIMUS HAS BEEN SHOWN TO BE EFFECTIVE in the management of patients with AKC and VKC who are refractory to conventional medications, including topical cyclosporine,^{24,25} and tacrolimus is therefore considered a promising agent for the management of intractable AKC. In the current study, tacrolimus demonstrated good results in the management of severe AKC resistant to cyclosporine. Consistent with previous reports, almost all patients in our study showed dramatic improvements in inflammatory signs and symptoms without developing any significant adverse effects. Although none of the patients in the current study had to use additional medications, including topical steroids, to obtain further relief, long-term use of tacrolimus was necessary to control the recurrence of the disease.

In 1 study, topical tacrolimus was used in 4 patients, and 1 of these patients was treated for a duration of 42 months.¹⁷ In the current study, all patients completed 49 months of follow-up, and none required the use of additional medications, such as antihistamines, steroids, or mast cell

stabilizers, to control disease activity. However, it may be possible to reduce or discontinue tacrolimus treatment if the disease is under control. Kymionis and associates¹⁹ showed that after 3 months of tapered treatment for giant papillary conjunctivitis, there was significant improvement without disease recurrence during the 6 months after the cessation of tacrolimus treatment. Burning sensations upon application of topical tacrolimus have been previously reported,^{18,19} and the most frequent tacrolimus-related adverse event in the present study was a mild burning sensation, which was seen in all patients upon topical application. However, this effect was well tolerated and improved rapidly after the third day of treatment. Because of the immunosuppressive effects of tacrolimus ointment, this effect may be associated with the activation of herpes simplex dendritic keratitis.²¹ However, none of the patients developed herpes simplex keratitis during the long-term follow-up period. Thus, the possibility for activation of herpes simplex dendritic keratitis resulting from tacrolimus treatment requires further study.

In previous studies, commercially available 0.03%-0.1% skin ointments have been applied to eyelids^{15,16,18,24} or to the fornix.¹⁹⁻²¹ In addition, the clinical study by Sengoku and associates²⁷ used 0.01%-1% eye drops that were formulated as an isotonic aqueous suspension using polyvinyl alcohol as a dispersive agent. Even at this low concentration of topical tacrolimus, a dramatic improvement was noted regarding the symptoms of patients with refractory AKC. In the current study, 9 patients (of 11) rapidly experienced itching relief (day 3) after the initiation of treatment (Figure 1). Miyazaki and associates²³ used 0.02% tacrolimus ointment in 5 patients with AKC and 1 patient with VKC who were refractory to conventional treatment and observed a marked improvement in patient symptoms within 2-4 weeks of treatment. In a multicenter, randomized clinical trial, Ohashi and associates²⁴ used a 0.1% ophthalmic suspension of tacrolimus twice daily for 4 weeks in 21 patients with AKC and 7 patients with VKC; compared to the placebo group, the treated eyes showed a marked improvement in symptoms after 4 weeks of treatment. In the present study, most symptoms were relieved to a remarkable extent 1 week after commencing tacrolimus treatment (Figure 1). In the current patient series, allergic symptoms recurred in 3 of 11 patients as a result of attempts to discontinue the medication. Therefore, these patients were kept on treatment for the entire follow-up period. Thus, although improvements in clinical findings have been reported after topical tacrolimus treatment, there is a paucity of data regarding the optimal drug concentration. Additionally, literature varies on the treatment duration as well. Although Kheirkhah and associates²⁶ have used topical tacrolimus for as few as 4 weeks, Miyazaki and associates²³ continued the treatment with topical tacrolimus for 26 months in patients with refractory VKC.

In the current study, improvement of papillary conjunctivitis was apparent as early as 1 week after the initiation of

tacrolimus ointment. These results are consistent with the previously published studies. Ohashi and associates have documented early improvement after the use of 0.1% tacrolimus ophthalmic suspension in patients with severe allergic conjunctivitis.²⁴ Likewise, Labcharoenwongs and associates reported good clinical response in as early as 1 week with the use of 0.1% tacrolimus (FK-506) ophthalmic ointment.²⁵ Similarly, Kheirkhah and associates reported improvement in as early as 2 weeks in eyes with moderate or severe giant papillae with topical 0.005% tacrolimus eye drops for treatment of refractory vernal keratoconjunctivitis.²⁶

The dramatic improvements provided by treatment with tacrolimus ointment in patients who failed to respond to topical steroids or topical cyclosporine treatments emphasize the beneficial role of tacrolimus. Thus, tacrolimus may be used as a steroid-sparing agent because it favorably alters the long-term prognosis of patients with AKC and may help patients to avoid complications associated with the chronic use of steroids. In fact, 1 patient developed secondary glaucoma with a total loss of vision in both eyes, attributable to the chronic use of steroids to control his AKC symptoms, but he became symptom-free just 1 week after beginning treatment with tacrolimus ointment. Of note, this treatment may have saved his vision if it had been used early enough. However, the potential risk of T cell lymphoma in patients using topical tacrolimus has been reported.²⁸ On the other hand, in another report, the blood concentration profiles of patients using 0.1% tacrolimus ointment were below the limit of quantification (0.5 ng/mL) in the majority of patients.²⁹ In the present study, no malignant cases were identified throughout the 5-year follow-up period, and the risk of developing malignancy after the application of 0.1% topical tacrolimus is likely extremely low. In fact, there is insufficient evidence in the epidemiologic literature to determine whether topical CIs may cause malignancy,³⁰ and the results from available literature suggest that tacrolimus skin ointment is a safe and effective treatment for patients with refractory AKC. Although the development of secondary resistance to tacrolimus after systemic use has been reported during the treatment course,³¹ no case of tacrolimus resistance was observed in this small series of 11 patients. Future studies with a large data set may provide suitable outcomes.

The small sample size and the lack of randomization and a control group were the main limitations of the current study. In conclusion, 0.1% tacrolimus skin ointment was effective in controlling the clinical signs and symptoms of severe allergic conjunctivitis refractory to topical antihistamine agents and topical cyclosporine. These results suggest that tacrolimus may be a promising agent for the treatment of refractory AKC, although further randomized controlled studies are required to evaluate the appropriate concentration and dosage of topical tacrolimus, as well as the long-term safety of this medication.

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Eye Disease on the Lewis and Clark Expedition

President Thomas Jefferson had Meriwether Lewis consult the famous physician Benjamin Rush in Philadelphia for advice on how to manage medical problems likely to occur on the long voyage to and from the Pacific. Lewis came away with a large supply of Rush's potent laxative prescription (known as "thunderclappers") and which turned out to be a godsend to men often restricted for weeks on end to an all-meat diet. Another particularly useful medication was Rush's prescription for a lead acetate solution to be applied topically for inflammatory eye disease. This condition was found frequently among the Indians that Lewis and Clark encountered in the two years of the expedition. In April, 1806, Lewis wrote in his journal:..."we gave them some

eye water which I believe will render them more esential sirvece [sic] than any other article in the Medical way which we had it in our power to bestow on them. Sore eyes seem to be a [serious] universal complaint among these people."

Rush's prescription proved to be a useful currency in obtaining the goodwill of the Indians, whom the explorers depended upon for topographical information as well as horses at critical points in the voyage.

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Submitted by Ronald Fishman MD from the Cogan Ophthalmic History Society.