

ORIGINAL ARTICLE

Tacrolimus ointment 0.1% in the treatment of allergic contact eyelid dermatitis

A Katsarou,* M Armenaka, V Vosynioti, E Lagogianni, D Kalogeromitros, A Katsambas

Department of Dermatology, University of Athens, 'A. Sygros' Hospital, Athens, Greece

*Correspondence: A Katsarou. E-mail: alkats.duoa@yahoo.gr

Abstract

Background Tacrolimus inhibits T-lymphocyte activation and dermal Langerhans' cells, without the side-effects of corticosteroids. The safety profile of tacrolimus makes it a promising therapeutic option for dermatitis affecting the delicate periorbital skin.

Objective To assess the efficacy and tolerability of tacrolimus ointment 0.1% in the treatment of allergic contact eyelid dermatitis.

Patients and methods Twenty adults (16 women, 4 men) with eyelid dermatitis and with at least one positive patch test reaction to relevant contact allergens were treated with topical tacrolimus in a prospective, open-label, non-comparative clinical study. Dermatitis was graded at baseline, at day 30 and day 60, using a 4-point grading system for the following parameters: erythema, oedema, scaling, lichenification, fissuring (investigator assessment) and burning/stinging and pruritus (patient assessment).

Results All patients completed the study. Erythema, oedema, scaling and lichenification showed improvement from baseline to 30 days of treatment ($P < 0.001$), but fissuring was not significantly affected. At 60 days, no further improvement of these investigator parameters was observed. Patient parameters improved significantly by day 30 ($P < 0.004$) and there was a trend for further improvement at the end of 60 days (for burning, $P = 0.046$; for pruritus, $P = 0.059$). Ten per cent of patients mentioned burning and itching, at the application site, during the first days of treatment. No other adverse events were observed.

Conclusion Topical tacrolimus is a promising alternative in patients with allergic contact eyelid dermatitis. Therapy was effective by 1 month and was well tolerated. These preliminary results merit a larger, controlled, study.

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Keywords

allergens, allergic contact dermatitis, eyelid, patch testing, periorbital, tacrolimus, therapy

Conflict of interest

This study was not funded by a drug company, and none of the investigators have received financial support/grants by the makers of the drug tacrolimus.

Introduction

Dermatitis of the eyelids may be an expression of allergic or irritant contact dermatitis, atopic dermatitis and systemic allergic contact dermatitis.^{1,2} Until now, the main treatment for eyelid dermatitis has been topical application of corticosteroids. However, prolonged use of corticosteroids around the eyes has been associated with side-effects such as local atrophy and telangiectasia, increased intraocular pressure and cataracts.³⁻⁵

Tacrolimus is a topical macrolactam immunosuppressant that inhibits calcineurin and the expression of genes for cytokine production.⁶ It has also been demonstrated to inhibit T-lymphocyte activation and dermal skin Langerhans' cells, but with a good safety profile and without the side-effects of corticosteroids.^{7,8} In

contrast to corticosteroids, tacrolimus effectively controls erythema and oedema, not as a result of vasoconstriction, but perhaps by a direct anti-inflammatory effect.⁹

The safety profile of tacrolimus makes it a promising therapeutic option for dermatitis affecting the eyelids. The present preliminary study was undertaken to examine the therapeutic efficacy of topical tacrolimus ointment 0.1% in adult patients with allergic contact eyelid dermatitis.

Methods

Study design

We performed a prospective, open-label, non-comparative, single-centre clinical study at a large city university hospital for dermatologic

and venereal diseases to assess the efficacy and tolerability of tacrolimus ointment 0.1% in the treatment of allergic contact dermatitis involving the eyelid and periorbital area. Patients were enrolled at the Department of Dermatology, Laboratory of Skin Allergy of the University of Athens, in Greece, after prior screening by a staff dermatologist. All patients provided informed consent to participate in the study, and the protocol was approved by the hospital institutional review board. The study was carried out from June 2005 to April 2006.

Participants

Patients with contact dermatitis that affected the eyelids and periorbital area and with one or more relevant positive patch tests reactions were enrolled in the study. As a relevant allergen, we defined a contact allergen with a positive patch test result that was related to the elicitation of eyelid dermatitis, in the past and/or the present time, according to the history. Patients with possible and probable relevance, according to the scoring system of Lachapelle, were included in this study.¹⁰ Those with an ambiguous history and with a positive patch test were excluded from the study. Patients with a personal or family history of atopic dermatitis and with total serum IgE levels > 200 IU/mL were also excluded from the study. Other exclusion criteria were coexisting serious chronic disease, seborrheic dermatitis and psoriasis. Before entering the study, medication washout periods were 2 weeks for topical corticosteroids and 4 weeks for systemic treatment for dermatitis.

Patch testing

All patients were patch tested with the European baseline series, the Greek series (am. mercury 1%, benzalkonium chloride 0.1%, ethylenediamine dihydrochloride 1%, imidazolidinyl urea 2%, thiomersal 0.1%), cosmetics series, preservatives/antioxidant series and, in some cases, with suspected allergens that were supplied by the patients (eye drops, undiluted, in four patients). A ROAT test was also performed with the eye drops, morning and night for 1 week, as previously described.¹¹

Allergens were supplied by Trolab (Hermal, Germany), and Finn Chamber on Scanpor tape was used, supplied by Epitest Ltd (Oy, Finland). Patch tests were performed according to ICDRG recommendations and read after 2 and 4 days.

Treatment interventions

Participants used tacrolimus ointment 0.1% ('Protopic 0.1%', Astellas Pharma GmbH, Munich, Germany), applied to the affected areas, twice daily for 15 consecutive days, followed by once daily application, at night, until the end of 1 month. Subsequently, patients were allowed to apply tacrolimus ointment, once daily, as needed, according to the clinical symptoms, until the end of the study. At the same time, they were advised to avoid the responsible allergens. Patients were not allowed to use other topical therapies or systemic corticosteroids during the study period.

Outcome measures

Participants were clinically evaluated before the onset of treatment (baseline, day 0, 'D0'), after the first month (day 30, 'D30') and after the end of the second month (day 60, 'D60') of treatment. Dermatitis was graded both by the investigator and by the patient. The chief dermatologist/investigator graded all patients. A digital photograph was taken on each of the three evaluation visits and stored as a patient record.

The clinical evaluation was based on the following five objective criteria (investigator's evaluation): erythema, oedema, scaling/dryness, lichenification and fissuring; as well as the following two subjective criteria (patient's evaluation): itching and burning/stinging sensation. Each criteria, was graded using a 4-point assessment scale, from 0 to 3, where 0 = absent, 1 = definite, but mild, 2 = intermediate and 3 = severe. In order to meet inclusion criteria, each patient had to have a total score of at least '4' at baseline.

Adverse events were recorded throughout the study period. Local cutaneous symptoms, ocular and skin infections were evaluated at all visits by the study dermatologist at the clinic.

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc. for Windows version 11.0). The Wilcoxon signed rank test was applied to investigate differences in mean scores from baseline. The level of significance was set at $P < 0.05$.

Results

Patients and patch tests

A total of 20 patients, 16 women and 4 men, aged 22–77 years (mean age, 44.3 years) were enrolled in the study. All patients finished the study. The mean duration of eyelid dermatitis was 19.2 months (range, 6 months to 3.5 years). Dermatitis was observed elsewhere on the face in eight patients and on the hands in five patients. The characteristics of the patients and results of patch tests are shown in Table 1. More than one relevant allergen was found by patch testing in 55% of the patients. The most common positive allergens were nickel sulphate (65%), fragrances (balsam of Peru 10%, fragrance mix 10%, balsam of Tolu 10%), and cobalt chloride (15%). Occupational exposure to nickel was evident in two patients – a bank teller and a repair worker for medical instruments. Occupational exposure to thiuram and to resins was present in two additional patients. Topical medications were involved in four cases.

Dermatitis severity assessment by investigator and patient

Total scores for investigator and patient evaluated parameters at baseline, at day 30 and at day 60 are shown in Fig. 1(a,b). Mean dermatitis severity scores for the seven parameters studied and the corresponding P -values are summarized in Table 2. There was statistically significant improvement in mean scores between day

Table 1 Baseline patient characteristics, dermatitis score, positive patch tests reactions and possible source of exposure

Number	Sex	Age (years)	Duration (months)	Total score	Positive allergens*	Source of exposure
1	F	22	24	6	Nickel sulphate 5%	Metal objects, cosmetics
2	F	51	6	5	Wool alcohols 30% [Am. mercury 1%, Potassium dichromate 0.5%]	Eye/face cream
3	F	36	8	6	Nickel sulphate 5%, Fragrance mix 8%, Balsam of Tolu 20%	Metal coins, cosmetics
4	F	54	6	10	Thiuram mix 1%	Latex gloves, fertilizers
5	F	30	24	5	Nickel sulphate 5%, Cobalt chloride 1%	Metal objects, cosmetics
6	F	27	12	7	Nickel sulphate 5%, Myroxylon pereirae (Balsam of Peru) 25%	Metal objects, face cream
7	F	51	32	11	Nickel sulphate 5%, Cobalt chloride 1%, [Hydroquinone 1%]	Eyeglass frame, metal, cosmetics
8	M	65	24	11	Nickel sulphate 5%	Metal objects
9	F	58	32	10	Nickel sulphate 5%	Metal objects, cosmetics
10	F	28	12	10	Cobalt chloride 1%, Ethylenediamine dihydrochloride 1%	Cosmetics, antifungal cream
11	M	69	24	13	Budesonide 0.1%	Cortisone cream
12	F	27	12	11	Nickel sulphate 5%	Metal objects, cosmetics
13	M	35	18	13	Epoxy resin 1%, Myroxylon pereirae (Balsam of Peru) 25%	Adhesives/resins, after-shave lotion
14	F	42	32	10	Nickel sulphate 5%	Metal objects, cosmetics
15	F	59	18	5	Nickel sulphate 5%, Paraben mix 16%, Tosylamide/formaldehyde resin 10%	Metal objects, nail polish
16	F	37	8	6	Nickel sulphate 5%, Sodium benzoate 5%	Medical instruments, cosmetics
17	F	32	24	4	Nickel sulphate 5%, Sodium benzoate 5%, Ethylenediamine dihydrochloride 1%	Cosmetics, antihistamine cream
18	F	24	5	5	Nickel sulphate 5%, Thiomersal 0.1%, [Am. mercury 1%]	Metal objects, contact lens solution
19	M	77	38	13	Xalatan (latanoprost) eye drops, tested as is	Ophthalmic drops
20	F	61	24	9	Fragrance mix 8%, Balsam of Tolu 20%	Face-eye cream

*Allergens in [brackets] are considered non-relevant.

0 and day 30 for all the parameters assessed ($P < 0.004$), except for fissuring. Differences remained significant at day 60 for the same parameters ($P = 0.001$). Fissuring did not reach significance even at the end of the study. For the physician-graded parameters, the differences between days 30 and 60 were not significant. In contrast, further improvement was observed between days 30 and 60 based on patient evaluations for burning/stinging ($P = 0.046$), while a trend for further improvement was seen for pruritus, but the P -value did not reach significance ($P = 0.059$). Photographic findings in representative subjects are shown in Fig. 2.

Tolerability evaluation

During the first days of treatment, two patients mentioned burning and itching after the use of tacrolimus ointment. Cutaneous or ocular infections were not seen. No other side-effect was reported by the patients or observed by the investigators.

Discussion

In this study, patients were carefully selected not to have atopic dermatitis. Although results of patch testing are not enough for

the diagnosis of allergic contact dermatitis, we studied only patients in whom allergic contact dermatitis was supported by a positive history of contact reactions to relevant patch test allergens. Furthermore, patients with an ambiguous history of contact reactions and with positive patch tests were excluded from the study. However, it is not possible to identify the coexistence of irritant dermatitis in our patients with contact allergy. In allergic contact eyelid dermatitis, allergen avoidance may be difficult because common contact allergens are often involved, as previously reported.^{1,12} Nickel is reported to cause periorbital dermatitis from use of metal eyelash curlers and eye cosmetics, such as eye shadows and eye pencils.¹ It may also be transferred to the eyelids, from the hands, after handling nickel containing metal objects, such as coins.¹³ Fragrances are so widely used in cosmetic products applied to the face or hands that effective avoidance is difficult.

It is noteworthy that some of our study patients had 3 years of eyelid dermatitis. Relapses often occur and long-term use of topical agents may be needed. Prolonged topical use of corticosteroids for dermatological conditions around the eyes has rarely been associated with ocular side-effects, which include raised

Table 2 Mean $\pm$ SD score for individual dermatitis parameters at day 0 (baseline), at day 30 and day 60. The *P*-values shown are for comparisons between days 0 vs. 30, days 0 vs. 60, and day 30 vs. 60, respectively

	Day 0	Day 30	Day 60	<i>P</i> -values
Erythema	1.75 (0.72)	0.55 (0.61)	0.30 (0.47)	< 0.001, < 0.001, 0.096
Oedema	1.40 (0.75)	0.40 (0.60)	0.25 (0.44)	< 0.001, < 0.001, 0.083
Scaling/Dryness	1.30 (0.73)	0.10 (0.31)	0.05 (0.22)	< 0.001, < 0.001, 0.317
Lichenification	1.0 (0.46)	0.25 (0.44)	0.10 (0.31)	< 0.001, < 0.001, 0.083
Fissuring	0.15 (0.37)	0.05 (0.22)	0.00 (0.00)	0.157, 0.083, 0.317
Pruritus	1.8 (1.06)	0.85 (0.59)	0.60 (0.58)	0.003, 0.001, 0.059
Burning/Stinging	1.10 (0.69)	0.30 (0.47)	0.10 (0.31)	0.002, 0.001, 0.046

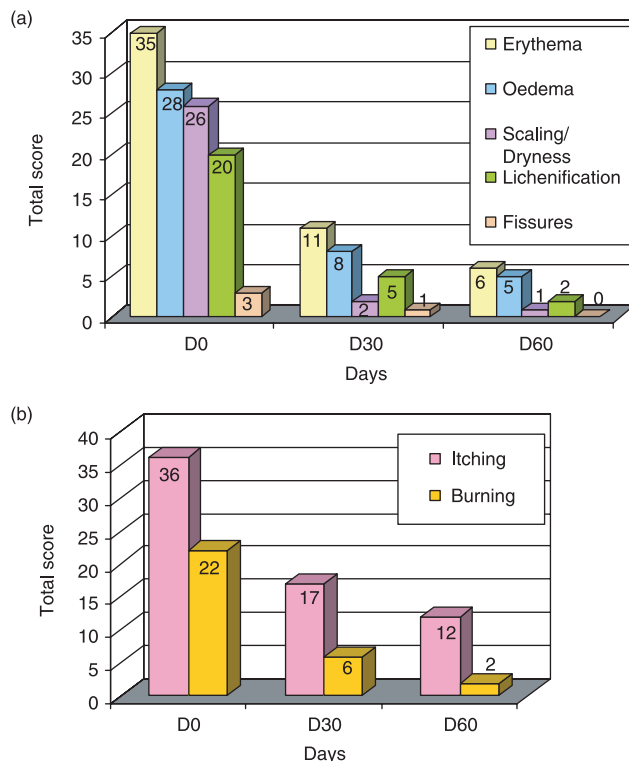


Figure 1 (a) Investigators' assessment of allergic eyelid dermatitis at day 0 (D0), day 30 (D30) and day 60 (D60). (b) Patients' assessment of pruritus and burning before treatment and after treatment (day 30 and day 60).

intraocular pressure and glaucoma.^{5,14} Although raised intraocular pressure is considered a rare complication in normal dermatology practice, one study suggests that pressure may not always return to normal upon discontinuation of the topical steroid.⁵ Therefore, there is a need for alternative effective treatments with few side-effects.

Tacrolimus ointment is a topical immunomodulator that is an effective treatment alternative for atopic dermatitis.^{15–17} Several recent reports also demonstrate promising effectiveness in allergic contact dermatitis, both for the prevention of the elicitation of

allergy¹⁸ and for active disease.^{19,20} Tacrolimus ointment has been shown to be effective in nickel sulphate–elicited allergic contact reactions, to a similar degree as mometasone furoate 0.1% in a patch test allergen challenge model.⁹ In eyelid dermatitis, tacrolimus ointment has been studied among patients with atopic dermatitis and was found to be effective and safe without causing skin atrophy, telangiectasia, or increased intraocular pressure.¹⁷

In this study of patients with allergic contact dermatitis and eyelid dermatitis, results showed that after treatment with tacrolimus ointment 0.1%, there was a significant improvement in dermatitis parameters. However, fissuring did not significantly improve with the therapy. This could be the consequence of the chronicity of the skin damage, or of the small sample size. Of the three patients that had fissures at baseline, two recovered by day 30 and the third recovered by day 60. We did not observe any further improvement for the physician-graded parameters at the end of 60 days, as compared to 30 days of treatment. A recent, double-blind, placebo-controlled, randomized study in 28 patients with steroid-resistant allergic contact dermatitis to nickel demonstrated significant improvement by 2 weeks of topical tacrolimus therapy.²¹

Topical application of the drug to the eyelids and periorcular skin was well tolerated. Transient burning and itching was reported by 10% of the patients in the study and this is in accordance with most other studies, which suggest excellent patient tolerance to the drug.^{9,15,18} Overall, our patients judged that pruritus and burning was significantly improved after 30 days of therapy, as compared to baseline. The lack of a placebo group with vehicle may have biased these findings. Tacrolimus has been shown to significantly lower patient itch-scores, as compared to placebo, in atopic dermatitis paediatric patients.¹⁶ In nickel-induced contact dermatitis, although improvement was seen with tacrolimus, it was not more than with the control vehicle.¹⁹

We did not follow our patients with ocular exams. This has been done in a previous study that has found tacrolimus did not increase intraocular pressure, after 8 weeks of periorcular application.¹⁷ Some reports have raised the possibility that topical macrolactams may, rarely, produce unusual manifestations of cutaneous fungal infections, similar to those seen with topical corticosteroids.²² There were no infectious complications seen in the patients we studied.



Figure 2 Dermatitis at baseline (a) and after 1 month of treatment with tacrolimus (b) in two patients.

One of our study patients had allergy to budesonide on patch testing. Topical tacrolimus is a valuable alternative in patients with corticosteroid allergy. However, contact allergy to tacrolimus has also been reported and may coexist with allergy to other related calcineurin inhibitors, including pimecrolimus.²³

There are several drawbacks of tacrolimus ointment that physicians must be aware of. It should not be used in pregnancy, since studies are lacking, according to the SPC of the product.²⁴ It is contraindicated in patients with eroded/ulcerous skin lesions, while exposure to ultraviolet light, UVA, UVB, or light from solarium should be minimized during use.²⁴ Drug concentrations in the systemic circulation are low with topical use. Levels are approximately 30-fold less than those seen with oral administration of the drug in kidney and liver transplant patients.²⁴ In the latter group, it is recommended to monitor laboratory parameters, including liver and renal function, blood glucose levels and serum electrolytes, particularly potassium levels.²⁵ However, there are no such recommendations with topical tacrolimus, neither are there official contraindications for topical use in patients with severe renal impairment or hyperkalemia, for example. Until further data are available regarding applications in humans, it may be wise to be cautious, having in mind that systemic exposure increases with increased treatment area and decreases as skin heals.

Tacrolimus ointment appears to be a promising alternative in patients with allergic contact dermatitis involving the eyelids, as it is effective from the first month of treatment and is well tolerated. Investigator bias cannot be excluded in this study. Despite the promising findings, results need to be confirmed by a larger, prospective, placebo controlled study, comparing conventional therapy vs. tacrolimus.

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