

Tacrolimus ointment vs steroid ointment for eyelid dermatitis in patients with atopic keratoconjunctivitis

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Abstract

Aims The main objective of this explorative study was to evaluate if tacrolimus ointment could be safer than corticosteroid ointment, with special reference to the intraocular pressure in the treatment of eyelid eczema in patients with atopic keratoconjunctivitis (AKC). Secondary aims were to compare the effects of the treatments on eyelid eczema and their potential impact on ocular surface inflammation.

Methods Tacrolimus 0.1% ointment and clobetasone butyrate 0.05% ointment were compared in a double-masked explorative crossover study. In total, 25 AKC patients were included. Each ointment was applied twice daily for 3 weeks, with 2 weeks of washout before, between, and after treatments. Efficacy was determined by eye examination and the patients' own symptom scoring. Cytology and cytokine measurements were performed on tear samples. Safety parameters were intraocular pressure, presence of bacteria and fungi, and the patients' reports of adverse events. The validity of the crossover design was explored with analysis of variance, and the effect of each medication was calculated with paired *t*-test and Wilcoxon paired test.

Results A total of 20 patients completed the study. Both treatments were effective in reducing signs and symptoms of eyelid eczema, with a near superior benefit for tacrolimus in terms of eczema (total skin score) signs ($P = 0.05$). No serious adverse events occurred and interestingly, intraocular pressure was not evidently affected by either treatment.

Conclusion Tacrolimus 0.1% ointment is a promising alternative therapy for eyelid eczema in AKC patients. Long-term studies are

needed to further determine the value of tacrolimus in this patient group.

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Keywords: atopic keratoconjunctivitis; steroids; cytokine; eyelid eczema; intraocular pressure; tacrolimus

Introduction

Eyelid eczema as part of the atopic dermatitis syndrome (AD) constitutes a therapeutic challenge. In general, the dermatitis has a chronic course with exacerbations causing considerable discomfort and cosmetic problems. The inflammatory activity of the eyelid margins may interact with the ocular surface-aggravating conjunctivitis and keratitis, the typical and potentially sight-threatening ocular manifestations of the syndrome, named atopic keratoconjunctivitis (AKC).¹ There are no available evidence-based therapeutic guidelines for eyelid eczema. Different or even conflicting management approaches may result from the fact that not only ophthalmologists but also dermatologists, allergists, and general practitioners provide care. Apart from emollients, the backbone of treatment for eyelid eczema is steroid ointments. Systemic immunosuppressants may be considered in more severe cases. There is a restriction for use of steroid ointments near the eye, warranted mainly by the propensity of steroid-containing eye-drops to cause increased intraocular pressure (IOP). In the worst-case scenario, this rise in IOP can cause irreversible glaucoma. Approximately 18–36% of the general population respond to steroid eye drops, with most often moderate elevations even after a short-term

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administration.^{2–5} With steroid application on eyelid skin, increased IOP seems less common, but there are no controlled prospective studies available and several case studies attest to the fact that in long-term treatment, this risk should not be overlooked.^{6–8} As a consequence, regular ophthalmologic examinations are recommended. Another feared complication following prolonged steroid treatment is skin atrophy.⁹ As an alternative to steroids, tacrolimus ointment is a valid therapeutic option for atopic dermatitis since more than 5 years.^{10–12} Successful treatment of eyelid eczema in AKC patients has further been documented in case series^{7,13} and three noncontrolled open-label studies.^{14–16} To the best of our knowledge, no comparative trial of tacrolimus ointment and steroid ointment for eyelid dermatitis has been performed. Moreover, no studies of inflammatory cells and cytokines in tears in response to these treatments have been presented. With the aim of investigating the potential benefits and side effects of tacrolimus in comparison with 'standard' care, that is a mid-potent steroid formulation, a prospective, randomized, double-blind crossover study was undertaken.

Materials and methods

Subjects

According to the defined criteria (Table 1), patients with a clinical diagnosis of AKC and who were regularly seen by one of the investigators (PM) in the outpatient clinic of St Erik's Eye Hospital were recruited. Written informed consent was obtained from each participant and the local ethics committee approved the project.

Study design

Tacrolimus ointment 0.1% (Protopic[®], Fujisawa GmbH, Munich, Germany) and a mid-potent steroid clobetasone

butyrate 0.05% (Emovat[®], GlaxoSmithKline AB, Mölndal, Sweden) were study treatments. Each ointment was given twice daily on the eyelids of both eyes for a 3-week period in a double-masked crossover manner to each participant. No other topical, periorbital, or systemic anti-inflammatory or anti-infective treatment was allowed during the study or during the washout periods (Figure 1). The trial was conducted from January to April 2004 and included five visits (Figure 1). At visit 1, after the initial 2-week washout, study eligibility according to inclusion and exclusion criteria (Table 1) was confirmed, and the patients were randomized to receive one of the study drugs. A research nurse managed randomization and drug distribution. Every visit included visual acuity testing, scoring of signs of eyelid dermatitis, blepharitis, conjunctivitis and keratitis, measurement of IOP, tear sampling for cytology and cytokine assessments, sampling for bacteria and fungi, and collections of patient diaries, *vide infra*. At the first visit, a serum sample was taken to analyse immunoglobulin E (IgE) antibodies against Staphylococcal enterotoxin B (SEB).

Assessment of symptoms and signs

A score system modified from European Tacrolimus Multicenter Atopic Dermatitis Study Group¹⁷ was designed for eyelid and eyelid margin signs. As for eyelid eczema, the following parameters were assessed: oedema, redness, excoriations, crusts/oozing, and lichenification. For blepharitis, oedema, redness, and crusts/oozing were assessed. All signs were scored 0–3: 0: no, 1: mild, 2: moderate, and 3: severe signs. Concerning ocular surface signs, the following grading system was used: Conjunctivitis: 0, no changes; 1, mild bulbar injection and superior sub tarsal fibrosis; 2, moderate mixed bulbar injection; and 3, severe mixed bulbar injection Keratitis: 0, no corneal affection; 1, a few

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
AKC with eyelid eczema and need for topical and/or periorbital steroid treatment during the last 6 months before the study and ability to sustain 2 weeks of washout of any anti-inflammatory and/or anti-infective treatment	Need for continuous local or systemic anti-inflammatory treatment, for example, steroids, cyclosporine. One functioning eye only Glaucoma diagnosis or IOP >25 mmHg Facial phototherapy

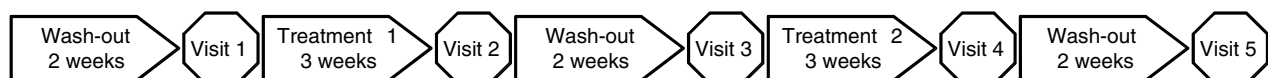


Figure 1 Study design.

superficial punctuate erosions; 2, multiple superficial punctuate erosions; and 3, confluent corneal ulcer. All patients had bilateral disease, and scores were recorded from both eyes and added together to obtain as robust data as possible. Maximal score for eyelid eczema was 15 + 15, for blepharitis 9 + 9, conjunctivitis 3 + 3, and for keratitis 3 + 3. One observer (EN) performed the examinations and evaluations at all but five of 105 occasions, and a second observer (PM) performed the remaining evaluations. The investigator did not have access to previous measurements for any of the parameters.

In terms of subjective symptoms, the patients were instructed to record eye region discomfort, regardless of type of sensation, twice daily on a visual analogue scale (VAS) graded 0–10: 0 corresponding to no discomfort and 10 to severe discomfort. The VAS scores, adverse events, and treatment application were documented in a diary. VAS scores from the examination days only were used for calculations.

IOP measurements

To ensure correct measuring of IOP, the same Goldmann tonometer was used at each visit. The calibration was controlled every week with prescribed equipment from Haag-Streit (Bern, Switzerland). To avoid influence of the circadian pressure rhythm, the patients were always examined at a specific time in the morning. The pressure was measured in both eyes and the mean was used for calculations. We defined an increase of 2 mmHg as a clinically relevant increase in IOP, see Statistics section.

Analyses of bacteria and assessment of cytology and cytokines

The presence of aerobic bacteria on eyelids, eyelid margins, and conjunctiva and the presence of *Malassezia* species on eyelid and eyelid margins were analysed as previously described.¹⁸

Tear fluid was collected from the external canthus with a glass blood capillary tube and transferred to Eppendorff tubes. A measure of 2 μ l were directly fixed with 2 μ l of 4% formaldehyde for cytology analysis according to a previously reported method.¹⁸ One masked observer (EN) counted the eosinophil and neutrophil numbers.

Tear fluid (30 μ l) was frozen on dry ice and stored at –80°C until analysis for cytokines. The levels of IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, GM-CSF, IFN- γ , and TNF- α were measured with Human Cytokine Premixed LINCOplex HCYTO-60K-PMX Kit from Linco Research Inc. (St Charles, MO, USA), according to the instructions and read on a Luminex™

100 instrument from Luminex corporation (Austin, TX, USA). The tear samples were diluted 1:2 with assay buffer and run in duplicates. Out of the 13 cytokines in the kit, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, IFN- γ , and TNF- α were chosen for further analyses.

Serum IgE against SEB was assessed with the Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden), according to the instructions of the manufacturer. A positive test was defined as 0.35 k_AU/L.

Statistics and sample size

The study was designed with the assumption that there would be a 30% proportion of steroid-treated patients with a clinically relevant rise of IOP, that is >2 mmHg, as opposed to no such rise in the tacrolimus group, leading to a statistically significant difference ($P < 0.05$) with the sign test for a sample of 22 individuals in a crossover study. In view of the crossover design, data from visits 1, 3, and 5 were considered as baseline values (Figure 1) and explored with analysis of variance (ANOVA) to exclude significant carryover or rebound phenomena of the treatments (Table 2). All post-treatment values were compared with the baseline values and analysed with parametric and nonparametric tests for dependent variables (paired t -test and Wilcoxon paired test) to

Table 2 Validity of the crossover design by control of baseline values

Parameter	P
IOP	0.278
Subjective score	0.278
Total skin score	0.107
Eczema	0.157
Blepharitis	0.375
Total eye score	0.022
Conjunctivitis	0.054
Keratitis	0.142
Eosinophils	0.211
Granulocytes	0.236
IL-2	0.039
IL-4	0.187
IL-5	0.171
IL-8	0.236
IL-10	0.035
IL-13	0.062
IFN- γ	0.028
TNF- α	0.019

P = probability value of differences between the visits 1, 3, and 5 analysed with ANOVA.

Table 3 Effect of treatment and differences between treatments

Parameter	Fitted baseline mean (SE)	Treatment	Effect on parameter	CI	P
IOP (mmHg)	12.38 (0.37)	T	0.08	-0.74, 0.90	0.849
		S	0.05	-0.66, 0.75	0.899
		T-S	0.03	-1.05, 1.12	0.950
Subjective score	4.34 (0.24)	T	-2.13	-2.99, -1.27	<0.001
		S	-1.86	-2.64, -1.08	<0.001
		T-S	-0.27	-1.42, 0.88	0.640
Total skin score ^a	14.05 (0.63)	T	-6.87	-8.48, -5.26	<0.001
		S	-4.48	-6.28, -2.67	<0.001
		T-S	-2.39	-4.79, 0.00	0.050
Eczema score	7.29 (0.35)	T	-4.10	-5.20, -3.00	<0.001
		S	-2.66	-3.84, -1.48	<0.001
		T-S	-1.44	-3.05, 0.17	0.087
Blepharitis score	6.76 (0.43)	T	-2.72	-3.64, -1.80	<0.001
		S	-1.82	-2.74, -0.90	<0.001
		T-S	-0.90	-2.19, 0.39	0.180
Total eye score ^b	3.58 (0.16)	T	-0.20	-0.67, 0.27	0.416
		S	0.05	-0.42, 0.52	0.835
		T-S	-0.15	-0.82, 0.52	0.513
Conjunctivitis score	2.88 (0.11)	T	-0.17	-0.54, 0.20	0.380
		S	-0.01	-0.38, 0.36	0.953
		T-S	-0.16	-0.69, 0.37	0.556
Keratitis score	0.85 (0.14)	T	-0.04	-0.31, 0.23	0.794
		S	0.07	-0.19, 0.33	0.652
		T-S	-0.11	-0.48, 0.26	0.566
Eosinophils (cells/ μ l tear fluid)	25.36 (7.54)	T	-10.78	-22.56, 1.00	0.073
		S	-8.80	-2.79, 20.38	0.135
		T-S	-1.98	-16.50, 14.54	0.811
Granulocytes (cells/ μ l tear fluid)	366.0 (92.18)	T	-64.4	-270.8, 141.95	0.535
		S	-101.3	-319.7, 117.1	0.358
		T-S	-36.91	-337.4, 263.6	0.806
IL-2 (pg/ml)	26.94 (2.76)	T	2.05	-6.87, 10.97	0.648
		S	-0.70	-8.20, 6.80	0.853
		T-S	2.75	-8.91, 14.41	0.638
IL-4 (pg/ml)	46.02 (6.59)	T	19.52	-1.84, 40.88	0.074
		S	18.37	-4.25, 41.00	0.111
		T-S	1.15	-14.41, 16.71	0.944
IL-5 (pg/ml)	1.49 (0.50)	T	-1.14	-3.82, 1.54	0.398
		S	-0.53	-3.07, 2.01	0.679
		T-S	-0.61	-4.31, 3.09	0.742
IL-8 (pg/ml)	367.8 (80.65)	T	-263.6	-538.6, 11.40	0.062
		S	-45.92	-322.5, 230.7	0.741
		T-S	-190.7	-580.7, 199.3	0.331
IL-10 (pg/ml)	55.16 (5.54)	T	3.57	-12.05, 19.19	0.650
		S	4.86	-10.32, 20.04	0.526
		T-S	-1.29	-23.07, 20.49	0.906
IL-13 (pg/ml)	160.3 (18.96)	T	-26.90	-77.46, 23.66	0.293
		S	-19.52	-77.40, 38.36	0.503
		T-S	-7.38	-84.24, 69.48	0.848
IFN- γ (pg/ml)	106.5 (10.08)	T	2.25	-23.19, 27.69	0.860
		S	-6.49	-27.77, 14.79	0.545
		T-S	8.74	-24.42, 41.90	0.599
TNF- α (pg/ml)	17.76 (1.46)	T	-1.24	-4.92, 2.44	0.504
		S	-1.16	-4.46, 2.14	0.483
		T-S	-0.08	-5.02, 4.86	0.513

The effects of tacrolimus treatment (T) steroid treatments (S) and the difference of T-S. Model-based fitted values after elimination of individual effects.

SE = standard error, CI = 95% confidence interval, P = probability value.

^aTotal skin score = eyelid eczema + blepharitis score.

^bTotal eye score = conjunctivitis + keratitis score.

compare the respective treatment effects within each individual (Table 3). Categorical data were analysed with the sign test. *Post hoc* analyses of baseline global objective scores in relation to treatment preference and to the presence of SEB were performed with the Mann–Whitney test. Spearman correlation test was used to explore various associations. A *P*-value <0.05 was defined as statistically significant.

Results

Patients, participant flow, assessment of baseline values

Overall, the disease activity in the study group was moderate. Twenty-five patients were recruited, of whom three patients could not withstand the first washout period without using steroid eye drops, and were consequently excluded. The remaining 22 were included and provided with study medication. One patient was lost to follow-up early in the study and another patient was excluded owing to use of steroid ointment as an add-on to study medications. Thus, 20 patients completed the trial (nine females and 11 males; average age \pm SD: 46 \pm 12 years, range 18–70 years). Compliance and documentation was generally satisfactory. One participant made a minor protocol deviation by taking oral antibiotics. He was therefore excluded from the microcolonization analyses. Additionally, four subjects took antihistamine tablets on few occasions because of general allergic symptoms. No one discontinued the trial owing to adverse events, but several patients found the washout periods almost intolerable, and two patients had such severe disease that the last period of washout could not be justified. To ascertain the validity of the crossover design, the three baseline values were compared. Neither scores for the eczema or blepharitis nor IOP values, bacterial or fungal flora differed significantly between nontreatment examination days. Conversely, there were significant alterations for ocular signs and for some inflammatory markers in tear fluid between baseline measurements (Table 2).

Effect on signs and symptoms

Both ointments provided significant improvement for eyelid eczema and blepharitis scores as well as for subjective symptoms (Table 3). No difference in effect between tacrolimus and steroid ointment could be proven, but the total skin (eczema + blepharitis) score was almost statistically significant in favour of tacrolimus, *P* = 0.05 (Table 3). No significant effect was shown for ocular surface scores after either treatment. Baseline values differed significantly for this parameter (Table 2), and therefore the first treatment period only

was further analysed. Once again, no treatment effect was detected, making carryover or rebound effects a less likely explanation of the significant baseline variability. After the last washout, the patients were asked to make a global evaluation of the therapies: four expressed no preference; 11 patients preferred tacrolimus ointment; and five favoured steroid ointment, *P* = 0.2. Patients who preferred tacrolimus ointment had higher total objective scores at inclusion, *P* = 0.03.

Effect on tear markers of inflammation

Owing to sampling difficulties and technical failure, 6/100 cytology slides were not amenable to analysis. No effect on eosinophil or neutrophil numbers was proven after either therapy. Four patients were excluded from the cytokine analysis because of insufficient tear volumes. No baseline variability was seen for IL-4, IL-5, IL-8, and IL-13 (Table 2). Trends of reduction for IL-4, *P* = 0.07, and IL-8, *P* = 0.06 were observed after tacrolimus treatment only (Table 3). For the other cytokines, there was a significant variability in analogy with the conjunctivitis scores. A *post hoc* analysis of the first treatment period revealed that only IL-2 and TNF- α were significantly responsive to treatment and only to tacrolimus. Consequently, no significant carryover or rebound effects are suspected for the cytokines in general. Expected associations between eosinophil numbers and IL-5 as well as neutrophil numbers and IL-8 were confirmed (data not shown).

Side effects/tolerance

IOP was not significantly changed by any of the ointments and no significant difference between the therapies was observed (Table 3). For these calculations, the mean pressure between the eyes was used. The IOP response variable, defined as an increase above 2 mmHg in either eye, was noted for 3/20 steroid- and for 5/20 tacrolimus-treated patients, of whom one responded to both treatments. No patient had an asymmetric response, that is a decrease of IOP in one eye and an increase in the other, but some patients had a larger difference in one eye than in the other. Two participants showed an increase of 5 mmHg, one on steroid and one on tacrolimus therapy. The pressure was normalized in both cases after washout. Seven patients reported initial skin burning during tacrolimus application, whereas no one on steroid experienced this untoward effect, *P* = 0.02. For six of these seven patients, the burning lasted for 2–5 days. In addition, two patients complained about a dry feeling of the eye and eyelids and another patient described fluctuating symptoms with red eyes and tearing during tacrolimus treatment. During steroid

treatment, eight patients reported increased itching. No other adverse events were reported.

Effects on microcolonization

Microcolonization was not influenced in a significant way by either treatment. The analysis was qualitative; hence, the presence of different species only and not the actual amount of bacteria could be assessed. *Coagulase-negative staphylococci* (CONS) were isolated from all patients and *Staphylococcus aureus* (SA) in 18/19 patients. Also in patients with an almost total clearing of signs and subjective symptoms, both CONS and SA were present. Other bacteria seen in few samples were *Haemophilus influenzae*, *Moraxella catarrhalis*, *Corynebacterium* species, and *Propionibacterium acnes*. In only two patients, *Malassezia sympodialis* was isolated. One patient reported a relapse of herpes on the eyelid during washout after tacrolimus treatment. This could not be confirmed as it had resolved before the following visit.

Serum IgE antibodies against *S. aureus* enterotoxin B antigen

Five out of 20 patients were tested positive for SEB, median 2.5 kAU/L and range 0.4–17 kAU/L. The five patients with positive SEB test had significantly higher disease scores, regarding both eczema and eye surface parameters, than those tested negative $P = 0.03$.

Discussion

There are no evidence-based guidelines for the treatment of eyelid eczema. This explorative short-term comparative crossover study investigated tacrolimus 0.1% *vs* a mid-potent steroid ointment for eyelid eczema of moderate severity in AKC patients. The main objective was to evaluate whether tacrolimus would be a safer alternative to steroid treatment in the eyelid region by not inducing a rise in IOP. Tacrolimus 0.1% was chosen because of significantly better effect than that of tacrolimus 0.03% without increase in adverse events,^{11,12} and because of proven similar anti-inflammatory properties to a mid-potent steroid.¹⁹ The clobetasone butyrate ointment was selected because of the ointment-base with White Vaseline that it shares with the tacrolimus formulation on sale in Sweden, thereby facilitating masking. The 3-week treatment periods were mainly warranted from a safety point-of-view, as we hypothesized that the steroid ointment could induce IOP elevations. Moreover, it is known from previous eczema studies that the onset of the anti-inflammatory effect occurs within the first 2 weeks with both treatments.^{17,19} The 2-week washout was justified from a patient comfort perspective.

Both treatments significantly reduced eczema signs and symptoms in agreement with the literature. Although tacrolimus was associated with tolerance problems, that is transient skin burning, the treatment was preferred by a majority of the patients. The hypothesized increase in IOP of at least 2 mmHg in 30% of the study population after steroid application could not be confirmed. Interestingly, one subject treated with tacrolimus and one receiving clobetasone butyrate reacted with a marked increase in IOP. The IOP was normalized on check-up, but clearly, this study suggests that the risk for IOP being affected by eyelid immune-modulating ointments needs to be elucidated in long-term settings also for tacrolimus, although previous reports do not indicate such a risk.^{7,20}

Results from studies with tacrolimus and steroid have indicated a reduction of SA colonization paralleling a decrease of inflammatory signs,²¹ which could not be confirmed in the present study. The role of SA in AKC is not fully known and there seems to be no simple relation between SA colonization and severity of AKC.¹⁸ Another aspect of the interaction between bacteria and atopic eczema is the risk for superinfection during immune-suppressive therapy. This was not observed in the present investigation, which is in line with previous findings.²² Finally, SEB has been implicated as a disease factor in AD and perhaps also in AKC.^{18,23} Such involvement was again apparent in this study where the subjects who had detectable levels of SEB in the serum had significantly higher disease activity scores than the other subjects.

In patients with AD²⁴ and AKC,²⁵ recurrent herpes simplex infections are not uncommon and a suspected increase of herpes simplex lesions during tacrolimus therapy has been a concern.^{26,27} This complication was therefore particularly examined, but apart from a reported recurrence of herpes on the eyelids, no viral lesions were observed in our trial.

Corneal disease is the major sight-threatening complication of AKC. There are at present no data suggesting that conjunctivitis and keratitis are generated by the eczema or closely interrelated, although in the present study a good correlation was seen between skin and eye affection (data not presented). It is quite plausible that at least blepharitis may induce and promote ocular surface changes in AKC, as has been substantiated in observational studies of other blepharitis entities.^{28,29} A positive effect of extended eyelid treatment with tacrolimus has also been reported on conjunctivitis and keratitis.^{13,16,20} Hence, we wanted to know whether a reduction of ocular surface inflammation could be produced by regional eczema treatment. Moreover, there seems to be a positive relationship between conjunctival disease and inflammatory cells as well as cytokines in

tear fluid,¹⁸ which was the reason why these objective measures were included in our protocol. However, neither the clinical signs nor the tear markers were significantly influenced by the study medications. Still, it cannot be entirely ruled out that eyelid eczema ointments may have these 'spin-off' benefits. First and mainly, there may have been too short a treatment period to achieve ocular surface effects. Second, the selection of patients with moderate conjunctivitis and keratitis manifestations and also the number of patients may have been decisive. Third, the cytokine analysis used herein appears to have been less sensitive than the one previously employed by our group.¹⁸ Finally, a significant effect on tear markers of inflammation could probably not be expected considering the lack of impact on the conjunctiva of the treatments.

In conclusion, both treatment concepts proved efficacious in reducing eczema signs and symptoms while not raising any immediate safety concerns. The lack of proven benefits on the ocular surface disease warrants studies over a longer period of time, preferably including AKC patients with severe manifestations, whose need to administer add-on steroid or cyclosporine eye-drops could be used as an efficacy criterion. Long-term studies are also called for to confirm safety regarding IOP changes.

The effects and safety profile of tacrolimus ointment used in an extended period of time are not known, which explains its current second-line status in AD. A serious safety signal of malignant tumour appearance has emerged for systemic tacrolimus treatment,³⁰ but concerning topical administration, several studies have demonstrated only a minimal absorption of the drug.^{12,17,19} However, carcinogenesis at the application site has been shown in a mouse model.³¹ In addition, single incidents of malignancy in humans after topical tacrolimus application have been reported,³² but to date there is no evidence of an increased risk.³³ A relation between these tumours and UV-light damage is suspected and ultraviolet exposure should hence be avoided during tacrolimus treatment. Until further knowledge is reached, the US Food and Drug Administration, FDA, has recommended a 'black box' warning,³⁴ whereas The European Agency for Evaluation of Medical Products, EMEA, has taken no such action.³⁵

Based on the presently reported data, we conclude that tacrolimus ointment is a promising alternative to steroid ointment for eyelid eczema in AKC patients, but the said safety and efficacy aspects warrant further exploration.

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