



Dermatologic tacrolimus ointment on the eyelids for steroid-refractory vernal keratoconjunctivitis

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Abstract

Purpose The study aims to evaluate the therapeutic effects of dermatologic tacrolimus ointment on eyelids to treat refractory vernal keratoconjunctivitis (VKC).

Method This institutional study examined the effects of steroid treatment for 10 patients diagnosed with severe VKC refractory to steroid treatment. Patients received 0.1% dermatologic topical tacrolimus treatment on their eyelids once or twice daily for concomitant atopic dermatitis. The therapeutic outcomes were evaluated according to change in severity of clinical findings recorded with serial external ocular photography and change in requirement for steroid treatment.

Results Clinical signs and symptoms improved substantially after tacrolimus treatment. Significant reduction in size of papillae, decrease of discharge, improvement in hyperemia, and shield ulcer healing with re-epithelization were observed in all patients. Six out of 10 (60%) patients did not receive steroid treatment. Long-term maintenance of tacrolimus was required to prevent episodic exacerbation. Patients' only treatment-related complaints were of mild burning sensations during medication application to eyelids, and this sensation disappeared a few days after treatment.

Conclusions Application of 0.1% dermatologic tacrolimus ointment to eyelids is effective and safe in the treatment of refractory VKC in patients with concomitant atopic dermatitis. This treatment may serve as a substitute for or decrease the requirement of steroid treatment.

Keywords Vernal keratoconjunctivitis · Steroid · Dermatologic tacrolimus ointment · Eyelid

Introduction

The treatment of vernal keratoconjunctivitis (VKC) is challenging for ophthalmologists because of the wide variation in the presentation of this disease, its recurrent nature, and complex comorbidities [1]. Bonini et al. [2] followed a case series of 195 patients with VKC for over 3 years and found that 27% of the patients experienced complete resolution, 35.4% showed improvement but mild-to-moderate persistence of symptoms, and 32% exhibited no change in signs or symptoms in response to

therapy. However, severe decline in visual acuity still occurred in patients with ulcerative keratitis, corneal scarring, and neovascularization [2]. Among such severe cases of VKC, especially in patients with Bonini grades 3 or 4, flares and exacerbations often threaten vision and may lead to eventual corneal ulceration and scarring [2, 3].

Treatment options for VKC encompass environmental control, the administration of medication, and surgery [4, 5]. Pharmacologic therapies exhibit low side-effect profiles and are easy to use; hence, they are suitable for the treatment of mild chronic symptoms of VKC. These therapies include topical vasoconstrictors [6], antihistamines [6], and mast cell stabilizers (such as 4% cromolyn sodium, 2% nedocromil sodium, and 0.1% lodoxamide) [7], selective histamine (H1) receptor antagonist (such as 0.05% levocabastine, 0.2% olopatadine, 0.05% epinastine, 0.025% ketotifen, and 0.25% alcaftadine) [8, 9], and 0.5% ketorolac or 0.1% diclofenac [10]. Stronger anti-inflammatory medications including 0.1% fluometholone, 0.5% loteprednol, 1% prednisolone acetate, and 0.1% dexamethasone phosphate are the primary

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treatment modalities for patients with flares or exacerbations of VKC [11–13]. However, prolonged topical steroid use induces cataracts and glaucoma in 2% of patients with VKC [2]. Supratarsal injection of dexamethasone sodium phosphate (2 mg) or triamcinolone acetonide (20 mg) has been demonstrated to improve symptoms of severe VKC [14, 15], but these injections may increase intraocular pressure and administration presents complications, such as the challenge of intraocular injection in children without anesthesia. Numerous clinical trials have demonstrated that topical 1–2% cyclosporine A decreases signs and symptoms of VKC [16–19]. However, topical 2% cyclosporine A is not commercially available and must be formulated by a compounding pharmacy. It is also not available in Taiwan. Tacrolimus ointment and eye drops have been identified as promising anti-inflammatory agents, and applied as effective treatments for patients with severe VKC who are resistant to topical cyclosporine [20–22]. In a Japanese study, tacrolimus eye drops were highly effective in treating refractory allergic conjunctivitis with proliferative lesions and corneal involvement, and the results suggested that the treatment reduced the requirement for or replaced topical steroid use [23].

Tacrolimus eye drops are effective for the treatment of severe VKC; however, these eye drops are only available in certain countries. Because of the limited availability of tacrolimus eye drops and side effects of long-term steroid use, we attempted to identify other options for the treatment of severe refractory VKC. Severe cases of VKC involve concomitant atopic eyelid dermatitis. Thus, in this study, we retrospectively identified patients in which topical tacrolimus dermatological ointment was used on the upper eyelid skin to treat severe VKC with concomitant atopic dermatitis. Here, we report 10 cases involving patients with VKC whose symptoms resolved significantly after dermatologic tacrolimus ointment was applied to their eyelids.

Patients and methods

A retrospective review was conducted of all patients diagnosed with severe VKC who received topical dermatological tacrolimus ointment on their upper eyelids between January 2016 and January 2018 at National Taiwan University Hospital. Diagnosis of VKC was based on the patients' history, age, and the presence of typical clinical signs and symptoms. Patients presenting with cobblestone-like papillae as well as a history of seasonal aggravation of ocular symptoms and signs received diagnoses of VKC [24]. The study adhered to the tenets of the Declaration of Helsinki. The Institutional Review Board of National Taiwan University Hospital approved this study.

The demographic data recorded were date of presentation and commencement of tacrolimus, duration of disease before starting tacrolimus treatment, previous immunosuppressive

treatment, concomitant use of other immunosuppressant medication, frequency and concentration of topical dermatologic tacrolimus applied, change in immunosuppressive agents after tacrolimus treatment, and duration of follow-up. Clinical data were the findings on standard ophthalmological examinations, serial external eye photography, and subjective changes in symptoms during follow-up. Slit-lamp photographs of upper tarsal conjunctiva and cornea were used to evaluate the clinical findings. The scoring system for clinical signs and severity of VKC was demonstrated in Table 1. The conjunctival reactions in VKC were assessed according to conjunctival injection, edema, the height of papillae, and mucous discharge on the upper tarsal conjunctiva, and were scored according to the following scale: 0, none; 1, mild injection, flat papilla (1 mm), discharge covering less than half the area; 2, moderate injection, giant papilla (2 mm), or discharge covering more than half the area; 3, severe injection, giant papilla in the eyelid (3 mm), or discharge covering the entire upper tarsal conjunctiva; and 4, very severe injection, giant papilla in the eyelid (4 mm), or considerable mucus discharge on the ocular surface or between papillae. Additionally, clinical severity of corneal involvement according to superficial punctate keratitis (SPK), corneal erosion, epithelial defect, calcium plaque formation, and shield ulcers was scored as follows: (0) clear cornea, (1) SPK in less than half of the cornea, (2) SPK in more than half of the cornea, (3) epithelial defect, and (4) shield ulcer or calcium plaque. Anti-inflammatory effects and dependence on immunosuppressive agents were scored as (0) none, (1) topical nonsteroidal anti-inflammatory drugs or mast cell stabilizers, (2) topical fluometholone, (3) topical betamethasone, or (4) systemic steroid or immune suppression with topical betamethasone. These scores are modifications of previously reported criteria [25]. The quiescent phase of uveitis was defined as no cell, flare, or keratic precipitate found in anterior chamber by slit lamp exam. The refraction before and after treatment were recorded if available (Table 2). The concentration of topical dermatologic tacrolimus ointment (Protopic, Astellas Pharma, Inc., Astellas Way, Northbrook, IL, USA) was 0.1% in this study.

All data were analyzed using SPSS (IBM Corp, New York, NY, USA). Quantitative variables are presented as mean $\pm$ SD, and qualitative variables are presented as percentages. Nonnormally distributed data were compared using the Wilcoxon signed-rank test. All the tests were two-tailed, and $P < 0.05$ was considered significant.

Results

In total, 10 patients received topical dermatologic ointment on their eyelids to treat refractory VKC (Table 2). The patients in our study were all categorized as exhibiting the tarsal form, except patient 8 presented both mixed tarsal and limbal form.

Table 1 Scoring system for clinical signs and severity of VKC

	Conjunctival reaction	Corneal reaction	Dependence on immunosuppressive agents
Score 0	None	Clear cornea	None
Score 1	Mild injection Flat papilla (1 mm) Discharge covering less than 1/2	SPK less than 1/2 area	Topical NSAID or mast cell stabilizers
Score 2	Moderate injection Giant papilla (2 mm) Discharge covering more than 1/2	SPK more than 1/2 area	Topical fluorometholone
Score 3	Severe injection Giant papilla in the eyelid (3 mm) Discharge covering the entire upper tarsal conjunctiva	Epithelial defect	Topical betamethasone
Score 4	Very severe injection Giant papilla in the eyelid (4 mm) Considerable discharge on the ocular surface or between papillae	Shield ulcer or calcium plaque	Systemic steroid or immune suppression with topical betamethasone

VKC Vernal keratoconjunctivitis, SPK Superficial punctate keratitis, NSAID Nonsteroidal ant-inflammatory drug

All patients were male. The mean age at evaluation was 10.5 ± 2.3 years (mean $\pm$ SD, range 7–14 years). The mean follow-up period was 15.10 ± 9.61 months (mean $\pm$ SD, range 1–26 months). All of these 10 patients were refractory to topical betamethasone before topical tacrolimus treatment (Table 2). Only one patient (patient 6) had been treated with topical cyclosporine in the past with disappointing results. There were no signs of uveitis in these 10 patients before and after treatment (Table 2). The refractive change before and after treatment is not statistically significant ($P = 0.785$, Wilcoxon signed-rank test; Table 2). The refractive change was not significant after treatment probably due to a small case number. Furthermore, refraction was difficult to obtain while patients had cornea complications, such as cornea epi-defect and vernal plaques.

Diffuse conjunctival injection, papillary reaction, superficial punctate keratopathy, and shield ulcer in the studied patients were refractory to standard treatment, which included 0.1% topical betamethasone eye drops. Additionally, after standard treatment, intraocular pressure spikes were observed in all patients. All patients presented with shield ulcer and giant papillary reaction of the upper eyelid (Fig. 1), and four patients (patients 2, 5, 9, and 10) exhibited associated calcium plaques in their corneas.

Patient demographic characteristics and treatment parameters are listed in Table 2. All patients tolerated the topical dermatologic tacrolimus ointment well. Administration of the drug was continued during follow-up. The duration of disease before tacrolimus treatment was 3 months to 9.3 years (mean $\pm$ SD, 51.60 ± 41.78 months), and the follow-up after tacrolimus treatment was 1 to 26 months (mean $\pm$ SD, 15.10 ± 9.61 months). None of the patient histories indicated herpetic keratitis.

Initially, all patients received concomitant topical betamethasone at low frequencies of one to four times a day,

except patient 7, who received topical betamethasone every 2 h; however, after 2 weeks, the treatment frequency of patient 7 was reduced to four times a day. Steroid administration for all patients was tapered to once every 1 or 2 days after papillae and corneal ulcer improvement. The treatment aim was to fully replace steroid administration with dermatologic ointment. Nonocular allergic manifestations were present in all of the patients with VKC. The most frequent associated disease was atopic dermatitis (10/10, 100%), followed by asthma (6/10, 60%), and allergic rhinitis (5/10, 50%).

All patients presented with shield ulcer complications, which, for all patients, was cured with full re-epithelialization or scattered SPKs after dermatologic topical tacrolimus treatment (Fig. 1). For example, in patients 4 and 7, ulcer re-epithelialization was completed 2 weeks after treatment commenced. Thus, the treatment dramatically decreased patients' pain and discomfort and enhanced their quality of life in a short time. In patients 5 and 9, band keratopathy and calcium plaque healed as soon as 2 months after treatment started. In patient 2, severe calcium plaque was resolved with almost total re-epithelialization within 3 months of tacrolimus treatment. In patient 10, calcium plaque disappeared within 5 months of treatment, enabling treatment of giant papillae-related band keratopathy without surgical debridement.

Regarding symptom relief, significant improvements in symptoms (e.g., itching, redness, photophobia, ocular discomfort, foreign body sensation, and tearing), decrease in discharge were observed within 2 weeks after treatment started. The biomicroscopic findings before and after treatment are presented in Fig. 1. Resolution of shield ulcer, reduced conjunctival hyperemia, and improvement of eyelid swelling were observed in all patients. Substantial flattening and decreases in papillae size were observed in all patients.

In patient 6, persistent cornea shield ulcer under topical 0.05% cyclosporine solution treatment was observed despite

Table 2 Demographic data and treatment responses of 10 patients with VKC

Patient	Age	Sex	Associated atopic disease	Diagnosis	Duration before Tacrolimus treatment (months)	Tacrolimus (concentration/- frequency)	Follow-up duration (months)	Conjunctival reaction score before treatment (R/L)	Conjunctival reaction score after treatment (R/L)	Cornea score before treatment (R/L)	Cornea reaction score after treatment (R/L)	Steroid score before treatment	Steroid score after treatment
1	13	M	AR, AD	VKC	24	0.1% BID		3/3	1/1	4/4	0/0	3	0
2	7	M	AR, AD, asthma	VKC	70	0.1% BID	22	3/3	2/2	4/2	0/0	3	3
3	11	M	AD, asthma	VKC	24	0.1% BID	20	1/2	0/1	2/4	0/0	3	0
4	12	M	AD, asthma	VKC	25	0.1% BID	4	2/1	1/1	4/1	0/0	3	0
5	7	M	AR, AD	VKC	4	0.1% BID	22	3/2	1/1	4/4	0/0	3	3
6	11	M	AR, AD, asthma	VKC	47	0.1% BID	21	2/2	1/1	4/4	0/0	3	0
7	10	M	AD, asthma	VKC	3	0.1% BID	1	2/1	1/1	4/0	0/0	3	3
8	10	M	AD, asthma	VKC	24	0.1% BID	11	4/4	3/3	4/3	1/2	3	0
9	10	M	AD	VKC	3	0.1% BID	2	3/1	2/1	4/0	1/0	3	0
10	14	M	AD, AR	VKC	112	0.1% BID	22	3/3	2/2	2/4	0/1	3	3
Patient	Age	Sex	Associated atopic disease	Diagnosis	Duration before Tacrolimus treatment (months)	Tacrolimus (concentration/- frequency)	Follow up duration (months)	Refraction before treatment (R/L)	Refraction after treatment (R/L)	Uveitis before treatment (R/L)	Uveitis after treatment (R/L)		
1	13	M	AR, AD	VKC	24	0.1% BID		-3.25/-2.0	-2.75/-1.5	Nil/Nil	Nil/Nil		
2	7	M	AR, AD, asthma	VKC	70	0.1% BID	22	-5/-3.75	-5.25/-4.0	Nil/Nil	Nil/Nil		
3	11	M	AD, asthma	VKC	24	0.1% BID	20	-6.5/-4.25	-7.0/-4.25	Nil/Nil	Nil/Nil		
4	12	M	AD, asthma	VKC	25	0.1% BID	4	NA	NA	Nil/Nil	Nil/Nil		
5	7	M	AR, AD	VKC	4	0.1% BID	22	+1.25/-0.75	+1.00/-1.25	Nil/Nil	Nil/Nil		
6	11	M	AR, AD, asthma	VKC	47	0.1% BID	21	-0.75/-0.25	-0.75/-0.5	Nil/Nil	Nil/Nil		
7	10	M	AD, asthma	VKC	3	0.1% BID	1	NA	NA	Nil/Nil	Nil/Nil		
8	10	M	AD, asthma	VKC	24	0.1% BID	11	NA	NA	Nil/Nil	Nil/Nil		
9	10	M	AD	VKC	3	0.1% BID	2	NA	NA	Nil/Nil	Nil/Nil		
10	14	M	AD, AR	VKC	112	0.1% BID	22	NA	NA	Nil/Nil	Nil/Nil		

AR atopic rhinitis, AD atopic dermatitis, R right eye, L left eye

AR atopic rhinitis, AD atopic dermatitis, R right eye, L left eye, NA not available

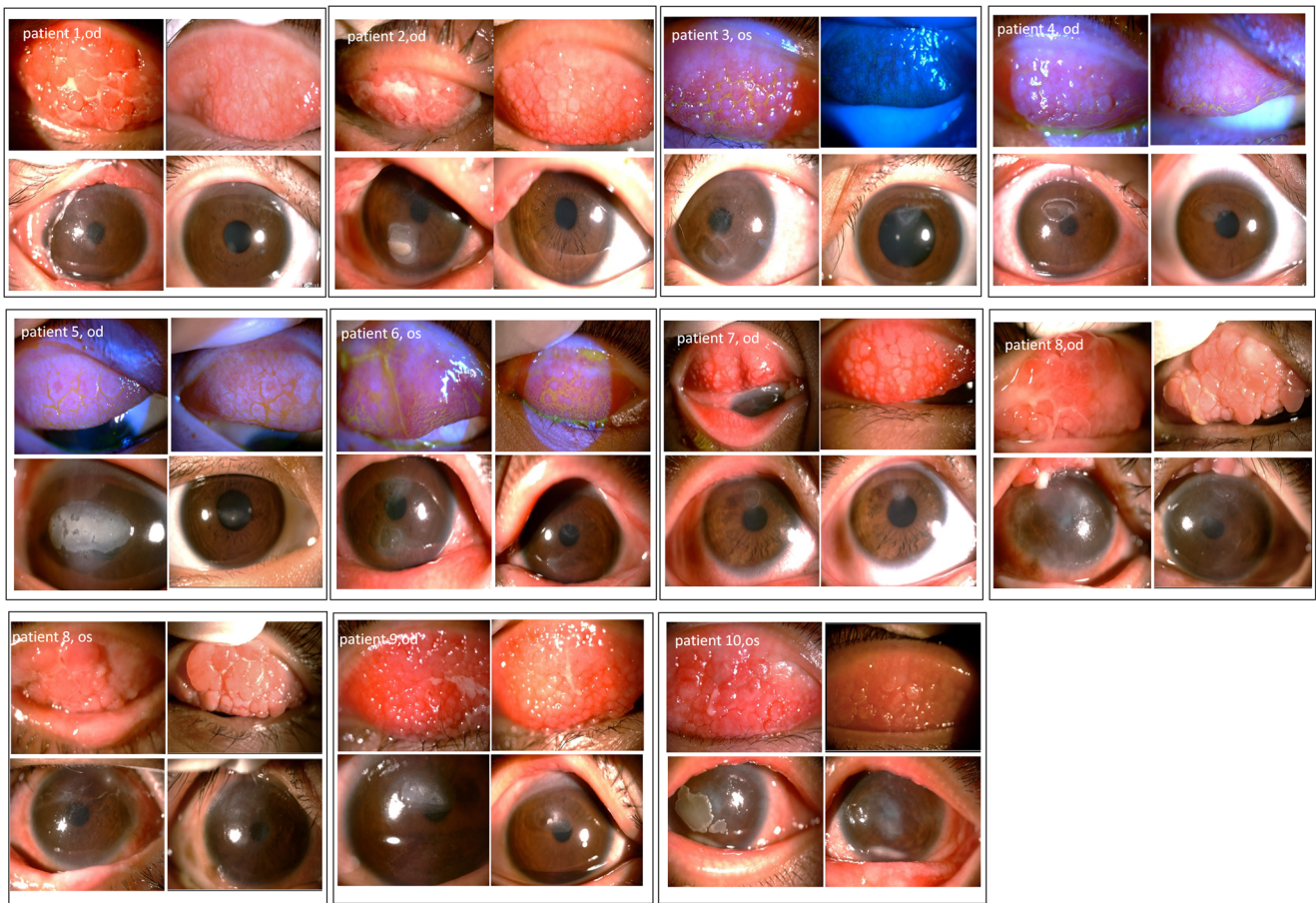


Fig. 1 External ocular photography of upper tarsal conjunctivas and corneas of 10 patients before and after tacrolimus treatment. The representations of patient's eyes are each a composite of four pictures: a picture of the upper tarsal conjunctiva before treatment in the left upper panel, a picture of the cornea before treatment in the left lower panel, a picture of upper tarsal conjunctiva after treatment in the right upper panel, and a picture of the cornea after treatment in the right lower panel. The conjunctival photos of patient 5 are exceptions; they were taken 3 months (left upper panel) and 1 year (right upper panel) after treatment. The photos of patients 1 to 4 are arranged from left to right in the first row. The second row comprises photos of patients 5 to 8 (od, right eye) arranged from left to right. The third row presents photos of patient 8 (os, left eye) to 10. Please refer to Table 1 for patient demographic data. All patients were refractory to topical 0.1% betamethasone treatment. All patients were diagnosed as having VKC. The photos indicate giant papillae formation in VKC patients before treatment (left upper panel of each patient). Before treatment, diffuse papillary hypertrophy was

observed in patients' upper tarsal conjunctivas, and some of which resembled cobblestones (left upper panel of patients 1, 2, 3, 4, 7, 8, 9, and 10). Shield ulcers were observed in all patients with prominent vernal plaques, as shown in the photos of patients 2, 5, 9, and 10 (left lower panel). After 0.1% tacrolimus ointment was applied on patients' upper eyelids, significant shrinkage and flattening of papillae (right upper panel), decreased conjunctival hyperemia (right upper panel), decreased discharge (right upper panel), and healing of shield ulcers (right lower panel) were observed in all of the patients. Vernal plaques were greatly reduced, with full epithelialization and faint scarring after treatment in patients 2, 5, 9, and 10 (right lower panel). Patient 6 exhibited persistent shield ulcer (left lower panel) and conjunctival hyperemia (left upper panel) with discharge (left upper panel) despite topical steroid and 0.1% cyclosporine treatment. Decreased conjunctival inflammation (right upper panel) and healed shield ulcer (right lower panel) were observed after tacrolimus treatment. No conjunctival scarring was observed after treatment

a decrease in the frequency of conjunctival injection. The patient's pediatrician had administered 0.03% tacrolimus ointment, but the treatment was ineffective. One month after the patient's treatment had been shifted from cyclosporine to 0.1% dermatologic tacrolimus ointment, the keratitis had healed. Tacrolimus is more potent than cyclosporine in treating shield ulcers. However, recurrence of signs and symptoms was observed in patient 6 when the patient discontinued the medication on his own after the first month of treatment. When the administration of the medication was resumed, the symptoms resolved quickly. Patient 2 also exhibited an

increased papillae size at 21 months of follow-up due to poor compliance with medication. Long-term maintenance of tacrolimus is necessary to prevent recurrence.

Representative parameters of treatment effects were evaluated in all 10 patients. The mean conjunctival reaction score was significantly reduced, from 2.40 ± 0.94 to 1.4 ± 0.75 , after treatment ($P = 0.0003$, Wilcoxon signed-rank test; Table 2). The mean corneal reaction score was significantly reduced from 3.10 ± 1.41 to 0.25 ± 0.55 after treatment ($P = 0.0002$, Wilcoxon signed-rank test; Table 2). In 6 out of the 10 patients, tacrolimus treatment enabled discontinuation of steroid

treatment. The other four patients continued to receive topical betamethasone at low frequencies of one to four times a day. The steroid score before tacrolimus treatment was significantly reduced after treatment, from 3.3 ± 0.2 to 0.4 ± 0.3 ($P < 0.05$, Wilcoxon signed-rank test; Table 2).

A common side effect of topical tacrolimus was a tolerable burning sensation on the eyelids, and this sensation disappeared a few days after continual use. No secondary bacterial or herpes simplex virus/varicella zoster virus infections were identified as of the follow-up recorded for this study.

Discussion

Tacrolimus is a 23-member macrolide lactone compound isolated from *Streptomyces tsukubaensis* and is 100 times as potent as cyclosporine [26]. Tacrolimus binds to immunophilin FK-binding protein (FKBP-12), inhibits calcineurin activity, and, subsequently, suppresses the formation of TH1 (interleukin [IL]-2, interferon γ) and TH2 cytokines (IL-4, IL-5) [27]. Tacrolimus also inhibits the release of histamines and other inflammatory mediators from basophils, thereby attenuating allergic symptoms [28]. Since 2000, topical 0.03% and 0.1% dermatologic tacrolimus ointments have been approved by the Federal Drug Administration as second-line agents for the treatment of atopic dermatitis [29]. However, tacrolimus is only available in eye drop and ointment forms in a few countries, such as Japan [30]. In Taiwan, neither tacrolimus eye drops nor ointments are available for ophthalmic use, but dermatologic tacrolimus ointments are available for patients with atopic dermatitis. In our case series, surprisingly, we revealed that dermatologic application of tacrolimus was not only effective in treating steroid-refractory VKC but also did not induce the ocular surface side effects caused by ophthalmic tacrolimus ointments or solutions. Long-term usage of tacrolimus ointment prevented recurrence. We also observed that dermatologic tacrolimus ointment was more effective as a treatment for shield ulcer than topical ophthalmic cyclosporine solution.

One incidental finding of dramatic AKC improvement after tacrolimus ointment treatment on the eyelids was reported by a dermatologist; however, they did not observe the same effect for VKC [31]. By contrast, our results indicated that 0.1% topical dermatologic tacrolimus ointment was a highly effective treatment for steroid-refractory VKC. In a study with a 10-year follow-up, topical dermatologic tacrolimus significantly reduced atopic dermatitis in the affected area, and also attenuated active asthma and rhinitis symptoms and improved bronchial hyperreactivity [32]. In addition, patients who responded to tacrolimus ($\geq 60\%$ improvement of the affected body surface area) also presented significant decreases in serum immunoglobulin E levels [32]. These findings suggest that long-term control with topical tacrolimus on the skin may terminate the inflammatory cascade. In addition,

tacrolimus was undetectable in blood after the administration of 5% tacrolimus eye drops in an animal study [33] and in children for whom 0.03% tacrolimus ointment had been applied in the conjunctival sac [34], which supported the safe use of topical tacrolimus. In patients with atopic dermatitis, drug delivery through the eyelid into the ocular surface may be enhanced by the disrupted skin barrier. In addition, tacrolimus is lipophilic, enabling drug penetration across the stratum corneum via intercellular spaces [35]. Additionally, a higher concentration of tacrolimus ointment, that is, 0.1% rather than 0.03%, facilitates distribution of the drug further into the conjunctiva. Medication is locally diffused through blood-vessel-abundant papillae and conjunctival tissue.

Tacrolimus ocular ointment and eye drops have been reported as safe and effective in the treatment of VKC [23, 28, 36]. However, in a study of 36 patients, Barot and colleagues reported that 13 (36%) complained of a transient burning sensation, and 3 experienced eye irritation (8%) during treatment with 0.1% tacrolimus eye ointment [37]. No corneal complications were observed in Barot's study [37]. Nevertheless, the risk of long-term tacrolimus use must be assessed. In a study of 41 patients, Hazarika and colleagues reported transient foreign body sensation in 16 (39%) patients, transient burning in 14 (34%) patients, and transient blurring of vision in 11 (26%) patients from treatment with 0.03% tacrolimus eye ointment [38]. Furthermore, Fukushima et al. [23] reported transient burning sensations in 46 patients, corneal involvement (bacterial and herpetic keratitis) in 10 patients, and hordeolum in 8 patients after the administration of 0.1% tacrolimus eye drops. According to Fukushima's study, eye drops at the lower concentration of 0.005% were effective in side-effect-free treatment of refractory VKC [23]. However, recurrence of patients' symptoms and signs was noted once the drug was discontinued [39]. Applying dermatologic tacrolimus ointment on the eyelids can treat refractory VKC and avoid the ocular surface complications caused by tacrolimus solution and eye ointments.

Dermatologic tacrolimus ointment exhibited high safety in our study. No secondary bacterial or virus infections were observed at the end of follow-up. Tacrolimus ointment slightly affects steroid treatment and may serve as an alternate treatment for steroid responders and those who are not tolerable to steroid treatment. The ointment has been revealed to induce a substantial treatment response in patients whose symptoms cannot be controlled with steroid or cyclosporine treatment. Tacrolimus ointment is relatively accessible, and dermatologic application may serve as an effective treatment for patients with atopic dermatitis and VKC. Extended follow-up is necessary to evaluate long-term treatment effect and safety.

In conclusion, 0.1% dermatologic tacrolimus applied to eyelids is an effective treatment for patients with refractory VKC and concomitant atopic dermatitis. Long-term maintenance of medication is necessary to prevent recurrence.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not present any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all participants included in the study.

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References

- Shaker M, Salcone E (2016) An update on ocular allergy. *Curr Opin Allergy Clin Immunol* 16:505–510. <https://doi.org/10.1097/ACI.0000000000000299>
- Bonini S, Bonini S, Lambiasi A, Marchi S, Pasqualetti P, Zuccaro O, Rama P, Magrini L, Juhas T, Bucci MG (2000) Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term follow-up. *Ophthalmology* 107:1157–1163
- Bonini S, Sacchetti M, Mantelli F, Lambiasi A (2007) Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* 7:436–441. <https://doi.org/10.1097/ACI.0b013e3282efb726>
- Takamura E, Uchio E, Ebihara N, Ohno S, Ohashi Y, Okamoto S, Kumagai N, Satake Y, Shoji J, Nakagawa Y, Namba K, Fukagawa K, Fukushima A, Fujishima H, Japanese Society of A (2017) Japanese guidelines for allergic conjunctival diseases 2017. *Allergol Int* 66:220–229. <https://doi.org/10.1016/j.alit.2016.12.004>
- Addis H, Jeng BH (2018) Vernal keratoconjunctivitis. *Clin Ophthalmol* 12:119–123. <https://doi.org/10.2147/OPTH.S129552>
- O'Brien TP (2013) Allergic conjunctivitis: an update on diagnosis and management. *Curr Opin Allergy Clin Immunol* 13:543–549. <https://doi.org/10.1097/ACI.0b013e328364ec3a>
- De Smedt S, Wildner G, Kestelyn P (2013) Vernal keratoconjunctivitis: an update. *Br J Ophthalmol* 97:9–14. <https://doi.org/10.1136/bjophthalmol-2011-301376>
- Verin P, Allewaert R, Joyaux JC, Piozzi E, Koliopoulos J, Bloch-Michel E, Lodoxamide Study G (2001) Comparison of lodoxamide 0.1% ophthalmic solution and levocabastine 0.05% ophthalmic suspension in vernal keratoconjunctivitis. *Eur J Ophthalmol* 11:120–125
- Corum I, Yeniad B, Bilgin LK, Ilhan R (2005) Efficiency of olopatadine hydrochloride 0.1% in the treatment of vernal keratoconjunctivitis and goblet cell density. *J Ocul Pharmacol Ther* 21:400–405. <https://doi.org/10.1089/jop.2005.21.400>
- D'Angelo G, Lambiasi A, Cortes M, Sgrulletta R, Pasqualetti R, Lamagna A, Bonini S (2003) Preservative-free diclofenac sodium 0.1% for vernal keratoconjunctivitis. *Graefes Arch Clin Exp Ophthalmol* 241:192–195. <https://doi.org/10.1007/s00417-002-0612-6>
- Tabbara KF, al-Kharashi SA (1999) Efficacy of nedocromil 2% versus fluorometholone 0.1%: a randomised, double masked trial comparing the effects on severe vernal keratoconjunctivitis. *Br J Ophthalmol* 83:180–184
- Oner V, Turkcu FM, Tas M, Alakus MF, Iscan Y (2012) Topical loteprednol etabonate 0.5% for treatment of vernal keratoconjunctivitis: efficacy and safety. *Jpn J Ophthalmol* 56:312–318. <https://doi.org/10.1007/s10384-012-0152-5>
- Tzu JH, Utine CA, Stern ME, Akpek EK (2012) Topical calcineurin inhibitors in the treatment of steroid-dependent atopic keratoconjunctivitis. *Cornea* 31:649–654. <https://doi.org/10.1097/ICO.0b013e32822481c2>
- Saini JS, Gupta A, Pandey SK, Gupta V, Gupta P (1999) Efficacy of supratarsal dexamethasone versus triamcinolone injection in recalcitrant vernal keratoconjunctivitis. *Acta Ophthalmol Scand* 77:515–518
- Holsclaw DS, Whitcher JP, Wong IG, Margolis TP (1996) Supratarsal injection of corticosteroid in the treatment of refractory vernal keratoconjunctivitis. *Am J Ophthalmol* 121:243–249
- Bleik JH, Tabbara KF (1991) Topical cyclosporine in vernal keratoconjunctivitis. *Ophthalmology* 98:1679–1684
- Gupta V, Sahu PK (2001) Topical cyclosporin A in the management of vernal keratoconjunctivitis. *Eye (Lond)* 15:39–41. <https://doi.org/10.1038/eye.2001.10>
- De Smedt S, Nkurikiye J, Fonteyne Y, Tuft S, De Bacquer D, Gilbert C, Kestelyn P (2012) Topical ciclosporin in the treatment of vernal keratoconjunctivitis in Rwanda, Central Africa: a prospective, randomised, double-masked, controlled clinical trial. *Br J Ophthalmol* 96:323–328. <https://doi.org/10.1136/bjophthalmol-2011-300415>
- Spadavecchia L, Fanelli P, Tesse R, Brunetti L, Cardinale F, Bellizzi M, Rizzo G, Procoli U, Bellizzi G, Armenio L (2006) Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood. *Pediatr Allergy Immunol* 17:527–532. <https://doi.org/10.1111/j.1399-3038.2006.00427.x>
- Anzaar F, Gallagher MJ, Bhat P, Arif M, Farooqui S, Foster CS (2008) Use of systemic T-lymphocyte signal transduction inhibitors in the treatment of atopic keratoconjunctivitis. *Cornea* 27:884–888. <https://doi.org/10.1097/ICO.0b013e3281872fbb1>
- Ueta M, Sotozono C, Koga A, Yokoi N, Kinoshita S (2014) Usefulness of a new therapy using rebamipide eyedrops in patients with VKC/AKC refractory to conventional anti-allergic treatments. *Allergol Int* 63:75–81. <https://doi.org/10.2332/allergolint.13-OA-0605>
- Pucci N, Caputo R, di Grande L, de Libero C, Mori F, Barni S, di Simone L, Calvani A, Rusconi F, Novembre E (2015) Tacrolimus vs. cyclosporine eyedrops in severe cyclosporine-resistant vernal keratoconjunctivitis: a randomized, comparative, double-blind, crossover study. *Pediatr Allergy Immunol* 26:256–261. <https://doi.org/10.1111/pai.12360>
- Fukushima A, Ohashi Y, Ebihara N, Uchio E, Okamoto S, Kumagai N, Shoji J, Takamura E, Nakagawa Y, Namba K, Fujishima H, Miyazaki D (2014) Therapeutic effects of 0.1% tacrolimus eye drops for refractory allergic ocular diseases with proliferative lesion or corneal involvement. *Br J Ophthalmol* 98:1023–1027. <https://doi.org/10.1136/bjophthalmol-2013-304453>
- Leonardi A, Secchi AG (2003) Vernal keratoconjunctivitis. *Int Ophthalmol Clin* 43:41–58
- Tanaka M, Dogru M, Takano Y, Miyake-Kashima M, Asano-Kato N, Fukagawa K, Tsubota K, Fujishima H (2006) Quantitative evaluation of the early changes in ocular surface inflammation following MMC-aided papillary resection in severe allergic patients with corneal complications. *Cornea* 25:281–285. <https://doi.org/10.1097/01.icc.0000183533.14899.8d>
- Ganong WF (2005) Review of medical physiology (LANGE basic science) 22nd Edition. McGraw-Hill Medical, New York City
- Sakuma S, Higashi Y, Sato N, Sasakawa T, Sengoku T, Ohkubo Y, Amaya T, Goto T (2001) Tacrolimus suppressed the production of cytokines involved in atopic dermatitis by direct stimulation of human PBMC system. (comparison with steroids). *Int Immunopharmacol* 1:1219–1226

28. Al-Amri AM (2014) Long-term follow-up of tacrolimus ointment for treatment of atopic keratoconjunctivitis. *Am J Ophthalmol* 157: 280–286. <https://doi.org/10.1016/j.ajo.2013.10.006>
29. FDA U (2000) US FDA advisory committee recommends approval of tacrolimus ointment. *Skin Therapy Lett* 6:5
30. Miyazaki D, Tominaga T, Kakimaru-Hasegawa A, Nagata Y, Hasegawa J, Inoue Y (2008) Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. *Ophthalmology* 115:988–992 e985. <https://doi.org/10.1016/j.ophtha.2007.07.025>
31. Zribi H, Descamps V, Hoang-Xuan T, Crickx B, Doan S (2009) Dramatic improvement of atopic keratoconjunctivitis after topical treatment with tacrolimus ointment restricted to the eyelids. *J Eur Acad Dermatol Venereol* 23:489–490. <https://doi.org/10.1111/j.1468-3083.2008.02933.x>
32. Mandelin JM, Remitz A, Virtanen HM, Malmberg LP, Haahtela T, Reitamo S (2010) A 10-year open follow-up of eczema and respiratory symptoms in patients with atopic dermatitis treated with topical tacrolimus for the first 4 years. *J Dermatol Treat* 21:167–170. <https://doi.org/10.3109/09546630903493329>
33. Yuan J, Zhai JJ, Chen JQ, Ye CT, Zhou SY (2009) Preparation of 0.05% FK506 suspension eyedrops and its pharmacokinetics after topical ocular administration. *J Ocul Pharmacol Ther* 25:345–350. <https://doi.org/10.1089/jop.2008.0125>
34. Attas-Fox L, Barkana Y, Iskhakov V, Rayvich S, Gerber Y, Morad Y, Avni I, Zadok D (2008) Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. *Curr Eye Res* 33:545–549. <https://doi.org/10.1080/02713680802149115>
35. Prausnitz MR, Langer R (2008) Transdermal drug delivery. *Nat Biotechnol* 26:1261–1268. <https://doi.org/10.1038/nbt.1504>
36. Miyazaki D, Fukushima A, Ohashi Y, Ebihara N, Uchio E, Okamoto S, Shoji J, Takamura E, Nakagawa Y, Namba K, Fujishima H (2017) Steroid-sparing effect of 0.1% tacrolimus eye drop for treatment of shield ulcer and corneal epitheliopathy in refractory allergic ocular diseases. *Ophthalmology* 124:287–294. <https://doi.org/10.1016/j.ophtha.2016.11.002>
37. Barot RK, Shitole SC, Bhagat N, Patil D, Sawant P, Patil K (2016) Therapeutic effect of 0.1% tacrolimus eye ointment in allergic ocular diseases. *J Clin Diagn Res* 10:NC05–NC09. <https://doi.org/10.7860/JCDR/2016/17847.7978>
38. Hazarika AK, Singh PK (2015) Efficacy of topical application of 0.03% tacrolimus eye ointment in the management of allergic conjunctivitis. *J Nat Sci Biol Med* 6:S10–S12. <https://doi.org/10.4103/0976-9668.166051>
39. Kheirikhah A, Zavareh MK, Farzbod F, Mahbod M, Behrouz MJ (2011) Topical 0.005% tacrolimus eye drop for refractory vernal keratoconjunctivitis. *Eye (Lond)* 25:872–880. <https://doi.org/10.1038/eye.2011.75>