Original Article

Topical tacrolimus versus dexamethasone in managing shield ulcer of vernal keratoconjunctivitis

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a bilateral, chronic, allergic inflammation of the ocular surface with debilitating ocular signs and symptoms. We compared the efficacies and safeties of 1% tacrolimus eye drops and 1% dexamethasone eye drops in managing unilateral shield ulcers and corneal epitheliopathy secondary to VKC.

Methods: We recruited patients with unilateral shield ulcer and corneal epitheliopathy secondary to VKC in a tertiary referral center in southeast Iran during a 12-month period. All eligible patients underwent a detailed eye examination. Participants were randomly assigned to receive either topical tacrolimus 1% or dexamethasone 1% twice daily. We recorded the best-corrected distance visual acuity (BCDVA) in decimal notation, area of the shield ulcer in square millimeters, presence or absence of re-epithelialization, and clinical symptoms of watering, mucus discharge, photophobia, burning, redness, and itching, along with any potential complications at five follow-up visits during a period of four months.

Results: Thirty patients (30 eyes) were allocated to each treatment group. The groups had comparable mean ages and sex distributions (both $P > 0.05$). Both groups experienced a decreasing trend in frequencies of all symptoms, and at most follow-up visits, ocular symptoms were less frequent in the tacrolimus group than in the dexamethasone group, reaching statistically significant differences at some time points (all $P < 0.05$). No re-epithelialization was detected in either group at the second week post-treatment. However, an increasing trend was observed thereafter in both groups, with significantly more re-epithelialization in tacrolimus-treated eyes at the second and third months post-treatment ($P < 0.05$). Re-epithelialization remained significantly more frequent in tacrolimus-treated eyes one month after cessation of treatment ($P < 0.05$). The mean BCDVA was significantly better in tacrolimus-treated eyes than in the dexamethasone group at all follow-up visits (all $P < 0.01$). The mean shield ulcer size tended to decrease in both groups, with lesser numerical values in tacrolimus-treated eyes at the one-, two-, three-, and four-month follow-up visits. The difference reached statistical significance at the last two follow-up visits (both $P < 0.05$).

Conclusions: Topical tacrolimus is superior to topical dexamethasone with regard to symptoms, visual acuity, shield ulcer size, and corneal epitheliopathy associated with VKC. This suggests that tacrolimus could be administered as monotherapy for managing this debilitating ocular inflammatory condition. Further studies are required to determine the long-term safety and efficacy of this promising treatment modality.

KEYWORDS

vernal keratoconjunctivitis, corneal epithelium, bowman's membrane, dexamethasone, tacrolimus, FK-506, topical administration.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, inflammatory ocular disease, with bilateral but asymmetric involvement, causing visual compromise [1]. The inflammatory mediators degrade corneal extracellular matrix proteins in the epithelial basement membrane, resulting in persistent epithelial keratopathy [2, 3]. Subsequently, Bowman's layer is compromised and type 1 stromal collagen is degraded, leading to the formation of an oval-shaped defect with elevated margins. This represents a shield ulcer, a vision-threatening VKC complication [3, 4].

Tacrolimus is an immunomodulatory macrolide with selective inhibition of calcineurin activity and blockade of interleukin-2 production and T-cell activation [5, 6]. It is widely used in the management of immune-mediated, inflammatory anterior segment entities such as VKC. Tacrolimus has satisfactory safety and efficacy profiles when administered in concentrations of 0.005%–0.1%, twice daily as eye drops or ointments, for an unlimited duration of treatment. The efficacy of topical tacrolimus without adjunctive topical steroids for shield ulcers and corneal epitheliopathy suggest that it may be administered alone for managing refractory allergic conjunctivitis [5, 7, 8].

Topical dexamethasone, a corticosteroid with a high relative anti-inflammatory potency compared with other steroids, is frequently used to treat anterior segment inflammation [9]. However, despite topical administration, dexamethasone eye drops could be associated with ocular [10] or systemic complications [9, 11]. These include increases in intraocular pressure (IOP) and elevation of blood glucose levels in patients with controlled diabetes mellitus [9-11]. Similar efficacies have been reported for topical dexamethasone and cyclosporine in managing acute VKC, whereas dexamethasone caused less stinging sensation than cyclosporine eye drops [12].

We compared the efficacies and safeties of 1% topical tacrolimus and 1% dexamethasone eye drops in managing unilateral shield ulcers and corneal epitheliopathy secondary to VKC.

METHODS

In this prospective, comparative, interventional study, we recruited patients with unilateral shield ulcer and corneal epitheliopathy secondary to VKC who were referred to Al Zahra Eye Hospital, Zahedan University of Medical Sciences, Zahedan, southeast Iran, during a 12-month period. The study protocol was approved by the University Ethics Committee and complied with the tenets of the Declaration of Helsinki. Each individual provided written informed consent outlining the participant's rights to cease involvement in the study at any time.

We recruited individuals aged > 18 years with eye-related symptoms of watering, mucus discharge, photophobia, burning, redness, and itching due to active VKC [13, 14]; a diagnosis of shield ulcer with an epithelial defect on fluorescein staining [4]; eligibility for a treatment washout interval of 10 days at the discretion of the corneal faculty supervisor after detailed ocular examination; and regular follow-up during a four-month period. We excluded patients with any previous ocular surgery or trauma; any ocular pathologies other than VKC with shield ulcer; contact lens wear; nonadherence to treatment or without regular follow-up; underlying connective tissue diseases, systemic chronic infections, malignancies, or immunodeficiencies; and coexisting infectious keratitis or other untreated ocular comorbidities that would affect re-epithelialization.

All eligible patients underwent detailed eye examinations. The best-corrected distance visual acuity (BCDVA) was measured using a Snellen illiterate "E" chart and recorded in decimal format. The anterior segment was examined under slit-lamp biomicroscopy (Haag-Streit AG, Koniz, Switzerland). IOP was measured in mmHg using a Goldmann applanation tonometer (GAT: Haag-Streit AG, Bern, Switzerland). A meticulous slit-lamp fundus examination was performed using a 78-D aspheric auxiliary lens (Volk Optical Inc., Mentor, OH, USA).

To calculate shield ulcer size in mm^2, the longest dimension (mm) was multiplied by the longest perpendicular dimension (mm). Re-epithelialization was defined as absence of an epithelial defect on corneal fluorescein staining [4]. Staining was performed after applying topical Anestocaine (Tetracaine 0.5% eye drop, Sina Daru, Tehran, Iran) to the impregnated paper strip (Fluorescein strip, Toos Negah Co., Mashhad, Iran).

Each recruited individual was randomly assigned using a permuted block randomization scheme [15], with equal probability, to receive topical tacrolimus 1% or dexamethasone 1% twice daily. Participants in both groups were advised to continue cold compresses and a similar regimen of preservative-free artificial tears, with avoidance of triggers. Tacrolimus and dexamethasone were purchased from the Iranian pharmaceutical companies of Zahravi (Zahravi Pharmaceutical Company, Tabriz, Iran) and Darou Pakhsh (Darou Pakhsh Pharmaceutical Company, Tehran, Iran), respectively.

Topical aqueous 1% tacrolimus [13, 16] and 1% dexamethasone sodium phosphate eye drop formulations were prepared. Both preparations were preservative free and dispensed from similar dropper bottles. Participants were instructed on digital punctal compression following eye drop administration. All study participants and the treating ophthalmologist were blinded to treatment allocation throughout the study.

Treatment was carried out for three months, with follow-up visits at two weeks, one month, two months, and three months after commencement of treatment. A final follow-up was conducted one month after treatment tapering and discontinuation. Patients were instructed that the follow-up schedule was not rigid, and they were free to come at other times if necessary. At each follow-up visit, we documented the presence or absence of re-epithelialization; clinical symptoms of watering, mucus discharge, photophobia, burning, redness, and itching; BCDVA; shield ulcer size; and any potential complications such as ocular infections and IOP increases.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (version 25, SPSS Inc., IBM Corp., Armonk, NY, USA). The statistician was unaware of group allocation and study arm. The Shapiro–Wilk test was used to assess the normality of data distribution. Quantitative and qualitative data are summarized as means and standard deviations (SDs) or frequencies (percentages), respectively. The independent *t*-test or its nonparametric version, the Mann–Whitney U test, was used to test the significance of differences between treatment groups. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Sixty eyes of 60 symptomatic patients with shield ulcer and corneal epitheliopathy associated with VKC completed four months of follow-up. Thirty patients were allocated to each treatment group, having comparable mean (SD) ages (25.7 [11.7] years in the tacrolimus group and 24.5 [10.4] years in the dexamethasone group; $P = 0.790$) and sex distributions (16 [53.3%] men and 14 [46.7%] women in the tacrolimus group and 14 [46.7%] men and 16 [53.3%] women in the dexamethasone group; $P = 0.606$).

Table 1 presents the trend of changes in the frequencies of ocular symptoms observed throughout the study in both groups. Both groups experienced a decreasing trend in the frequencies of all symptoms, reaching a maximum of 33.3% (n = 10 eyes) and minimum of 0.0% (n = 0) at final follow-up. Likewise, in most follow-up visits, the frequencies of ocular symptoms were less in the tacrolimus group than in the dexamethasone group, reaching statistically significant differences at some time points (all $P < 0.05$; Table 1). However, no individual in either group experienced an improvement in itching up to one month after commencement of treatment; thereafter, itching was significantly less frequent in the tacrolimus group at the two subsequent follow-up visits (both $P < 0.05$; Table 1). At one month after treatment discontinuation, the frequency of ocular symptoms tended to decrease in both groups, with absence of photophobia in both treatment groups and absence of mucus discharge, burning, or redness in the tacrolimus group (both $P < 0.05$; Table 1).

Table 2 summarizes trends in the frequencies of re-epithelialization observed throughout the study in both groups. While no re-epithelialization was detected at two weeks after treatment commencement in either group, the frequency increased thereafter in both groups. Significantly more re-epithelialization occurred in tacrolimus-treated eyes at two and three months after treatment commencement, and it remained significantly more frequent (n = 30, 100%) in tacrolimus-treated eyes one month after cessation of therapy (all $P < 0.05$; Table 2). However, in the dexamethasone group, 23 eyes (76.7%) displayed re-epithelialization at the final follow-up (Table 2).

Table 3 summarizes trends in the BCDVA and shield ulcer size observed throughout the study in both groups. The mean BCDVA was significantly better in the tacrolimus group than in the dexamethasone group at all follow-up visits (all $P < 0.01$). Despite an improving trend in the mean BCDVA among tacrolimus-treated eyes, measurements remained nearly stationary in dexamethasone-treated eyes. Likewise, at the final visit, the mean change in BCDVA compared to the baseline value was significantly greater in the tacrolimus group than in the dexamethasone group ($P < 0.001$; Table 3).

The mean shield ulcer area demonstrated a decreasing trend in both groups; however, numerical values were less in the tacrolimus group at one, two, three, and four months, reaching statistically significant differences at the last two follow-up visits (both $P < 0.05$; Table 3). Likewise, at the final visit, the mean change in shield ulcer area compared to the baseline value was significantly greater in the tacrolimus group than in the dexamethasone group ($P < 0.05$; Table 3). We observed no ocular infections or IOP increases in either group at any point.

Table 1. Comparison of symptom frequencies between study groups

Variables	Time point	Dexamethasone (n = 30)	Tacrolimus (n = 30)	*P*-value
Watering, n (%)	Second weeks	30 (100)	30 (100)	> 0.99
	First month	30 (100)	26 (86.7)	0.038
	Second months	26 (86.7)	13 (43.3)	**< 0.001**
	Third months	14 (46.7)	6 (20.0)	0.028
	Forth months	2 (6.7)	1 (3.3)	0.554
Mucus discharge, n (%)	Second weeks	30 (100)	25 (83.3)	**0.020**
	First month	30 (100)	20 (66.7)	**0.001**
	Second months	28 (93.3)	1 (3.3)	**< 0.001**
	Third months	12 (40.0)	0 (0.0)	**< 0.001**
	Forth months	2 (6.7)	0 (0.0)	0.150
Photophobia, n (%)	Second weeks	29 (96.7)	12 (40.0)	**< 0.001**
	First month	27 (90.0)	9 (30.0)	**< 0.001**
	Second months	22 (73.3)	4 (13.3)	**< 0.001**
	Third months	9 (30.0)	0 (0.0)	**0.001**
	Forth months	0 (0.0)	0 (0.0)	> 0.99
Burning (%)	Second weeks	30 (100)	25 (83.3)	**0.020**
	First month	29 (96.7)	18 (60.0)	**0.001**
	Second months	28 (93.3)	11 (36.7)	**< 0.001**
	Third months	19 (63.3)	1 (3.3)	**< 0.001**
	Forth months	7 (23.3)	0 (0.0)	**0.005**
Redness, n (%)	Second weeks	30 (100)	29 (96.7)	0.313
	First month	28 (93.3)	26 (86.7)	0.389
	Second months	26 (86.7)	10 (33.3)	**< 0.001**
	Third months	23 (76.7)	5 (16.7)	**< 0.001**
	Forth months	10 (33.3)	0 (0.0)	**0.001**
Itching, n (%)	Second weeks	30 (100)	30 (100)	> 0.99
	First month	30 (100)	30 (100)	> 0.99
	Second months	30 (100)	22 (73.3)	**0.002**
	Third months	20 (66.7)	8 (26.7)	**0.002**
	Forth months	10 (33.3)	5 (16.7)	0.136

Abbreviations: n, number; %, percentage. Note: *P*-values < 0.05 are shown in bold; Dexamethasone, eyes treated with 1% dexamethasone sodium phosphate eye drop; Tacrolimus, eyes treated with 1% topical ocular aqueous tacrolimus drop.

Table 2. Comparison of re-epithelialization frequencies between study groups

Variable	Time point	Dexamethasone (n = 30)	Tacrolimus (n = 30)	*P*-value
Re-epithelialization, n (%)	Second weeks	0 (0.0)	0 (0.0)	> 0.99
	First month	4 (13.3)	10 (33.3)	0.067
	Second months	14 (46.7)	29 (96.7)	**< 0.001**
	Third months	20 (66.7)	30 (100)	**0.001**
	Forth months	23 (76.7)	30 (100)	**0.005**

Abbreviations: n, number; %, percentage. Note: *P*-values < 0.05 are shown in bold; Dexamethasone, eyes treated with 1% dexamethasone sodium phosphate eye drop; Tacrolimus, eyes treated with 1% topical ocular aqueous tacrolimus drop.

Table 3. Comparison of BCDVAs and shield ulcer sizes between study groups

Variables	Time point	Dexamethasone (n = 30)	Tacrolimus (n = 30)	*P*-value
BCDVA (decimal), Mean ± SD	Second weeks	0.20 ± 0.09	0.36 ± 0.15	**< 0.001**
	First month	0.21 ± 0.09	0.40 ± 0.19	**< 0.001**
	Second months	0.29 ± 0.10	0.50 ± 0.17	**< 0.001**
	Third months	0.32 ± 0.10	0.56 ± 0.17	**< 0.001**
	Forth months	0.39 ± 0.13	0.66 ± 0.16	**< 0.001**
BCDVA improvement from the baseline to last follow-up (decimal), Mean ± SD		0.19 ± 0.06	0.30 ± 0.06	**< 0.001**
Shield ulcer size (mm^2), Mean ± SD	Second weeks	2.25 ± 1.17	2.38 ± 1.38	0.668
	First month	2.11 ± 1.15	1.84 ± 1.35	0.415
	Second months	1.43 ± 0.83	1.11 ± 0.90	0.152
	Third months	0.99 ± 0.80	0.53 ± 0.52	**0.011**
	Forth months	0.58 ± 0.67	0.16 ± 0.23	**0.002**
Shield ulcer size improvement from the baseline to last follow-up (mm^2), Mean ± SD		1.67 ± 0.70	2.23 ± 1.21	**0.032**

Abbreviations: BCDVA, best-corrected distance visual acuity; SD, standard deviation. Note: *P*-values < 0.05 are shown in bold; Dexamethasone, eyes treated with 1% dexamethasone sodium phosphate eye drop; Tacrolimus, eyes treated with 1% topical ocular aqueous tacrolimus drop.

DISCUSSION

Our outcomes indicate that topical tacrolimus therapy yields earlier and more frequent improvement in most VKC symptoms when compared with topical dexamethasone. Tacrolimus therapy also results in a higher frequency of re-epithelialization and better BCDVA. The mean shield ulcer area was significantly less in the tacrolimus group than in the dexamethasone group at the last two follow-up visits, with a significantly greater mean change in ulcer size throughout the study period.

In a double-blind, comparative, crossover clinical trial, Pucci et al. [17] investigated the efficacy of 0.1% topical tacrolimus in 30 patients with severe VKC refractory to 1% cyclosporine eye drops. They found a significant improvement in objective and subjective scores among eyes treated with 0.1% topical tacrolimus three times per day, and patients experienced a significant improvement in quality of life despite only half the eyes being successfully treated. The authors concluded that topical tacrolimus is effective and safe in the short term for patients with severe VKC resistant to 1% cyclosporine eye drops [17].

Vichyanond et al. [18] conducted an open-label trial using 0.1% topical tacrolimus ointment applied to the lower conjunctival sac of both eyes, once or twice daily dependent on disease severity, for four weeks in ten children with recalcitrant VKC. They observed a significant reduction in the mean size of the tarsal papilla, chemosis, conjunctival swelling, and conjunctival injection at the end of the treatment period. The patients' and physicians' high preference for this therapy was documented at the end of treatment [18]. Likewise, in the current interventional study, eyes treated with 1% tacrolimus eye drops two times daily experienced a significant improvement in subjective and objective manifestations of VKC with shield ulcer and epitheliopathy.

Miyazaki et al. [8] retrospectively reviewed the medical records of 791 patients with refractory allergic conjunctivitis and epitheliopathy or shield ulcers followed at 330 ophthalmological institutions in Japan within nine years. They detected a significant reduction in the epitheliopathy score one month after treatment with 0.1% topical tacrolimus eye drops alone, yet adjunct topical or oral steroids had no significant effect on the time course of the epitheliopathy score. Furthermore, they assessed the steroid-sparing effect of 0.1% topical tacrolimus in 238 patients with shield ulcers and found comparable outcomes for the adjusted mean epitheliopathy score one month after administration of tacrolimus alone, tacrolimus with adjuvant fluorometholone, and tacrolimus with adjuvant betamethasone. The outcomes favored tacrolimus without adjuvant steroids for the treatment of corneal complications caused by refractory allergic conjunctivitis, eliminating the plausible complications associated with steroid administration [8]. Despite the advantage of a large sample size, the study by Miyazaki et al. [8] was not a randomized, interventional, comparative, prospective investigation. However, the current prospective, comparative study confirms the safety and superior efficacy of 1% tacrolimus eye drops monotherapy over topical 1% dexamethasone, a potent and long-acting steroid [9, 19], in managing VKC complicated with shield ulcers and epitheliopathy.

Tacrolimus is more conveniently used as an eyedrop than as an ointment [13]. In a pioneer in vivo study, Sengoku et al. [20] applied 0.01–1% tacrolimus versus steroid eye drops (0.1% betamethasone sodium phosphate and 0.1% fluorometholone eye drops) in experimental models of ocular allergy. They observed an anti-inflammatory effect of tacrolimus on late and delayed-type responses [20]. Twice-daily topical 0.1% tacrolimus treatment for VKC suppresses allergic inflammation associated with chemokines such as eotaxin-2 and thymus and activation-regulated chemokine [21]. In a prospective study on 20 eyes of 10 patients with refractory VKC, active symptomatic disease, and a mean age of 21.3 years, Kheirkhah et al. [13] assessed the efficacy and safety of four-times-daily topical 0.005% tacrolimus eye drops at the first visit, three days post-treatment, and every 2–4 weeks thereafter. They observed substantial relief of all symptoms including itching, redness, photosensitivity, foreign body sensation, and mucus discharge throughout a mean (SD) follow-up of 10.7 (3.7) months (range: 6–15 months). No adjunct medications such as steroids were required for further relief, and itching was the first symptom to resolve [13]. In contrast, our participants experienced improvement in itching at the third post-treatment visit (second month after treatment commencement), whereas the other symptoms improved earlier, at the first or second post-treatment visit. Kheirkhah et al. [13] encountered no ocular complications related to tacrolimus and recommended topical 0.005% tacrolimus eye drops as a safe and effective treatment for steroid-resistant refractory VKC [13]. We observed similar significant outcomes in symptom relief, BCDVA improvement, reduction in shield ulcer size, and re-epithelialization by administering twice-daily 1% tacrolimus eye drops in our participants. The magnitude of improvements in the tacrolimus group was greater than that of 1% dexamethasone eye drop monotherapy throughout the study. We did not record any safety concerns in either group during the four-month study period.

In a case series, conjunctival sac application of twice-daily topical tacrolimus 0.1% skin ointment yielded optimal outcomes in managing steroid responders with diagnoses of VKC, atopic keratoconjunctivitis, post-glaucoma implant surgery, and corneal graft rejection [22]. Liu et al. [23] retrospectively reviewed the medical records of 10 male participants with a mean (SD) age of 10.5 (2.3) years (range: 7–14 years) and mean (SD) follow-up duration of 15.10 (9.61) months (range: 1–26 months) with a diagnosis of steroid-resistant (0.1% topical betamethasone) refractory VKC with shield ulcer. Participants received 0.1% topical dermatological tacrolimus ointment on the eyelids once or twice per day. A tapering strategy was implemented to fully substitute steroids with tacrolimus. All patients experienced a cured shield ulcer with full re-epithelialization or scattered superficial punctate keratopathy, reduced conjunctival hyperemia, substantial flattening and reduced papillae size, and improvement in eyelid swelling. Likewise, significant relief of itching, redness, photophobia, ocular discomfort, foreign body sensation, tearing, and discharge were observed within two weeks after commencement of treatment. Concerning safety profile, a burning sensation on the eyelids was a common side effect that disappeared a few days after continual administration of tacrolimus. Bacterial or herpes simplex virus/varicella-zoster virus superinfections were not detected during the study follow-up [23]. Likewise, our study confirmed the safety of tacrolimus eye drops using a 10-fold greater concentration in a similar cohort of patients with VKC.

Dry eye may coexist in patients with VKC [14]. In fact, twice-daily topical 0.03% tacrolimus eye drops improved tear film stability and ocular surface status 90 days after treatment in patients with dry eyes associated with Sjögren syndrome [6]. We did not document dry eye signs and symptoms in our participants. However, given the possible coexistence of dry eye among individuals with VKC [14] and the confirmed therapeutic effect of topical tacrolimus on managing dry eye [6], our observed superior efficacy of tacrolimus over dexamethasone for VKC treatment could be attributable to its therapeutic effect on ocular complications of dry eye. Further trials are deemed necessary to prove this justification.

Remitz et al. [24] conducted a retrospective review of medical records of 28 patients (mean [range] age: 45.9 [19–84] years and 13 [46.4%] men) with a diagnosis of steroid-resistant refractory atopic blepharoconjunctivitis, ten of whom were steroid responders. After a mean 10-week interval between the commencement of topical tacrolimus 0.03% ointment, applied to the eyelids, and the first follow-up visit (range: 4–17 weeks), participants were followed up once daily for the first month and then intermittently, depending on individual symptoms, from six months to two years. They observed a statistically significant IOP decrease in all participants, and to a greater magnitude in steroid responders. Likewise, the clinical score decreased significantly between the commencement of tacrolimus therapy and the first follow-up visit, with no occurrence of lens opacities or vision deterioration. All patients experienced symptom relief and tolerated treatment well without marked adverse events. Only mild burning sensation was reported by three patients (11%) at the onset of treatment [24]. In parallel with their outcomes, we observed no ocular infections or IOP

increases throughout four months of follow-up. Our participants experienced significant improvement in their symptoms and visual acuities.

The safety profile of 0.1% tacrolimus ophthalmic suspension was confirmed by its low blood concentrations, acceptable efficacy profile, and tolerability, justifying it as an important treatment modality for severe allergic conjunctivitis [25]. In a multicenter, randomized, double-masked, placebo-controlled clinical trial, Ohashi et al. [26] randomly assigned 56 individuals with severe steroid- and antiallergic-resistant allergic conjunctivitis to receive twice-daily 0.1% tacrolimus ophthalmic suspension or placebo for four weeks. They detected a significant improvement in symptoms (itching, discharge, hyperemia, lacrimation, and foreign body sensation), a change in mean total score for objective signs, and improvement in giant papillae and corneal involvement. Concerning safety profile, a mild ocular irritation upon drop administration was a common but well-tolerated side effect [26]. We administered tacrolimus in a greater concentration and encountered no ocular complications; however, we did not measure blood concentrations of the drug. Further studies are required to determine blood concentrations corresponding to this formulation.

In a case series of five patients with varying severities of VKC, twice-daily topical tacrolimus 0.03% ointment yielded substantial relief of symptoms and signs, and in one patient with a large shield ulcer, healing was observed within three weeks [27]. Using a similar treatment regimen for two months, a 32-year-old patient with long-standing, severe, intractable atopic disease experienced resolution of symptoms, significant decrease in papillae size, and no side effects. The patient remained asymptomatic with no evidence of reactivation up to eight months post-treatment [28]. Likewise, a 73-year-old man with refractory atopic blepharoconjunctivitis experienced a dramatic relief of symptoms and no side effects with continuous administration of 0.03% tacrolimus dermatologic ointment for 12 months [29]. In a three-year-old female patient with coexistence of chronic anterior uveitis and VKC, administration of 0.1% tacrolimus eye drops three times daily for six months led to resolution of both diseases and no relapses within ten months of treatment cessation [30]. Our study, with a larger sample size and robust design, replicated the outcomes of previous reports, thus justifying tacrolimus monotherapy as an effective and safe treatment modality for VKC and its associated ocular complications. However, further multicenter, randomized, clinical trials investigating the efficacy and safety of various concentrations and regimens of topical tacrolimus could provide valid and practical clinical guidelines.

Our prospective, comparative, interventional study verifies the superior efficacy of twice-daily 1% tacrolimus eye drops over twice-daily 1% dexamethasone eye drops in managing VKC associated with subjective symptoms, shield ulcers, and epitheliopathy. However, a small sample size, single-center design, and short follow-up duration limit the generalizability of our findings. Further multicenter clinical trials incorporating longer follow-up and more objective measurements, such as changes in the size of papillae, could provide robust evidence of long-term efficacy and safety of 1% tacrolimus eye drops in managing this debilitating and sight-threatening severe inflammatory ocular disease.

CONCLUSIONS

The superior effects of topical tacrolimus monotherapy over topical dexamethasone on symptoms, visual acuity, shield ulcer size, and corneal epitheliopathy associated with VKC support its potential in managing this debilitating ocular inflammatory condition. However, further multicenter, longitudinal, randomized, clinical trials are needed to confirm these promising safety and efficacy profiles.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the University Ethics Committee and complied with the tenets of the Declaration of Helsinki. Each individual provided written informed consent outlining the participant's rights to cease involvement in the study at any time.

Conflict of interest: None.

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