Original Article

Safety and Efficacy of Tacrolimus Ointment 0.03% as a Steroid-Sparing Regimen in Patients with Severe or Refractory Vernal Keratoconjunctivitis (VKC): A study from Quetta, Balochistan

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a chronic, seasonally exacerbated ocular surface disease of childhood for which steroid-sparing therapy is desirable. We evaluated the safety and efficacy of tacrolimus 0.03% ointment in severe or refractory VKC over 12 months.

Methodology: This was a single-arm, non-randomized, prospective interventional study (no comparator group) conducted over 12 months (July 2024–June 2025) at Helpers Eye Hospital, Quetta, Pakistan. Ninety children (5–20 years) with severe or refractory VKC, enrolled by consecutive sampling, received tacrolimus 0.03% ointment nightly for 4–6 months. Symptom and sign scores (0–12 composite) and intraocular pressure (IOP) were recorded at baseline, 6, and 12 months and analyzed in SPSS v25.0 using paired t-tests. Primary outcome: change in composite symptom and sign scores from baseline; secondary outcomes: symptom, sign, and composite responder rates (≥50% reduction) at 12 months, and overall safety status.

Results: Lost to follow-up at 12 months was 13/90 (14.4%). Composite symptom scores improved by 4.66 at 6 months and 5.56 at 12 months (both $p<0.001$); composite sign scores improved by 1.77 and 2.78, respectively (both $p<0.001$). IOP remained stable at both time points. At 12 months, symptom responders were 69%, sign responders 3%, and composite responders 1%; safety was observed in 94%.

Conclusions: In severe/refractory pediatric VKC, tacrolimus 0.03% ointment was associated with large symptom improvement, moderate sign improvement, and favorable safety through 12 months, with stable IOP. When composite thresholds are strict, domain-specific responder reporting is helpful in clarifying clinical benefit. The results are supportive of tacrolimus 0.03% ointment being a practical steroid-sparing treatment.

Keywords: Conjunctivitis, Allergic; Tacrolimus; Immunosuppressive Agents; Child; Intraocular Pressure

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, seasonally exacerbated, T-cell–mediated ocular surface disease of childhood that is most prevalent in warm, dry climates and disproportionately affects boys, with a substantial impact on quality of life and schooling.[1-3] Contemporary global consensus statements and systematic reviews emphasize its inflammatory allergic pathobiology, characteristic palpebral and limbal forms, and the risk of vision-threatening corneal involvement in severe or refractory disease.[1-3]

Initial therapy typically combines topical antihistamines and mast-cell stabilizers, but many children with severe VKC require topical corticosteroids for symptom control, with attendant risks of ocular hypertension and steroid-induced glaucoma, concerns that have accelerated the search for steroid-sparing strategies.[1-3] In this steroid-sparing context, calcineurin inhibition with tacrolimus provides targeted immunomodulation by suppressing T-cell activation and downstream cytokines, addressing the inflammatory drivers of VKC while potentially reducing reliance on steroids.[1,3-5] Evidence from randomized and observational studies, as well as meta-analyses, indicates that tacrolimus improves symptoms and clinical signs across disease severities, with acceptable tolerability in pediatric populations.[4-7]

Both ophthalmic (0.1%) and dermatologic ointment (0.03%) preparations are used in practice. Pediatric data on the subject of the present study, 0.03% tacrolimus

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ointment, are also shown. Adverse events are generally mild, with meaningful symptom improvement and variable sign responses. The prevalence of mild and transient (e.g., burning/tingling) adverse events is comparable in head-to-head pediatric comparisons (0.03%).[6,8,9] versus 0.2% report a clinical benefit at either dosage. Real-world series reported by real-world versus report a clinical benefit at either dosage. In high-burden settings, good results are found using ointment formulations.[6,8,9] Recent syntheses still uphold the use of tacrolimus as an effective steroid-sparing option in A heterogeneous variety of formulations, dosing regimens and outcomes, moderate to severe VKC. Standardized, real-world evaluations, reporting quantitative scores, continue to exist.[4,10] Changes (composite symptom/sign scores) and clinically intuitive responder outcomes, in addition to safety data like intraocular pressure (IOP) and any adverse events, are still a part of the data collected. On this background, we assessed tacrolimus 0.03% ointment in a prospective study of children with severe or refractory VKC.[1,2,10] Efficacy was assessed at 6 and 12 months (mean change and responder analyses focusing on both symptoms and signs) and safety was assessed at 12 months (overall status and IOP). However, it is difficult to manage severe VKC on a day-to-day basis. Children often experience flares that tend to happen in warm and dusty periods, and caregivers need to try to account for this in their balance at clinic. Access, cost and school attendance. A steroid-free, home-based alternative to keep control. It is therefore desirable to reduce the rise in IOP. The 0.03% dermatologic ointment formulation, rather than the 0.1% ophthalmic preparation, was selected for this study as being more suitable for use. Prior pediatric studies suggest that the 0.03% dermatologic ointment is more readily available and affordable in a resource-limited setting. The mild and transient application discomfort and lack of ocular tolerance reports in series are negligible. Significant systemic absorption is unlikely at this lower concentration.[6,8,9] The ointment also allows adaptable, adjustable dosage; slight discomfort during application, which is later reduced; continued use and counselling. The observation period of 12 months is intentional, being the time it takes for at least one seasonal cycle and to test durability beyond the short time frame used in previous studies.

Accordingly, we pre-specified complementary endpoints: continuous change in composite scores and intuitive responder proportions, together with practical safety readouts, including global safety status and IOP.

METHODOLOGY

This prospective, single-arm, non-randomised interventional study with no comparator (control) group was conducted between July 2024 and June 2025 at Helpers Eye Hospital, Quetta. Ethical approval was obtained from the institutional review board, and the study adhered to the tenets of the Declaration of Helsinki. A total of 90 patients (n = 90) aged 5–20 years, diagnosed with severe or refractory, uncontrolled vernal keratoconjunctivitis (VKC), were recruited. The sample size was 90 patients, calculated for the paired comparison of composite VKC scores (baseline vs 12 months), using a two-sided α=0.05 and 80% power; we assume a standardised mean difference of 0.33 (small–moderate). The required evaluable sample is ≈72. Allowing 20% attrition at 12 months, the target enrollment = 72 / 0.80 ≈ 90 participants. Consecutive patients meeting the inclusion criteria aged between 5 and 20 years, clinically confirmed severe VKC (grade ≥ 3 on standardized VKC grading scale), either refractory to topical corticosteroids (no improvement after two weeks of standard steroid therapy) or presence of steroid-related complications (steroid-induced glaucoma or keratoconus). Patients were excluded if there was an active ocular infection (bacterial, viral or fungal), a history of ocular surgery within the preceding six months, systemic immunosuppressive therapy, or known hypersensitivity to tacrolimus or other macrolides.

All enrolled patients received tacrolimus 0.03% ointment daily HS for 4–6 months. In week 1, application was limited to the eyelid margin near the lashes to minimize initial conjunctival irritation. From week 2 onward, patients were instructed to apply a 1 cm ribbon of ointment directly into the inferior conjunctival sac, using aseptic technique. Concomitant use of previous topical steroids was tapered off over the first four weeks.

Detailed history, slit-lamp examination, intraocular pressure (IOP) measurement (Goldmann applanation tonometry), and grading of the signs and symptoms of VKC (conjunctival hyperemia, giant papillae, Trantas dots, corneal involvement and itching, redness, photophobia, tearing) on a 0–3 scale were performed during the baseline evaluation. Follow-up visits occurred at 2 and 4 weeks, then monthly, then at 6 months and finally at one year. Patients and caregivers received structured counselling on application technique and adherence at each visit, and a telephonic reminder call was made the day before every scheduled follow-up appointment to support retention. At each visit, the following were recorded: Symptom score (0–12 composite), Sign score (0–12 composite), IOP. Any adverse events (burning, stinging, infection, further IOP rise). Primary efficacy

endpoint was change in composite symptom and sign scores from baseline to month 6 and 1 year. Secondary endpoints: Reduction/discontinuation of topical steroids; incidence of adverse events; control of IOP in steroid-induced glaucoma patients. Efficacy was operationalized as the change in composite symptom and sign scores from baseline and as responder proportions (≥50% reduction) at 12 months. Safety was operationalized as the absence of any adverse event, including a clinically significant IOP rise, requiring treatment modification or discontinuation. Data were analysed using SPSS v. 25.0 (IBM Corp., Armonk, NY, USA). Normality of data was checked by the Shapiro-Wilk test. Continuous variables are presented as mean ± SD or median IQR, depending on the normality of data. Categorical variables were presented as frequencies and percentages. Paired t-tests (or Wilcoxon signed-rank tests for non-normal data) compared baseline versus post-treatment scores; composite symptom/sign scores and IOP were normally distributed on Shapiro-Wilk testing ($p>0.05$), so paired t-tests were used throughout. Analyses were performed on available cases at each time point, without imputation of missing follow-up data. A p-value < 0.05 was considered statistically significant.

RESULTS

Ninety children with severe or refractory VKC were enrolled. Baseline demographic and clinical characteristics – including sex distribution, disease severity, corneal involvement, steroid use, and baseline composite symptom/sign scores and IOP – are summarized in Table 1.

Follow-up and attrition. At 6 months, approximately 85 (94.4%) had paired data; at 12 months, 77 (85.6%) were evaluable, with 13 (14.4%) lost to follow-up. Efficacy—quantitative change from baseline. Composite symptom scores improved substantially at both 6 and 12 months: mean change (Baseline − 6 months) 4.6576 (95% CI 4.4588–4.8565) and (Baseline − 12 months) 5.5610 (95% CI 5.2793–5.8428), both $p<0.001$. Composite sign scores also improved, with mean changes of 1.7682 (95% CI 1.6033–1.9332) at 6 months and 2.7753 (95% CI 2.5775–2.9732) at 12 months (both $p<0.001$). Intraocular pressure remained stable on average at both time points ($\Delta=-0.1471$ mmHg at 6 months, $p=0.095$; $\Delta=-0.1013$ mmHg at 12 months, $p=0.311$) (Table 2).

Table 1: Demographics & baseline clinical characteristics (n=90)

Characteristic	Frequency n (%)
Sex	
Male	56 (62.2%)
Female	34 (37.8%)
Baseline severity	
Severe	35 (38.9%)
Very severe	55 (61.1%)
Corneal involvement	
Yes	42 (46.7%)
No	48 (53.3%)
Steroid use at baseline	
Yes	50 (55.6%)
No	40 (44.4%)
Age (years)	11.76 ± 2.94
Baseline composite symptom score (0–12) (Mean ± SD)	9.999 ± 1.204
Baseline composite sign score (0–12) (Mean ± SD)	9.587 ± 1.334
Baseline IOP (mmHg) (Mean ± SD)	14.516 ± 2.443

Table 2: Change from baseline at 6 and 12 months (paired t-test analyses; available participants)

Characteristic	Baseline, Mean ± SD (n=85)	6 months, Mean ± SD (n=85)	Change, Mean (95% CI)*	p-value
Change from baseline to 6 months				
Composite symptom score (0–12)	10.01 ± 1.21	5.35 ± 1.46	4.66 (4.46–4.86)	<0.001
Composite sign score (0–12)	9.58 ± 1.34	7.81 ± 1.57	1.77 (1.60–1.93)	<0.001
IOP (mmHg)	14.59 ± 2.37	14.74 ± 2.44	−0.15 (−0.32 to 0.03)	0.095
Change from baseline to 12 months				
Composite symptom score (0–12)	9.98 ± 1.20	4.42 ± 1.77	5.56 (5.28–5.84)	<0.001
Composite sign score (0–12)	9.55 ± 1.39	6.77 ± 1.67	2.78 (2.58–2.97)	<0.001
IOP (mmHg)	14.65 ± 2.42	14.75 ± 2.56	−0.10 (−0.30 to 0.10)	0.311

*Change = baseline – follow-up. Change >0 for symptoms/signs indicates improvement;
The p-values from paired t-tests. 6-month pairs used ~n=85; 12-month pairs used ~n=77 after attrition.

Table 3: Twelve-month safety and efficacy (available participants n=77; LTFU 13/90 = 14.4%)

Endpoint (12 months)	n/N (%)
Reduction of symptoms domain (≥50% reduction)	53/77 (68.8%)
Reduction of sign domain (≥50% reduction)	2/77 (2.6%)
Reduction of composite (≥50% in both symptom & sign)	1/77 (1.3%)
Safety	72/77 (93.5%)

Percentages are based on valid (available) participants at 12 months (n=77).

Efficacy—domain-specific responder analyses at 12 months. Using a ≥50% reduction threshold, 53 (68.8%) were symptom responders, whereas 2 (2.6%) were sign responders. Applying a composite definition requiring ≥50% improvement in both domains, 1 (1.3%) met the responder criterion. Safety at 12 months. Overall safety status was observed in 72 (93.5%) patients, with issues in 5 (6.5%) among available patients; IOP findings were consistent with stability over time (Table 3).

DISCUSSION

In this prospective pediatric case series with severe or refractory VKC, tacrolimus 0.03% ointment was associated with large, durable reductions in composite symptoms, moderate improvements in objective signs, and no clinically meaningful rise in IOP over 12 months, with an overall favorable safety profile. This is in line with the modern Management guidance and regional consensus that focus on steroid-sparing. Treatment of children who may develop steroid-induced ocular hypertension and vision loss: immunomodulation.[1-3] Efficacy signals are consistent with the quantitative syntheses and controlled comparisons of tacrolimus. Across disease severities, randomised trials,4 a double blind study design,5 and head-to-head data in pediatric cyclosporine-resistant VKC are available for crossover versus cyclosporine. 0.03% vs 0.1% ointment,[6] and outcomes at longer term with 0.1% drops in severe allergic conjunctival disease.[7] Ointment cohorts in real-world data from Middle East and South American countries. Asian settings—likewise report symptomatic improvement with acceptable tolerability.[8,9] In addition, these strands have been incorporated into the latest systematic review and meta-analysis specific to: VKC,[10] as also experience in the region with ointment gives pragmatic support for routine. Pharmacokinetic data show that there is low systemic exposure, which is also a safety concern.[11] In conjunction with the use of tacrolimus ophthalmic suspension, this is further evidence of its suitability as a steroid-sparing agent for the treatment of keratitis. paediatrics.[12]

Our quantitative efficacy pattern faster, larger relief in symptoms, with steadier regression of signs – mirrors pediatric clinical experience with 0.03% ointment[13] and controlled work with 0.1% suspension.[14] Additional non-randomized controlled data with 0.03% ointment in VKC bolster the case for benefit in refractory disease.[15] Comparative evidence further contextualizes positioning in care pathways: tacrolimus has performed favorably against topical steroids in pediatric settings,[16] against antihistamine/mast-cell stabilizers such as olopatadine,[17] and as a first-line option versus cyclosporine in some cohorts.[18,19] Beyond VKC, systematic review of topical tacrolimus across corneal/ocular surface inflammation supports class-level biological plausibility and ocular tolerability;[20] randomized data in high-risk corneal transplantation provide additional safety-efficacy context on the ocular surface.[21] Earlier reports of 0.03% dermatologic preparations for VKC from Pakistan[22] and pediatric refractory cases from the Middle East[23] are consistent with more recent single-center experience [24] and comprehensive corneal/ocular surface reviews.[25] State-of-the-art VKC updates and mechanistic summaries underscore the inflammatory–allergic pathobiology that tacrolimus targets,[26,27] while quasi-experimental pediatric data with 0.03% ointment highlight real-world symptom relief with largely transient application discomfort.[28] Against the backdrop of steroid-related ocular hypertension and blindness described in pediatric VKC receiving repeated corticosteroids,[29] our 12-month stability of IOP is clinically meaningful. Finally, concrete recommendations regarding the timing of starting tacrolimus ointment and the way of tapering ointment use during seasonal surges can facilitate the implementation of these findings in clinical practice.[30]

One continuing problem in the VKC literature is the way that "response" is defined. We prespecified that on the symptom and sign scores, the stringent composite responder group (≥50% improvement) had the largest overall reduction. As expected, this conservative criterion yielded a low proportion despite clear mean improvements. This pattern reflects heterogeneity in responder thresholds and composite rules across studies (e.g., per-domain vs composite, 30% vs 50% cut-offs), which limits cross-study comparability and underscores the need for standardized endpoints.[3,4,6,10] To aid clinical interpretability, we also reported domain-specific responders at 12 months, which many clinicians find more intuitive when making decisions about tapering steroids through long, dusty seasons typical of high-burden regions. Our results suggest that patients and families can anticipate early symptomatic relief and gradual sign

improvement, aligning with both mechanistic expectations and published pediatric series.[6,7,13–15,22–24,28].

Strengths of this study include a clearly defined severe/refractory pediatric population; a 12-month observation window spanning at least one seasonal cycle; and complementary reporting of continuous change (paired analyses with confidence intervals) alongside clinically intuitive responder outcomes, plus pragmatic safety (global safety status and IOP). Limitations include the absence of a parallel comparator (control) group (so causal inference relies on effect sizes and concordance with prior work), the absence of formal statistical adjustment for potential confounders (e.g., baseline steroid use, corneal involvement), available-case analyses with attrition that is typical of long-distance pediatric follow-up, and a strict composite responder that may underestimate clinically meaningful benefit when domains improve asynchronously. These cautions reinforce the recent syntheses for the harmonization of the definition of responders and the standardization of the measurement of individual's reactions to the same events. Categorized by outcome sets, multicenter designs, and direct comparisons of the 0.03 vs 0.1 regimens Steroid-sparing step-down algorithms are also integrated into these algorithms.[3,6,7,10,20,21,25,30]

CONCLUSIONS

This study showed that 12 months of tacrolimus 0.03% ointment in severe/refractory pediatric VKC resulted in sustained symptom improvement, moderate sign improvement and good safety, with no change in IOP. In the context of steroid-sparing strategies and regional practice realities, these data suggest that tacrolimus 0.03% ointment is a practical and home-use steroid-sparing therapy, and that routine IOP monitoring and/or standardized multicenter studies with comparator/control arms are warranted to further optimize protocols.

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Authors Contribution

MM: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, and final approval.

HA: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval, and proofreading.

AAM: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval, and proofreading.

AM: Conception and design, analysis and interpretation of data.

AP: Analysis and interpretation of data, and drafting the article.

G: Acquisition of data, conception and design, and analysis and interpretation of data.

Artificial Intelligence (AI) Use Disclosure

ChatGPT (OpenAI) was used during the preparation of this manuscript for language editing and improvement of manuscript clarity. The AI tool was not used to generate or manipulate original research data, perform statistical analysis, or independently develop scientific conclusions or interpretations. All AI-assisted text and suggestions were critically reviewed, edited, and approved by the authors. The authors remain fully responsible for the accuracy, originality, integrity, scientific content, data interpretation, and conclusions of the manuscript.

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