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Systematic Review

Efficacy and Safety of Topical Tacrolimus for Vernal Keratoconjunctivitis: A Systematic Review

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Abstract

Objectives: Vernal keratoconjunctivitis (VKC) poses a significant challenge in ocular inflammation management, necessitating potent anti-inflammatory interventions. Despite its restricted utilization, tacrolimus has emerged as a promising agent in inflammation control. However, the specific efficacy of topical tacrolimus in VKC remains underexplored.

Methods: A systematic review was conducted to evaluate the impact of topical tacrolimus on VKC, adhering meticulously to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies were meticulously retrieved from comprehensive databases including Cochrane Library, PubMed, EBSCO Host, ProQuest, and Google Scholar, with a focus on English-language publications. This systematic review protocol was prospectively registered with PROSPERO (CRD42022302291).

Results: The review encompassed 11 studies involving 607 participants, with an average age of 8.45 years. Tacrolimus concentrations utilized in the interventions spanned from 0.005% to 0.1%, delivered through eye ointment or drops. Across the studies, topical tacrolimus demonstrated significant reductions in both the total objective signs score and total subjective symptoms score. Adverse events reported encompassed sensory experiences such as burning sensation, ocular stinging, pain, redness, and sporadic photophobia.

Conclusion: This systematic review underscores the notable efficacy of topical tacrolimus in ameliorating the clinical manifestations and symptomatic burden associated with VKC. Furthermore, tacrolimus exhibited a favorable safety profile, with minor adverse effects reported infrequently.

Keywords: Topical tacrolimus, vernal keratoconjunctivitis, clinical effectiveness

Introduction

Vernal keratoconjunctivitis (VKC) is an ocular immunologic condition that affects approximately 0.1–0.5% of individuals in developed countries. It predominantly occurs in warm and arid tropical and subtropical regions, including Africa, the Middle East, Latin America, and Asia (1). The prevalence of VKC is notably higher among children and adolescents, reaching rates of 33% and 90%, respectively (2). VKC is characterized by the presence of superior tarsal papillae and chalky white deposits known as Horner–Trantas dots, with common symptoms including eye itching, photophobia, eye discharge, tearing, and the sensation of a foreign body. Although typically bilateral, VKC can occasionally be unilateral (3). This severe form of allergic conjunctivitis involves both type I immediate hypersensitivity and type IV hypersensitivity reactions (1).

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Tacrolimus, also referred to as FK-506, is a macrolide derivative with anti-inflammatory and immunomodulatory properties (4). It is a potent, non-steroidal immunosuppressant derived from the fungus Streptomyces tsukubaensis (5). Tacrolimus functions by suppressing T-cell activation and interleukin-2 (IL-2) production through its binding to immunophilin, thereby inhibiting the enzymatic activity of calcineurin (4). The inhibition of calcineurin prevents the dephosphorylation of the nuclear factor of activated T-cells and its translocation to the nucleus, which subsequently suppresses the formation of T-helper (Th) 1 (IL-2, interferon γ) and Th2 cytokines (IL-4, IL-5). In addition, tacrolimus inhibits histamine release from mast cells, alleviating allergic symptoms. It has proven effective in managing VKC patients who are unresponsive to conventional treatments, including topical cyclosporine (5). Topical tacrolimus has been recognized as a safe and effective alternative to topical corticosteroids, given its mild side effects and minimal systemic absorption (6).

Initially approved for treating atopic dermatitis, topical tacrolimus has also demonstrated efficacy in treating giant papillary conjunctivitis, atopic keratoconjunctivitis, and VKC, with minimal adverse reactions such as transient burning and pruritus at the application site (5,7). However, its use remains limited, particularly in low- and middle-income countries. The authors of this review aim to inform stakeholders, government officials, clinicians, and patients about the critical benefits and essentials of topical tacrolimus for VKC management. This study is registered with PROSPERO under the identifier CRD42022302291 and was previously posted to the Research Square preprint server on March 15, 2023.

Objectives

The objective of this systematic review is to evaluate the efficacy of topical tacrolimus therapy, either as a standalone intervention or in comparison to a placebo or alternative treatment regimen, in managing VKC among pediatric and adolescent populations.

Methods

Eligibility Criteria

This systematic review encompassed studies involving children and adolescents aged up to 18 years diagnosed with active VKC through clinical assessment by ophthalmologists. Specifically, studies featuring topical tacrolimus as a sole monotherapy were included for comparison with both placebo and other pharmacological interventions. Inclusion criteria comprised assessments of patients' clinical manifestations and adverse events associated with therapy over a minimum period of 3 weeks following the initial evaluation. Exclusion criteria were applied to articles that were unattainable.

Literature Search

Two researchers independently conducted a comprehensive search for randomized controlled trials (RCTs) published between 2012 and 2022. The search encompassed databases such as the Cochrane Library, PubMed/MEDLINE, EBSCOhost, ProQuest, and Google Scholar, focusing on studies from 2012 to 2023 specifically for Google Scholar. Only English-language publications were considered for inclusion in this systematic review. The search strategy employed Medical Subject Heading (MeSH) terms, specifically targeting "topical tacrolimus" and "vernal keratoconjunctivitis." The findings were documented in a structured flow diagram (Fig. 1).

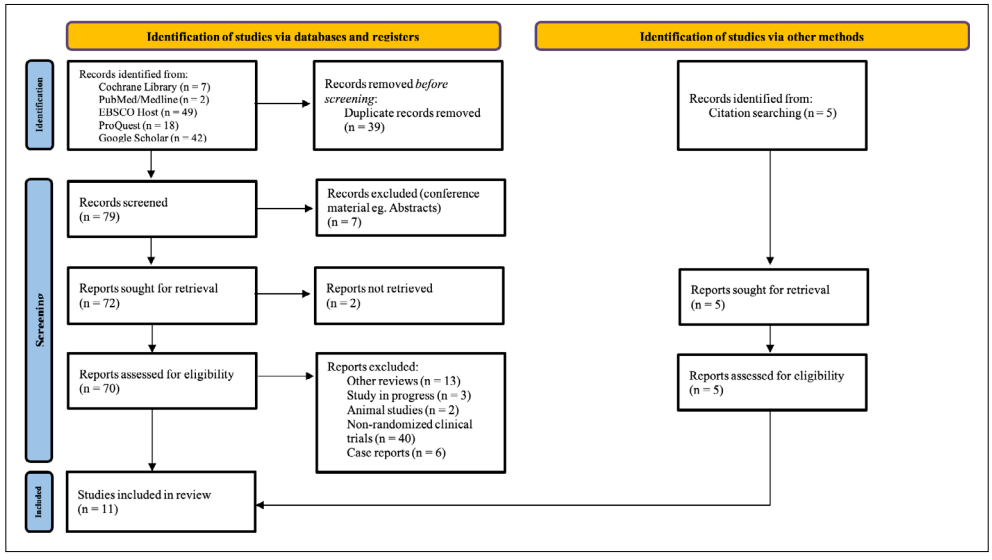

Figure 1. Flow chart demonstrating the study's selection process.

Data Extraction and Quality Assessment

One researcher extracted pertinent information regarding study design, participant demographics, intervention modalities, outcome measurement frequency, clinical endpoints, and potential adverse events into an evidence table. Another researcher independently verified the accuracy of the extracted data. Discrepancies were resolved through consensus discussions.

Data Items and Effect Measures

The mean clinical changes from baseline to the conclusion of the treatment regimen were identified. Clinical parameters encompassed symptoms (itching, tearing, photophobia, discharge, and foreign body sensation) and signs (conjunctival hyperemia, punctate keratitis, tarsal papillary reaction, limbal neovascularization, and conjunctival fibrosis) (8).

Bias Assessment

Two researchers evaluated each study's risk of bias using RevMan 5.4 software, employing Cochrane's risk of bias assessment tool (9). Components assessed included sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Risk judgments were categorized as "low risk," "high risk," or "uncertain risk."

Data Synthesis

A qualitative synthesis was performed, and evidence pertaining to the primary objective was tabulated. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist guided reporting standards. Ethical clearance was not required for this study as it did not involve human or animal participants.

Results

Study Selection

On February 24, 2022, a thorough search was conducted by two investigators across four databases, namely the Cochrane Library, PubMed, EBSCO Host, and ProQuest. In addition, on October 12, 2023, the Google Scholar database was incorporated to broaden the scope of the study. The retrieved records and the search terminologies utilized are delineated in Table 1. Initially, 118 records were retrieved, from which six studies were considered appropriate for inclusion (8,10-14). Subsequently, a "snowball" search strategy was employed, yielding five additional eligible studies (15-19). The flow diagrams are illustrated in Figure 1.

Study Characteristics

All included studies in this review had randomization and encompassed a total of 607 participants, with participant numbers ranging from 16 to 200 individuals. The mean age across all included studies was 8.45±4.0 years, with a predominance of male participants. The intervention doses of tacrolimus ranged from 0.005% to 0.1%, with the most commonly utilized dose being 0.03%. Among the 11 studies, five compared tacrolimus with cyclosporine, whereas others compared it with various medications such as lower concentration tacrolimus, olopatadine, a combination of tacrolimus and olopatadine, sodium cromoglycate, conventional therapies, and interferon alpha-2b. Tacrolimus formulations included ointments in eight studies and eye drops in the remaining studies. Treatment durations varied from 3 to 12.8 weeks across the studies, all of which incorporated assessments of objective, subjective, and adverse event parameters. Detailed characteristics of the included studies are outlined in Table 2.

Risk of Bias in Studies

The risk of bias in each of the included studies was evaluated using the RoB 2.0 tool, and a summary of the bias assessment is illustrated in Figure 2.

Random Sequence Generation

All 11 randomized controlled trials (RCTs) were assessed as having a low risk of bias for random sequence generation. Each RCT reported that participant allocation was determined through randomization.

Table 1. Articles retrieved from each database using the predetermined search terms

Databases	Search terms	Records retrieved
Cochrane Library	topical tacrolimus in Title Abstract Keyword AND vernal keratoconjunctivitis in Title Abstract Keyword - in Trials	7
PubMed	(topical tacrolimus[Title/Abstract]) AND (vernal keratoconjunctivitis[Title/Abstract])	2
EBSCO Host	(TI topical tacrolimus OR AB topical tacrolimus) AND (TI vernal keratoconjunctivitis OR AB vernal keratoconjunctivitis)	49
ProQuest	(ti(topical tacrolimus) OR ab(topical tacrolimus))AND (ti(vernal keratoconjunctivitis) OR ab(vernal keratoconjunctivitis))	18
Google Scholar	allintitle:"topical tacrolimus"|"tacrolimus ointment"|"tacrolimus eye drop"|"tacrolimus suspension" "vernal keratoconjunctivitis"|"vkc"|"allergic conjunctivitis"	42
	Total	118

Table 2. Characteristics of the included study, study design, country, sample size, setting mean age, intervention, comparison, treatment duration, and outcomes

Study	Study Design	Country	Sample Size	Mean Age (years)	Intervention	Comparison	Treatment Duration (weeks)	Outcomes		
								TSSS	TOSS	AE
Panadda et al., 2012	RCT	Thailand	24 patients (M:23 F:1)	9.6±2.6	Tacrolimus eye ointment 0.1%	Cyclosporine eye drops 2%	8 weeks	✓	✓	✓
Singla et al., 2017	RCT	India	56 patients (M:44 F:12)	8.3±1.7 (I) 8.0±1.6 (C)	Tacrolimus eye ointment 0.1%	Cyclosporine eye drops 2%	6 weeks	✓	✓	✓
Kumari et al., 2021	RCT	India	60 patients (M:53 F:7)	7.9±2.7 (I) 8.4±3.1 (C)	Tacrolimus eye ointment 0.1%	Tacrolimus eye ointment 0.03%	12 weeks	✓	✓	✓
Pucci et al., 2015	RCT	Italy	30 patients (M:24 F:6)	9.1±2.1	Tacrolimus eye drop 0.1%	Cyclosporine eye drops 1%	3 weeks	✓	✓	✓
Heikal et al., 2021	RCT	Egypt	59 patients (M:49 F10)	9.9±4.2 (I) 10.8±4.7 (C)	Tacrolimus eye ointment 0.03%	Cyclosporine eye drops 2%	12 weeks	✓	✓	✓
Kumari et al., 2017	RCT	India	32 patients (M:28 F:4)	7.6 ±1.8	Tacrolimus eye ointment 0.03%	Cyclosporine eye drops 0.05%	6 weeks	✓	✓	✓
Manzoor et al., 2023	RCT	Pakistan	200 patients (M:134 F:66)	5.1±0.9 (I) 5.9±1.9 (C)	Tacrolimus skin ointment 0.03%	- Fluoromethalone acetate 0.1% (25); - Dexamethasone sodium phosphate 0.1% (25); - Prednisolone acetate 1% (25); - Sodium cromoglycate 4% (25)	12 weeks	✓	✓	✓
Müller et al., 2014	RCT	Brazil	21 patients (M:14 F:7)	10.4±2.8	Tacrolimus eye ointment 0.03%	Tacrolimus eye ointment 0.03% + Olopatadine solution 0,1%	4.2 weeks	✓	✓	✓
Hassan et al., 2021	RCT	Pakistan	69 patients (M:54 F:15)	12.7±5.4	Tacrolimus eye ointment 0.03%	Olopatadine eye drop 0.2%	12 weeks	✓	✓	✓
Eduardo et al., 2017	RCT	Brazil	16 patients (M:13 F:3)	11.6±2.4	Tacrolimus eye drop 0.03%	Sodium cromoglycate eye drop 4%	12.8 weeks	✓	✓	✓
Habibollah et al., 2017	RCT	Iran	40 patients (M:31 F:9)	11.1±5.2	Tacrolimus eye drop 0.005%	Interferon alpha-2b (1.000.000 U/cc)	8 weeks	✓	✓	✓

TSSS: Total Subjective Symptoms Score; TOSS: Total Objective Sign Score; AE: Adverse Events; RCT: Randomized Controlled Trial.

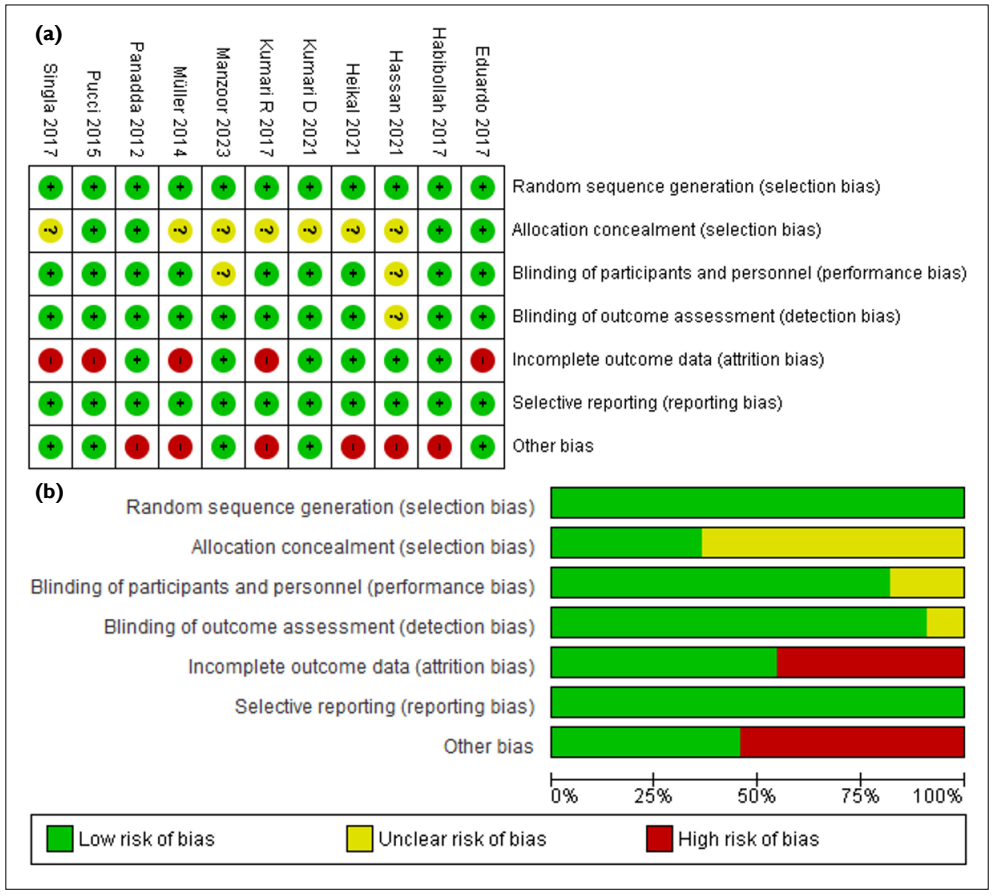

Figure 2. **(a)** Risk of bias summary: review authors' judgments about each risk of bias item for each included study. **(b)** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies (8,10-19).

Allocation Concealment Before Assignment

Four RCTs indicated that allocation was concealed before random assignment (Panadda 2012; Pucci 2015; Eduardo 2017; and Habibollah 2017). Among the remaining seven RCTs, six did not specify the method of concealing treatment allocation (Kumari R. 2017; Hassan 2021; Singla 2017; Kumari D. 2021; Heikal 2021; and Manzoor 2023), whereas the remaining RCTs did not clarify whether drug-containing envelopes were sealed (Müller, 2014), resulting in these three RCTs being categorized as unclear.

Masking (Performance Bias and Detection Bias)

Two RCTs were deemed unclear in terms of masking as there was no information regarding participant or personnel masking (Hassan 2021; Manzoor 2023). Seven RCTs reported both participant and personnel masking (Panadda 2012; Müller 2014; Pucci 2015; Eduardo 2017; Habibollah 2017; Kumari R. 2017; and Singla 2017), whereas the remaining RCTs stated that investigators were unaware of the corresponding therapy (Kumari D. 2021; and Heikal 2021), leading to these studies being judged as having a low risk of performance and detection bias.

Incomplete Outcome Data

Six RCTs were deemed to have a low risk of attrition bias as there were no missing outcome data (Panadda 2012; Habibollah 2017; Hassan 2021; Kumari D. 2021; Heikal 2021; and Manzoor 2023). However, attrition bias was considered high for Müller 2014 and Eduardo 2017 due to participants being excluded for requiring rescue therapy with corticosteroids, and for Pucci 2015 due to participant dropout resulting from lack of efficacy. Kumari R. 2017 was also assessed as high risk due to participant loss to follow-up, whereas Singla 2017 had high risk due to participant dropout.

Selective Reporting

All eleven RCTs were assessed as having a low risk of reporting bias as they reported all expected outcomes.

Other Potential Sources of Bias

Müller 2014; Kumari R. 2017; Hassan 2021; and Heikal 2021 were assessed as having a high risk of other bias due to baseline imbalances potentially affecting intervention effects. In addition, Panadda 2012 and Habibollah 2017 were considered high-risk due to pre-randomization administration of interventions, whereas the remaining studies were categorized as low-risk.

Results of Synthesis

Subjective Outcomes

All of the tacrolimus preparations significantly decreased the Total Symptom Severity Scores (TSSS) across studies (11-15,17-19). Five out of 11 studies exhibited notable mean subjective differences between treatment groups (10,11,14,16,17). In comparison to cyclosporine, two randomized controlled trials (RCTs) involving 0.1% tacrolimus eye drops and 0.03% tacrolimus eye ointment demonstrated statistically significant differences in subjective outcomes ($p<0.05$) (10,14). However, three other studies employing either 0.1% or 0.03% tacrolimus eye ointment reported insignificant variations in TSSS (12,18,19). When contrasted with olopatadine, one RCT featuring 0.03% tacrolimus eye ointment revealed significant subjective outcome disparities ($p<0.05$) (17). In addition, the use of 0.03% tacrolimus eye ointment as a standalone treatment yielded insignificant TSSS in comparison to its combination with olopatadine (8). Compared to sodium cromoglycate or conventional therapies, two RCTs utilizing 0.03% tacrolimus ointment and 0.03% tacrolimus eye drops respectively, exhibited noteworthy discrepancies in subjective outcomes ($p<0.05$) (11,16). One RCT comparing 0.1% tacrolimus eye ointment with 0.03% tacrolimus eye ointment revealed insignificant differences in subjective outcomes (13). Another study comparing 0.005% tacrolimus eye drops with interferon alpha-2b also reported insignificant differences (15) The summary of subjective outcomes is presented in Table 3.

Objective Outcomes

All formulations of tacrolimus significantly reduced the Total Objective Severity Score (TOSS) across studies (10-15,17-19). Two out of five studies comparing tacrolimus (0.03% eye ointment and 0.1% eye drop) with cyclosporine reported significant objective differences ($p<0.05$) (10,14). Compared to sodium cromoglycate or conventional therapies, significant disparities were observed in objective outcomes ($p<0.05$) (11,16). In contrast, compared to olopatadine, one RCT utilizing 0.03% tacrolimus eye ointment revealed a significant objective difference (17). However, other studies indicated insignificant objective differences ($p>0.05$) (8,12,13,15,18,19). The summary of objective outcomes is presented in Table 4.

Adverse Events

Among the nine studies employing tacrolimus eye ointment at concentrations of 0.03% and 0.1%, varying ocular complications and side effects were reported. Specifically, among those using 0.03% tacrolimus eye ointment, three studies reported no ocular complications or side effects (11,14,19). whereas one study noted burning sensations (81%) upon application of tacrolimus (8). In addition, occasional photophobia was reported in some patients in one study, (17) and

Table 3. Summary of clinical subjective

Study	Treatment duration (weeks)	Mean subjective						
		Intervention			Comparison		p	Comparison, p
		Initial	Evaluation	p	Initial	Evaluation		
Panadda 2012	8	6.07±3.95	N/A	p<0.05	6.05±2.26	N/A	p<0.05	p>0.05
Singla 2017	6	7.43±0.97	1.27±0.45	p<0.05	6.96±0.96	1.19±0.40	p<0.05	p>0.05
Kumari D. 2021	12	7.54±1.01	-	p<0.05	7.01±1.50	-	p<0.05	p>0.05
Pucci (A) 2015	3	6.30±3.42	1.83±3.18	p<0.05	6.56±3.35	5.75±4.57	p>0.05	p<0.05
Pucci (B) 2015	3	6.32±3.61	2.00±2.77	p<0.05	6.20±3.76	5.72±3.37	p>0.05	p<0.05
Heikal 2021	12	2.53±0.15	0.15±0.11	p<0.05	2.57±0.19	0.35±0.20	p<0.05	p<0.05
Kumari R. 2017	6	7.06±2.59	1.31±0.60	p<0.05	7.75±2.90	1.18±0.66	p<0.05	p>0.05
Manzoor 2023	12	2.80±0.12	0.12±0.21	p<0.05	2.93±0.14	1.23±0.28	p>0.05	p<0.05
Müller 2014	4.2	4.55	2.82	-	3.80	3.20	-	p>0.05
Hassan 2021	12	9.00±2.04	0.11±0.32	p<0.05	8.88±2.18	1.70±0.77	p<0.05	p<0.05
Eduardo 2017	12.8	4.63	0.38	-	4.50	3.17	-	p<0.05
Habibollah 2017	8	9.60±3.10	1.10±1.80	p<0.05	9.70±3.20	2.20±2.10	p<0.05	p>0.05

*(A) first phase of cross-over study; (B) second phase of cross-over study after the washout period.

Table 4. Summary of clinical objective

Study	Treatment duration (weeks)	Mean objective						Comparison, p
		Intervention			Comparison			
		Initial	Evaluation	p	Initial	Evaluation	p	
Panadda 2012	8	13.58±4.48	N/A	P<0.05	13.55±6.14	N/A	P>0.05	P>0.05
Singla 2017	6	4.13±1.17	2.07±0.74	P<0.05	4.19±0.63	2.04±0.60	P<0.05	P>0.05
Kumari 2021	12	6.08±1.33	-	P<0.05	5.75±1.27	-	P<0.05	P>0.05
Pucci (A) 2015	3	6.02±1.13	2.43±1.34	P<0.05	6.00±1.12	5.60±1.66	P>0.05	P<0.05
Pucci (B) 2015	3	6.64±1.89	2.42±1.78	P<0.05	6.04±1.81	5.32±1.55	P>0.05	P<0.05
Heikal 2021	12	2.03±0.49	0.17±0.12	P<0.05	2.16±0.45	0.36±0.33	P<0.05	P<0.05
Kumari 2017	6	4.88±1.50	2.88±0.88	P<0.05	4.50±1.15	2.50±1.03	P<0.05	P>0.05
Manzoor 2023	12	2.56±0.25	0.23±0.37	P<0.05	2.54±0.28	0.81±0.69	P<0.05	P<0.05
Müller 2014	4.2	4.00	2.91	-	3.70	4.00	-	P>0.05
Hassan 2021	12	3.93±1.93	0.08±0.28	P<0.05	4.36±1.90	0.64±0.55	P<0.05	P<0.05
Eduardo 2017	12.8	5.88	3.00	-	7.50	4.67	-	P<0.05
Habibollah 2017	8	7.70±3.00	1.20±0.90	P<0.05	8.90±3.00	2.70±2.00	P<0.05	P>0.05

* (A) first phase of cross-over study; (B) second phase of cross-over study after the washout period.

another study reported herpetic keratitis (1.6%) as an ocular complication, alongside side effects of a burning sensation (3.3%) and ocular stinging (3.3%) (13). Regarding the use of 0.1% tacrolimus eye ointment, one study reported herpetic keratitis (3.3%) and punctate keratitis (1.6%) as complications, along with side effects including burning sensation (10%), ocular stinging (8.3%), redness (6.6%), watering (5%), and ocular pain (3.3%) (13). However, the two remaining studies did not report any complications or side effects (12,18).

In the three remaining studies utilizing tacrolimus eye drops at concentrations of 0.005%, 0.03%, and 0.1%, adverse events were also documented. One study reported burning sensation (100%), ocular stinging (36.6%), and ocular pain (26.6%) upon administration of 0.1% tacrolimus eye drops (10). Another study noted a burning sensation following instillation of 0.03% tacrolimus (16). Conversely, no complications or side effects were reported in the third study (15). The summary of adverse events is presented in Table 5.

Discussion

VKC represents one of the more severe manifestations of ocular allergy. In our study, all participants received topical tacrolimus (either in the form of eye ointment or eye drops) along with other topical medications such as cyclosporine, olopatadine, interferon alpha-2b, sodium cromoglycate, or corticosteroids, with the aim of determining the most effective treatment for managing VKC (8,10-19). Despite one study employing a cross-over design, we maintain the appropriateness of its results, as neither topical medication nor systemic corticosteroids were permitted during the cross-over trial (10). In addition, there was a 1-week washout period between the applications of the two drugs to each eye.

Our findings indicate that regardless of variations in time, concentration, and vehicle, topical tacrolimus led to reductions in both subjective and objective scores of VKC (10-15,17-19). The application of topical tacrolimus significantly decreased TOSS and TSSS in VKC patients as early as 3 weeks following initiation. Moreover, both eye drops and eye ointment formulations demonstrated equal efficacy for VKC. Among studies utilizing 0.03% tacrolimus eye ointment, three studies found a correlation between duration of application and efficacy, indicating that longer durations led to greater improvements in TSSS and TOSS.

Table 5. Summary of adverse events

Intervention	Study	Adverse events
Tacrolimus eye drop 0.005%	Habibollah 2017	No major ocular complications or side effects.
Tacrolimus eye drop 0.03%	Eduardo 2017	No major ocular complications or side effects (burning sensation).
Tacrolimus eye drop 0.1%	Pucci 2015	No major ocular complications or side effects (burning sensation 100%, ocular stinging 36.6%, ocular pain 26.6%).
Tacrolimus eye ointment 0.03%	Kumari R. 2017*, Heikal 2021*, Manzoor 2023* Müller 2014[a] Hassan 2021[b] Kumari D. 2021[c]	*No major ocular complications or side effects [a]No major ocular complications or side effects (burning sensation 81%) [b]No major ocular complications or side effects (occasional photophobia) [c]No major ocular complications (herpetic keratitis 1.6%) or side effects (burning sensation 3.3%, ocular stinging 3.3%)
Tacrolimus eye ointment 0.1%	Panadda 2012*, Singla 2017* Kumari D. 2021[d]	*No major ocular complications or side effects

[d]Herpetic keratitis (3.3%), punctate keratitis (1.6%); side effects of a burning sensation (10%), ocular stinging (8.3%), redness (6.6%), watering (5%), ocular pain (3.3%)..

However, Kumari et al. observed a significant decline in TSSS and TOSS after 6 weeks of applying 0.03% tacrolimus ointment, but these scores returned to baseline levels after 2 weeks of discontinuation (19). A similar trend was noted by Pucci et al., who utilized 0.1% tacrolimus eye drops, resulting in an increase in TSSS and TOSS numbers 1 week after discontinuation (10). These findings are consistent with tacrolimus's short half-life, which ranges from 4 to 41 h (with an average of 12 h), highlighting the need for maintenance dosing strategies to sustain its effects (20). For instance, Kumari et al. initiated treatment with tacrolimus eye ointment at concentrations of 0.1% and 0.03% twice daily for 3 months, followed by maintenance dosing at the same concentration and frequency, but applied once daily (13).

In comparisons with cyclosporine, both 0.03% and 0.1% tacrolimus eye ointments exhibited equally effective reductions in TOSS and TSSS (12,18,19). Although Pucci et al. reported a significant mean difference between 0.1% tacrolimus eye drops and 1% cyclosporine eye drops, this finding could be biased as the study participants were cyclosporine-resistant and had undergone unsuccessful cyclosporine treatment for at least 15 days (10). In addition, no correlation was observed between the study origin and the effectiveness of topical tacrolimus for VKC.

Adverse events reported in this systematic review included burning sensation, ocular stinging, ocular pain, watering, redness, and occasional photophobia, irrespective of whether the preparation was in the form of eye ointment or eye drops (8,10,13,16,17). Interestingly, our study found that 0.005% tacrolimus eye drops did not produce any side effects, suggesting that side effects may emerge with increasing concentrations (0.03% and 0.1%). Hence, our results imply that the side effects of tacrolimus eye drops may be dose-dependent, as demonstrated by Kumari et al., who observed increasing ocular complications and side effects proportional to concentration increments (13). However, it is important to note that this study utilized tacrolimus ointment, necessitating further investigation to validate these findings in the context of eye drops.

In contrast, our findings regarding adverse events associated with tacrolimus eye ointment revealed intriguing variations. Kumari et al., Heikal et al., and Manzoor et al. reported no side effects with the application of 0.03% tacrolimus eye ointment, whereas Muller et al. reported a burning sensation during the application of the same concentration, and Hassan et al. noted occasional photophobia (8,11,14,17,19). However, no side effects were reported with 0.1% concentration of tacrolimus eye ointment (18). As previously mentioned, Kumari et al. suggested the occurrence of dose-dependent ocular complications and side effects (13). Nonetheless, Saha et al. reported mild burning and stinging sensation in three patients using 0.1% tacrolimus eye ointment, while no side effects were observed with 0.03% tacrolimus eye ointment (21). Further research is warranted to resolve these inconsistencies.

Some studies have proposed that the vehicles used in tacrolimus formulations, such as castor oil, may contribute to side effects (22). Alternative vehicles, including beta-cyclodextrin, sesame oil, olive oil, linseed oil, almond oil, and petroleum jelly, have been suggested (23). However, due to the lack of information regarding the vehicles used in both

ointments and eye drops in our studies, conclusive determinations cannot be made. Despite the occurrence of adverse effects with topical tacrolimus, the majority of participants continued treatment. In our studies, involving various concentrations and forms of tacrolimus, both eye drops and eye ointments significantly improved ocular signs and symptoms, consistent with the findings of Heikal et al. (14).

The mechanisms underlying burning sensation and ocular stinging remain unclear. One study proposed that tacrolimus may induce mast cell degranulation, releasing histamine and tryptase, which could stimulate sensory nerve fibers and result in a burning sensation. However, pre-cooling the topical tacrolimus in the refrigerator for 15–20 min before application has been suggested as a method to alleviate this sensation (24). Moreover, the preservative used in topical ophthalmic solutions, such as benzalkonium chloride, may also contribute to stinging and burning sensations (25). The occasional photophobia reported by Hassan et al. remains ambiguous, whether it was triggered by exposure to topical tacrolimus or VKC itself (17). Tacrolimus-induced herpetic keratitis may occur due to compromised local immunity (23). However, no studies are available to elucidate the mechanism of occasional photophobia following topical tacrolimus instillation.

Furthermore, in refractory cases of VKC, where symptoms persist despite treatment with anti-histamines, mast-cell stabilizers, topical steroids, cyclosporine, and decongestants, topical tacrolimus was found to be effective in reducing signs and symptoms in the majority of studies (10,11,14,26-28). No study identified the ineffectiveness of topical tacrolimus for refractory VKC. Gupta et al. described the effectiveness of interferon alpha-2b eye drops (1 million IU/mL) compared with 0.03% tacrolimus eye ointment in refractory VKC; however, this study had a high risk of bias due to its unrandomized method (29). Similarly, an RCT by Habibollah et al. reported significant effectiveness of interferon alpha-2b eye drops (1 million IU/mL) for refractory VKC, with no significant difference compared to 0.005% tacrolimus eye drops (15). These findings necessitate further research and clinical trials with larger sample sizes.

Although corticosteroids have been used in some studies to effectively treat VKC, long-term corticosteroid use must be avoided to prevent adverse complications such as glaucoma, cataracts, corneal damage, and increased susceptibility to infection (21,30,31). To address these concerns, clinicians often seek alternative steroid-sparing agents. At present, two notable steroid-sparing agents widely used in ophthalmology are cyclosporine and tacrolimus, with the latter being ten to a hundred times more potent than the former (23,31). Tacrolimus, as a steroid-sparing agent, has been shown to reduce mean intraocular pressure (IOP), thereby mitigating the risk of cataract and glaucoma formation. In addition, tacrolimus exhibits fewer side effects compared to corticosteroids and is effective for steroid-resistant refractory VKC. Yazu et al. found that 0.1% tacrolimus eye drops had better IOP control performance compared to when combined with topical corticosteroids (32). Similarly, Kumar et al. supported this finding by demonstrating that topical tacrolimus could be used without additional drugs such as steroids in refractory VKC (26).

Limitations

One limitation of this systematic review lies in its focus solely on English-language literature. Furthermore, some of the reviewed studies had small sample sizes, and there was inconsistency in the scoring systems employed across these studies. In addition, a notable challenge was the high dropout rate observed in several studies due to low participant compliance (10,19). Given the short half-life of topical tacrolimus, continuous administration of this medication is necessary (19,20). In summary, while the efficacy of topical tacrolimus holds promise for the management of VKC in clinical practice, robust evidence from large-scale randomized trials is imperative to establish its effectiveness conclusively. Further investigations are warranted to address the disparity between tacrolimus dosage and side effects, as well as its efficacy in refractory cases. In addition, comparative analyses regarding the cost-effectiveness of topical tacrolimus vis-à-vis other treatments are needed. If proven cost-effective, the inclusion of topical tacrolimus in clinical guidelines could be warranted.

Conclusion

The findings of this systematic review indicate that topical tacrolimus, regardless of its formulation or dosage, effectively mitigated the clinical signs and symptoms of VKC. Tacrolimus emerges as a potent steroid-sparing agent capable of averting the potential complications associated with prolonged corticosteroid usage. Moreover, tacrolimus demonstrated favorable safety profiles with minimal adverse effects and complications.

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