



## Clinical study of role of topical tacrolimus 0.03% eye ointment in vernal keratoconjunctivitis

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### Abstract

**Background:** Vernal keratoconjunctivitis (VKC) is recurrent bilateral allergic inflammation of conjunctiva and cornea. It is more prevalent in hot dry climate like Indian subcontinent. Antihistaminics and mast cell stabilizers are the first line treatment of VKC. In severe cases corticosteroids are used. But because of severe side effect of steroids immunomodulators have been used as substitutes for corticosteroids. The aim of this study is to determine the clinical efficacy of topical 0.03% tacrolimus as a sole therapy in VKC.

**Material and methods:** 50 patients of VKC were selected & divided into two subgroup.

**Group A:** In which 0.03% tacrolimus ointment was applied twice a day with tear drops as placebo.

**Group B:** In which 0.1% olopatadine ophthalmic solution was applied twice a day along with 0.03% tacrolimus ointment. Each patient was examined on slit lamp and symptom and sign was graded on a scale from 0 to 3 before the introduction of therapy, on day 7, 30 and 90. The student's T-test for independent sample was used to compare the results between two groups.

**Results:** There is significant reduction in the signs (conjunctival hyperaemia, tarsal papillary reaction, punctate epithelial keratitis, limbal gelatinous infiltrate) and symptoms (itching, tearing, foreign body sensation, photophobia, discharge) in both the group on day 7, 30 and 90 days. (P<0.05)

**Conclusion:** The isolated use of tacrolimus and the combined use of tacrolimus with olopatadine have similar efficacy in reducing clinical symptoms and signs in cases of VKC which are refractory to conventional therapy.

**Keywords:** Vernal keratoconjunctivitis, tacrolimus, immunomodulators, olopatadine

### Introduction

Allergic eye disease has been considered as a common ocular condition encountered in clinical practice. Vernal keratoconjunctivitis (VKC) is recurrent, bilateral interstitial, self-limiting, allergic inflammation of the conjunctiva having a periodic seasonal incidence which subsequently affects cornea. Worldwide the incidence of VKC has been reported in most of the continents. Indian population is also significantly present with VKC [1, 2].

Reports indicate the wide variation in prevalence, severity, course of the disease and treatment response. As per various studies this condition is more prevalent in hot, dry climatic zone [2].

VKC differs from seasonal allergic conjunctivitis and perennial allergic conjunctivitis because it is a condition mediated by Th2 lymphocytes. However, the precise roles of mast cells, eosinophils, fibroblasts, and their cytokines in the inflammatory process and the remodelling of conjunctival tissue remain poorly established [3-5].

The topical use of antihistamines, mast cell stabilizers (MCSs), and, more recently, drugs with both effects, termed dual-action drugs (DADs), represent the first-line treatment for VKC. In the more severe forms, corticosteroids are used for a short period to induce the remission of the allergic crisis. However, there are characteristic features of VKC coming in department of pediatric ophthalmology & strabismus at a tertiary eye care centre located in Rajasthan, India will be studied. As this region is with hot,

cases where it is not possible to withdraw the corticosteroid without any clinical worsening, thus leaving patients susceptible to risks caused by the prolonged use of these drugs, such as cataract, glaucoma, and corneal complications. For the past two decades, immunomodulators have been used as substitutes for corticosteroids in allergic crisis control and the maintenance of asymptomatic VKC patients [6].

Tacrolimus, a macrolide derived from the bacterium *Streptomyces tsukubaensis*, is a potent immunomodulator capable of decreasing the production of inflammatory mediators by T lymphocytes through the inhibition of calcineurin, an intracytoplasmic protein essential for interleukin (IL)-2 and IL-4 transcription [7, 8].

There are numerous reports of the successful use of tacrolimus for the treatment of autoimmune diseases of the ocular surface, such as dry eye, scleritis, Mooren ulcer, cicatricial conjunctivitis, atopic, and VKC [9-13]. Recent clinical trials have also shown that, like corticosteroids, tacrolimus and other immunosuppressive drugs have similar efficacy in allergic crisis control and maintenance therapy for VKC but with a low incidence of side effects [14-16].

This study is focused on determining the efficacy of Tacrolimus as a sole therapy in VKC. A group of patients with windy and dry climatic condition, the prevalence of VKC is higher over here.

Material and methods

The study group consisted of all VKC patients refractory to conventional therapy coming in the out-patient department at a tertiary eye hospital. Refractory, in this context, meant that the clinical condition was maintained or worsened during the use of topical corticosteroids or that there was a relapse after withdrawal. Randomly 50 patients were selected & divided into two subgroups A and B consisting of 25 each.

**Group A (Experimental Group):** In which 0.03% tacrolimus ointment was applied twice a day with tear drops as placebo.

**Group B (Control Group):** In which 0.1% olopatadine ophthalmic solution was applied twice a day along with 0.03% tacrolimus ointment.

Both eye drops had similar flasks, with no identification and were given to the patients together with the ointment. For double masking of the study, the eye drop flasks were numbered and contained no identification of the drug. The content of the flasks was only revealed after the end of the data collection period. The randomization was performed using a block system.

Each patient was examined on slit lamp and each symptom and sign was graded on a scale from 0 to 3 (Table 1 and Table 2). The symptoms and signs were assessed before the introduction of therapy, after 30 days and after 90 days.

Clinical impression of the progress of each case and the self-assessment provided by the patient will be noted using an objective 0 to 3 scale. To assess the safety and side effects of the treatment, itching, burning, intraocular pressure, lens opacification, secondary infections, or other possible complications were assessed.

The Institutional Ethics Committee on Human Subjects Research, 2014-15, granted approval, subsequent to which data collection for the study was initiated. The Student's *T* test for independent samples was used. To compare the results for the two assessment times, within each group, the Student *T* test for paired samples was used. When comparing the 2 groups regarding the qualitative variables, Fisher exact test and the chi-square test were used. *P*-values less than 0.05 were considered significant. The statistical software, statistical product and

service solutions (SPSS 15.0) was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables, etc.

## Results

In the study group the age of the patients were ranging from 6 to 20 years. Majority of the patients were found between 6 years to 15 years. 41 out of 50 (82.0%) were male and 09 (18.0%) were female. Large numbers of patients were of school going children (82.0%) followed by preschool children (12%) and working outdoors with their parents (6%). Most of the patients were from rural area (80.0%). Majority of the patients were of bulbar variety (46.0%) of VKC followed by palpebral (34.0%) and mixed (20%). Total 11 out of 50 (22%) patients were presented with corneal involvement in which three out of twenty three (13.04%) cases were of bulbar form, four out of seventeen (23.52%) cases were of palpebral form and four out of ten (40.00%) cases were of mixed form shows corneal involvement. Superficial punctate keratitis in seven cases and epithelial scarring in four cases were observed. Corneal involvement was observed more among patients having palpebral or mixed type of disease.

## Result of therapeutic trial with drugs

50 patients were divided into two groups and symptoms & signs were assessed on day 0 (base line) and at day 7, day 30, day 90. Mean scores of symptoms (itching, tearing, foreign body sensation, photophobia, discharge) and signs (conjunctival hyperaemia, tarsal papillary reaction, punctate epithelial keratitis, limbal gelatinous infiltrate) and their comparison in between two groups with *p* value are summarised in table-3 & 4. There is significant reduction in the signs and symptoms in both the group on day 7, 30 and 90 days.

In this study in group A (Tacrolimus with placebo) and group B (Tacrolimus with olopatadine) severity of signs and symptoms were found to be reduced at day 90. (Fig-1)

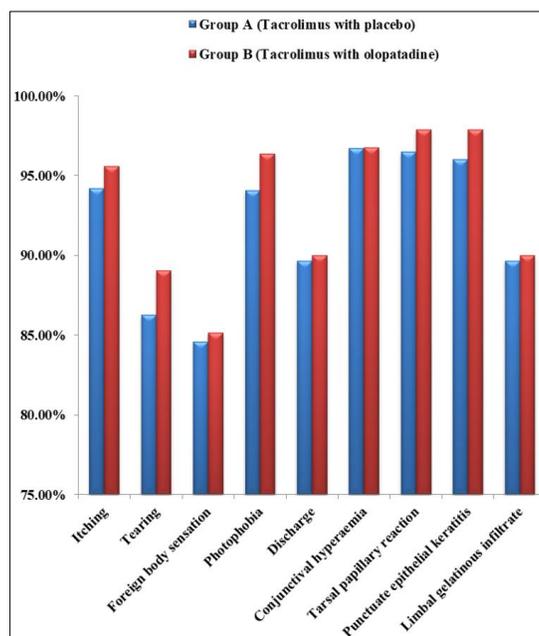


Fig 1

**Table 1**

	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>Itching</b>	<b>Absent</b>	<b>Occasional desire to rub or scratch</b>	<b>Frequent need to scratch or rub the eye</b>	<b>Constant need to rub or scratch the eye</b>
Tearing	Normal tear production	Positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant, spilling of tears over the lid margins
Foreign body Sensation	Absent	Mild	Moderate	Severe
Photophobia	Absent	Mild difficulty with light	Moderate difficulty, necessitating dark glasses	Extreme photophobia, cannot stand natural light even with dark glasses
Discharge	Absent	Mild, occasionally discharge accumulates	Moderate, noted in the lower cul-de-sac	Severe, eyelids tightly matted together upon awakening

**Table 2**

	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>Conjunctival hyperaemia</b>	<b>Absent</b>	<b>Minimal redness</b>	<b>Diffuse redness</b>	<b>Very marked diffuse redness</b>
Tarsal papillary reaction	Absent	Mild mosaic flat appearance	Elevated papillae	Cobble stone appearance of papillae
Punctate epithelial keratitis	Absent	Up to one quadrant	Up to two quadrants	three or more quadrants
Limbal gelatinous infiltrate	Absent	Upto one quadrant	Upto two quadrants	three or more quadrants

**Table 3**

<b>Symptoms</b>	<b>Group</b>	<b>Day 0 mean score (Base line)</b>	<b>Day 30 mean score</b>	<b>Day 90 mean score</b>
Itching	Group A	2.76	1.04P<0.05	0.16P<0.05
	Group B	2.72	0.84P<0.05	0.12P<0.05
	P Value	0.753(P>0.05)	0.231(P>0.05)	0.691(P>0.05)
Tearing	Group A	2.80	1.08P<0.05	0.44P<0.05
	Group B	2.88	1.00P<0.05	0.20P<0.05
	P Value	0.451(P>0.05)	0.645(P>0.05)	0.07(P>0.05)
Foreign body sensation	Group A	2.76	1.08P<0.05	0.48P<0.05
	Group B	2.96	0.88P<0.05	0.44P<0.05
	P Value	0.042(P>0.05)	0.060(P>0.05)	0.782(P>0.05)
Photophobia	Group A	2.76	1.00P<0.05	0.44P<0.05
	Group B	2.84	1.00P<0.05	0.42P<0.05
	P Value	0.49 (P>0.05)	1 (P>0.05)	0.98 (P>0.05)
Discharge	Group A	2.32	0.84P<0.05	0.24P<0.05
	Group B	2.40	0.68P<0.05	0.24P<0.05
	P Value	0.565(P>0.05)	0.485(P>0.05)	1(P>0.05)

**Table 4**

<b>Signs</b>	<b>Group</b>	<b>Day 0 mean score (base line)</b>	<b>Day 30 mean score</b>	<b>Day 90 mean score</b>
Conjunctival Hyperemia	Group A	2.44	0.56P<0.05	0.08P<0.05
	Group B	2.48	0.60P<0.05	0.08P<0.05
	P value*	0.837(P>0.05)	0.780(P>0.05)	1(P>0.05)
Tarsal Papillary Reaction	Group A	2.28	0.48P<0.05	0.08P<0.05
	Group B	1.88	0.36P<0.05	0.04P<0.05
	P value*	0.226(P<0.05)	0.40(P<0.05)	0.307(P<0.05)
Punctate Epithelial Keratitis	Group A	0.52	0.04P<0.05	0.00P<0.05
	Group B	0.84	0.08P<0.05	0.00P<0.05
	P value*	0.876	0.801	1
Limbal Gelatinous Infiltrates	Group A	2.04	0.44P<0.05	0.12P<0.05
	Group B	2.28	0.52P<0.05	0.12P<0.05
	P value*	0.565(P>0.05)	0.485(P>0.05)	1(P>0.05)

**Discussion**

Refractory VKC is difficult condition to treat. Steroid relieves sign and symptoms effectively but long term use of them is known to cause serious side effects. In this study, we compared

the efficacy of isolated tacrolimus with combined use of tacrolimus and olopatadine. The majority of VKC occurs in patients between the ages of 5-25 years old with an age of onset between 10-12 years old; however there are reports of patients as

young as 5-months-old [17-19]. It generally resolves after puberty, usually around 4–10 years after onset [20, 21]. In a prospective double masked comparison Labcharoenwongs P *et al.* enrolled 24 patients into the study. Their mean age was 9.61 years [16]. Pucci N *et al.* reported mean age  $9.05 \pm 2.12$  years in their study [22]. In the present study 41 (82%) patients out of 50 were between ages of 6 to 15 years of age.

Males are affected more than females, but this difference becomes smaller as age increases [23]. Harada N *et al.* reported 24 men and 6 women of VKC in their study [24]. Marey HM *et al.* reported male-to-female ratio of 2.3:1 in school going age group in their study [25]. In a study of Shoughy SS *et al.* there were 62 patients with VKC comprising 49 male and 13 female patients [26]. In the present study 41 out of 50 (82.0%) were male and 09 out of 50 (18.0%) were female.

The increased incidence in hot regions is speculated to be secondary to a higher level of pollution by pollens and various other allergens [20]. Depending on region and climate, prevalence of VKC can vary widely [27]. As Rajasthan state of India is the region with hot, windy and dry climatic condition, the prevalence of VKC is higher over here. In this study there were 40 out of 50 (80%) patients from rural area and 10 out of 50 (20%) patients from urban area. Although the name vernal suggests a seasonal, springtime occurrence, this allergic condition frequently persists throughout the year and usually increases in intensity in warmer weather [28, 29]. In present study most of the patients (82%) have reported in month of April to July considered as they are hot months in Rajasthan, India.

VKC is known to be one of the most severe forms of ocular allergy, with the potential to cause corneal damage and permanent visual loss. Sacchetti *et al.* [29] observed that VKC patients with corneal involvement or more than one recurrence per year have an increased risk of permanent visual loss. In present study 11 out of 50 (22%) patients were with corneal involvement.

Generally VKC is a rather benign and self-limiting disease that may resolve with age or spontaneously at puberty. Nonetheless, the sometimes debilitating nature of this disease when it is active necessitates therapy to control symptoms [17, 18].

The aim of this study is to review the effectiveness of currently available treatment option mainly newer medication that is alone effective in VKC cases which are resistant to conventional treatment e.g. Tacrolimus eye ointment.

Several studies have considered topical tacrolimus an effective and safe alternative for allergic crisis control and the maintenance of VKC symptoms [15, 29, 30]. In a randomized clinical trial, Ohashi *et al.* [14] obtained significant clinical improvement in the group that used tacrolimus in comparison with the placebo group. Labcharoenwongs *et al.* [16] compared 0.1% tacrolimus with 2% cyclosporine and reported clinical improvement in both groups, with no significant difference between the two drugs. However, Moscovici *et al.* [9] showed that absorption of tacrolimus 0.03% eye drops were well below that at which adverse effects were reported when administered systemically. In this study in group A (Tacrolimus with placebo) and group B (Tacrolimus with olopatadine) severity of signs and symptoms were found to be reduced at day 90 in both the groups. Itching has reduced by 94.20%, tearing by 86.28%, foreign body sensation by 82.60%, photophobia by 84.06%, discharge by 89.65%, conjunctival hyperaemia by 96.72%, tarsal papillary reaction by 96.49%,

punctuate epithelial keratitis by 96.00%, limbal gelatinous infiltrate by 89.65% in group A and by 95.59%, 89.05%, 85.13%, 96.37%, 90.00%, 96.77%, 97.87%, 97.87%, 90% respectively in group B. Prompt and considerable improvement in symptoms of refractory VKC has found in both group A and group B.

Itching has been seen to be mostly relieved in all patients after 7 days of treatment. Majority of symptoms have been alleviated. There was marked improvement in objective signs with time, such as: decreased hyperaemia within 7 days; improved conjunctival papillary hypertrophy and giant papillae within 1 month and improved limbal hypertrophy and corneal signs in a month. In present study it has found that group A (tacrolimus with placebo) and group B (tacrolimus with olopatadine) have similar efficacy in reducing signs and symptoms of VKC with minimum discomfort.

Improvement in clinical picture was reported in 50 (100%) cases though 20 (40%) cases reported burning sensation in eyes while applying tacrolimus ointment.

So the main complaint was associated with burning during the application of tacrolimus. During the study period, there was no significant change regarding intraocular pressure, lens opacification, secondary infections, or other factors.

Also, no great complications have been described in literature about ocular use of tacrolimus (ointment or drops). Only one case of herpes keratitis and other with throat irritation were described in one study [14].

This study was limited by small number of cases. We used tear drops as placebo which itself relieves signs and symptoms of VKC by some extent. This study was not powered to assess either systemic absorption of tacrolimus cause any side effect.

## Conclusion

The isolated use of tacrolimus and the combined use of tacrolimus with olopatadine have similar efficacy in reducing clinical symptoms and signs in cases of VKC which are refractory to conventional therapy.

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