Original Article

Efficacy of 0.03% Dermatological Tacrolimus Ointment for Refractory Vernal Keratoconjunctivitis

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Purpose: To determine the efficacy of 0.03% dermatological tacrolimus ointment in patients with refractory vernal keratoconjunctivitis.

Study Design: Quasi-experimental study.

Place and Duration of Study: Eye Department, DHQ-Teaching Hospital, Gujranwala, Pakistan from April 2018 to March 2019.

Material and Methods: After approval from hospital ethical committee and obtaining written informed consent from each patient/guardian, patients of either gender between 4-16 years of age with VKC not responding to conventional treatment for more than 8 weeks or having steroid-induced complications were included in this study. Dermatological tacrolimus ointment 0.03% was placed in inferior fornix in BD dose frequency along with topical lubricants. Patients were followed up on a regular schedule. Individual symptoms score was assessed from the questionnaire and signs score from observer's clinical assessment. Data were analyzed using SPSS v23.0. P-value <0.05 was considered as statistically significant.

Results: Forty eyes of 20 patients were included in this study. Out of 40, four (20%) were female and 16 were male (80%). Mean baseline score for clinical symptoms was 6.65 ± 1.81 that reduced to 1.65 ± 0.81 after 12 weeks' treatment course of tacrolimus with a significant p-value of 0.006 ($p < 0.05$). Mean baseline score for clinical signs was 5.9 ± 1.59 that improved to 1.80 ± 0.83 after 12 weeks' treatment course with a statistically significant p-value of 0.003 ($p < 0.05$).

Conclusion: In conclusion, topical tacrolimus dermatological ointment 0.03% is highly effective in refractory VKC and can be safely used as an alternative in VKC patients who are steroid-responders.

Key Words: Tacrolimus, Vernal keratoconjunctivitis, mast cell stabilizers, antihistamines.

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, bilateral conjunctival inflammation that has seasonal exacerbations in summer and late spring and involve both type I as well as type IV hypersensitivity reactions[1]. It mainly affects children between 3 and 16 years of age with remission by late teens in 95% of cases. Young boys in dry and hot climates are generally affected[2]. Patients with VKC suffer from significant morbidity. Symptoms include severe itching, foreign body sensation, mucoid discharge, photophobia, and blurred vision. Common clinical signs of VKC are conjunctival hyperemia, papillary hypertrophy, mucous discharge, Horner-trantas dots, and corneal involvement[3].

Treatment options available for Vernal keratoconjunctivitis include topical antihistamines, mast cell stabilizers, NSAIDS, steroids, and immunomodulators[4]. Prolonged treatment course with multiple remissions is the major threat faced among VKC patients. Secondly, as topical steroids are the mainstay of management for moderate to severe VKC but their injudicious and prolonged use can lead to secondary glaucoma, cataract, and secondary infections[5]. Risk of these complications is particularly high among children who are the most commonly affected age group in VKC.

To prevent the occurrence of steroid-induced complications in VKC patients, certain immunomodulators are in use.[6] Two being cyclosporine and tacrolimus, of which tacrolimus is strong, nonsteroidal, macrolide immunomodulator isolated from *Streptomyces tsukubaensis* that has 100 times more potency than cyclosporine[7]. Though uncertainty exists about its mechanism of action but it is known to interact with 12-kDa FK506-binding protein in T-cells and thus inhibits calcineurin activity that ultimately leads to reduced de-phosphorylation of the nuclear factor of activated T-cells and hence T_H1 (IL-2, interferon- γ), as well as T_H2 cytokines (IL-4, IL-5) production is reduced[8]. Tacrolimus is also known to inhibit histamine release from mast cells thus alleviating the symptom of itching[9].

In ophthalmic practice, topical tacrolimus in doses of 0.001–0.1% are in use for many refractory inflammatory ocular surface diseases including vernal keratoconjunctivitis (VKC)[10]. Its proper dosage, frequency, duration and adverse events in the eye still lie in an undiscovered domain.

The rationale of this study was to confirm efficacy and safety of low dose topical tacrolimus ointment 0.03% for refractory vernal keratoconjunctivitis non-responding to conventional treatment and also to find out an alternative treatment for VKC eyes suffering from steroid-induced complications.

MATERIAL AND METHODS

After approval from the hospital ethical committee, a written informed consent with demographic variables was collected from patients/guardians. Patients of either gender between 4-16 years of age with VKC not responding to conventional treatment (anti-histamines/mast cell stabilizers/NSAIDS/steroids) for more than 8 weeks or having steroid-induced complications were included in this study. Exclusion criteria was immunocompromised patients, pregnant females, recent ocular surgery in previous 3 months and infectious ocular disease in particular, herpes infection. This study included 40 eyes of 20 patients and was conducted at eye department of DHQ-Teaching Hospital Gujranwala during 12 months (April 2018 – March 2019).

All patients underwent routine ophthalmic examination including Visual acuity, BCVA, Slit lamp Biomicroscopy with Fluorescein staining as well as photography, Fundus evaluation, and Applanation Tonometry. Diagnosis of VKC was made on a clinical basis with 4 symptoms of itching, redness, photophobia, mucoid discharge and 4 clinical signs of conjunctival hyperemia, papillary hypertrophy, Horner-Trantas dots, and corneal involvement.

Before starting treatment with tacrolimus and at each visit thereafter, all patients/guardians were given a questionnaire to grade all four symptoms into scale 0 (none), scale 1 or mild, scale 2 or moderate, and scale 3 or severe[11]. Similarly, clinical signs were also categorized by one observer into scale 0 (none), scale 1 (mild), scale 2 (moderate), or scale 3 (severe) in following way[11].

Table 1: Signs score grading.

Signs	Score	Description
Conjunctival Hyperemia	3	Diffuse dilated vessels over entire bulbar conjunctiva
	2	Dilatation of many vessels
	1	Dilatation of few vessels
	0	None
Papillae	3	Papillae size > 0.3 mm
	2	Papillae size 0.2-0.3mm
	1	Papillae size <0.2mm
	0	None
Trantas	3	> 6 dots
	2	4-6 dots
	1	1-3 dots
	0	None
SPK	3	Total corneal surface
	2	More than half corneal surface
	1	Less than half corneal surface
	0	None

Dermatological Tacrolimus ointment 0.03% was advised to be placed in inferior fornix in BD dose while all other conventional topical medications (anti-histamine, mast cell stabilizers, NSAIDS) were discontinued except for steroids that were tapered off. Topical lubricants were also prescribed in BD frequency to reduce irritation, which is seldom observed with tacrolimus ointment.

Patients were followed up at 3 days after starting the medication and then at 2 weeks, 4 weeks, 8 weeks and final follow up at 3 months. In each visit, the above mentioned questionnaire and ophthalmic examination were repeated to attain final clinical score along with photographs and the patients were also specifically asked about the discomfort associated with the use of tacrolimus ointment.

Improvement of each symptom or sign was defined as at least 1-score reduction in severity compared with values before the treatment. Paired t-test was used to statistically analyze the changes in mean clinical score before and after treatment. Data was analyzed using SPSS v23.0. Results were expressed as Mean ± SD and percentages. P-values of 0.05 or less were considered as statistically significant.

RESULTS

Average age of the participants of the study was 9.05 ± 3.58 (range 4-16) years. Eleven (55%) patients were between 4-8 years of age, 5 (25%) between 9-12 years of age and 4 (20%) between 13-16 years of age.

Mean duration of conventional treatment before starting tacrolimus ointment was 10 months with SD of ± 5.96. While using conventional treatment, 4 patients (20%) were only on topical steroids, 9 patients (45%) were using anti-histamines, mast cell stabilizers and NSAIDS and 7 (35%) were on combination of all.

Most common symptom found in this study was itching that was present in 90% of total study population and it also first responded to treatment within 2 weeks. Least common symptom observed was photophobia that was present in 40% of cases.

Most common sign observed in this study was papillary hypertrophy that was present in 80% of total study population and it slowly responded to treatment within 8 weeks' duration. Least common sign observed was corneal involvement that was present in 30% of cases.

Symptoms sore was calculated from questionnaire. Each symptom (total 4) was graded on a scale of 0-3 thus rendering individual symptoms score out of 12. Mean symptoms score at baseline was 6.65 ± 1.81 that reduced to 6.25 ± 1.68 after three days post-treatment with insignificant p- value of 0.354. At 4 weeks follow up, p-value turned out statistically significant (p = 0.009) with symptoms score of 3.30 ± 1.17 that markedly reduced to 1.65 ± 0.81 with significant p-value of 0.006.

Signs score was calculated from observer's clinical response at each visit in which each clinical sign (total 4) was graded by observer on a scale of 0-3, again rendering the total score of 12. Mean signs score at baseline was 5.90 ± 1.59 that reduced to 5.45 ± 1.38 three days post-treatment with insignificant p-value of 0.233. At 4 weeks follow up, p-value turned out statistically significant (p = 0.035) with signs score of 3.30 ± 1.08 that markedly reduced to 1.80 ± 0.83 with significant p-value of 0.003.

At baseline, mean score for symptoms was 6.65 while that for

Table 2: Individual symptoms and signs in percentages.

Symptoms / Signs	Percentage (%)	Total No. (n)
Itching	90%	36 eyes of 18 pts.
Redness	70%	28 eyes of 14 pts.
Mucoid Discharge	50%	20 eyes of 10 pts.
Photophobia	40%	16 eyes of 8 pts.
Papillary Hypertrophy	80%	32 eyes of 16 pts.
Conjunctival Hyperemia	70%	28 eyes of 14 pts.
Trantas Dots	40%	16 eyes of 8 pts.
Corneal involvement (SPK)	30%	12 eyes of 6 pts.

Table 3: Symptoms score at different intervals.

Symptoms Score at Different Intervals	Mean	Std. Deviation	p-value
Symptoms score at baseline	6.65	1.81	
Symptoms score after 3 days	6.25	1.68	0.354
Symptoms score after 2 weeks	4.45	1.23	
Symptoms score after 4 weeks	3.30	1.17	0.009
Symptoms score after 8 weeks	2.45	1.19	
Symptoms score after 12 weeks	1.65	0.81	0.006

Table 4: Signs score at different intervals.

Signs Score at Different Intervals	Mean	Std. Deviation	p-value
Signs score at baseline	5.90	1.59	
Signs score after 3 days	5.45	1.36	0.233
Signs score after 2 weeks	4.10	1.07	
Signs score after 4 weeks	3.30	1.08	0.035
Signs score after 8 weeks	2.60	1.05	
Signs score after 12 weeks	1.80	0.83	0.003

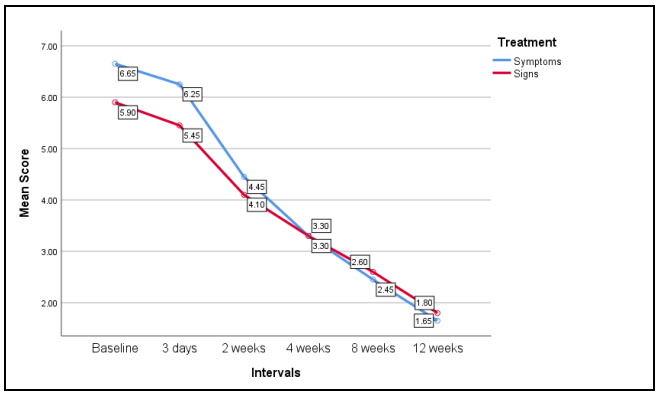
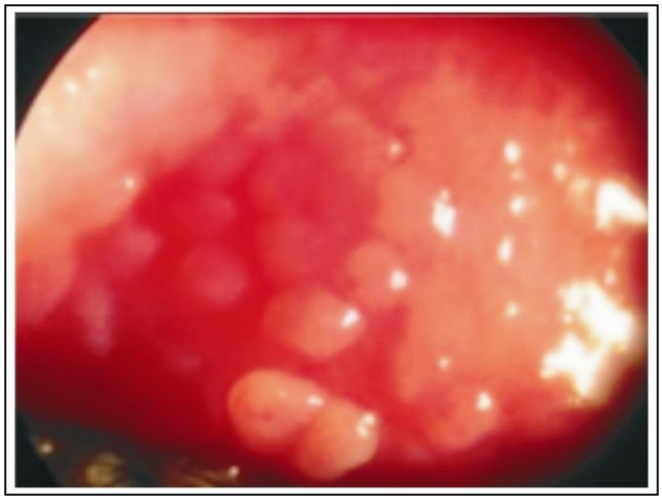
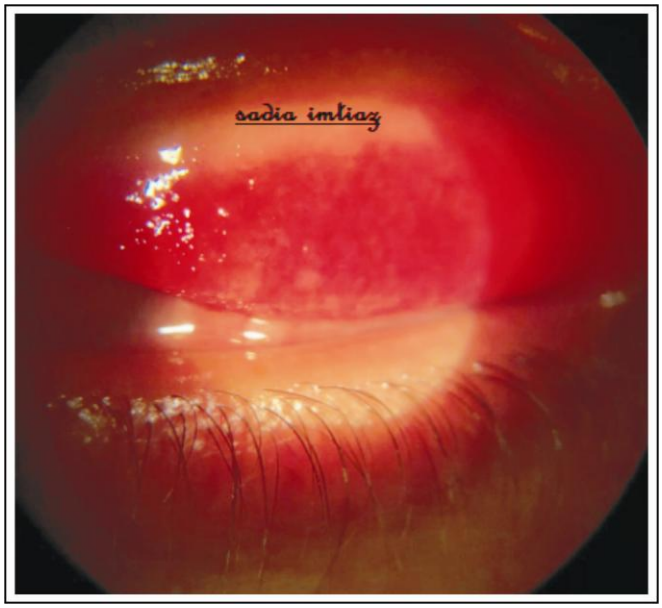


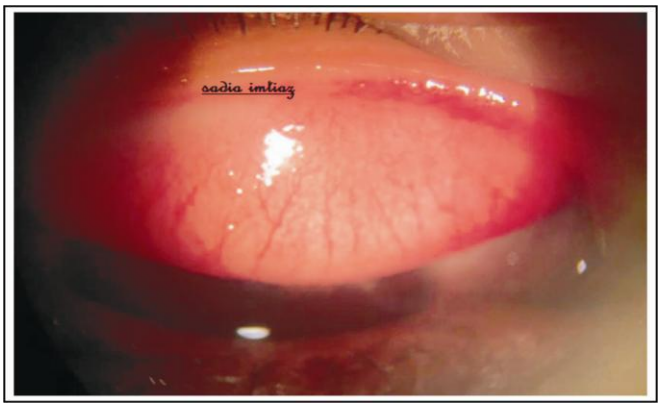
Fig. 1: Line Chart showing Gradual Decline in Symptoms and Signs Score.



2A): Grade III Papillary Hypertrophy at Baseline.

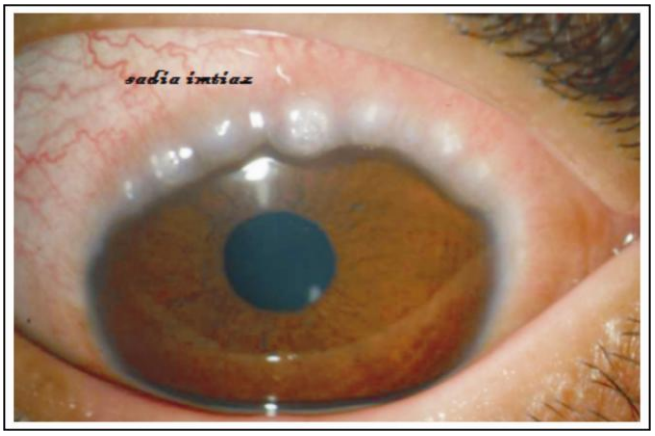


2B): Grade I Papillary Hypertrophy at 4 Weeks.

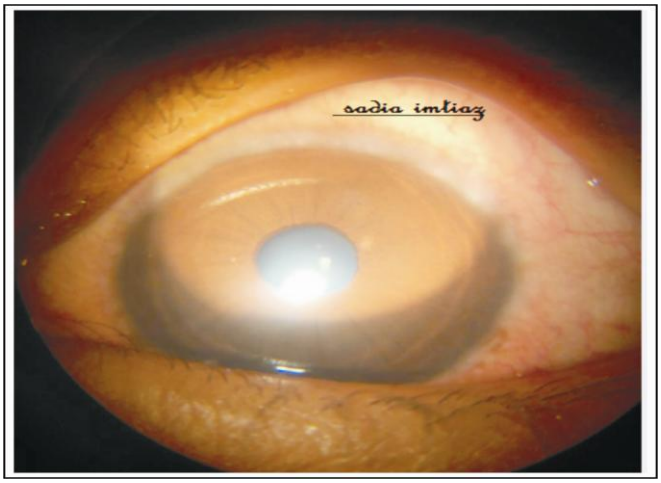


2C): Grade 0 Papillary Hypertrophy at 8 Weeks Duration.

Fig. 2(A-C): Resolution of Papillary Hypertrophy with Tacrolimus.



3A): Grade III Trantas Dots at baseline.



3B): Grade I Trantas Dots at 8 weeks duration

Fig. 3(A-B): Resolution of Limbal Trantas Dots with Tacrolimus.

signs was 5.90. At 4 weeks interval both mean scores were found to be 3.30. While after 4 weeks, symptoms score reduced more markedly than signs score and at final follow up, mean score for symptoms was 1.65 and that for signs was 1.80.

DISCUSSION

This study confirmed the efficacy and safety of topical tacrolimus 0.03% in VKC, which were refractory to conventional treatment. All patients showed marked improvement in signs and symptoms without developing any significant adverse effects. Mild irritation was noted in 4 patients initially with the use of tacrolimus ointment but that subsided after one week. Chatterjee et al. also reported mild transient stinging sensation in their study population but that also lasted only for few days[12].

Most common symptom in our study was itching that was noted in 90% (36 eyes of 18 patients) of patients and it was also first to resolve within 2 weeks duration. In a similar study by Al-Amri et al 17 out of 20 patients complained of itching and all cases improved within 1 week[13].

Most common clinical sign noted was papillary hypertrophy that was present in 80% of patients (32 eyes of 16 subjects) and it resolved in relatively longer period of about 8 weeks. Conjunctival hyperemia responded to treatment first and resolved within 4 weeks in 12 out of 20 patients. Barot et al. also reported conjunctival hyperemia to get resolved within 1 month in 60% of patients.[14] Corneal involvement was least observed among participant patients probably due to early visit to Ophthalmologist.

In our study, Mean baseline score for clinical symptoms was 6.65 ± 1.81 that reduced to 1.65 ± 0.81 after 12 weeks treatment course of topical tacrolimus with significant p-value of 0.006 ($p < 0.05$). Mean baseline score for clinical signs was 5.9 ± 1.59 that improved to 1.80 ± 0.83 after 12 weeks treatment course with statistically significant p-value of 0.003 ($p < 0.05$). Results of this study are also supported by few other recently conducted studies[15,16,17]. Fukushima et al. carried out similar study on large population including 1436 patients with refractory allergic conjunctivitis and concluded that 0.1% tacrolimus eye drops are highly effective in treating this refractory condition with corneal involvement thus alleviating need for topical steroids use.[15] Muller et al. suggested topical tacrolimus 0.03% as sole therapy in VKC by dividing study population in two groups; One with only topical tacrolimus ointment and other with topical tacrolimus ointment + olopatadine eye drops and found out same efficacy with no significant difference between the two groups[16]. Kheirkhah et al. used low dose 0.005% topical tacrolimus drops in refractory VKC cases and results showed it effective and safe alternative for steroid resistant cases[17].

Tacrolimus is widely used in many refractory ophthalmic conditions other than vernal keratoconjunctivitis. Al-Amri reported the successful use of 0.1% dermatological tacrolimus ointment in 22 patients with Atopic kertoconjunctivitis[18]. Many studies have concluded the therapeutic efficacy of tacrolimus ointment in chronic ocular graft versus host disease (GVHD)[19,20,21]. Choi et al. reported the effective role of 0.03% tacrolimus eye drops in refractory dry eye disease associated with chronic ocular GVHD[21].

The limitation of our study is the off-label use of drug, as its ophthalmic preparation is not available in Pakistan. But many other authors also safely recommended the use of this skin preparation for ophthalmic usage[18,22]. Second limitation of this study is relatively small sample size and that is due to patient's/guardian's reluctance towards use of off-label drug. Third being short duration of follow up (3 months) as it cannot be determined the risk of recurrence after drug has been stopped. In the end, the author suggests that its ophthalmic preparation should be available in our country like elsewhere so similar studies can be carried out on large scale for a long period of time for better determination of its efficacy and safety.

CONCLUSION

In conclusion, topical tacrolimus dermatological ointment 0.03% is effective in relieving signs and symptoms of refractory VKC cases that are not responding to conventional treatment and also that topical tacrolimus can be safely used as an alternative in VKC patients who are steroid-responders, to lower the risk of steroid-induced complications.

CONFLICT OF INTEREST

The author has no financial or personnel conflict of interest in this study.

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