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To Assess Efficacy and Safety of 0.1% Tacrolimus Ophthalmic Ointment in Refractory Cases of VKC

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ABSTRACT

Introduction: Vernal kerato-conjunctivitis (VKC) is a chronic, bilateral allergic inflammation of the conjunctiva and cornea. For refractory cases, oral or subtarsal corticosteroids are indicated, immunotherapeutic agents like cyclosporine are also used. Recently Tacrolimus is used for the treatment of refractory VKC. It is an immunomodulator with more potency than cyclosporine.

Aim & Objective: To assess efficacy and safety of 0.1% tacrolimus ophthalmic ointment in refractory cases of VKC

Material and Methods: Present study was a prospective study carried out on refractory cases of vernal kerato-conjunctivitis. Patients were divided into two groups. Group A Patients received Tacrolimus 0.1% ophthalmic ointment twice daily and anti-allergic medications and Group B patients received only allergic medication. Patients were followed up for up to 6 months. At every follow-up, symptoms and signs of both groups were compared.

Results: Mean age of the patients in group A was 14.5±2.4 years and in the group, B was 15.4±3.1 years. Males predominated females in both groups. Patients with tacrolimus treatment showed a statistically significant decrease in symptom score and sign score over 6 months. ($p<0.05$).

Conclusion: Tacrolimus ophthalmic ointment 0.1% is well tolerated and effective in improving objective clinical signs and subjective symptoms of severe VKC refractory to topical antiallergic agents.

Key Words: Tacrolimus, Vernal kerato-conjunctivitis, Refractorycases, Steroid, Cyclosporine

INTRODUCTION

Vernal kerato-conjunctivitis (VKC) is a chronic, bilateral allergic inflammation of the conjunctiva and cornea. Prevalence of VKC is more in the 3-25 years age group with peak incidence at 11-13 years.[1] Patient commonly present with itching, slight drooping of the upper lid, ropy discharge, photophobia and blurry vision.[2] Signs observed in VKC are cobblestone papillae on the upper tarsal conjunctiva, discrete or confluent papillary hypertrophy on limbal conjunctiva, white chalky appearing concretions, called Horner-Granta's dots, corneal erosions and shield ulcer.[3] Histopathologically it is characterized by a dense inflammatory infiltrate consisting of eosinophils, lymphocytes, basophils, dendritic cells and macrophages within microvessel, outside microvessel and in the epithelium. Lymphocytes are aggregated to form follicles. [4]

Treatment modalities included measures to control inflammation. Various pharmacological agents used are topical steroids, mast cell stabilizers and topical Non-steroidal anti-inflammatory drugs.[5] Most of these treatments are ineffective in refractory VKC. Refractory VKC is defined as symptoms and signs that are persistent after conventional treatment. For refractory cases, oral or subtarsal corticosteroids are indicated, immunotherapeutic agents like cyclosporine are also used,[6] but chronic use of topical corticosteroids may increase intraocular pressure (IOP) and susceptibility to opportunistic infections.

Novel treatment therapy for severe allergic ocular diseases with potent anti-inflammatory effects as well as sufficient safety is thus needed. Recently Tacrolimus is used for the treatment of refractory VKC. It is an immunomodulator with more potency than cyclosporine. It suppresses T-cell activation, T helper cell-mediated B-cell proliferation, and

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formation of cytokines, especially interleukin-2.[7] In ophthalmology, tacrolimus has mainly been used to suppress immune reactions in corneal and limbal transplantations, uveitis, and allergic eye disease. [8-10]

The good safety profile of 0.1% tacrolimus ophthalmic suspension based on the low blood concentration of tacrolimus, coupled with demonstrated better efficacy, make it an important tool for treating severe allergic conjunctivitis. Therefore we chose 0.1% tacrolimus ointment in this study.

Side effects noted in the use of tacrolimus ointment are burning sensation, activation of herpes simplex dendritic keratitis and development of molluscum contagiosum[11,12].

Material & methods: Present study was a prospective study carried out to assess the efficacy of 0.1%tacrolimus ophthalmic ointment in refractory cases of VKC at the Department of Ophthalmology at Saraswathi Institute of Medical Sciences. Patients were enrolled from November 19 to September 2020. The study population was refractory cases of vernal keratoconjunctivitis.

Inclusion criteria: 1. Patients with VKC refractory to conventional treatment for 3 weeks 2. Patients willing to participate in the study and followup

Exclusion criteria: 1. Patients with trachoma 2. Patients with infectious diseases of eye 3. Patients with hypersensitivity to tacrolimus 4. Patients who had less than 6 months follow up 5.Systemic administration of immunosuppressants within 2 weeks before study.6.pregnant or lactating females7.patients with any cardiac, renal or hepatic disease or diabetes.

This study was conducted in compliance with the Declaration of Helsinki. The study was approved by the ethical committee of the institute. A valid written consent was taken from patients after explaining the study to them.

Total of 66 patients was included in the study. Out of 66 patients, 6 patients lost to follow up so data of 60 patients was included in the study. Patients were divided into two groups randomly. Group A patients received Tacrolimus 0.1% (Talimus-Ajanta Pharmaceuticals, India) twice daily and anti-allergic medications (sodium cromoglycate eye drop, ketotifen fumarate eye drop) and Group B patients received only antiallergic medications (sodium cromoglicate eye drop, ketotifen fumarate eye drop). All participants were followed up for 6 months.

At every follow-up, symptoms and signs of vernal keratoconjunctivitis were noted. Five symptoms (itching, discharge, lacrimation, photophobia, foreign body sensation) were scored (0 to 3) depending on severity. Total score for symptoms (0 to 15) was noted at the initiation of treatment (Baseline), 2 wk, at one month, 3 month and six months.

Slit-lamp examination findings were used to grade (0=none, 1=mild, 2=moderate and 3=severe) each of the eight clinical signs. Score range (0 to 24). (table 1). For each patient, the eye with a higher total score for clinical findings was selected for efficacy assessment. The reduction in total signs and symptoms scores (from baseline) was used as the determinant of efficacy.

Table 1: Score for clinical sign in patients with refractory VKC

Signs	Score	Definition
Palpebral conjunctiva Hyperaemia	3	Impossible to distinguish individual blood Vessels
	2	Dilatation of many vessels
	1	Dilatation of several vessels
	0	None
Follicles	3	20 or more follicles
	2	10–19 follicles
	1	1–9 follicles
	0	None
Papillae	3	Papillae size: 0.6 mm or more
	2	Papillae size: 0.3–0.5 mm
	1	Papillae size: 0.1–0.2 mm
	0	None
Giant Papillae (papillae Size≥1 mm)	3	Elevated papillae in 1/2 or more of the Upper Palpebral conjunctiva
	2	Elevated papillae in <1/2 of the upper Palpebral conjunctiva
	1	Flat papillae
	0	None
Bulbar Conjunctiva Hyperaemia	3	Diffusely dilated blood vessels over the entire bulbar conjunctiva
	2	Dilatation of many vessels
	1	Dilatation of several vessels
	0	None
Oedema	3	Bullous oedema
	2	Thinner diffuse oedema
	1	Localized oedema
	0	None
Limbus Trantas dot	3	9 > dots
	2	5-8 dots
	1	1-4 dots
	0	None
Corneal Epithelial signs	3	Shield ulcer or corneal erosion
	2	Exfoliation superficial punctate keratitis
	1	Superficial punctate keratitis
	0	None

To assess the safety and side effects of the treatment, intraocular pressure, lens opacification, secondary infections, or other possible complications were assessed. Data were entered in an excel sheet and analysed by SPSS version 20.

RESULTS

In our study, we studied 60 patients. Group A patients received Tacrolimus 0.1%Ophthalmic ointment twice daily and anti-allergic medications(sodium cromoglycate eye drop, ketotifen fumarate eye drop). Group B patients received anti-allergic medications(sodium cromoglycate eye drop, ketotifen fumarate eye drop) only.

In group A there were 18 males and 12 females and in group B there were 20 males and 10 females. Both the groups were comparable concerning age. The mean age of the patients in group A was 14.5±2.4 years and in the group, B was 15.4±3.1 years. The age of the patient ranged from 1 -27 years.

Table 2 shows the comparison score of symptoms in group A and group B. Participants were followed at 2 weeks, 1 month, 3 months and 6 months. Symptom score ranged from 0-15. In the group, A mean score of symptoms at baseline was 10.56±1.73. It decreased over follow up and was found to be 5.93±0.78 (2 weeks), 4.23±0.67 (1 month), 2.86±0.68 (3 months) and 1.7±0.65 (6 months). Thus in the group, A patients showed a significant decrease in symptom score over the follow-up period

In Group B, the mean symptom score at baseline was 10.53±1.67. At 2 weeks it was 8.73±1.28. The score decreased to 7.93±1.04 at 1 month, 7.13±0.77 at 3 months and 6.8±0.71 at 6 months. We observed decreased symptom score in Group B over follow up to 6 months.

In the comparison of both the groups, we found patients in Group A showed a more significant decrease in symptom score as compared to Group B.Resuts were statistically significant ($p<0.05$)

Table 3 shows comparison score of signs in group A and group B. we assessed the 8 clinical signs with the score ranging from 0-24.

In Group A, the mean sign score at baseline was 19.56±1.95. At 2 weeks it significantly decreased to 9.93±1.31. The score decreased to 5.96±1.24 at 1 month, 3.36±1.03 at 3 months and 1.66±0.6 at 6 months. Group A patients showed a significant decrease in sign score.

In group, B the mean score of symptoms at baseline was 19.5±1.94. It decreased over follow up and was found to be 17.13±1.94 (2 weeks), 15.4±1.47 (1 month), 14.16±1.55 (3 months) and 13.6±1.52 (6 months). Thus in group B patients showed a decrease in symptom score.

In comparison of both the groups, we found patients in Group A showed a statistically significant decrease in sign score as compared to Group B. ($p<0.05$)

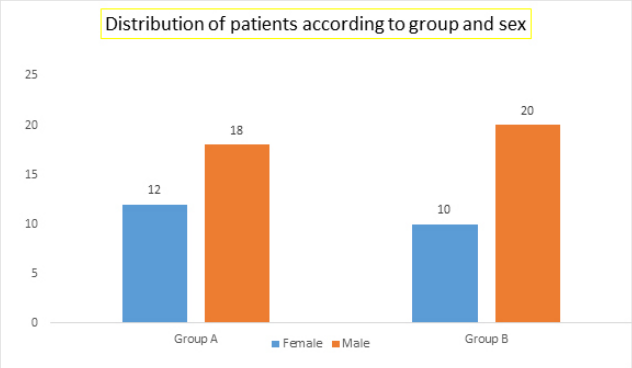

Figure 1: Distribution of patients according to group and sex.

Table 2: Comparison of Symptom score in both the groups of patients with refractory VKC

Group	0 Day (baseline)	2 week	1 month	3 Month	6 Month	P value
Group A	10.56±1.73	5.93±0.78	4.23±0.67	2.86±0.68	1.7±0.65	<0.05
Group B	10.53±1.67	8.73±1.28	7.93±1.04	7.13±0.77	6.8±0.71	

Table 3: Comparison of Sign score in both the groups of patients with refractory VKC

Group	0 Day (baseline)	2 week	1 month	3 Month	6 Month	P value
Group A	19.56±1.95	9.93±1.31	5.96±1.24	3.36±1.03	1.66±0.6	<0.05
Group B	19.5±1.94	17.13±1.94	15.4±1.47	14.16±1.55	13.6±1.52	

An assessment of visual acuity, IOP, pupil diameter, and clinical findings for the iris, lens, anterior chamber, and fundus, no abnormal change related to testing drugs was observed. In our study, 8 patients from group A developed side effect (7 had transient burning sensation one patient developed burning sensation)which was managed with the addition of lubricating eye drop.

DISCUSSION

In our study, we studied 60 patients with refractory VKC for testing the efficacy of tacrolimus 0.1% ointment. Previous studies have used different concentrations. A study by Joseph MA[12] used 0.02% concentration while a study by Müller GG used 0.03% concentration[13]. Kheirkhah A used topical 0.005% tacrolimus eye drop for the treatment of VKC[14]. The good safety profile of 0.1% tacrolimus ophthalmic suspension based on the low blood concentration of tacrolimus, coupled with demonstrated better efficacy, make it an important tool for treating severe allergic conjunctivitis[15]. Not many studies have been done on Indian eyes to test the efficacy of tacrolimus 0.1% for the treatment of ocular allergic diseases. Therefore we chose 0.1% tacrolimus ointment in this study

Topical tacrolimus has been used for different durations in previous studies. Duration ranged from 1-7 months. In our study, we followed the patients for 6 months.

The mean age of the patients in group A was 14.5±2.4 years and in group B was 15.4±3.1 years. Males predominated females in both the groups. Both the groups were comparable with respect to age and sex.

In group A mean score of symptoms at baseline was 10.56±1.73. It decreased over follow up and found to be 5.93±0.78 (2 weeks), 4.23±0.67 (1 month), 2.86±0.68 (3 months) and 1.7±0.65 (6 months). In Group B, mean symptom score at baseline was 10.53±1.67. At 2 weeks it was 8.73±1.28. Score decreased to 7.93±1.04 at 1 month, 7.13±0.77 at 3 months and 6.8±0.71 at 6 months.

Patients with tacrolimus treatment showed a statistically significant decrease in symptom score($p<.05$)

In Group A, the mean sign score at baseline was 19.56±1.95 and it decreased to 1.66±0.6 at 6 months. In group, B the mean score of symptoms at baseline was 19.5±1.94 which decreased to 13.6±1.52 at 6 months. Patients with tacrolimus treatment showed a statistically significant decrease in sign score over 6 months. ($p<0.05$).

Similar to our study, in the study by Ohashi Yand others, 0.1% twice-daily dose of tacrolimus showed improvement in symptoms of VKC[16].

A study by Miyazaki N and others studied effects of 0.02% Tacrolimus ointment for refractory ocular surface inflammatory diseases and found that there was a lower incidence of elevated intraocular pressure and no adverse side effects during 2–26 months of continuous treatment[18].

Muller and Jose [13] reported no difference in the improvement of symptoms or signs in 2 groups of patients with severe VKC treated with tacrolimus and olopatadine or tacrolimus alone.

In contrast to a study by Muller GG,[13] Tam PMK [19] reported the additional use of mast cell stabilizers in 2 of 5 patients. A study by Fukushima [20] reported the continued requirement of steroids in nearly half of their patients.

In our study tacrolimus ophthalmic ointment 0.1% was well-tolerated, 8 patients from group A developed side effect(7 had transient burning sensation one patient developed burning sensation) which was managed with the addition of lubricating eye drop. Previous studies have also reported burning sensation upon application of topical tacrolimus.[21]This study findings suggest the usefulness of topical tacrolimus 0.1% as a steroid-sparing substitute for treating severe allergic conjunctivitis due to its potent immunosuppressive effect,

CONCLUSION

In this study, we conclude that Tacrolimus ophthalmic ointment 0.1% is well tolerated and effective in improving objective signs and subjective symptoms in cases of severe VKC who are refractory to other topical antiallergic agents.

Conflict of interest: NIL

The Source of the funding: The study was carried out at Saraswathi Institute of Medical Sciences, Hapur and no extra financial support was required

Ethical Clearance: Ethics committee approval was obtained before the study.IECSIMS/FMT/ETHI/22/19

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