Efficacy and Safety of Tacrolimus Eye Ointment in Refractory Vernal Keratoconjunctivitis in Eastern India

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ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a common allergic inflammation of eye involving tarsal and/or bulbar conjunctiva, affecting children and young adults. Many patients with VKC are refractory to conventional treatment including steroids. So this study was done to evaluate the efficacy and safety of topical 0.03% tacrolimus eye ointment in patients with refractory VKC.

Material and Methods: Patients with VKC refractory to conventional treatment were included in this study retrospectively. Tacrolimus 0.03% eye ointment was administered to patients twice daily after discontinuation of all previous topical medications. The symptoms and signs of VKC were graded as 0 (normal), 1+ (mild), 2+ (moderate), or 3+ (severe). Evaluation of symptoms and signd were done before starting treatment and at 1 week, 4 weeks and on the last follow-up after treatment.

Results: There were 54 patients with VKC comprising 39 male and 15 female patients. The mean age of the patients was 16.3±7.4 years. After treatment with Tacrolimus 0.03% eye ointment, there was statistically significant improvement in symptoms of VKC including itching and redness of eyes, foreign body sensation and ocular discharge (P<0.001). There were also significant improvement in clinical signs of VKC including conjunctival congestion, conjunctival papillae, Trantas dots and superficial punctate keratopathy (P<0.001). None of the patients developed any complications related to tacrolimus use.

Conclusion: Topical tacrolimus 0.03% ointment is highly safe and effective in VKC refractory to conventional treatment. It can be used for longer duration to avoid steroid related complications.

Keywords: Tacrolimus, Vernal keratoconjunctivitis, Allergy

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a common allergic inflammation of eye involving tarsal and/or bulbar conjunctiva, affecting children and young adults. It is usually bilateral and chronic with seasonal exacerbation.[1] Symptoms of VKC are itching and redness of eyes, foreign body sensation, photophobia, watering and discharge. Common conjunctival signs of VKC are conjunctival hyperemia, giant papillae, ropy discharge, and trantas dots.

VKC has been described as a classical IgE-mediated disease (type I hypersensitivity). But recent studies of VKC shows more complex pathogenesis with particular involvement of Th2 lymphocytes.[2,3]

Treatment of VKC includes antihistamines, mast-cell stabilizers, corticosteroids, and immunomodulators. Long-term treatments are needed in most patients with VKC. Topical steroids are the mainstay of treatment for moderate to severe forms of VKC. Long term use of topical steroids may lead to glaucoma, cataract, and secondary infections.[4]

Tacrolimus is an immunomodulator agent which suppresses Th2 lymphocyte activation, T helper cell-mediated B-cell proliferation, and formation of cytokines.[5] Previous studies had shown that topical tacrolimus is effective for treatment of VKC.[6-14] However these studies evaluated the either relatively high concentration of topical tacrolimus (topical tacrolimus 0.1%) or had short term follow-up. The purpose of this study was to assess the long term efficacy and safety of topical tacrolimus ointment (0.03%) in patients with refractory VKC.

MATERIAL AND METHODS

Fifty two consecutive patients with VKC refractory to conventional treatment who presented to the Regional institute of ophthalmology, Rajendra institute of medical sciences, Ranchi, India between January 2013 and July 2015 were retrospectively analyzed. Patients with minimum 6 months of follow-up after starting treatment were included in the study. Informed consent and clearance from the Institute ethics committee for the study were taken.

Refractory to conventional treatment was defined as persistence of symptoms and signs despite the use of conventional treatment prior to presentation. Conventional treatment included anti-histamines, mast-cell stabilizers, topical steroids, cyclosporine and decongestants.

Each patients underwent a complete ophthalmic examination including measurement of best corrected visual acuity (BCVA), slit-lamp biomicroscopy and

photography, fluorescein staining, and applanation tonometry. Symptoms and signs of VKC were assessed and the severity was graded as 0 (normal), 1+ (mild), 2+ (moderate), or 3+ (severe). Patients with known hypersensitivity to tacrolimus, trachoma or other infectious eye disease, and patients who had less than 6 months of follow-up were excluded from the study.

Tacrolimus 0.03% eye ointment was applied twice daily after discontinuation of all previous topical medications. Patients were followed up at 1week and thereafter every 4 weeks. At each follow-up visits, change in clinical symptoms, including itching and redness of eyes, foreign body sensation, and discharge were studied. Change in clinical signs, including conjunctival congestion, conjunctival papillae, Trantas dots and superficial punctate keratopathy were also studied. To assess the safety and side effects of the treatment, intraocular pressure, lens opacification, secondary infections, or other possible complications were assessed.

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STATISTICAL ANALYSIS

Statistical analysis was done using SPSS for Windows software (version 18.0, SPSS Inc., Chicago, IL, USA). To analyse the changes in mean score of symptoms and signs of VKC before and after treatment paired t-test were used. P-values of 0.05 or less were considered as statistically significant.

RESULTS

The study included 108 eyes of 54 patients with refractory VKC. There were 39 males (72.2 %) and 15 females (27.8 %) patients. Age of the patients ranged from 7–26 years (mean 16.3±7.4 years). On presentation, all patients had bilateral VKC that was refractory to conventional topical treatment, including antihistamines, mast-cell stabilizers, decongestants, cyclosporine, and steroids. The main presenting symptoms were itching in 44 (81.4%) patients, redness in 42 (77.7%) patients, discharge in 21 (38.8%) patients, and foreign body sensation in 12 (22.2%) patients. Clinical signs included conjunctival hyperemia in 45 (83.3%) patients, conjunctival papillary hypertrophy in 29 (53.7%) patients, Trantas dots in 30 (55.5%) patients, limbal hypertrophy in 34 (62.9%) patients, and superficial punctuate keratitis in 14 (25.9%) patients.

After starting 0.03% tacrolimus eye ointment, the patients were followed for a mean duration of 9.3±3.7 months (range, 6–14 months). All symptoms significantly improved after treatment with tacrolimus eye ointment (Table-1, figure-1). Improvement in all symptoms was statistically highly significant.

In addition to relief of symptoms, there was improvement in objective signs after starting tacrolimus eye ointment (table-2, figure 2). Improvement in all signs was statistically highly significant.

Patients on treatment with tacrolimus, doesn't required any additional medications during entire period. Four (7.4%) out of 54 patients reported mild irritation and/or transient burning sensation at the time of instilling the tacrolimus ointment, which subsided during treatment. None of the patients in our study developed ocular infection, cataract, or increased intraocular pressure. Although tacrolimus ointment were used during entire study period, none of the patients discontinue tacrolimus due to any side effects.

DISCUSSION

Tacrolimus is an effective agent for the management of patients with AKC and VKC who are refractory to conventional medications, including topical cyclosporine. This study showed that 0.03% tacrolimus eye ointment is highly effective treatment for patients with refractory VKC. All patients in our study showed significant improvement of clinical symptoms and signs. Also tacrolimus eye ointment is highly safe agent for long term use as none of the patients had any significant side effect. Tacrolimus has been used in different forms and concentrations

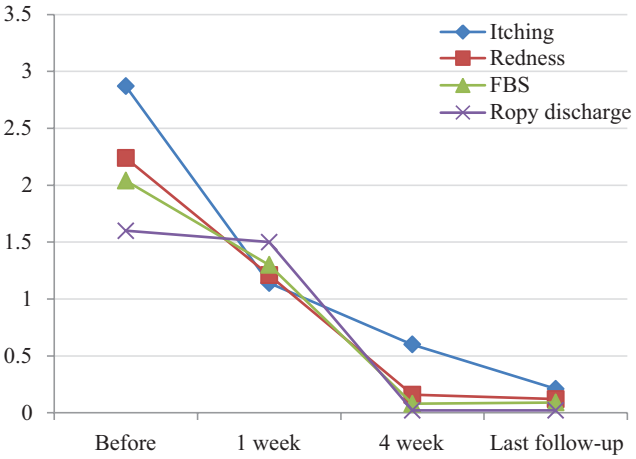

Figure-1: Mean score of symptoms in patients with refractory VKC before and after treatment with topical 0.03% tacrolimus eye ointment

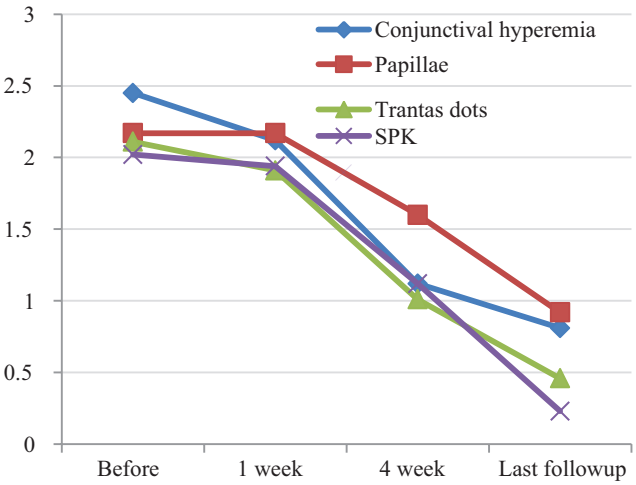

Figure-1: Mean score of signs in patients with refractory VKC before and after treatment with topical 0.03% tacrolimus eye ointment

Symptoms	Before	1 week	4 week	Last follow-up	p-value
Itching	2.87±0.31	1.14±0.21	0.60±0.40	0.21±0.13	<0.001
Redness	2.24±0.41	1.21±0.24	0.16±0.11	0.12±0.11	<0.001
FBS†	2.04±0.53	1.30±0.34	0.08±0.12	0.09±0.16	<0.001
Ropy discharge	1.60±0.68	1.50±0.41	0.02±0.04	0.02±0.04	<0.001
*VKC – Vernal keratoconjunctivitis, †FBS – Foreign body sensation					

Table-1: Mean score of symptoms in patients with refractory VKC* before and after treatment with topical 0.03% tacrolimus eye ointment

Signs	Before	1 week	4 week	Last follow-up	p-value
Conjunctival hyperemia	2.45±0.42	2.12±0.37	1.12±0.41	0.81±0.24	<0.001
Papillae	2.17±0.46	2.17±0.46	1.60±0.38	0.92±0.48	<0.001
Trantas dots	2.11±0.27	1.91±0.26	1.01±0.27	0.46±0.32	<0.001
SPK†	2.02±0.25	1.94±0.45	1.12±0.35	0.23±0.21	<0.001
*VKC – Vernal keratoconjunctivitis, †SPK – Superficial punctuate keratopathy					

Table-2: Mean score of signs in patients with refractory VKC* before and after treatment with topical 0.03% tacrolimus eye ointment

in the treatment of allergic eye diseases, including refractory VKC. Most of the studies have used 0.1% concenteration.[6-10] Some studies used lower concentrations of tacrolimus, including 0.02% and 0.03%.[11,12] Kheirkhah A et al[8] in their study have used topical 0.005% tacrolimus eye drop for treatment of VKC. However, it was prescribed four times daily. In our study, we used 0.03% topical tacrolimus ointment twice daily, which may increase compliance.

In our study, none of the patients on tacrolimus required any additional medications, which showed its potential role as steroid sparing agent. In a study Guilherme Gubert Müller et al[12] showed that the isolated use of tacrolimus and the combined use of tacrolimus and olopatadine have the similar efficacy.

Topical tacrolimus has been used for varying duration in different studies, ranging from 1-7 months.[6,9,14] Topical tacrolimus has been used for longer duration in the treatment of allergic diseases of eyelids.[15,16] In our study, tacrolimus eye ointment were used during the entire follow-up period for sustained relief of sign and symptoms of VKC. Further studies are needed to determine the optimal duration of treatment with topical tacrolimus.

In our study 4 (7.4%) patients reported mild irritation and/or transient burning sensation at the time of instilling the tacrolimus ointment, which subsided during treatment. Burning sensation upon application of topical tacrolimus has been reported before also.[6,10,15] Although various complication related to use of tacrolimus has been reported including activation of herpes simplex dendritic keratitis[11] and development of molluscum contagiosum.[16] None of the patients in our study developed any ocular infection, cataract, or increased intraocular pressure.

CONCLUSION

In conclusion, our study showed that topical tacrolimus 0.03% ointment is highly safe and effective in VKC refractory to conventional treatment. It can be used for longer duration to avoid steroid related complications.

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