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TO EVALUATE THE EFFICACY OF TOPICAL 0.03% TACROLIMUS OINTMENT FOR TREATMENT OF REFRACTORY VERNAL KERATOCONJUNCTIVITIS

KEYWORDS: Refractory, Vernal keratoconjunctivitis (VKC), Tacrolimus

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ABSTRACT

Introduction- Conjunctivitis is the most common eye disease worldwide. As the treatment of vernal keratoconjunctivitis is still a dilemma, there is a need for devising a treatment modality that is safe as well as effective in refractory vernal keratoconjunctivitis (VKC).

Aim- To study the efficacy and safety profile of 0.03% tacrolimus eye ointment in refractory vernal keratoconjunctivitis.

Material &methods-70 eyes of 35 patients with refractory VKC were included in the study. 0.03% tacrolimus eye ointment was given two times a day and patients were followed up at 1st,3rd,6th and 12th week .

Results- At the end of 12 weeks there was a marked reduction in the mean score of symptoms and signs ($p<0.001$). The drug was well tolerated and no complication was reported in any patient.

Conclusion-0.03% tacrolimus ointment is safe and effective in treatment of refractory vernal keratoconjunctivitis VKC.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, bilateral allergic ocular inflammation that primarily affects children and young adults with male preponderence (Jones, 1961). VKC has traditionally been considered as a classical IgE mediated disease (Type I hypersensitivity) but recent findings implicate more complex pathogenesis with particular involvement of Th-2 lymphocytes (Bieolory & Frohman, 1992).

A wide range of therapeutic modalities are available for treatment of vernal keratoconjunctivitis which include cold compresses, tear substitutes, antihistamines, mast cell stabilisers and non-steroidal anti-inflammatory drugs. Nevertheless, topical steroids are the mainstay of treatment for moderate-severe forms of VKC (Tabbara, 1999). However, some cases remain symptomatic despite treatment with topical steroids. Further more, prolonged use of topical steroids may be associated with various complications such as glaucoma, cataract and secondary infections. To avoid steroid related complications, immunomodulatory agents such as topical cyclosporine A (Secchi et al, 1990) and Tacrolimus (Hooks, 1994) have recently been used for treatment of refractory VKC.

Tacrolimus has been isolated from the fermentation broth of streptomyces tsukubaenis (Kino et al, 1987). Tacrolimus (formerly, FK-506) is an immunomodulatory agent, which is similar to cyclosporine A in mechanism but with much higher potency (up to 100 times) (Schreiber and Crabtree, 1992). It suppresses T- cell activation, T helper cell mediated B- cell proliferation and formation of cytokines, especially interleukin-2. In ophthalmology, tacrolimus has mainly been used to suppress immune reactions in corneal and limbal transplantations (Yalcindag et al, 2008) in uveitis (Mochizuki et al, 1992) and allergic eye disease (Iwamoto et al, 1999).

Topical tacrolimus with concentration of 0.02% - 0.1% in ointment form has been successfully been used for treatment of atopic keratoconjunctivitis (Zribi et al, 2009), giant papillary conjunctivitis (Kymionis et al, 2008) and vernal keratoconjunctivitis (Vichyanond et al, 2004).

This study has been undertaken to study the efficacy and safety profile of 0.03% topical tacrolimus eye ointment in patients with refractory vernal keratoconjunctivitis.

MATERIAL METHODS

This observational study included 70 eyes of 35 patients with refractory VKC attending the outpatient Department of Ophthalmology Subharti Medical College, Meerut during the period of August 2014 to April 2016. An informed consent was taken from attendant of all the patients included in the study and ethical clearance was taken from the institutional ethical committee.

Patients with refractory VKC diagnosed on the basis of typical history and slit lamp examination were included in the study. Refractory VKC was defined as disease not responding or inadequately responding to month long topical therapy including steroids. Patients with a history of active infection or any other allergic disorder and those already on any form of immunosuppressants were excluded..

Before starting treatment with tacrolimus eye ointment and at each visit thereafter, all patients were asked a questionnaire regarding the symptoms of itching, redness, photophobia, foreign body sensation, and mucus discharge. The patients were graded on a grading score of score 0 (none), score 1 or mild (occasional symptoms), score 2 or moderate (frequent symptoms), and score 3 or severe (constant symptoms) to report the severity of each individual symptom. In addition they underwent a complete ophthalmic examination including measurement of best spectacle-corrected visual acuity (BCVA), slit lamp biomicroscopy and photography, fluorescein staining and intra ocular pressure. All the patients had a wash off period of 1 week prior to treatment in which all topical drugs were discontinued.

The treatment included 0.03% tacrolimus eye ointment two times a day along with lubricant eye drops. Patients were advised to instil lubricating eye drop prior to tacrolimus eye ointment so as to reduce burning sensation. The patients were evaluated at 1st , 3rd , 6th , and 12th weeks after starting treatment.Improvement of each symptom or sign was defined as atleast 1-score reduction in severity compared with values before the treatment.

Paired t-test was used to statistically analyse the changes in mean score of symptoms and signs and p value of 0.05 or less was considered as statistically significant.

OBSERVATION AND RESULTS

A total of 35 patients were included in the study out of which there were 3 dropouts. Disease was bilateral in all cases.

The maximum cases 19 patients i.e (59.37%) were in the age group of

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6-10 yrs -Mean age of the patients was 9.03 yrs.

Out of 32 patients included in the study, majority i.e 22 patients (68.75%) were males.

Mixed form of disease was found to be most common i.e 22 patients (68.75%) followed by palpebral form in 6 patients (18.75%) and bulbar form in 4 patients (12.50%).

Table 1: CHIEF PRESENTING COMPLAINTS

Chief complaints	No. of Patients	Percentage
Itching	32	100.0
Watering	29	90.6
Redness	20	62.5
Foreign Body Sensation	20	62.5
Ropy Discharge	18	56.3
Photophobia	9	28.1

Itching was found to be most prominent symptom seen in 100% cases followed by watering in 29 patients (90.60%). Photophobia was least common seen in 9 patients (28.12%) cases.

Table 2: CLINICAL SIGNS AT PRESENTATION

Clinical Signs	No. of Patients	Percentage
Conjunctival Hyperaemia	28	87.25
Tarsal Conjunctival Changes	22	68.75
Limbal Changes	21	65.62
Keratopathy	6	18.75

Most common clinical sign of disease was conjunctival hyperaemia seen in 28 patients (87.25%) followed by tarsal conjunctival changes seen in 22 patients (68.75%). Keratopathy was least common seen in 6 patients (18.75%).

Table 3: MEAN SCORE OF SYMPTOMS

SYMPTOMS	DAY 1	1st WEEK	3rd WEEK	6th WEEK	12th WEEK	p-value
Itching	2.90±0.31	0.20±0.42	0	0	0	<0.001
Watering	2.70±0.27	0.40±0.45	0.20±0.32	0	0	<0.001
Redness	2.00±0.82	1.70±0.82	0.70±0.48	0.60±0.50	0.30±0.53	<0.001
FB Sensation	1.80±0.63	1.50±0.53	0.30±0.48	0.20±0.36	0.10±0.32	<0.001
Ropy Discharge	1.80±0.79	1.60±0.52	0.20±0.42	0.20±0.42	0.20±0.42	<0.001
Photophobia	1.50±0.85	0.60±0.85	0.30±0.42	0	0	<0.001

Significant improvement in all the symptoms of patients was seen after 12 weeks.

- The first symptom to show dramatic relief was itching and it was completely relieved by the end of 3rd week, p value (<0.001).
- Marked improvement in watering and photophobia was seen by 3rd week and they were completely relieved by 6th week, p value (<0.001).
- Redness, FB Sensation and Ropy Discharge showed significant improvement by 6th week, p value (<0.05) and by the end of the 12th week p value was (<0.001). The patients remained mostly symptom free while under treatment and during follow up. However, in some cases mild symptoms persisted even after 12 weeks.

Table 4: MEAN SCORE OF SIGNS

SIGNS	DAY 1	1st WEEK	3rd WEEK	6th WEEK	12th WEEK	p-value
Conjunctival hyperaemia	2.60±0.52	0.50±0.52	0.30±0.42	0.10±0.46	0	<0.001
Tarsal conjunctival changes	2.70±0.48	2.0±0.48	1.30±0.67	1.0±0.58	0.60±0.52	<0.001
Limbal changes	1.70±1.29	1.20±1.29	0.80±1.13	0.40±0.50	0.20±0.42	0.005
Keratopathy	0.80±1.23	0.60±1.23	0.50±0.85	0.40±0.66	0.30±0.48	0.036

Significant improvement in signs of patients was seen after 12 weeks.

- Conjunctival hyperaemia was the first sign to show improvement and by the end of the 1st week, p value was (<0.05). It completely resolved by the end of 12th week, p value (<0.001).
- Tarsal Counjunctival changes, Limbal changes and Keratopathy also showed improvement after treatment and were significantly improved by the end of 12th week, p value (<0.001, 0.005 and 0.036) respectively.
- No ocular complication related to tacrolimus eye ointment was reported in any patient.

DISCUSSION

Refractory VKC poses a great challenge for the treating ophthalmologist especially when patients remain markedly symptomatic and debilitated despite maximum medical therapy. A variety of drugs are being used for VKC but none of them is ideal. Thus, there is a need for devising a treatment modality that is safe as well as effective in refractory VKC.

When patients with refractory VKC were treated with (0.03%) tacrolimus eye ointment, there was a marked improvement in symptoms and signs of patients. There was statistically significant improvement in symptoms of itching (p<0.001), watering (p <0.001), redness (p <0.001), foreign body sensation (p <0.001), ropy discharge (p<0.001) and photophobia (p<0.001). Statistically significant improvement was also observed in clinical signs of conjunctival hyperaemia (p <0.001), tarsal conjunctival changes (p <0.001), limbal changes (p <0.005) and keratopathy (p<0.036). The patients remained mostly symptom free while under treatment and during follow up. The drug was well tolerated and no complication was reported in any patient.

Promising results have been reported in other studies also. Vichyanond et al (2004) evaluated the efficacy of topical 0.1% tacrolimus ointment in 10 patients with recalcitrant VKC and found marked improvement in mean score of symptoms at the end of the 4 weeks. Shoughy et al (2016) reported statistically significant improvement in symptoms and signs of patients with refractory VKC after treatment with low dose 0.01% tacrolimus solution. Our results are also consistent with Hazarika et al (2015) and Attas Fox et al (2008) who found 0.03% tacrolimus eye ointment safe and effective in the treatment of refractory allergic conjunctivitis. Similarly Kheirkhah et al (2011) reported 0.005% tacrolimus eye drop as an excellent alternative in refractory vernal keratoconjunctivitis.

CONCLUSION

Thus, we conclude that topical tacrolimus 0.03% eye ointment is an effective and safe modality for treatment of patients with refractory VKC. But our study has certain limitations. The sample size is relatively small and follow up period is also short. Moreover there was no control group in our study. So, more studies should be conducted to assess the long term efficacy and safety profile of 0.03% tacrolimus eye ointment in vernal keratoconjunctivitis.

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