Clinical study to evaluate safety and efficacy of tacrolimus 0.1% eye ointment in treatment of vernal keratoconjunctivitis

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Abstract

Introduction: Vernal keratoconjunctivitis is a seasonally recurring, chronic, allergic bilateral inflammatory disorder of the conjunctiva and cornea caused due to immune mediated hypersensitivity reaction. Tacrolimus is an immunomodulator which induces suppression of T lymphocytes activity and causes reduction of ocular inflammation. Hence, in our present study we aim to evaluate the efficacy of 0.1% tacrolimus eye ointment as first line therapy in the management of Vernal Keratoconjunctivitis.

Materials and Methods: This was a clinical, prospective and interventional study including 100 eyes of 50 patients with VKC which were serially selected. 0.1% tacrolimus eye ointment was instilled twice daily over a period of 12 weeks. On every fortnightly follow up, patients were assessed for 5 symptoms and 4 signs and the severity was graded as 0 (normal), 1+ (mild), 2+ (moderate), or 3+ (severe)in order to evaluate the efficacy of the drug.

Results: There were 50 patients with VKC comprising of 41 males and 09 females. After treatment with Tacrolimus 0.1% eye ointment, there was statistically significant improvement in symptoms of VKC including itching, redness, photosensitivity, foreign body sensation and mucus discharge (P<0.001). Significant improvement in clinical signs of VKC including conjunctival hyperaemia, papillary hypertrophy, giant papillary conjunctivitis and limbal involvement (P<0.001) was seen at the end of the study. No significant adverse effects of tacrolimus were seen in these patients.

Conclusion: Topical 0.1% tacrolimus eye ointment is very effective in the treatment of Vernal Keratoconjunctivitis with minimal long term side effects.

Keywords: Allergy, Immunosupressant, Inflammatory, Tacrolimus, Vernal keratoconjunctivitis.

Introduction

Vernal keratoconjunctivitis is a seasonally recurring, chronic, allergic bilateral inflammatory disorder of the conjunctiva and cornea caused due to immune mediated hypersensitivity reaction. The disease has a male preponderance[1,2] usually manifesting between 4 to 16 years of age.

The disease may manifest in palpebral, limbal or mixed form. Conjunctival redness, intense itching, photophobia, watering and sticky mucus discharge are typical symptoms of VKC, whereas conjunctival hyperemia, papillary hypertrophy, giant papillary conjunctivitis and limbal involvement are the most common signs associated with the disease. Of these, giant papillae with a cobblestone- like appearance in the upper tarsal conjunctiva and Trantas' dots (the aggregates of epithelial cells, eosinophils and CD4+ T cells) at the limbus are considered hallmarks of the disease.[3-5] VKC is a sight threatening allergic condition associated with subconjunctival fibrosis, symblepharon, conjunctival keratinization, superficial keratopathy or the presence of corneal shield ulcers (occurring in approximately 3–11%) and neovascularization if left untreated.[6,7]

VKC has a complex pathogenesis, not merely type 1 hypersensitivity reaction involving over-expression of mast cells, eosinophils, neutrophils but also increase in Th2-derived cytokines, chemokines, adhesion molecules, growth factors, fibroblast and lymphocytes. Interleukins are mainly involved in the formation of giant papillae by inducing the production of extra-cellular matrix and the proliferation of conjunctival fibroblasts.

Management of VKC is difficult and often a dilemma for the practitioners as we have multiple topical medications in our armamentarium. Topical medications include Antihistaminics (levocabastine 0.05%, emedastine 0.05%), Mast Cell Stabilizers (sodium cromoglycate 2%-4%, lodoxamide 0.1%), drugs with both antihistaminics and mast cell stabilizing effect (olopatadine 0.1%), Mucolytic agents (acetylcysteine 5%-10%),[9,10] Corticosteroids (fluoromethalone 0.1%, loteprednol 0.5%) and Immunomodulators (cyclosporine 0.05%). Oral monoclonal antibodies (omalizumab), oral steroids and drugs like aspirin (PGD_2 inhibiting action) have also been used in VKC.

In severe cases subtarsal injection of steroid like triamcinolone acetonide (0.1ml of 40mg/ml) or surgical excision of the papillae have also been attempted with good results. In blinding form of the disease with corneal involvement, debridement of shield ulcers with amniotic membrane graft, lamellar keratectomy or penetrating keratoplasty can also be done.

Tacrolimus, an immunomodulator, is a macrolide isolated from a strain of Streptomyces species and a lipophilic molecule which blocks the early phase of T-cell activation, thus inhibitng both T-lymphocyte signal transduction and IL-2 transcription by inhibiting the

production of cytokines particularly IL-2, IL-3, IL-5, TNF-alpha and IFN-gamma. It also inhibits the IgE dependent release of histamine from mast cells and impairs prostaglandin synthesis.[8] These actions are mediated via cyclophillin receptors. Tacrolimus has shown to be effective in the treatment of immune-mediated diseases such as corneal graft-rejection, ocular inflammation, ocular pemphigoid and uveitis.

Use of topical tacrolimus has shown promising results, with studies reporting impressive and rapid reduction in the size of the giant papillae. It also appeared to be more easily tolerated than cyclosporine in its side-effect profile.[11,12] In our present study, we aim at evaluating the safety and efficacy of 0.1% tacrolimus as a first line therapy for the management of patients with Vernal Keratoconjunctivitis.

Materials and Methods

All newly diagnosed patients of the age of 9 to 20 years with VKC who met the inclusion and exclusion criteria were included in the study carried out at the Department of Ophthalmology, Sumandeep Vidyapeeth University from 7/10/2016 to 27/4/2017 during which all the patients were treated with tacrolimus 0.1% eye ointment twice a day. Sumandeep Vidyapeeth Institutional Ethics Committee approval was obtained on 23/09/16 date for the same.

Those patients with history of ocular surgery; infective, degenerative or dystrophic ocular surface pathology; history of ocular trauma; or patients on any kind of topical treatment for allergic conjunctivitis or otherwise were excluded from the study.

Out of the 70 patients that were screened, 60 patients between the age of 5 to 25 years with at least one of the 5 symptoms (itching, redness, photosensitivity, foreign body sensation, mucous discharge) and one of the 4 signs (Conjunctival hyperaemia, papillary hypertrophy, giant papillary conjunctivitis, limbal involvement) of VKC with no history of ocular medication usage in the past 3 months were included in the study. Even from these, 50 patients completed the study and 10 patients were lost on follow up.

All the enrolled patients underwent ophthalmic examination at baseline visit and at all 6 follow up visits thereafter at fortnightly intervals (2, 4, 6, 8, 10 and 12 weeks). At the baseline visit the patients were prescribed tacrolimus eye ointment 0.1% twice daily and Carboxy-methyl cellulose eye drops four times a day by the clinician.

The grading of the signs was done on each follow up after a thorough slit lamp examination according to the criteria given in [Table 1]

Each of 4 clinical signs [Table 1] was scored on a four-point scale using the following criterion: 0=none, 1=mild, 2=moderate and 3=severe. On the other hand, grading of the symptoms was subjective on the basis of the patient's complaints and was also done on a similar four point scale.

Table 1: Clinical grading of VKC

Clinical Grading of Vernal Keratoconjunctivitis				
	0=absent	**1=mild**	**2=moderate**	**3=severe**
Conjunctival hyperaemia	No evidence of bulbar hyperaemia	Mild bulbar hyperaemia	Moderate bulbar Hyperaemia	Severe bulbar hyperaemia
Papillary hypertrophy	No papillary hypertrophy in palpebral conjunctiva	Few papillae of <0.2	0.2-1mm	1 to 3mm in entire tarsal conjunctiva
Giant papillary conjunctivitis	No giant papillae seen	Few giant papillae of 3 to 4mm	Giant papillae 3 to 4 mm throughout the entire tarsal conjunctiva	Giant papillae of 4 to 6mm throughout the entire tarsal conjunctiva
Limbal involvement	No evidence of trantas' dots	1 to 2 trantas' dots	3 to 4 trantas' dots	4 trantas' dots
Corneal Involvement	No corneal involvement	Fine superficial epithelial defects involving <1/2 of cornea	Fine superficial epithelial defects involving >1/2 of cornea	Confluent epithelial defects, mucous plaques formation, oval ulcer

Results and Discussion

The treatment for allergic ocular diseases like Vernal keratoconjunctivitis has been a challenge for ophthalmologists.[13,14] Variety of topical medications have been used including anti-histamines, mast-cell stabilisers, non-steroidal anti-inflammatory drugs, steroids and immunosuppressants.[13,14] Amongst the various treatment modalities available, topical steroid eye drops are used as first drug of choice for the treatment of VKC. However, topical steroids are associated with increased adverse effects like raised intraocular pressure, cataract formation, retardation of wound healing, secondary infections, stem cell loss and corneal scarring. Moreover, the misuse or overuse of

these drugs also increases the probability of their adverse effects. Hence, the development of a new safe treatment strategy especially for chronic version of the disease is essential. [15]

Tacrolimus was discovered in 1987.[16] It was among the first novel macrolide immunosuppressants. Tacrolimus is produced by the fermentation of Streptomyces tsukubaensis. It has been used systemically in Sjogren's syndrome, bone marrow transplant, atopic dermatitis, and hepatic and renal transplantation.[17-23] It's use in ophthalmology has also evolved over the years and now is used for several ophthalmic conditions like corneal graft rejection, atopic and vernal keratoconjuctivitis, uveitis, graft-versus-host disease, Mooren's ulcer, proliferative vitreoretinopathy and after glaucoma filtering surgery. Rakesh K Barot et al, in their study "Therapeutic effect of 0.1% Tacrolimus Eye Ointment in Allergic Ocular Diseases "concluded that topical 0.1% Tacrolimus eye ointment is well tolerated and effective in management of patients with AOD (Allergic ocular diseases). In a similar consensus, our present study was aimed at finding out the therapeutic efficacy of Tacrolimus 0.1% eye ointment in management of VKC.

The demography of 50 patients has been included in the analysis of the study. There were 82% males and 18% females in the study [Fig. 1]. The mean age of the patients in our study was 13.4 ± 5.11 Years. The total score of the 5 clinical signs (range 0–15) and 4 clinical symptoms (range 0–12) decreased significantly from baseline to 3 month follow-up after beginning Tacrolimus eye ointment therapy.

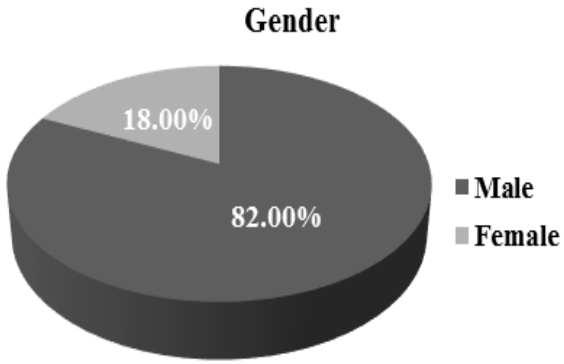

Fig. I: Demography of the sex of the patients

Total score of all 5 clinical symptoms was 379 at the start of treatment and decreased to 44 at the last observation (median score at baseline was 2 and median score at end of visit was 0). The total clinical sign score decreased from 308 at baseline to 54 at the last observation. [Table 2/Fig. 2,3] (evaluated by Wilcoxon rank test, p value: <0.001).

Table 2: Reduction in symptom and sign score from baseline to the last visit

Clinical features	Score	
	Baseline visit	End of Visit
Symptoms	379	44
Signs	308	54

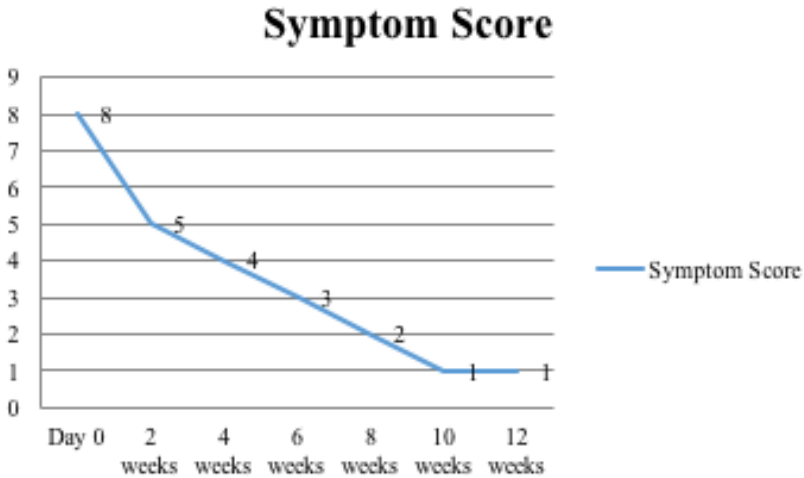

Fig. 2: Symptom score (Median)

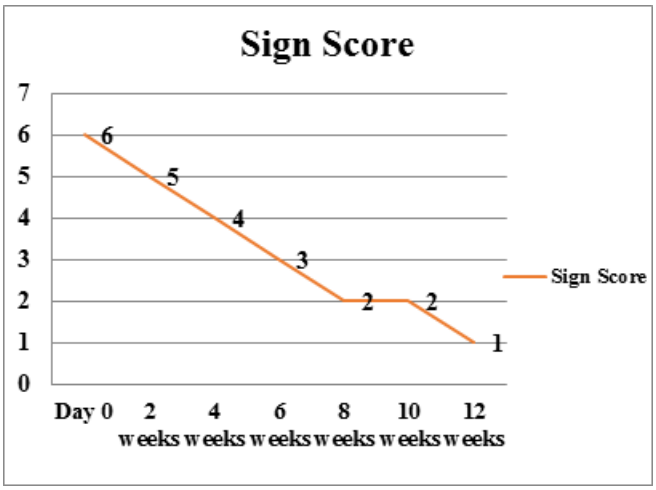

Fig. 3: Sign score (Median)

Amongst the various symptoms the patients most frequently complained of itching, redness and foreign body sensation. 49 out of total 50 patients complained of itching, of which 11(22.44%) had mild, 23 (47.93%) had moderate and 15 (30.61%) had severe itching. At the end of 12 weeks follow up 35 patients (70%) had no complaint of itching [Table 3]. 49 out of 50 patients complained of redness of which 9 (18.36%) complained of mild, 30 (61.22%) moderate and 10 (20.40%) complained of severe redness which reduced to just 11 (22.44%) patients at the end of the study. Of the 30 patients with moderate redness 24 (80%) had no redness at the end of 12 weeks while 6 (20%) had mild redness [Table 4]. 37 out of 50 patients complained of foreign body sensation of which 16 (43.24%) had mild, 16 (43.24%) had moderate and 5(13.51%) had severe foreign body sensation. This number reduced to 4 patients having persistent symptoms at the end of 12 weeks. Similarly, in the patients with symptoms of mucus discharge and photosensitivity a statistically significant reduction was observed at the last visit.

Table 3: Itching score indicating increase in the number of patients with no symptoms from 1 to 35 at the end of 3 months of the use of tacrolimus eye ointment

Score	Itching						
	Day 0	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
No Symptoms	1	8	10	10	14	28	35
Mild	11	17	20	29	30	18	15
Moderate	23	20	17	11	6	4	0
Severe	15	5	3	0	0	0	0

Table 4: Photosensitivity score indicating marked reduction in photosensitivity at the end of 3 months

Score	Photosensitivity						
	Day 0	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
No Symptoms	15	21	21	24	35	41	45
Mild	16	18	23	24	13	8	4
Moderate	16	11	6	2	2	1	1
Severe	3	0	0	0	0	0	0

Out of the total 50 patients, 49 had conjunctival hyperaemia. Of these 13 (26.53%) had mild conjunctival hyperaemia. Maximum number of patients which were 28 (57.14%) had moderate conjunctival hyperaemia while 8 (16.32%) had severe conjunctival hyperaemia. Amongst the 28 patients with moderate severity, 21 (75%) were completely relieved while mild signs persisted in 6 (21.42%) and 1 (3.57%) patient showed no improvement [Table 5/Fig. 4]. 46 patients had papillary hypertrophy of which 5(10.86%) had mild, 28 (60.86%) had moderate and 13(28.26%) had severe papillary hypertrophy. Of the 28 with moderate papillary hypertrophy 19 (67.85%) had no symptoms while 9 (32.14%) had mild hypertrophy at the end of 3 months also. Of the 46 patients, 16 (34.78%) still had mild to moderate papillary hypertrophy at the end of the study [Table 6]. Amongst the patients with giant papillary conjunctivitis also marked reduction was observed at the

end of 3 months. 36 of 50 patients had limbal involvement of which 7(19.4%) had mild, 20 (55.55%) had moderate and 9(25%) had severe involvement. At the end of 12 weeks 9 (25%) still had mild sign while 1(2.77%) had persistent severe limbal involvement [Fig. 5].

Table 5: Score of conjunctival hyperaemia indicating increase in the number of patients with no symptoms from 1 to 35 at the end of 3 months follow up

Score	Conjunctival Hyperaemia						
	Day 0	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
No Symptoms	1	5	6	6	16	23	35
Mild	13	18	25	33	25	23	14
Moderate	28	21	17	10	9	4	1
Severe	8	6	2	1	0	0	0

Table 6: Score indicating reduction in the number of patients having papillary hypertrophy from 46 to 30 at the end of the treatment

Score	Papillary Hypertrophy						
	Day 0	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
No Symptoms	4	3	5	7	15	26	34
Mild	5	17	23	31	29	21	15
Moderate	28	24	20	11	5	2	1
Severe	13	6	2	1	1	1	0

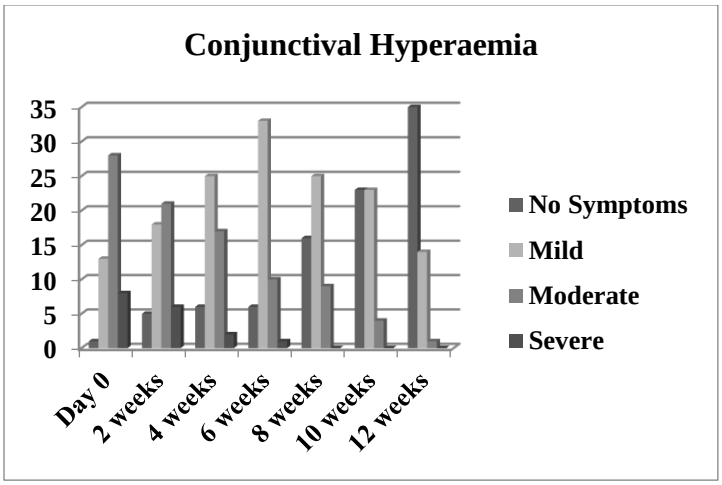

Fig. 4: Conjunctival hyperaemia in patients from baseline till 3 months indicating significant decrease inseverity

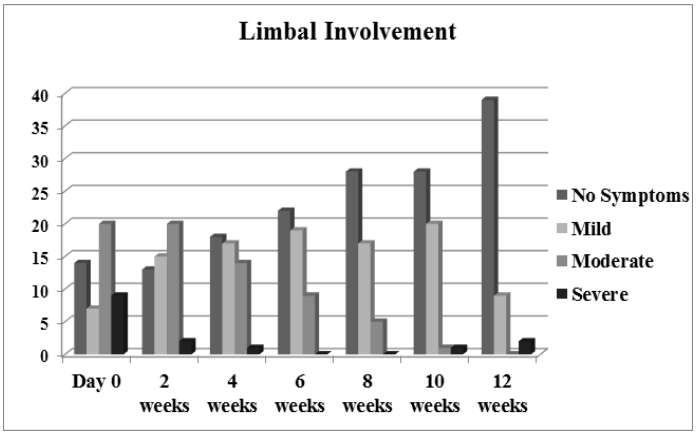

Fig.5: Limbal involvement in patients from baseline till 3 month follow up

Tacrolimus is known to cause local adverse effects like stinging, burning sensation and certain systemic side effects in the form of headache, nausea, insomnia, diarrhoea, renal dysfunction, tremors and increased blood glucose levels. However, in our study we did not encounter such complaints after the use of the drug. Burning sensation was an important adverse effect during our study and hence to prevent the discontinuation of the use of the drug for the same, Carboxy-methyl cellulose eye drops were instilled with the drug simultaneously from the baseline visit itself.

Conclusion

Our study suggests the safety and efficacy of topical tacrolimus as first line of management in patients with VKC. It has topical steroid sparing effect which avoids the vision threatening complications associated with steroid use. As our study has limitation of a short duration of follow-up, the long term effects as well as adverse effects of the use of tacrolimus could not be assessed.

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