Assessment of the efficacy of 0.03% tacrolimus eye ointment in refractive vernal Keratoconjunctivitis with corneal involvement in a tertiary eye care hospital in north India

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Abstract

Background: Vernal keratoconjunctivitis (VKC) is an acute – on – chronic inflammatory disease of the conjunctiva and cornea, encountered usually in the very first decade of life in children.

Aims and Objectives: To determine the clinical efficacy of 0.03% tacrolimus eye ointment in refractive Vernal Keratoconjunctivitis (VKC) in patients with corneal involvement, based on a study done on children in their first and second decade of life.

Materials And Methods: Prospective observational study of 110 patients aged 7- 18yr (I2±5yrs). After taking history, 8 clinical signs and 5 symptoms were noted and graded. Patients were started with 0.03% tacrolimus eye ointment twice daily and followed up for 6 months.

Results and Observations: Statistically significant improvement was noted in patients with corneal involvement and giant papillary lesions ($p<0.001$), 47 patients (43%) showed improvement after 1 month. After 6 months, 105 patients (95%) showed improvement in signs and symptoms. The only side effect observed was burning sensation in 3 patients, which was relieved with lubricating drops (0.5% Carboxy-Methyl-cellulose) given four times a day.

Conclusion: 0.03% Tacrolimus eye ointment was safe and effective in VKC cases, resistant to anti-allergic/steroid/cyclosporine eye drops, especially with proliferative lesions and corneal involvement.

Key words: Cyclosporine eye drops, Corneal involvement, Vernal Keratoconjunctivitis(VKC), Refractive, Tecrolimus, Eye ointment, Allergic inflammatory disorder.

Introduction: Vernal keratoconjunctivitis (VKC) is an acute – on – chronic inflammatory disease of the conjunctiva and cornea, [1,2] usually encountered in the very first or early second decade of life. Vernal keratoconjunctivitis (VKC) is a bilateral recurrent chronic allergic inflammatory disorder of the ocular surface which is seasonally exacerbated mostly involving tarsal and bulbar conjunctiva often present with corneal involvement mostly affecting children.

Previously its etiology was considered a classical igE-mediated type 1 hypersensitivity reaction, but now, complex etiology involving T2-lymphocytes are also involved. The predominant eye symptoms are itching, ropy discharge, tearing, eye irritation, redness of the eyes, and to a variable extent photophobia. Conjunctival signs include hyperaemia and giant papillary cobblestone lesions in bulbar conjunctiva with congestion, gelatinous limbal membrane and Horner-Trantas spots. Corneal lesions can range from punctuate epithelial erosions to shield ulcer, scarring and corneal plaques. Various treatment modalities had been tried ranging from topical antihistamines, mast-cell stabilizers, NSAID, topical low and high-potency steroids (1% Methyl Prednisolone). Steroids in particular cannot be used for a long period because of their side-effects (such as early onset cataract and open angle glaucoma). Keeping this in mind newer immunomodulating drugs like tacrolimus are being advocated for the management of VKC. This study aims at highlighting the role of tacrolimus in the management of VKC with corneal involvement in young children.

Materials And Methods: It is a prospective observational study which includes 110 consecutive VKC patients (between the ages of 7-18 years) attending the department of Ophthalmology Maharishi Markandeshwar Institute of Medical Sciences and research, Mullana, Ambala, Haryana, India, in between July 2021 and December 2022.

Results and Observations: After taking the history, total signs and symptoms score was noted. 0.03% Tacrolimus eye, ointment was started in patients meeting inclusion criteria twice daily and studied for 6 months. Total of 8 clinical signs (Palpebral congestion hyperaemia, follicles, papillae, giant papillae bulbar hyperemia, edema, Trantas dot, corneal signs) and 5 symptoms (itching, foreign body sensation, tearing, discharge and photophobia) were graded as none, mild, moderate, and severe. Baseline examination was done on day 0 using slit-lamp biomicroscope and then again after 1 month, 3 months, and 6 months. Patients with clinical diagnosis of refractive VKC whose symptoms did not subside with antihistaminic/mast-cell stabilizer/topical steroids and patients who did respond to topical steroids but developed ocular steroid toxicity were included in this study. Patient having only one useful eye, patients using contact lens for long term, patients with any other active ocular inflammatory condition, and patients with hypersensitivity reaction against the study medication were excluded from the study in written informed consent was obtained from the each of the participants (or from their legal guardians in cases of minors) before the start of study medication. Institutional ethical committee permission was obtained before the start of the study. Statistically significant improvement was seen in patients with corneal involvement and giant papillary lesions ($p<0.001$) Out of 110 patients around 50(45%), 69(63%), 105 patients (95%) showed improvement in symptoms and signsafter application of 0.03% Tacrolimus ointment at 1st month, within 3rd month and within 6th month respectively (Table 1). Follicles were observed in 75 patients, giant papillae in 58 patients, edema in 42 patients, Trantas dot in 62 patients and corneal signs in 69 patients. Only few side-effects were seen such as mild burning sensation seen in 3pts (2.5%) seen in 1st month which subsided in few weeks (Table)

Table 1: Comparative study on observation of relief and regression of signs and symptoms seen in patients under observation following treatment with 0.03% Tacrolimus at 1 month, 3 months and 6 months following treatment.

Symptoms and Signs	At 1 Month	At 3 Months	At 6 Months
Conjunctival hyperaemia	52(47%)	70(64%)	**104**(95%)

Photophobia	**51**(47%)	**71**(65%)	**102**(93%)
Discharge	**50**(45%)	**69**(63%)	**103**(94%)
Tearing	**49**(45%)	**70**(64%)	**105**(95%)
Fb sensation	**51**(47%)	**70**(64%)	**102**(93%)
Itching	**51**(47%)	**71**(65%)	**103**(94%)
Corneal signs (n=69)	**26**(38%)	**43(62%)**	**67**(97%)
Trantas dot (n=62)	**27(44%)**	**36(58%)**	**55(89%)**
Oedema (n=42)	**18(43%)**	**24(57%)**	**36(86%)**
Bulbar hyperemia	**48**(44%)	**68**(62%)	**104**(95%)
Giant papillae (n=58)	**26(45%)**	**36(62%)**	**49(85%)**
Papillae	**46**(42%)	**68**(62%)	**103**(94%)
Follicles (n=75)	**35(47%)**	**47(63%)**	**72(96%)**
Mean	45.53%	63.32%	95.3%

Table 2: Comparative study of symptoms and signs seen in patients under treatment at presentation (0 month) and at end of study (6 months) in respective with mild, moderate and severe grade in conjunctival and corneal involvement.

Symptoms and Signs	Grade 1(Mild)		Grade 2(Moderate)		Grade 3(Severe)	
	At 0 Month	At 6 Months	At 0 Month	At 6 Months	At 0 Month	At 6 Months
Conjunctival hyperemia	37	17	49	8	24	5
Photophobia	50	13	35	9	25	7
Discharge	53	15	34	10	23	9
Tearing	13	12	50	11	47	9
Fb sensation	16	13	57	9	37	7
Itching	21	16	58	6	31	5
Corneal signs (n=69)	31	12	33	12	5	5
Trantas dot (n=62)	27	9	25	6	10	17
Oedema (n=42)	22	10	16	6	4	10
Bulbar hyperemia	26	10	36	8	48	5
Giant papillae (n=58)	21	15	25	12	12	3
Papillae	22	23	29	24	58	3
Follicles (n=75)	23	24	36	7	16	2

Discussion: Tacrolimus is a highly potent immunomodulator agent produced by the fungus Streptomyces tsukubensis. It suppresses T-cell activation, T helper cell-mediated B-cell proliferation, and the formation of cytokines, especially that of interleukin-2. Initially approved as a skin applicant for treatment of atopic dermatitis (AD) it has also been used with good effect in below quantifiable levels with no evidence of cancer risk or significant local side effects and only occasional reports of transient burning or pruritus at the application site. Safer alternatives for topical steroids had been on, especially in view of the chronic and indolent nature of VKC.

Fukusnima et al. used 0.1% tacrolimus in their study and placed it superior to cyclosporine in managing refractory VKC10. They reported a significant reduction of total signs and symptoms, including corneal lesions at one month after tacrolimus application. Burning sensation(transient) was the most commonly documented side effect in 3.20% (2.5% in our study). Results of 0.1 % tacrolimus in refractory VKC cited by Abaysiri et al. are similar to our study11. They concluded the excellent safety profile of tacrolimus and its efficacy is as good as any high-potency topical steroids. Improvement of corneal lesions had been reported (like our study) by Kheirkhah et al12. The major limitation of our study is that we have a small sample size and lack of a control arm. 0.03% Tacrolimus eye ointment was found safe and effective in vernal keratoconjunctivitis cases resistant to anti-allergic /steroid/ cyclosporine eye drops, especially with proliferative lesions and corneal involvement with mild side-effects of burning sensation which subsided within few weeks.

Conclusion: 0.03% Tacrolimus eye ointment was safe and effective in VKC cases resistant to anti-allergic/steroid/cyclosporine eye drop especially with proliferative lesions and corneal involvement.

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