A Comparative Evaluation of Tacrolimus versus Steroids in the Treatment of Vernal Keratoconjunctivitis

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ABSTRACT

BACKGROUND

Vernal keratoconjunctivitis (VKC) is a bilateral, chronic, conjunctival inflammatory condition of children and young adults. It is an IgE and T cell mediated disease leading to chronic inflammation in which eosinophil, lymphocyte and structural cell activation are involved. Treatment of VKC requires mast cell stabilisers, antihistamines, steroids and topical immunomodulators. This study was designed to compare topical tacrolimus ointment 0.03% and low potent steroids like Fluorometholone in the treatment of VKC.

METHODS

In this randomised double masked clinical trial, 60 eyes of 30 patients with VKC were treated in a tertiary referral centre in Chennai. Patients were randomly assigned to receive either 0.03% tacrolimus ointment or low potency topical steroids. Chi-square & t tests were used for comparison of outcomes between the two groups.

RESULTS

Mean age was 10.2 ± 2 yrs. in study group and 9.2 ± 2 yrs. in control group. The mean duration of disease was 4.2 ± 2.5 years. In this study, signs and symptoms were significantly reduced in patients after treatment in both groups (p=0.0001). Significant improvements in clinical signs and symptoms were achieved in all patients 4 weeks after starting treatment with topical tacrolimus. Significant improvement was noted in the control group too. In the tacrolimus group all patients except one responded to treatment. Side effects in the tacrolimus group were minimal and tolerable. Side effects in the steroids group were slightly severe.

CONCLUSIONS

Both 0.03% topical tacrolimus ointment and steroids are effective in the treatment of VKC. However, long term complications in the tacrolimus group are fewer and milder when compared with the steroids group.

KEYWORDS

Vernal Keratoconjunctivitis, Tacrolimus, Papillae, Steroids

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BACKGROUND

Allergic eye disease (AED) is a type 1 hypersensitivity reaction, that occurs following exposure to environmental triggers with a spectrum encompassing mild seasonal allergies to severe sight threatening keratoconjunctivitis.[1,2] Vernal keratoconjunctivitis (VKC) is a chronic, bilateral inflammation of the conjunctiva that predominantly affects children between 3 and 16 years of age.[3] It usually resolves at puberty, but can continue into adulthood.[3] This allergic condition frequently persists throughout the year and usually increases in intensity in warmer climate.[4] 40 to 75% of these patients have some atopy manifestations. Patients with VKC experience significant morbidity. Symptoms include intense itching, tearing, mucous secretions, and photophobia. Common conjunctival signs of VKC are hyperemia, papillary hypertrophy, giant papillae, discharge, and Horner Trantas dots.[5,6] For the treatment of VKC several treatment options are available like anti histamines, mast cell stabilisers and topical steroids.[5,6] For moderate to severe cases topical steroids are the mainstay of treatment. Prolonged steroid therapy is fraught with complications like cataract and glaucoma. To avoid these complications steroid sparing immunomodulatory agents like cyclosporine and tacrolimus have been used.

Tacrolimus is a strong, nonsteroidal immune suppressant isolated from Streptomyces tsukubaensis.[7] It binds to FK506-binding proteins in T-lymphocytes and inhibits calcineurin activity. Tacrolimus is up to 100 times more potent than cyclosporine.

METHODS

This prospective, randomized, case series study followed 60 eyes from 30 patients with active VKC refractory to conventional treatment. Written informed consent was obtained from the patients who were recruited for the study. Exclusion criteria were coexisting conjunctival disorders, chemical injury, Stevens-Johnson syndrome, corneal diseases, uveitis, ocular infections, contact lens use, a history of systemic NSAID or steroids use and ocular surgery in the previous 3 months, pregnant patients, patients who had other infectious/inflammatory eye diseases, known cases of allergy to tacrolimus, cases who had prior steroid injection within 6 months.

VKC was diagnosed by (1) symptoms (chronic, bilateral itching, redness); and (2) signs (Trantas dots, papillae on the upper tarsal conjunctiva, corneal erosions). Complete ophthalmic examinations were performed, including best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy, fluorescein staining, fundoscopy, tear film evaluation, and applanation tonometry. Patients in the first study group received topical tacrolimus ointment 0.03% twice daily and the control group received topical soft steroids like fluorometholone eye drops 4 times daily for a study period of 4 weeks. The tacrolimus dose was twice daily for 1-month followed by a taper to once daily for 1 week, twice a week for 1 week and then once a week. The soft steroids were also tapered after 4 weeks and then stopped. During treatment, patients returned for evaluation after 1-week, 4 weeks, 6 weeks, and then every 6 months. The primary efficacy endpoint was change from baseline with topical treatment.

Objective signs and subjective symptoms were observed at baseline (before treatment) and 1, 2, 4 & 6 weeks after treatment. Objective parameters included conjunctival hyperemia, papillary reaction and severity of limbal hyperplasia. Each sign was graded as scale 0 (none), scale 1 (mild), scale 2 (moderate), or scale 3(severe). Subjective ocular symptoms (included redness of the eyes, itching, photophobia) and side-effects were recorded by patients once daily, during the entire period. They were graded on a scale of scale 0 (none), scale 1 or mild (occasional symptoms), scale 2 or moderate (frequent symptoms), and scale 3 or severe (constant symptoms).

The primary outcome measure was the difference in score for the symptoms and objective signs between study group and control group at the end of 4 weeks. The secondary outcome measure was the safety and tolerance of the tacrolimus ointment.

Ethics

Written informed consent has been obtained from patients for using their details for the study purpose. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given the consent for their images and other clinical information to be reported in the journal. The patients understand the names and initials will not be published and due efforts will be made to conceal the identity, anonymity cannot be guaranteed. The study has been approved by the Institutional Ethics Committee.

RESULTS

Objective Parameters - Study Group

Score	Pre-Treatment	Post-Treatment
Severe	17	5
Moderate	13	10
Mild	10	25
	40	40

Table 1. Conjunctival Hyperemia Pre- and Post-Treatment

The Chi ^ 2 value is 38.7. The p-value is <0.001. The result is significant at p =<0.05.

Score	Pre-Treatment	Post-Treatment
Severe	25	10
Moderate	13	10
Mild	2	20
	40	40

Table 2. Papillary Reaction Pre- and Post-Treatment

The Chi ^ 2 value is 39.6. The p-value is <0.001. The result is significant at p = <0.05.

Score	Pre-Treatment	Post-Treatment
Severe	20	5
Moderate	12	20
Mild	8	15
	40	40

Table 3. Limbal Hyperplasia Pre- and Post-Treatment

The Chi ^ 2 value is 51.467. The p-value is < 0.001. The result is significant at p =<0.05.

Objective Parameters - Control Group

Score	Pre-Treatment	Post-Treatment
Severe	14	12
Moderate	16	18
Mild	10	10
	40	40

Table 4. Conjunctival Hyperemia Pre- and Post-Treatment

The Chi^2 value is 0.556. The p-value is 0.75. The result is not significant at p =<0.05.

Score	Pre-Treatment	Post-Treatment
Severe	20	19
Moderate	12	11
mild	8	10
	40	40

Table 5. Papillary Reaction Pre- and Post-Treatment

The Chi ^2 value is 0.544. The p-value is 0.762. The result is not significant at p =<0.05.

Score	Pre-Treatment	Post-Treatment
Severe	14	10
Moderate	13	18
Mild	13	12
	40	40

Table 6. Limbal Hyperplasia Pre- and Post-Treatment

The Chi ^2 value is 3.072. The p-value is 0.215. The result is not significant at p =< 0.05.

Subjective Parameters - Study Group

Score	Pre-Treatment	Post-Treatment
Severe	20	8
Moderate	12	10
Mild	8	14
None	0	8
	40	40

Table 7. Redness Pre- and Post-Treatment

The Chi ^2 value is 28.971. The p-value is < 0.001. The result is significant at p =<0.05.

Score	Pre- treatment	Post-Treatment
Severe	17	10
Moderate	13	10
Mild	9	4
None	1	16
	40	40

Table 8. Itching Pre- and Post-Treatment

The Chi ^2 value is 26.112. The p-value is <0.001. The result is significant at p =<0.05.

Score	Pre-Treatment	Post-Treatment
Severe	12	4
Moderate	10	6
Mild	10	10
None	8	20
	40	40

Table 9. Photophobia Pre- and Post-Treatment

The Chi ^2 value is 25.867. The p-value is <0.001. The result is significant at p =<0.05.

Subjective Parameters - Control Group

Score	Pre-Treatment	Post-Treatment
Severe	13	12
Moderate	14	15
Mild	10	13
None	3	0
	40	40

Table 10. Redness Pre- and Post-Treatment

The Chi ^2 value is infinity. The p-value is <0.001. The result is significant at p =<0.05.

Score	Pre-Treatment	Post-Treatment
Severe	16	10
Moderate	7	10
Mild	13	17
None	4	3
	40	40

Table 11. Itching Pre- and Post-Treatment

The Chi ^2 value is 5.775. The p-value is 0.123. The result is not significant at p =<0.05.

Score	Pre-Treatment	Post-Treatment
Severe	10	9
Moderate	12	11
Mild	10	10
None	8	10
	40	40

Table 12. Photophobia Pre- and Post-Treatment

The Chi ^2 value is 0.602. The p-value is 0.896. The result is not significant at p =<0.05.

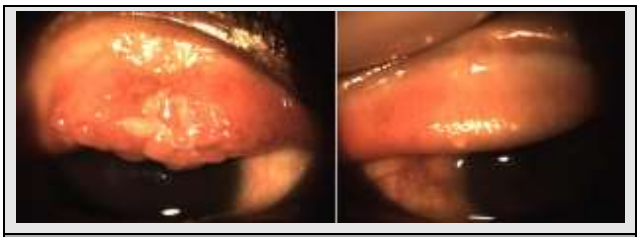

Figure 1a) Significant Palpebral Conjunctival Papillae. 1b) Reduction of Conjunctival Papillae Following Treatment in Tacrolimus Group

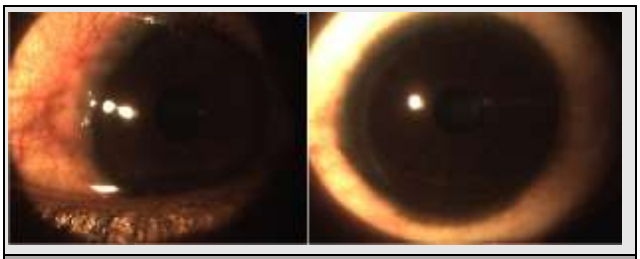

Figure 2a) Limbal Hyperplasia and Conjunctival Hyperemia 2b) Reduction of the Same

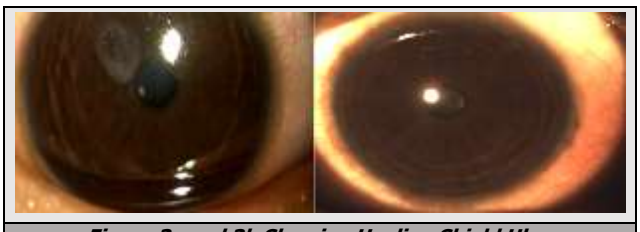

Figure 3a and 3b Showing Healing Shield Ulcer at the End of 2 Months

In this clinical trial, all 60 patients completed the study in two groups of study (n=30) and control (n=30). Male patients predominated in both (20/30) study and (22/30) control groups. Mean age was 10.2 ± 2 yrs. in study group and 9.2 ± 2 yrs. in control group. All patients had received topical antiallergic agents (olopatadine) within 4 weeks prior to treatment, and continued to use them during the treatment period. These results clearly show statistically significant improvement with both tacrolimus in the study group and steroids in the study group after 4 weeks of treatment. (Figure 1a, 1b, 2a, 2b, 3a, 3b) One male patient in the Tacrolimus study group with giant papillae did not respond to treatment and he was considered as a failure, however he responded well to a Supratarsal injection of triamcinolone. Side effects in the tacrolimus group were mild and tolerable.

Four patients in the tacrolimus group had mild irritation which resolved with lubricants. 4 patients in the steroid group had developed an intraocular pressure raise at the end of 6 weeks and were treated for the same. One patient in the steroid group developed Punctate epithelial erosions, steroid therapy was discontinued for him temporarily and he was started on lubricants.

DISCUSSION

The two main topical immunomodulators commonly used to treat allergic eye diseases such as VKC and AKC are topical 2% Cyclosporine A and topical tacrolimus 0.03% eye ointment. Tacrolimus is a potent drug similar to cyclosporine A in it's mode of action, but chemically distinct. Tacrolimus is a strong, nonsteroidal immune suppressant isolated from Streptomyces tsukubaensis. It binds to FK506-binding proteins in T-lymphocytes and inhibits calcineurin activity. Calcineurin inhibition suppresses the formation of T-helper (Th) 1 (interleukin (IL)-2, interferon γ) and Th2 cytokines (IL-4, IL-5). It also inhibits histamine release from mast cells and basophils through a reduction in IL 5 production. A prospective double masked randomised comparative trial comparing the efficacy of 0.1% tacrolimus ophthalmic ointment with Cyclosporin A 2% showed that both were equally effective in the treatment of VKC.[8]

In a multicentre randomized clinical trial, Ohashi et al applied 0.1% ophthalmic suspension of tacrolimus twice daily for 4 weeks in 21 patients with AKC and 7 patients with VKC.[9] Compared with placebo the treated eyes showed marked improvement in symptoms. Initial evidence show that tacrolimus is more effective than Cyclosporin A .Topical steroid therapy with soft steroids like Fluorometholone or Loteprednol in VKC down regulates conjunctival inflammation. However studies show that one third of the normal population can become a steroid responder with an increase of an IOP between 6 and 15 mm Hg.41 of 145 (28.30%) patients with severe VKC in a Singapore case series developed a steroid response, of which 8 progressed to glaucoma.[10] The incidence of posterior subcapsular cataract in these cases are also high.

In our study, both the study group which used tacrolimus and the control group which used steroids responded well to treatment. There was significant improvement of not only conjunctival signs like hyperaemia and papillae, but also improvement of corneal signs like limbal hypertrophy. Topical steroids were the mainstay of therapy previously for refractory cases of VKC. However the adverse effects with the tacrolimus group were very minimal. Although burning sensation upon application of topical tacrolimus has been reported before with the 0.1% percent tacrolimus, no patient in our study experienced any burning sensation with tacrolimus 0.03%. 4 patients in the tacrolimus group reported only mild irritation.

The complications reported in literature with steroids can be avoided by using a steroid sparing immunomodulator like tacrolimus in the treatment of Vernal keratoconjunctivitis. Most of the patients of VKC belong to the younger age group, hence avoiding these complications will go a long way in improving the quality of life.

CONCLUSIONS

0.03% tacrolimus as well as low potency steroids are efficacious in the management of VKC. But even low potency topical steroids can cause complications like cataract and glaucoma. We can avoid such complications by using a steroid sparing agent like Tacrolimus.

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