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Therapeutic Effects of 0.1% Tacrolimus Eye Drops for Refractory Vernal Keratoconjunctivitis

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Abstract :
Background: *To investigate the efficacy of topical 0.1% tacrolimus in treating refractory vernal keratoconjunctivitis.*
Material and Methods: *This prospective study included 20 patients with refractory VKC. Patients having refractory VKC were started with topical 0.1% tacrolimus eye drop twice daily. Changes in subjective symptoms and objective signs after treatment were evaluated.*
Results: *Total signs and symptoms score significantly decreased after 1 month of treatment ($p<0.001$). The drug proved effective in treating refractory cases of VKC and also helped in weaning the patients from steroid therapy. No significant and hazardous adverse drug reactions were noticed in the study participants during the study period, so making the tacrolimus 0.1% eye drops safe for use in vernal keratoconjunctivitis patients in twice a daily doses.*
Conclusion: *Topical 0.1% tacrolimus eye drop seemed to be a safe and effective treatment for steroid-resistant refractory VKC.*
Keywords*: efficacy, refractory, steroid, topical, tacrolimus, vernal keratoconjunctivitis*

I. Introduction

Vernal keratoconjunctivitis (VKC) is a sight-threatening inflammatory disease of conjunctiva and cornea in young children with the onset usually occurring in the first decade of life. Mild cases of VKC tend to remit with nonspecific and supportive therapy. In contrast, severe cases are usually more protracted with remission/relapse occurring for a prolonged period of time. Pathogenesis of VKC involves roles for IgE, cytokines, chemokines, and inflammatory cells (T and B lymphocytes, mast cells, basophils, neutrophils, and eosinophils) with the release of their granular proteins, proliferation of fibroblasts, and laying down exuberant amounts of collagen fibers in the conjunctival tissue. Topical corticosteroids, often required for controlling symptoms and signs in severe VKC, can lead to serious ocular complications.

Tacrolimus is a 23-member cyclic macrolide lactone and was isolated from Streptomyces tsukubaensis in 1984.[1] Tacrolimus is an immunosuppressant that binds to FK506-binding proteins within T lymphocytes and inhibits calcineurin activity. Calcineurin inhibition suppresses dephosphorylation of the nuclear factor of activated Tcells and its transfer into the nucleus, which results in suppressed formation of T helper 1 (Th1) (interleukin (IL)-2, interferon γ) and Th2 cytokines (IL-4, IL-5).[2] Tacrolimus has also been reported to inhibit histamine release from mast cells and is thought to alleviate allergic symptoms through these mechanisms.[3]

II. Objectives

- To study the therapeutic efficacy and safety of 0.1% tacrolimus eye drop in treating refractory cases of VKC
- To study the effectiveness of tacrolimus therapy in sparing steroid therapy.

III. Material And Methods

- **Type of study:** Hospital based prospective study.
- **Place of study:** out patient department of M.L.B. Medical college,Jhansi.
- **Duration of study:** April to September 2015.
- **Study population:** 20 patients satisfying the eligibility criteria and diagnostic guidelines of Vernal keratoconjunctivitis.[4]
- **Inclusion criteria:** Patients satisfying the following requirements were included in analysis: presence of conjunctival giant papillae, limbal swelling, and/or Trantas dots; persistent or relapsing conjunctivitis sign; and younger than 20 years of age.

- **Exclusion criteria:** Patients with a known sensitivity to tacrolimus hydrate or any tacrolimus eye drop component, an infectious eye disease, or a confirmed or possible pregnancy.
- **Methodology:** Patients younger than 20 years of age satisfying the diagnostic criteria of VKC were included in the study.[4] One drop of tacrolimus was administered twice a day to patients with refractory vernal keratoconjunctivitis. The maximum observation period was 6 months. Each of 6 clinical signs (Table 1) was scored on a four-point scale using the following definitions: 0=none, 1=mild, 2=moderate and 3=severe. Grades were assigned based on photographic criteria (Table 1). In addition, each of six symptoms, including itching, discharge, lacrimation, photophobia, foreign body sensation and eye pain, was scored on a four-grade scale. Scoring was done at baseline (therapy initiation) and at 1, 2, 3 and 6 months into tacrolimus eye drop therapy. Demographic variables collected and examined included gender, age, allergic disease complications, previously used drugs, concomitant drugs and adverse reactions. The primary efficacy was evaluated in the terms of change in total signs and symptom scores from baseline.

Table 1: Grading Scale For Clinical Signs

SIGNS	SCORE	DEFINITION
Palpebral conjunctiva Hyperaemia	3	Impossible to distinguish individual blood Vessels
	2	Dilatation of many vessels
	1	Dilatation of several vessels
	0	None
Papillae	3	Papillae size: 0.6 mm or more
	2	Papillae size: 0.3–0.5 mm
	1	Papillae size: 0.1–0.2 mm
	0	None
Giant papillae (papillae size ≥1 mm)	3	Elevated papillae in 1/2 or more of the upper palpebral conjunctiva
	2	Elevated papillae in <1/2 of the upper palpebral conjunctiva
	1	Flat papillae
	0	None
Bulbar conjunctiva Hyperaemia	3	Diffuse dilated blood vessels over the entire bulbar conjunctiva
	2	Dilatation of many vessels
	1	Dilatation of several vessels
	0	None
Limbus Trantas' dot	3	9 or more dots
	2	5–8 dots
	1	1–4 dots
	0	None
Corneal epithelial signs	3	Shield ulcer or corneal erosion
	2	Exfoliation superficial punctuate keratitis
	1	Superficial punctate keratitis
	0	None

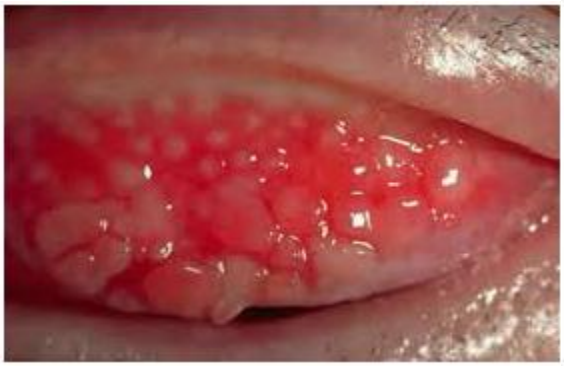

Figure 1 Giant papillae

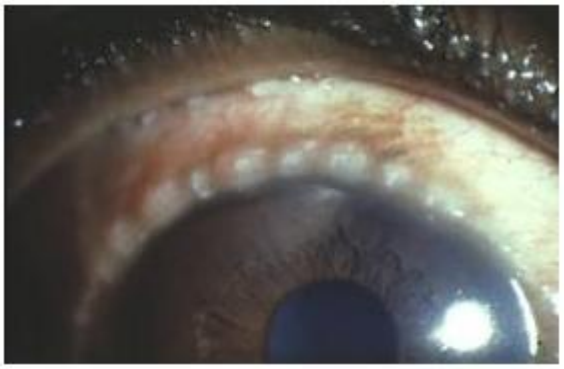

Figure 2 Horner tranta's spots

- **Statistical analysis:** Data are presented as mean±SD. Statistical analyses were performed using epi info (version 7.1.3.0). Statistical significance was defined as a two-sided p value of <0.05. Efficacy *assessments* were based on measurements obtained from the eye with a higher total ocular findings score (worse disease)[5] and the Wilcoxon signed rank test was used to compare total scores before and after treatment.

IV. Result & Observation

The majority of the patients with vernal keratoconjunctivitis who participated in our study were males (65%). 75% of our patients were already using anantiallergic topical medications and 65% were taking topical steroids for vernal keratoconjunctivitis.(Table 2)The study participants showed a marked decrease in the symptom and sign score after 1 month of initiation of topical tacrolimus therapy from the baseline values of 8.1 and 9.2 to 3.0 and 4.3 respectively(p value< 0.05). Thereafter both the symptoms and sign score decreased progressively at the subsequent follow up visits, finally coming to a value of 1.8 and 2.8 at the end of 6 months respectively(p value< 0.05).(Fig.3)

In our study we also found that use of topical tacrolimus therapy reduced the steroid dependence of our patients. Before initiation of topical tacrolimus eye drops to vernal keratoconjunctivitis patients, 83% of our patients were using topical steroid therapy for the same, but after initiation of tacrolimus therapy the patients using topical steroid eye drops dcreased to 53.5% at the end of 1 month which subsequently decreased to a value of 33.8% at the end of 6 months of starting the tacrolimus eye drops.(Fig.4) In this study, 10% of study participants showed adverse drug reactions with transient burning sensation(2.20%) being the commonest followed by irritation, pain, itching, foreign body sensation to name a few.(Table 3)

Table 2- Socio-demographic profile of study participants (n=20)

CHARACTERISTICS	FREQUENCY (%)
Sex Male Female	 13(65%) 7 (35%)
Mean age (years)± SD	12.8±7.2
Mean age of onset (years)±SD	10.6±4.2
Pretreatment* Antiallergic eye drops Topical steroids	 15 (75%) 13 (65%)

*= multiple responses

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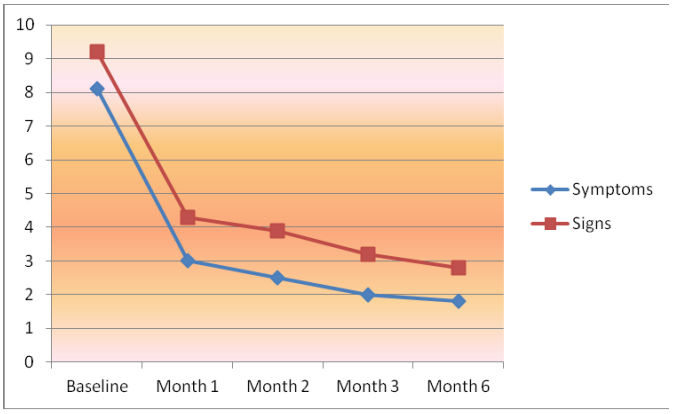

Figure-3 Change from baseline in total symptom and sign scores during the 6-month study period. The statistical significance of each score change was evaluated using the Wilcoxon signed rank test.

Figure-4 Proportions of patients using topical steroids at baseline and throughout the 6-month period during which the patients received topical tacrolimus eye drops.

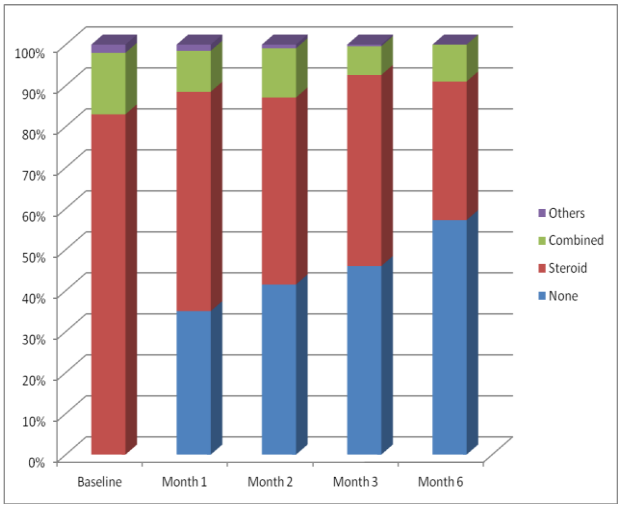

Table 3- Adverse drug reactions

Adverse reaction	Frequency (%)
Transient burning sensation	4 (2.2%)
Eye irritation	3 (1.5%)
Pain in eye	3 (1.5%)
Foreign body sensation	3 (1.5%)
Eye itching	3 (1.5%)
Lacrimation	2 (1%)
Blurred vision	2 (1%)

V. Discussion

In the past, antiallergic drugs and/or steroid therapy have been used to treat severe VKC with proliferative lesions. Unfortunately, antiallergic drug therapy is often insufficient without concomitant steroid use. However, topical steroids put patients at high risk of developing cataracts and/or glaucoma. For severe disease, VKC most frequently occurs in children and young adults. Therefore, it is desirable to avoid long-term

steroid use, particularly during childhood, to reduce the lifelong risk of developing steroid-related complications. Tacrolimus has long been used in organ transplant patients and has been shown to have potent immunosuppressive activity. Moreover, tacrolimus has also been reported to inhibit calcineurin 100 times more effectively than cyclosporine.[1] To evaluate the risks and benefits of tacrolimus eye drop use in patients with refractory vernal keratoconjunctivitis, the present study was conducted in a routine clinical setting. Changes in 6 clinical signs and 6 clinical symptoms were evaluated before and after tacrolimus eye drop therapy in 20 patients. Twice daily treatment with tacrolimus eye drops resulted in a significant reduction in the score 1 month after the start of treatment. Our data showed that 49.2% of patients using steroids were successfully weaned from topical steroid therapy. Thus, tacrolimus eye drops appear to have a steroid-sparing or replacing effect. Because those in infancy or early childhood are at high risk for steroid-induced elevation of intraocular pressure, tacrolimus eye drops may be a very effective, alternative treatment for VKC that does not impose the risk of developing glaucoma. Tacrolimus treatment may cause adverse reactions, including renal failure, when used systemically.[5] In our study, no serious systemic adverse events were observed. This is likely because the percentage of tacrolimus reaching the bloodstream with twice- daily topical use is very low.[6,7]

VI. Conclusion

Tacrolimus therapy is safe and effective in treating patients with refractory VKC

Acknowledgements

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