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VERNAL KERATOCONJUCTIVITIS: ROLE OF TACROLIMUS 0.1% OINTMENT IN SEVERE VKC

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ABSTRACT **Purpose:** To evaluate the safety and efficacy of tacrolimus 0.1% ointment for the treatment of refractory vernal keratoconjunctivitis (VKC). **Materials and Methods:** This prospective, nonrandomized case series enrolled 50 patients with severe VKC, who were treated with Tacrolimus 0.1% ointment. Each patient completed a follow-up period of at least 12 months. The main outcome measure was the clinical response to treatment. **Results:** Significant improvements in clinical signs and symptoms were achieved in all patients 6 weeks after starting treatment with topical tacrolimus. Treatment was gradually reduced, with increasing intervals between applications. VKC recurred in all patients who attempted to discontinue treatment. No additional medications were required and no significant changes in visual acuity or refraction were documented. One patient discontinued treatment due to a severe burning sensation and therefore was excluded from the study. **Conclusions:** Tacrolimus 0.1% ointment, is a safe and effective treatment for VKC refractory to standard treatment and may be used as a substitute for steroid treatments as long term corticosteroids may cause severe side effects. However, adverse effects could cause poor patient compliance.

KEYWORDS : Tacrolimus 0.1% , Keratoconjunctivitis

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a bilateral, chronic inflammation of the conjunctiva that particularly affects children between 3 and 16 years of age. It is seen to resolve at puberty, but can continue into adulthood. Although the name vernal suggests a seasonal, springtime occurrence but this is a misnomer as this allergic condition frequently persists throughout the year and usually increases in warm, humid weather[1,2].Significant morbidity is experienced by VKC patients [3].Severe scratching, tearing, mucous discharges, and photophobia are symptoms [4].Typical conjunctiva hyperemia, papillary hypertrophy, giant papillae, discharge, and Horner Trantas spots are symptoms of VKC[5]. Three types of the disease have been noted: limbal, tarsal, and mixed VKC, depending on the primary area of the ocular surface affected.

Tacrolimus is a strong, nonsteroidal immunosuppressant which is isolated from *Streptomyces tsukubaensi.*[6] It suppresses the action of calcineurin by attaching to FK506-binding proteins found in T cells. Nuclear factor dephosphorylation is inhibited by calcineurin of T-cells that have been activated and its entry into the nucleus, which inhibits the production of T-helper (Th) 1 (interleukin [IL]]-2, interferon gamma , and Th2 (IL-4, IL-5) cytokines[7]. Tacrolimus also prevents mast cell histamine release, which is thought to lessen allergic symptoms.[8]. Topical tacrolimus (0.02–0.1%) has also been used to treat giant papillary conjunctivitis, atopic keratoconjunctivitis (AKC), and VKC.

Recently topical cyclosporine A also been tried for VKC, which has immunomodulatory effects and may be used as an alternative to corticosteroids in circumstances when they are ineffective[9,10,11,12,13]. Furthermore, a tacrolimus 0.1% ophthalmic suspension has been used for the treatment of AKC and VKC with only 4 weeks of follow-up[14]

MATERIAL AND METHODS

This was a prospective observational study that involved 50 patients with vernal keratoconjunctivitis complaining of itching, discharge, redness. Patients were selected after all the criterias were fulfilled, from Department of Ophthalmology of M.L.B. Medical college, Jhansi , Uttar Pradesh and were followed from 1st May 2022 - 1st May 2023. The study was performed under the Helsinki Declaration of 1975, as revised in 2000. The necessary permission from the Ethical and Research Committee was obtained for the study. Despite receiving tacrolimus treatment or other standard therapies such antihistamines, mast cell stabilisers, topical steroids, or other medications, all research subjects had active illness and were steroid dependent, were on topical steroids and nonsteroidal anti-inflammatory medications.

Inclusion Criteria

- Children having vernal keratoconjunctivitis with previous history of treatment
- Patients who were symptomatic,
- Who are able to follow study related advices
- Patient must be able to understand and give consent for study.

Exclusion Criteria

- Coexisting conjunctival disorders,
- Chemical injury,
- Stevens-Johnson syndrome,
- Corneal diseases,
- Uveitis,
- Ocular infections,
- Contact lens use,
- H/O systemic nonsteroidal anti-inflammatory or immunosuppressive drug use,
- Any ocular surgery recently

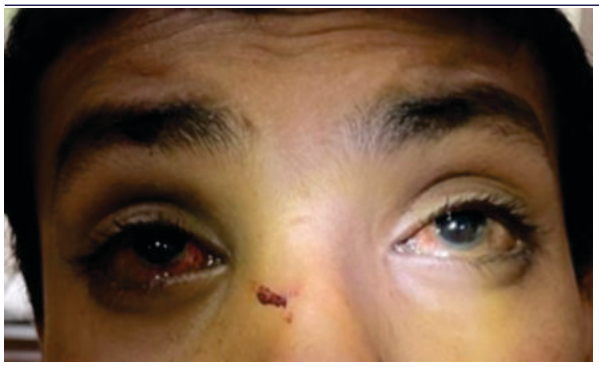
VKC was diagnosed by symptoms (bilateral itching with redness) and signs (Horner-Trantas dots, papillae on the upper tarsal conjunctiva, there may be corneal erosions). Complete ophthalmic examinations were performed which included best corrected visual acuity, slit-lamp biomicroscopy, fluorescein staining, and fundus examination. Study participants were told to discontinue all their medications one week before beginning the treatment. The participants were instructed to apply Tacrolimus 0.1% dermatologic ointment (Astellas Toyama, Toyama, Japan) in the inferior conjuctival fornix of each eye. During treatment, patients were told about follow up for further evaluation in 1-week,4 weeks, 6 weeks, and then every 6 months.

Using a 4-grade scale (0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe), the main outcomes were rated according to the severity of the signs and symptoms at baseline (before treatment) and at each visit as shown in Table 1.

Table 1 showing grading scales of clinical signs.

Sign	Score	Definition
Conjunctival hyperemia	3	Diffuse dilated blood vessels over entire bulbar conjunctiva
	2	Dilatation of many vessels
	1	Dilatation of few vessels
	0	None
Papillae	3	Papillae size >0.3 mm
	2	Papillae size 0.2-0.3 mm
	1	Papillae size <0.2 mm
	0	None
Trantas dots	3	6 dots
	2	4-6 dots
	1	1-3 dots
	0	None
SPK	3	Total corneal surface
	2	More than half corneal surface
	1	Less than half corneal surface
	0	None

SPK: Superficial punctate keratopathy



(This picture was taken at Dept. Of Ophthalmology in M.L.B. Medical College, Jhansi, where this 14 year old boy presented to our OPD wing with Severe VKC presenting with C/O watering, redness, watering and itching from Both Eyes).

Statistical Analysis

After data collection completion, data analysis was conducted using the SPSS version 19.0 (IBM Corporation, Armonk, NY, USA). Discrete variables such as symptoms and signs of vernal keratoconjunctivitis were expressed as counts (percentage)

RESULTS

There were 50 patients with refractory VKC comprising 39 (78%) male and 11(22%) female patients. The median age was 12 years. All patients exhibited bilateral VKC at presentation that was resistant to standard topical medications such antihistamines, mast-cell stabilisers,steroids and decongestants. The primary symptoms that presented were itching in about 42(84%) patients, redness in about 39(78%), discharge in 25(50%), foreign body sensation in 22(44%) patients.Clinical signs included conjunctival hyperemia in 42 (84%) patients, conjunctival papillary hypertrophy in 30(60%) patients, Trantas dots in 22 (44%)patients and superficial punctuate keratitis in 32 (64%) patients. In mild cases, the improvement in clinical indications was seen after two weeks, while in severe cases, it took four weeks to start seeing improvement.

Table 2 shows Effect of topical tacrolimus 0.01% on symptoms of vernal keratoconjunctivitis

Symptoms	No. Of Affected Patients	No. Of Improved Patients
Itching	42	40
Redness	39	35
Discharge	25	24
Foreign body sensation	22	22

Table 3 shows the effect of topical tacrolimus 0.01% on signs of vernal keratoconjunctivitis

Signs	No. Of Affected Patients	No. Of Improved Patients
Conjuctival Hyperemia	42	32
Conjuctival papillary hypertrophy	30	15
Superficial punctuate keratitis	32	28
Trantas Dots	22	18

DISCUSSION

Patients with VKC who are unresponsive to traditional treatments can get benefit from Tacrolimus[14]. Similar to earlier studies, almost all of the patients in our trial shown remarkable improvements in inflammatory signs and symptoms without experiencing major negative effects. Despite the fact that none of our patients needed other medications, such as topical steroids, for more alleviation, tacrolimus had to be used on a long-term basis to prevent disease recurrence.

Ohashi et al.utilised tacrolimus 0.1% ophthalmic suspension twice daily for 4 weeks in 21 patients with AKC and 7 patients with VKC in a multicenter, randomised clinical trial and compared the results to a placebo group. After 4 weeks of treatment, they 17 discovered that the symptoms in the treated eyes had significantly improved[15]. Tacrolimus 0.1–1% eye drops were used in a clinical research by Sengoku et al.16 to significantly reduce the symptoms of patients with refractory VKC[16].

The symptoms of most of the patients in our study were relieved 4 weeks after beginning tacrolimus ointment treatment. Allergic symptoms recurred in those patients who discontinued Tacrolimus. when acute exacerbations of AKC and VKC make topical tacrolimus treatment inadequate, treatment of allergic inflammation needs to be augmented with a steroid regimen. Notably, Miyazaki et al reported on the significant effects.

Although the specifics are unknown, there is significant worry regarding the negative effects of chronic usage of tacrolimus ophthalmic suspension 0.1%. The negative effects since the results from this study are comparable to those that have already been published it may be concluded that continuous use of tacrolimus ophthalmic suspension 0.1% does not cause any particular side effects. Tacrolimus ophthalmic suspension 0.1% was necessary for lengthy treatment in patients with severe VKC who developed enormous papillae in the upper tarsal conjunctiva. Significant palpebral conjunctival symptoms, like large papillae, may be a risk factor for treatment resistance, it was suggested. Tacrolimus skin ointment is a safe and efficient treatment for patients with refractory VKC, according to data from the literature[17]. However, topical tacrolimus therapy alters the local immune response at the ocular surface, which theoretically could lead to an increase in risk with infections.[18] An increased risk of herpes simplex virus keratitis linked to topical tacrolimus may be of special concern. As a result, care must be taken to during long-term treatment, avoid potential recurrence[14,18]. None of our patients developed herpetic keratitis.

Patients with atopic dermatitis receiving tacrolimus skin ointment may have a higher chance of developing T-cell lymphoma[19]. But there isn't any proof in the literature of a rise in the risk of cancer brought on by calcineurin inhibitor topical therapy. No instances in our study underwent malignancy over the follow-up period up to 12 months[20,21]

CONCLUSION

Our study suggests that tacrolimus has equal potentials to be used as first line drugs in vernal keratoconjunctivitis. Since the effect of drugs is short lasting so the duration of treatment needs to be investigated further with respect to drug concentration to maintain the phase of remission. The major limitation of this study is small sample size. This study found tacrolimus to be clinically better drug for treatment of VKC and is cost effective too. In our study, we used 0.1% topical tacrolimus twice daily, which may increase compliance. Tacrolimus may be thought of as a first-line treatment for patients with VKC due to its great efficacy and safety even after prolonged use.

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