e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2024; 16(8); 763-767

Original Research Article

Therapeutic Efficacy of Tacrolimus in Vernal Keratoconjunctivitis in a Tertiary Care Center

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Received: 25-05-2024 / Revised: 23-06-2024 / Accepted: 25-07-2024
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Conflict of interest: Nil

Abstract:

Objectives: The present study was to evaluate the therapeutic efficacy of tacrolimus in vernal keratoconjunctivitis patients of different age group in a tertiary care center.

Methods: Tacrolimus 0.03% ophthalmic solution was administered to patients twice daily after discontinuation of all previous topical medications. The duration of treatment ranged from 1 month to 9 months. The variation in the duration of treatment with topical tacrolimus solution was attributed to the differences in the response to treatment among patients. The treatment was continued during active disease with periodic attempts to withdraw tacrolimus eyedrops whenever possible. On the last follow-up visit, all patients were evaluated for improvement in subjective symptoms, including itching, redness, foreign body sensation, and discharge. They were also evaluated for improvement in clinical signs, including conjunctival hyperemia, conjunctival papillary hypertrophy, limbal infiltration, Trantas dots, and superficial punctate keratopathy.

Results: A total of 50 patients with age group 5 to 45 years were included. Most of the patients were in age group of 5 to 15 years 20(40%) and 16 to 25 years 14(28%). Most of the cases 36(72%) were males. The main presenting symptoms were itching in 42(84%) patients, redness in 40(80%) patients, discharge in 28(56%) patients, and foreign body sensation in 11(22%) patients. Each of the symptoms were significantly ($p<0.05$) reduced by the application of topical tacrolimus 0.03%. Clinical signs included conjunctival hyperemia in 34(68%) patients, conjunctival papillary hypertrophy in 29(58%) patients, Trantas dots in 28(56%) patients, limbal hypertrophy in 31(62%) patients, and superficial punctuate keratitis in 13(26%) patients. Each of the clinical signs were significantly reduced ($p<0.05$) by the application of topical tacrolimus 0.01%. which was evaluated in last follow up.

Conclusions: The male childhood to young age populations is preponderance to VKC. And the 0.03% topical tacrolimus is the most effective for treatment of clinical signs and symptoms of all levels (mild to severe) of Vernal keratoconjunctivitis patients.

Keywords: VKC, 0.03% Topical Tacrolimus, Age Group.

Introduction

VKC is a chronic, bilateral (though at times asymmetrical), seasonally exacerbated, allergic inflammation of the tarsal conjunctiva, bulbar conjunctiva, or both. It is more common in children and young adults [1]. It is categorized into three types: tarsal, limbal, and mixed. Patients with VKC complain of itching, watering, burning, perceived redness, foreign-body sensation, discharge, and photophobia. Signs include inflamed limbus, tarsal papillae, punctate keratitis, hyperemia, and Horner–Trantas dots [2].

The prevalence of conjunctivitis varies according to its condition type. Allergic conjunctivitis is common, affecting 15–40% of the US population, and is more prevalent in the spring and autumn [3]. It is a recurrent inflammatory disease that can be stratified into mild forms—seasonal conjunctivitis, perennial conjunctivitis—and severe forms—vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis [4].

Tacrolimus is a strong, nonsteroidal immune suppressant isolated from Streptomyces tsukubaensi [5]. It binds to FK506-binding proteins in T-lymphocytes and inhibits calcineurin activity. Calcineurin inhibition suppresses dephosphorylation of the nuclear factor of activated T-cells and its transfer into the nucleus, which suppresses the formation of T-helper (Th) 1 (interleukin [IL]-2, interferon γ) and Th2 cytokines (IL-4, IL-5) [6]. Tacrolimus also inhibits histamine release from mast cells, which is thought to

alleviate allergic symptoms [7]. Tacrolimus is up to 100 times more potent than cyclosporine [5,8]. Tacrolimus ointment is used widely for the treatment of atopic dermatitis. Topical tacrolimus (0.02–0.1%) has also been used to treat giant papillary conjunctivitis, atopic keratoconjunctivitis (AKC), and VKC with good results [9,10]. Objective of our study was to evaluate the therapeutic efficacy of tacrolimus in vernal kerato-conjunctivitis patients in a tertiary care center.

Material & Methods

The present study was conducted in the Department of Ophthalmology, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar during a period from April 2023 to December 2023.

A total of 50 patients of vernal keratoconjunctivitis with irrespective of age and sex were enrolled. Patients with known hypersensitivity to tacrolimus; patients with infectious eye diseases, including trachoma; pregnant or lactating women; patients on systemic therapy for other atopic diseases; and patients who had recent surgical procedures were excluded from the present study.

The diagnosis of VKC was based on the clinical findings of symptoms of itching, redness, discharge, and foreign body sensation and signs of conjunctival hyperemia, papillae in the upper palpebral conjunctiva, limbal infiltration, Trantas dots, and superficial punctate keratopathy. Each clinical symptom and sign were assessed and the severity was graded as 0 (normal), 1+ (mild), 2+ (moderate), or 3+ (severe). Clinical assessment was carried out before, during, and on the last visit after treatment.

Procedures: Tacrolimus 0.03% ophthalmic solution was administered to patients twice daily after discontinuation of all previous topical medications. The duration of treatment ranged from 1 month to 9 months. The variation in the duration of treatment with topical tacrolimus solution was attributed to the differences in the response to treatment among patients. The treatment was continued during active disease with periodic attempts to withdraw tacrolimus eyedrops whenever possible. On the last follow-up visit, all patients were evaluated for improvement in subjective symptoms, including itching, redness, foreign body sensation, and discharge. They were also evaluated for improvement in clinical signs, including conjunctival hyperemia, conjunctival papillary hypertrophy, limbal infiltration, Trantas dots, and superficial punctate keratopathy.

Improvement in each symptom or sign was defined as control of symptoms and signs without the need for an additional therapy. Ocular surface temperature was measured in selected patients who had serum levels of tacrolimus and IgE. Tacrolimus eyedrops were compounded by adding balanced salt solution to 1,000 µg tacrolimus capsule to achieve 0.01% concentration. No preservative was added. The final pH of the compounded tacrolimus solution was 6. The compounding of the eyedrops was carried out under sterile condition and laminar flow hood. The patients were asked not to use the tacrolimus eyedrops after 1 month from opening the bottle. They were strictly instructed to keep the bottle clean and to keep it in the refrigerator. Cultures of selected tacrolimus 0.01% eyedrops were carried out at days 0 and 30 that revealed no growth. Response to treatment was assessed based on at least 1-grade reduction in severity compared to values before the treatment. The improvement in the clinical signs was noted after 2 weeks of initiation of therapy in mild cases and after 4 weeks of initiation of therapy in severe cases. The mean duration of treatment was 6 months.

Statistical Analysis

Data was analysed with the help of latest version of SPSS software. Mean and standard deviation were calculated. Chi square test was applied. P-value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

Results

A total of 50 patients with age group 5 to 45 years were included in the present study. Most of the patients were in age group of 5 to 15 years 20(40%) and 16 to 25 years 14(28%). Most of the cases 36(72%) were males.

Table 1: Age wise distributions of VKC patients

Age group	No. of patients	Percentage
5-15	20	40%
16-25	14	28%
26-35	10	22%
36-45	6	14%
Total	50	100%

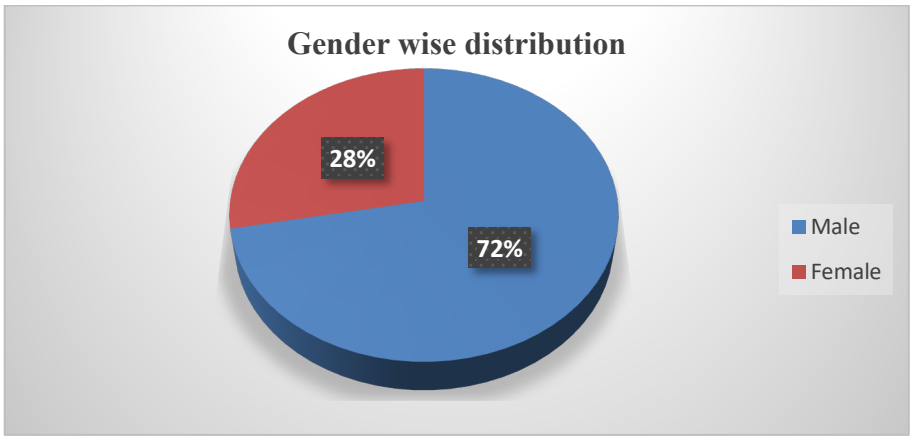

Figure 1: Gender wise distribution of VKC patients

The mean visual acuity at presentation was 20/30. The mean intraocular pressure at presentation was 13 mmHg. On presentation, all patients had bilateral VKC that was refractory to conventional topical treatment, including antihistamines, mast-cell stabilizers, decongestants, cyclosporine, and steroids.

Table 2: Therapeutic response of topical tacrolimus 0.01% on symptoms of vernal keratoconjunctivitis

Symptoms	No. VKC patients	Improved patients	P-value
Redness	40	28(70%)	0.000
Itching	42	33(78.57%)	0.001
Discharge	28	20(71.43%)	0.002
Foreign body sensation	11	7(63.63%)	0.030

The main presenting symptoms were itching in 42(84%) patients, redness in 40(80%) patients, discharge in 28(56%) patients, and foreign body sensation in 11(22%) patients. Each of the symptoms were significantly ($p<0.05$) reduced by the application of topical tacrolimus 0.03%. Which was evaluated in last follow up.

Table 3: Therapeutic response of topical tacrolimus 0.01% on signs of vernal keratoconjunctivitis.

Signs	No. VKC patients	Improved patients	P-value
Conjunctival papillary hypertrophy	29	5(17.25%)	<0.000
Conjunctival hyperemia	34	24(70.59%)	0.000
Limbal hypertrophy	31	25(80.65%)	0.010
Trantas dots	28	21(75%)	0.005
Superficial punctate keratitis	13	9(69.23%)	0.033

Clinical signs included conjunctival hyperemia in 34(68%) patients, conjunctival papillary hypertrophy in 29(58%) patients, Trantas dots in 28(56%) patients, limbal hypertrophy in 31(62%) patients, and superficial punctuate keratitis in 13(26%) patients. Each of the clinical signs were significantly reduced ($p<0.05$) by the application of topical tacrolimus 0.01%. which was seen in last follow up.

The mean visual acuity on the last visit was 20/24. The mean intraocular pressure on the last visit was 12 mmHg. 2(4%) out of 50 patients reported mild irritation and/or transient burning sensation at the time of instilling the eyedrop, which subsided during treatment. 1(2%) patient developed ocular infection.

Discussions

Patients with VKC present with a typical set of complaints comprising intense itching, watering, burning sensation, ropy discharge, and a red eye. Typical conjunctival signs consist of hyperaemia, giant papillae on superior palpebral conjunctiva, papillary hypertrophy or Horner–Trantas dots that consist of accumulation of gelatinous inflammatory infiltrates around the limbus [11]. The disease may sometime lead to corneal involvement in form of superficial keratitis, shield ulcer or corneal vascularization that causes foreign body sensation, pain and photophobia6 Although, VKC is a self-limiting disorder resolving around puberty, the characteristic episodes of exacerbation and remission of the inflammatory phase of the disease is generally bothersome [1]. Besides increased risk of vision threatening complications, the quality of life gets severely compromised [12]. The treatment options of VKC usually include anti-histamines, mast cell stabilizers and non-steroidal anti-inflammatory offered in different permutations and combinations [13]. Moderate to severe sight-threatening cases frequently need topical steroids, or but being chronic disease, long-term use of steroids has notable side effects like glaucoma, cataract and secondary infections [14]. To prevent such complications, steroid-sparing agents like immunosuppressants are a better alternative [15].

They not only inhibit histamine release from mast cell and basophils but also block proliferation of Th2 lymphocyte and subsequent interleukin-2 production.10 Two members evaluated in this category are tacrolimus and cyclosporine with encouraging results [16,17]. Potency of tacrolimus is reported to be 100 times more than cyclosporine-A. For this reason, it has been useful even in cases refractory to cyclosporine [17,18]. Besides being used in steroid resistant, it has even been used as first line therapy in VKC [19]. Strength of topical tacrolimus being used in clinical practice for the treatment of VKC ranges from 0.005% to 0.1% [20].

In the present study, we were used 0.03% topical tacrolimus for the treatment of vernal keratoconjunctivitis patients. We enrolled 50 VKC patients with age group of 5 to 45 years. Most of the VKC patients (40%) were in age group of 5-15 years. VKC was commonly seen in (72%) male.

Fiorentini S F et al. [21] stated in their study, VKC affects children between 3 and 16 years of age, though it may appear earlier and continue into adulthood. In most cases, symptoms resolve at puberty and the prevalence is more in males. Epidemiological studies do not consider it as a seasonal disease since frequently this persists throughout the year with increase intensity in warmer weather [21]. In many parts of Africa, Latin America and Asia, VKC represents an important cause of hospital attendance, ranging from 3% to 6% of patients of all ages, rising to 33% and 90% in children and adolescents [22,23].

In the present study, there was statistically significant improvement in symptoms and signs of VKC. In addition to conjunctival signs, there was significant improvement in limbal hypertrophy, Trantas dots, and corneal signs such as corneal punctate epithelial erosions. Improvement in corneal signs was associated with a change in visual acuity from 20/30 to 20/24 following treatment with topical tacrolimus 0.03%. Among the various clinical signs of our patients, conjunctival papillary hypertrophy was found to have the least response to topical tacrolimus 0.03%. However, previous studies reported improvement in conjunctival papillary reaction. These studies evaluated the efficacy of a higher concentration of topical tacrolimus (0.1%) and also included patients with concomitant use of topical steroids [22, 24].

In the study by Ohashi et al with 0.1% twice daily dose, showed improvement in symptoms of both atopic keratoconjunctivitis and VKC [22]. In another study by Miyazaki et al the effects of 0.02% Tacrolimus ointment for refractory ocular surface inflammatory diseases have been reported to presents the lower incidence of elevated intraocular pressure in steroid responders and there were no adverse side effects during 2–26 months of continuous treatment, same as in our study, with the mean follow-up of 6 months [25].

The majority of the studies have used 0.1% concenteration [22, 26]. Some other studies evaluated lower concentrations of tacrolimus, including 0.02% and 0.03% [11, 27]. The lowest concentration of topical tacrolimus evaluated for treatment of VKC was 0.005%. The authors found that topical 0.005% tacrolimus eyedrop seemed to be a safe and effective treatment for steroid-resistant refractory VKC [28]. However, it was prescribed four times daily. In our study, we used 0.03% topical tacrolimus twice daily, which may increase compliance. Despite the efficacy of topical tacrolimus, almost all patients reported immediate recurrence of symptoms on discontinuation of therapy.

In the present study, intraocular pressure remained normal and the rest of eye examination had no clinical or structural changes. One patient developed infectious conjunctivitis that responded well to antimicrobial therapy. None of the cases developed malignancy throughout the follow-up period.

Tacrolimus has been documented safe for longterm use. However, there are reports of complications like stinging, burning, watering, ocular pain or sometimes herpetic keratitis [29]. Our study found only mild burning and stinging sensation in two patients. The strength of our study was the management of VKC as a chronic eye condition using a single agent with a high success rate. Small sample size and short follow-up were the major limitations of our study.

Conclusions

The present study concluded that the male childhood to young age populations is preponderance to VKC. And the 0.03% topical tacrolimus is the most effective for treatment of clinical signs and symptoms of all levels (mild to severe) of Vernal keratoconjunctivitis patients.

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