Original Article

The efficacy of Topical Tacrolimus Ointment 0.03% as Monotherapy for the Treatment of Severe Cases of Vernal Keratoconjunctivitis

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Abstract

Purpose: The aim of this study was to evaluate the efficacy of Tacrolimus ointment 0.03% as monotherapy for the treatment of severe cases of Vernal Keratoconjunctivitis

Setting DAR EL TAMUS private ophthalmology clinic in Benghazi Libya

Methods: A prospective observational study of 32 eyes of 16 patients was carried out in the period from (01-01 2017) to (31-12- 2017).

All the patients attended DAR EL TAMAIUS private ophthalmology clinic in Benghazi Libya, the clinical subjective ocular signs and the objective ocular symptoms of severe cases of vernal Keratoconjunctivitis were assessed.

All patients were treated only with Tacrolimus ointment 0.03% applied to the conjunctival sac once at night in each eye for consecutive 8 weeks, where the signs and symptoms of vernal Keratoconjunctivitis followed prospectively at 1st week, 1st month, 2nd month, 3rd month, 6th month and 12th month.

Result: By the end of 8th weeks there was a dramatic relief in the total score of symptoms and signs from baseline were recorded at each visit and no need for further treatment up to the end of this study period 12th months. No relevant adverse effects were reported except mild burning sensation.

Conclusion:Tacrolimus ointment 0.03% was well tolerated and effective as monotherapy in reducing the signs and symptoms of severe cases of vernal Keratoconjunctivitis and a valuable treatment option for this condition that may substitute for steroids treatment with its adverse effect.

Keywords: Efficacy Topical Tacrolimus Monotherapy Vernal Conjunctivitis

Introduction

Vernal keratoconjunctivitis (VCK) is a chronic recurrent allergic inflammation of the conjunctiva affecting children and young adults. It shows more affinity towards males and is seen commonly in the hot, dry regions of the Middle East, Mediterranean basin, Africa, Japan and India. [1]

Patients usually complain of severe itching, tearing, redness of the eyes, and photophobia. Clinically, it is characterized by the presence of papillary hypertrophy of the palpebral and/or the limbal conjunctiva, with conjunctival hyperemia, Horner Trantas dots, and mucous discharge. [2]

The pathogenesis of VKC is multifactorial in which Th2 derived cytokines (IL-3, IL-4, IL-5 and IL-13) are increased; in addition, Th2 lymphocytes stimulate B lymphocytes leading to mast cell, eosinophil and neutrophil activation through IgE production. [3]

VKC can be treated by topical antihistaminics and dual action agents (e.g. olopatadine), but moderate to severe forms need to be treated with corticosteroids, which may often need to be taken for long periods of time. This is associated with visual morbidities such as glaucoma and cataracts.. [4]

This led to the use of drugs with potent anti-inflammatory effects and less steroid induced side-effects such as cyclosporine A and tacrolimus.

Tacrolimus is an immunomodulator with a much more potent immunosuppressive effect than cyclosporine and better tolerance profile. It is a macrolide, isolated from the bacteria Streptomyces tsukubaensis. It acts by suppressing the activation of T-cells, the proliferation of B –cells, and the formation of inflammatory mediators (cytokines) especially interleukin2. [5]

Studies had reported promising results in the treatment of VCK with tacrolimus; [6,7,8,9] and therefore this study was designed to evaluate the efficacy of Tacrolimus ointment 0.03% as monotherapy for the treatment of severe cases of vernal keratoconjunctivitis.

Methods:

A prospective study conducted at Dar El Tamaius Private Ophthalmology Clinic in Benghazi Libya, during the period from the 1st January 2017 to the 31st December 2017.

According to the tenets of the Declaration of Helsinki for research in human subjects, written informed consent was obtained from all the patients, or their legal representatives before inclusion in the study. In addition official ethics approval was obtained from

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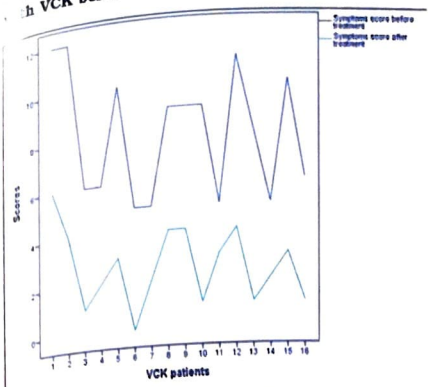
ure.1 Total score of symptoms in sixteen patients h VCK before and after treatment



the Martyr Sohail Al Atrash Eye Hospital authorities. Only patients with severe VKC were included in this study.

VKC was defined as the presence of chronic or recurrent conjunctivitis characterized by itching, photophobia, watering, and foreign body sensation in the presence of conjunctival hyperemia, keratitis, giant papillae on the upper tarsal plate and/ or limbitis (gelatinous limbal infiltration or Horner- Trantas dots).

Study exclusion criteria were cases with mild to moderate VCK, patients who had received systemic or sub-conjunctival corticosteroids, patients with a history of herpetic keratitis, glaucoma or ocular hypertension due to previous therapy, developmental cataract or any systemic illness.

Complete ophthalmic examination was performed, including visual acuity, slit-lamp biomicroscopy, fluorescein staining, fundoscopy, and tonometry.

A protocol for the scoring of signs and symptoms, which was modified from clinical trials with similar methods and objectives, was applied. [10,11,12]

Grading the severity of the symptoms of itching, lacrimation, photophobia and a foreign body sensation was done as follow: 0 (none), 1 for mild (occasional symptoms), 2 for moderate (frequent symptoms), and 3 for severe (constant symptoms).

Also, the severity of the signs (conjunctival hyperemia, keratitis, giant papillae on the upper tarsal plate and/ or limbitis) was evaluated and graded as follows: 0 (none), 1 (mild), 2 (moderate), and 3 severe. Table 1

The whole evaluation was based on the examination of both eyes.

All patients were treated only with tacrolimus ointment 0.03% (Astellas Pharma. Europe B.V), patients were instructed to apply the ointment to the conjunctival sac once at night in each eye for eight consecutive weeks, and the signs and symptoms of vernal keratoconjunctivitis were then followed prospectively at the first week, first month, secondmonth, third month, sixth month, and finally the twelfth month.

Side effects of treatment were monitored by measuring visual acuity, intraocular pressure, presence of secondary infection, patient tolerance to the new treatment and other complications if any emerged. At the end of the second month, the change in the mean of total scores of signs and symptoms from baseline was recorded.

STATISTICAL ANALYSIS

Data were presented as frequencies and mean ±SD. Statistical analyses were performed using SPSS version 20. A nonparametric paired-samples test

Table1: Severity scores for signs of VKC

SIGNS	SEVERITY SCORE
CONJUNCTIVAL HYPEREMIA	3 Impossible to distinguish individual blood vessels
	2 Dilatation of many vessels
	1 Dilatation of several vessels
	0 None
PAPILLAE	3 Giant papillae predominance on the upper tarsal conjunctiva
	2 Thickened conjunctival surface with many papillae (some giant) on the upper tarsal conjunctiva
	1 Prominent papillary reaction in the upper tarsal conjunctiva with thickening, impeding observation of the vascular pattern
	0 Micropapillae of the upper tarsal conjunctiva
LIMBITIS	3 Horner-Trantas dots
	2 Limbal hyperemia and papillae
	1 Limbal hyperemia
	0 No limbal inflammatory activity
KERATITIS	3 Shield ulcer or corneal erosion
	2 Exfoliation superficial punctate keratitis
	1 Superficial punctate keratitis
	0 None

Table 2: Mean of the total score of signs and symptoms in patients with vernal-keratoconjunctivitis before and after treatment with topical 0.03% tacrolimus ointment.

	Before treatment	After treatment	P-value
Symptoms			
Mean of total score	8±2.58	2.56±1.59	<.0001
Signs			
Mean of total score	8.19±1.10	2.19±1.22	<.0001

* P < .05 is statistically significant

(Wilcoxon signed-ranks) was used to statistically analyze the changes in the mean of total score of symptoms and signs after treatment with topical 0.03 % tacrolimus.

P-values of 0.05 or less were considered as statistically significant.

Results

A total number of 16 patients was involved in this study with a mean age of 11.81±4.06 years (range,5-18 years); males were 12 in number (75%), and females were 4 (25%).

Out of these 16 patients; 6 (37.5%) had the palpebral form, and 10 (62.5%) had the mixed form.

The mean duration of VKC symptoms was 3.75± 1.77 years (range,1-7 years) and mean follow up time was 9.25 ±3.76 months (range, 3-12 months).

A few patients reported a mild burning sensation on using the treatment; but all could tolerate it and none stopped the drug.

By the end of eight weeks a dramatic decrease in the total score of symptoms and signs in the was noted in all sixteen patients (Figures1and2).

The improvement in the mean of the total score of symptoms and signs was statistically significant with P<.0001. (Table2).

Discussion

The treatment of severe forms of VKC is usually done by the use of topical corticosteroids which carry a risk of ocular complications such as glaucoma and cataracts. This necessitated the introduction of steroid- sparing drugs like tacrolimus.

Tacrolimus has emerged as an effective and safe drug that can control immune reactions responsible for the pathogenesis of VKC. [13-18]

This study was done to evaluate the efficacy of tacrolimus ointment 0.03% as monotherapy for the treatment of severe cases of vernal keratoconjunctivitis. The changes in the clinical symptoms and signs were assessed in sixteen patients before and after the use of the ointment once at night for two months. There was a statistically significant improvement (P<.0001) in the mean of the total score of symptoms and signs at the end of the second month.

There was no recurrence reported after stopping the treatment with a mean follow up time of 9.25 ±3.76 months; although previous studies showed that symptoms recur after stopping treatment and advised to either tapper it, [5], or increase the duration of its use to decrease recurrence. [19]

No side effects were noted except for a mild burning sensation. This may have been due to the nature of the ointment which is a dermatological preparation (Protopic®) and not an ophthalmic preparation (as it is not available in Libya), and is consistent with the reports from other researchers. [14,20,21]

Many studies used different concentrations of tacrolimus with more frequent applications, but this study used the 0.03% concentration applied only once at night which had the advantage of increasing the compliance of patients. [22-24]

Conclusion

Tacrolimus ointment 0.03% is an effective and safe drug that can be used to alleviate the symptoms and signs of severe cases of VKC, and as an alternative to topical corticosteroids.

Since this study was limited by a small sample size and the absence of a control group; further studies having a control group and a larger number of patients need to be done to confirm our results.

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