Tacrolimus Ointment for Treatment of Vernal Keratoconjunctivitis

Abdulrahman M. Al-Amri, Aleem Gulzar Mirza, Ahmed Mossa Al-Hakami

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 20 patients (40 eyes) with severe VKC, who were treated with tacrolimus 0.1% ointment. The mean age of the patients was 18.25 ± 4.2 years (range, 9–31 years). Each patient completed a follow-up period of at least 24 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. Five patients discontinued treatment due to a severe burning sensation and were 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 used to control disease activity. However, adverse effects could cause poor patient compliance.

Key words: Allergy, Tacrolimus, Vernal Keratoconjunctivitis

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a bilateral, chronic inflammation of the conjunctiva that predominantly affects children between 3 and 16 years of age. It usually resolves at puberty, but can continue into adulthood. Although the name vernal suggests a seasonal, springtime occurrence, this allergic condition frequently persists throughout the year and usually increases in intensity in warmer weather.1,2 Patients with VKC experience significant morbidity.3 Symptoms include intense itching, tearing, mucous secretions, and photophobia.4 Common conjunctival signs of VKC are hyperemia, papillary hypertrophy, giant papillae, discharge, and trantas dots.5 Tacrolimus is a strong, nonsteroidal immune suppressant isolated from Streptomyces tsukubaensis.6 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).7 Tacrolimus also inhibits histamine release from mast cells, which is thought to alleviate allergic symptoms.8 Tacrolimus is up to 100 times more effective than corticosteroids at blocking cell proliferation and preventing the release of cytokines and chemotactic factors.9

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more potent than cyclosporine.\textsuperscript{9-11} 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\textsuperscript{12-18} with good results. Furthermore, a tacrolimus 0.1% ophthalmic suspension has been used for the treatment of AKC and VKC with only 4 weeks of follow-up.\textsuperscript{18}

The purpose of this study was to evaluate the long-term clinical outcomes of tacrolimus ointment as a treatment for refractory VKC.

MATERIALS AND METHODS

This prospective, nonrandomized, noncontrolled case series study followed 40 eyes from 20 patients with active VKC refractory to conventional treatment. The Institutional Review Board of King Khalid University, Abha, Saudi Arabia approved the study protocol. Patients were recruited from Magrabi Aseer Hospital after written informed consent was obtained. This study adhered to the tenets of the declaration of Helsinki.

All study participants had active disease and were steroid dependent, despite treatment with cyclosporine or conventional treatments such as antihistamines, mast-cell stabilizers, topical nonsteroidal anti-inflammatory drugs, and topical steroids. Exclusion criteria were coexisting conjunctival disorders, chemical injury, Stevens-Johnson syndrome, corneal diseases, uveitis, ocular infections, and contact lens use, a history of systemic nonsteroidal anti-inflammatory or immunosuppressive drug use, and ocular surgery in the previous 3 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, and applanation tonometry.

Study participants discontinued all medications, 1-week before beginning treatment. All participants were instructed to apply tacrolimus 0.1% dermatologic ointment (Astellas Toyama, Toyama, Japan) to the inferior conjunctival fornix of each eye. The dose for severe AKC was once daily for 1-month followed by a taper to every other day for 1-week; then twice a week for 1-week; then once a week. The dose for moderate AKC was once every other day for 1-month followed by a taper to twice a week for 1-week; then once a week. The dose for mild AKC was twice a week for the 1\textsuperscript{st} month and then once a week. 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 tacrolimus 0.1% ointment. Patients were followed for a mean duration of 27.20 ± 0.70 months [Table 3].

There were significant improvements in the clinical signs and symptoms of disease after starting treatment with tacrolimus [Table 4]. Itching was the first symptom to decrease. At baseline, 17 of 20 patients complained of itching (14 severe, 3 moderate), however, after 1-week of treatment, all patients improved. After 6 weeks, all patients achieved complete resolution of their symptoms of itching [Table 3]. At the end of the follow-up period, all patients remained asymptomatic but continued to apply topical tacrolimus ointment. No additional

**RESULTS**

Forty eyes from 20 patients (18 males) with bilateral VKC (mean ± standard deviation duration; 61.25 ± 4.24 months) were included in this study. The mean age was 23.14 ± 3.8 years [Table 2]. All patients had active, perennial, symptomatic disease that was refractory to medication, including antihistamines, mast-cell stabilizers, topical cyclosporine, and steroids. Itching was the most prominent symptom (17/20); other complaints included redness and foreign body sensation. All eyes had lid thickening, conjunctival hyperemia, and papillary conjunctivitis, and 10% of patients had a history of atopy. After starting treatment with tacrolimus 0.1% ointment, patients were followed for a mean duration of 27.20 ± 0.70 months [Table 3].

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<th>Table 1: Grading scales of clinical signs</th>
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SPK: Superficial punctate keratopathy

All data were analyzed using SPSS (IBM Corp, New York, NY, USA). Analysis of variance and the Wilcoxon test were to analyze changes in the mean scores of signs and symptoms following treatment with topical tacrolimus 0.1% ointment. \( P \leq 0.05 \) was considered statistically significant.
of itching [Table 3]. When Miyazaki et al.\textsuperscript{19} used tacrolimus 0.02% ointment to treat 5 patients with AKC and 1 patient with VKC who were refractory to conventional treatment, there was a marked improvement in symptoms within 2–4 weeks of treatment.

The symptoms of most of the patients in our study were relieved 4 weeks after beginning tacrolimus ointment treatment [Table 3]. Allergic symptoms recurred in all patients who attempted to discontinue tacrolimus. Consequently, they were kept on treatment for the entire follow-up period. Although a risk of T-cell lymphoma in patients using topical tacrolimus has been reported,\textsuperscript{20} there is insufficient epidemiological evidence to determine if topical calcineurin inhibitors can cause malignancy.\textsuperscript{21} Moreover, there is a scarcity of data regarding the optimal dose and duration of treatment. In fact, the blood concentration profiles of patients using tacrolimus 0.1% ointment were below quantifiable limits (0.5 ng/ml) in the majority of patients.\textsuperscript{22} In our study, no malignancies occurred during the 2 years follow-up period, and the risk of developing malignancy after the application of topical tacrolimus 0.1% ointment is extremely low. Results from the available literature suggest that tacrolimus skin ointment is a safe and effective treatment for patients with refractory VKC.\textsuperscript{23} The small sample size and the lack of randomization and a control group were the main limitations of the current study.

**CONCLUSION**

Tacrolimus, 0.1% ointment, was effective in controlling the clinical signs and symptoms of severe VKC refractory to topical antihistamine agents and topical cyclosporine. Our results demonstrate that tacrolimus is a promising alternative for the treatment of severe VKC. Further randomized controlled studies are required to evaluate the appropriate concentration and dosage of topical tacrolimus, as well as the long-term systemic safety of this medication.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**