



ORIGINAL ARTICLE

Efficacy and safety of topical tacrolimus 0.03% ointment in thygeson superficial punctate keratitis.

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ABSTRACT... Objective: To assess the effectiveness of topical tacrolimus (TCL) 0.03% dermatological ointment in the treatment of patients with Thygeson superficial punctate keratitis. **Study Design:** Retrospective Review. **Setting:** Eye OPD of Qazi Hussain Ahmad Medical Complex, Nowshera. **Period:** Jan 2019 to Jan 2021. **Material & Methods:** Twelve patients with Thygeson superficial punctate keratitis (TSPK) were included retrospectively by reviewing their medical records. Eight patients were unresponsive to topical steroids and/or lubricants. Diagnosis was made based on the history and clinical findings. All patients were treated with topical tacrolimus 0.03% dermatological ointment twice a day. We took the following subjective features for assessment i.e. watering of eyes and light sensitivity, while for objective features reduction in the no. of epithelial keratitis, healing of keratitis, surface leveling of the lesion and reduced corneal staining with fluorescein. **Results:** Out of total 12 patients, 4 were male and 8 females with a mean age of 21 ± 9.42 years. All were having bilateral involvement. Duration of therapy ranged from 02 to 40 weeks (mean 08 weeks). All patients improved symptomatically with resolution of watering of eyes and light sensitivity, while in ocular signs we noted improvement in corneal lesions. The efficacy of therapy was observed 3 days, post application among all patients. No, side effects reported in any of our patients treated with topical TCL dermatological ointment. **Conclusion:** The safety and efficacy of topical tacrolimus 0.03% dermatological ointment has been observed in patients with Thygeson superficial punctate keratitis who were refractory to conventional therapy.

Key words: Dermatological, Ointment, Topical Tacrolimus, Thygeson Superficial Punctate Keratitis.

INTRODUCTION

In 50s, Phillips Thygeson diagnosed Thygeson superficial punctate keratitis (TSPK) as long-lasting corneal condition involving both eyes with the appearance of pin point epithelial erosions diffusely spread over the entire cornea. These lesions are numerous and well demarcated and made up of intra-epithelial opacities, with no sub-epithelial oedema and sub-epithelial infiltrations.¹ These lesions are evolving in nature and preferably involves pupillary region. The punctate erosions stain variably with florescein, and the corneal sensitivity is intact. Conjunctiva is not involved in TSPK. Typical symptoms of this condition includes light sensitivity, ocular grittiness, ocular irritation, watery eyes, and blurry vision.^{2,3}

Topical steroids are the mainstay of treatment.⁴

But, long standing use is associated with a higher incidence of adverse effects like cataractous changes in lens, raised intra-ocular pressure (IOP) and high risk of ocular infetions.⁵ Additionally, some cases of TSPK does not effectively respond to topical corticosteroids.

The primary objective of this work is to assess the effectiveness of topical TCL 0.03% dermatological ointment in the therapy of TSPK.

MATERIAL & METHODS

We conducted a retrospective review of the medical records of 12 consecutive patients with TSPK who presented to the Ophthalmology dept. of Qazi Hussain Ahmad Medical Complex, Nowshera from Jan. 2019 to Jan. 2021. The study was granted approval by the Institutional Ethical

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Review board (IERB) (0414/R&D/IERB/NMC) and was adherent to the tenets of Helsinki declaration and guidelines of good clinical practice. All the patients were given informed consent regarding the trial. Eight patients were having refractory to therapy (conventional treatment) TSPK. Refractory to therapy was defined as presence of both subjective and objective features of the disease, even with adherence to standard therapeutic regimen. Detection of TSPK was based upon the subjective features of watering and light sensitivity and the objective features of numerous raised, greyish-white, nodular, intra-epithelial corneal lesions with no inflammation of conjunctiva. All subjects were treated with topical TCL 0.03% dermatological ointment (Crolimus[®], Valor Inc. Pak) twice a day. None of the subjects were simultaneously treated with any other immuno-modulatory or anti-inflammatory agents. Outcome variables included betterment/resolution in the subjective features like watering and light sensitivity, whereas resolution in objective features included reduction in the no. of epithelial keratitis, healing of keratitis, surface leveling of the lesion and reduced corneal staining with fluorescein. Clinical assessment was undertaken at baseline, during trial, and on the final follow up after cessation of therapy.

RESULTS

There were 4 male and 8 female patients with an age range of 12 to 44 yrs. and mean age 21 ± 9.42 yrs. Both eyes were involved in all the subjects. The length of disease before presentation were ranging from 12 weeks to 52 weeks. The subjective features taken for assessment included watering of eyes and light sensitivity with slight visual deterioration. The objective features on Slit-lamp bio-microscopy revealed multiple-elevated, greyish-white, nodular, intra-epithelial corneal lesions. The lesions had variable staining pattern with florescein dye. There wasn't any stromal/conjunctival inflammation. The therapy ranged from 02 to 40 weeks (mean 08 weeks).

We observed betterment in subjective features of watering in eye and light sensitivity and healing of the SPK in all subjects. Therapeutic efficacy of topical TCL was fast and effective. The therapy

was continued during flare ups with periodic attempts of withdrawal when feasible. Topical TCL therapy was well tolerated in all subjects with no bothersome burning/stinging sensation. None of the patient developed cataracts, raised IOP or corneal infections. Interestingly none of our subjects developed any systemic toxicity throughout the trial.

DISCUSSION

The cause of TSPK is still unclear. Several postulated mechanisms exists to delineate the patho-physiology of the disease, these include viral infections and localized immune deregulation.⁶ In a quest to explore the etiology, several scientists failed to reveal viral infections as the etiological agent in causation of the disease using tissue- culture techniques.^{3,7,8} In one of the study it was revealed that not a single patient out of 15 with TSPK turned out positive for HSV-1, HSV-2, HZV and adeno-virus in the epithelial cells of cornea using PCR. They negated the previous fact that TSPK is due to viral etiology but is due to an immune hypersensitivity reaction to a latent or intra-cellular epithelial infestation with the above mentioned viruses.⁹

The immune-mediated mechanisms are favored due to the fact that patients with TSPK are non-responsive to anti-viral drugs and the presence of an increased frequency of HLA-DR which is prevalent in different autoimmune diseases.^{10,11}

Topical corticosteroids are the mainstay therapy for TSPK. But, there are two main issues related to these drugs. Firstly the length of therapy with its associated adverse effects on eye, secondly is non-responsiveness to topical steroids in some of the cases.^{12,13} Eight (66.6%) of our 12 cases were refractory to corticosteroids and responded well to topical TCL. The real mechanism of the better response of topical TCL compared to topical steroids is unclear. Both steroids and TCL inhibits several inflammatory pathways including T-lymphocytes activation and proliferation. Possibly, the better response of TCL may be because of its powerful inhibitory effect against Langerhans cells which are considered to play a vital role in the immune-pathogenesis of TSPK.

Similarly in one of the study it was observed that eyes affected by TSPK have a marked increase in no. of Langerhans cells in the basal epithelial layer and in the Bowman's layer compared with the uninvolved eyes. Interestingly, Langerhans cells vanished from the involved eyes after topical steroids therapy.⁶ Regarding the therapeutic effectiveness TCL, one of the study revealed that this drug is approx. 100 times more powerful than betamethasone at inhibiting human epidermal Langerhans cell activation. This explains the superiority of topical TCL over steroids in the treating TSPK.¹⁴

TCL and cyclosporine-A are both calcineurin inhibitors which primarily acts on T-lymphocytes by blocking the production of inflammatory mediators and inhibiting the activation of other immune cells and compliment cascades. Both of these agents were proven effective in numerous studies having beneficial effect in the management of immune mediated ocular surface disorders including TSPK, with no steroid induced side effects in the long run.^{13,15-19} However, the immuno-suppressive activity of TCL is superior to cyclosporine-A.¹⁶ TCL also gets better and rapid absorption into corneal and conjunctival tissues.¹⁸

In the quest for exploration of topical TCL ointment 0.03% in the treatment of TSPK, one study concluded that ointment has the advantage over eye-drops due to prolonged ocular retention and contact resulting in better tissue absorption and bioavailability, but it increases the incidence of ocular surface irritation comparatively. Two out of 12 patients included in his study developed transient FB-sensation and stinging in eyes.¹⁹ We haven't observed any local side effect from topical application of TCL 0.03% ointment. All of our patients did well to twice a day therapy. The postulated mechanism that we derived from our study is that the local ocular irritation and watering is due to the underlying disease severity and not exclusively due to topical TCL application. We reported in one of our study the incidence of side effects in 2 out of 42 children with refractory vernal kerato-conjunctivitis treated with topical TCL 0.03% ointment. There was mild irritation and/or transient burning sensation at

the time of application, which subsided after few days of therapy.²⁰ There are some concerns about the increased risk of HSV-keratitis associated with topical TCL and slightly higher risk of T-cell lymphoma and skin malignancies in atopic dermatitis patients treated with TCL skin ointment.

Our study, has certain limitations, including small sample size, lack of control group and masking effect. Further prospective, randomized control clinical trials are needed to further elucidate the role of topical TCL 0.03% ointment in the treatment of TSPK.

CONCLUSION

It is concluded from this study that topical tacrolimus 0.03% dermatological ointment is safe and efficacious in the treatment of Thygeson superficial punctate keratitis who are refractory to conventional therapy.





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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Adnan Ahmad	Study design, Final draft of manuscript & Review.	
2	Shams Ul Haq	Literature review, manuscript, Editing & references management	
3	Jamal Hussain	Data analysis & interpretation, Statistical analysis.	
4	Javed Rasool	Data analysis & interpretation acquisition.	
5	Mubashir Rehman	Critical review, Manuscript drafting.	