Original Article

Therapeutic effects of topical 0.03% Tacrolimus ointment in children with refractory vernal keratoconjunctivitis in Middle East

Sandra Flavia Fiorentinia,⇑; Darakhshanda Khurram

Abstract

Objective: The purpose of this paper is to review the efficacy and safety profile in children treated with topical 0.03% Tacrolimus ointment for vernal keratoconjunctivitis in Middle East and to propose a treatment posology. According to recent studies, a complex non-IgE dependent mechanism plays a relevant role in the pathogenesis of vernal keratoconjunctivitis. Numerous cells and mediators have been found in the serum, conjunctiva and tears of patients with Vernal keratoconjunctivitis.

Design: This case series included 10 patients from a single centre, pediatric department of a tertiary hospital with active symptomatic vernal keratoconjunctivitis. All the patients had proliferative lesions and corneal involvement despite conventional medications, including topical steroids. All other medications, systemic and topical: steroids, antihistamines and cyclosporine, were unsuccessful. Patients were treated with topical 0.03% Tacrolimus ointment twice daily for 8 weeks and then once a day for the next two month followed by thrice a week for two months. The changes in symptoms and signs after treatment were evaluated, also the development of possible complications was assessed.

Results: The results showed a significant reduction in signs and symptoms after 4 weeks of the treatment. Clinical resolution of giant papillae and corneal lesions were seen within eight weeks and no additional drug was required during that period, except tear substitutes. Treatment was continued for period of two months and then slowly reduced.

Conclusion: The use of 0.03% Tacrolimus ointment is safe and effective in children refractory to conventional treatment of vernal keratoconjunctivitis even in high temperature climate as Middle East. Due to the effectiveness of the treatment, the dosage used may be proposed for conventional use.

Keywords: Vernal keratoconjunctivitis, Allergy, Tacrolimus, Middle East

Introduction

Vernal keratoconjunctivitis (VKC) is a severe chronic inflammatory ocular disease that involves the anterior ocular surface in different grades of severity in both eyes, asymmetrically. It can affect the eyes as the severe end of the spectrum of allergy.1–3 However, despite its pathogenesis traditionally been considered as a classical IgE- mediated disease, it is not totally allergy related and recent studies have revealed particular...
involvement of Th2 lymphocytes. 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. It is typically characterized by the presence of giant “cobblestone” papillae in the upper palpebral conjunctiva (tarsal form) or at the limbus (bulbar form) with a corneal involvement ranging from superficial keratitis to plaque ulcers and late corneal vascularization and scars. Epidemiological studies do not consider it as a seasonal disease since frequently this persists throughout the year with increase intensity in warmer weather. 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.

The treatment arsenal includes a variety of agents including anti-histamines, mast cell stabilizers, and non-steroidal anti-inflammatory drugs, mainly for the mild cases. For moderate to severe cases, the disease can be a sight threatening, due to the development of corneal ulcers and scars topical steroids have been the treatment of choice, however prolonged use of steroids may cause complications, such as glaucoma, cataract, and secondary infections. Topical cyclosporine A in last decade started to be an option of treatment to avoid all the steroid related complications and several studies have demonstrated efficacy and safety at 1% to 2% concentrations.

Tacrolimus is a calcineurin inhibitor that blocks T-lymphocyte activation and it has been used for the prophylaxis of organ rejection in transplanted patients. There is also topical Tacrolimus that is indicated as a second-line treatment of atopic dermatitis in non-immunologically compromised patients over two years old. The mechanism of action of Tacrolimus has not been fully elucidated yet. It is known that Tacrolimus binds to FKBP-12 (12-kDa FK506-binding protein) in T cells 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 TH1 (interleukin [IL]-2, interferon γ) and TH2 cytokines (IL-4, IL-5). Tacrolimus monohydrate ointment is used for dermatologic treatment of atopic dermatitis worldwide. The same topical Tacrolimus in doses that varies from 0.02% to 0.03% in medical literature has been prescribed “off label” and it has been shown as an effective treatment for a number of refractory inflammatory ocular surface diseases, including VKC.

Methods

This prospective non-comparative study included 20 eyes of 10 patients with active symptomatic vernal keratoconjunctivitis was conducted in a single centre, in a pediatric department of a tertiary care hospital in Dubai and Abu Dhabi, between August 2016 to January 2017. The study was approved by the ethics committee of Moorfields Eye Hospital Dubai and the patients were recruited followed by a written informed consent. This study adhered to the tenets of the Declaration of Helsinki. All patients with active disease presenting with corneal involvement, and no improvements of the symptoms after at least 3 months under topical anti-histamines, cyclosporine and steroid (Prednisolone Acetate 1%) drops were included in this study. The exclusion criteria included the patients with co-existing ocular diseases like corneal infections, chemical injuries, Steven Johnson syndrome, uveitis and patients under VKC remission.

Topical Tacrolimus 0.03% ointment was started twice a day for 8 weeks and then once a day for the next 2 months followed by thrice a week for 8 weeks. The changes in subjective symptoms and objective signs were evaluated after Tacrolimus started and also the development of possible complications was assessed in each follow up. The follow up was dependent on the severity of the disease but all the patients were assessed in 1 week, one month, 3 and 6 months of treatment. The disease severity was classified in a scale of grades created for this study according to Table 1, in order to quantify the clinical signs and symptoms improvements.

Results

Before Tacrolimus 0.03% ointment introduction, all the patients were under Prednisolone acetate 1% drops which usually brought all of them a significant clinical response

Table 1. Scale of severity.

| Grade | Cornea signs | Conjunctiva signs | Symptoms |
|-------|--------------|-------------------|----------|
| 0     | Clear        | White             | None     |
| 0.5   | Very mild punctate keratopathy (localized fluorescein staining) | Mild bulbar redness and small tarsus papillae | Mild itchiness |
| 1.0   | Mild punctate keratopathy affecting the whole cornea | Moderate bulbar redness and moderate bulbar papillae and/or mild Trantas nodules | Mild ichiness, burning sensation, no photophobia, normal UCVA |
| 1.5   | Moderate punctate keratopathy | Moderate bulbar redness and moderate bulbar papillae and/or moderate Trantas nodules | No photophobia, moderate itchiness |
| 2.0   | Severe punctate keratopathy | Giant tarsal papillae and moderate bulbar redness, limbal involvement but not 360 degrees | Mild photophobia, moderate itchiness, normal UCVA |
| 2.5   | Severe punctate keratopathy with continuous epithelial defects | Giant tarsal papillae and severe bulbar redness with 360 degrees limbal involvement | Moderate photophobia, severe itchiness, fluctuation of UCVA |
| 3.0   | Shield ulcer with Severe punctate keratopathy | Cobblestone papillae with mucus, discharge and severe bulbar redness | Severe photophobia, severe itchiness, reduced UCVA |
but when its posology started to be tapered, the remission of the disease did not last more than one week and the disease control was unsuccessful. Significant reduction in signs and symptoms of all patients were reported after 4 weeks of commencement of the treatment. Clinical resolution of giant papillae and corneal lesions were seen within eight weeks. No additional drug was required during that period, except tear substitutes to stabilize the tear film. Treatment was continued for period of six months and slowly reduced after 3 months. At the end of the follow up period, all patients remained asymptomatic but continued to apply topical Tacrolimus. Fig. 1 shows the effect of 0.03% Tacrolimus ointment on the severity of signs and symptoms during 6 months follow up.

No additional medications, such as mast cell stabilizers, topical cyclosporine, or steroids, were required to provide additional relief. No local or systemic side effect was observed during the entire 6 months of treatment.

Discussion

The use of topical Tacrolimus for VKC treatment has substantially changed the management of this disease, which was difficult to control without steroids before and was considered a sight threatening condition, either due to the severity of some cases or due to the side effects of the steroids. Many studies have shown the effectiveness and safety of Tacrolimus topical use for this indication. However, there is no consensus regarding the better posology, administration and concentration of the still “off label” indication. In the study by Ohashi et al with 0.1% twice daily dose, showed improvement in symptoms of both atopic keratoconjunctivitis and VKC. 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 case series, with the follow-up of 6 months. In Middle East, due to almost a year round warm weather, including very high temperatures of above 40-Celsius degrees in summer time, VKC is more prevalent and we suspected that the environment could play a role in delaying the patient’s response to Tacrolimus treatment. However, all the patients showed improvement at the same average time after initiation of Tacrolimus 0.03% treatment, as described in medical literature. Our case report series corroborate with literature regarding the time of action for the results to be achieved. All the patients achieved dramatic improvements in inflammatory signs and symptoms without significant adverse effects, except for the stinging sensation, that also is in accordance with the literature review. There was a significant improvement on the severity of the disease. The grade changed from 2.5 (pre-treatment) to 1.5 at the first three months of topical 0.03% Tacrolimus use and gradually improved to 1.0 after three/four months of treatment.

Patients completed 6 months of follow-up and none required additional medications, such as anti-histamines, steroids, or mast cell stabilizers, to control disease activity proving that Tacrolimus was very effective in the disease control (Fig. 1).

Studies have reported risk of T-cell lymphoma associated with the use of systemic and intravenous Tacrolimus in patients with immunocompromised status, however epidemiological evidence is not sufficient to know the topical calcineurin inhibitors can cause malignancy. In our study, no malignancy occurred during the 6 months of follow-up period and this is very unlikely to be a risk factor as Hui RL at el described a retrospective cohort study of over 950,000 patients with atopic dermatitis or eczema and found that Tacrolimus skin ointment was a safe and effective treatment for patients with refractory VKC.

In conclusion, a 0.03% Tacrolimus ointment is effective in controlling the clinical signs and symptoms of all levels of VKC in this study in Middle East, especially the severe cases and this should be considered as an alternative to steroids.

Declaration of Competing Interest

There is no conflict of interest in this study. There is no sponsor in this study.

References

1. Pucci N, Novembre E, Cianferoni A, et al. Efficacy and safety of cyclosporine eye drops in vernal keratoconjunctivitis. Ann Allergy Asthma Immunol 2002;89:298–303.
2. Kosriukvongs P, Vichyanond P, Wongsawad W. Vernal keratoconjunctivitis in Thailand. Asian Pac J Allergy Immunol 2003;21:25–30.
3. Lambiase A, Minchietti S, Leonardi A, et al. Prospective, multicenter demographic and epidemiological study on vernal keratoconjunctivitis: a glimpse of ocular surface in Italian population. Ophthalmic Epidemiol 2009;16:38–41. A recent large study examining epidemiology of VKC from Italy.
4. Bielory L, Frohman LP. Allergic and immunologic disorders of the eye. J Allergy Clin Immunol 1992;89(1 Part 1):1–15.
5. Pucci N, Caputo R, Di Grande L, et al. Tacrolimus vs. Cyclosporine eye drops in severe cyclosporine-resistant vernal keratoconjunctivitis: a randomized, comparative, double-blinded, crossover study. Pediatr Allergy Immunol 2015;26:556–61.
6. Tabbara AK, El-Astal A. Immunopathogenesis of ocular allergy. Progress in allergy and clinical immunology. Seattle: Hogrefe & Huber; 1997. p. 381–5.
7. McMoli T, Assonganyi T. Limbal vernal kerato-conjunctivitis in Yaounde, Cameroon. A clinic-immunology study. Rev Int Trach Pathol Ocul Trop Subtrop Sante Publique 1991;68:157–70.
8. Diallo J-S. La limbo-conjunctivite endemique des tropiques. Rev Int Trachome 1976;3:4–71–9.
9. Dantas PEC, Alves MR, Nishiwaki-Dantas MC. Topographic corneal changes in patients with vernal conjunctivitis. Arq Bras Oftalmol 2005;68:593–8.
10. Uchio E, Kimura R, Migita H, et al. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. *Graefes Arch Clin Exp Ophthalmol* 2008;291–6.

11. Sacchetti M, Baiardini I, Lambiase A, et al. Development and testing of the quality of life in children with vernal keratoconjunctivitis questionnaire. *Am J Ophthalmol* 2007;144:557–63.

12. Leonardi A. Vernal keratoconjunctivitis: Pathogenesis and treatment. *Prog Retin Eye Res* 2002;21:319–39.

13. Stahl JL, Barney NP. Ocular allergic disease. *Curr Opin Allergy Clin Immunol* 2004;4:455–9.

14. Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term follow up. *Ophthalmolology* 2000;107:1157–63.

15. Akdnis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL consensus report. *Allergy* 2006;61:969–87.

16. Sakuma S, Higashi Y, Sato N, Sasakawa T, Sengoku T, et al. Tacrolimus suppressed the production of cytokines involved in atopic dermatitis by direct stimulation of human PBMC system. (Comparison with steroids). *Int Immunopharmacol* 2001;1:1219–26.

17. Joseph MA, Kaufman HE, Insler M. Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. *Cornea* 2005;24:417–20.

18. Mayer K, Reinhard T, Reis A, Bühringer D, Sundmacher R. FK 506 ointment 0.1% A new therapeutic option for atopic blepharitis. Clinical trial with 14 patients. *Klin Monbl Augenheilkd* 2001;218:733–6.

19. Tam PM, Young AL, Cheng LL, Lam PT. Topical tacrolimus 0.03% monotherapy for vernal keratoconjunctivitis – case series. *Br J Ophthalmol* 2010;94:1405–6.

20. Kheirkhah A, Zavareh MK, Farzbod F, Mahbod M, Behrouz MJ. Topical 0.005% tacrolimus eye drop for refractory vernal keratoconjunctivitis. *Eye (Lond)* 2011;25:872–80.

21. Ohashi Y, Ebihara N, Fujishima H, Kumagai N, et al. A randomized, placebo controlled clinical trial of tacrolimus ophthalmic suspension 0.1% in severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2010;26:165–74.

22. Miyazaki D, Tominaga T, Kakimaru- Hasegawa A, Nagata Y, et al. Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. *Ophthalmology* 2008;115:988–92.

23. Stumpf T, Luqmani N, Sumich P, Cook S, Tole D. Systemic tacrolimus in the treatment of severe atopic keratoconjunctivitis. *Cornea* 2006;25:1147–9.

24. Al-Amri AM, Fiorentini SF, Albary MA, Bamahfouz AY. Long-term use of 0.003% Tacrolimus suspension for treatment of vernal keratoconjunctivitis. *Oman J Ophthalmol* 2017;10:145–9.

25. Kymionis GD, Goldman D, Ide T, Yoo SH. Tacrolimus ointment 0.03% in the eye for treatment of giant papillary conjunctivitis. *Cornea* 2008;27:228–9.

26. Vichyanond P, Kosirukvongs P. Use of Cyclosporine A and Tacrolimus in treatment of vernal keratoconjunctivitis. *Curr Allergy Asthma Rep* 2013;13:308–14.

27. Akilov OE, Geskin L. Therapeutic advances in cutaneous T-cell lymphoma. *Skin Therapy Lett* 2011;16:1–5.

28. Radovic TC, Kostovic K, Ceovic R, Mokos ZB. Topical calcineurin inhibitors and malignancy risk. *Int J Cancer Manage* 2017;10(4).

29. Hui RL, Lide W, Chan J, Schottinger J, Yoshinaga M, Millares M. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother* 2009;43:1956–63.