TACROLIMUS OINTMENT FOR TREATMENT OF VKC

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ABSTRACT

BACKGROUND

Vernal Keratoconjunctivitis (VKC) is a bilateral recurrent chronic allergy inflammatory disorder of ocular surface, which is seasonally exacerbated mostly involving tarsal and bulbar conjunctiva in chronic and severe cases involves cornea as well. Affects mostly children and young adults with male predominance. Tacrolimus (FK-506) is a highly potent immune modulatory agent produced by the fungus Streptomyces tsukubaensis.

MATERIALS AND METHODS

This prospective, nonrandomised 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 12 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.

CONCLUSION

Tacrolimus 0.1% ointment is a safe and effective treatment for VKC refractory to standard treatment and maybe used as a substitute for steroid treatments used to controlled-disease activity. However, adverse effects could cause poor patient compliance.

KEYWORDS

Allergy, Tacrolimus, Vernal Keratoconjunctivitis.

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BACKGROUND

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 hyperaemia, papillary hypertrophy, giant papillae, discharge and Trantas dots.[5]

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Tacrolimus is a strong, nonsteroidal immune suppressant isolated from Streptomyces tsukubaensi.[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 potent than cyclosporine.[9,10] 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[11,12,13,14,15,16] 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.

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

It is a prospective observational study attending Nalanda Medical College OPD. After taking history, total signs and symptoms score was noted. 0.03% tacrolimus eye ointment was started in patients meeting inclusion criteria twice daily and studied for 12 months. Total of 8 clinical signs and 5 symptoms were graded as none, mild, moderate and severe.

Signs are palpebral conjunctival hyperaemia, follicles, papillae, giant papillae, bulbar hyperaemia, oedema, Trantas dot and corneal signs. Symptoms include itching, foreign body sensation, tearing, discharge and photophobia.

Inclusion Criteria

Patients with clinical diagnosis of refractive VKC whose symptoms did not subside with anti-histaminic/mast cell stabiliser/topical steroids.

Patients who respond to steroid, but develop toxicity.

Exclusion Criteria

Patient having one useful eye.

Patients using contact lens.

Patients with any other active ocular inflammatory condition.

Patients with hypersensitivity reaction.

Those patient who lost to follow up.

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. All patients had active, perennial, symptomatic disease that was refractory to medication including antihistamines, mast cell stabilisers, topical cyclosporine and steroids. Itching was the most prominent symptom (15/20); other complaints included redness and foreign body sensation. All eyes had lid thickening, conjunctival hyperaemia, 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 month.

There were significant improvements in the clinical signs and symptoms of disease after starting treatment with tacrolimus. Itching was the first symptom to decrease. At baseline, 15 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. At the end of the followup period, all patients remained asymptomatic, but continued to apply topical tacrolimus ointment. No additional medications, such as mast cell stabilisers, topical cyclosporine or steroids were required to provide additional relief.

Prior to treatment, conjunctival hyperaemia was present in 38 eyes (28 severe, 6 moderate, 4 mild). Conjunctival hyperaemia was completely resolved in 37/40 eyes, 6 weeks after the initiation of treatment.

Improvement in conjunctival papillary hypertrophy was seen in 20 eyes and 6 weeks after starting treatment. After 3 months, 8 patients had only mild papillary hypertrophy. Twenty one eyes that had moderate or severe lid thickening at baseline showed improvements in clinical signs, 6 weeks after starting treatment. All patients (20/40 eyes) with moderate or severe corneal punctate epithelial erosions showed improvement 8 weeks after starting treatment. All these eyes had mild corneal punctate epithelial erosions after 2 months of treatment, which completely resolved at the last follow-up visit. At the end of the study, all patients with VKC were still using tacrolimus ointment due to recurrence while attempting to discontinue treatment. However, these patients experienced a dramatic improvement when they resumed a once weekly tacrolimus treatment regimen. Five patients discontinued treatment because of a severe burning sensation and were excluded from the study. BSCVA and refraction remained unchanged throughout the followup period.

DISCUSSION

Tacrolimus is an effective agent for the management of patients with AKC and VKC who are refractory to conventional medications, including topical cyclosporine.[11,12,13,14,15,16] In our study, topical tacrolimus achieved good results in the management of severe cyclosporine-resistant VKC. Previously, Daniel et al reported that 0.05% topical cyclosporine was not an effective steroid-sparing agent in steroid-dependent allergic conjunctivitis. Consistent with previous reports, almost all patients in our study showed dramatic improvements in inflammatory signs and symptoms without significant adverse effects. Although, none of our patients required additional medications including topical steroids for additional relief, long-term use of tacrolimus was needed to control disease recurrence. In a multicenter, randomised clinical trial, Ohashi et al[16] used tacrolimus 0.1% ophthalmic suspension twice daily for 4 weeks in 21 patients with AKC and 7 patients with VKC and compared to the outcome to a placebo group. They[16] found the treated eyes showed a marked improvement in symptoms after 4 weeks of treatment.

In our study, all patients completed 12 months of follow-up and none required additional medications such as antihistamines, steroids or mast cell stabilisers to control disease activity. In the present study, 5 patients were excluded because they were intolerant to the severe burning sensation caused by the application of tacrolimus ointment. This effect maybe associated with the activation of herpes simplex dendritic keratitis by the immunosuppressive properties of tacrolimus ointment.[15] However, none of our patients developed herpes simplex keratitis during the long-term followup period. The possibility of activation of herpes simplex dendritic keratitis by tacrolimus treatment requires further study. In a clinical study conducted by Sengoku et al,[15] use of tacrolimus 0.1-1% eye drops achieved a dramatic improvement in the symptoms of patients with refractory VKC. In our study, 20 patients experienced initial mild conjunctival hyperaemia (which subsides thereafter) for the first 3 days after initiation of treatment followed by relief of itching. When Miyazaki et al used tacrolimus 0.02% ointment to treat 5 patients with AKC and one patient with

VKC who were refractory to conventional treatment. There was a marked improvement in symptoms within 2-4 weeks of treatment.

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 randomised 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.

REFERENCES

[1] Tabbara AK, El-Asrar A. Immunopathogenesis of ocular allergy. Progress in allergy and clinical immunology. Seattle: Hogrefe and Huber 1997:381-385.
[2] Clark AF. Basic sciences in clinical glaucoma: steroids, ocular hypertension, and glaucoma. J Glaucoma 1995;4(5):354-369.
[3] 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(4):557-563.
[4] Bielory L. Allergic and immunologic disorders of the eye. Part II: ocular allergy. J Allergy Clin Immunol 2000;106(6):1019-1032.
[5] Stahl JL, Barney NP. Ocular allergic disease. Curr Opin Allergy Clin Immunol 2004;4(5):455-459.
[6] Kino T, Hatanaka H, Hashimoto M, et al. FK-506, a novel immunosuppressant isolated from a Streptomyces. I. fermentation, isolation, and physicochemical and biological characteristics. J Antibiot (Tokyo) 1987;40(9):1249-1255.
[7] Sakuma S, Higashi Y, Sato N, 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(6):1219-1226.
[8] Muller GG, Jose NK, de castro RS. Topical tacrolimus 0.03% as sole therapy in vernal keratoconjunctivitis: a randomized double-masked study. Eye Contact Lens 2014;40(2):79-83.
[9] Vidyachand P, Pacharn P, Player U, et al. Vernal keratoconjunctivitis: a severe allergic eye disease with remodelling changes. Pediatr Allergy Immunol 2014;25(4):314-322.
[10] Ezeamuzie CI. Anti-allergic activity of cyclosporin-A metabolites and their interaction with the parent compound and FK 506. Int J Immunopharmacol 1996;18(4):263-270.
[11] Tam PM, Young AL, Cheng LL, et al. Topical tacrolimus 0.03% monotherapy for vernal keratoconjunctivitis- case series. Br J Ophthalmol 2010;94(10):1405-1406.
[12] Mayer K, Reinhard T, Reis A, et al. FK 506 ointment 0.1% - A new therapeutic option for atopic blepharitis. Clinical trial with 14 patients. Klin Monbl Augenheilkd 2001;218(11):733-7336.
[13] Kymionis GD, Goldman D, Ide T, et al. Tacrolimus ointment 0.03% in the eye for treatment of giant papillary conjunctivitis. Cornea 2008;27(2):228-229.
[14] Joseph MA, Kaufman HE, Insler M. Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. Cornea 2005;24(4):417-420.
[15] Sengoku T, Sakuma S, Satoh S, et al. Effect of FK506 eye drops on late and delayed-type responses in ocular allergy models. Clin Exp Allergy 2003;33(11):1555-1560.
[16] Ohashi Y, Ebihara N, Fujishima H, et al. A randomized, placebo-controlled clinical trial of tacrolimus ophthalmic suspension 0.1% in severe allergic conjunctivitis. J Ocul Pharmacol Ther 2010;26(2):165-174.