Original Article

To Assess the Efficacy and Safety of Tacrolimus Skin Cream, 0.03% in Moderate to Severe Vernal Keratoconjunctivitis

Sameera Irfan, Arsalan Ahmed, Faiza Rasheed

Pak J Ophthalmol 2015, Vol. 31 No. 1

See end of article for authors affiliations

Correspondence to:
Sameera Irfan
Mughal Eye Trust Hospital
301, H3/A, Johar Town, Lahore.
sam.irfan48@gmail.com

Purpose: To determine the efficacy and safety of Tacrolimus skin cream (Ecczemus 0.03%) in the resolution of moderate to severe Vernal Keratoconjuctivitis (VKC).

Material and Methods: A prospective clinical trial was conducted at the oculoplastics department of a tertiary care centre, from Sep 2013 – Oct 2014. In this, 54 consecutive cases (108 eyes) with moderate to severe VKC, between the ages of 4 – 18 (mean 7 years) years were included. There were 13 newly diagnosed cases and 41 recurrent. After discontinuing their previous medications, they were treated with Tacrolimus skin cream, 0.03% applied into the lower conjunctival fornix twice a day along with lubricants for a period of 4 – 8 months. Clinical signs and symptoms were recorded at the beginning of the treatment and at all follow-ups which were conducted weekly for one month and then every month for one year.

Results: The duration of therapy was 4 – 8 months (mean 6 months). The patients were followed-up for a mean duration 10 ± 1.5 months. There was marked subjective as well as objective improvement in all cases within one month of therapy. There was no need for any additional therapy. No toxic effects of Tacrolimus were observed in any case.

Conclusion: It can be concluded that Tacrolimus skin cream (0.03%) is an effective therapy for moderate to severe cases of vernal keratoconjuctivitis. It acts as a safe alternative to topical steroids.

Key words: Tacrolimus Vernal Keratoconjunctivitis, Allergy

Vernal keratoconjunctivitis (VKC)is an acute – on – chronic inflammatory disease of the conjunctiva and cornea,[1,2]encountered usually in the first decade of life .in children. The patients are visually handicapped because of intense burning and itching along with lacrimation, a stringy mucoid discharge, photophobia and heaviness of eyelids due to involvement of the tarsal conjunctiva. The symptoms are accentuated when patient goes to a warm, humid environment. Mild cases of VKC show improvement with nonspecific, supportive therapy. But severe cases show frequent remissions and relapses, run a protracted course, and if not treated properly, usually result in sight–threatening complications[3] over a period of time.

VKC starts as a Type I (immediate) hypersensitivity reaction[4] (histamine mediated). This occurs when a sensitized individual comes into contact with a specific antigen resulting in degranulation of mast cells in the conjunctiva and the release of histamine. Histamine causes watery, red eyes with intense itching in children; later there is super-imposed involvement of T lymphocytes[2,4] which results in chronicity of the disease, corneal and tarsal conjunctival signs. There is involvement of both eyes which may be asymmetrical. The disease is notorious for recurrence when the treatment is stopped. It needs to be differentiated from Seasonal Allergic Conjunctivitis which is an acute Type 1 hypersensitivity reaction and involves only the conjunctiva. In comparison to VKC, it shows marked

chemosis, conjunctival injection and eyelid edema due to the release of histamine from conjunctival mast cells resulting in .increased vascular permeability.

Patients with VKC exhibit large amounts of circulating Immunoglobulin E (IgE); the cross-linking of 2 adjacent IgE molecules by the antigen triggers mast cell degranulation. This releases various preformed mediators of the inflammatory cascade like histamine, prostaglandins, leukotrienes, tryptase, chymase, heparin and chondroitin sulfate. These mediators cause increase vascular permeability with migration of eosinophils, polymorphs, T and B lymphocytes and proliferation of fibroblasts which lay down of exuberant amounts of collagen in conjunctival tissue. Hence the ocular tissues exhibit the following changes :

Conjunctiva shows cellular infiltration with hyperplasia of epithelium and dilatation of conjunctival vessels along with increased permeability.

The upper Tarsus is typically affected by the proliferation of fibrous layer of conjunctiva and its hyalinization resulting in the formation of giant papilla, more than 0.3 mm in diameter, giving the classic 'cobble – stone' appearance. In severe cases, these papillae may hypertrophy producing cauliflower-like excrescences (giant papillae) which may produce mechanical ptosis. These giant papillae are randomly distributed over the whole tarsus while those resulting from wearing of hard contact lenses are present only at the edge of the tarsus.

The limbal involvement comprises of papillae which are thick, gelatinous along with multiple white spots which are collections of degenerated epithelial cells and eosinophils called Horner – Trantas dots. They do not last longer than a week from their initial presentation as they .undergo rapid dissolution.

The corneal involvement is variable: It may show Punctate epithelial keratopathy (PEK) due to toxic effect of inflammatory mediators released from the conjunctiva. These fine punctate erosions coalesce, resulting in larger erosions or a shield ulcer, which is typically shallow with white irregular epithelial borders. The giant tarsal papillae are a major contributing factor in its development by causing chronic mechanical irritation. Vernal pseudogerontoxon, a degenerative lesion in the peripheral cornea resembling corneal arcus, may be seen. *Keratoconus* is a frequent complication in chronic cases, due to chronic eye rubbing and superimposed corneal thinning by injudicious use of topical steroids. Corneal vascularizuation or pannus formation may also be seen.

In the acute but milder form of VKC, topical antihistamines, mast cell stabilizers, mucolytics, ANSAIDS and lubricants are used as the first line of therapy. However, in the severe and chronic disease, corticosteroids [5] have to be added and they have to be used for a long term to control the symptoms; corticosteroid withdrawal leads to clinical worsening while their long term use is associated with side-effects like cataract, glaucoma, corneal thinning, corneal ectasia / keratoconus. Hence a marked ocular morbidity results from the prolonged use of steroids topically.

Immuno-modulators have been introduced for the past two decades into the armamentarium of drugs for the management of VKC.[6] They are mainly used as steroid – sparing drugs. Tacrolimus[7,8] is one such immunomodulating drug, the other being Cyclosporin eye drops. Tacrolimus is known to be 10 – 100 times more potent than Cyclosporin. It is a macrolide, discovered in 1984 from the bacteria streptomyces tsukubaensis. It is very affective in suppressing the activation and proliferation of B & T lymphocytes and formation of inflammatory mediators like cytokines, especially interleukin$_2$.

At first Tacrolimus was used as an immuno-suppressant in liver transplants and subsequently in other solid – organ transplants. For more than 10 years it has been used in the treatment of skin disorders such as vitiligo and atopic dermatitis etc. It is available as a skin cream 0.03% and 0.1% for the treatment of atopic dermatitis (eczema), vitiligo. It suppresses inflammation as affectively as topical steroids, with the major advantage for not causing skin thinning (atrophy) and other steroid related side-effects. On initial applications, it can produce mild burning or itching sensation, with increased sensitivity to sunlight and heat.; no other side effects have been reported. Patients should minimize or avoid exposure to natural or artificial light. There may be an increased risk of activation of skin infections which should be cleared up prior to its application.

According to numerous clinical studies,[9-12] Tacrolimus has been successfully used in the treatment of autoimmune diseases of the ocular surface such as dry eyes, mooren's ulcer, scleritis, cicatricial conjunctivitis atopic and vkc. Its ophthalmic preparation is not available in Pakistan so we

conducted this study to find out the efficacy and safety of tacrolimus skin cream 0.03% (Ecczemus, Brooke Pharma) applied in the lower conjunctival fornix in treating moderate to severe VKC.

MATERIAL AND METHODS

A prospective clinical trial was conducted at the oculoplastics department of Mughal Eye Trust Hospital, Lahore, Pakistan, from Sep 2013 – O ct 2014. This is a tertiary referral centre. 54 consecutive cases with moderate to severe VKC (108 eyes), between the ages of 4 – 18 years were included. The male to female ratio was 2:1. There were 13 newly diagnosed cases and 41 recurrent, being refractory to their previous therapy consisting of topical antihistamines, mast cell stabilizers and steroids. The study inclusion criteria was moderate to severe cases of VKC presenting with the symptoms of chronic, recurrent, bilateral red eyes with itching, redness, watering and mucus discharge with papillae found on the upper tarsal conjunctiva, along with limbal changes. Study exclusion criteria were cases of seasonal allergic conjunctivitis (histamine mediated) and mild VKC with only palpebral conjunctivitis; patients who had received systemic or sub-conjunctival corticosteroids, glaucoma or ocular hypertension due to previous therapy, developmental cataract or any systemic illness.

Before starting the trial, all patients were given a questionnaire to grade the severity of their symptoms of itching, redness, watering, mucus discharge, photophobia and a foreign body sensation (Table 1), as 0 (none), 1 for mild (occasional symptoms), 2 for moderate (frequent symptoms), and 3 for severe (constant symptoms). They all underwent a thorough ophthalmic examination including the measurement of best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy, conjunctival/corneal fluorescein staining and applanation tonometry. The clinical signs like conjunctival injection, limbitis, papillary hypertrophy or giant papillae, punctate corneal erosions, corneal pannus formation were graded (Table 2 and 3) as 0 (none), 1 (mild), 2 (moderate), 3 (severe). The patients and / or their parents were fully explained the advantages and disadvantages of the treatment and a verbal consent was obtained.

After discontinuing the previous medications in recurrent cases, all were treated with Tacrolimus skin cream, 0.03% applied into the lower conjunctival fornix twice a day along with lubricants (Visol eye gel 4 × / day and Lacrilube eye ointment at night) for a period of 4 - 8 months (mean of 6 months). Efficacy of treatment was evaluated subjectively by assessing patient's symptoms and objectively by noting an improvement in the clinical signs. The need for any additional therapy was noted. Any side effects of the treatment particularly ocular discomfort were specifically asked and possible complications such as intraocular pressure, lens opacification, secondary bacterial infections were noted. All these findings were recorded at the beginning of the treatment and at all follow-ups conducted weekly for the first month and then after every month, for 1 year. Any recurrence of symptoms and / or signs after stopping all therapy was also noted during the follow-up period.

Table 1: Grading of symptoms of VKC patients before and after 1 month's therapy with 0.03% tactolimus skin cream.

Symptoms	Grade Prior to Rx				Grade after 1 Month Rx				Improvement %
	0	1	2	3	0	1	2	3	
Itching	0	–	n = 22	n = 86	–	–	–	–	100
Redness	–	–	n = 32	n = 76	98	10	–	–	90.74
Watering	–	–	n = 56	n = 52	108	–	–	–	100
Discharge	–	n =16	n = 32	–	108	–	–	–	100
Photophobia	–	–	n = 45	n = 53	102	6	–	–	94.4
Grittiness	–	n = 62	n = 30	n = 16	103	5	–	–	95.3

Grade 0 = None, 1 = mild, 2 = moderate, 3 = severe

RESULTS

In all 54cases (108 eyes) included in the study, the commonest presenting symptom was itching and watering of eyes in addition to other symptoms shown in Table1. Papillary hypertrophy was noted in all cases while giant papillae were found only in 25 recurrent cases (moderate = 24 eyes and severe = 26 eyes), Table 2. Limbitis was found in all cases (mild = 12,

Table 2: Grading of clinical signs of VKC prior to therapy and after 1 month's therapy with Tacrolimus 0.03% skin cream.

Signs	Grade Prior to Rx				Grade after 1 Month Rx				Improvement %
	0	1	2	3	0	1	2	3	
Conj. injection	–	–	n = 22	n = 86	96	12	–	–	88.8
Limbitis	–	n = 12	n = 42	n = 54	108	–	–	–	100
PEK	–	n = 15	n = 52	n = 41	108	–	–	–	100
Corneal pannus	–	–	n = 62	–	108	–	–	–	100
GPC	–	–	n = 24	n = 26	108	–	–	–	100
Shield Ulcer	–	–	n = 2	–	108	–	–	–	100

Grade 0 = none, 1 = mild, 2 = moderate, 3 = severe

Table 3: Grading scales for objective clinical signs.

Signs	Score	Definition
Conjunctival injection	3	Impossible to distinguish individual blood vessels
	2	Dilatation of many vessels
	1	Dilatation of several vessels
	0	None
Limbitis	3	7 or more limbal papillae
	2	4 - 6 limbal papillae
	1	1 - 3 limbal papillae
	0	None
SPK	3	Diffusely scattered on Whole cornea
	2	Half of cornea spared
	1	Only a few punctae erosions
	0	None
Giant papillae (papillae size ≥ 1 mm)	3	Elevated papillae in ½ or more of the upper palpebral conjunctiva
	2	Elevated papillae in < ½ of the upper palpebral conjunctiva

moderate = 42, severe = 54 eyes), corneal involvement in the form of punctate erosions was seen in all cases (mild = 15, moderate = 52, severe = 41 eyes), corneal pannus in 42 cases (62 eyes) and shield ulcer, unilateral, in 2 cases.

After starting 0.05% Tacrolimus skin cream, the patients were followed up for 8 – 12 months (mean duration 10 ± 1.5 months). All symptoms significantly improved after treatment though itching was the first to be relieved. Percentage improvement of symptoms after treatment has been shown in Table 1. By 1 month after treatment, the residual symptoms only included mild redness in ten eyes (90.74% improvement), mild photosensitivity in 6 eyes and mild foreign body sensation in 5 eyes which disappeared after a further one month's therapy. The patients remained mostly symptom-free during the remaining period of therapy. However, when Tacrolimus was stopped after 2 – 3 months of continuous use, almost all of them had a recurrence of the disease though in a milder form. Hence it was continued for a further 2 months and then tapered gradually over another one month. After stopping all treatment, 26 cases developed mild recurrence after 3 – 4 months during the follow-up period which was of mild severity and was managed with anti-histamine eye drops only. While during treatment with Tacrolimus, none of the cases needed additional medications like topical steroids, anti-histamines or mast-cell stabilizers, for symptomatic relief.

Marked improvement was noted objectively, Table 2; conjunctival injection was the first sign to show improvement in all cases within two weeks of therapy. In addition, conjunctival papillary hyper-trophy showed improvement in all eyes. All 25 cases (50 eyes) with moderate to severe giant papillae, all showed reduction in size of the papillae as early as 2 weeks of therapy which flattened by1 month and disappeared by the end of 4 months of therapy. There was improvement in limbitis (limbal papillary hypertrophy) in all 54 cases (108 eyes), corneal punctate epithelial erosions in 54 cases (mild = 15 moderate = 52, severe = 41 eyes), and corneal pannus in 42 cases (62 eyes) after one month treatment which cleared fully after 2 months of therapy. Both cases (2 eyes) with a shield ulcer healed after two months therapy. All cases showed improvement in visual acuity by two Snellen's lines.

Only three cases complained of mild discomfort on instillation of the cream; the remaining 51 cases did not complain of any discomfort or burning sensation when asked specifically. Intraocular pressure remained normal in all cases and no other ocular complication related to Tacrolimus skin cream was seen in any case. No patient had to discontinue the medication due to any adverse effect.

DISCUSSION

Since VKC is an immune – mediated disease with marked ocular morbidity, the use of an immuno-modulating drug to control the debilitating symptoms of itching and watering in children becomes necessary in moderate to severe cases. The disease is known for its recurrence when therapy is stopped, hence the medications have to be used on a long – term basis. Topical steroids have been the preferred choice to – date to control symptoms in such cases, but their prolonged use results in vision-threatening complications like glaucoma, cataracts, corneal thinning and ectasia. Hence Tacrolimus has emerged as a very safe and effective steroid-sparing option which inhibits all immune reactions responsible for the pathogenesis of VKC.[9-12] Though an ophthalmic preparation is not available in Pakistan; this study confirms that Tacrolimus skin cream (0.03%) in such a mild concentration is a safe and effective therapeutic alternative to topical steroids for moderate to severe VKC.

We opted for Tacrolimus after its effectiveness in VKC has been demonstrated in other studies. Tacrolimus 0.1% 'skin' cream applied to the skin of lower eyelid in previous studies[13,14] had effectively controlled VKC. Sengoku *et al*[15] used 0.01 – 1% eye drops in an animal study for ocular allergy while Ohashi *et al*[16] used an 0.1% ophthalmic suspension in another clinical study.

This study shows that not only there was an effective control of patient's symptoms in all cases (Table 1) but a subjective improvement was also noted soon after starting the treatment (Table 2). Conjunctival injection was the first sign to show improvement within 2 weeks of therapy while conjunctival papillary hypertrophy also improved in all eyes within one month of therapy. A similar improvement was noted in giant papillae which started regressing after one month of therapy and disappeared after 4 months in all case. Corneal signs like punctate epithelial erosions, pannus, and to some degrees, the opacities in corneal stromal showed improvement. Similar results have been shown in a study by Ohashi *et al*[16] Kymionis *et al*[17] who used an

ophthalmic preparation.

2 cases in our series had a shield ulcer which also resolved after treatment with Tacrolimus and lubricants as has been reported previously[18]. Improvement in BSCVA in 21 out of 27 cases, who had an initial BSCVA less than 6/18, was seen due to the improvement of corneal status and ocular surface in general. However, the 6 cases which did not show improvement in VA had keratoconus which was confirmed by an Orbscan (due to constant rubbing of eyes and a thinned cornea due to previous use of topical steroids).

In our study, an attempt to discontinue Tacrolimus after 2 – 3 months of continuous use resulted in recurrence of a milder form of VKC hence they were asked to use it for at least 4 – 5 months and then gradually taper it over a further one month. In other studies, topical Tacrolimus has been stopped after 4 weeks in VKC and no recurrence was documented.[15,16] In a study by Miyazaki *et al,*[18] topical Tacrolimus was continued for 7 months while in another study, in patients with AKC,[13,18] it was used for up to 42 months and no side effects were reported. In our study, none of our cases needed additional medications like anti-histamines or mast cell stabilizers. Since its long-term use has been shown to be safe, it can be used as a prophylactic drug in less severe disease as well to prevent its aggravation during the hot, humid season of the year.

Upon initial application of tacrolimus, a local burning sensation has been reported,[16-18] it was seen in only 4 cases in our study and it disappeared after one week of therapy. During the follow-up period of 8 – 12 months (mean duration 10 ± 1.5 months), none of the cases developed any other side effects. However, because of its local immunosuppressive effect, it may result in activation of viral infections. Hence we excluded patients from our study who gave a history of previous herpes infection.

CONCLUSION

The use of Tacrolimus eye drops / ointment in the treatment of VKC has been a topic of extensive research. Consistent with previous reports, we found out that Tacrolimus skin cream 0.03% used twice daily in the lower conjunctival fornix shows marked improvement in VKC; all patients had an effective relief of their symptoms within one month of therapy. Since the nature of the disease requires long term usage, it was safe and easy to taper off the dosage and eventually stop it after 6 months with no adverse effects. There was no need to add additional medications like antihistamines or steroids in any case during the study.

Author's Affiliation

Dr. Sameera Irfan
Consultant Oculoplastic Surgeon
Mughal Eye Trust Hospital
301, H3/A, Johar Town, Lahore

Dr. Arsalan Ahmed
Mughal Eye Trust Hospital
301, H3/A, Johar Town, Lahore

Dr. Faiza Rasheed
Mughal Eye Trust Hospital
301, H3/A, Johar Town, Lahore

REFERENCES

1. **Bonini S, Coassin M, Aronni S, et al.** Vernal keratoconjunctivitis. Eye (Lond) 2004; 18: 345–51.
2. **Kumagai N, Fukuda K, Fujitsu Y, et al.** Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. ProgRetin Eye Res 2006; 25: 165–87.
3. **Kumar S.** Vernal keratoconjunctivitis: A major review. Acta Ophthalmo. 2009; 87: 133–47.
4. **Barney NP.** Vernal and atopic keratoconjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea: Fundamentals, Diagnosis and Management. 3nd ed. Philadelphia, PA, Elsevier/Mosby, 2011, pp 1–2
5. **Carnahan MC, Goldstein DA.** Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophthalmol. 2000; 11: 478–83.
6. **Kino T, Hatanaka H, Hashimoto M, et al.** FK-506, a novel immunosuppressant isolated from a Streptomyces. I. Fermentation, isolation, and physic-chemical and biological characteristics. J Antibiot (Tokyo). 1987; 40: 1249–55.
7. **Bertelmann E, Pleyer U.** Immunomodulatory therapy in ophthalmology: Is there a place for topical application? Ophthalmologica. 2004; 218: 359–67.
8. **Joseph MA, Kaufman HE, Insler M.** Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. Cornea 2005; 24: 417–20.
9. **Zhai J, Gu J, Yuan J, et al.** Tacrolimus in the treatment of ocular diseases. Bio Drugs. 2011; 25: 89–103.
10. **Kheirkhah A, Zavareh MK, Farzbod F, et al.** Topical 0.005% tacrolimus eye drop for refractory vernal keratoconjunctivitis. Eye (Lond). 2011; 25: 872–80.
11. **Lee YJ, Kim SW, Seo KY.** Application for tacrolimus ointment in treating refractory inflammatory ocular surface diseases. Am J Ophthalmol. 2013; 155: 804–13.

12. **Müller GG, José NK, Castro RS de.** Topical Tacrolimus 0.03% as sole therapy in vernal keratoconjuctivitis. Eye Contact Lens. 2014; 40: 79-83.
13. **Virtanen HM, Reitamo S, Kari M, Kari O.** Effect of 0.03%Tacrolimus ointment on conjunctival cytology in patients with severe atopic blepharoconjunctivitis: a retrospective study. Acta Ophthalmol Scand. 2006; 84: 693–5.
14. **Zribi H, Descamps V, Hoang-Xuan T, Crickx B, Doan S.** Dramatic improvement of atopic keratoconjunctivitis after topical treatment with tacrolimus ointment restricted to the eyelids. J Eur Acad Dermatol Venereol. 2009; 23: 489–90.
15. **Sengoku T, Sakuma S, Satoh S, Kishi S, Ogawa T, Ohkubo Y, et al.** Effects of FK506 eye drops on late and delayed-type responses in ocular allergy models. Clin Exp Allergy.2003; 33: 1555–60.
16. **Ohashi Y, Ebihara N, Fujishima H, Fukushima A, Kumagai N, Nakagawa Y, 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.
17. **Kymionis GD, Goldman D, Ide T, Yoo SH.** Tacrolimus ointment 0.03% in the eye for treatment of giant papillary conjunctivitis. Cornea. 2008; 27: 228–29.
18. **Myazakai, Vichyanond P, Tantimongkolsuk C, Dumrongkigchaiporn P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P.** Vernal keratoconjunctivitis: result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment. J Allergy Clin Immunol. 2004; 113: 355–8.