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Research Article

Comparative Evaluation of Tacrolimus 0.03% Ointment and Bepotastine 1.5% Eye Drops in the Management of Vernal Keratoconjunctivitis

Dr. Shabana Khan[1], Dr. Abdul Wahab Bhat[2], Dr. Aarij Zaffar Khan[3], Dr. Sheikh Saddait Hamid*

1. Assistant Professor, Department of ophthalmology, GMC Baramulla, J&K.
2. Associate professor, Department of ophthalmology, GMC Baramulla, J&K.
3. Senior Resident, Department of ophthalmology, GMC Baramulla, J&K.

***Correspondence to:** Dr. Sheikh Saddait Hamid, DNB 2nd year Resident, Tawheed Gunj, Baramulla, J&K Pin-193101.

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Abstract:

Objective: *To compare the therapeutic outcomes between tacrolimus 0.03% ointment and bepotastine 1.5% eye drops in treatment of vernal keratoconjunctivitis,*

Study Design: *Prospective cross-sectional study.*

Place and Duration of Study: *GMC Baramulla, (March-June) 2023.*

Methodology*: This study involved 30 vernal keratoconjunctivitis (VKC) patients. Half received 0.03% tacrolimus ointment, and the other half received bepotastine. Patients were randomly assigned, and chi-square and one-way ANOVA tests were employed for intergroup comparison.*

Results: *The study group, with a mean age of 8.3 ± 2 years, and the control group, averaging 8.1 ± 2 years, showed a notable reduction in signs and symptoms after treatment (p=0.0001). Disease duration averaged 4.2 ± 2.5 years. Within four weeks of topical tacrolimus treatment, the study group demonstrated marked improvements, and the control group also showed significant enhancement. The majority in the tacrolimus group responded well to treatment, with minimal side effects noted in both study and control groups.*

Conclusions: *While both 0.03% topical tacrolimus ointment and bepotastine demonstrate efficacy in treating VKC, the tacrolimus was significantly superior in comparison to the bepotastine.*

KEYWORDS*: Vernal Keratoconjunctivitis, Tacrolimus, Papillae, bepotastine*

Background

Allergic eye disease (AED) is a hypersensitivity reaction of type 1 that occurs when exposed to environmental triggers.[1,2] It can range from mild seasonal allergies to severe keratoconjunctivitis, which poses a threat to vision. Vernal keratoconjunctivitis (VKC) is a chronic inflammation of the conjunctiva that mainly affects children aged 3 to 16.[3,7] Although it often resolves during puberty, it can persist into adulthood.[3] VKC tends to be year-round and worsens in warmer climates.[4] The disease is seen mostly in tropical climate such as in countries surrounding the Indian sub- continent, the Middle-East, the Mediterranean, in West African nations and in Japan[8].The prevalence of VKC in the tropical regions of the world may be up to 5%[9].

About 40 to 75% of VKC patients also experience other manifestations of atopy. VKC causes significant discomfort, including intense itching, tearing, mucous discharge, and sensitivity to light. Conjunctival signs of VKC include redness, enlarged papillae, discharge, and Horner Trantas dots.[5,6] Various treatment options are available for VKC, such as antihistamines, mast cell stabilizers, and topical steroids. In moderate to severe cases, topical steroids are the primary treatment. However, prolonged steroid use carries the risk of complications like cataracts and glaucoma.[5,6] To mitigate these risks, steroid-sparing immunomodulatory agents like cyclosporine and tacrolimus have been utilized.

Tacrolimus is a potent immune suppressant derived from Streptomyces tsukubaensis, a type of bacteria. It acts by binding to specific proteins called FK506-binding proteins in T-lymphocytes, thereby blocking the activity of an enzyme called calcineurin. Compared to cyclosporine, another commonly used immunosuppressant, tacrolimus is exceptionally strong and can be up to 100 times more potent in its effects.

Methods

In this study, researchers closely monitored and examined 30 patients with active VKC who did not respond to conventional treatment. Before participating in the study, the patients provided written consent after being fully informed about the study's objectives and procedures. Certain criteria were established to exclude individuals from the study, such as having other conjunctival disorders, chemical injury, Stevens-Johnson syndrome, corneal diseases, uveitis, ocular infections, currently using contact lenses, recent use of systemic NSAIDs or steroids, recent ocular surgery within the past 3 months, pregnancy, presence of other infectious/inflammatory eye diseases, known allergy to tacrolimus, and receiving a steroid injection within the past 6 months.

VKC was diagnosed based on two main criteria: (1) the presence of chronic, bilateral symptoms including itching and redness, and (2) the identification of specific signs such as Trantas dots, papillae on the upper tarsal conjunctiva, and corneal erosions. The patients underwent thorough ophthalmic examinations, including assessments of best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy, fluorescein staining, fundoscopy, tear film evaluation, and applanation tonometry. In the first study group, patients received topical tacrolimus ointment 0.03% twice daily, while the control group received topical bepotastine 1.5% eye drops two times daily. The study duration was four weeks, with the tacrolimus dose initially administered twice daily for one month, followed by a gradual taper to once daily for an additional

week.The treatment regimen for the patients involved applying the tacrolimus ointment twice a week for the initial week, followed by once a week. Throughout the treatment period, patients were scheduled for evaluations at specific intervals, including one week, four weeks, six weeks, and subsequently every six months. The primary focus of evaluation was to measure the change from baseline using topical treatment.

Baseline assessments were conducted to observe objective signs and subjective symptoms, which were further evaluated at one, two, four, and six weeks after initiating the treatment. Objective parameters encompassed factors such as conjunctival hyperemia, papillary reaction, and the severity of limbal hyperplasia. Each sign was graded on a scale ranging from 0 (none) to 3 (severe). Subjective ocular symptoms, including redness, itching, and photophobia, as well as any side effects, were recorded by the patients on a daily basis throughout the entire treatment period. These symptoms and side effects were graded on a scale from 0 (none) to 3 (severe), with intermediate levels indicating the frequency and severity of symptoms.

The primary outcome measure focused on assessing the difference in scores for symptoms and objective signs between the study group and the control group at the conclusion of the four-week period. The secondary outcome measure aimed to evaluate the safety and tolerability of the tacrolimus ointment.

Clinical Scoring System

A clinical scoring system was utilized in this study as the primary outcome measure. The total subjective symptom scores and total objective ocular sign scores were assessed at each visit, as shown in Tables I and II. The scores from each visit were summed, with the maximum values for subjective symptoms and objective signs being 15 and 12, respectively. The comparison between groups was conducted based on these scores.

Table-I: Subjective symptom scores.

Symptoms	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Itching	1-2 times/day	3-5 times/day	5-9 times/day	>10 times/day
Grittiness sensation	1-2 times/day	3-5 times/day	5-9 times/day	>10 times/day

Symptoms	Grade 0	Grade 1	Grade 2	Grade 3
Photophobia	1-2 times/day	3-5 times/day	5-9 times/day	>10 times/day
Tearing	1-2 times/day	3-5 times/day	5-9 times/day	>10 times/day
Burning	1-2 times/day	3-5 times/day	5-9 times/day	>10 times/day

Table-II: Objective ocular sign scores.

Signs	Grade 0	Grade 1	Grade 2	Grade 3
Conjunctival inflammation	None	Dilation of some vessels	Dilation of many vessels	Not able to distinguish different vessels
Corneal involvement	None	Only few punctate erosion	Half cornea involved	Diffusely scattered on whole cornea
Giant papillae	None	Very few giant papillae	Giant papillae in less than half of upper palpebral conjunctiva	Giant papillae in more than half of upper pulpebral conjunctiva
Limbitis	None	1-3 Limbal papilae	4-6 Limbal papilae	7 or more Limbal papilae

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23. Quantitative analysis involved the utilisation of independent sample t-tests and one-way ANOVA. A significance level of $p \leq 0.05$ was considered statistically significant.

Ethics

Ethical considerations were upheld throughout the study by obtaining written informed consent from the patients. The authors ensured that all necessary patient consent forms were obtained, clearly explaining the purpose of the study and the potential use of their images and clinical information in the journal publication. Patients were made aware that their identities would be protected through the use of pseudonyms and efforts

to maintain confidentiality; however, complete anonymity could not be guaranteed. The study protocol was approved by the Institutional Ethics Committee, ensuring that it adhered to established ethical guidelines

Results

Group	Week 0	Week 12	p-value
Tacrolimus (study) 15 patients	10.90	0.013	<0.001
Bepotastine (control) 15 patients	8.89	1.7	<0.001

Table-III : Intra-group comparison of mean scores in subjective symptoms

Group	Week 0	Week 12	p-value
Tacrolimus (study) 15 patients	3.9	0.07	<0.001
Bepotastine (control) 15 patients	4.2	0.64	<0.001

Table-IV: Intra-group comparison of mean scores in objective symptoms

Score	Tacrolimus	Bepotastine	p-value
Mean subjective symptoms score (week 12)	0.013	1.7	<0.001
Mean objective symptoms score (week 12)	0.07	0.64	<0.001

Table-V: Inter-group comparison of scores by one-way ANOVA.

Out of the total of 30 patients, 11 were males, and the remaining 19 were females. The mean age of patients

in group A was 8.3 ±2 years, while for group B, it was 8.1 ± 2.18 , respectively. This indicates that both groups were similar in terms of age and the severity of the disease.

Significant reductions in both subjective symptoms and objective signs scores were observed within both the tacrolimus and bepotastine groups when compared to their initial values. These reductions started becoming statistically significant at the fourth week of the study and continued throughout the entire 12-week period. Refer to Table I & II for more detailed information.

The overall improvement in scores, measured as a percentage of the baseline values, was 98.3% in the tacrolimus group and 83% in the bepotastine group. When comparing the two groups, a statistically significant difference was found, highlighting the superior effectiveness of tacrolimus over bepotastine.

While no major ocular complications or systemic side effects related to the use of tacrolimus or bepotastine were observed, some patients in the tacrolimus group did report occasional photophobia. It is worth noting that none of the patients needed to discontinue the medication due to severe adverse effects. However, in the tacrolimus group, one patient and in the bepotastine group, four patients (15.15%) required local steroid treatment for a duration of three days to manage severe redness and itching.

Discussion

In the management of vernal keratoconjunctivitis (VKC), various approaches are employed, including preventive measures, medical interventions, and, in severe cases, surgical procedures.[15] Prevention strategies involve measures like vaccination and avoiding allergens such as house dust mites, pollen, and dust. Surgical options, although reserved for severe cases, may involve the removal of upper tarsal giant papillae or debridement of non-healing shield ulcers.[1,15] Medical therapy is the preferred approach for acute VKC and typically includes topical antihistamines, mast cell stabilizers, mucolytics, and lubricants as first-line treatment.[16.] However, in severe and chronic cases, the addition of topical corticosteroid drops and supratarsal steroid injections may be necessary to manage symptoms.[16] It is important to exercise caution and avoid prolonged use of topical steroids to prevent potential complications such as glaucoma, cataracts, and secondary infections.[20] Children with VKC are particularly vulnerable to the adverse effects of steroids, as they are the most commonly affected age group.[17]

Bepotastine is currently one of the most commonly prescribed drugs, along with topical steroids, for the treatment of allergic conjunctivitis. It acts by selectively blocking the histamine H1 receptor, which helps inhibit the release of histamine and stabilize mast cells.[18] The US Food and Drug Administration has approved bepotastine 1.5% for the treatment of allergic conjunctivitis. [19]

On the other hand, Tacrolimus is a potent nonsteroidal macrolide immunosuppressant derived from Streptomyces tsukubaensis.[10] It is approximately 100 times more potent than cyclosporine. The exact mechanism of action of tacrolimus is not fully understood, but it is believed to suppress the activation of Th2 lymphocytes (which are key cells in VKC), inhibit T helper cell-mediated B-cell proliferation, and reduce the production of cytokines. Initially used as an immunosuppressant in organ transplants, it is now being utilized in the treatment of various skin disorders such as vitiligo and atopic dermatitis.[11] The efficacy and safety of tacrolimus have been evaluated in different types and concentrations, yielding varying overall efficacy results.

In our study, significant improvement was observed in all patients receiving 0.03% tacrolimus and those treated with 0.2% bepotastine. The severity of their symptoms significantly decreased, indicating that both drugs are effective options for patients with VKC. However, there was a statistically significant difference between the two drugs, with the tacrolimus group exhibiting fewer remaining signs and symptoms after three months of treatment compared to the bepotastine group.

Similar to our study, Sameera Irfan et al[12]. demonstrated that topical use of 0.03% tacrolimus skin ointment was a safe and effective treatment for moderate to severe VKC. However, their study reported a cumulative percentage of improvement in signs and symptoms of 90.43%, which is lower compared to the 98.3% improvement observed in our study. This disparity could be attributed to differences in the study locations and weather conditions. Another study by Lab-charoenwongs et al. showed that 0.1% tacrolimus eye ointment was effective in treating active VKC in children after four weeks of treatment, with a significant total improvement of symptoms (86.49% improvement compared to baselines).

Vichyanond et al[13]. also conducted a study using tacrolimus for the long-term treatment of severe VKC without significant adverse effects. Prolonged use of tacrolimus not only reduced symptoms but also decreased papillary hyperplasia. Other comparative studies conducted found that adding bepotastine to 0.03% tacrolimus did not provide additional effects.

While there are various studies on the efficacy of tacrolimus in treating VKC, there is currently no comparative study on the efficacy of tacrolimus versus bepotastine. Our study is the first to compare the effectiveness of these two drugs for the treatment of VKC.

Although there have been recorded complications associated with tacrolimus, such as reactivation of herpes simplex keratitis and increased susceptibility to molluscum contagiosum,[14] none of the patients in our study experienced any serious ocular complications. While our study has some limitations, including a lack of diversity in the sample size and a relatively short follow-up period, its significance lies in the inclusion of both subjective and objective data from a relatively large sample size. Further studies with long-term follow-up are needed to confirm the safety and efficacy of this drug in the future.

Conclusion

In summary, our findings demonstrate that bepotastine 1.5% eye drops are less effective compared to tacrolimus 0.03% ointment in relieving the symptoms and clinical signs of individuals with VKC.

References

1. BuckleyRJ.Allergiceyedisease-aclinicalchallenge.Clin Exp Allergy 1998;28(Suppl 6):39-43.

2.Bremond-Gignac D, Donadieu J, Leonardi A, et al. Prevalence of vernal keratoconjuntivtis: a rare disease? Br J Ophthalmol 2008;92(8):1097-1102.

3.Al–Amri AM, Mirza AG, Al-Hakami AM. Tacrolimus ointment for treat-ment of Vernal keratoconjunctivitis. Middle East Afr J Ophthalmol 2016;23(1):135-138.

4.Tabbara AK, El-Asrar A. Immunopathogenesis of ocular allergy. In: Jo-hansson SGO, (ed). Progress in allergy and clinical immunology. Seattle: Hogrefe and Huber 1997:381-385.

5.Leonardi A, Bogacka E, Fauquert JL, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. Allergy 2012;67(11):1327-1337.

6.Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. Prog Retin Eye Res 2002;21(3):319-339.

7.Labcharoenwongs P, Jirapongsananuruk O, Visitsunthorn N. Adouble-masked comparison of 0.1%

tacrolimus ointment and 2% cyclo-sporine eye drops in the treatment of vernal kerato con- junctivi-tisin children. Asian Pac J Allergy Immunol 2012; 30(3): 177–84.

8.Collum MT. Vernal keratoconjunctivitis. Acta Ophthalmol Scand 1999; 228(Suppl): 14-16.

9.Bremond-Gignac D, Donadieu J, Leonardi A. Prevalence of ver- nalk-eratoconjunctivitis: a rare disease?. Br J Ophthalmol 2008; 92(1): 1097–02.

10. William F. Review of medical physiology. 22nd ed. Lange Medi- cal Books; 2005. Ganong"s; [Internet]. http:// hdl.handle. net/ 123456789/425.

11. Peters DH, Fitton A, Plosker GL, Faulds D. Tacrolimus. A rev- iew of its pharmacology, and therapeutic potential in hepatic and renal transplantation. Drugs 1993; 46(2): 746–94.

12. Irfan S. To Study the Efficacy & Safety of Tacrolimus Skin Cream, 0.03%, in VKC. Pak J Ophthalmol 2015; 31(1): 15-22.

13. Vichyanond, P. Kosrirukvongs, P. Use of Cyclosporine A and Tac-rolimus in Treatment of Vernal Keratoconjunctivitis. Current Allergy Asthma Report 2013; 13(3): 308-14.

14. Zribi H, Descamps V, Hoang-Xuan T, Crickx B, Doan S. Drama- tic improvement of atopic keratoconjunctivitis aftertopical treat- ment with tacrolimus ointment restricted to theeyelids. J Eur Acad Derma-tol Venereol 2009; 23(4): 489–90.

15 Leonardi, A. Management of Vernal Keratoconjunctivi-tis. Ophthalmol Ther 2, 73–88 (2013). https://doi.org/10.1007/s40123-013-0019-y

16 Chigbu, D. I. (2009). The management of allergic eye diseases in primary eye care. Contact Lens and Anterior Eye, 32(6), 260-272.

17 Kaur, S., Dhiman, I., Kaushik, S., Raj, S., & Pandav, S. S. (2016). Outcome of ocular steroid hypertensive response in chil-dren. Journal of Glaucoma, 25(4), 343-347.

18. Ackerman, S., Smith, L. M., & Gomes, P. J. (2016). Ocular itch asso-ciated with allergic conjunctivitis: latest evidence and clinical man-agement. Therapeutic advances in chronic disease, 7(1), 52-67.

19. Macejko, T. T., Bergmann, M. T., Williams, J. I., Gow, J. A., Gomes, P. J., McNamara, T. R., ... & Bepotastine Besilate Ophthalmic Solu-tions Clinical Study Group. (2010). Multicenter clinical evaluation of bepotastine besilate ophthalmic solutions 1.0% and 1.5% to treat al-lergic conjunctivitis. American journal of ophthalmology, 150(1), 122-127.

20 Holland, E. J., Fingeret, M., & Mah, F. S. (2019). Use of topical ster-oids in conjunctivitis: a review of the evidence. Cornea, 38(8), 1062-1067.

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