ORIGINAL ARTICLE

Comparison of 0.1% Topical Tacrolimus with 0.05% Topical Cyclosporine in Treatment of Vernal Keratoconjunctivitis

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Abstract:

Objective: To compare the effectiveness of 0.1% tacrolimus skin ointment with 0.05% cyclosporine eye drops in the initial management of moderate to severe vernal keratoconjunctivitis.

Methods: This quasi-experimental study was conducted at a tertiary care Hospital in Bannu, from Sep 22 to Apr 23. Total 46 patients (96 eyes) with moderate to severe VKC were enrolled. Consecutive sampling was done. All patients were off treatment before enrolment. Patients were divided into two groups. One group was given 0.1% tacrolimus dermatologic ointment and the other was given 0.05% cyclosporine eye drops. Subjective and objective signs were scored according to criteria and recorded pretreatment, at 2 weeks and 4 weeks with treatment. Data was analysed by using SPSS version 20.

Results: Mean age of the patients was 8.6 years ± 3.8 SD. Subjective and objective scores were analyzed by using paired sample T test and comparison between both medicines was done by applying independent sample T test. Both of the drugs showed statistically significant improvement at 2 and 4 weeks of treatment (p value< 0.001). Both of the drugs were found to be equally effective at 2 and 4 weeks (p value >0.05 %) except for photophobia and giant papillae which were improved better in cyclosporine group at 2 weeks. However, at 4 weeks there was no significant difference.

Conclusion: Both tacrolimus 0.1% ointment and 0.05% cyclosporine eye drops are equally effective in the treatment of VKC and can be used in the initial management of moderate to severe VKC.*Al-Shifa Journal of Ophthalmology 2025; 21(4): 239-246. Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan.*

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Originally Received: 05 July 2025
Revised: 27 July 2025
Accepted: 3 August 2025

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Introduction:

Vernal keratoconjunctivitis VKC is a chronic recurrent ocular inflammatory condition affecting mostly children and adolescents. The patients present with itching, redness, discharge, grittiness and photophobia. If untreated or improperly treated it can lead to various sight threatening complications like shield corneal ulcer, irregular astigmatism and keratoconus due to frequent eye rubbing.[1] Various topical antiallergic like antihistamine and mast cell stabilizer and topical anti-inflammatory agents like steroids and immune modulators are used to control the disease.[1] Since the disease has a chronic and relapsing course long term treatment is generally required to keep it under control and prevent disease related complications.

VKC is more common in warm and dry climate. Bannu, Khyber Pakhtunkhwa (KPK) is amongst those areas of Pakistan which have same climate. Due to rapid symptomatic relief and effectiveness steroids are judiciously used by patients of VKC. They are either prescribed by general practitioners, pharmacist or quacks.

Many a times they are used by the patients without any advice since it provides a quick relief, since they are unaware of the sight threatening complications of such practice. In our clinical practice many cases of VKC report to ophthalmologist when they already had developed vision threatening complications of self-medication with steroids like glaucoma, cataract and infections. This has led to the urge of using steroid sparing agents as first line treatment for VKC.

Various immune modulators like Cyclosporine have found to be safe and effective for the treatment of VKC. The only side effect observed with it was burning of eyes.[2] Calcinurin inhibitors like tacrolimus has also been found to be safe and effective in the treatment of VKC. Qi Wan et al found 0.1% tacrolimus eye drops to be efficacious in treating tarsal form of VKC with few side effects like tingling and burning sensation.[3] Tacrolimus ophthalmic ointment/eye drops are not available in Pakistan. However various studies have found the dermatological tacrolimus ointment can be used to treat VKC effectively and it is also commercially obtainable in Pakistan.[4] In another study conducted in Saudi Arabia 0.1% tacrolimus skin ointment has been found to be safe and effective in the treatment of VKC on long term follow up of 24 months.[5] To compare the efficacy of both drugs various studies have been carried out. In one of the studies in Nepal, Kumari R et al has evaluated and compared the efficacy and safety of tacrolimus eye ointment 0.03% and cyclosporine eye drops 0.05% in the treatment of VKC and has found both of them to be equally effective.[6]

The aim of this study is to compare the effectiveness of 0.1% tacrolimus skin ointment with 0.05% cyclosporine eye drops in the initial management of moderate to severe VKC. Both are non-steroidal preparations and are commercially easily available in Pakistan. No local study has been done so far in this regard.

Methodology:

This quasi-experimental study was conducted at Tertiary Care Hospital Bannu from September 2022 to April 2023. Ethical approval was taken from ethical review committee of the hospital. Consecutive sampling was done. 96 eyes of 48 patients were included in the study. Patients were randomly assigned into 2 groups by lottery method.

Patients with moderate to severe conjunctivitis were included in the study. Patients presenting with bilateral recurrent episodes of itching, redness, watering, grittiness, foreign body sensation and photophobia were included in the study. Along with these symptoms, they had conjunctival congestion, papillae including limbal, palpebral or giant papillae and corneal epithelial erosions.

Patients with mild allergic symptoms of short duration, patients with other ophthalmic diseases like glaucoma, patients with previous treatment with subconjunctival steroid injections were excluded. Patients were given a questionnaire for grading of their symptoms including redness, itching, discharge, grittiness and photophobia as 0 = None, 1 = Mild (occasional symptoms), 2 = Moderate (frequent symptoms) and 3 = Severe (constant symptoms)

Table 1: Objective Signs Assessment.

Objective signs	Score	Definition
Conjunctival hyperemia	0	None
	1	Few dilated blood vessels (up to 10)
	2	Several dilated blood vessels (>10)
	3	Unable to distinguish individual blood vessels
Papillae <1mm size	0	None
	1	Few scattered micropapillae
	2	Few scattered macropapillae <1mm
	3	Several macropapillae, diffuse velvety appearance
Punctate epithelial erosions	0	None
	1	Few scattered erosions
	2	Half of the cornea involved
	3	Erosions all over cornea
Limbitis	0	None
	1	1 to 3 limbal papillae
	2	4 to 5 limbal papillae
	3	6 or more limbal papillae
Giant papillae >1mm size	0	None
	1	1 to 3 giant papillae
	2	>3 giant papillae involving <1/2 of palpebral conjunctiva
	3	Giant papillae involving >1/2 of palpebral conjunctiva

After taking consent from the parents/guardian of the patients, all of the patients underwent thorough ocular examination including vision, intraocular pressure and anterior segment examination with corneal staining. Pre-treatment findings were noted. Patients and their parents were counselled regarding treatment like mode of application, its benefits being steroid sparing agents and possible side effects. Tacrolimus dermatologic 0.1% ointment was used since ophthalmic ointment is not available in Pakistan.

All of the patients were off treatment at least 2 weeks prior to inclusion in study. Patients were randomly divided into 2 groups. One group was given Tacrolimus 0.1% dermatological ointment twice daily in the inferior fornix along with Olopatadine 0.2% eye drops TDS, the other group was given cyclosporine 0.05% eye drops TDS with Olopatadine 0.2% eye drops TDS. Olopatadine eye drops were discontinued after 2 weeks, because by that time both immune modulating agents have started their full effects, and only tacrolimus ointment and cyclosporine eye drops were given along with a lubricant to continue up till 4 weeks.

On follow up visit patients were asked about the compliance to treatment and symptoms according to scale. They were examined for any possible side effect like glaucoma, lenticular opacity and secondary infections. Any need for additional medicines was also noted. All of these findings were recorded before starting treatment, at 2 weeks and 4 weeks with treatment.

Results:

Total 60 patients were enrolled initially at the start of study, 30 in each group. Six patients of the tacrolimus group and two of cyclosporine group did not report at first follow up. They were excluded from the study. Demographic study revealed that they were from remote areas of KPK. Data was analysed by using SPSS version 20.

Total 96 eyes of 48 consecutive patients of VKC who were fulfilling the inclusion criteria were enrolled. 70% of the patients were male while 30% were female. Confidence interval was kept 95%. Mean age of the patients was 8.6 years ± 3.8 SD. 78 eyes had treatment previously for episodic aggravation of disease, in the form of topical steroid, topical anti-histamine and mast cell stabilizers. 18 eyes were newly diagnosed cases. Tarsal VKC was most common form of presentation (n= 50) followed by mixed (n= 34) and then limbal (n = 12). Five major complaints recorded by patients were redness, itching, discharge, grittiness were present in all cases (n=96) however photophobia was present in 82 cases.

Symptomatic improvements were observed and analyzed by using paired sample T test and compared between both medicines by applying independent sample T test. Paired sample T test showed P value at 2 weeks and 4 weeks to be less than 0.001. These values are less than 0.05 so both medicines are statistically highly significant for efficacy. Improvement in the mean subjective symptoms score on follow up is shown in Figure 1.

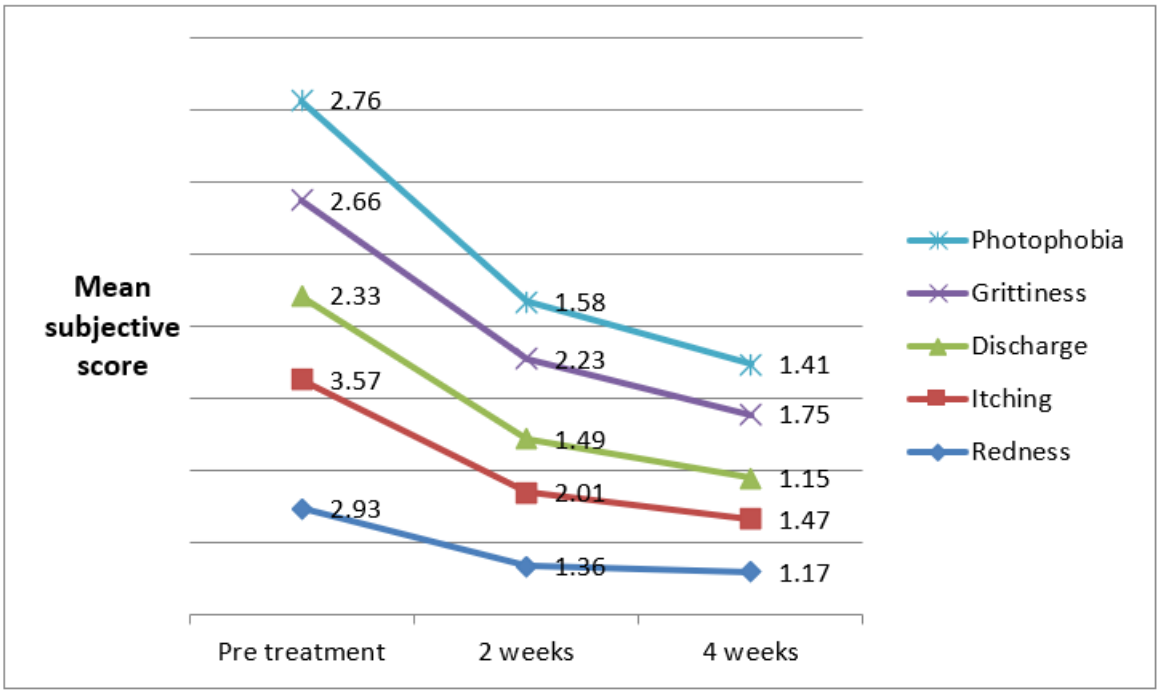

Figure 1: Improvement in mean subjective score

Based on the independent sample T test results shown in table 2, both medicines demonstrated comparable overall efficacy, as the P value for all symptoms were greater than 0.05. This indicates no statistically significant difference between the two treatment groups. However, a significant difference was observed for photophobia at 2 weeks (P=0.01), where cyclosporin produced greater improvement than tacrolimus. By 4 weeks, this difference was no longer present, as the P value increased to 0.15, showing that both medicines were equally effective in reducing photophobia at that stage.

Table 2: Independent sample T test for symptoms at 2 and 4 weeks

Symptoms	P value at 2 weeks CI 95%	P value at 4 weeks CI 95%
Redness	0.29	0.59
Itching	0.51	0.54
Discharge	0.84	0.08
Grittiness	0.77	0.64
Photophobia	0.01	0.15

Objective improvements were observed and analyzed by using paired sample T test at 2wks and 4 wks. At 2 weeks of treatment all parameters improved statistically significant (P value 0.001) except Giant papillae (P value 0.083). However, all parameters improved at 4wks, P value being less than 0.05. Fig 2

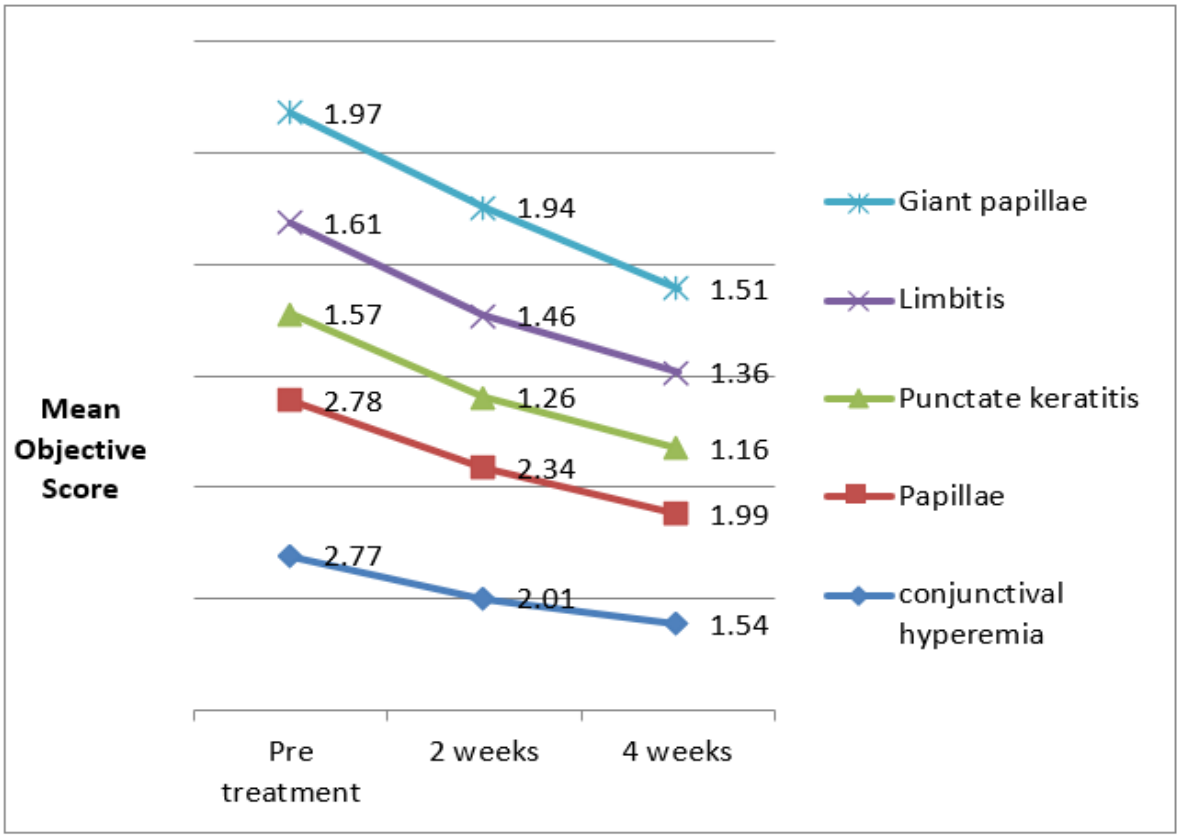

Figure 2: improvement in mean objective score

Efficacy of both drugs was compared by using independent sample T test. Both of the drugs are found to be equally effective in improving objective signs including papillary reaction, punctate keratitis, limbitis and giant papillae P values > 0.05 as shown in table. However conjunctival hyperemia was improved more in the cyclosporine group than in the tacrolimus group at both 2 and 4 weeks.

Table 3: Independent sample T test at 2 and 4 weeks for objective signs

Objective signs	At 2 weeks P value CI 95%	P value at 4 weeks CI 95%
Conjunctival hyperemia	0.043	0.014
Papillary reaction	0.283	0.883
Punctate keratitis	0.818	0.404
Limbitis	0.173	0.834
Giant papillae	0.636	0.173

Burning of eyes was the main side effect reported by 83.3% (n=20) at 2 weeks and 62.5% (n= 15) of the patients in tacrolimus group and 33.3% (n=8) of the patients in cyclosporine group at 2 weeks and 16.6% (n=4)

Discussion:

Allergic conjunctivitis is one of the commonly presenting ocular disorders in ophthalmic outpatient departments. Its prevalence varies in different areas of the world; however, it is more prevalent in areas with hot and humid climate. Asia is the region of the world with highest prevalence of allergic conjunctivitis.[7] In one of the studies conducted in Karachi its prevalence was found to be 19.2%.[8] Vernal keratoconjunctivitis is one of the variants of allergic conjunctivitis which has a chronic, recurrent and bilateral involvement of eyes.[9] The diagnosis of the disease is clinical. Major presentation symptoms are redness, itching, discharge, photophobia and grittiness of eyes. Continuous itching and watering greatly affects the quality of life. The clinical signs for diagnosing vernal keratoconjunctivitis are conjunctival injection, conjunctival papillae, giant papillae and corneal involvement like punctate erosions and shield ulcer etc. if the conjunctival papillae are mainly in tarsal conjunctiva it is called tarsal VKC, if papillae are more in limbal conjunctiva then it is called as limbal VKC however if they are distributed in both limbal and tarsal conjunctiva then it is called mixed VKC.[10] VKC is more prevalent in boys than girls.[11] In our study also 70% of the patients were boys.

VKC is a self-limiting disease and it spontaneously resolve after puberty but there are chances of developing vision threatening complications if untreated.[9] Topical anti histamine and mast cell stabilisers are used to control the disease but they have only transient effect.[12] Immune modulation is the main stay of treatment. Cyclosporine topical preparations have been studied for the treatment of VKC by many researchers with varying results. Bourcier T et al have studied the effect os 1% 1nd 2% cyclosporine eye drops for treatment of VKC and found them to be equally effective in improving the subjective and objective signs even upto 12 months follow up and reduced corticosteroid use.[13] 1% cyclosporine was used to treat the resistant cases of VKC in a long-term study of 6 months and significant improvement was noted from the first month of treatment.[14] In another study by Yücel OE and Ulus ND 0.05 % cyclosporine eye drops were used to treat resistant VKC cases and found significant clinical improvement in symptoms and signs at 4 weeks of treatment and helped to reduce corticosteroid use.[15] In our study we used 0.05% cyclosporine eye drops, significant clinical improvement was noted at 2 and 4 weeks even in the newly diagnosed cases as well (p value <0.05). The stinging sensation has reported as one of its side effects in various studies.[13,14] Our patients also complained of it at the start of treatment only. They experienced it for few minutes after instillation and it disappeared in a few days i,e 3-5 days.

Tacrolimus has been studied extensively as an immune modulator and corticosteroid sparing agent by many researchers. Dr Sameera Irfan studied the efficacy of 0.03% tacrolimus skin cream in treatment of VKC and found it to be highly efficacious

without any side effects.[4] In another study by Al-Amri AM et al clinical improvement was noted as early as 1 week with treatment with the use of 0.1% tacrolimus dermatologic ointment. However, 25% of their patients lost follow up due to severe burning sensation.[16] In a long-term study 0.1% tacrolimus eye drops were used to treat severe allergic conjunctivitis for a longer period of time of average 8.4 years. Significant clinical improvement was noticed from 2 week of treatment onwards and patients only experienced mild, well tolerated burning sensation on instillation. However, none of the patient discontinued treatment due to these mild side effects.[17] These differences could be due to various drug preparations used in different studies. Different strengths of tacrolimus have also been studied to find out their efficacy and it was found that amongst the dermatologic preparations of tacrolimus 0.03% qnd 0.1% when used to treat recalcitrant, both were found out to be equally effective however the conjunctival papillae responded better to 0.1%.[18] In our study we used 0.1% dermatological tacrolimus ointment which showed significant clinical improvement which is consistent with the above-mentioned studies.[4,16,17,18]

In our study all of the symptoms were improved significantly at 2 weeks and 4 weeks in both groups, however on comparison of both drugs cyclosporine improved photophobia earlier than tacrolimus. This can be due to the burning sensation which was reported by 83.3% of the patients in tacrolimus group. Cause of this could be either use of 0.1% tacrolimus ointment or use of dermatologic preparation instead of ophthalmic preparation due to non-availability. The burning sensation was treated with the ophthalmic lubricant eye drops. However, none of the patients stopped treatment due to this side effect. Objective signs were improved in both of the groups at 2 weeks and 4 weeks however the improvement in giant papillae papillae was not statistically significant at 2 weeks but it was significantly improved at 4 weeeks. These findings are not consistent with the findings of Qi Wan et al who observed significant improvement in giant papillae after 8 weeks of treatment rather than 4 weeks[3]. This earlier response in our study can be due to the use of tacrolimus ointment instead of eye drops.

Conclusion:

Our study suggests that both tacrolimus 0.1% ointment and 0.05% cyclosporine eye drops are equally effective in the treatment of VKC. However long-term studies are required to access the use of these drugs for a longer period of time.

References:

1. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol (Auckland, N.Z.) 2018;12:119–23.
2. N Pucci, R Caputo, F Mori et al. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):865-71. doi: 10.1177/039463201002300322.
3. Wang Q, Tang J, Han Y et al. Therapeutic Effect of 0.1% Tacrolimus Eye Drops in the Tarsal Form of Vernal Keratoconjunctivitis. Ophthalmic Res 2018;59(3):126-134. doi: 10.1159/000478704. Epub 2017 Aug 12.
4. Irfan S, Ahmed A and Rasheed F. To Assess the Efficacy and Safety of Tacrolimus Skin Cream, 0.03% in Moderate to Severe Vernal Keratoconjunctivitis. Pak J Ophthalmol 2015, Vol. 31 No. 1;Jan – Mar; 15-21.
5. Al-Amri AM, Mirza AG, Al-Hakami AM. Tacrolimus Ointment for Treatment of Vernal Keratoconjunctivitis. Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):135-8. doi: 10.4103/0974-9233.164616.
6. Kumari R et al. Tacrolimus versus Cyclosporin. Nepal J Ophthalmol 2017; Vol 9 (18): 128-135. DOI:

http://dx.doi.org/10.3126/nepjoph.v9i2.19257
7. Miyazaki D, Fukagawa K, Okamoto S et al. Epidemiological aspects of allergic conjunctivitis. Allergology International 69 (2020) 487e495. https://doi.org/10.1016/j.alit.2020.06.004
8. Baig R, Walayat A, Ali T et al. prevalence of allergic conjunctivitis in school children of Karachi. JPMA (2010), 60(5), 371-373.
9. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol. 2018 Jan 11;12:119-123. doi: 10.2147/OPTH.S129552. PMID: 29391772; PMCID: PMC5769567.
10. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. Curr Opin Allergy Clin Immunol. 2007 Oct;7(5):436-41. doi: 10.1097/ACI.0b013e3282efb726.
11. Sacchetti M, Plateroti R, Bruscolini A, Giustolisi R, Marenco M. Understanding Vernal Keratoconjunctivitis: Beyond Allergic Mechanisms. Life (Basel). 2021 Sep 26;11(10):1012. doi: 10.3390/life11101012.
12. Mehta JS, Chen WL, Cheng ACK et al. Diagnosis, Management, and Treatment of Vernal Keratoconjunctivitis in Asia: Recommendations From the Management of Vernal Keratoconjunctivitis in Asia Expert Working Group. Front Med (Lausanne). 2022 Aug 1;9:882240. doi: 10.3389/fmed.2022.882240.
13. Bourcier T, Dory A, Dormegny L, Alcazar J, Gaucher D, Sauer A. Efficacy and Safety of 0.1% Cyclosporine versus 2% Cyclosporine in the Treatment of Severe Vernal Keratoconjunctivitis in Children. Clin Ophthalmol. 2022;16:3589-3596.https://doi.org/10.2147/OPTH.S370414
14. H. Fujishima, Y. Takano, D. Murat, M. Tanaka, N. Okada, A. Igarashi, K. Tsubota, K. Fukagawa; 0.1% Cyclosporine Eye Drops for Patients With Vernal Keratoconjunctivitis. Invest. Ophthalmol. Vis. Sci. 2007;48(13):5845.
15. Yücel OE, Ulus ND. Efficacy and safety of topical cyclosporine A 0.05% in vernal keratoconjunctivitis. Singapore Med J. 2016 Sep;57(9):507-10. doi: 10.11622/smedj.2015161. Epub 2015 Nov 13.
16. Al-Amri AM, Mirza AG, Al-Hakami AM. Tacrolimus Ointment for Treatment of Vernal Keratoconjunctivitis. Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):135-8. doi: 10.4103/0974-9233.164616.
17. Yazu, H., Fukagawa, K., Shimizu, E. et al. Long-term outcomes of 0.1% tacrolimus eye drops in eyes with severe allergic conjunctival diseases. Allergy Asthma Clin Immunol 17, 11 (2021). https://doi.org/10.1186/s13223-021-00513-w
18. Saha BC, Kumari R, Ambasta A. Comparision of efficacy and safety of 0.03% and 0.1% tacrolimus ointment in children with vernal keratoconjunctivitis. Ther Adv Ophthalmol. 2023 May 26;15:25158414231173532. doi: 10.1177/25158414231173532.

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