Efficacy of topical tacrolimus ointment 0.03% as monotherapy for the treatment of vernal keratoconjunctivitis

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ABSTRACT

Background: Given the potential adverse effects associated with long-term corticosteroid use, there was need for alternative treatment options that can effectively manage VKC while minimizing the risk of complications. Tacrolimus, a potent immunosuppressive agent, had emerged as a promising alternative due to its ability to modulate the immune response.

Purpose: The purpose of this study was to evaluate the effect of tacrolimus ointment 0.03% as a monotherapy in the treatment of vernal keratoconjunctivitis.

Methodology: Consent was taken from participants. patients who were diagnosed by recurrent vernal keratoconjunctivitis was recruited for study. Slit lamp examination was done to assess the categories of vernal keratoconjunctivitis. Study participants discontinued all the medications one week before beginning treatment. Tacrolimus 0.03% ointment was given for three months and effect on VKC was assessed after 1st week, 1st month, 2nd month and 3rd month.

Results: In this study minimum age was 5 years and maximum age was 20 years. Gender wise 89% was male and 11% were females. The mean scores of effect of tacrolimus was statistically significant (P Value=0.00). Subjective ocular symptoms and objective ocular signs at the baseline, first week, first month, second and third month had significant association by the usage of tacrolimus ointment. During the follow-

ups, no other topical medications were required and no significant changes in visual acuity were documented. No cataracts or elevation of intraocular pressures were detected.

Conclusion: The findings of this study demonstrate the efficacy and safety of topical tacrolimus ointment 0.03% as monotherapy for the treatment of VKC, it could offer an alternative treatment option to corticosteroids and potentially reduce the long-term complications associated with their use. The results of this study may contribute to improving the management and quality of life for individuals affected by VKC, particularly children and young adults.

Keywords: Allergy, Photophobia, Pruritus, Tacrolimus

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a severe, long-lasting inflammatory eye condition. VKC is an allergic eye disorder that mostly affects youngsters and is prevalent in warmer countries (1). It is distinguished by chronic corneal and conjunctival inflammation. On average, it affects three out of every four males in their first decade of life before fading away by late adulthood. Ocular symptoms include itching, burning, redness, photophobia and mucous discharge are the most prominent (2). On inspection, it's usual to see large papillae on the upper tarsal conjunctiva (which gives the appearance of cobblestones) and gelatinous infiltrations around the limbus enclosing the cornea known as the Horner-Trantas dot in certain patients. Clinical data and immunohistochemistry investigations imply a complicated, immune-mediated pathology, but the etiology and pathophysiology of VKC are still unknown (3). Weather, sunlight, male gender, socioeconomic position, dust and wind exposure, underlying atopy, kerosene/wood fire smoke, and intimate animal interaction have all been linked to an increased risk of VKC (4)

Among developed-world, VKC accounts for just 0.1% to 0.5%. The incidence of VKC is rather low in Europe, at 1.2-1.06 per 100,000 people. Its prevalence is greater in the subtropical and tropical regions of Africa, the Middle East, Latin America, and Asia, where temperatures are often high (5).

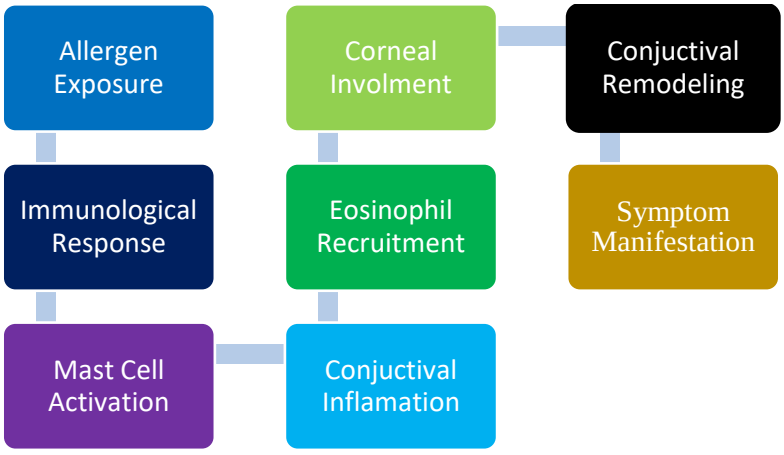

Figure 1.1 Pathophysiology of VKC

If left untreated, VKC may result in irreparable visual loss. Untreated, 4.6% of people with VKC result in some degree of vision impairment or complete blindness. Complications from severe VKC, including as keratitis, shield ulcers, keratoconus, corneal hydrops, astigmatism, cataract, and glaucoma, make it a potentially blinding illness in impoverished nations (6). One of the most popular therapies for treatment is the dual-action antihistamine/anti-inflammatory medication combination of lodoxamide and olopatadine (7). To treat flare-ups when these are ineffective, topical corticosteroids may be required. Infections, glaucoma, cataracts, and increased intraocular pressure are a few other possible side effects of prolonged topical steroid use.

Tacrolimus is an immunomodulators that may replace standard VKC therapy (). It has been discovered that tacrolimus applied topically works by preventing gene transcription and altering T cell signal transduction pathways. T cells' sensitivity to antigens is reduced as a result. At dosages between 0.03% and 0.3%, tacrolimus ointment has been shown to be helpful in reducing the severity and symptoms of atopic dermatitis in both adults and children (8).

Tacrolimus, a powerful immunosuppressant, inhibits the calcium-dependent calcineurin (CaN)-calmodulin (CaM) complex to stop T cells from signaling. The CaN-CaM complex, a phosphatase that activates the nuclear factor of activated T cells (NFAT), is effectively inhibited by tacrolimus. Tacrolimus interacts to FK506-binding proteins when it reaches the cytoplasm of T cells, preventing the CaN- CaM complex from performing its usual role. Recent studies have linked the galectin-3 protein, which causes mast cells, macrophages, and basophils to become activated, to allergic eye diseases. Galectin-3 has been found to have an antimigratory effect on neutrophils, and in mice with allergic conjunctivitis, a lack of endogenous galectin-3 caused a sharp increase in cytokines in the tear fluid, a result that was reversed by tacrolimus administration (9).

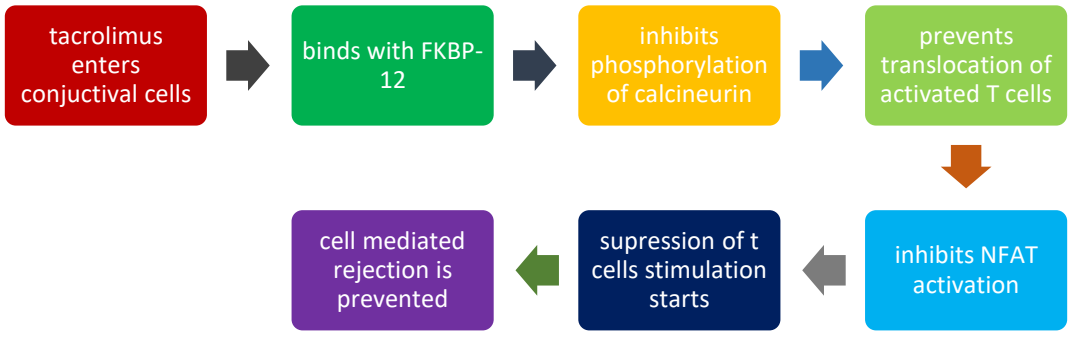

Figure 1.2: Mode of action of tacrolimus

Many pediatricians and allergists are unaware of VKC despite the fact that it has substantial clinical symptoms and indicators. Eye care professionals must be knowledgeable with VKC's diagnosis, available treatments, and side effects in order to assist their young patients achieve clinical remission.

OBJECTIVE

To evaluate the effect of tacrolimus ointment 0.03% as a monotherapy in the treatment of vernal keratoconjunctivitis.

MATERIALS AND METHODS

Study design: It was a Quasi experimental study.

Place of study: This study was carried out at the Kot Khawaja Saeed DHQ, Hospital Lahore.

Duration of study: Study was conducted from September 2022-June 2023.

Population of study: Population of study was the patients taking vernal keratoconjunctivitis medication.

Sample size: A sample of 45 participants was selected. The sample size was calculated using the Rao soft calculator with confidence interval of 95% and a margin error of 5%.

Sampling technique: A non-probability Purposive Sampling Technique was used to select sample.

Inclusion criteria

- Age 05-20 years
- Both male and female patients
- Refractory vernal keratoconjunctivitis (Micropapillae**,** Macropapillae, mucus accumulation, corneal vascularization**,** Macroerosion, sheild ulcer, persistant severe inflamation)

Exclusion criteria

- Adeno viral keratitis
- Seasonal allergy
- Steven Johnson syndrome
- Uveitis
- Atopic keratoconjunctivitis

Data collection instruments: These instruments were used in this research study

1. LogMAR chart (ASF Universal)
2. Slit lamp biomicroscopy (Ziess SL 220)

Research tool

This research was carried out by self-structured examination based proforma.

Data collection method

After taking permission from the hospital ethical committee, patients who were diagnosed by recurrent vernal keratoconjunctivitis was recruited for study. Slit lamp examination was done to assess the vernal keratoconjunctivitis. Study participants discontinued all the medications one week before beginning treatment. Tacrolimus 0.03% ointment was given for three months and effect on VKC was assessed after 1st week, 1st month, 2nd month and 3rd month. In order to ensure that the subjects who was included in the study understood the goals and design of the study and were willing to volunteer as subjects, both verbal and written consent was obtained from the patients after sufficiently informed them of the study's objectives and its design and giving them enough time to consider all of their options. On completion of the study, all subjects' responses were recorded.

Data analysis method

The input and analysis of the data were done using SPSS statistical software version 26.0.

Ethical consideration

After explaining the purpose, methods, and potential outcomes of the research to each participant, informed permission was acquired in accordance with the Declaration of Helsinki. After sufficiently explaining the study's goals and design to the patients, both verbal and written consent was obtained. This allowed for ample time to consider all the available options, to make sure that the subjects who volunteered to participate in the study understood this information, to continue providing information and to continue exchanging information and asking questions.

RESULTS

This study included 45 patients taking vernal keratoconjunctivitis medication. Participants of 5- 20 year were included in the study. There was no gender specification.

4.1 Age distribution

The mean value of age and standard deviation of participants was 11.2889±4.27265.

Table 4.1 Frequency of Age Distribution

	Minimum	Maximum	Mean	Std. Deviation
AGE	5	20	11.2889	4.27265

4.2: GENDER DISTRIBUTION

There was no gender specification. Both male and female were included in the study. There were 40 male participants and 5 female participants. Table show the frequency distribution with respect of gender.

Table 4.2 Frequency Distribution of respondent with respect of Gender

Gander	Frequency	Percent
Male	40	89

Female	5	11
Total	45	100

4.3: Frequency distribution of subjective score (itching) of VKC against tacrolimus ointment from baseline to three months

In the "Severe" category: There is only one occurrence recorded during the one-month period, with zero occurrences in all other time periods. The total count for the "Severe" category is 1.
In the "Moderate" category: There are 8 occurrences during the base line and one-week periods. However, there are no occurrences recorded during the one-month, two-month, and three-month periods, resulting in a total count of 16.
In the "Mild" category: The count fluctuates slightly over time, ranging from 8 to 12 occurrences. The count starts at 9 during the base line period and ends at 8 after three months, with a total count of 46 across all time periods.
In the "On/Off" category: The count starts at 28 during the base line period and increases gradually over time. By the end of three months, the count reaches 37, with a total count of 162 across all time periods.

Table 4.3 VKC related itching having tacrolimus monotherapy in comparison to five point times

	Base Line	**One Week**	**One Month**	**Two Months**	**Three Months**	**P Value**
On/Off	28	29	32	36	37	0.00
Mild	9	8	12	9	8	
Moderate	8	8	0	0	0	
Severe	0	0	1	0	0	
Total	45	45	45	45	45	

Df = 12
Pearson chi-square 158.965[a]

4.4: Frequency distribution of subjective score (Foreign body sensation) of VKC against tacrolimus ointment from baseline to three months:

In the "Severe" category: The count primarily occurs during the base line and one-week periods, with 23 and 8 occurrences, respectively. There are no occurrences recorded during the one-month, two-month, and three-month periods, resulting in a total count of 31.
In the "Moderate" category: The count also varies across time periods, with a range of 0 to 16 occurrences. The count starts at 8 during the base line period and ends at 0 after two months, with a total count of 33.

In the "Mild" category: The count varies across time periods, ranging from 7 to 15 occurrences. The count starts at 14 during the base line period and ends at 8 after three months, with a total count of 54 across all time periods.
In the "On/Off" category: There are no occurrences during the base line period (0). The count increases over time, reaching 37 after three months, with a total count of 107 across all time periods. The provided "P Value" of 0.00 suggests that there is a statistically significant association between the "On/Off" category and the time periods.

Table 4.4 VKC related foreign body sensation having tacrolimus monotherapy in comparison to five point times

	Base Line	One Week	One Month	Two Months	Three Months	P Value
On/Off	0	14	21	35	37	0.00
Mild	14	7	15	10	8	
Moderate	8	16	9	0	0	
Severe	23	8	0	0	0	
Total	45	45	45	45	45	

Df = 12

Pearson chi-square 141.088[a]

4.5: Frequency distribution of subjective score (photophobia) of VKC against tacrolimus ointment from baseline to three months:

In the "Severe" category: The count varies across time periods, with the highest count of 10 occurring during the base line and one-week periods. There are no occurrences recorded during the two-month and three-month periods, resulting in a total count of 28
In the "Moderate" category: The count varies across time periods, ranging from 2 to 23 occurrences. The count starts at 23 during the base line period, decreases to 2 during the one-month period, and then increases again, ending at 8 after three months. The total count is 46.
In the "Mild" category: The count varies across time periods, with the highest count of 18 occurring during the one-week and one-month periods. There are no occurrences recorded during the three-month period, resulting in a total count of 38.
In the "On/Off" category: The count starts at 12 during the base line period and gradually increases over time. By the end of three months, the count reaches 37, with a total count of 113 across all time periods.

Table 4.5 VKC related photophobia having tacrolimus monotherapy in comparison to five point times

	Base Line	One Week	One Month	Two Months	Three Months	P Value
On/Off	12	12	17	35	37	0.00
Mild	0	18	18	2	0	

Moderate	23	5	2	8	8	
Severe	10	10	8	0	0	
Total	45	45	45	45	45	

Df = 12

Pearson chi-square 122.807[a]

4.6: Frequency distribution of subjective score (blurring of vision) of VKC against tacrolimus ointment from baseline to three months:

In the "Severe" category: There is only one occurrence recorded during the one-month period, with zero occurrences in all other time periods. The total count for the "Severe" category is 1.

In the "Moderate" category: There are 8 occurrences during the base line and one-week periods. However, there are no occurrences recorded during the one-month, two-month, and three-month periods, resulting in a total count of 16.

In the "Mild" category: The count fluctuates slightly over time, ranging from 8 to 12 occurrences. The count starts at 9 during the base line period and ends at 8 after three months, with a total count of 46 across all time periods.

In the "On/Off" category: The count starts at 28 during the base line period and gradually increases over time. It reaches 37 after three months, with a total count of 162 across all time periods. The provided p-value of 0.00 suggests that there is a statistically significant association between the "On/Off" category and the time periods.

Table 4.6: VKC related blurring of vision having tacrolimus monotherapy in comparison to five point times

	Base Line	**One Week**	**One Month**	**Two Months**	**Three Months**	**P Value**
On/Off	28	29	32	36	37	0.00
Mild	9	8	12	9	8	
Moderate	8	8	0	0	0	
Severe	0	0	1	0	0	
Total	45	45	45	45	45	

Df = 12

Pearson chi-square 31.186[a]

4.7 Frequency distribution of subjective score (mucous discharge) of VKC against tacrolimus ointment from baseline to three months:

In the "Severe" category: The count starts at 9 during the base line period and remains the same during the one-week period. There are no occurrences recorded during the one-month, two-month, and three-month periods, resulting in a total count of 17.

In the "Moderate" category: The count starts at 6 during the base line period and drops to 1 during the one-week period. There are no occurrences recorded during the one-month, two-month, and three-month periods, resulting in a total count of 7.

In the "Mild" category: The count varies across time periods, with the highest count of 24 occurring during the one-week and one-month periods. The count drops to 8 during the three-month period, resulting in a total count of 83.
In the "On/Off" category: The count starts at 12 during the base line and one-week periods. It increases to 21 during the one-month period and further to 36 during the two-month period. Finally, it reaches 37 after three months, with a total count of 118 across all time periods. The provided p-value of 0.00 suggests that there is a statistically significant association between the "On/Off" category and the time periods. This indicates that the observed differences in counts between time periods are unlikely to occur by chance alone.

Table 4.7 VKC related mucous discharge having tacrolimus monotherapy in comparison to five point times

	Base Line	One Week	One Month	Two Months	Three Months	P Value
On/Off	12	12	21	36	37	0.00
Mild	18	24	24	9	8	
Moderate	6	1	0	0	0	
Severe	9	8	0	0	0	
Total	45	45	45	45	45	

Df = 12

Pearson chi-square 85.540[a]

4.8: Frequency distribution of objective score (micropapillae, macropapillae, mucus accumulation, corneal vascularization, macroerosion, sheild ulcer, persistant severe inflammation) of VKC against tacrolimus ointment from baseline to three months

45 patients presenting with micropapllae, there's no recovery after one week. Out of 45 patients, 14 persons showed positive reaction to tacrolimus after one month. After 3rd month, 32 persons recovers from micropapllae.

Out of 45 patients only 30 patients presenting with macropapillae, 15 persons showed effective response to tacrolimus after first week. After one month of using tacrolimus, 41 persons are recovered from Macropapillae and remaining 4 are cured in 3rd month of follow up.

Out of 45 patients 12 pts are cured from mucus accumulation after 1st follow up. After 2nd follow 15 are recovered 2 months later, 37 are recovered from mucus accumulation. Out of 45, 23 are cured after 1st follow up. After 2nd fellow up, 30 are recovered. In 3rd follow up 32 are cured.

30 pts out of 45 presenting with corneal vascularization. 23 cured at 1st follow up of 1st week. 30 are recovered from after one month 32 person got recovery after 2nd month of follow up.

8 persons presenting with macroerosions. No recovery after one week. 8 patients completely recovered from macroerosions after one month.

There's no patient came with complain of shield ulcer and persistent severe inflammation.

Table 4.8 VKC related micropapillae, macropapillae, mucus accumulation, corneal vascularization, macroerosion, sheild ulcer, persistant severe inflammation having tacrolimus monotherapy in comparison to five point times

		Base Line	One Week	One Month	Two Month	Base Line	Pearson Chi Squre	P Value
Micropapillae	Yes	45	45	31	13	8	8	
	No	0	0	14	32	37		
Macropapillae	Yes	30	15	4	0	0	8	0.00
	No	15	30	41	45	45		
Mucus accumulation	Yes	45	33	30	8	8	12	
	No	0	12	15	37	37		
Corneal vascularization	Yes	30	22	15	12	10	6	
	No	15	23	30	32	35		
Macroerosion	Yes	8	8	0	0	0	12	
	No	37	37	45	45	45		
Sheild ulcer	Yes	0	0	0	0	0	A	
	No	45	45	45	45	45		
Persistant severe inflamation	Yes	0	0	0	0	0	A	
	No	45	45	45	45	45		

a. No statistics are computed because shield ulcer

and persistant severe inflammation are constant.

DISCUSSION

Wan Q et al carried a study in 2019. This study's objectives were to assess the effectiveness and safety of 0.1% tacrolimus eye drops in treating the tarsal type of vernal keratoconjunctivitis (VKC) and to examine, using in vivo confocal imaging, the alterations in dendritic cells at the palpebral conjunctiva in individuals with VKC. There were 17 individuals (34 eyes) with the tarsal variety of VKC included in this prospective, nonrandomized case series. They received twice-daily administration of 0.1% tacrolimus eye drops after discontinuing all previous topical therapies. In vivo confocal microscopy was used to evaluate the characteristics of the dendritic cells in each right eye at the palpebral conjunctiva before treatment and at the first, second, fourth, and eighth weeks after treatment. Subjective ocular symptoms and objective ocular signs were graded on a 4-point scale by one ophthalmologist. After one week of treatment with eye drops containing 0.1% tacrolimus, the scores for all patients' symptoms dramatically improved (p 0.001), and 13 patients (76%) reported having considerable symptom relief. Aside from big papillae, the clinical sign score greatly decreased (p 0.001) after 4 weeks of therapy, and after 8 weeks of therapy, the gigantic papillae score significantly improved (p 0.001). Dendritic cell characteristics, such as cell count, total area, average size, perimeter, and diameter, significantly decreased (p 0.05) after two weeks of treatment. The results of the current study also point to tacrolimus use's significant (P= 0.00) effectiveness. Throughout the follow-up, no more topical medications were required, and no discernible changes in visual acuity were noted. There were no indications of cataracts or increased intraocular pressure. Only 5 individuals (or 29%) indicated any tingling or pain. For the tarsal variety of VKC, tacrolimus 0.1% eye drops are an effective and secure treatment. Rapidly reducing dendritic cell activity, symptom relief, reducing papillary hyperplasia, and palpebral conjunctiva injury are all possible outcomes. The negative effects could have an influence on certain patients' compliance. These results suggest that clinicians discuss the advantages of tacrolimus and that more study is needed (10).

Roumeau I et al done this study in 2021. Random-effect meta-analyses were computed on changes in clinical ratings of symptoms and signs between the start of therapy and subsequently, stratified by treatment classes. We looked for possible influencing factors in meta-regressions. A total of 45 research (27 randomized controlled trials, 18 prospective

cohort studies, and 1749 individuals, 78% of whom were male, with a mean age of 11.2 years) and 12 distinct therapy groups were used. Tacrolimus, cyclosporine, and mast cell stabilizers (MCSs; often regarded as first-line treatment) were the three medications that were investigated the most frequently in 75% of the research. Overall, every clinical evaluation became better. There were no discernible differences between the therapy groups in terms of concentration, age, sex, baseline activity ratings, or atopy. Studies on the sensitivity came to similar conclusions. This research supports the efficacy of MCSs in the treatment of VKC. The current study shown that tacrolimus significantly affected the treatment of VKC. Following treatment, the signs and symptoms of the patients significantly improved (P = 0.000). The mean age of the participants and their corresponding standard deviations were 11.2889 and 4.27265. Since tacrolimus is an acceptable cyclosporine alternative for severe cases of VKC, both cyclosporine and tacrolimus were equally efficacious (11).

5.2: CONCLUSION

It was concluded that

- Tacrolimus 0.03% ointment is a safe and effective therapy for the tarsal variant of VKC. It may quickly decrease dendritic cell activity, alleviate symptoms, lessen papillary hyperplasia and repair damage to the palpebral conjunctiva.
- The results of this study show the effectiveness and safety of topical tacrolimus ointment 0.03% as monotherapy for the treatment of vernal keratoconjunctivitis; it may provide an alternative to corticosteroids and lessen the potential side effects of their use. The findings of this research may help those with VKC, especially children and young people, better manage their condition and live happier, healthier lives.
- Tacrolimus may be used alone, without any additional medications, to treat VKC. By using tacrolimus alone, we achieved meaningful results.

5.3: LIMITATIONS OF STUDY

There are some limitations in this study:

- Tacrolimus can be relatively expensive, especially in some regions or healthcare systems where it may not be readily available or covered by insurance.

Affordability and accessibility can limit its widespread use as a monotherapy for VKC, particularly in areas with limited resources.

- A continuing barrier is the absence of commercial tacrolimus ocular drops or ointments. The production of such formulations would be very helpful in the treatment of inflammatory ocular surface illnesses including allergies.
- There was no constant concentration of tacrolimus was found.
- Duration of usage of tacrolimus was also a limitation.

5.4: RECOMMENDATIONS

There are some recommendations:

- For patients who have not responded to conventional VKC therapies, take into account tacrolimus 0.03% as a possible monotherapy alternative. To make an educated choice, consider the patient's medical history, prior treatment results, and personal traits. Further research is needed to assess the potential risks associated with its long-term usage.
- Future research should demand a more objective test result, such as a tear break-up time, Shirmer test, and impression cytology, since this study is reliant on the subjective opinion of an observer.
- Inform patients on the usage of protective eyewear such as sunglasses, hats, visors, umbrellas, and protective goggles in addition to avoiding allergens that cause symptoms.
- Emphasize the value of complementary treatments that are not pharmaceutical, including cold compresses and proper lid hygiene.

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