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Outcomes of Using Tacrolimus Topical Preparation in Treatment of Vernal Keratoconjunctivitis in Pediatric Age Group

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a chronic hypersensitive condition of the eye that affect conjunctiva and cornea. The symptoms of vernal keratoconjunctivitis can vary but typically include itching, hyperemia, photophobia and foreign body sensation. This study concentrates on the effect of tacrolimus 0.03% ointment in treatment of VKC in children.

Objective: This study aimed to assess the efficacy as well as safety of using tacrolimus 0.03% ointment in treatment of VKC in children.

Subjects and methods: We conducted this prospective case study on a random group of 30 patients (60 eyes) of pediatric age group with vernal keratoconjunctivitis using tacrolimus topical preparation.

Results: The mean age was 13 ± 3 years. The mean visual acuity improved from 0.8 ± 0.2 to 0.9 ± 0.1 after the treatment. Statistically significant improvement was found in symptoms of redness, foreign body sensation, itching, as well as tearing. Statistically significant improvement was also revealed among the clinical signs of conjunctival hyperemia, Tranta's dots, limbal infiltration, superficial punctate keratitis, as well as conjunctival papillary hypertrophy. No side effects were recorded as cataract, or infectious keratitis. Mild and moderate relapse of symptoms and signs were seen in 8 patients (26.7%) after 6 months during their follow up and all of them were considered to be severe at the beginning of the study.

Conclusion: Tacrolimus 0.03% ointment could be an effective safe treatment option for VKC in children and could be a steroid sparing agent.

Keywords: Tacrolimus ointment, Vernal keratoconjunctivitis, Steroid sparing.

INTRODUCTION

The symptoms of chronic bilateral inflammation of the conjunctiva and cornea, known as VKC, include photophobia, thick and sticky mucous discharge, hyperaemia of the conjunctiva, and chemosis of the conjunctiva [(1)]. Although there may be some variations in intensity between the eyes, VKC is typically bilateral in 98% of patients. Wind, dust, strong light, and physical exertion that cause perspiration may amplify itching, which can range from moderate to severe [(2)].

At this time, there are no gold-standard ways to identify this illness. In most cases, VKC manifests with hyperaemia, itching, photophobia, tears, and discharge of mucus. The upper tarsal conjunctiva and corneoscleral junction are sites where large or medium papillae can be seen, which are characteristics of verrucous Keratoconus. Many mild or unusual instances may go undetected because diagnosis is based on standard clinical signs and symptoms [(3)].

Some of the eye problems that can develop as a result of VKC include steroid-induced cataracts and glaucoma, scarring on the cornea, infectious keratitis, and hyperplasia of the limbal tissues [(4)]. Corneal opacity, irregular astigmatism, and keratoconus are potential causes of amblyopia associated with VKC [(5)].

Signs of allergic inflammation are easily visible in the tarsal and bulbar conjunctiva because they are abundant in immune cells like mast cells, eosinophils, macrophages, and lymphocytes [(6)].

Antigenic proteins are able to easily penetrate it because its barrier qualities are inferior to those of the skin and cornea [(7)]. Multiple biological investigations have established that eosinophils, lymphocytes, and structural cell activation are involved in VKC, which is a disease mediated by T-helper (TH) 2 lymphocytes [(8)].

A wide range of medications, including antihistamines, mast-cell stabilizers, dual acting medicines, corticosteroids, and immunomodulators like tacrolimus and cyclosporine-A, are presently accessible for the treatment of VKC [(4)].

Streptomyces tsukubaensis is the source of the powerful non-steroidal macrolide immunosuppressant tacrolimus [(9)].

Tacrolimus inhibits several immune system processes, including stimulation of T cells and T helper cell-mediated responses, proliferation of B cells, and secretion of cytokines, most notably interleukin-2. By combining with its cytosolic partner FK506-binding protein 12. This medicine inhibits the activation and proliferation of immune cells by binding to calcineurin and preventing the production of cytokines and the expression of their receptors [(10)].

In this study, children with VKC were treated with topical tacrolimus 0.03% ointment, and the clinical outcomes of this treatment were studied over a short-term follow-up. This study aimed to study the safety and efficacy of using tacrolimus 0.03% ointment in treatment of VKC in children.

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PATIENTS AND METHODS

This prospective case series study included 30 patients with VKC in the pediatric age group with age range from 6-17 years old, who underwent treatment with topical tacrolimus 0.03% ointment at Benha University Hospitals during the period from September 2022 to August 2023.

Inclusion criteria: Patients with significant symptoms and sign of VKC of both sexes. Patients aged less than 18 years old (pediatric age group) with optically clear corneas.

Exclusion criteria: patients with previous ocular trauma or previous eye surgery, patients with coexisting conjunctival disorders or chemical injuries, patients with Stevens-Johnson syndrome, patients with history of contact lens wear within 3 months before the study and patients unwilling to give informed consent.

METHODOLOGY

Patients or their parents were asked to fill out a detailed medical history form, and after parents were given a clear explanation of the study's purpose and methods in simple terms, they were asked to sign a consent form. A comprehensive ophthalmic evaluation was performed for each patient, which included measuring best-corrected visual acuity, examining the anterior segments with fluorescein staining and a slit lamp, and examining the dilated posterior segments using an indirect ophthalmoscope.

The scoring of symptoms was done according to interference with patient's daily routine as in mild cases the discomfort was barely noticeable, in moderate cases, patients reported discomfort for most of the day with no interference with daily activities while in severe cases there was disrupted daily routine.

Clinical signs included conjunctival hyperemia in most participants: Moderate (70%, n=21) and severe (30%, n=9). Regarding conjunctival papillary hypertrophy 46.7% (n=14) of participants had no conjunctival lesions, while the remainder exhibited varying degrees of severity: 10% (n=3) mild (flat papilla = 1mm), 20% (n=6) moderate (Giant papilla = 2 mm), and 23.3% (n=7) severe (Giant papilla=3mm). Trantas dots were found in 23 (76%) patients and limbal infiltration in 23 (76%) patients. Distribution of punctate keratitis severity was varied, with 43.3% (n=13) of participants experiencing mild (punctate keratitis (PK) less than ½ cornea), 40% (n=12) moderate (PK more than ½ cornea), and 16.7% (n=5) severe (cornea showed epithelial defect) symptoms. At least a one-grade improvement in severity relative to values obtained prior to treatment was used to evaluate treatment response.

Patients were advised to apply a 0.03% ointment of dermatologic tacrolimus, which is available on the market, to the inner corners of their eyes once a day before bed for one week. After that, the frequency was tapered down to once a week, every other day for another week, twice a week, and finally once a week. Then, the tapering was continued for another six months. This is an off label use of the dermatologic ointment due to lack of availability of a tacrolimus ophthalmic ointment in Egypt.

Ethical approval: Benha Medical Ethics Committee and Mansoura Faculty of Medicine gave its approval to this study (Approval code: MS 15-11-2022). All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Software from IBM (Armonk, New York, USA) called SPSS version 28 was used for data administration and statistical analysis. Using both direct data visualization tools and the Shapiro-Wilk test, we checked the quantitative data for normalcy.

The quantitative data was summarized using means and standard deviations in accordance with the principle of normalcy. Numbers and percentages were used to summarize ordinal and categorical data. Repeated measures ANOVA was used to compare quantitative data at several time points. Using Friedman's test, ordinal data were compared across various time intervals. Each statistical test had two possible outcomes. Significance was determined by $p \leq 0.05$.

RESULTS

The study enrolled 30 patients (60 eye). The mean age was 13 ± 3 years ranged from 6 to 17 years. Regarding gender distribution, most participants were males, accounting for 73.3% (n=22) of the total, while females represented 26.7% (n=8). Notably, all participants (100%, n=30) had a history of receiving previous treatment. The mean visual acuity at presentation was 0.8 ±0.2 SD (**Error! Reference source not found.**).

Table (1): General characteristics of the studied patients

General characteristics		
Age (years)	Mean ± SD, Range	13 ± 3, (6-17 years)
Sex		
Males	n (%)	22 (73.3)
Females	n (%)	8 (26.7)
Previous treatment	n (%)	30 (100)

All patients presented with bilateral VKC that did not respond to standard topical treatments such as steroids, antihistamines, decongestants and mast-cell stabilizers, or cyclosporine.

The main presenting symptoms were itching that was moderate in (60%, n=18) patients and severe in (40%, n=12) patients and redness that was reported moderate in (70%, n=21) patients and severe in (30%, n=9) patients. Regarding tearing it was reported that most participants experienced moderate (70%, n=21) and severe (30%, n=9) tearing and foreign body sensation it was reported that more than half of the participants had moderate (53.3%, n=16), and nearly half had severe (46.7%, n=14) foreign body sensations.

The scoring of these symptoms was done according to interference with patient's daily routine as in mild cases the discomfort was barely noticeable, in moderate cases, patients reported discomfort for most of the day with no interference with daily activities while in severe cases there was disrupted daily routine.

Clinical signs included conjunctival hyperemia in most participants experienced moderate (70%, n=21) and severe (30%, n=9) hyperemia. Regarding conjunctival papillary hypertrophy, 46.7% (n=14) of participants had no conjunctival lesions, while the remainder exhibited varying degrees of severity: 10% (n=3) mild (flat papilla = 1mm), 20% (n=6) moderate (Giant papilla = 2 mm), and 23.3% (n=7) severe (Giant papilla=3mm). Trantas dots were found in 23 (76%) patients and limbal infiltration in 23 (76%) patients.

Distribution of punctate keratitis, severity was varied with 43.3% (n=13) of participants experiencing mild (PK less than ½ cornea), 40% (n=12) moderate (PK more than ½ cornea), and 16.7% (n=5) severe (cornea showed epithelial defect) symptoms.

When results were at least one grade lower after treatment than they had been before, it was considered a response to treatment. Associated allergic diseases were noted in 12 patients (40%) (Allergic rhinitis, asthma and atopic dermatitis). There was no reported family history of VKC in any of the patients (Table 2).

Table (2): Baseline assessment of symptoms and signs of VKC in studied patients

Symptoms and signs	N (%) of affected patients
Itching	
Moderate	18 (60)
Severe	12 (40)
Red eye	
Moderate	21 (70)
Severe	9(30)
Foreign body sensation	
Moderate	16 (53.3)
Severe	14 (46.7)
Burning sensation	
Moderate	19 (63.3)
Severe	11(36.7)
Tearing	
Moderate	21 (70)
Severe	9 (30)
Photophobia	
Mild	9 (30)
Moderate	8 (26.7)
Severe	13 (43.3)
Limbal infiltration	
No infilteration	7 (23.3)
Mild	3(10)
Moderate	12(40)
Severe	8(26.7)
Trantas dots	
No dots	7 (23.3)
Moderate	13(43.3)
Severe	10(33.3)
Punctate keratitis	
Mild	13 (43.3)
Moderate	12(40)
Severe	5(16.7)

Each of the following symptoms of itching, redness, tearing, and foreign body sensation showed there was a marked improvement in severity after applying tacrolimus 0.03% ointment. Similarly, there was a statistically significant improvement in the severity of all of the clinical symptoms, including conjunctival hyperemia, limbal infiltration, Trantas dots, superficial punctate keratopathy, conjunctival papillary hypertrophy, and limbal hyperemia (P, 0.001). When treating mild cases, clinical signs began to improve by the end of the first week of therapy. When treating severe cases, clinical indicators began to improve after four weeks of therapy (Table 3 & **Error! Reference source not found.**s 1-6).

Table (3): Follow up of symptoms and signs of VKC in studied patients

Symptoms and signs	N (%) of affected patients after 1st week	N (%) of affected patients after 1st month	N (%) of affected patients after 6 months	P-value
Itching				<0.001*
No itching	0	20 (66.7)	22 (73.3)	
mild	10 (33.3)	10 (33.3)	8 (26.7)	
Moderate	15 (50)			
Severe	5 (16.7)			
Red eye				<0.001*
No red eye	0	15 (30)	19 (63.3)	
Mild	9 (30)	15 (30)	11 (36.7)	
Moderate	17 (56.7)			
Severe	4 (13.3)			
Foreign body sensation				<0.001*
No foreign body sensation	0	21 (70)	22 (73.3)	
Mild				
Moderate	13 (43.3)	9 (30)	8 (26.7)	
Severe	12 (40)			
	5 (16.7)			
Burning sensation				<0.001*
No burning sensation	0	21 (70)	22 (73.3)	
Mild	13 (43.3)	9 (30)	8 (26.7)	
Moderate	12 (40)			
Severe	5 (16.7)			
Tearing				<0.001*
No tearing	0	30 (100)	22 (73.3)	
Mild	7 (23.3)		8 (26.7)	
Moderate	15 (50)			
Severe	8 (26.7)			
Photophobia				<0.001*
No photophobia	5 (16.7)	27 (90)	22 (73.3)	
Mild	7 (23.3)	3 (10)	8 (26.7)	
Moderate	16 (53.3)			
Severe	2 (6.7)			
Limbal infiltration				<0.001*
No infiltration	7 (23.3)	16 (53.3)	30 (100)	
Mild	3 (10)	14 (46.7)		
Moderate	15 (50)			
Severe	5 (16.7)			
Trantas dots				<0.001*
No dots	7 (23.3)	16 (53.3)	30 (100)	
Mild	0	14 (46.7)		
Moderate	16 (53.3)			
Severe	7 (23.3)			
Punctate keratitis				<0.001*
No PK	0	30 (100)	30 (100)	
Mild	18 (60)			
Moderate	12 (40)			
Severe				

*Significant P-value; † significantly different from baseline

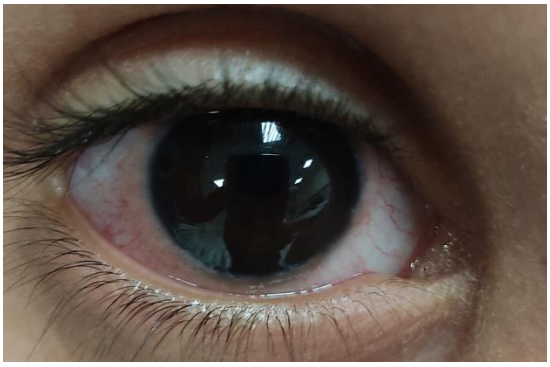

Figure (1): Patient showing signs of hyperemia before treatment with tacrolimus 0.03% ointment

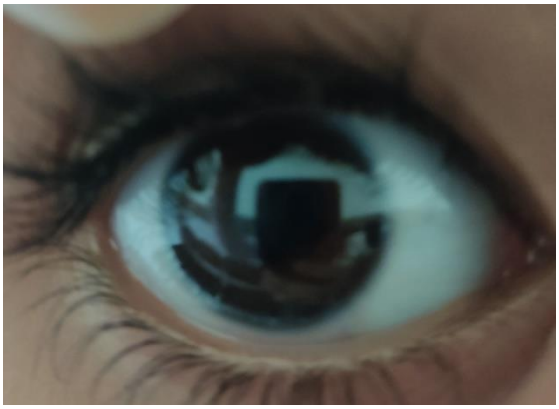

Figure (2): Same patient showing improvement of hyperemia after four weeks of treatment with tacrolimus 0.03% ointment.

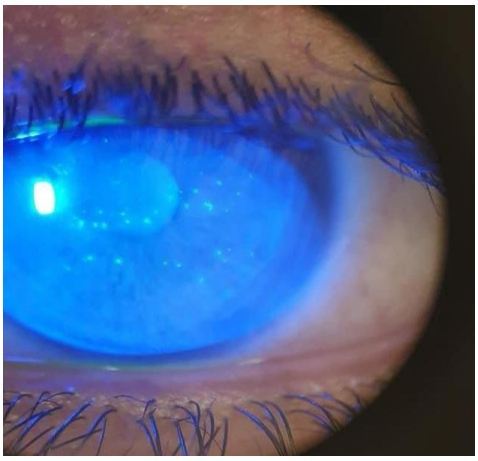

Figure (3): Patient showing signs of punctate keratitis before treatment with tacrolimus 0.03% ointment

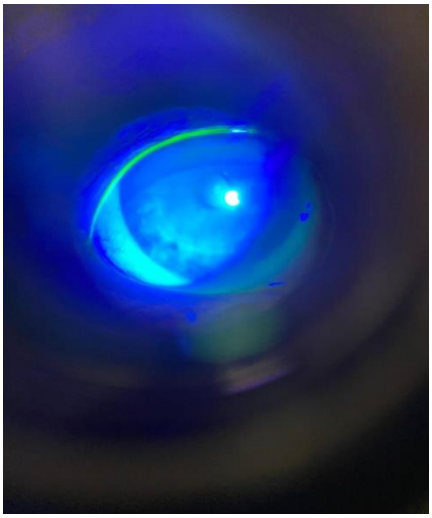

Figure (4): Same patient showing improvement of punctate keratitis after four weeks of treatment with tacrolimus 0.03% ointment

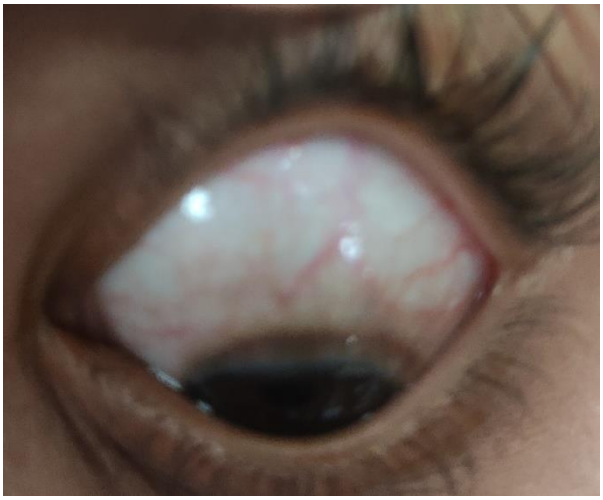

Figure (5): Patient showing signs of hyperemia and limbal infilterates before treatment with tacrolimus 0.03% ointment.

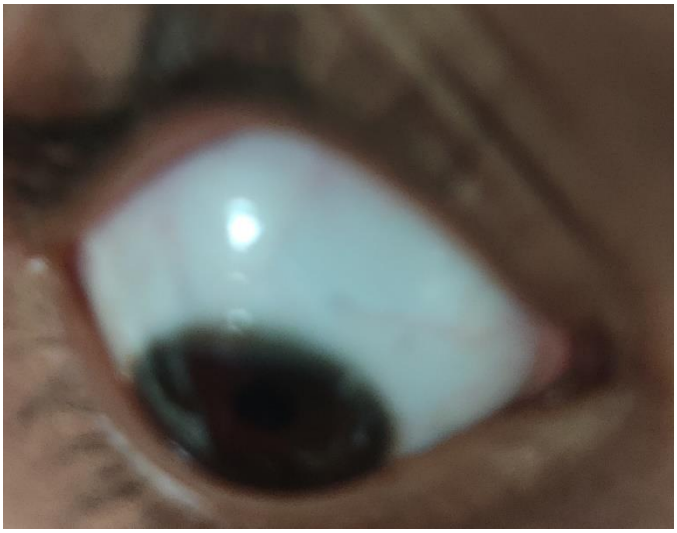

Figure (6): Same patient showing improvement of hyperemia and limbal infilterates after four weeks of treatment with tacrolimus 0.03% ointment.

At baseline, the mean best corrected visual acuity (BCVA) was recorded at 0.8 ± 0.2. This initial measurement differed significantly from the follow-up measurements ($P < 0.001$).

Interestingly, no change was observed in BCVA one-week post-baseline, maintaining a mean of 0.8 ± 0.2. However, significant improvements were noted at one month and six months follow-up, with the mean BCVA increasing to 0.9 ± 0.1 at these time points. Mild and moderate relapse of symptoms and signs were seen in 8 patients (26.7%) after 6 months during the follow up and all of them were considered to be severe according to their scored symptoms and signs, there was 3 patients who discontinued treatment due to irritation and were excluded of the study (Table 4).

Table (4): BCVA at baseline and follow-up

BCVA	Mean ±SD	P-value
Baseline	0.8 ±0.2	**<0.001***
One week	0.8 ±0.2	
One month †	0.9 ±0.1	**<0.001***
Six months †	0.9 ±0.1	**<0.001***

*Significant P-value; BCVA: Best corrected visual acuity; † Significant difference from baseline.

DISCUSSION

One immunomodulator that has been studied for the treatment of VKC is tacrolimus in an ocular topical formulation. Most cases of severe VKC respond to topical tacrolimus within a month of starting treatment. Most patients can safely utilize topical tacrolimus for an extended period of time in VKC without experiencing any major negative effects. Topical tacrolimus is a game-changer for the treatment of severe VKC, an allergic eye disease that severely impacts children and young adults [(11)].

One such study compared the effectiveness of two different eye treatments for vernal keratoconjunctivitis in children: 2% cyclosporine eye drops and 0.1% tacrolimus eye ointment. Twenty-four patients with VKC were given the tacrolimus ointment twice a day for eight weeks. The researchers used a double-masked design to ensure the accuracy of the results. Results showed that, comparable to cyclosporine A, tacrolimus therapy improved VKC symptoms in this trial. Furthermore, this study found that patients treated with tacrolimus experienced a fleeting burning sensation, whereas those treated with cyclosporine A reported burning and discomfort upon administration.

Tacrolimus therapy was found to have a greater impact in improving objective ocular symptoms [12]. Not only that, but our study, along with a plethora of others, has shown that tacrolimus has a positive impact on symptoms, particularly conjunctival papillary size.

Within two to four weeks of starting treatment with 0.02% tacrolimus ointment, five patients with atopic keratoconjunctivitis (AKC) and one with VKC showed significant improvement in their symptoms, according to a retrospective research. No negative side effects were reported over the 2-26 months of continuous treatment, and steroid responders had a decrease in increased intraocular pressure after steroid therapy was discontinued [13].

The results of our study showed that a topical tacrolimus ointment with a concentration of 0.03% was an effective treatment for moderate to severe VKC that was resistant to anti-histamines and mast cell stabilizers. Almost every single one of our patients had a marked improvement in their inflammatory symptoms and signs with no serious side effects at all. After the first four weeks of follow-up, no more medicine, including steroids, was necessary. Only tacrolimus ointment was able to keep the patients under control.

Our study included 60 eyes of 30 patients with VKC in the pediatric age group, the patients were scored according to the eye showing more severe symptoms and signs and were allocated to one group that received the tacrolimus 0.03% topical dermatologic ointment. The average age of the participants was 13 ± 3 years. Regarding gender distribution, most participants were males, accounting for 73.3% (n=22) of the total, while females represented 26.7% (n=8). Notably, all participants (100%, n=30) had a history of receiving previous treatment. Different modalities of treatment including corticosteroids, antihistamines, cromoglycates and surgical scraping were used in the management of almost all our patients before being included in our study and the patients were advised to stop any medications one week before beginning treatment with tacrolimus 0.03% topical preparation.

All symptoms and signs except palpebral conjunctival lesion started to improve from the first week, severe forms disappeared from the second to third week, in the fourth week only mild symptoms and signs were present in few cases. By the end of the first month, all symptoms disappeared in 100% of patients. Palpebral conjunctival lesion started to improve from the third week in all patients, but relapse was seen in severe forms after 3 to 6 months during their follow up. There was a mild and moderate relapse of symptoms and signs in some patients during their follow up, all of which were considered to be severe according to their scored symptoms and signs at the time of presentation and they were resistant to treatment with topical corticosteroids and antihistamines. None of our patients developed any kind of complications resulting from using tacrolimus 0.03% ointment. However some patients reported having some itching and irritation immediately after application of the ointment that disappeared shortly after the application.

CONCLUSION

Tacrolimus 0.03% ointment is a safe and effective alternative for treating symptoms and signs of VKC in children resistant to antihistaminic agents and topical mast cell stabilizers. Tacrolimus is a promising alternative for the treatment of severe VKC and has the potential of being a steroid sparing agent for treatment of VKC. However, more studies should be conducted to assess the long term safety of using this drug for treatment of VKC.

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Conflict of Interest: Nil.

REFERENCES

1. **Bonini S, Coassin M, Aronni S *et al.* (2004):** Vernal keratoconjunctivitis. Eye, 18 (4): 345-51.
2. **Bonini S, Bonini S, Lambiase A *et al.* (2000):** Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. Ophthalmology, 107 (6): 1157-63.
3. **Bonini S, Sacchetti M, Mantelli F *et al.* (2007):** Clinical grading of vernal keratoconjunctivitis. Current Opinion in Allergy and Clinical Immunology, 7 (5): 436-41.
4. **Kumar S (2009):** Vernal keratoconjunctivitis: a major review. Acta Ophthalmologica, 87 (2): 133-47.
5. **Tabbara K (1999):** Ocular complications of vernal keratoconjunctivitis. Canadian journal of ophthalmology. Journal Canadien D'ophtalmologie., 34 (2): 88-92.
6. **Allansmith M, Ross R (1986):** Ocular allergy and mast cell stabilizers. Survey of Ophthalmology, 30 (4): 229-44.
7. **Kumagai N, Fukuda K, Fujitsu Y *et al.* (2006):** Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. Progress in Retinal and Eye Research, 25 (2): 165-87.
8. **Leonardi A (2002):** Vernal keratoconjunctivitis: Pathogenesis and treatment. Prog Retin Eye Res., 21: 319–39.
9. **William F (2005):** Review of medical physiology. 2nd ed. Lange Medical Books; Ganong; Mcgraw-hill, Pp: 530. https://search.worldcat.org/title/Ganong's-review-of-medical-physiology/ oclc/ 430823856
10. **de Paulis A, Stellato C, Cirillo R *et al.* (1992):** Anti-inflammatory effect of FK-506 on human skin mast cells. Journal of Investigative Dermatology, 99 (6): 723-8.
11. **Vichyanond P, Kosrirukvongs P (2013):** Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. Current Allergy and Asthma Reports, 13: 308-14.
12. **Labcharoenwongs P, Jirapongsananuruk O, Visitsunthorn N *et al.* (2012):** A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis in children. Asian Pacific Journal of Allergy and Immunology, 30 (3): 177-84.
13. **Miyazaki D, Tominaga T, Kakimaru-Hasegawa A *et al.* (2008):** Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. Ophthalmology, 115: 988-92.