



Topical Use of Olopatadine and Cyclosporine a in Treatment of Vernal Keratoconjunctivitis

Vernal Keratokonjonktivit Tedavisinde Topikal Olopatadin ve Siklosporin Kullanımı

The Treatment of Vernal Keratoconjunctivitis

Knatova Zaire¹, Kantarci Feride Aylin², Akata Fikret³, Vieru Eugeniu⁴

¹Private Rehamer Hospital,

²Department of Ophthalmology, Fatih University Medicine Faculty, İstanbul,

³Department of Ophthalmology, Gazi University, Faculty of Medicine, Ankara,

⁴Department of Neurology, Private KAS Hospital, Ankara, Türkiye

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Özet

Amaç: Vernal Keratokonjonktivit (VKK) tedavisinde Olopatadin hidroklorid (0.1%) ile Siklosporin A (0.05%) göz solüsyonunun (0.05%) etki ve güvenilirliğini değerlendirmektir. **Gereç ve Yöntem:** VKK olan 25 hasta prospektif olarak değerlendirildi. Her hastanın bir gözüne Olopatadin hidroklorid (0.1%), diğer gözüne Siklosporin A (0.05%) damlatıldı. Kaşıntı, sulanma, yabancı cisim hissi ve mucus sekresyon gibi subjektif semptomların varlığı kaydedildi ve skorlandı. Tarsal konjonktivada dev papilla varlığı, bulber konjonktiva hiperemisi, keratit, limbal hipertrofi, korneal vaskularizasyon ve konjonktival skar oluşumu gibi objektif belirtiler kaydedildi ve skorlandı. **Bulgular:** Olopatadin ve Siklosporin gruplarında subjektif semptomlarda anlamlı bir düzelme görüldü. İki grup arasında subjektif semptomlar açısından arasında 3., 6., 12. ve 18. ayda anlamlı fark görülmedi. Gruplar arasında objektif bulgular açısından anlamlı fark izlenmedi. Geç dönemde Siklosporin grubunda anlamlı bir iyileşme görüldü. **Tartışma:** VKK uzun dönem tedavisinde Olopatadin ve Siklosporin A kullanımı ile subjektif semptomlarda benzer etkiler görüldü. Objektif bulguların iyileşmesinde ise geç dönemde Siklosporin A'nın daha etkili olduğu izlendi.

Anahtar Kelimeler

Korneal Damarlanma; Olopatadin Hidroklorid; Vernal Keratokonjonktivit; Siklosporin A; Tarsal Dev Papilla

Abstract

Aim: To compare the efficacy and safety of Olopatadine hydrochloride (0.1%) with Cyclosporine A ophthalmic solution (0.05%) in treating the signs and symptoms of VKC. **Material and Method:** Twenty-five patients with VKC were included in a prospective study. One eye of each patient was treated with Olopatadine while the other eye was treated with Cyclosporine A. Subjective symptoms of the patients such as itching, tearing, foreign body sensation, and mucus discharge were recorded and scored. The objective signs, such as the presence of giant papillae on the tarsal conjunctiva, bulbar conjunctival hyperemia, keratitis, limbal hypertrophy, corneal vascularization, and conjunctival cicatrization, were scored. **Results:** There was no significant difference between the Olopatadine group and the Cyclosporine A group regarding subjective symptoms at the 3rd, 6th, 12th, and 18th month. There was a significant improvement in the subjective symptoms of both groups. No significant difference was seen between the groups with regard to objective signs. A significant improvement was observed in the Cyclosporine group in the late period of the study. **Discussion:** In long-term therapy of VKC, similar effects were seen regarding improvement in the subjective symptoms during the use of topical Olopatadine and Cyclosporine A. In terms of improvement regarding the objective signs, Cyclosporine A was seen to be more effective in the late period.

Keywords

Corneal Vascularization, Cyclosporine A, Olopatadine Hydrochloride, Vernal Keratoconjunctivitis, Tarsal Giant Papillae

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Corresponding Author: Feride Aylin Kantarci, Department of Ophthalmology, Fatih University Medicine Faculty, 34844, İstanbul, Turkey.

T.: +90 2164589000 E-Mail: ferideaylin@gmail.com

Introduction

Vernal keratoconjunctivitis (VKC) is a common severe allergic eye disease mainly affecting children and adolescents with seasonal recurrence [1,2]. The symptoms are characterized by hyperemia, itching, tearing, photophobia, chemosis, and filamentous and sticky mucous discharge. An important clinical sign of VKC is the presence of giant papillae (cobblestones) on the upper tarsal conjunctiva (tarsal form) or at the limbus (bulbar form) [2,3]. VKC may have mild or severe chronic forms. Furthermore, if not diagnosed and treated properly, VKC can induce irreversible corneal changes that profoundly impair vision [4]. Some patients with VKC have spontaneous resolution of their symptoms. However, others may require treatment to control the course of the disease [1]. The therapy administered to the patient should not only treat the disease but it should also be safe and should provide relief from the symptoms of VKC [1,2]. Pathophysiological studies suggest that allergic inflammation probably plays a role in the etiology of VKC. However, VKC has a more complex pathogenic mechanism, unlike a classic type 1 immunoglobulin-E (IgE)-mediated allergic disease [4,5]. Results of immunohistochemical studies inform us that VKC is an allergic inflammatory disease involving mast cells, eosinophils, lymphocytes, basophils, dendritic cells, and macrophages that infiltrate the conjunctival epithelium and stroma [6,7]. Pharmacological treatment options for VKC include antihistamines, mast-cell stabilizers, dual-acting agents, corticosteroids, and immunomodulators such as Cyclosporine A and Tacrolimus [8]. As far as we know, topical corticosteroids are very effective in the treatment of VKC. However, these agents may lead to steroid-induced glaucoma and cataracts in patients with prolonged use. Consequently, these drugs should not be administered as a first-line treatment in VKC patients [2,9]. Olopatadine hydrochloride (0.1%), which has mast-cell stabilizing and selective histamine H1-receptor antagonist effects, was shown to be effective in the treatment of VKC [10]. In recent years, Cyclosporine A has been preferred in the treatment of VKC due to its immunosuppressive effect. The mechanism is to abrogate proliferation of T lymphocytes by suppressing synthesis of interleukin α and blocking expression of IL-2 receptors. It has also been shown to suppress IgE production by interfering with the T cell dependent mechanisms [7,11]. VKC decreases an individual's quality of life due to disturbing long-term symptoms [3,12]. Therefore, effective long-term treatment is necessary. In the literature, there are no previous studies comparing the efficacy and safety of topical Cyclosporine A with Olopatadine hydrochloride that show it to have no significant adverse effects and to be an effective and safe drug. Therefore, in our study, we aimed to perform a prospective comparison of the long-term effects of the use of Olopatadine hydrochloride ophthalmic solution (0.1%) and Cyclosporine A ophthalmic solution independent of steroids in the treatment of VKC cases.

Material and Methods

Twenty-five patients with VKC and concurrent diseases were included in a prospective study. Seventeen patients were boys and 8 patients were girls with a mean age of 16.5 years (range: 7 to 26).

Patients were randomized in a single-blinded clinical trial at a single center and the eye of each patient was assigned to one of two different treatment regimens. One eye of each patient was treated with Olopatadine hydrochloride twice daily and the fellow eye was treated with Cyclosporine A four times daily. None of the patients had taken systemic steroids or other anti-inflammatory or immunosuppressive drugs. None of the patients used contact lenses. An informed consent form was obtained from all of the patients prior to inclusion in the study. These consent forms adhered to the tenets of the Declaration of Helsinki. The study was approved by an Ethics Committee. During the enrollment, age, gender, and family history of an allergic disease were noted and a detailed history of symptoms was obtained from all of the patients. All the patients underwent a complete ophthalmic examination which included determination of visual acuity, slit-lamp biomicroscopy, and indirect ophthalmoscopy. The anterior segment of the eyes of all patients were photographed. All clinical signs of the patients were recorded. The symptoms of the patients included itching, tearing, foreign body sensation (FBS), and mucous discharge. They were recorded and scored based on a scale from grade 0 to grade 4 (grade 0: free of symptoms, grade 1: mild, grade 2: moderate, grade 3: severe and grade 4: very severe) (Table 1). The objective signs were recorded based on the presence of the giant papillae (cobblestone appearance) on the tarsal conjunctiva, bulbar conjunctival hyperemia, limbal hypertrophy, corneal vascularization, and conjunctival cicatrization (superficial scarring of the conjunctiva) and then scored based on a scale from grade 0 to 3 (grade 0: free of symptoms, grade 1: mild, grade 2: moderate and grade 3: severe). The results are shown in Table 1. After the initiation of treatment, clinical evaluations were performed at the 3rd, 6th, 12th, and 18th month of the treatment.

Table 1. Scores of objective signs

Item	0	1	2	3
Tarsal papillary hypertrophy	No	Mild	Moderate	Severe
Bulbar hyperemia	No	Mild	Moderate	Severe
Limbal hypertrophy	No	One quadrant	Two quadrants	>2 quadrants
Neovascularization of cornea	No	One quadrant	Two quadrants	>2 quadrants
Conjunctival cicatrization	No	Subepithelial fibrosis	Fornix foreshortening	Symblepharon formation

Statistical Analysis

During the evaluation of the data obtained from the study, NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) programs were used for statistical analysis. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods, the Mann Whitney U test was used for the intergroup comparisons of parameters without normal distribution. Group evaluations were performed using Friedman test and Wilcoxon Signed-Rank tests. A significance level of $P<0.05$ was used.

Results

Overall topical drop application compliance was 100% both in

the Olopatadine group and Cyclosporine A group. The difference between the two groups was not significant regarding the subjective scores prior to treatment ($P>0.05$) (Table 2). The efficacy of Olopatadine and Cyclosporine A treatments administered for 18 months with regard to subjective symptoms, such as itching, tearing, FBS, and mucous discharge, was evaluated. At the end of the study, no significant difference in the two groups was found between the levels of itching, tearing, foreign body sensation, and mucous discharge at baseline, 3rd, 6th, 12th, or 18th months. ($p>0.05$) (Table 2). A significant difference was observed between the levels of

itching, tearing and mucous discharge of the two groups according to the month ($p<0.01$). Significant decreases were determined at the 3rd, 6th, 12th and 18th month compared to baseline ($p<0.01$) (Table 2). When an assessment was performed regarding the FBS symptom, no significant difference was observed between the levels of FBS according to the months of treatment in the Olopatadine group ($p>0.05$). A significant difference was observed between the levels of FBS according to the months in the Cyclosporine A group ($p>0.05$). While significant decreases were determined at the 6th month as compared to the baseline ($p<0.01$), no significant difference was observed at the 3rd, 12th or 18th months compared to baseline ($p>0.05$) (Table 2).

Table 2. Evaluation of subjective symptoms between the two groups

	Olopatadine Mean±SD	Cyclosporine A Mean±SD	ap	p	Cyclosporine p
ITCHING					
Baseline	3.8±0.8	3.4±0.9	0.902		
3rd month	1.5±1.5	1.1±1.3	0.334		
6th month	1.3±1.2	0.8±1.1	0.124		
12th month	1.3±1.2	1.1±1.3	0.436		
18th month	1.1±0.9	0.7±0.9	0.189		
+Baseline-3rd month				0.001**	0.001**
+Baseline-6th month				0.001**	0.001**
+Baseline-12th month				0.001**	0.001**
+Baseline-18th month				0.001**	0.001**
TEARING					
Baseline	2.5±0.9	2.6±0.9	0.835		
3rd month	1.1±1.0	0.9±0.8	0.383		
6th month	0.5±0.9	0.5±0.9	1.000		
12th month	1.0±0.9	0.8±0.9	0.350		
18th month	0.5±0.8	0.4±0.8	0.539		
+Baseline-3rd month				0.001**	0.001**
+Baseline-6th month				0.001**	0.001**
+Baseline-12th month				0.001**	0.001**
+Baseline-18th month				0.001**	0.001**
FOREIGN BODY SENSATION					
Baseline	0.6±0.76	0.6±0.9	0.965		
3rd month	0.3±0.5	0.3±0.5	1.000		
6th month	0.2±0.5	0.1±0.3	0.127		
12th month	0.5±0.7	0.3±0.9	0.143		
18th month	0.4±0.6	0.2±0.4	0.693		
+Baseline-3rd month				0.088	0.059
+Baseline-6th month				0.059	0.008**
+Baseline-12th month				0.710	0.124
+Baseline-18th month				0.212	0.083
MUCOUS DISCHARGE					
Baseline	1.9±1.2	1.9±1.2	0.831		
3rd month	0.8±0.8	0.5±0.6	0.220		
6th month	0.6±0.8	0.4±0.8	0.488		
12th month	0.5±0.7	0.4±0.8	0.517		
18th month	0.5±0.8	0.6±0.8	0.756		
+Baseline-3rd month				0.001**	0.001**
+Baseline-6th month				0.001**	0.001**
+Baseline-12th month				0.001**	0.001**
+Baseline-18th month				0.001**	0.001**

a Mann-Whitney U test
+Wilcoxon Signed Ranks test ** $p<0.01$
* $p<0.05$

Tarsal conjunctiva was assessed regarding the objective signs such as the presence of papillae, bulbar conjunctival hyperemia, limbal hypertrophy, corneal neovascularization, conjunctival cicatrization, and corneal involvement. When the tarsal conjunctiva was assessed according to the presence of the giant papillae, although there was no significant difference between the tarsal conjunctival papillae levels at the baseline and the 3rd month according to the groups ($p>0.05$), it was determined that the 6th month levels of the Olopatadine group were significantly higher than those of the Cyclosporine A group (at a level of $p<0.05$), and that the 12th and 18th month levels were also significantly higher than the Cyclosporine A group (at a level of $p<0.01$) (Table 3). In the Olopatadine and Cyclosporine A groups, no significant difference was observed between the tarsal conjunctival papillae levels according to the months ($p<0.01$). Significant decreases were determined at the 3rd, 6th, 12th and 18th month as compared to the baseline ($p<0.01$) (Table 3). When an assessment was performed regarding the levels of bulbar conjunctival hyperemia, no significant difference was found between the bulbar conjunctival hyperemia levels at the baseline and at the 3rd, 6th, 12th and 18th month according to the Olopatadine and Cyclosporine A groups ($p>0.05$). The 12th-month levels of the Olopatadine group were determined to be significantly higher than those of the Cyclosporine A group ($p<0.05$) (Table 3). When an assessment was performed regarding the limbal hypertrophy, no significant differences were found between the levels of limbal hypertrophy at the baseline and the 3rd, 6th, 12th and 18th month according to the groups ($p>0.05$) (Table 4). A significant difference was observed between the levels of limbal hypertrophy according to the months in the Olopatadine and Cyclosporine A groups ($p<0.01$). While significant decreases were observed in the 12th and 18th month as compared to the baseline ($p<0.01$), a significant difference was not determined in the 3rd or 6th month as

compared to baseline ($p>0.05$) (Table 3).
When an assessment was performed regarding the corneal neo-

vascularization, no significant difference was found between the levels of corneal neovascularization at the baseline and the 3rd, 6th, 12th and 18th months according to the groups ($p>0.05$) (Table 5). A significant difference was not observed between the levels of corneal neovascularization according to the months in the Olopatadine group ($p>0.05$). A significant difference was observed between the levels of corneal neovascularization according to the months in the Cyclosporine A group ($p<0.01$). While significant decreases were observed at the 6th, 12th and 18th months as compared to baseline ($p<0.05$), no significant difference was determined at the 3rd month as compared to the baseline ($p>0.05$) (Table 3).

When an assessment was performed regarding the conjunctival cicatrization, no significant difference was found between the levels of the conjunctival cicatrization at the baseline and the 3rd, 6th, 12th and 18th months according to the groups ($p>0.05$). A significant difference was not observed between the levels of the conjunctival cicatrization according to the months in the Olopatadine group ($p>0.05$). However, a significant difference was observed between the levels of the conjunctival cicatrization according to the months in the Cyclosporine A group ($p<0.01$). While significant decreases were observed at both the 12th month with a level of ($p<0.05$) and at the 18th month with a level of $p<0.01$ as compared to the baseline, a significant difference was not observed at the 3rd or 6th month as compared to baseline ($p>0.05$) (Table 3).

In the photo of the anterior segment of an eye in a case whose right eye was treated with Olopatadine and left eye was treated with Cyclosporine A due to VKC, hyperemia and limbal hypertrophy (Figure 1A and 1B) and papillary reaction on the tarsal conjunctiva (Figure 1C and 1D) are seen before treatment. At the 12th month after treatment, improvement was seen in the hyperemia and limbal hypertrophy (Figure 2A and 2B), as well as a decrease in the papillary reaction (Figure 2C and 2D).

Discussion

VKC is a severe chronic allergic inflammatory disease characterized by recurrent, bilateral, occasionally asymmetrical, seasonally exacerbating ocular inflammation [13]. It may also be seen in severe chronic forms that can inflict irreversible corneal changes, profoundly impairing vision [2]. We know from previous studies that the management of allergic eye disease is aimed at blocking the release of allergic mediators in order to control the allergic inflammatory cascade and to prevent ocular surface damage secondary to the allergic response. In addition, we also need to min-

Table 3. Evaluation of objective signs between the two groups

	Olopatadine	Cyclosporine A		Olopatadine	Cyclosporine
	Mean±SD	Mean±SD	ap	p	p
Tarsal Conjunctival Papillae					
Baseline	1.7±0.5	1.8±0.6	0.847		
3rd month	1.5±0.6	1.3±0.5	0.214		
6th month	1.4±0.5	1.0±0.5	0.017*		
12th month	1.2±0.3	0.7±0.6	0.006**		
18th month	1.0±0.3	0.5±0.5	0.001**		
+Baseline-3rd month				0.034*	0.001**
+Baseline-6th month				0.007**	0.001**
+Baseline-12th month				0.001**	0.001**
+Baseline-18th month				0.001**	0.001**
Bulbar Conjunctival Hyperemia					
Baseline	2.2±0.8	2.4±0.8	0.362		
3rd month	2.1±0.8	1.8±0.8	0.192		
6th month	1.7±0.6	1.3±0.8	0.081		
12th month	1.4±0.6	1.0±0.5	0.046*		
18th month	1.0±0.7	0.6±0.6	0.177		
+Baseline-3rd month				0.655	0.002**
+Baseline-6th month				0.008**	0.001**
+Baseline-12th month				0.001**	0.001**
+Baseline-18th month				0.001**	0.001**
Limbal Hypertrophy					
Baseline	1.4±1.1	1.3±1.1	0.622		
3rd month	1.4±1.1	1.3±1.1	0.532		
6th month	1.3±1.0	1.2±1.0	0.579		
12th month	1.2±1.0	0.8±0.8	0.168		
18th month	1.2±1.1	0.8±0.8	0.200		
+Baseline-3rd month				1.00	1,000
+Baseline-6th month				0.317	0.025*
+Baseline-12th month				0.083	0.038*
+Baseline-18th month				0.083	0.038*
Corneal Neovascularization					
Baseline	0.6±0.9	0.5±0.9	0.808		
3rd month	0.6±0.9	0.5±0.9	0.808		
6th month	0.5±0.8	0.3±0.6	0.415		
12th month	0.5±0.7	0.2±0.5	0.260		
18th month	0.4±0.7	0.2±0.5	0.300		
+Baseline-3rd month				1.000	0.317
+Baseline-6th month				1.000	0.157
+Baseline-12th month				0.317	0.014*
+Baseline-18th month				0.157	0.008**
Conjunctival Cicatrization					
Baseline	0.8±0.5	0.8±0.5	0.771		
3rd month	0.8±0.5	0.8±0.5	1.000		
6th month	0.8±0.5	0.7±0.5	0.779		
12th month	0.7±0.5	0.6±0.5	0.312		
18th month	0.7±0.6	0.5±0.6	0.324		
+Baseline-3rd month				1.000	0.317
+Baseline-6th month				1.000	0.157
+Baseline-12th month				0.317	0.014*
+Baseline-18th month				0.157	0.008**

a Mann-Whitney U test +Wilcoxon Signed Ranks test ** $p<0.01$ * $p<0.05$

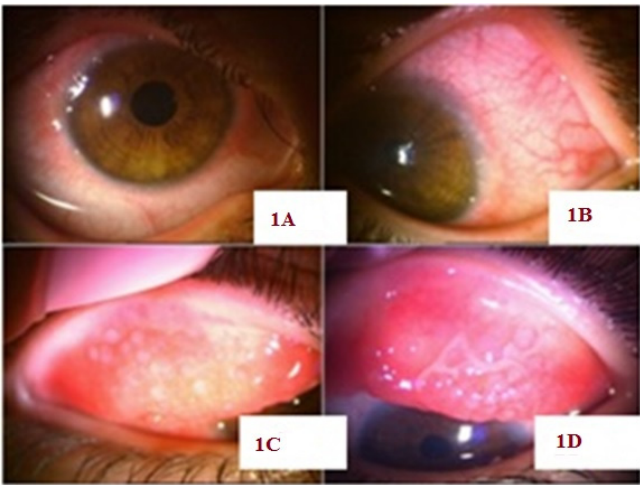


Figure 1. Photos of the anterior segment before the treatment

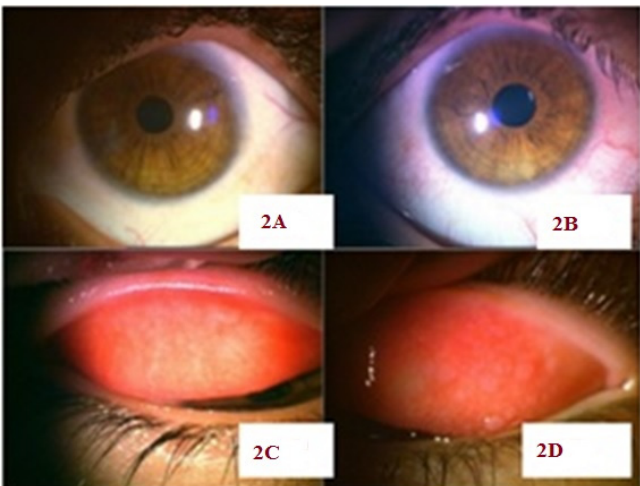


Figure 2. Photos of the anterior segment at the 12th month after the treatment

imize the impact of the allergic reaction on the quality of life of the individual [2-4]. There are studies showing that Olopatadine and Cyclosporine A, which are dual-acting drugs, are effective in the treatment of VKC. It is reported that Olopatadine is inadequate to control the severe cases and to prevent recurrence. Development of tolerance to Cyclosporine A and high cost is a disadvantage [2]. In our prospective study, we evaluated the long-term effects of Olopatadine and Cyclosporine A treatments on the signs and symptoms of VKC cases. When an assessment was performed regarding the subjective symptoms such as itching, tearing, FBS, and mucous discharge, no statistically significant differences were found between the baseline and the 3rd, 6th, 12th, and 18th months when comparing the Olopatadine and Cyclosporine A groups. While no difference was seen regarding the FBS according to the month in the Olopatadine group, a significant decrease was observed with the treatment in the Cyclosporine A group. A significant decrease was observed regarding the itching, tearing, and mucous discharge in both of the groups with the treatment. We could not find any previous studies comparing topical Cyclosporine A and antihistaminic Olopatadine in the literature. Several comparative studies between antiallergy medications and design model studies suggested topical treatment of Olopatadine hydrochloride for use in allergic eye diseases. The effects

of Olopatadine in the treatment of allergic conjunctivitis on signs such as itching and redness were shown [14-16]. When the antihistaminic medications were compared, it was reported that Olopatadine hydrochloride 0.1% caused less discomfort for patients during the use of the drug [3]. It was shown that Cyclosporine A inhibited inflammatory cell infiltration and fibrosis by suppressing T helper cells (Th2) cytokine release in allergic conjunctivitis [17]. It is known that Cyclosporine A has an immunomodulator effect and is effective in the improvement of symptoms in the treatment of VKC [18-22]. In our study, it was seen that Cyclosporine A was effective in the improvement of subjective symptoms such as itching, tearing, FBS, and mucous discharge. Development of a tolerance to Cyclosporine A or development of a corneal complication was not observed during long-term treatment. Pucci et al. investigated the long-term safety and efficacy of Cyclosporine A 2%. In their study, it was reported that Cyclosporine A 2% was effective in the improvement of the children's symptoms on average over 24 months and no side effects were seen due to the treatment [23]. In a study comparing topical Cyclosporine A 0.5% and anti-inflammatory Ketorolac tromethamine, it was stated that cyclosporine was slow-acting in decreasing the symptoms [24]. In a prospective study comparing topical Cyclosporine A 2% and Dexamethasone 0.1%, including 366 VKC cases, no significant difference was seen in the decrease of symptoms over 4 weeks [2]. In our study, the respective efficacy levels of Olopatadine and Cyclosporine A were compared with regard to objective symptoms such as papillary reaction on the tarsal conjunctiva, bulbar conjunctival hyperemia, corneal vascularization, and conjunctival cicatrization. No significant difference was observed between the levels of bulbar conjunctival hyperemia, limbal hypertrophy, corneal vascularization, or conjunctival cicatrization at the baseline and at the 3rd, 6th, 12th and 18th months, according to the groups. A significant decrease was observed in the giant papillary reaction on the tarsal conjunctiva beginning in the 6th month in the Cyclosporine A group. No significant difference was observed between the levels of corneal vascularization and conjunctival cicatrization in the Olopatadine group according to the month. A significant decrease was seen in the Cyclosporine group after the 6th month. A significant difference was also observed between the levels of the other objective symptoms in both of the groups according to the month. In previous studies, it has been shown that Olopatadine was effective in improving conjunctival hyperemia and edema [15,25]. In the study performed by Khurana et al., it was reported that Olopatadine was effective in treating papillary conjunctivitis related to contact lens wear [24]. It has also been shown that Cyclosporine A is effective in causing regression of the objective symptoms, particularly the giant papillae on the tarsal conjunctiva due to VKC [26,27]. The inhibitory effect of Cyclosporine A in the development of conjunctival fibrosis is previously known [16]. Cyclosporine A inhibits the development of corneal vascularization [28]. In our study, it was seen that Olopatadine and Cyclosporine A were effective in instigating the regression of signs and symptoms during the follow-up treatment for VKC cases for 18 months. Regression of the tarsal papillary reaction was found

to be significantly different in the Cyclosporine A group. Significant decreases were observed in due course in both the Olopatadine and Cyclosporine A groups, except for corneal vascularization and conjunctival fibrosis.

Limitations of the study include the small number of cases, a higher dosage of Cyclosporine A (four times daily), and also the absence of a pathological study to support the findings. In order to conclude that Cyclosporine A is effective in the treatment of VKC, further studies are required.

Olopatadine and Cyclosporine A were seen to be similarly effective in treating the subjective symptoms due to VKC in the long-term. Although the difference in the regression of the objective symptoms was not significant, it was seen that Cyclosporine A was more effective and its effect tended to increase during the late period.

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Competing interests

The authors declare that they have no competing interests.

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