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Is Topical Interferon Alpha-2b Eye Drop Effective in Refractory Vernal Keratoconjunctivitis

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ABSTRACT

Purpose: To evaluate the efficacy and safety of topical interferon alpha-2b (IFN alpha-2b)for the treatment of long-standing steroid-resistant and steroid-dependent vernal keratoconjunctivitis (VKC).

Methods: Inthis prospective interventional case series,patients with refractory VKC from one referral center in Rasht, Iran were included. All patients had active symptomatic disease despite conventional medical therapyincluding topical steroids (steroid-resistant group) or were dependent on topical steroids (steroid-dependent group). After discontinuationof all medications for at least 1 week,patients were treated with topical Interferon Alpha-2beye drop at least for 6 months. Changes in subjective symptoms and objective signs were evaluated 1 week,1 and 6 months after treatment. Possible ocular and systemic complications wereevaluated.

Results: Twenty-eight eyes of 14 patients (10males and 4 female) were included. Mean age of the patients was 22 ± 8 years (11 to 38 years).Mean duration of VKC was12 ± 6 years (5 to 23 years). Patients were followed for 10±2 months (6-12 months). All symptoms including itching,burning, redness, photosensitivity, foreign body sensation, and mucus discharge were improved (P<.001).Conjunctival hyperemia was the first sign, which improved 1 week after treatment. Other objective signs including conjunctivalandlimbalpapillary hypertrophy, corneal punctate epithelial erosions, and corneal pannus improved at least one month after treatment. There were not any changes in corneal opacityduring follow-up period (p> 0.05).No ocular or systemic side effect was observed.

Conclusion: Topical IFN alpha-2b eye dropis a safe and effective medication for refractory VKC. It might be better to apply earlier in these cases before occurrence of the complications including irreversible limbal stem cell deficiency,corneal opacity, and steroid-induced complications.

KEYWORDS

Vernal Keratoconjunctivitis,Topical Interferon Alpha-2b,VKC, Refractory,Steroid Resistant, Steroid Dependent.

Introduction

Vernal keratoconjunctivis (VKC) is a severe form of ocular allergy, characterized by acute and chronic corneoconjunctival inflammation that may lead to visual sequel. VKCis an ocular allergic disease mostly affecting children and young adults living in warm climates[1].Currently available drugs to treat VKC include antihistamines, mast-cell stabilizers, corticosteroids, and immunomodulators. VKC requires long-term treatment in many cases. Topical steroids are the mainstay of treatment for moderate to severe forms of VKC. Steroids, however, cannot be administered for a long period[2]. Furthermore, steroid dependency is a frequent finding in these patients, who make them prone to steroid-induced complications including cataract, glaucoma especially in children under the age of 10 years, as well as infections.These complications may contribute to severe visual impairment in these young individuals.Therefore, finding the ways including high potency steroid sparing medications, which subside their chronic inflammation and decrease their dependency to steroids might potentially reduce their visual impairment and drug-induced complications[3].Recently, topical immune-modulatory medications including cyclosporine and tacrolimus eye drops have been used for its treatment [4-10].In a recalcitrant case of VKC, use of other immunosuppressant may be the optimal method[11-14].Interferons are a group of natural proteins that act as immunomodulatory agents[15]. Tacrolimus in multiple studies and interferon alpha-2b(IFN alpha-2b) in few studies have been successfully used for treatment of such cases. In one comparative study, 2 immunomodulatory agents, tacrolimus and IFN alpha-2b compared in the treatment of VKC that had an equal effect in that's therapeutic effects[16].The efficacy of topical IFN drops in the treatment of ocular diseases such as pterygium has been evaluated[14, 15].Accordingly, in this study, the efficacy and safety of IFN alpha-2bwere evaluated to determine better treatment for VKC in a steroid resistant and steroid dependent cases.

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Methods

This prospectiveinterventional case series included consecutive patients with severerefractory VKC who received topicalIFN alpha-2b with at least 6months of follow-up.Thestudywas conducted at AmiralmomeninOphthalmology Center fromApril 2018 to May 2020. The study protocol was based on the tenets of the Declaration of Helsinki. It was approved by the institutional review board and ethics committee of the Ophthalmic Research Center, GuilanUniversity of Medical Sciences, Rasht, Iran. All possible risks and benefits were clearly explained to the patients before enrollment, and informed consent were obtained from all of them.

Patient'sSelection

Refractory VKC cases that referred to our cornea clinic, categorized into two groups; steroid-resistant and steroid-dependent groups. Steroid resistant VKC was defined as cases unresponsive to topical steroids (at least two weeks' topical steroids every 6 hours). Cases who also needed to at least1month steroid usage to control symptoms and signs were also included (steroid dependent group). Patients who received systemic administration or sub-conjunctival injection of corticosteroids, and/or ophthalmic or systemic administration of immune-suppressants within 2 weeks prior to the study,who were receiving desensitization or immune modulation therapy,infectious eye disease, pregnant patients, lactating, or planning pregnancy during the study period,diabetic, cardiac, renal, hepatic, and pancreatic disease were excluded.

Signs and Symptoms Scoring

The severity of symptoms and signs were evaluatedat baseline (before treatment) and 1 week, 1 and6 months after treatment.The severity of subjective symptoms (itching, burning, redness, foreign body sensation, photophobia, and mucus discharge) was assessed on the basis of a 4-grade scale. The patients were asked to use a grading scale of 0 (none), 1 or mild (occasional symptoms), 2 or moderate (frequent symptoms), and 3 or severe (constant symptoms) to report the severity of each individual symptom. Severity of objective signs in palpebral and bulbar conjunctiva, limbus, and corneal involvementwere also assessed.Bulbar conjnctivalhyperemia, tarsal papillary hypertrophy, limbal papillary hypertrophy (including Horner-Trantas' dots), punctate epithelial erosion and keratitis,corneal pannus and corneal opacity were assessed using 4-grade scale (0 = normal; 1+ = mild; 2+ = moderate; or 3+ = severe)(*table 1)*.

Table 1. Grading score of the ocular signs

Signs	Score0	Score1	Score2	Score3
Bulbarconjnctivalhyperemia	Absent	Mild	Moderate	Severe
Tarsal papillary hypertrophy	No	<1mm	1-3mm	>3mm
Limbal papillary hypertrophy	No	<3 h	3-6 h	>6 h
Corneal pannus	No	1 quadrant	2quadrants	> = 3 quadrants
Corneal punctate erosion	No	1 quadrant	2 quadrants	> = 3 quadrants
Corneal opacity	No	peripheral	mid-peripheral	central

Managementand Follow-up

All medications including topical corticosteroids, antihistamines, mast cell stabilizers, vasoconstrictors, and non-steroidal anti-inflammatory agents were discontinued at least 1 week before treatment. Only IFN alpha-2bdrop 4 times per day was started. The drop was continued 4 times per day for 1 month. The dose was then tapered according to ocular surface inflammation and subjective symptoms. The patients were kept on a minimum maintenance dose. The patients were visited on a regular basis on post-treatment days of 3, 7, 14, 28, and every month thereafter. Changes in subjective symptoms and objective signs scoreswere evaluated 1 week, 1 and 6 months after treatment (main follow up visits). In each main follow up visit, complete eye examination including best spectacle-corrected visual acuity (BSCVA) measurement,slit-lamp biomicroscopy, fluorescein staining, and applanation tonometry were performed. Digital photography(Imagenet; Topcon SL-8Z, Tokyo, Japan) was performed in each follow up visit. The patients were also specifically questioned about the discomfort associated with the use of IFN eye drops. Developments of possible ocular and systemic complications were also assessed.Ocular safety was assessed based on

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changes in visual acuity, IOP, and clinical findings for the iris, lens, anterior chamber, and fundus.

Preparation of IFN Alpha-2bEye Drop

In this study, 1,000,000 IU/mL IFN alpha-2b ophthalmic preparations were used for topical treatment. It was prepared with a dilution of 3,000,000 IU/mL IFN alpha-2b solution (3 MIU/cc PDferon-B; Pooyesh Daru Co, Iran) in artificial tears (Tear lose; Sinu Daru Co, Iran). It should be stored in 2–8°C.

Statistical Analysis

To describe the data, we used frequency (percent), mean ± SD, and median. To evaluate the changes when considering the correlation between the eyes of a subject we used GEE (Generalized Estimating Equation) model. Correction for mutiple comparison was performed by Bonferroni method. All statistical analyses performed by STATA software (Version 12.0).

Results

Twenty-eight eyes of 14 patients (11male and3 female) were included.Mean age of the patients was 22 ± 8 years (11 to 38 years). Mean duration of VKC was12 ± 6 years (5 to 23 years). Mean follow up period was 10±2 months (6-12 months).

The mean BSCVAwas0.25 ± 0.39 LogMAR at baseline. It was 0.26 ± 0.46 Log MAR and 0.27 ± 0.43LogMAR, 1 and 6 months after surgery,respectively (p>0.05).All symptoms (itching, burning, redness, photosensitivity, foreign body sensation, and mucusdischarge)significantly improved 1 week after treatment (P<0.001)(*table 2*).There was also significant improvement in objective signs ofconjunctival hyperemia, conjunctival papillary hypertrophy, limbal hypertrophy, corneal punctate epithelial erosions, and corneal pannus1 month after treatment (p< 0.001) (Fig 1). Conjunctival hyperemia was the first sign to show improvement 1 week after treatment (Fig 2).Corneal neovascularization was the last and most resistant sign to decrease. There were not any changes in corneal opacity during follow-up period (P >0.05) (*table 3) (Fig 3)*.Improvement in symptom scores was faster and more significant than objective signs (*chart 1*). Any attempt to taper and discontinue IFN alpha-2b eye drop was associated with recurrence of patients' symptoms and signs necessitating continued use of the medication during the entire follow-up period on a low maintenance dose. No ocular and systemic complication was seen.There were not any complaints.

Table 2. Subjective symptoms scores during follow up

Time		Itching	Burning	Redness	Photo sensitivity	Foreign body Sensation	Mucus Discharge
Baseline	0	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)
	1	0 (.0)	2 (7.1)	0 (.0)	2 (7.1)	0 (.0)	2 (7.1)
	2	16 (57.1)	16 (57.1)	24 (85.7)	15 (53.6)	20 (71.4)	14 (50.0)
	3	12 (42.9)	10 (35.7)	4 (14.3)	11 (39.3)	8 (28.6)	12 (42.9)
Week 1	0	6 (21.4)	3 (10.7)	4 (14.3)	2 (7.1)	2 (7.1)	4 (14.3)
	1	14 (50.0)	18 (64.3)	16 (57.1)	21 (75.0)	20 (71.4)	19 (67.9)
	2	8 (28.6)	7 (25.0)	8 (28.6)	5 (17.9)	6 (21.4)	5 (17.9)
	3	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)
P-values†		<.001	<.001	<.001	<.001	<.001	<.001
Month 1	0	18 (64.3)	22 (78.6)	14 (50.0)	18 (64.3)	6 (21.4)	7 (25.0)
	1	10 (35.7)	6 (21.4)	12 (42.9)	10 (35.7)	22 (78.6)	21 (75.0)
	2	0 (.0)	0 (.0)	2 (7.1)	0 (.0)	0 (.0)	0 (.0)
	3	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)
P-values†		<.001	<.001	<.001	<.001	<.001	<.001
Months 6	0	18 (64.3)	22 (78.6)	19 (67.9)	20 (71.4)	10 (35.7)	15 (53.6)
	1	10 (35.7)	6 (21.4)	7 (25.0)	8 (28.6)	18 (64.3)	13 (46.4)
	2	0 (.0)	0 (.0)	2 (7.1)	0 (.0)	0 (.0)	0 (.0)
	3	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)
P-values†		<.001	<.001	<.001	<.001	<.001	<.001

†Based on GEE analysis.

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Table 3. Objective signs scores during follow up

Time		Conjunctival Hyperemia	Tarsal papilary Hypertrophy	Limbal Hypertrophy	Corneal Punctate Epithelial Erosion	Corneal Pannus	Corneal Opacity
Baseline	0	0 (.0)	0 (.0)	0 (.0)	0 (.0)	0 (.0)	7 (25.0)
	1	0 (.0)	15 (53.6)	9 (32.1)	15 (53.6)	17 (60.7)	17 (60.7)
	2	8 (28.6)	13 (46.4)	16 (57.1)	11 (39.3)	9 (32.1)	2 (7.1)
	3	20 (71.4)	0 (.0)	3 (10.7)	2 (7.1)	2 (7.1)	2 (7.1)
Week 1	0	0 (.0)	4 (14.3)	0 (.0)	2 (7.1)	0 (.0)	8 (28.6)
	1	11 (39.3)	19 (67.9)	13 (46.4)	20 (71.4)	18 (64.3)	16 (57.1)
	2	16 (57.1)	4 (14.3)	13 (46.4)	4 (14.3)	8 (28.6)	2 (7.1)
	3	1 (3.6)	1 (3.6)	2 (7.1)	2 (7.1)	2 (7.1)	2 (7.1)
P-values†		.001	.029	.320	.029	.797	.440
Month 1	0	9 (32.1)	8 (28.6)	6 (21.4)	3 (10.7)	2 (7.1)	9 (32.1)
	1	14 (50.0)	16 (57.1)	20 (71.4)	21 (75.0)	22 (78.6)	15 (53.6)
	2	5 (17.9)	4 (14.3)	2 (7.1)	2 (7.1)	2 (7.1)	2 (7.1)
	3	0 (.0)	0 (.0)	0 (.0)	2 (7.1)	2 (7.1)	2 (7.1)
P-values†		<.001	.001	<.001	.003	.017	.122
Months 6	0	9 (32.1)	8 (28.6)	6 (21.4)	3 (10.7)	2 (7.1)	9 (32.1)
	1	15 (53.6)	16 (57.1)	20 (71.4)	21 (75.0)	22 (78.6)	15 (53.6)
	2	4 (14.3)	4 (14.3)	2 (7.1)	4 (14.3)	2 (7.1)	2 (7.1)
	3	0 (.0)	0 (.0)	0 (.0)	0 (.0)	2 (7.1)	2 (7.1)
P-values†		<.001	.001	<.001	.001	.017	.122

†Based on GEE analysis.

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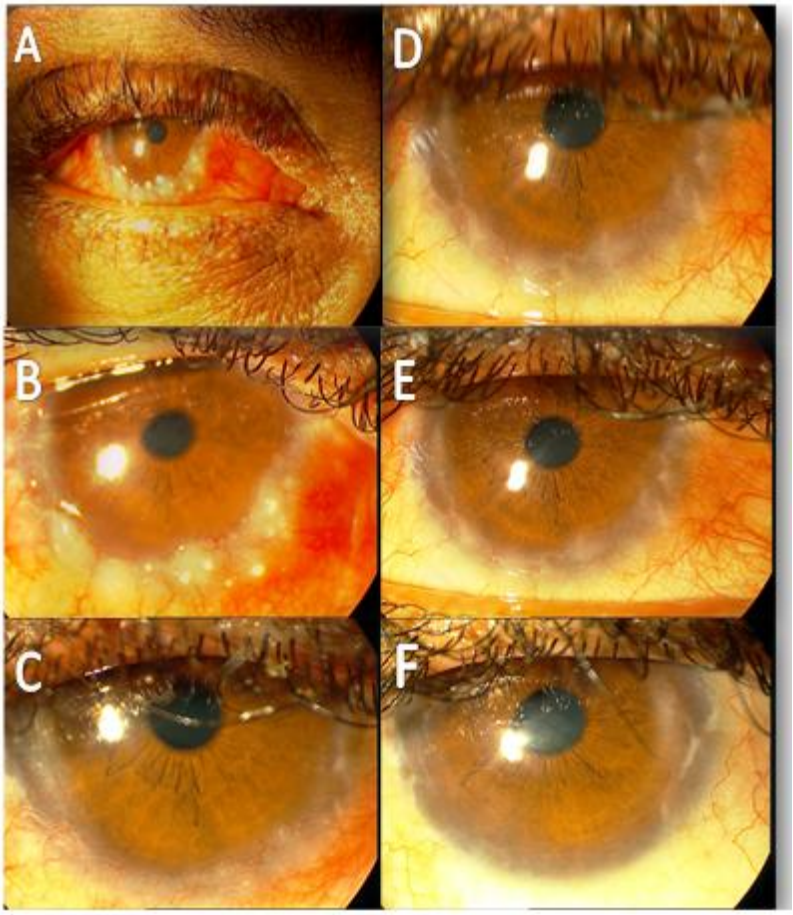

Figure 1. Limbal papillary hypertrophy with Horner-trantas' dots and severe conjunctival hyperemia at baseline (A),and 1week(B), 1(C), 2(D), 3 (E), and 6 (F) month after treatment.

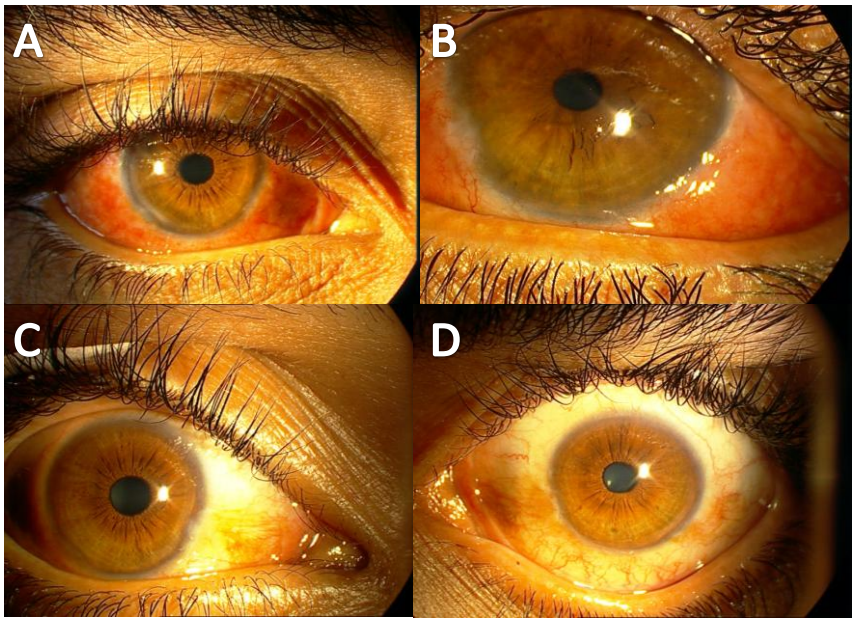

Figure 2. Bulbar conjunctival hyperemia and severe edema in the right and left eyes before (A,B) and 1 month after treatment (C,D).

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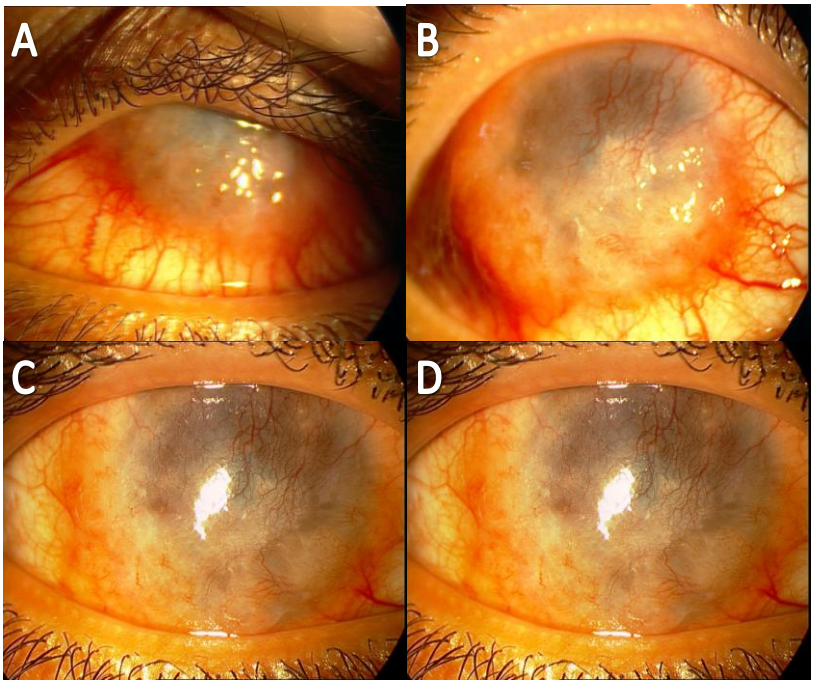

Figure 3. Severe limbal hypertrophy with vascularization and opacification of the cornea in the right and left eyes of a patient, before (A,B) and 6 months after treatment (C,D).

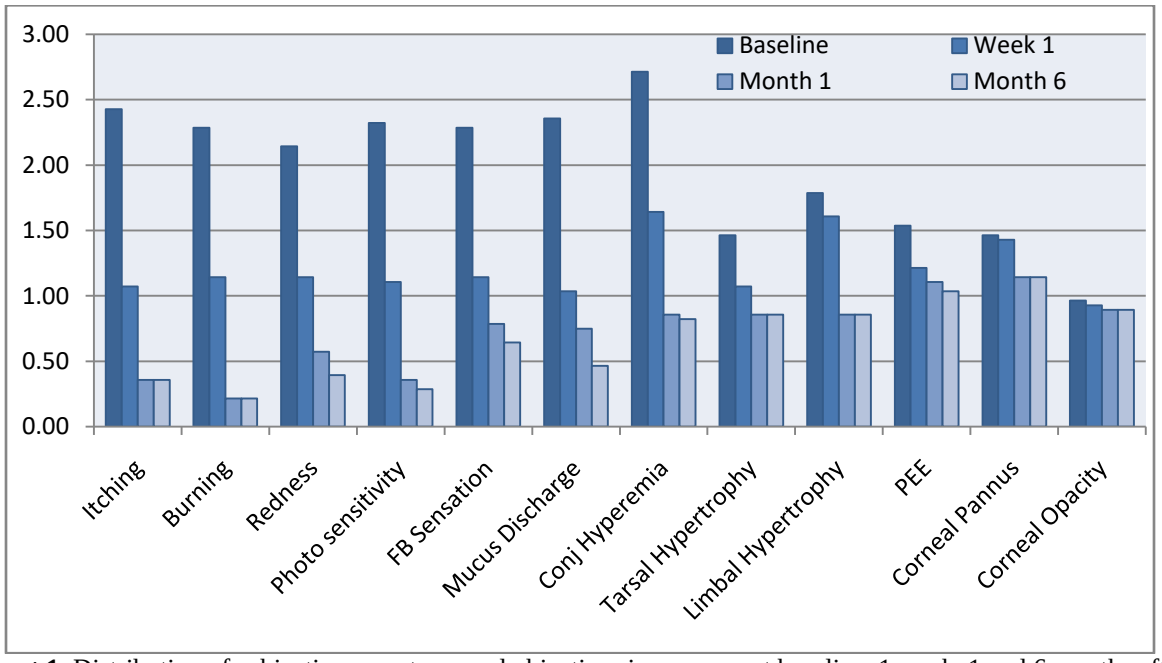

Chart 1. Distribution of subjective symptoms and objective signs scores at baseline, 1 week, 1 and 6 months after treatment.

Discussion

In our study, all the patients who received IFN alpha-2b eye drops, had significant improvement, and the severity of their signs and symptoms significantly decreased, so this drugis effective options for patients with refractory VKC.

Treatment of patients with VKC is a challenge for ophthalmologists. Current drug treatment for ocular allergy targets the key mechanisms involved in the development of clinical disease: mast cells with mast cell stabilizers, histamine

with histamine receptor antagonists,moderate inflammation with corticosteroids, and severe inflammation with steroids and immunomodulators. None of these agents lacks side effects and none abolishes signs and symptoms completely. New therapeutic strategies are still needed to respond to the complex pathogenesis of severe especially chronic forms of VKC[12, 15, 17].“High steroid response” in VKC can lead to a secondary open-angle glaucoma, which may persist even after corticosteroid therapy is discontinued[1, 2].The chronic inflammation and long standing nature seen in severe limbal VKC patients may lead to partial or total limbal stem cell deficiency (LSCD). This may occur due to impaired mechanical stromal support or direct damage to the stem cells by the toxic products of eosinophils and other inflammatory cells infiltrating the limbus [17, 18].

Recently, Turan-Vural et alshowed good efficacy and safety of short-term treatment with IFN alpha-2b in the management of resistant VKC[19]. The result of this study is compatible to our result. In the study of Turan-Vural et al,although most of the beneficial effects achieved were during the 2-month treatment with IFN alpha-2b, they were maintained after discontinuation of the treatment until 6 months[19].This contrary to our study, that reduction in signs and symptoms of the disease was dependent on the continuation of this drug treatment. Although there are different studies on efficacy of tacrolimus in treatment of VKC, there is only one comparative study on efficacy of tacrolimus versus IFN alpha-2b[16].

We used IFN alpha-2b eye drop in a refractory and steroid resistant VKC cases. It suggests that the drop may potentially be used as a main part of VKC treatment. It is steroid sparing and can decrease steroid dependency and itslong-termcomplications.Refractory and steroid-dependent cases of VKC with favorable response to IFN alpha-2bdrop may show kind of dependencyto it which may be better than steroid dependency with lower doses and moresafety.It may also decrease the need to other medications including antihistamines and mast cell stabilizers. Even it may be used as monotherapy. To prevent irreversible sequelae of the cornea and limbus such as corneal opacification and limbal stem cell deficiency, topical immune-modulators such asIFN alpha-2bmay be better to apply earlier in long standing refractory and steroid-resistant VKC cases.

In multiple studies show that,topical tacrolimus can help in reducing corticosteroid usage and is a safe and effective alternative for the treatment of resistant VKC[5, 12] but this drop is not easily available in very countries. In our study, VKC cases were resistant to topical steroids and we used the topical IFN alpha-2b ophthalmic eye drops that well tolerated and rapidly subsided the ocular surface inflammation and shrinkage of the limbal papillary hypertrophy. IFN alpha-2b is a type of IFN considered to be an immunomodulatory cytokine[20-22] and this drop can be prepared more easily than tacrolimus eye drop that is another valuable drug for the treatment of recalcitrant VKC cases, therefore IFN alpha-2b eye drop is a more accessible than tacrolimus eye drops and this can be a great advantage for using this drug in these complicated cases.

Recently, Turan-Vural et al showed good efficacy and safety of short-term treatment with IFN alpha-2b in treatment of resistant VKC[19]. The result of this study is compatible to our result. In this study although most of the beneficial effects achieved were during the 2-month treatment with IFN alpha-2b, they were maintained after discontinuation of the treatment until 6 months. They concluded that the use of IFN alpha-2b could be considered as a promising treatment for short-term therapy[19]. In another comparative study, 2 immunomodulatory agents, tacrolimus and IFN alpha-2b compared with tacrolimus eye drop in the treatment of VKC that had an equal effect in that’s therapeutic effects[16].
In our refractory cases, all symptomsand signs except the corneal opacitycompletely healed after 1-month of topical IFN alpha-2b treatment. We observed that this medication is so effective in the refractory VKC and alleviate all signs and symptoms of severe cases that was resistant and dependent to topical steroid treatment;however, we need more studies with a larger sample size and long-term follow-up times to confirm this drug efficacy and safety in the future.We used IFN alpha-2b drops in a small series of patients with medium-term follow up. Despite that, our sample size and follow up period is longer than most of the published studies. More randomized clinical trials with longer follow-ups and larger sample sizes are recommended to define its optimum concentration and treatment protocol.

In conclusion, in a refractory VKC, IFN alpha-2b eye drop is a safe and effective medication for these cases. It might be better to apply earlier in these cases before occurrence of the complications including irreversible limbal stem cell deficiency, corneal opacity, and steroid-induced complications. However, long-term use may be needed to control the disease. This study indicated that IFN alpha-2b is more available and cheaper than topical tacrolimus in the treatment of recalcitrant VKC.

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