

Is Interferon α -2b 1 MillionIU/mL Truly Better Than Tacrolimus 0.03% for Steroid-Resistant VKC?: Our 2-Year Experience at a Tertiary Health-Care Centre

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Purpose: To compare the efficacy of eye-drop interferon (IFN) α -2b 1 millionIU/mL with eye-ointment tacrolimus 0.03% in refractory vernal keratoconjunctivitis (VKC).

Materials and Methods: Fifty patients with VKC refractory to conventional treatment with topical corticosteroids and antihistamines after 4 weeks of regular use were selected retrospectively. Patients were divided into two groups depending on whether they received eye-ointment tacrolimus 0.03% three times a day or eye-drop IFN α -2b 1 millionIU/mL three times a day and were followed up for 24 months. The main outcome measures were total subjective symptom score (TSSS) and total objective ocular score (TOSS).

Results: Mean baseline TSSS was 7.24 ± 1.98 in Group A (tacrolimus group) and 7.84 ± 1.82 in Group B (IFN group), and it reduced to 1.12 ± 0.83 in Group A and 0.62 ± 0.41 in Group B at 6 months, which was statistically significant compared to the baseline score ($p < 0.05$) as well as between the two groups. Mean baseline TOSS was 6.72 ± 2.07 in Group A and 6.56 ± 2.04 in Group B, and it improved to 1 month onwards to 1.52 ± 0.87 in Group A and 1.0 ± 0.71 in Group B at 6 months, which was statistically significant compared to the baseline score ($p < 0.05$) as well as between the two groups. Side effects like stinging and burning sensations were seen in the tacrolimus group only.

Conclusion: Our study suggests that while both eye-drop IFN α -2b 1 millionIU/mL and eye-ointment tacrolimus eye ointment 0.03% are both safe and effective steroid-sparing agents in steroid-resistant VKC. IFN α -2b results in greater improvement in subjective symptoms and objective signs, has fewer side effects in long term and is better tolerated as compared to tacrolimus.

Keywords: refractory vernal keratoconjunctivitis, tacrolimus, interferon α -2b, VKC

Plain Language Summary

What is Already Known About the Subject

The treatment cocktail for vernal keratoconjunctivitis (VKC) usually includes antihistamines, mast cell stabilizers, and non-steroidal anti-inflammatory drugs for mild disease. For moderate to severe sight threatening cases, topical steroids are the treatment of choice but their long-term use may result in side effects like glaucoma, cataract and secondary infections. To prevent such complications, steroid-sparing agents may be a better option.

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What are the New Findings and How Would These Results Change Clinical Practice

Interferon (IFN) α -2b leads to greater reduction in both subjective symptoms as well as objective signs than tacrolimus at 6 months which is statistically significant. This improvement, both subjective and objective, persisted even till the end of follow-up period at 24 months.

While both IFN α -2b eye drops 1 millionIU/mL and tacrolimus eye ointment 0.03% are both safe and effective steroid-sparing agents in steroid-resistant VKC, IFN α -2b eye drops result in greater improvement in subjective symptoms and objective signs, have fewer side effects in the long term and are better tolerated as compared to tacrolimus eye ointment.

Introduction

Vernal keratoconjunctivitis (VKC) is a recurrent, bilateral, chronic ocular inflammatory condition that primarily affects boys in their first and second decade, living in warm dry climate countries. It is a severe allergic condition in which both IgE and cell mediated immune mechanisms play a role.¹⁻⁵ The prevalence of VKC in tropical regions is around 5%.⁶ VKC persists throughout the year but the symptoms usually get worse during warm seasons.^{7,8} Most of the patients with VKC have a significant history of atopy and/or a family history of atopy. Although, VKC is a self-limiting disorder which usually resolves after puberty, some patients can have sight threatening complications if it is left untreated.

The treatment cocktail usually includes antihistamines, mast cell stabilizers, and non-steroidal anti-inflammatory drugs for mild disease. For moderate to severe sight threatening cases, topical steroids are the treatment of choice but their long term use may result in side effects like glaucoma, cataract and secondary infections.⁹ To prevent such complications, steroid-sparing agents may be a better option.

Tacrolimus (FK506) is a non-steroidal macrolide immunosuppressant and, like cyclosporin, it inhibits T-cell activation and IgE dependent histamine release via cyclophilin receptors.^{10,11} Topical tacrolimus 0.02–0.1% are being used in clinical practice for the treatment of VKC. IFNs are natural proteins that act as immunomodulatory agents. IFN α -2b is a cytokine with endogenous anti-inflammatory and anti-anaphylactic effects. It blocks the IgE-mediated release of histamine, stabilises mast cells

and inhibits the arachidonic acid metabolism. IFN is known to exert anti-inflammatory property by inhibiting the release of IL-4 and IL-5 from Th2 cells¹² and release of IL-10 from monocytes. Hence, this new drug has proven to be effective in the treatment of VKC.¹²

Our study was aimed to compare the efficacy of eye drop IFN α -2b 1,000,000 IU/mL to that of tacrolimus eye ointment 0.03% in a group of patients with refractory VKC.

Materials and Methods

Written and informed consent was taken from parents/guardians of all patients. This study was approved by the Institutional Ethics Committee and Institutional Review Board (IEC.IRB/VMMC/SJH/10/2019-17) of V.M.M.C & Safdarjung Hospital, NewDelhi. All procedures performed our study involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

This retrospective, comparative, observational study was conducted on patients visiting Speciality Cornea Clinic at tertiary health-care hospitals, i.e., V.M.M.C & Safdarjung Hospital, Department of Ophthalmology from 1January 2019 to 31December 2020.

Inclusion Criteria

All patients, 5–15 years of age, having VKC refractory to conventional treatment with topical corticosteroids and topical antihistamines after 4 weeks of regular use were shortlisted. There was a wash-out period of 2 weeks so as to allow the effects of topical corticosteroids to wear off while patients were prescribed topical decongestants and lubricants for temporary symptomatic relief. Of these shortlisted patients, only those who had been prescribed Eye-ointment tacrolimus 0.03% three time a day and eye-drop IFN α -2b 1 millionIU/mL three time a day were selected to be included in final analysis. Patients were matched for age, sex, and any confounding factors and then classified into two groups according to the medication they received.

Exclusion Criteria

Patients with any ocular disease namely uveitis, glaucoma, ocular infection, hypersensitivity to any drug, on any immunosuppressive therapy (topical/ systemic), history of herpetic keratitis, any systemic disease except coexisting asthma/ atopic dermatitis/ allergic rhinitis, and contact lens wearers were excluded from the study.

Procedure and Data Collection

Patients of steroid-resistant VKC who had been put on tacrolimus or IFN α -2b were selected for the study comparison and final analysis. Individuals were then assigned to Group A or Group B as follows:

Group A patients: Eye-ointment tacrolimus 0.03% three times a day.

Group B patients: Eye-drop IFN α -2b 1 millionIU/mL QID.

IFN α -2b eye drop was prepared by diluting 3 millionIU/0.5mL IFN injection (Reliferon © Reliance Formulation Pvt. Ltd) with 2.5 mL artificial tear drops 0.5% Carboxymethylcellulose (RefreshTears © Allergan India Pvt. Ltd.) The IFN α -2b eye drop was stored in the refrigerator (2–8°C) and fresh formulation was prepared after 3 weeks (considering that volume of a drop is 0.05mL so that 1mL has equivalent of 20 drops). After complete general, physical and ocular examination, patients were scored using objective assessment of the signs and symptoms, adapted from similar clinical trials.^{3,4,13,14} Total subjective symptom score (TSSS) and total objective sign score (TOSS) were recorded according to severity from 0 to 3, with higher score indicating greater severity of the disease (Table 1).¹³ These scores were used for comparison within each group and between the two groups on each visit. Evaluations done at 1 week, 1 month, 6 months, 12 months, 18 months, 24 months were taken into consideration and any change in TSSS and TOSS and any side, if present were noted.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm SD. Quantitative variables were compared using Independent-*t*-test for inter-group comparisons and Paired-*t*-test was used for intra-group comparisons. Qualitative variables were compared using Chi-Square test. A *p* value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Demographic Data

Twenty-five patients included in Group A were treated with tacrolimus 0.03% and 25 patients included in Group B were treated with IFN α -2b eye drops 1 millionIU/mL

Table 1 VKC Scoring System

TOTAL SUBJECTIVE SYMPTOM SCORE = TSSS	
Symptom	Severity Score
Itching	0: Absent, no desire to scratch 1+: Intermittent desire to scratch 2+: Frequent desire to scratch 3+: Constant desire to scratch
Photophobia	0: Absent, no photophobia 1+: Mild, squints in bright light 2+: Moderate, improves with use of sunglasses 3+: Severe, improves only with total eye occlusion
Foreign body sensation	0: Absent, no foreign body sensation 1+: Discrete, similar to dust 2+: Mild, similar to sand 3+: Severe, constant and similar to rock
Tearing	0: Absent 1+: Humid, no epiphora 2+: Intermittent epiphora 3+: Constant epiphora
TOTAL OBJECTIVE SIGN SCORING = TOSS	
Sign	Severity Score
Conjunctival hyperemia	0: Absent, calm conjunctiva 1+: Mild, increase in vessel diameter, difficult to notice 2+: Moderate, increase in diameter and number of vessels 3+: Diffuse and intense hyperemia
Upper tarsal papillae	0: Absent on the central tarsal conjunctiva 1+: Present on the central tarsal conjunctiva 2+: Some giant papillae 3+: Giant papillae predominance
Limbus	0: No limbal inflammatory activity 1+: Limbal hyperemia 2+: Limbal hyperemia and papillae 3+: Horner-Trantas dots
Keratitis	0: Absent, no epitheliopathy 1+: Superficial punctate keratitis 2+: Confluent punctate keratitis 3+: Shield ulcer
Discharge	0: Absent, no discharge 1+: Little amount in the fornix 2+: Moderate amount in the fornix 3+: Great amount in the fornix, sticky eyes in the morning

Table 2 Demographic Data of Patients Included in Study

	Group A	Group B	p value	Total
Sample size	25	25		50
Sex				
Males	19	22	0.463	41 (82%)
Female	6	3		9 (18%)
Mean age (years)	8.68 ± 2.53	7.92 ± 2.33	0.274	8.3 ± 2.43
Duration of disease before treatment (years)	3.04 ± 1.21	2.96 ± 1.14	0.810	3 ± 1.16
Associated allergic condition				
Atopic dermatitis	1	0	1	1 (2%)
Allergic rhinitis	8	6	0.753	14 (28%)
Asthma	2	1	1	3 (6%)
VKC-subtype				
Tarsal	15 (60%)	17 (68%)		32 (64%)
Limbal	2 (8%)	4 (16%)	0.346	6 (12%)
Mixed	8 (32%)	4 (16%)		12 (24%)

(Table 2). All were examined at regular visits for 24 months (2 years).

The mean age of patients was 8.68 ± 2.53 years in Group A and 7.92 ± 2.33 years in Group B, the difference between the two groups being not significant statistically (p value = 0.274). Patients had the disease since 3.04 ± 1.21 years, and 2.97 ± 2.6 years in Group A and Group B, respectively (p value = 0.810).

Both groups of patients had predominantly tarsal VKC as compared to the limbal or mixed type, but the difference was not statistically significant. Eighteen out of 50 patients enrolled had a history of some associated allergic conditions.

Scoring (TSSS and TOSS)

TSSS was 7.24 ± 1.98 in Group A and 7.84 ± 1.82 in Group B, respectively, at baseline visit (Table 3), the difference being not significant statistically (p value = 0.271). TSSS improved to 1.12 ± 0.83 in Group A and 0.62 ± 0.41 in Group B respectively at 6 months which was statistically significant compared to baseline score ($p < 0.05$) in respective intra-group. Also, the IFN group (Group B) showed more improvement in subjective symptoms as compared to the tacrolimus group (Group A), which was statistically significant at 6 months ($p = 0.042$). This difference was maintained throughout the period of observation at 24 months.

TOSS was 6.72 ± 2.07 in Group A and 6.56 ± 2.04 in Group B, respectively, at baseline visit, the difference being not significant statistically (p value = 0.785). TOSS improved consistently from 1 month onwards and decreased to $1.52 \pm$

0.87 in Group A and 1.0 ± 0.71 in Group B, respectively, at 6 months, both of which were statistically significant when compared to baseline ($p < 0.05$) in respective intra-group. Also, the IFN group (Group B) showed more improvement in objective signs as compared to the tacrolimus group (Group A), which was statistically significant at 6 months ($p = 0.025$). This difference was maintained throughout the period of observation at 24 months.

There were no major side effects noted except a stinging sensation in 3 patients (12%) and a burning sensation in 8 patients (36%) of the tacrolimus group (Group A) which gradually reduced with time. There were no serious adverse effect requiring withdrawal from the study in either group. Intraocular pressures were within normal limits at each visit in both groups. No patient developed exacerbation of symptoms during the study period.

Discussion

VKC is one of the more severe forms of ocular allergy which can cause vision loss, either due to disease itself or due to indiscriminate use of corticosteroids for years. It usually occurs in children, lasts for 2–10 years and is resolved by puberty. Males are affected more than females. It is usually observed in warm climates and hence is common in India. Many patients with VKC have a significant history of atopy, such as atopic dermatitis, asthma or allergic rhinitis.

The pathogenesis of VKC is multifactorial and involves conjunctival infiltration with eosinophils, mast cells, lymphocytes and macrophages. It is Th_2 lymphocyte-mediated

Table 3 Comparative Data of TSSS and TOSS Between Study Groups

	Group A	Group B	Intergroup Comparison (p value)
At entry (baseline)	TSSS: 7.24 ± 1.98 TOSS: 6.72 ± 2.07	TSSS: 7.84 ± 1.82 TOSS: 6.56 ± 2.04	TSSS: 0.271 TOSS: 0.785
1 Month	TSSS: 3.48 ± 1.48 TOSS: 2.76 ± 1.54	TSSS: 3.16 ± 1.28 TOSS: 3.08 ± 1.22	TSSS: 0.417 TOSS: 0.419
6 Months	TSSS: 1.12 ± 0.83 TOSS: 1.52 ± 0.87	TSSS: 0.62 ± 0.41 TOSS: 1 ± 0.71	TSSS: 0.042 TOSS: 0.025
24 Months	TSSS: 1.08 ± 0.94 TOSS: 1.46 ± 0.79	TSSS: 0.68 ± 0.32 TOSS: 0.98 ± 0.89	TSSS: 0.038 TOSS: 0.011
Intra-group comparison (p value)			
Baseline vs 1 Month	TSSS: <0.0001 TOSS: <0.0001	TSSS: <0.0001 TOSS: <0.0001	
Baseline vs 6 Months	TSSS: <0.0001 TOSS: <0.0001	TSSS: <0.0001 TOSS: <0.0001	
Baseline vs 24 Months	TSSS: <0.0001 TOSS: <0.0001	TSSS: <0.0001 TOSS: <0.0001	

mechanism and long standing, severe inflammation that can lead to fibrovascular reaction, tissue remodelling, corneal complications and permanent visual impairment.¹⁵ This insight has led to use of many drugs like IFN α -2b, tacrolimus, cyclosporine along with conventional therapy like topical steroids, anti-histamines, mast cell stabilisers for the treatment of VKC. Topical steroids remain the first line of treatment of VKC, especially in a flare-up, but their use for long term results in serious complications like glaucoma, cataract and ocular infections. Steroid induced glaucoma can potentially lead to blindness and hence, alternative drugs are needed to avoid such complications.

Tacrolimus is an immunosuppressant agent that reduces inflammatory cytokine production and inhibits several immune reactions involved in pathogenesis of VKC. Tacrolimus, in different concentrations and types, has been proven to be safe and effective for the treatment of refractory VKC.^{16,17} In 2019, Fiorentini et al showed that tacrolimus eye ointment 0.03% can be used as a safe and effective agent for the treatment of refractory VKC in children.¹⁸ IFN α -2b is a cytokine with anti-proliferative, anti-inflammatory and immunomodulator effects, which inhibits arachidonic acid metabolism, stabilises mast cells and inhibits IgE-mediated release of histamine. The role of IFN α -2b has been established in allergic asthma, atopic dermatitis and in conjunctival neoplasias. In 2012, Tarun-Vural et al showed that topical IFN α -2b eye drops reduced the signs and symptoms in steroid-resistant-VKC patients and thus, can be used as

a promising alternative to steroids for treatment of VKC patients resistant to conventional treatment for short periods. The improvement in signs and symptoms was maintained even 6 months after discontinuation of treatment.¹⁹ But the most important drawback of this study was that it had a very small sample size of 12. The second important drawback of this study was that it neither had any comparative nor control group. Similar to our study, in 2017, Zanjani et al conducted a double-masked randomised study in which they compared IFN α -2b and tacrolimus for the treatment of steroid resistant VKC in 40 patients and found that both 0.005% tacrolimus eye ointment and IFN eye drops were equally effective.²⁰ The results of our study are consistent with their results. However, there were certain inherent drawbacks in their study protocol. Firstly, the follow up duration in their study was only 2 months. Secondly, they used tacrolimus eye drops 0.005% formulated from injection tacrolimus, perhaps because such low concentration is not commercially available. Also, they concluded that this ultra-low concentration of tacrolimus was as equally effective as IFN α -2b 1 million IU/mL, which would logically still leave the comparison of commercially available low-dose tacrolimus eye ointment 0.03% vs IFN α -2b unanswered. Thirdly, as Gupta PC. and Ram J. pointed out, no mention has been made of the number of patients in each group in the entire article. Fourth, there is discrepancy of the demographic data within the article abstract and the main text. Also, the dosage frequency of tacrolimus and IFN in each group has not been elucidated. And finally, contact lens

wearers and patients with history of HSV dendritic keratitis were not excluded from the study.²¹

In our study, each patient was followed up at 1 week to check for compliance and side effects. Since no change in TOSS and TSSS was noted at 1 week, these results were not included in study analysis tables. Both 1 million IU/mL IFN α -2b eye drops and 0.03% tacrolimus eye ointment showed a significant improvement in TSSS and caused a significant reduction in TOSS from 1 month onwards. Moreover, IFN α -2b caused more reduction in both subjective symptoms TSSS as well as objective signs TOSS than tacrolimus at 6 months which was statistically significant. This improvement, both subjective and objective, persisted even until the end of the follow-up period at 24 months.

The ophthalmic impact of our study is worth mentioning here. Firstly, the adverse effects noted with tacrolimus were burning and stinging sensation but no such adverse effects were noted with IFN α -2b. There was no increase in intraocular pressure with both tacrolimus and IFN α -2b even after long duration of use. Thus, it is reasonable to believe that both IFN and tacrolimus are equally safe for use in patients with glaucoma or those with steroid-induced raised intraocular pressure. Secondly, IFN α -2b was well tolerated by the patients. As it is more convenient and comfortable to use an eye drop compared to an eye ointment, thus patient compliance and satisfaction was better with IFN α -2b. Both these considerations are significant as the cohort that we are catering to, is the 5- to 15-year-old paediatric group as well as adolescent age group and not only tolerance but also comfort are significant variables in long-term compliance of treatment of steroid-resistant VKC.

Nevertheless, there are a few inherent limitations to the study. Firstly, our study cohort was steroid-resistant and recalcitrant VKC and hence it may be difficult to extrapolate the results of our study to the general population. The second important drawback of our study was that it was a retrospective analysis and the scientific yield of a prospective randomised clinical trial would definitely have been much higher than a retrospective one. Further studies would be warranted to determine if IFN α -2b should be advocated as the main first-line therapy in VKC or whether it should be reserved for severe, recalcitrant and steroid-resistant VKC cases. It is expected that future research would be directed towards newer and better topical steroid-sparing agents that would be safer even in long-term use.

Conclusion

IFN α -2b leads to greater reduction in both subjective symptoms TSSS as well as objective signs TOSS than

tacrolimus at 6 months which is statistically significant. This improvement, both subjective and objective, persisted even until the end of follow-up period at 24 months.

Our study suggests that while both IFN α -2b eye drops 1 million IU/mL and tacrolimus eye ointment 0.03% are both safe and effective steroid-sparing agents in steroid-resistant VKC, IFN α -2b eye drops result in greater improvement in subjective symptoms and objective signs, have fewer side effects in long term and are better tolerated as compared to tacrolimus eye ointment.

Patient and Public Statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethical Clearance

Obtained from Ethical Clearance Committee, Institution Review Board. IEC.IRB/VMMC/SJH/10/2019-17.

Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from parents/guardians all individual participants included in the study.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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