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Case Report

Is there an alternative therapy for refractory vernal keratoconjunctivitis?

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ABSTRACT

We describe a case of severed and steroid-resistant limbal vernal keratoconjunctivitis (VKC) with deficient limbal stem cells, limbal papillary hypertrophies, and its pattern of management with topical eye drops of tacrolimus (TAC) and interferon alpha-2b (IFN-∝2b). The present study is a case report and review of the literature. A woman aged 20 years with a complaint of decreased vision, ocular surface burning, and photophobia in both eyes since childhood age was referred to our cornea clinic. According to corneal impression cytology and incisional biopsy of the limbal hypertrophic lesions, the limbal VKC with deficient limbal stem cells had been diagnosed. She was resistant to topical steroid therapy, therefore topical tacrolimus 0.05% since 4 years ago improved her signs and symptoms, but the tacrolimus eye drop was not available many times and we have to replace it with topical IFN-∝2b eye drop and eventually the good visual acuity achieved with penetrating keratoplasty (PKP) and amniotic membrane transplantation (AMT) surgeries. In a severed and refractory VKC, topical tacrolimus can be replaced by IFN-∝2b and enhanced remission that can resolve patient's complaints and graft survival in such complex cases.

Keywords: Vernal keratoconjunctivitis, Limbal stem cell deficiency, Interferon tacrolimus, Refractory

Introduction

Vernal keratoconjunctivitis (VKC) as an ocular allergic condition occurs in children and young adults predominantly in warm regions. Approximately 50% of patients suffer from concurrent other allergic complications. The illness depends on the season, and the perennial cases that are likely to continue for the whole year, in particular those who are living in a climate of subtropical or desert, are not uncommon [1].

The extra activity and inflammatory responses in the immunity have important functions in the pathophysiology of various ocular surface diseases like VKC [2]. The chronic inflammatory responses in the patients with acute limbal VKC can gradually result in dysfunction of corneal limbal stem cells, probably because of direct disturbance in the stem cells through toxic products from eosinophils and other inflammatory cells that penetrate limbus [3]. Prolong ocular surface inflammations (like VKC) can partially or completely cause limbal stem cell deficiency (LSCD), resulting in an acute visual problem in young people. This ocular surface condition may occur due to the chronic long-lasting nature of the disease, which clinically causes LSCD [3, 4].

Corticosteroids are the main agents for the treatment of anterior inflammation and are the most extensively administered topical anti-inflammatory medications. Often the long-term use of this class of drugs is limited due to unwanted complications like cataracts and glaucoma [5]. In a recalcitrant case of VKC, a suitable immunosuppressant can be an effective strategy. Tacrolimus (TAC) and cyclosporine A are Calcineurin inhibitors extensively prescribed for the prevention and treatment of diseases as topical "steroid-sparing" agents using T-cell-mediated pathophysiology of common eye diseases [6]. To avoid steroid-related complications and in resistance cases, topical TAC and cyclosporine A as routine immunomodulatory medications have

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been reportedly effective strategies to manage the VKC [6, 7]. TAC blocks the immune responses and impedes transplanted organ rejection, with various therapeutic purposes in the ocular surface and corneal chronic inflammations [8].

Interferon alpha-2b (IFN-∝2b) is an immunomodulatory cytokine, whose topical drops are effective agents to manage ocular surface conditions like VKC and pterygium [9]. TAC in many and IFN-∝2b is limited investigations have been successful agents in the management of such cases [10]. In one comparative study 2-immunomodulatory agents, TAC and IFN-∝2b compared in the treatment of VKC that had an equal effect in that are therapeutic effects, these two recently introduced medications may effectively control the VKC based on immunosuppressive strategies [11].

In this case report, we present a rare case of severe and steroid-resistant limbal VKC with a severed limbal stem cell deficiency that managed with topical tacrolimus 0.05% and consequently IFN-∝2b witch prepared the eyes for surgical procedures such as penetrating keratoplasty (PKP) for the patient's visual rehabilitation.

Case report

The patient was a 20 years-old lady with a complaint of decreased vision, ocular burning, and photophobia in both eyes since many times ago that referred to our cornea clinic for 4 last years. Her complaints were aggravated. Her past medical history was unremarkable. She was under medical treatment by topical steroids by several physicians at that time, but her complaints aggravated despite these medications. Her vision was 2 meters finger count in both eyes.

In a slit-lamp examination of eyes, severe corneal haziness, vascularization, and limbal hypertrophy at least 2 corneal quadrants were seen **(Figure 1)**. Extensive vascularized corneal opacity and negligible integrity of epithelium (repeated deficiencies in epithelium) with chronic irritation, lowered visual acuity, and redness.

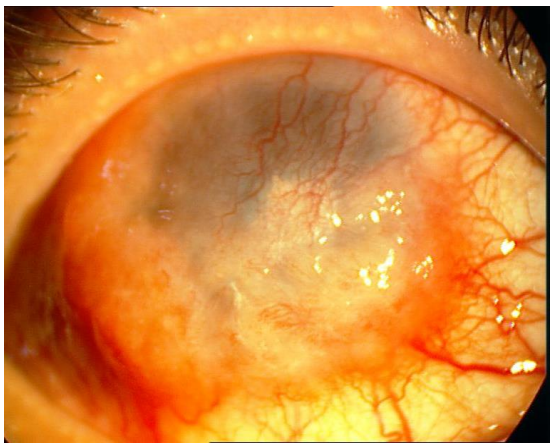

Figure 1. Severed limbal hypertrophy and corneal vascularization in the right eye.

The differential diagnosis of limbal hypertrophic lesions that we saw in this patient may have many categories of allergic, inflammatory, infectious, and neoplastic diseases [12]. In the first step, our approach for the diagnosis was obtaining impression cytology (IC). Many goblet cells and few eosinophils could be seen on IC in some parts of the cornea, according to this finding of IC, limbal stem cells deficiency (LSCD) was confirmed [6]. Small incisional biopsy was obtained from the limbal lesion that in the histopathology exam, many eosinophils were seen on the specimen. The histopathological causes of this mass, including hyperplastic epithelium plus thickened subepithelial stroma and eosinophilic infiltration, was uneven hyperplastic collagen connective tissue scattered with plenty of eosinophils and inflammatory cells. Limbal pseudoepitheliomatous hyperplasia, the lining epithelium did not show any evidence of dysplasia. According to this report of the pathology, the diagnosis was limbal vernal keratoconjunctivitis with a hypertrophic limbal papillary reaction. Interestingly there was not any evidence of tarsal conjunctiva papillary lesions.

The LSCD in this patient was diagnosed in accordance with determined clinical manifestations and confirmed by classic impression cytology. The fluorescein staining was used to assess the ocular surface epithelial integrity and the pattern of epithelial healing. Findings from all follow-p visits were recorded by digital corneal photography (Imagenet; Topcon SL-8Z, Tokyo, Japan). All risks and benefits were clearly explained to obtain informed written consent.

After the diagnosis of refractory VKC since 4 years ago, she was treated with topical tacrolimus 0.05% in our service that continued until 3 years. She was resistant to topical steroid therapy, therefore topical tacrolimus 0.05% improved her signs and symptoms, but the tacrolimus eye drop was not available many times and we have to replace it with topical interferon alpha-2b (IFN-∝2b), 1,000,000 IU/ml eye drop that we could easily prepare it.

Four years ago, her allergic inflammatory reaction was resistant to steroid therapy that was previously prescribed and we started the tacrolimus 0.05% eye drop every 4 hours that continued for 3 years. At that time more signs and symptoms except the corneal opacity were reduced and the limbal papillary hypertrophy was regressed. After 3 years along with decreasing ocular surface inflammation and shrinkage of limbal papillary hypertrophy with the use of topical tacrolimus the tacrolimus eye drop was not available and we started the IFN-∝2b 1000,000 unit/ml with continued controlling of the signs and symptoms **(Figure 2)**. After full control of ocular surface inflammations, the right eye operated with penetrating keratoplasty (PKP) and amniotic membrane transplantation (AMT) for visual recovery **(Figure 3)**. Topical IFN-∝2b therapy continued for another year after surgery, and visual acuity achieved to 20/30 in the right eye.

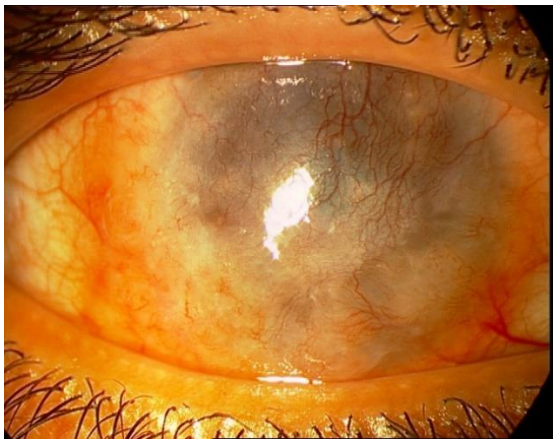

Figure 2. Limbal papillary hypertrophy shrinkage after treatment with topical tacrolimus 0.05%, consequently topical interferon eye drops.

Figure 3. Clear graft, 6 months after penetrating keratoplasty and amniotic membrane transplantation.

Tacrolimus 0.05% eye drop preparation

A balanced salt solution was added to a TAC vial (Prograf, Astellas Pharma Inc.; Dublin; Ireland) to prepare 0.05% eye drop aseptically, followed by refrigeration.

IFN-∝2b eye drop preparation

Topical treatment was fulfilled through IFN alpha-2b ophthalmic preparations (1,000,000 IU/ml), whose preparation was performed by diluting IFN alpha- 2b (3,000,000 IU/ml) solution (3 MIU/cc PDferon-B; Pooyesh Daru Co.; Iran) with the artificial tears (Tear lose; Sinu Daru Co.; Iran). It should be stored in 2–8°C.

Results and Discussion

The prevalence of limbal VKC is lower than palpebral, which is characterized by a thickened, wide, and opacified limbus. The tissues contain basophils, macrophages, plasma cells, lymphocytes, and many eosinophils. About 50% of cases suffer from corneal involvements such as corneal shield ulcers, superficial pannus, and punctuate epithelial keratitis. Reportedly, 10% of patients experience corneal ulcers. The VKC is diagnosed by clinical principles following history taking and ocular tests. Scratching the conjunctiva, showing eosinophils can be useful in the confirmation, but not necessarily for detection [1, 2]. Papilla enlargement and prolonged bulbar type of inflammatory responses indicated a very weak prognosis, elevating complication rates like limbal stem cells deficiency (LSCD) [3, 4].

The pathogenesis of VKC inflammatory responses depends on many parameters on the control of mast cells, IgE, eosinophils, Th2 lymphocytes, and numerous cell mediators and interleukins. In most cases, the clinical course of VKC is self-limiting and may disappear following puberty [13]. Some long-standing limbal VKC patients such as our presented case will face sight-threatening complications, which are mainly due to corneal involvement and LSCD, like our patient who had some goblet cells in the corneal impression cytology with severe corneal vascularisation that represented as partially LSCD.

Many therapeutic agents have been developed to treat VKC, such as antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), and mast cell stabilizers. Topical steroids have been introduced as the main agents to treat moderate to severe VKC types [5]. Several cases are still symptomatic despite management via topical steroids. Long-term administration of topical steroids may lead to many side effects like secondary infections, cataracts, and glaucoma. In cases of refractory and preventing steroid side effects, the VKC has been treated in recent years through immunomodulatory medications like TAC, topical cyclosporine A, and IFN alpha- 2b [13-16].

Topical TAC 0.05% can decrease the usage of corticosteroids, which is effectively and safely used as an alternative to treat refractory VKC [17]. In our case that was resistant to topical steroids, we used the topical 0.05% tacrolimus and consequently topical IFN alpha- 2b ophthalmic eye drops that well-tolerated and rapidly resolved the inflammation and shrinkages of the limbal papillary hypertrophies.

TAC is a non-steroidal immune-modulator capable of blocking the activity of calcineurin, significantly inhibiting the release of different activated T cell-mediated cytokines. Atopic dermatitis is broadly treated by the TAC ointment [17]. Topical TAC 0.02–0.1% can strongly control many refractory inflammatory diseases of the eye surface, such as VKC and atopic keratoconjunctivitis (AKC) [18, 19]. However, there is no information on the optimum treatment dose and long-lasting impacts of the treatment at mentioned doses. Some investigators investigated topical TAC effectiveness to treat acute allergic ocular conditions. Different concentrations from 0.005% to 0.1% have been used [20]. A multicenter double-blinded placebo-controlled randomized clinical trial was conducted to evaluate the effectiveness of TAC ophthalmic suspension 0.1% to treat highly allergic conjunctivitis. The TAC group showed better objective and subjective findings and symptoms compared to the placebo group [21].

Similar findings to our study results have previously been reported in many studies. In a study by Vichyanond *et al.*, topical TAC ointment 0.1% was applied to patients with recalcitrant VKC for a month [22]. Kymionis *et al.* published a case report

after applying TAC skin ointment 0.03% two times per day in a boy suffering from VKC-mediated giant papillary conjunctivitis, the results of which eliminated the giant papillae after 15 days, without any evidence of papilla after one month of treatment [23].

The IFN-∝2b is an immunomodulatory cytokine, whose topical drops are effective agents to control the ocular surface conditions like VKC and pterygium [24]. In a recent study by Turan-Vural *et al.*, short-term IFN alpha-2b therapy for refractory VKC indicated an admirable efficacy and safety, which is in line with our findings. Although most positive impacts were seen within two months of IFN alpha-2b therapy, they persisted for up to 6 months after cessation of treatment. They concluded that the use of IFN alpha-2b could be considered as a potential short-term therapeutic strategy [25]. In another comparative study, 2 immunomodulatory agents, tacrolimus and IFN-∝2b compared in the treatment of VKC that had an equal effect in that's therapeutic effects [11] that were similar to our case study.

In our patient, the limbal lesion was due to an allergic inflammatory process that was diagnosed according to clinical presentations and impression cytology (IC). It was resistant to topical steroids, we used the topical tacrolimus 0.05% eye drops and topical IFN-∝2b that well-tolerated and equally subsided the inflammation and shrinkage of limbal papillary hypertrophy. In such cases, the limbal inflammation in limbal VKC should be controlled as soon as possible especially in steroid-resistant cases that topical tacrolimus and IFN alpha-2b are one of the proper tools in these situations. In our case, papillary hypertrophic lesions completely regressed after 3-years of tacrolimus therapy that consequently followed with topical IFN-∝2b. Ultimately the cornea was prepared for visual reconstructive surgical intervention. We observed that the topical tacrolimus and IFN-∝2b are so effective in the steroid-resistant VKC and the reduction of acute topical steroid-resistant VKC symptoms. On the other hand, topical IFN-∝2b is more available and cheaper than topical tacrolimus in the treatment of recalcitrant VKC.

In our patient, the limbal lesion was more than 2 quadrants that required for amniotic membrane transplantation after keratoplasty for proper corneal surface epithelialization [4]. The epithelial defect completely healed after 4-weeks. The cornea was clear one year later without any conjunctivalization. Our case had more than 2 quadrant stem cells deficiency but still had enough reserve of viable stem cells that responded to AMT application for graft epithelialization after PKP.

Surgically removal of the lesions in the recalcitrant VKC cases, where the signs appear to be due to an increase in mass, is of the therapeutic modalities, probably eliminating chronic VKC-caused symptoms [26], but in our case, the lesion was too extensive that could not be removable and for the preservation of limbal stem cells, we were not done this procedure.

In this case, we found that topical tacrolimus 0.05% and IFN-∝2b 1000,000 IU/ml had the same efficacy in reducing the topical steroid-resistant VKC signs and symptoms. The limbal inflammation in limbal VKC should be controlled as soon as possible especially in steroid-resistant cases that IFN alpha-2b is one of the proper tools in these situations. In our case, papillary hypertrophic lesions completely healed after treatment with topical tacrolimus and consequently topical IFN-∝2b. Ultimately the corneal graft was clear without any conjunctivalization. Because IFN-∝2b is more available and cheaper than topical tacrolimus in the treatment of recalcitrant VKC.

Conclusion

In a refractory VKC, topical tacrolimus as well as IFN-∝2b can be used to enhance remission in such recalcitrant and complex cases and can resolve patient's complaints and induced visual recovery.

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Conflict of interest: None

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Ethics statement: The ethics committee of Guilan University of Medical Science approved this study.

The patient signed informed written consent before the preparation of the current case report.

References

1. Villegas BV, Benitez-Del-Castillo JM. Current Knowledge in Allergic Conjunctivitis. Turk J Ophthalmol. 2021;51(1):45-54.
2. AlHarkan DH. Management of vernal keratoconjunctivitis in children in Saudi Arabia. Oman J Ophthalmol. 2020;13(1):3-12.
3. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol. 2018;12:119-23.
4. Baradaran-Rafii A, Akbari M, Shirzadeh E, Shams M. Single block conjunctival limbal autograft for unilateral total limbal stem cell deficiency. J Ophthalmic Vis Res. 2015;10(1):90-2.
5. Yazu H, Fukagawa K, Shimizu E, Sato Y, Fujishima H. Long-term outcomes of 0.1% tacrolimus eye drop in eyes with severe allergic conjunctival diseases. Allergy Asthma Clin Immunol. 2021;17(1):11.
6. Chatterjee A, Bandyopadhyay S, Kumar Bandyopadhyay S. Efficacy, Safety and Steroid-sparing Effect of Topical Cyclosporine A 0.05% for Vernal Keratoconjunctivitis in Indian Children. J Ophthalmic Vis Res. 2019;14(4):412-8.
7. Ghasemi H, Djalilian A. Topical Calcineurin Inhibitors. J Ophthalmic Vis Res. 2019;14:398-9.
8. Shoughy SS. Topical tacrolimus in anterior segment inflammatory disorders. Eye Vis (Lond). 2017;4(1):1-7.
9. Al Bayyat G, Arreaza-Kaufman D, Venkateswaran N, Galor A, Karp CL. Update on pharmacotherapy for ocular surface squamous neoplasia. Eye Vis (Lond). 2019;6(1):24.

10. Gupta S, Singh P, Singh M, Naik M, Srivastava K. 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. Clin Ophthalmol. 2021;15:2993-9.
11. Zanjani H, Aminifard MN, Ghafourian A, Pourazizi M, Maleki A, Arish M, et al. Comparative Evaluation of Tacrolimus Versus Interferon Alpha-2b Eye Drops in the Treatment of Vernal Keratoconjunctivitis: A Randomized, Double-Masked Study. Cornea. 2017;36(6):675-8.
12. Akbari M, Elmi R. Herpes simplex virus and human papillomavirus coinfections in hyperimmunoglobulin E syndrome presenting as a conjunctival mass lesion. Case reports in medicine. 2017; Article ID 1650841.
13. Zicari AM, Capata G, Nebbioso M, De Castro G, Midulla F, Leonardi L, et al. Vernal Keratoconjunctivitis: an update focused on clinical grading system. Ital J Pediatr. 2019;45(1):64.
14. Akbari M, Moghadam RS, Elmi R, Nosrati A, Taghiabadi E, Aghdami N. Adjunctive Tacrolimus for Herpetic Stromal Keratitis. J Ophthalmic Vis Res. 2019;14:400-11.
15. Haddadi S, Shahrokhirad R, Ansar MM, Marzban Sh, Akbari M, Parvizi A. Efficacy of Preoperative Administration of Acetaminophen and Melatonin on Retrobulbar Block Associated Pain in Cataract Surgery. Anesth Pain Med. 2018;8(5):e61041.
16. Foroutan A, Ghafourian A, Habibi A, Foroutan P, Ashrafkhorasani M, Alemzadeh SA. Successful treatment of allergic conjunctival granuloma by topical tacrolimus: A clinicopathologic case report. Indian J Ophthalmol. 2018;66(4):578-80.
17. Siegl C, König-Schuster M, Nakowitsch S, Koller C, Graf P, Unger-Manhart N, et al. Pharmacokinetics of topically applied tacrolimus dissolved in Marinosolv, a novel aqueous eye drop formulation. Eur J Pharm Biopharm. 2019;134:88-95.
18. Yazu H, Fukagawa K, Shimizu E, Sato Y, Fujishima H. Long-term outcomes of 0.1% tacrolimus eye drops in eyes with severe allergic conjunctival diseases. Allergy Asthma Clin Immunol. 2021;17(1):11.
19. Koh K, Jun I, Kim TI, Kim EK, Seo KY. Long-term results of topical 0.02% tacrolimus ointment for refractory ocular surface inflammation in pediatric patients. BMC Ophthalmol. 2021;21(1):247.
20. Kheirkhah A, Zavareh M, Farzbod F, Mahbod M, Behrouz MJ. Tpical 0.005%tacrolimus eye drop for refractory vernal keratoconjunctivitis. Eye 2011;25(7):872-80.
21. Flynn T, Dahlmann Noor A, Bunce C, Tuft S. Topical treatments for vernal keratoconjunctivitis. Cochrane Database Syst Rev. 2017;2017(8).
22. Vichyanond P, Kosrirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. Curr Allergy Asthma Rep. 2013;13(3):308-14.
23. Kymionis GD, Goldman D, Ide T, Yoo SH. Tacrolimus ointment 0.03% in the eye for treatment of giant papillary conjunctivitis. Cornea. 2008;27(2):228-9.
24. Esquenazi S. Treatment of early pterygium recurrence with topical administration of interferon alpha-2b. Can J Ophthalmol. 2005;40(2):185-7.
25. Turan-Vural E, Acar BT, Acar S. The efficacy of topical interferon-alpha 2b treatment in refractory vernal keratoconjunctivitis. Ocul Immunol Inflamm. 2012;20(2):125-9.
26. Sangwan VS, Jain V, Vemuganti GK, Murthy SI. Vernal keratoconjunctivitis with limbal stem cell deficiency. Cornea. 2011;30(5):491-6.