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Case Report

Topical interferon alpha-2b is a proper alternative for management of adenoviral keratitis: A case report

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ABSTRACT

We describe a case of long-standing and steroid-dependent adenoviral sub-epithelial corneal infiltrations (SEIs), and its management pattern with topical eye drops interferon alpha-2b (IFN-∝2b), and tacrolimus. There is no compressive study about the role of IFN-∝2b in the management of adenoviral corneal SEIs. The present study is a case report and review of literatures. A woman aged 31 years suffering from ocular surface burning, decreased vision, and photophobia in her both eyes with a history of two years after acute adenoviral keratoconjunctivitis was referred to our cornea clinic. According to corneal lesions, the adenoviral SEIs had diagnosed. She was dependent on topical steroid therapy, therefore topical tacrolimus 0.05% improved her signs and symptoms, but the tacrolimus eye drop was not available for that time and we have to replace it with 1,000,000 IU/ML eye drop, topical IFN-∝2b, and eventually the good visual acuity achieved. In steroid-dependent and refractory adenoviral SEIs, topical tacrolimus and IFN-∝2b can equally enhance remission and achieve an excellent visual acuity.

Keywords: Adenovirus, Keratoconjunctivitis, Interferon, Cornea, Infiltration, Tacrolimus

Introduction

Adenovirus causes epidemic keratoconjunctivitis (EKC), with impacts on patients' quality of life over a long period [1]. Half of such patients experience sub-epithelial infiltrations (SEIs); thereby developing blurred vision, reduced visual acuity, photophobia, glare, and halos [2]. SEIs are developed following the immune response to virus replication in the sub-epithelial keratocytes. Such infiltrates are formed from a histological view of antigen-presenting Langerhans, histocytes, and lymphocytes [3]. For years it is possible to observe sub-epithelial infiltrates secondary to adenoviral keratoconjunctivitis, thereby developing blurred vision, photophobia, glare, and halos. The immune response to the virus due to the reaction to topical steroids leads to the formation of these infiltrates. Reportedly, adenovirus SEIs can be effectively treated by cyclosporine A and tacrolimus [4-6]. It may be possible to see this clinical presentation for months to years after conjunctivitis has cleared up, thus developing subjective vision disorders like photophobia, blurred vision, irregular astigmatism, and halos. Considering their chronic nature and visual effect, there are immunosuppressive and anti-inflammatory drugs for the treatment and prevention of SEI. However, they are improved finally without scarring or corneal neovascularization [7-10].

Topical tacrolimus and cyclosporine A have been reported to be effective strategies to manage the adenoviral corneal SEIs to prevent the side effects of steroid therapy and, in cases of resistance. These drugs block the immune response and are used for various therapeutic purposes in chronic inflammation of the surface of the eye and cornea [11].

Interferon alpha-2b (IFN-∝2b) is an immunomodulatory cytokine, whose topical drops are effective agents to manage ocular surface conditions like ocular surface squamous neoplasia (OSSN), vernal keratoconjunctivitis (VKC), and the pterygium surgery [12-15]. In a comparative work, topical IFN-∝2b and

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topical tacrolimus agents compared for VKC therapy, which had the same impact on the therapeutic response, these two recently introduced medications may effectively control the ocular surface inflammations based on immunosuppressive strategies [16].

Unfortunately, there is no compressive study about the role of IFN-∝2b in the management of adenoviral corneal SEIs. In this case report, we present a long-standing and steroid-dependent adenoviral SEIs and its management pattern with IFN-∝2b eye drops and topical tacrolimus that seems to have equal efficacy in the control of adenoviral SEIs.

Case report

A 31-year-old woman was admitted to our corneal clinic with complaints of vision loss, eye irritation, and photophobia in her both eyes with a history of two years, whose complaints intensified recently after discontinuing the topical steroids. Her past medical history was unremarkable except for a history of bilateral EKC since 2 years ago. She was under medical treatment by topical steroids by several physicians at that time, but her complaints aggravated after steroid discontinuation. The vision was 20/30 in both of her eyes.

Figure 1 shows multiple corneal SEIs located in the center under a biomicroscope equipped with a slit lamp. Normal findings were found on the IOP measurements in both eyes. The patient reported the previous consumption of artificial tears without preservative agents, corticosteroids, and topical antibiotics for a year due to the presence of adenoviral SEIs. Fluorescein staining was used to assess the ocular surface epithelial integrity. A digital Imagenet Topcon SL-8Z corneal photography (Tokyo, Japan). The advantages and disadvantages were all clearly described for informed written consent.

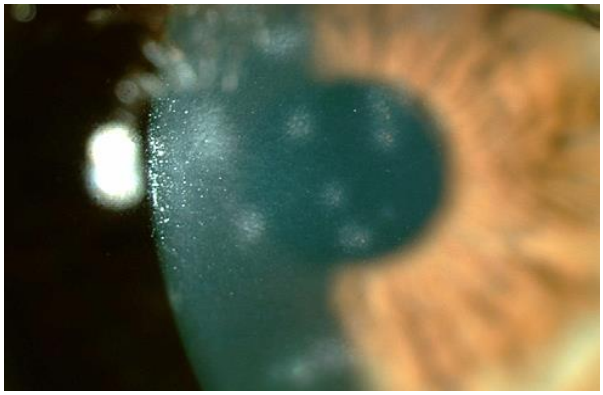

Figure 1. Corneal adenoviral sub-epithelial infiltrations 2 weeks after discontinuing of topical tacrolimus.

After diagnosing corneal adenoviral SEIs, we discontinued the topical steroid and started topical tacrolimus 0.05% that continued until 6 months. Topical tacrolimus 0.05% improved her signs and symptoms. Still, the tacrolimus eye drop was not available for that time. The SEIs quickly recurred after discontinuation of topical tacrolimus and the patient had elevated intraocular pressure (IOP) with restarted topical steroid therapy. So we used another suitable alternative drug and replaced tacrolimus with topical interferon alpha-2b (IFN-∝2b). INFα-2b was administered four times per day, with 1,000,000 IU/ml eye drops that we could easily prepare. After 2 months used and control of corneal inflammations and SEIs, the BCVA achieved 20/20 in both eyes **(Figure 2)**. Topical IFN-∝2b therapy continued for another month with good control of inflammation.

Tacrolimus 0.05% eye drop preparation: A vial of Prograf tacrolimus (Astellas Pharma Inc.; Dublin; Ireland) was added by a balanced salt solution to prepare 0.005% eye drop aseptically, followed by refrigeration.

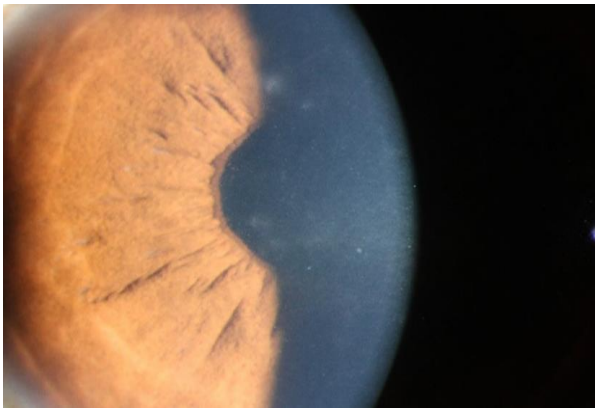

Figure 2. Improvement of corneal sub-epithelial infiltrations 2 weeks after topical interferon alpha- 2b usage.

IFN-∝2b eye drop preparation: Topical treatment was fulfilled through IFN alpha-2b ophthalmic preparations (1,000,000 IU/ml), whose trial was performed by diluting 3,000,000-IU/ml IFN alpha- 2b (3 MIU/cc PDferon-B solution; Pooyesh Daru Co.; Iran) with the Tear Lose artificial tears (Sinu Daru Co.; Iran), followed by keeping at a temperature of 2 to 8°C.

Results and Discussion

Epidemic keratoconjunctivitis (EKC) is the most common symptom of adenovirus-induced eye infections. Visual acuity is commonly reduced due to multifocal SEIs in 50% of cases. Keratitis in EKC is characterized by several corneal infiltrates in the sub-epithelial stroma that begins one to two weeks following the initiation of conjunctivitis [1, 2]. Such SEIs exhibit a cell-mediated immune response to antigens of the virus on the corneal stroma beneath the Bowman's membrane for several weeks to years. Severe ocular morbidity can occur as a result of corneal infiltrates of EKC. Months to years later there is a possibility of seeing photophobia, decreased vision, and foreign body sensation following infection [3]. Corticosteroids suppress the inflammatory response and delay infiltrate formation, thus relieving symptoms caused by SEI.

However, when corticosteroid use is discontinued, the infiltrates return. There is often the possibility of recurrence for opacities, possibly due to the effective suppression of the host immunological response following the administration of steroids, which have no concomitant antiviral impact. The corneal opacity

recurrence could not be prevented even years after the initial acute stage of the disease due to long-term reduction of topical steroids. The other risks of topical steroid use include increased intraocular pressure (putting the eye at risk for developing glaucoma) and cataract formation [5, 6]. Accordingly, and due to unwanted complications of long-term administration of topical steroids like secondary glaucoma and cataract, the steroid therapy cannot be considered for the chronic stage of adenoviral SEIs. Topical cyclosporine A and tacrolimus may both modulate and suppress corneal inflammatory responses. A study of the effects of topical cyclosporin yields the same results as corticosteroids with improved symptoms during medication use, but recurrence of SEI occurs when the medication was discontinued [6, 9]. The SEIs can be treated by topical tacrolimus. One-year follow-up showed that the 60% size and the number of SEIs were decreased after six-month administration of tacrolimus ointment or drops and were eliminated in 32%. The visual acuity was improved significantly following the treatment procedure [17, 18]. Stopping the drug administration for seven months caused a recurrence of almost 19% of the eyes [18]. Interferon-b, an immunomodulator secreted by virally infected cells, may act by inducing an antiviral state or modulating the immune response [19].

Topical Cyclosporin A and tacrolimus are appreciable immunosuppressive agents, with a history of 25 years to prevent the rejection of the transplant. They have been useful to manage persistent corneal opacities in adenoviral SEIs. The topical cyclosporine has shown no complications to date. After slow tapering, the opacities recurred in one-third of primary respondents. Another period of topical cyclosporin (1-2 drops per day) can effectively eliminate opacities in all these patients [6, 20, 21]. Interferons have multiple immunomodulating properties with antiviral and anti-inflammatory effects. Topical interferon may effectively prevent adenovirus infection, but there is not any compressive study in this regard on the impact of interferon on the control and elimination of SEIs.

Based on the results of this study, the majority of signs and clinical outcomes significantly improved following topical IFN-∝2b in those with refractory adenoviral SEIs. In addition, many of the beneficial impacts obtained within two-month therapy have been preserved so far. The patient did not require steroids, so prevented the complications of this therapy. Topical TAC 0.005% and IFN-∝2b can decrease the usage of corticosteroids, which are effectively and safely used as an alternative to treat SEIs. In the topical steroid-dependent case in our study, the patient was administered with topical tacrolimus 0.005%. Then topical IFN-b2b eye drops tolerated well and resolved fast corneal inflammation of SEIs.

The topical drops of IFN-∝2b as an immunomodulatory cytokine are effective agents controlling ocular surface conditions like VKC and pterygium [12, 15]. In a comparative work [16], IFN-∝2b and topical tacrolimus as a 2-immunomodulatory agent compared with VKC therapy had the same impact on the therapeutic response, in line with our case. Unfortunately, there is no comprehensive study on the role of interferon in the treatment of adenoviral SEIs. Administration of IFN-α2b 1,000,000 IU/ml ophthalmic solutions in our research is well tolerated and there was no associated complications, like follicular conjunctivitis, redness, hyperemia, or minor irritation and keratitis.

In our patient, she was dependent on topical steroids and at the same time was a steroid responder with IOP rising. So we used the topical tacrolimus 0.005% eye drops and topical IFN-∝2b subsequently that well-tolerated and equally subsided the corneal inflammation. In such cases, SEIs should be controlled as soon as possible before irreversible sub-epithelial fibrosis mainly occurs in steroid responders that topical tacrolimus and IFN-∝2b are appropriate means in such circumstances. We found that topical IFN-∝2b was as effective as topical tacrolimus in steroid-dependent adenoviral SEIs. On the other hand, the topical IFN-∝2b has high accessibility and affordability compared with topical tacrolimus in the management of these lesions in our country. So we found that topical tacrolimus 0.005% and topical IFN-∝2b 1,000,000 IU/ml had the same efficacy in reducing the topical steroid dependency and SEIs signs and symptoms.

In conclusion, in refractory adenoviral corneal SEIs, topical IFN-∝2b and tacrolimus can be administered to elevate remission in these recalcitrant cases and can eliminate patients' complaints and trigger the visual recovery.

Conclusion

In steroid-dependent and refractory adenoviral SEIs, topical tacrolimus and IFN-∝2b can equally enhance remission and achieve an excellent visual acuity.

Consent

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

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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.

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