Treatment of corneal neovascularization with topical aflibercept in a case of exposure keratopathy following cerebellar astrocytoma surgery

Sibel Aksoy

In this report, we report the case of a 7-year-old boy with corneal neovascularization due to exposure keratopathy following cerebellar astrocytoma surgery. Corneal surface healing was achieved with topical treatment and therapeutic contact lens, after which topical steroid was administered for stromal haze and corneal neovascularization. After 2 months of steroid therapy failed, corneal neovascularization responded well to topical aflibercept administration, showing complete regression.

Key words: Aflibercept, anti-VEGF, corneal vascularization

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_418_18

Department of Ophthalmology, Saglik Bilimleri University, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

Correspondence to: Dr. Sibel Aksoy, Department of Ophthalmology, Saglik Bilimleri University, Fatih Sultan Mehmet Training and Research Hospital, Istanbul- 34752, Turkey. E-mail: sibelaksoymd@gmail.com

Manuscript received: 20.03.18; Revision accepted: 11.09.18

Case Report

A 7-year-old boy was admitted to our clinic with complaints of incomplete eye closure, low vision, and redness in the left eye. Six months before onset, he had undergone suboccipital craniotomy surgery for pilocytic astrocytoma in the left cerebellar hemisphere. Since the surgery, he experienced left facial paralysis and left eye problems associated with lagophthalmos. He was treated with artificial tear drops and topical antibiotic in the intensive care unit and after discharge.

Cite this article as: Aksoy S. Treatment of corneal neovascularization with topical aflibercept in a case of exposure keratopathy following cerebellar astrocytoma surgery. Indian J Ophthalmol 2019;67:145-7.

Despite these treatments, he was referred to our clinic owing to worsening complaints. In initial ophthalmologic examination, he had House-Brackmann grade 3 facial weakness and his parents reported nocturnal lagophthalmos in his left eye. Best corrected visual acuity (BCVA) was 20/20 in the right eye and counting fingers from 1 m in the left eye. Schirmer test results were 10 mm and 3 mm in the right and left eyes, respectively. Slit-lamp biomicroscopy revealed a persistent paracentral epithelial defect, stromal haze, and corneal neovascularization (CNV). We recommended topical sodium hyaluronate hourly, topical dexpanthenol gel twice daily, topical netilmicin twice daily, and eye closure with topical carbomer gel during sleep. There were no changes in the patient's findings after 1 week, so a therapeutic silicone hydrogel soft contact lens (SCL) (Bausch and Lomb Ultra, USA) was fitted and the same topical therapy was maintained.

On examination 2 weeks after SCL application, we observed that the epithelial defect had completely healed. Loteprednol etabonate 5% twice daily was then added to the patient's topical therapy. Despite 2 months of steroid treatment, the superficial/deep stromal vascularization and corneal haze increased. Topical 2 mg/0.05 ml aflibercept (Eylea, Bayer, Germany) was started 3 times daily. The patient's parents were informed about the efficacy of the treatment and possible complications, and a written informed consent form was obtained. Temporary punctal plugs were placed in both puncta to reduce the systemic circulation of the drug.

Eylea is produced for intravitreal injection as a vial containing 40 mg/ml aflibercept in a volume of 278 µl. Topical aflibercept was prepared daily in sterile conditions in the operating room by combining volumes remaining in the vials after intravitreal injection procedures. Remaining volumes of approximately 100 µl per vial were combined in a 1 ml syringe and placed in single-dose artificial tear drop vials that provided 50 µl volumes per application.

Fig. 1 shows the anterior segment image of the patient before topical aflibercept treatment. Significant regression of the neovascularization was observed 3 days after starting treatment and nearly all of the vessels disappeared within 1 week [Fig. 2]. The topical treatment was discontinued after 1 week. No deterioration of the corneal epithelial wound healing, new epithelial defects, or systemic side effects associated with the drug were observed during topical aflibercept therapy. Treatment with sodium hyaluronate artificial tears, dexpanthenol gel, and loteprednol etabonate once daily was continued for 6 months. After 1 year of follow-up, the patient's left eye closed without effort, and Schirmer test result was 10 mm. BCVA of the left eye was 20/40 with +3.00 diopter astigmatism at 90 degrees. Superficial leucoma was noted in the central cornea [Fig. 3]. No neovascular progression was observed at the 1-year follow-up, and no further aflibercept treatment was needed.

Discussion

Several medical approaches are available for treating CNV, all of which are off-label uses.[1] Topical steroids remain the first-line therapy because CNV is assumed to be secondary to some degree of inflammation. In the present case, we also initially used topical loteprednol etabonate, but observed active progression of the vascularization.

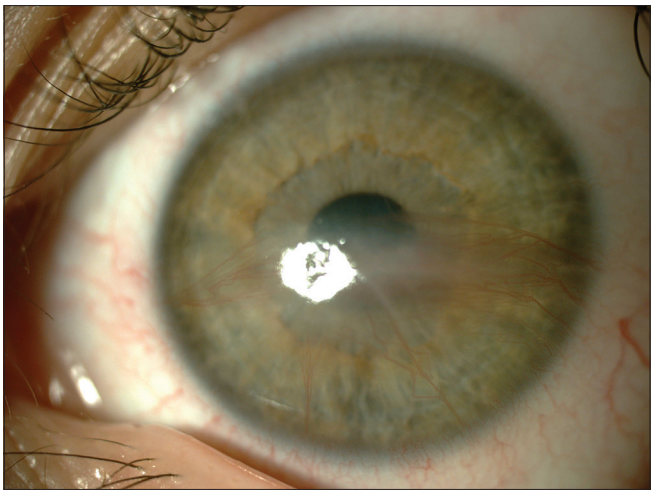

Figure 1: A baseline photograph shows superficial and deep corneal neovascularization affecting the visual axis

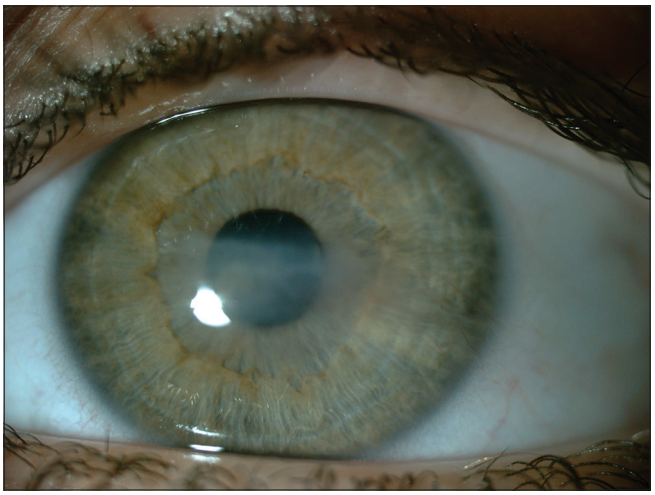

Figure 2: Complete resolution of corneal neovascularization is observed 7 days after initiating topical aflibercept

Figure 3: At 1-year follow-up, the only apparent finding is superficial leucoma in central cornea

Steroids do not specifically target the molecular mediators of angiogenesis and increase the risk of infection, glaucoma, and cataract.[2] High-potency steroids might be more effective in the treatment of vascularization, but we avoided them owing to the potential side effects.

Vascular endothelial growth factor (VEGF) has been proven to be a major inducer of CNV, especially in inflamed and vascularized corneas.[3] Topical and/or subconjunctival administration of bevacizumab or ranibizumab has shown good short-term safety and efficacy.[1] Aflibercept binds to VEGF-A and VEGF-B with higher affinity than any other anti-VEGF agents, and it also inhibits placental growth factor.[4] We speculated that topically applied aflibercept, an intermediate-sized VEGF-Trap molecule, could penetrate neovascularized cornea and more effectively induce regression of neovascularization. We observed complete and permanent regression on CNV after topical aflibercept treatment.

Anti-VEGFs are seemed to be only effective against actively growing blood vessels in an angiogenically stimulated cornea because established vessels are thought to not require VEGF for proliferation. The covering of blood vessels by pericytes marks the end of a sensitive period in which the absence of angiogenic factors such as VEGF can lead to selective apoptosis and the regression of vessels. According to Cursiefen *et al*.'s results, sensitive period seems to be within the first 3 months after onset of CNV, probably within the first few weeks.[5] Antiangiogenic therapy usually involves blocking angiogenic growth factors. In contrast, the goal of *angioregressive* therapy to induce regression of nascent or established corneal blood vessels. Our patient exhibited an actively progressive neovascular process despite steroid therapy, suggesting the presence of newly formed immature vessels, and anti-VEGF therapy was initiated approximately 2.5 months after the patient admitted. Topical aflibercept was effective in this case owing to both its antiangiogenic and angioregressive activity. In human corneal diseases, obviously old and new vessels can be mixed if the angiogenic stimulus is still active. It might be possible to inhibit the further progression of vascularization, in both settings of old and new CNV, by using antiangiogenic treatments.

To our knowledge, there are no previous studies conducted in humans on the use of topical aflibercept to treat CNV. There are two experimental animal studies in the literature that investigate the effect of topical aflibercept on CNV. In a rabbit model of CNV created by placing silk suture in the stroma, 0.1% and 0.01% topical aflibercept significantly reduced CNV compared to the control group. The effect of 0.1% topical aflibercept was equivalent to that of 0.1% topical bevacizumab. No complications were reported.[4] Another study in which CNV was induced by chemical burn in rats demonstrated that topical aflibercept more efficiently prevented CNV compared to bevacizumab. This study also showed that aflibercept suppressed the infiltration of CD68-positive macrophages into the corneal stroma, suggesting that aflibercept reduces inflammation by inhibiting these pathways. The authors reported no significant adverse effects on corneal epithelial wound healing or nerve fiber density.[6] A concentration of 40 mg/ml (2 mg/0.05 ml) was selected for our case because dilution can cause pharmacological instability. We did not observe any clinically evident toxicity to the ocular surface during the aflibercept treatment. Similarly, no complications were reported in a recent pilot study investigating the ability of high-dose (2.5 mg to 7.5 mg) repeated intralesional ziv-aflibercept to cause regression of inflamed or recurring pterygia.[7] In another study that investigated the effects of commonly used anti-VEGF antibodies on the proliferation index and viability of mesenchymal stem cells, a statistically significant adverse effect on mesenchymal stem cell viability was observed only with concentrations of anti-VEGF 10 times the clinically used dosage.[8] These data indicate that the topical application of anti-VEGF is safe at commonly used doses.

Conclusion

In summary, in the presented case, 7 days of 2 mg/0.05 ml topical aflibercept therapy resulted in complete and permanent regression of CNV that did not previously respond to topical steroid therapy. Topical aflibercept seems to be a safe and effective method for the treatment of CNV. Further, clinical studies are needed to demonstrate its efficacy for the treatment of stable, established corneal neovascularization, safety, minimal effective dose, and superiority over other VEGF antagonists.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Giulio F, Chiara G, Paolo R. Corneal neovascularization: A translational perspective. J Clin Exp Ophthalmol 2015;6:387-95.
2. Gupta D, Illingworth C. Treatments for corneal neovascularization: A review. Cornea 2011;30:927-38.
3. Philipp W, Speicher L, Humpe C. Expression of vascular endothelial growth factor and its receptors in inflamed and vascularized human corneas. Invest Ophthalmol Vis Sci 2000;41:2514-22.
4. Park YR, Chung SK. Inhibitory effect of topical aflibercept on corneal neovascularization in rabbits. Cornea 2015;34:1303-7.
5. Cursiefen C, Hofmann-Rummelt C, Küchle M, Schlötzer-Schrehardt U. Percyte recruitment in human corneal angiogenesis: An ultrastructural study with clinicopathological correlation. Br J Ophtahmol 2003;87:101-6.
6. Sella R, Gal-Or O, Livny E, Dachbash M, Nisgav Y, Weinberger D, *et al*. Efficacy of topical aflibercept versus topical bevacizumab for the prevention of corneal neovascularization in a rat model. Exp Eye Res 2016;146:224-32.
7. Mansour AM. Regression of inflamed pterygia by frequent high-dose intralesional ziv-aflibercept. Cornea 2017;36:1002-5.
8. Acar U, Erginturk AD, Alpaslan PF, Demir MN, Beyazyildiz E, Ozdemir O, *et al*. Effects of commonly used intravitreal anti-vascular endothelial growth factor drugs on mesenchymal stem cells derived from the limbus and ciliary body. Clin Exp Ophthalmol 2016;44:587-96.