

Subconjunctival bevacizumab for corneal neovascularization

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Abstract

Objective To report the efficacy of subconjunctival bevacizumab injection in patients with corneal neovascularization (NV).

Methods This retrospective interventional case study included two eyes of two patients with corneal NV due to aqueous-deficient dry eye with filamentary keratitis in the first case, and corneal graft failure in the second case. Patients received a subconjunctival injection of 2.5 mg (0.1 ml) bevacizumab. Morphologic changes were investigated by slit-lamp biomicroscopy and corneal photography.

Results Corneal NV was dramatically regressed a week after injection in the first case. In the second case, minor vessels were regressed while the major one did not. No infection or inflammation was observed. No relapse was seen within the follow-up of two to three months.

Conclusion Subconjunctival injection of bevacizumab may offer an additional strategy for the treatment of corneal NV.

Keywords Bevacizumab · Corneal neovascularization

Introduction

During corneal NV, an up-regulation of angiogenic factors must be present, most likely in association with a down-regulation of anti-angiogenic molecules. Vascular endothelial growth factor (VEGF) is a secreted growth factor

peptide generated by alternative splicing in five isoforms (VEGF115, VEGF121, VEGF 165, VEGF 189, and VEGF 206) [4]. It plays a major angiogenic role in several ocular pathologies characterized by NV [6]. It was recently shown that VEGF was up-regulated in inflamed and vascularized corneas in humans and animal models [2, 6]. Interestingly, requirement of VEGF in corneal NV was shown by the inhibition of NV after stromal implantation of an anti-VEGF blocking antibody in a rat model [2]. VEGF promotes several steps of angiogenesis, including proteolytic activities, endothelial cell proliferation, migration, and capillary tube formation [4].

Bevacizumab, a recombinant humanized monoclonal antibody developed against VEGF, binds to soluble VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation [7].

In the present study, we therefore evaluated, for the first time in the literature, the efficacy of bevacizumab as an alternative treatment to reduce corneal NV after subconjunctival administration.

Materials and methods

This retrospective study adhered to the tenets of the Declaration of Helsinki and institutional review board approval was obtained to review the patient data. Patients opted to have the injection after receiving detailed information about other therapeutic options and signed informed consent. The standard protocol for subconjunctival injections included topical anesthesia, disinfection, and lid speculum. Approximately 2.5 mg (0.1 ml) of commercially available bevacizumab solution (Altuzan, Roche, Istanbul, Turkey) was injected into the subconjunctival space close to the corneal limbus near the corneal NV.

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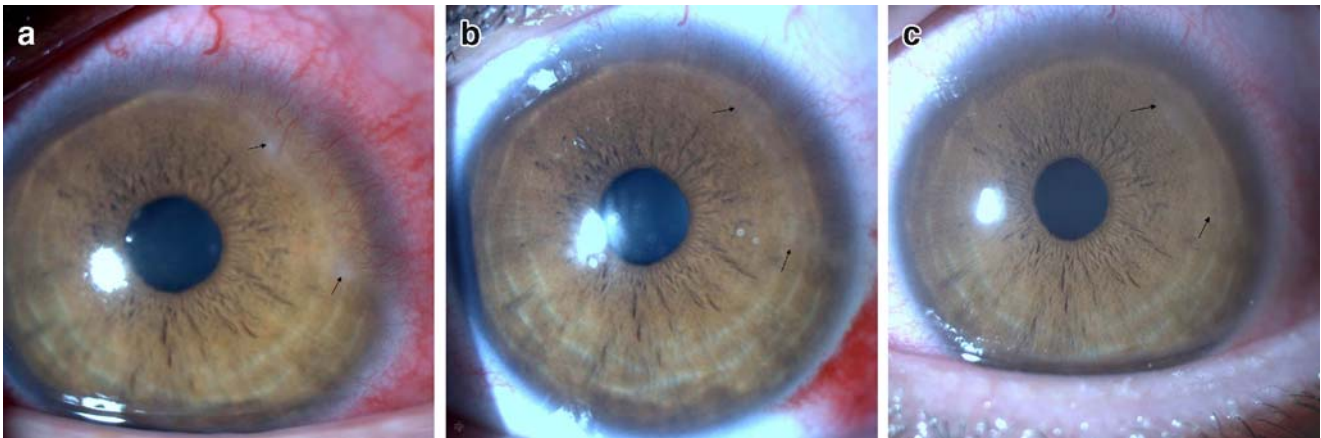


Fig. 1 Corneal neovascularization (NV) due to aqueous-deficient dry eye with filamentary keratitis (**a**). It was rapidly resolved, one week after subconjunctival bevacizumab injection (**b**). No relapse was seen at the end of three months of follow-up (**c**)

Results

Case 1 A 27-year-old man presented with foreign body sensation, grittiness, discomfort, photophobia, and blepharospasm in his left eye. Slit-lamp examination showed corneal NV between 1 and 3 o'clock position with corneal filaments and severe conjunctival hyperemia (Fig. 1a). He had no history of trauma, ocular surgery, or disease. He had been on topical artificial tears and steroid therapy for about two weeks. The diagnosis of filamentary keratitis was made based on the clinical findings of positively staining mucus strands attached to the superior cornea. The patient was also found to have aqueous-deficient dry eye, and blepharitis. Complete examination of anterior and posterior segments of both eyes revealed no other ocular pathology. A single dose of 2.5 mg (0.1 ml) of bevacizumab was injected into the subconjunctival area 1–2 mm behind the limbus near the corneal NV. The patient received an antibiotic eye drop and artificial tear preparation four times a day after subconjunctival drug administration. He was more comfortable even one day after injection. Filamentary lesions and corneal NV was rapidly resolved within one week (Fig. 1b). No relapse was seen at the end of three months of follow-up (Fig. 1c). No signs and symptoms were

detected, and no ocular inflammation and complications were observed throughout the follow-up.

Case 2 An 80-year-old man presented with blurred vision and redness in his right eye. He had a longstanding history of trachoma. Partial penetrating keratoplasty and entropion correction was made because of corneal opacity and cicatricial entropion occurring two years previously. Slit-lamp examination showed suture-induced corneal NV along 360 degrees circumferentially in his right eye. At 6 o'clock position, there was a major branch of corneal NV extending to the central cornea with surrounding lipid keratopathy (Fig. 2a). He had been on topical artificial tears and steroid therapy for about a year. A single dose of 2.5 mg (0.1 ml) of bevacizumab was injected into the subconjunctival area at the 6 o'clock position, 1–2 mm behind the limbus under the main branch of the corneal NV. He was given the same medication and dosage preparation as in case 1. Minor neovascular branches disappeared within one week (Fig. 2b), while the major vessel did not markedly regress during the follow-up of two months (Fig. 2c). No ocular inflammation and complications were observed throughout the follow-up period.



Fig. 2 Corneal neovascularization (NV) due to corneal graft failure (**a**). Minor branches of the corneal NV appear to be rapidly resolved one week after subconjunctival bevacizumab injection (**b**), while the major branch did not markedly regress within the two months of follow-up (**c**)

Discussion

Recent studies using intravitreal injections of bevacizumab for neovascular age-related macular degeneration showed promising results [1, 3]. Iliev et al. [5] also confirmed the regression of iris and iridocorneal angle NV after intravitreal bevacizumab injection and they speculated that it may provide an additional strategy for the treatment of neovascular glaucoma.

We have first reported the inhibitory effect of bevacizumab on corneal NV in two patients, due to aqueous-deficient dry eye with filamentary keratitis and corneal graft failure. Only a single subconjunctival application of the drug caused a dramatic reduction of corneal NV within the first week, with no evidence of inflammation or visual disturbance. In the first case, all the vessels invading the cornea were resolved completely within one week after injection and the cornea remained clear over the following three months. In the second case, however, only the small vessel branches originating from the major vessel dissolved one week after injection, but the major vessel did not regress markedly through the follow-up period. Briefly, a dramatic regression of corneal NV in all eyes was confirmed by slit-lamp biomicroscopy within just a week after injection and no relapse was seen within the follow-up period of 2–3 months.

We used 2.5 mg (0.1 ml) of bevacizumab solution for corneal NV in our patients. The results suggested that this dosage may be enough for corneal NV and could be repeated if necessary. Although some portion of bevacizumab might have been passed into the systemic circulation via subconjunctival vessels, a sufficient amount seemed to be maintained to lessen the corneal NV.

Finally, the present study confirmed that subconjunctival application of bevacizumab can reduce the degree of corneal NV, which implies that bevacizumab may have an additional application for the treatment of corneal NV.

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References

1. Abraham-Marin ML, Cortes-Luna CF, Alvarez-Rivera G, Hernandez-Rojas M, Quiroz-Mercado H, Morales-Canton V (2006) Intravitreal bevacizumab therapy for neovascular age-related macular degeneration: a pilot study. *Graefe's Arch Clin Exp Ophthalmol* [Epub ahead of print]
2. Amano S, Rohan R, Kuroki M, Tolentino M, Adamis AP (1998) Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization. *Invest Ophthalmol Vis Sci* 39:18–22
3. Bashshur ZF, Bazarbachi A, Schakal A, Haddad ZA, El Haibi CP, Nouredin BN (2006) Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 142:1–9
4. Chang JH, Gabison EE, Kato T, Azar DT (2001) Corneal neovascularization. *Curr Opin Ophthalmol* 12:242–249
5. Iliev ME, Domig D, Wolf-Schnurrbursch U, Wolf S, Sarra GM (2006) Intravitreal bevacizumab (Avastin) in the treatment of neovascular glaucoma. *Am J Ophthalmol* 142:1054–1056
6. Philipp W, Speicher L, Humpel C (2000) Expression of vascular endothelial growth factor and its receptors in inflamed and vascularized human corneas. *Invest Ophthalmol Vis Sci* 41:2514–2522
7. Wang Y, Fei D, Vanderlaan M, Song A (2004) Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. *Angiogenesis* 7:335–345