Topical Bevacizumab Therapy for Corneal Neovascularization

Angiogenesis has been defined as the formation of new blood vessels from preexisting vascular structures. Corneal neovascularization (NV) occurs when the balance between angiogenic and antiangiogenic factors shifts toward angiogenic factors. Vascular endothelial growth factor (VEGF) has been found to be a significant angiogenic factor in corneal NV in human and animal models. Therapy specifically aimed at VEGF may suppress corneal NV and increase the chance of transplant survival. We report the use of a topical formulation of bevacizumab, a humanized monoclonal antibody to VEGF, in 2 patients with significant corneal NV.

Report of Cases. Case 1. A 20-year-old man was seen at Duke University Eye Center approximately 1 year after ocular trauma to the left eye from carbonized debris expelled from a high-pressure hose. Examination revealed a best-corrected visual acuity of 20/20 OD and counting fingers OS. Slitlamp examination in the left eye revealed extensive residual debris in the conjunctiva and cornea. Diffuse superficial and deep stromal corneal NV with significant corneal scarring was observed (Figure 1A). The NV was unresponsive to 8 months of corticosteroid therapy. The conjunctival and corneal epithelia were intact. The remainder of the anterior and posterior examination findings were within normal limits.

Case 2. The second case involved a 41-year-old man with a history of ocular cicatricial pemphigoid and corneal neurotrophic ulceration in the right eye. The patient had previously undergone corneal biopsy and amniotic membrane graft to the affected eye with resolution of the ulcer. Examination prior to topical bevacizumab therapy revealed a best-corrected visual acuity of counting fingers in the OD and 20/70 OS. The patient had diffuse scarring, superficial and stromal corneal NV, band keratopathy, and punctate epitheliopathy secondary to the ocular cicatricial pemphigoid in the affected eye (Figure 2A). The corneal NV was unresponsive to several months of topical corticosteroid therapy.

The compassionate off-label use of bevacizumab as well as the potential risks, benefits, and adverse effects of this medication were discussed extensively with each patient. The goal of treatment was to reduce corneal NV to improve the prognosis of future corneal transplantation. To further minimize systemic absorption, silicone punctal plugs were placed in the lower eyelids. The Duke University Hospital pharmacy assisted with the topical formulation of bevacizumab, which consisted of the intravenous solution (25 mg/mL) mixed with stock benzalkonium chloride solution, 0.5% (5 mg/mL), and sterile saline. The final formulation provided 5 mL of bevacizumab, 1.0% (10 mg/mL), with a 0.01% concentration of benzalkonium chloride (0.1 mg/mL) and a pH of 6.2. The patients applied topical bevacizumab, 1%, 4 times a day. All concurrent therapies were discontinued for at least 6 months prior to initiation of topical bevacizumab therapy. The patients were examined at 3 days, 1 week, 2 weeks, and 25 days after initiation of treatment. Slitlamp examination, tonometry, systemic blood pressure measurement, and slitlamp photography were completed at all visits.

Superficial and deep stromal corneal NV was markedly reduced in

Figure 1. Patient 1. A, The patient’s cornea is shown prior to topical bevacizumab treatment, displaying extensive neovascular vessels, most evident inferiorly. B, Dramatic reduction in vascularization resulted after 25 days of topical therapy.
successful results demonstrated with anti-VEGF therapy, used to reduce corneal angiogenesis, has recently garnered interest based on the potential effectiveness of bevacizumab in treating corneal NV. Amano et al reported a potent suppression of corneal NV after stromal implantation of anti-VEGF antibodies using a rat model. Ren et al also used a rat model to show the effects of topical bevacizumab (+ mg/mL) in decreasing corneal NV when applied twice daily for 1 week.

To our knowledge, this case series represents the first successful topical application of bevacizumab in reducing corneal NV in human patients. An obvious reduction in established corneal NV occurred to a different degree in each patient, and topical bevacizumab therapy was very well tolerated. With studies involving a larger sample of patients, one may find a varying response based on the amount of scarring, the chronicity and extent of corneal NV, the disease process, and the formulation and/or route of administration of the medication.

Successful reduction or elimination of corneal NV with topical anti-VEGF therapy could play an important role in improving graft survival in patients who have pre-existing corneal NV or NV of the peripheral cornea that develops after penetrating keratoplasty. Topical anti-VEGF therapy could also potentially treat corneal NV associated with contact lens wear. The reduction or elimination of corneal NV could therefore allow for corneal transplantation or refractive surgery in those patients who were previously considered high risk and had contraindications to surgery. Although promising, the role of bevacizumab and other anti-VEGF agents in corneal angiogenesis needs to be further investigated.

Our preliminary findings provide evidence that anti-VEGF therapy could potentially offer a safer and more effective alternative or adjunct to conventional therapies in treating corneal NV without the potential adverse effects. Although the duration and long-term effects of this therapy remain to be determined, the initial impressive short-term response and the high tolerance to topical bevacizumab therapy offer encouraging results for the potential role of topical anti-VEGF therapy in treating corneal diseases associated with corneal NV.

Comment. Corneal NV remains a significant risk factor for corneal transplantation and subsequent graft failure after transplantation. The Collaborative Corneal Transplantation Study identified, in addition to several other factors, the extent of stromal vessel (quadrants) involvement as a strong risk factor for corneal graft failure. Corneal NV also affects millions of long-term contact lens wearers, many of whom are forced to reduce or discontinue contact lens use so that regression of corneal NV may occur. Various medical and surgical therapies have been attempted to reduce corneal angiogenesis, including corticosteroids, nonsteroidal anti-inflammatory agents, laser photocoagulation, and needle diathermy. Many of these therapies are associated with adverse effects and risks, and most of these therapies have demonstrated limited success. Furthermore, none of these treatments specifically target the inhibition of VEGF.

Anti-VEGF therapy, used to reduce corneal angiogenesis, has recently garnered interest based on the successful results demonstrated with intravitreal bevacizumab. Preliminary in vivo animal data have shown the potential effectiveness of bevacizumab in reducing corneal NV. Successful reduction or elimination of corneal NV may occur. Various medical and surgical therapies have been attempted to reduce corneal angiogenesis, including corticosteroids, nonsteroidal anti-inflammatory agents, laser photocoagulation, and needle diathermy. Many of these therapies are associated with adverse effects and risks, and most of these therapies have demonstrated limited success. Furthermore, none of these treatments specifically target the inhibition of VEGF.

Patient 1 (Figure 1B) and to a lesser degree in patient 2 (Figure 2B). Systemic blood pressure remained at baseline level during the treatment period in both patients. No adverse ocular effects, including conjunctivitis, increased epitheliopathy, or burning on instillation, were noted. The patients did not report any systemic adverse effects.

Figure 2. Patient 2. A, The patient’s cornea is shown prior to topical bevacizumab treatment, displaying neovascular vessels, scarring, and band keratopathy. B, Reduction in vascularization resulted after 25 days of topical therapy.
Vitreous Band Formation and the Sustained-Release, Intravitreal Fluocinolone (Retisert) Implant

The fluocinolone acetonide implant (Retisert; Bausch & Lomb, Rochester, NY) is a sustained-release, intravitreal steroid implant developed to treat chronic noninfectious uveitis.1

Two, 3-year, phase 3, randomized, multicenter clinical trials have demonstrated a statistically significant decrease in the recurrence of uveitis and the need for additional corticosteroids or other immunosuppressive agents after implantation.2

During these studies, 50% to 90% of patients experienced an adverse event after implantation, most commonly cataract formation and increased intraocular pressure.2 Within 2 years of implantation, nearly 100% of phakic eyes required cataract surgery and one third of patients required a glaucoma surgical procedure. Other adverse events included ptosis, eyelid edema, conjunctival hemorrhage, chemosis, corneal edema, vitreous opacities, vitreous hemorrhage, macular edema, retinal hemorrhage, hypotony, and choroidal detachment.2 We describe 4 patients with an adverse ocular event not previously described after Retisert implantation: the formation of vitreous bands from the posterior pole to the implant.

Methods. A retrospective medical chart review of patients who received a Retisert implant at the Cole Eye Institute, Cleveland, Ohio, was conducted. Inclusion criteria included patients with clinically visible vitreous bands extending from the posterior pole to the Retisert implant.

Results. Of the 33 patients who received the Retisert implant, 4 (12%) developed vitreous bands that were visible on clinical examination. Case 1. A 46-year-old white woman received an implant in her left eye for idiopathic uveitis. Prior therapies included posterior sub-Tenon triamcinolone injections and oral cyclosporine. Repositioning of the implant was required 1 month after implantation for slight extrusion of the suture tab. The BCVA improved from 20/80 to 20/70 OS and intraocular inflammation was controlled without the need for additional surgical procedures.

Case 2. A 55-year-old white woman received an implant in her left eye for idiopathic uveitis. Prior systemic medications included prednisone, cyclophosphamide, and mycophenolate mofetil. After implant, BCVA improved from 20/40 to 20/25 OS and intraocular inflammation was controlled without systemic immunosuppression. Three years later, the implant was exchanged owing to increasing inflammation. The patient developed steroid-induced ocular hypertension requiring an Ahmed...