Treatment of Corneal Neovascularization

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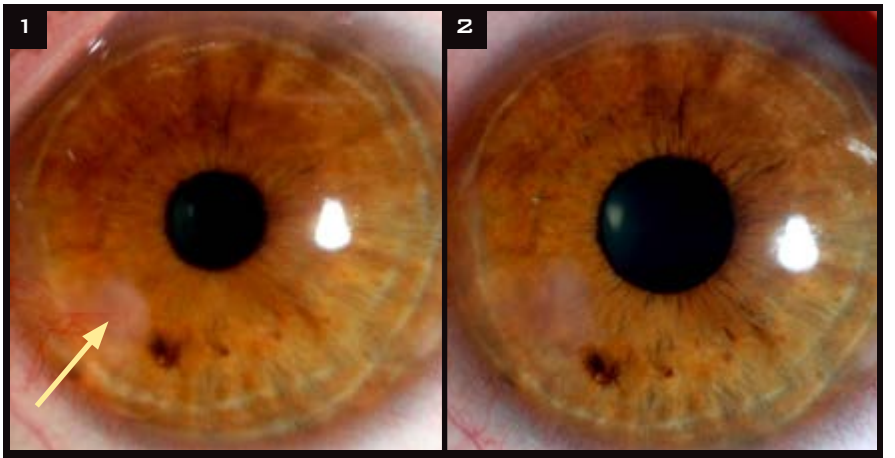
Corneal neovascularization (NV) is characterized by the invasion of new blood vessels into the cornea from the limbus. It is caused by a disruption of the balance between angiogenic and antiangiogenic factors that preserves corneal transparency. Immature new blood vessels may lead to lipid exudation, persistent inflammation, and scarring, thus threatening corneal transparency and visual acuity. Advanced stages, in which ingrown blood vessels reach the visual axis, can become permanently vision-threatening and, in patients with corneal grafts, may contribute to rejection.

This review covers the various treatment options available to patients with corneal NV, ranging from medical management to surgical interventions.



RESPONSE TO THERAPY. Corneal neovascularization in a 41-year-old man with limbal stem cell deficiency, after superficial keratectomy and autologous limbal stem cell transplant with amniotic membrane transplantation. The patient received topical 1 percent bevacizumab four times a day for three weeks. (1) Baseline photograph taken at week 0 (arrow indicates blood vessel invasion area). (2) Photograph taken at week 12, nine weeks after cessation of treatment.

Etiology

Blood vessel formation in the cornea generally involves upregulation of angiogenic cytokines. Extracellular matrix and basement membrane degradation by metalloproteinases and other proteolytic enzymes permits vascular endothelial cells to enter the subepithelial and stromal spaces within the cornea. Corneal NV is typically secondary to one of two types of conditions, inflammation or hypoxia.

Inflammation. Inflammatory NV is commonly caused by traumatic injury, bacterial and viral infection, or chemical burns. Other inflammatory causes of corneal NV include autoimmune conditions such as Stevens-Johnson syndrome, graft rejection, and cicatricial pemphigoid. Degenerative disorders—including pterygium, Terrien marginal degeneration, and limbal stem cell deficiency—also may be involved.

Under inflammatory conditions, corneal epithelial and endothelial cells, macrophages, and inflammatory cells produce angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factors. VEGF upregulates production of matrix metalloproteinases (MMPs) by endothelial cells in the limbal vascular plexus and stimulates blood vessel formation. Inflammation can also induce Langerhans cell migration into the cornea, leading to additional production of angiogenic cytokines and recruitment of immune cells. The angiogenic cascade, amplified by inflammation, tips the balance between pro- and antiangiogenic factors in favor of angiogenesis.

Hypoxia. Most hypoxic corneal NV cases are the result of contact lens wear. Under hypoxic conditions, VEGF is upregulated by corneal epithelial cells in an attempt to enhance the supply of oxygen to the cornea.

Treatment: Medical Options

Several medical approaches, all of which are used off label, are available for treating corneal NV. We recommend that these options be explored fully before considering more inva-

sive surgical interventions. If contact lens–related hypoxia is suspected, it is important to cease contact lens use while the NV is addressed. Lenses with higher gas permeability may be prescribed after corneal NV resolution.

Anti-inflammatory drugs. Topical administration of steroids and/or nonsteroidal anti-inflammatory drugs (NSAIDs) should be first-line treatment for corneal NV. These drugs are best administered within 24 hours following the initial corneal insult, before leukocyte infiltration and recruitment occurs. Results, however, are highly variable. Steroids increase the risk of infection, glaucoma, cataract, and herpes simplex recurrence, while aggressive NSAID use increases the risk of corneal ulceration and melting. As a result, patients should be monitored closely for these complications.

Anti-VEGF agents. Recent studies involving monoclonal anti-VEGF antibodies have shown promising results for the reduction of corneal NV. Topical and/or subconjunctival administration of bevacizumab or ranibizumab has demonstrated good short-term safety and efficacy,[1,2] although long-term data are lacking. Anti-VEGF therapy for corneal NV is still considered experimental and off label, special consents are required, and insurance coverage may be denied.

MMP inhibitors. Under inflammatory conditions, suppression of enzymes that compromise corneal structural integrity may block corneal NV. The combination of orally administered doxycycline (a nonselective MMP inhibitor) plus topical corticosteroids has been shown to suppress neovascularization.

Treatment: Surgical Options

Several laser and surgical solutions are available for corneal NV treatment. Because of the invasive nature of these procedures, they should be reserved for patients in whom medical therapies have failed to produce desirable results.

Laser ablation. Argon and Nd:YAG lasers may be used to occlude invading blood vessels by coagulating blood vessels and ablating tissue. Careful attention must be paid to avoid excessive irradiation and damage to adjacent tissues, as complications such as corneal hemorrhage and corneal thinning may develop. Occlusion of afferent vessels is often unsuccessful because of vessel depth, size, and high blood flow rates. Paradoxically, thermal damage may trigger an inflammatory response, exacerbating neovascularization. Failure due to vessel lumen reopening is common, and new shunt vessels may form.

Photodynamic therapy. Irradiation of a previously injected photosensitive dye causes a reaction that produces reactive oxygen species in the vessel lumen, inducing apoptosis and necrosis of the endothelium and basement membrane. The highly specific tissue damage, combined with the resulting thrombogenic response, seals off the vessel. Although it is effective, photodynamic therapy has limited clinical acceptance due to high costs and potential complications related to laser irradiation and generation of reactive oxygen species.

Diathermy and cautery. A fine needle may be inserted into feeder vessels at the limbus. Vessels are occluded either by application of a coagulating current through a unipolar diathermy unit or by thermal cautery using an electrolysis needle. Although initial studies found these techniques to be safe and effective, additional data from multi-institutional studies are required.

Reducing Graft Rejection

Corneal NV greatly elevates the risk of graft rejection and, ultimately, failure in patients undergoing corneal transplants. Blood vessels at the graft junction provide easy access to donor antigens for host immune effector lymphocytes. The subsequent immune response can trigger inflammation and angiogenesis in the donor cornea. In a large histocompatibility crossmatching study, the frequency of rejection was shown to increase with the number of quadrants of corneal NV present as well as with the number of blood vessels present at the graft junction.[3]

Measures can be taken to mitigate the effect of corneal NV in the host corneal bed and the risk of an immune response. Preoperative occlusion of invasive blood vessels with an argon laser has shown good effect in combination with aggressive postoperative administration of steroids and immunosuppressants such as cyclosporine. In two 2012 studies, patients with corneal NV following penetrating keratoplasty (PK) who received topical bevacizumab or ranibizumab showed decreases in both neovascular area and vessel caliber after 24 weeks of follow-up, without adverse ocular or systemic effects.[1,4]

Use of a Keratoprosthesis

The Boston Keratoprosthesis introduces a clear window of manmade material in the center of a neovascularized cornea. A 3-mm trephine hole in the center of a donor corneal graft accommodates a clear cylinder of the keratoprosthesis front plate, fixed in place with a back plate, which is then secured to the neovascularized recipient corneal bed by interrupted sutures, similar to the technique used in PK. Vision is spared regardless of whether the donor cornea becomes vascularized peripheral to the prosthesis. Placement of a keratoprosthesis may be the treatment method of choice for patients with repeated graft failure or rejection due to recalcitrant central corneal NV. ■

1 Stevenson W et al. *Ocul Surf.* 2012;10(2):67-83.
2 Doctor PP et al. *Cornea.* 2008;27(9):992-995.
3 The Collaborative Corneal Transplantation Studies Research Group. *Arch Ophthalmol.* 1992;110(10):1392-1403.
4 Cheng SF et al. *Am J Ophthalmol.* 2012;154(6):940-948.

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