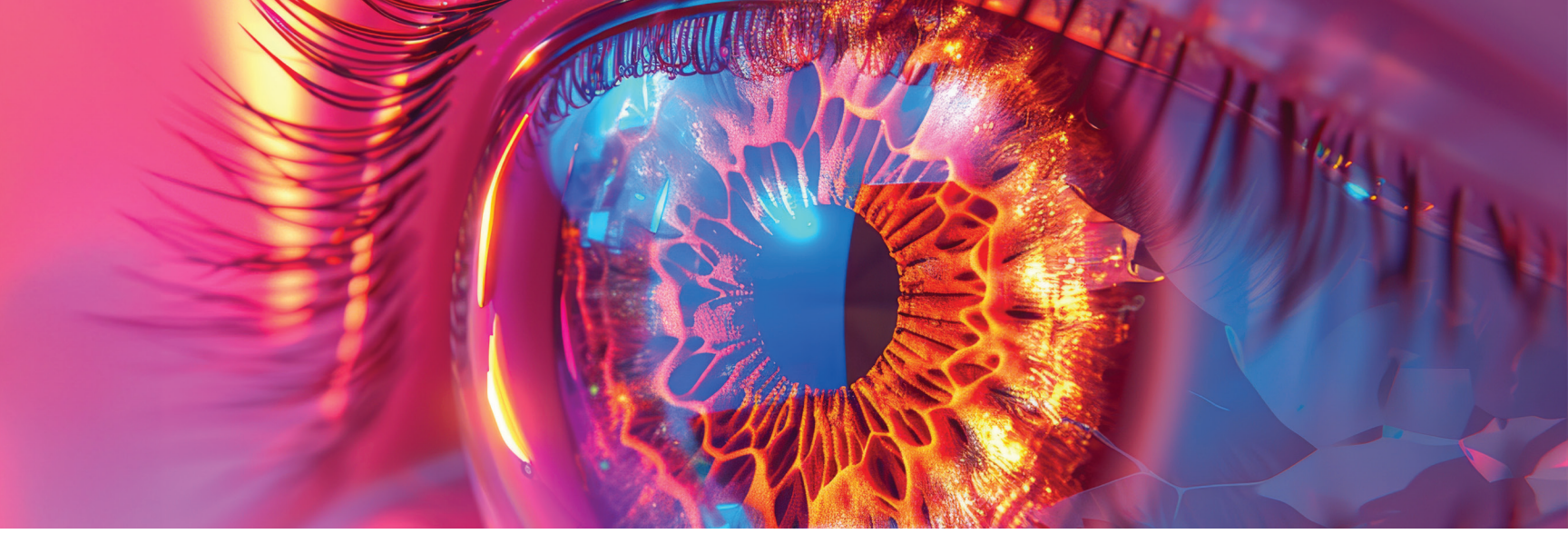

WHAT'S OUT AND WHAT'S IN FOR TREATING CORNEAL FIBROSIS

Emerging regenerative therapies are expanding.

BY NOA ROBSON, OD, MBA

The cornea is an avascular membrane that, when damaged, undergoes a cascade of inflammatory responses, remodeling, and healing. A new extracellular matrix is formed when an insult occurs, which leads to corneal fibrosis and scarring. Severe corneal scarring, especially in the line of sight, can lead to significant visual impairment and even blindness. Treatments for corneal fibrosis, both surgical and pharmacological, have many downsides; however, emerging regenerative therapies are showing promise. This article identifies the limitations of current treatment options and offers an update on newer therapies in development.

PITFALLS OF STANDARD TREATMENTS

Pharmacological treatment with topical steroids or mitomycin C has been the standard for treating mild to moderate corneal opacities. The downside of these medications is that they are ineffective once the corneal epithelium is intact and corneal haze is established. Therefore, unless treatment is initiated prophylactically with the expectation of haze post-operatively or after another form of insult, such options are insufficient.

For severe corneal scarring, corneal transplant is the standard treatment, but it comes with a multitude of potential early complications (eg, raised IOP, infection, wound leak), as well as various late complications (eg, graft failure and/or rejection, infiltrate formation, epithelial ingrowth, astigmatism, and possible disease recurrence, depending on the etiology) that can develop years after surgery. Left untreated, the extensive procedure and recovery process entailed with corneal transplants only provides a 15-year survival rate of approximately 50%.[1]

EMERGING THERAPIES

Pharmacological Approach

Losartan has been used for years as an angiotensin 2 receptor blocker to treat systemic hypertension. Steven Wilson, MD, a cornea and refractive surgeon, investigated the off-label

use of topical losartan to treat corneal scarring with the proposed mechanism of action being the inhibition of TGF-beta signaling, which promotes myofibroblast development and leads to scarring and fibrosis of the cornea.[2] Of note, losartan differs from the standard pharmacological therapies mentioned earlier because it can penetrate an intact corneal epithelium and basement membrane.[3] Oral losartan was not shown to be effective in clinical trials, as only topical penetration supported the proposed mechanism of action.[3]

Topical losartan is being used to treat corneal fibrosis from various causes, including trauma (Figure 1), refractive surgery complications, chemical burns, and infectious etiologies.[4] It is also being used to treat fibrosis from Reis Buckler corneal dystrophy (lattice or granular) and even severe scarring conditions, such as trachoma or Steven Johnson syndrome. The use of topical losartan to treat fibrosis due to glaucoma surgery complications, such as bleb scarring or shunt encapsulations, as well as fibrotic retinal diseases, is also being investigated.[2]

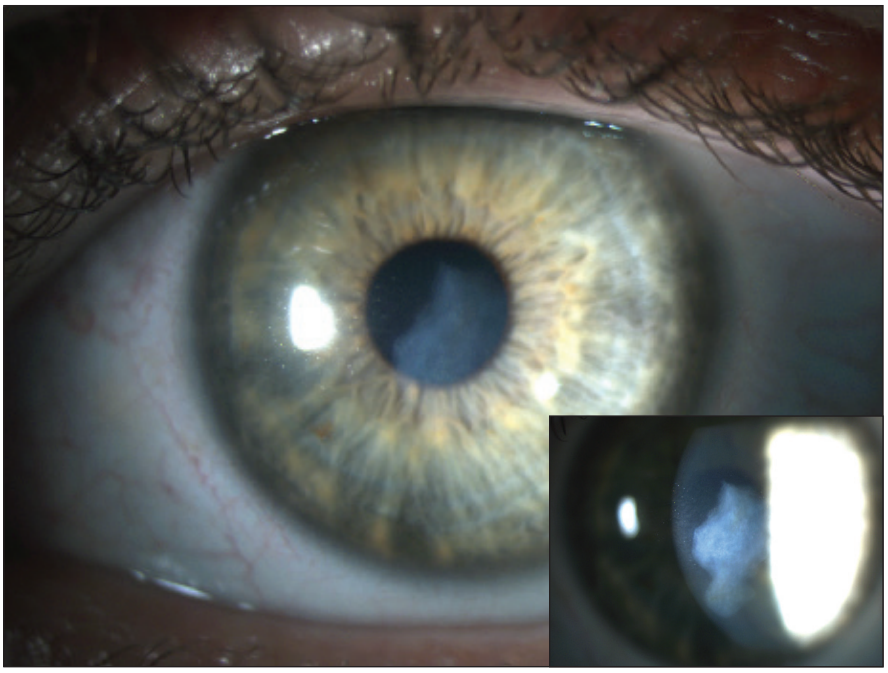

Figure 1. A 28-year-old male with history of ocular trauma developed central subepithelial opacity extending to the posterior stroma (Inset).

Topical losartan must be prescribed through a compounding pharmacy, and all clinical trials recommend 0.8 mg/mL dosed at six times daily.[5] The length of dosage varies depending on density and size of fibrosis, but many patients notice improvement in visual acuity and symptoms within about 2 months, although it may take up to 6 months, in my experience (Figure 2). The six-times daily dosage may be a compliance challenge for some patients, but I have found many are motivated, as they are grateful to finally have a treatment option. Further studies are needed to evaluate dosing, duration, and long-term implications of treatment.

AT A GLANCE

- Corneal fibrosis can occur due to various mechanisms. The standard treatments, consisting of topical antibiotics, steroids, and mitomycin C, are no longer sufficient for management.
- Topical losartan may be able to treat corneal scarring by inhibiting TGF-beta signaling, a pathway that promotes myofibroblast development, leading to fibrosis.
- Autologous limbal stem cell transplantation, in which limbal stem cells are obtained from the patient's contralateral healthy eye, has shown promise for restoring persistent corneal epithelial defects, but more research is needed.
- Nerve-based therapeutic approaches have focused on blocking the interaction between corneal nerves and immune cells to decrease corneal inflammation.

Cell-Based Approach

Interest in corneal and non-corneal stem cell treatments for corneal fibrosis is increasing. The corneal epithelium can regenerate due to the limbal stem cells located at the peripheral limbus, specifically the palisades of Vogt. Autologous limbal stem cell transplantation, where limbal stem cells are obtained from the contralateral healthy eye,

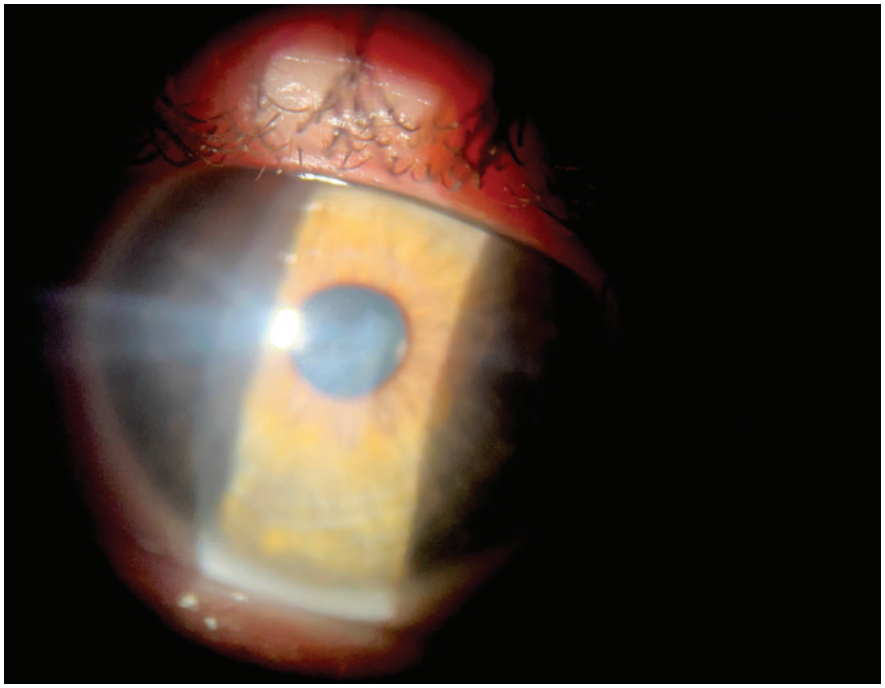

Figure 2. Eight-week follow-up after prescribing topical losartan six times daily. The size of the opacity had mildly decreased, but more significantly, the opacity density had decreased, particularly in the central area.

has shown promise in restoring persistent corneal epithelial defects; however, more research is needed on stromal and corneal endothelial stem cell regeneration properties.[6] Allogenic limbal epithelium had a lower success rate and requires systemic immunosuppression.

Non-corneal–derived cells are being researched extensively and can come from multiple sources, such as oral mucosa, adipose tissue, bone marrow, and amniotic membranes.[7] Embryonic stem cells have many limitations, as their proliferation is uncontrolled and less specific; thus, there is a higher incidence of graft rejection.[8] Although graft-versus-host disease and ocular surface disease are two significant complications associated with stem cell-based therapy, optimism still remains for this approach to restore sight in patients with corneal fibrosis. The use of 3D printing to generate biomaterials is on the rise, which may be the missing puzzle piece to help allow stem cell transplantation to become more compatible.

Nerve-Based Approach

Corneal nerves and immune cells interact to form corneal opacities in cases of bacterial, viral, and fungal corneal infections.[9] Research has focused on attempting to block the interaction between corneal nerves and immune cells to offer therapies that decrease corneal inflammation.[10] The corneal sensory nerve has many critical functions, such as blink reflex and tear production, and a disruption in the reflex can cause advanced ocular surface disease, severe corneal inflammation, and, eventually, corneal scarring. The treatment for patients with decreased corneal sensory nerves is steroids and/or a lateral tarsorrhaphy to decrease corneal exposure. However, neither of these treatments is effective in regenerating corneal nerves, and, therefore, disruptions persist.[11] Of note, patients with diabetic macular edema typically have decreased corneal sensitivity, as anti-VEGF injections impair regeneration of the corneal sub-basal nerve plexus.[12]

A RAY OF HOPE

The standard treatments for corneal fibrosis, consisting of topical antibiotics, steroids, and mitomycin C, are no longer sufficient for management. Research on corneal fibrosis is being directed toward a better understanding of the underlying mechanism of action to better enhance treatment and reduce the reliance on surgical therapy, especially considering the limited global supply of donor tissue.

Future studies may offer a better understanding of the exact process of corneal fibrotic formation, which may offer hope to patients with debilitating corneal scarring who were previously told there were no options for treatment. ■

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