PAINTING A CLEARER PICTURE OF CORNEAL SCARRING IN KERATOCONUS


Topical losartan may offer a new treatment option.

BY ETHIN S. KIEKHAFER, OD, FAAO, AND JACOB R. LANG, OD, FAAO

Keratoconus is a corneal dystrophy commonly diagnosed in early adolescence and adulthood characterized by progressive apical thinning, corneal scarring, irregular astigmatism, visual distortion, and decreased visual acuity. With early diagnosis and therapeutic intervention such as corneal crosslinking (CXL), when indicated, many patients perform well using rigid gas permeable or scleral lenses. However, corneal scarring can complicate the clinical picture, affecting an estimated 20% of patients with keratoconus.[1] Corneal transplantation has historically been the only option for achieving visual improvement for these patients. Recently, the off-label use of losartan, an angiotensin II receptor blocker (ARB) commonly used in hypertension, has emerged as a promising intervention for reducing corneal scarring in keratoconus and possibly other pathologies of the cornea. Let's take a look at some of the research.

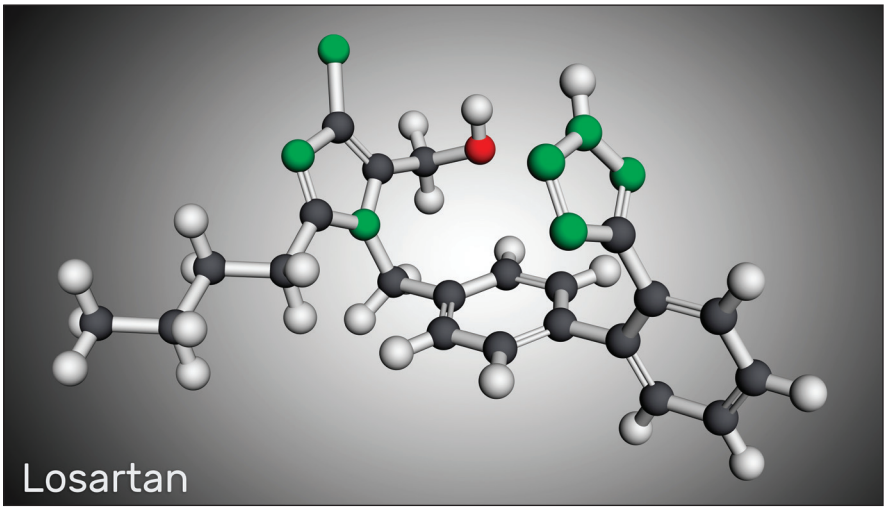
CORNEAL SCARRING

The etiology and pathogenesis of keratoconus is complex and not fully understood. In simplest terms, it is considered a multifaceted amalgamation of factors including systemic conditions, genetic predispositions, and environmental factors such as contact lens wear, chronic eye rubbing, and allergies.[2] Although each case is likely to have its own unique etiology, progressive or untreated keratoconus results in stromal collagen thinning, basement membrane (BM) disorganization, Bowman layer breaks, corneal fibrosis, and ultimately, vision loss.[2] Other keratoconus-associated complications, such as acute corneal hydrops, can

also result in visually debilitating corneal fibrosis. These factors have allowed keratoconus to persist as a leading indication for corneal transplantation in Western countries.[1]

At the molecular level, corneal fibrosis is driven by matrix metalloproteinase activity and other inflammatory mediators, damaging the extracellular matrix and exacerbating fibrosis. Another important key player in this process is transforming growth factor-beta (TGF-β), a cytokine that is absent in a healthy stroma, which is safeguarded by the epithelial and endothelial (Descemet) BMs.

Following injury to either membrane, TGF-β1 present in the epithelium, tears, aqueous humor, and endothelial cells invades the stroma, leading to myofibroblast activation.[3] In any nonhealing or chronic injury with persisting BM damage, adequate stromal TGF-β concentrations allow the relatively opaque myofibroblasts to persist. Over time, these myofibroblasts secrete large amounts of irregular extracellular matrix, leading to the characteristic fibrosis and haze seen clinically. Previous studies have indicated the TGF-β signaling pathway as a developing target for reducing and preventing corneal fibrosis seen in keratoconus.[4-6]



More recent animal studies and clinical trials further identified that topical losartan indirectly inhibits stromal TGF-β, thereby reducing corneal fibrosis.[3] By inhibiting TGF-β signal transduction, losartan attenuates myofibroblast stimulation, triggering apoptosis or reversion back to keratocytes and eventual clearing of the corneal fibrosis.[3,7,8]

This mechanism has sparked interest in losartan as an off-label therapeutic indicated in the case of any fibrotic process caused by myofibroblasts, including keratoconus, post-surgical haze, thermal or chemical burns, microbial keratitis, herpes-related scarring, and other corneal dystrophies.[3,9]

AT A GLANCE

- The off-label use of losartan has emerged as a promising intervention for reducing corneal scarring in keratoconus and possibly other pathologies of the cornea.
- Topical losartan indirectly inhibits stromal transforming growth factor-beta, thereby reducing corneal fibrosis.
- By targeting the underlying signal transduction responsible for scarring, losartan can function as an adjunct to the mechanical stabilization achieved by corneal crosslinking.

NOT YOUR AVERAGE ARB

Losartan possesses several unique characteristics and properties that make it the ARB of choice for treating corneal fibrosis. Most conveniently, it is an affordable and readily available medication that maintains high solubility in balanced salt solutions while remaining clinically effective at low concentrations (0.1 - 0.8 mg/mL).[3,7] To date, clinical studies have reported no corneal toxicity or unexpected side effects when dosed six times daily for several months.[3]

Because it does not require a special vehicle, ophthalmic losartan 0.8 mg/mL can be prepared by local compounding pharmacies for roughly $70 to $140 for a 1-month supply.

Determining treatment duration and frequency will likely vary with each case; however, the level of remaining corneal fibrosis can be a valuable tool in guiding clinical decision making. It is essential to continue treatment through full fibrotic resolution. Any unresolved haze may indicate ongoing myofibroblast activity, which increases the likelihood of relapse after discontinuation. It is postulated that corneal fibrosis resolution often precedes that of the compromised BM in question. It is for this reason that therapy should continue for up to 6 months after corneal scarring

> THE MOST AUSPICIOUS CHARACTERISTIC SURROUNDING LOSARTAN IS NOT ONLY ITS ABILITY TO PENETRATE AN INTACT CORNEA, BUT ALSO TO MAINTAIN THERAPEUTIC CONCENTRATIONS IN ALL CORNEAL LAYERS.

has cleared, albeit at a reduced frequency with monthly monitoring.[3] Corneal scarring is likely to return if therapy is discontinued prior to BM regeneration. In corneas where the BM never completely heals, surgical intervention should be considered to address the resulting recurrent episodes of haze.[3]

The most auspicious characteristic surrounding losartan is not only its ability to penetrate an intact cornea, but also to maintain therapeutic concentrations in all corneal layers. This was highlighted in the two initial animal models demonstrating topical losartan's safety and efficacy in descemetorhexis without graft placement or full-thickness alkali burns.[9] With regard to keratoconus, this indicates promise for patients experiencing deep stromal scarring or damage to the endothelial BM.

CLINICAL IMPLEMENTATION

Keratoconus is treated using rigid gas permeable contact lenses, scleral lenses, and CXL in more advanced or progressive cases. While these treatment modalities are imperative in managing the visual and mechanical complications of keratoconus, they do nothing to address the corneal scarring once it has occurred. The potential integration of topical losartan into existing keratoconus management could indicate a pivotal advancement in patient care.

By targeting the underlying TGF-β signal transduction responsible for scarring, losartan can function as an adjunct to the mechanical stabilization achieved by CXL. Combining CXL and losartan in dual therapy could prevent continued corneal thinning while also reducing overall fibrosis. For patients, this could mean clearer and more consistent long-term visual results and a reduced likelihood of more invasive surgical interventions.

FUTURE OUTLOOK

Early reports on topical ophthalmic losartan are exciting; however, they use limited ocular conditions, small sample sizes, short treatment intervals, and short follow-up periods. Larger-scale animal models and clinical trials investigating losartan and keratoconus will better define the drug's safety and efficacy profiles and improve clinical guidelines.

Looking to the future, the off-label role of topical losartan in optometry offers a promising novel alternative for those experiencing corneal scarring related to keratoconus or other fibrotic conditions. For now, the focus remains on ongoing clinical research and the careful implementation of losartan into existing treatment protocols. ■

1. Santodomingo-Rubido J, Carracedo G, Suzaki A, Villa-Collar C, Vincent SJ, Wolffsohn JS. Keratoconus: an updated review. *Cont Lens Anterior Eye*. 2022;45(3):101559.
2. Davidson AE, Hayes S, Hardcastle AJ, Tuft SJ. The pathogenesis of keratoconus. *Eye (Lond)*. 2014;28(2):189-195.
3. Wilson SE. Topical losartan: practical guidance for clinical trials in the prevention and treatment of corneal scarring fibrosis and other eye diseases and disorders. *J Ocul Pharmacol Ther*. 2023;39(3):191-206.
4. Priyadarsini S, McKay TB, Sarker-Nag A, Karamichos D. Keratoconus in vitro and the key players of the TGF-β pathway. *Mol Vis*. 2015;21:577-588.
5. Sharif R, Hjortdal J, Sejersen H, Frank G, Karamichos D. Human in vitro model reveal the effects of collagen cross-linking on keratoconus pathogenesis. *Scientific Reports*. 2017;7(1).
6. Engler C, Chakravarti S, Doyle J, et al. Transforming growth factor-β signaling pathway activation in keratoconus. *Am J Ophthalmol*. 2011;151(5):752-759.e2.
7. Martinez VV, Dutra BAL, Santhiago MR, Wilson SE. Effect of topical losartan in the treatment of established corneal fibrosis in rabbits. *Transl Vis Sci Technol*. 2024;13(8):22.
8. Wilson SE. Coordinated modulation of corneal scarring by the epithelial basement membrane and Descemet's basement membrane. *J Refract Surg*. 2019;35(8):506-516.
9. Sampaio LP, Hilgert GSL, Shiju TM, Santhiago MR, Wilson SE. Topical losartan and corticosteroid additively inhibit corneal stromal myofibroblast generation and scarring fibrosis after alkali burn injury. *Transl Vis Sci Technol*. 2022;11(7):9.

ETHIN S. KIEKHAFER OD, FAAO
- Optometrist, Associated Eye Care, Stillwater, Minnesota
- eyedoc.kiek@gmail.com
- Financial disclosure: None

JACOB R. LANG OD, FAAO
- Optometrist, Associated Eye Care, Stillwater, Minnesota
- Member, *Modern Optometry* Editorial Advisory Board
- drjakelang@gmail.com; Instagram @seeoneteachone
- Financial disclosure: None