Strengthening Weak Corneas With CXL

If approved in the United States, corneal collagen cross-linking may become the procedure of choice for stabilizing thinning corneas.

BY SPENCER THORNTON, MD

Treatments to stop or reverse the degenerative changes induced by corneal surgery (radial incisions, limbal relaxing incisions, LASIK, lamellar keratoplasty) and diseases such as keratoconus are of high interest to the ophthalmic community because of an increasing number of patients with corneal and limbal thinning. Current methods to ameliorate thinning of the cornea and limbus include surgical and nonsurgical modalities such as vitamin therapy, ultraviolet (UV) light therapy, and corneal collagen cross-linking (CXL). Originally developed to strengthen corneas weakened by keratoconus, CXL has also been shown to strengthen the cornea in eyes with post-LASIK ectasia and those with corneal dystrophies and microbial ulcers.[1]

STRENGTHENING A WEAK CORNEA

In CXL, the term *cross-linking* refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. CXL naturally occurs in the cornea with aging (as in other parts of the body), but chemical agents such as UV-activated riboflavin produce an immediate therapeutic effect. CXL has been shown to stop the progression of ectasia after an excimer laser ablation. In an early CXL study, the procedure halted the refractive and topographic progression of ectasia.[1]

During CXL, the cornea is saturated with riboflavin and then illuminated with UVA light at a frequency of 365 nm, a wavelength that is strongly absorbed by riboflavin. The vitamin produces free radicals that cause cross-linking of the stromal collagen. CXL creates stable new bridges between collagen molecules, reinforces the corneal structure, and prevents significant levels of UV light from penetrating deeper into the eye (Figure 1). The cross-linked collagen filters UV light better than normal stroma (Joseph Colin, MD, personal communication, April 2012).

The photosensitizer riboflavin and UV irradiance strengthen corneal tissue by increasing collagen covalent bonds, as in photopolymerization in polymers, significantly increasing the collagen fiber's diameter and reducing its elasticity. Immunofluorescent confocal microscopy has shown a pronounced compacting of collagen fibers in the anterior stroma after exposure to riboflavin and UVA light (Figure 2). The compacted collagen fibers act as a new entity of conjoined fibers, as in a multiple-strand cable.

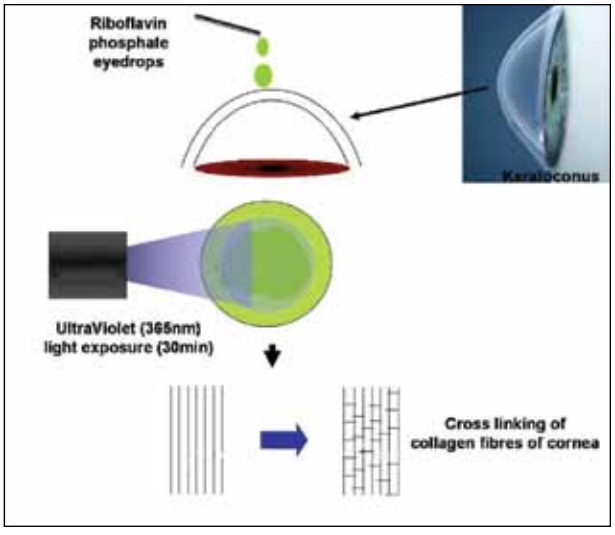

Figure 1. The technique of cross-linking.

Eyes with irregular astigmatism caused by ectasia have been treated initially with CXL followed by customized topography-guided surface ablation.[2-4] This method, which has been shown to stabilize ectasia and improve patients' visual, refractive, and topographic outcomes, may eliminate the need for corneal transplantation.[2-4]

Potentially 50% of corneal transplants necessitated by postoperative ectasia or keratoconus would be eliminated in the United States if the FDA approved CXL (Doyle Stulting, MD, personal communication, September 2012). In Europe, CXL technology received CE Mark approval in 2006.

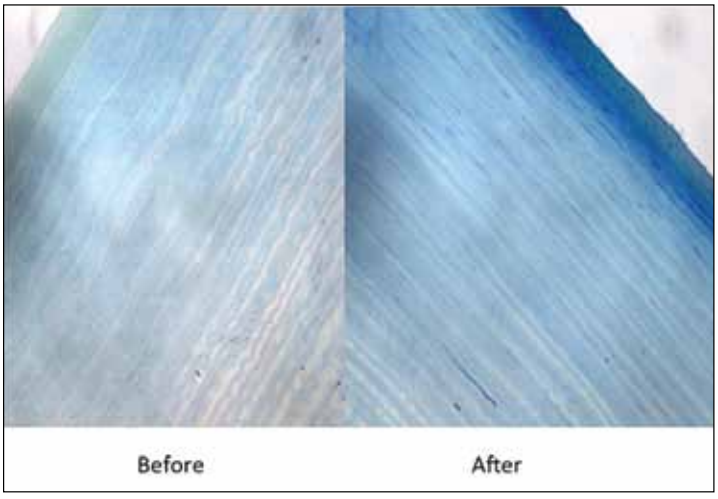

Figure 2. The effect of UV light-activated riboflavin on collagen fibers in the anterior stroma after cross-linking.

EFFICACY AND COMPLICATIONS

Because UVA light can damage the inner endothelial cellular layer of the cornea, the corneal thickness of the stroma needs to be at least 350 µm for a standard CXL treatment.[5] Although UVA light is potentially harmful to the lens and retina, it is believed that the riboflavin soaking the stromal layer blocks the transmission of UVA light to an extent that no measurable damage will occur.[5] Consistent improvement in coma and anterior corneal higher-order aberrations indicates efficacy of the CXL procedure in eyes with ectasia.[6]

Possible complications of CXL include diffuse lamellar keratitis, nonhealing epithelium, infiltrates, stromal haze, and endothelial disturbances.[7] Immediate postoperative hyperemia, foreign-body sensation, and photophobia usually resolve spontaneously.[1] Stromal demarcation lines have been noted at depths of 100 to 300 µm without significant visual effects. The treatment's failure rate is less than 3%, and the complication rate is less than 1%.[7]

TRANSEPITHELIAL CXL

In ongoing studies, investigators are leaving the epithelium intact or performing "epi-on" or transepithelial CXL. Some surgeons familiar with the procedure believe that patients endure less pain, heal faster, and are at a lower risk for adverse events with epi-on compared with the epithelium-off or epi-off technique.[8] Riboflavin is a hydrophilic compound and cannot easily cross the intact epithelial barrier, so buffers and ethylenediaminetetraacetic acid enhancers are added to the riboflavin solution to help it penetrate an intact epithelium.[9]

Pinelli compared the results of epi-on versus epi-off CXL.[10] Riboflavin 0.1% was applied to the cornea via a saturated Merocel sponge (Medtronic ENT) for 5 minutes before the start of UVA light administration and reapplied every 3 minutes during the procedure. Six and 9 months postoperatively, there were no significant differences between the two groups. Mean keratometry, spherical equivalent, and root mean square error decreased in both groups. Additionally, patients in both groups gained lines of UCVA and BCVA, and no loss of endothelial cells was observed in the two groups.

Riboflavin formulations with modified physiochemical properties that enhance penetration through the epithelium are currently being produced outside the United States and are available at Leiter's Compounding Pharmacy and Avedro, Inc. Avedro's new formulations reportedly reduce the time required to perform CXL and, in some applications, improve CXL's utility.

WHAT COULD FDA APPROVAL MEAN?

CXL could be used to stabilize corneal biomechanics before any further clinical progression of ectasia is observed. Because of FDA restraints, further uses of CXL in the United States are considered off label.

I believe that, when approved, CXL will become the treatment of choice for stabilizing thinning or unstable corneas, and I expect its popularity to match that of RK in the latter part of the 20th century.[11] ■

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