Combining Corneal Cross-linking

When keratoconus and corneal ectasia are beyond the early stages, CXL combined with refractive surgeries can improve visual outcomes

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In the world of cornea care, keratoconus (KC) and corneal ectasia are two of the most dreaded conditions, as they cause progressive vision loss. (See "KC and Post-Refractive Corneal Ectasia: An Overview," p.19.) Thankfully, corneal cross-linking (CXL) has been shown to stabilize the ectatic process by halting the progress of the disease and, in some cases, partially reversing the corneal steepening.

Specifically, CXL strengthens the collagen fibers in the cornea, gradually inducing changes in the anterior corneal curvature that stabilize between 6 to 12 months postoperatively.[1] Currently, there is one FDA-approved CXL, which follows the Dresden protocol, however many off-label variations exist.[2] Additionally, the procedure has been shown to improve the optical quality of the eye. (It is not uncommon to see improvements in KC indices after CXL.[3]) Further, the procedure seems to be effective in improving uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) in eyes that have progressive KC by significantly reducing corneal average pupillary power, apical keratometry, and corneal and total wavefront aberrations at 1 year postoperatively.[4]

Given these findings, performing CXL early in the disease process is clearly advantageous. The problem: Many patients undergo the procedure once their condition has already significantly affected their UCVA or, worse, their BCVA.

The good news: Combining CXL with other surgeries has been shown to improve visual outcome when, postoperatively, the BCVA has been negatively affected, and there is irregular shape or astigmatism of the cornea.

Here, we discuss the most utilized combination surgeries, often referred to as "CXL Plus" procedures.

Conducive Keratoplasty (CK)

CK is a noninvasive procedure that utilizes radiofrequency energy to alter biomechanical properties of the cornea.[5] **(Figure 1)** Originally intended to correct presbyopia and low hyperopia by flattening the peripheral corneal to steepen the central cornea, the same principle can be applied to a cornea that has a decentralized cone when combined with CXL.

While the CK treatment on its own results in almost certain corneal shape regression, it is theorized that CXL makes the corneal tissue stiffer, and, thus prevents regression. In fact, reports by Rubinfeld et al. showed improvements in BCVA when CK is followed by CXL over the course of 1 to 3 years postoperatively.[6] That said, a large sample pool is needed to determine the long-term stability of this procedure.

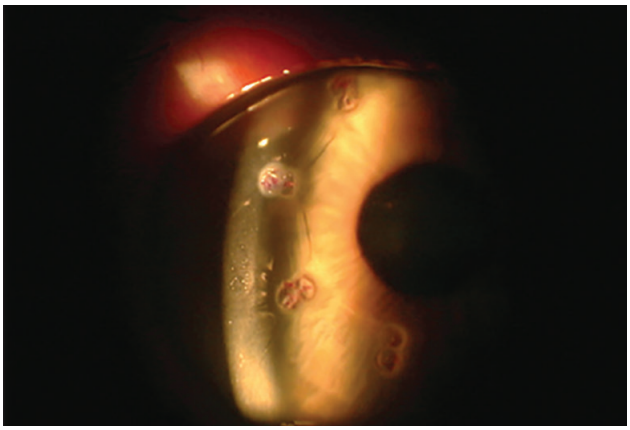

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FIGURE 1: CK's principal of correcting presbyopia and low hyperopia by flattening the peripheral cornea to steepen the central cornea can be applied to a cornea that has a decentralized cone when combined with CXL.

FIGURE 2: When combined with CXL, ICRS have been shown effective in improving both BCVA and UCVA in KC by regularizing and decreasing pathologic corneal steepening and irregular astigmatism.

Intrastromal Corneal Ring Segments

ICRS are polymethyl methacrylate pieces implanted in the mid-peripheral deep stroma to reduce central corneal curvature and were originally developed as a treatment for myopia. **(Figure 2).**

When combined with CXL, done to halt the progression of KC, ICRS have been shown effective in improving both BCVA and UCVA in KC by regularizing and decreasing pathologic corneal steepening and irregular astigmatism.[7] Studies have shown that insertion of ICRS prior to CXL may have a stabilizing effect on the visual outcomes from

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the ICRS and further enhance its effect, whereas prior CXL may have already fixed the cornea into a suboptimal configuration, which ICRS may have difficulty in reversing.[8] More studies that have larger cohorts would need to be done to further elucidate these effects.

PRK

PRK is a corneal refractive procedure in which the corneal reshaping is done by ablating the cornea from the surface without the need for a corneal flap. Its mechanism of action makes it ideal for patients who have thin corneas. The surface ablation also allows for treatment protocols that could address surface irregularities. The Athens protocol was developed to perform topography-guided PRK followed immediately by CXL to optimize the refractive outcomes of KC, whilst the cornea was stabilized by the CXL.[9] Many prospective studies noted significant improvement in BCVA, UCVA and keratometric values in the PRK-CXL group.[10,11] Also, corneal higher-order aberration analysis showed better reduction in root mean square values after topo-guided PRK-CXL (with a planned ablation stromal depth between 18 µm and 49 µm) than after CXL alone.[10] Another study comparing conventional CXL to simultaneous combined PRK and CXL (Athens protocol) showed nearly equivalent results in visual outcomes and refractive improvement after 2 years.[12]

It is difficult to properly determine the precise ablation pattern or refraction that simultaneous topography-guided PRK should target, as the combination of procedures introduces significant unpredictability in how the cornea responds. Further study is necessary to elucidate optimal treatment conditions for this combined procedure and to identify specific disease subgroups more likely to benefit. Based on the published data, topo-guided PRK-CXL treatment can be considered to stabilize disease progression, as well as normalize the corneal surface in keratoconic eyes by reducing the irregular astigmatism, and potentially reducing the refractive error.[13,14]

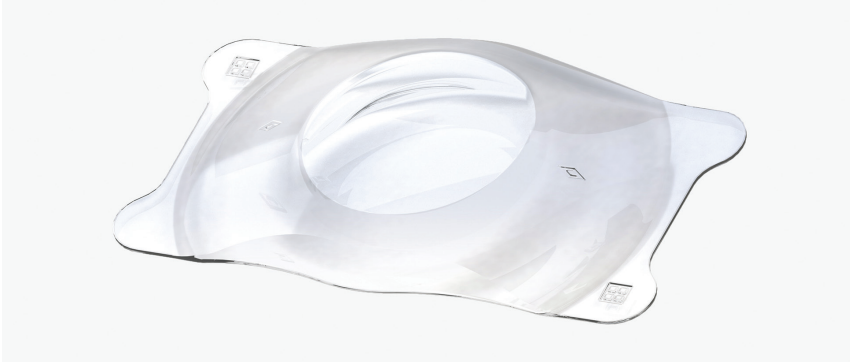

FIGURE 3: When a post-CXL patient develops presbyopia or cataract, an option is to replace the crystalline lens with a pseudophakic IOL.

Phakic IOL

The use of a phakic IOL to correct significant refractive error post-CXL has been shown promising. For example, short to long-term outcomes of an implantable collamer lens following CXL showed significant improvement in refractive error.[15,16] Additionally, none of the eyes needed explantation or repositioning of the ICL during the 3-year follow-up.[17] After achieving post-CXL stability of refractive error, typically around 3 months, ICL implantation can be considered in patients whose vision can be corrected to a level acceptable to the patient with manifest refraction alone. If the patient prefers the vision with hard contact lenses, an ICL will not be comparable, and may be used only to debulk the myopic refractive error for a more acceptable residual correction correctable with rigid contact lenses. Toric ICLs should be considered only if the astigmatism being corrected is mostly regular and bowtie, as measured in the central corneal topographic images.

Pseudophakic IOL

When a post-CXL patient develops presbyopia or cataract, an option is to replace the crystalline lens with a pseudophakic IOL. **(Figure 3)** Once stability of the cornea has been determined, lens replacement may be considered. A caveat: Due to the highly irregular shape and astigmatism of an ectatic cornea, obtaining accurate keratometry and axial length may prove challenging.[18] A comprehensive consensus of which formula is the best in moderate and severe KC cases is not available, as the literature is limited on this subject.[19] Technology that might help obtain more accurate IOL selection can include intraoperative aberrometry and utilizing a light-adjustable lens. Similar to phakic IOL consideration, if there is a potential need for a rigid gas permeable lens, a toric IOL should be avoided. On the other hand, if the central corneal topographic cylinder is mostly bowtie and regular, and especially if the measured cylinder and axis are consistent across other diagnostic tools (i.e., biometry, manual keratometry topography), one can consider a toric IOL to correct or debulk the astigmatic refractive error.

Keeping a Watchful Eye

The initial outcomes of combining CXL with the aforementioned surgeries are promising, though require

more prospective long-term randomized controlled studies to confirm the superiority and stability of the combinational custom CXL approach. Additionally, standardization of treatment strategy needs to be elucidated to determine the most effective approach. To more accurately predict the final refractive outcome of combined CXL protocols, a laser ablation nomogram needs to be developed that takes into account all the possible variables, including patient age, refractive status, CXL status, and KC stage. Short of producing a cure, there is great hope and evidence that we now have the capability to not only halt the progression of KC and ectasia, but also improve upon vision by expanding on the applications of previously known surgical options. **CP**

KC AND POST-REFRACTIVE CORNEAL ECTASIA: AN OVERVIEW

The exact etiology and pathogenesis of KC is still unclear; however, it is suspected to be a result of inherent corneal collagen structural weakness and biomechanical instability.[20] Many genetic, hormonal, and mechanical factors have been proposed as possible causes of KC development and progression. For example, the literature has shown a significant correlation between KC progression and hormonal changes, as in pregnancy, lactation and thyroid eye disease.[21,22] It is also worth noting that KC treatment failures have been associated with vernal keratoconjunctivitis, chronic eye rubbing, dry eye disease and limbal stem cell deficiency.[23]

Corneal ectasia can occur independently in an eye that has had no previous surgical history, or it can happen following refractive surgery. The current understanding for post-refractive corneal ectasia is that there exists a dynamic between the inherent structural integrity of the cornea and the degree of alteration introduced by surgery. If there is inherent structural weakness within the cornea, surgical alteration can destabilize the cornea toward ectasia, or accelerate a latent pre-ectatic process.

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