Combined collagen crosslinking treatments for keratoconus

The landscape of keratoconus treatment has changed profoundly since the introduction of corneal collagen crosslinking (CXL). A decade ago, a newly diagnosed keratoconus patient could expect a treatment plan that involved gradual escalation from spectacle correction to contact lens wear, perhaps followed by an attempt to improve contact lens tolerance or spectacle acuity with intrastromal corneal ring segments (ICRS) and then, for some patients, keratoplasty. This path is beset with frustrations for patients and clinicians alike. Contact lens intolerance, multiple fitting attempts, and temporal gaps in visual function while waiting for special-order lenses are a few of the difficulties faced by patients who would otherwise be enjoying some of the healthiest and most productive years of their lives. Keratoconus carries the additional burden of significant medical expenses that are often passed along as out-of-pocket expenses because of inconsistent insurance coverage for ICRS and contact lenses. When patients do reach the point of keratoplasty, they are often disappointed by the discrepancy between their post-transplant vision and the expectation that transplantation will “cure” their disease and reverse all the optical distortion that makes keratoconus a leading cause of impaired vision-related quality of life.1

Not long ago, disease progression was accepted as an inevitability for predisposed patients, and one that could be addressed only post facto. Crosslinking has fundamentally altered this former truth. Originally envisioned for stabilizing early disease, CXL is increasingly used across the spectrum of keratoconus severity and in combination with other therapies. Questions about who to treat, when to treat, how to treat, and why to treat are increasingly important given the dizzying number of possible treatment combinations.

In their prospective study of staged ICRS, CXL, and toric phakic intraocular lens (pIOL) implantation, Coşkunseven et al. (pages 722–729) report impressive refractive and visual results while providing a unique opportunity to study the incremental effects of each treatment not afforded in studies of simultaneous procedures. The 14 eyes treated in the study demonstrated very high myopia with a mean spherical equivalent (SE) refractive error of $-16.40$ diopter (D) and a range up to $-22.50$ D. Study eyes also had steeper corneas (mean keratometry value was 60.57 D) than those in most CXL studies, and progression of at least 0.75 D was required prior to initiation of treatment. In such eyes, CXL alone—even with the associated benefit of 1 D to 2 D of keratometric flattening reported in many studies—might promote stability but would do little to rehabilitate vision.

With a mean delay of 7 months between ICRS and CXL, Coşkunseven et al. demonstrated the effectiveness of ICRS in reducing overall corneal curvature, spherical refractive error, refractive astigmatism, and keratometric astigmatism while improving corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA). With another 8 months between CXL and pIOL implantation, an additional 1.70 D of keratometric flattening was observed after CXL without significant changes in refractive error or keratometric astigmatism. One year after placement of toric pIOLs, marked gains in UDVA and CDVA and reductions of refractive error were achieved, with 86% of eyes gaining 3 or more lines of CDVA. In the time between the 6- and 12-month examinations after toric pIOL implantation, no eye experienced a shift in SE refractive error greater than 0.50 D.

These results reinforce the complementary functional goals of each treatment modality in addressing the different optical manifestations of keratoconus. Intrastromal corneal ring segments are used to reduce irregular corneal astigmatism. Corneal CXL is delayed to allow some normalization of corneal shape after ICRS before stabilizing an otherwise biomechanically and optically unstable cornea. Finally, after another delay to allow early resolution of post-CXL corneal changes, a more refined intraocular correction of residual spherocylindrical refractive error is performed with a toric pIOL. A separate study by Coşkunseven et al. of patients with lower levels of ametropia and less severe keratoconus used transepithelial topography-guided photorefractive keratectomy (PRK) rather than a toric pIOL as the final step of a staged 3-step approach to keratoconus treatment. Compared with PRK, the advantages of a pIOL include avoidance of tissue ablation, the capability to correct higher degrees of spherical and astigmatic refractive error, lower levels of surgically induced aberrations, no risk of corneal haze, and a degree of reversibility. Disadvantages of a posterior chamber toric pIOL include a potentially higher lifetime risk of cataract formation in a younger recipient group, the potential for rotational instability (which might be mitigated by an iris-fixated pIOL), and the inability to offer further correction of irregular astigmatism that is not corrected by ICRS. This latter limitation, which
also applies to pseudophakic toric IOLs in keratoconus patients, might explain why patients in the ICRS-CXL-PRK study achieved UDVA and CDVA that was on average 1 line better than the ICRS-CXL-toric pIOL patients. However, a reasonable selection bias toward pIOL in patients with high ametropia limits the ability to compare these studies directly.

The worthy goal of these and other combined approaches is to provide a comprehensive surgical solution for the optical blur and instability that drive visual symptoms in keratoconus. The cost-effectiveness of multiple procedures, long-term outcome stability, patient-reported visual function, and time required to achieve ultimate vision (which is comparable to keratoplasty in the cited series) should be explored in these cohorts and others to strengthen the case for or against certain combination therapies. In comparing approaches, it is essential to consider the disease characteristics of the patients in each study, particularly the degree of keratoconus severity and evidence of disease progression prior to treatment. To this point, judicious selection of patients for combination treatments involving ICRS implantation is important given evidence that patients with low-grade keratoconus could be more prone to loss of CDVA because of induced irregularity.

The great promise of CXL for keratoconus is its potential to prevent loss of vision that is only partially reversible later with more expensive and invasive treatments. For today's patients who have already experienced significant visual loss, it is increasingly clear that carefully selected combinations of treatments can provide both stability and meaningful visual recovery.

William J. Dupps Jr, MD, PhD

REFERENCES