Corneal Collagen Cross-linking: New and Expanding Applications

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Corneal collagen cross-linking (CXL) for adult corneal ectatic disorders has come of age. With more than 300 publications appearing in the peer-reviewed literature, this procedure is well vetted, has an excellent safety profile, and is reasonably predictable in clinical outcomes when the standard protocol is applied. In this issue of the Journal of Refractive Surgery (JRS), we have a series of articles that move CXL beyond its traditional borders, into the realm of pediatric keratoconus, treatment of nonectatic clinical disorders, and as adjunctive treatment with refractive surgical procedures.

Cross-linking is not, per se, a refractive procedure, as improvements in acuity and refractive error are modest in the best scenarios. A logical question might therefore arise: if CXL is not a refractive procedure, why does it occupy so many pages of a journal devoted solely to refractive surgery? The reasons are many currently, as refractive surgeons are frequently the individuals with whom patients with ectatic corneal disease initially interact, and these reasons may grow as refractive surgical procedures and CXL become increasingly linked together in our treatment armamentarium. The newer applications of CXL are simultaneously of great interest to our profession and also remain to be thoroughly evaluated; hence, the number of articles in this issue of JRS.

CXL FOR PEDIATRIC KERATOCONUS

Because keratoconus is by definition a progressive corneal disease, it logically follows that the process begins early in life, and earliest intervention provides the best opportunity to provide visual stability. Given the varying ages being studied (ranging from 8 to 19 years in the literature) as well as the variety in potentially correct nomenclature (children, kids, adolescents, young, juvenile), which will only serve to confuse the issue as future studies arise, I recommend all of these studies be grouped under the generic heading “Pediatric CXL” to maximize the exchange of information by simplifying and thus facilitating complete literature searches. Timing of treatment, optimal treatment protocol, and long-term efficacy are topics of active investigation.

Chatzis and Hafezi found that 88% of pediatric patients demonstrated progression from their initial evaluation, suggesting that treatment at onset of diagnosis may be appropriate as opposed to waiting for signs of progression as is commonly done in adults. Recent publications have found improvements in visual acuity, steepest keratometry, and refraction similar to that reported for adult treatment, with stability or improvement maintained for 24- to 36-month follow-up when treated with the standard protocol, including epithelial removal. Chatzis and Hafezi found similar outcomes over 24 months; however, they noted some regression by 36 months. The significance remains to be determined, but it is possible that pediatric CXL may not enjoy the longevity of stability comparable to adult treatment.

EFFICACY (OR LACK THEREOF) OF TRANSEPITHELIAL CXL

Although the standard protocol has resulted in good, predictable success for CXL, the major drawbacks to the procedure are related to epithelial removal. A variety of transepithelial or modified epithelial removal approaches have been attempted; however, to date, none have been close to reaching the efficacy of full epithelial removal. Buzzonetti and Petrocelli report similarly limited outcomes for transepithelial pediatric CXL, and Touboul and colleagues found essentially no corneal morphological changes after transepithelial CXL as compared to standard and accelerated CXL. Using in vivo optical coherence tomography, Malhotra and colleagues compared complete and partial epithelial removal and found no riboflavin penetration in regions without epithelial removal. Thus, although enticing, transepithelial CXL...
appears to have limited, if any, efficacy using current techniques and technology.

**CXL FOR NONECTATIC CORNEAL DISORDERS**

Last month, Price and colleagues\(^9\) reported an excellent safety profile when adding CXL as adjunctive therapy for infectious keratitis. This month, Bettis and colleagues\(^10\) provide an excellent summary of the literature to date on using CXL for nonectatic disorders, including persistent corneal edema and infectious keratitis. The particulars remain to be determined, but CXL appears promising as either adjunctive or potentially primary therapy for these disorders.

**CXL AS A “STABILIZER” FOR REFRACTIVE SURGICAL PROCEDURES**

A novel application for CXL involves utilizing it in combination with corneoplastic procedures to maintain the induced curvature alteration in otherwise unstable procedures, including thermal keratoplasty, or to further stabilize already stable procedures such as routine LASIK. The degree to which this adjunctive use will be necessary or effective remains uncertain. Vega-Estrada and colleagues\(^11\) report early outcomes of CXL combined with a microwave procedure intended to flatten the cornea centrally to treat keratoconus; however, they found that adjunctive CXL did not prevent significant regression and thus was only minimally effective as an adjunct to this procedure. Time will tell whether CXL proves effective as an adjunctive “stabilizing” therapy for any refractive procedures.

**REFERENCES**


