The Case for CXL: Is it a Standalone or a Combination Procedure?

A review of the history and an overview of current treatments.

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For several years, surgeons have used corneal collagen crosslinking (CXL) with riboflavin to stop the progression of keratoconus.[1] This treatment, which strengthens the weakened corneal structure, can stop the cornea from becoming steeper and more irregular. In some cases, it can prevent these effects of keratoconus altogether.

It is postulated that degradation of normal collagen and synthesis of abnormal collagen contribute to the pathogenesis of keratoconus.[2] Therefore, it is argued, strengthening the collagen's crosslinks should alleviate the effects of the disease. But CXL is a rather new treatment; its mechanism of action is not fully understood, and the protocol is still somewhat experimental. What is standard at this point is the instillation of riboflavin and the use of ultraviolet-A (UV-A) light to project 3 mW/cm^2 of radiance onto the surface of the cornea.[3] The UV-A light activates the riboflavin, which in turn increases the amount of collagen crosslinking in the cornea. The use of riboflavin increases UV-A absorption in the cornea[4,5] and enhances the effect of the treatment, which is most noticeable in the anterior 300 µm of the corneal stroma.[6]

Surgeons continue to debate certain aspects of the procedure, including the amount and length of riboflavin exposure, the amount and length of UV-A light exposure, and the role of the epithelium. Additionally, surgeons' opinions differ between using CXL as a standalone treatment or in combination with another refractive procedure, such as PRK or intrastromal corneal ring segments (ICRSs).

Following CXL alone, patients typically enjoy better quality of vision with contact lenses or glasses and in general are satisfied with their results. In combination with other procedures, however, CXL often takes away the guesswork of what the final shape of the cornea will be.

CXL ALONE

Wollensak and colleagues were the first to treat patients with progressive keratoconus using CXL alone.[1] In their patient population, the progression of keratoconus halted in 100% of eyes and the keratoconus regressed in 70%. Additionally, the mean refractive error decreased by 1.14 D by 23 months after treatment, and the maximum keratometry (K) reading decreased by 2.01 D. Since this groundbreaking study, other surgeons including Caporosi,[7] Coskunseven,[8] and Vinciguerra,[9] have published similar results. Caporossi showed that 6 months after treatment patients had a mean K reduction of 2.10 D in the central 3 mm of the cornea and a gain of 3.6 lines of UCVA.[7] Mean spherical equivalent decreased by 2.50 D. In addition to an improvement in UCVA, BCVA, and mean spherical equivalent at 9 months, Coskunseven's study[8] also showed a decrease in astigmatism in eyes treated with CXL compared with those left untreated. Vinciguerra[9] noted no significant changes in corneal wavefront measurements until 12-month follow-up.

These studies suggest that patient outcomes continue to improve over time. In one long-term study with maximum follow-up of 6 years, Raiskup-Wolf[10] determined that maximum K decreased and BCVA continued to improve 3 years after CXL.

COMBINATION TREATMENT

In the United States, the current protocol in clinical trials is to use CXL as a standalone treatment. However, surgeons in Europe are using CXL as a combination treatment—either before, during, or after PRK or in conjunction with ICRSs. The benefit to combining CXL with another refractive procedure, in most cases, is to provide more rapid visual rehabilitation and potentially better final visual results.

CXL and PRK. A. John Kanellopoulos, MD, of Athens, Greece, began using CXL as a standalone procedure in 2002. He introduced the use of partial topography-guided PRK as a means to further normalize the stabilized cornea some months following CXL.[11-13] His team transitioned to same-day simultaneous topography-guided partial PRK and CXL, using the treatment as a therapeutic intervention. In this technique, the Athens Protocol, the cornea is first normalized with PRK and then treated with CXL.[13-16] He uses the protocol in patients with highly irregular corneas with keratoconus or progressive post-LASIK ectasia.[13]

A description of the Athens Protocol follows. After an aspirating lid speculum is placed, the surgeon performs a 50-µm phototherapeutic keratectomy (6.5-mm optical zone) to remove the corneal epithelium. Next, customized partial topography-guided PRK is performed with the WaveLight Allegretto (Alcon Laboratories, Inc., Fort Worth, Texas). The result is normalization of the corneal surface, including reduction of irregular astigmatism and partial treatment of the refractive error. Unlike routine PRK or LASIK with an effective optical zone diameter of 6.5 mm, the Athens Protocol decreases the effective optical zone to 5.5 mm, ensuring that only the minimal amount of tissue is removed. Additionally, the protocol treats cylinder (up to 70%) and sphere (up to 70%) so that the amount of stroma removed does not exceed 50 µm.

The ablated tissue is then covered with a cellulose sponge soaked in mitomycin C 0.02% for 20 seconds, and irrigation (10 mL of chilled balanced saline solution) is performed. The next step is to apply 0.1% riboflavin sodium phosphate (Priavision, Inc., Menlo Park, California) topically every 2 minutes for a total of 10 minutes.

The last step of the Athens Protocol is to radiate the cornea with UV-A light for 30 minutes. The four diodes of the Keracure prototype device (Priavision, Inc.), emitting UV-A light at 365 to 375 nm, projects 3 mW/cm^2 of radiance at a distance of 2.5 cm onto the surface of the cornea. At the end of the treatment, a bandage contact lens is placed and remains on the cornea until complete reepithelialization is achieved, which is usually around day 5.

Dr. Kanellopoulos counsels patients to use topical ofloxacin (OcuFlox, Allergan, Inc., Irvine, California) four times daily for the first 10 days following surgery and prednisolone acetate 1% (Pred Forte; Allergan, Inc.) for 60 days. He recommends that patients wear sunglasses to protect their eyes from natural light and consider taking 1,000 mg vitamin C daily for 60 days.

CXL can also be used prior to PRK treatments; however, Dr. Kanellopoulos compared the Athens Protocol with sequential CXL and PRK in his latest series of just under 400 eyes with significant follow-up (average, 3 years) and found that improvements in the mean UCVA and BCVA, and reduction in spherical equivalent refraction, haze score, and K were better in the Athens Protocol group.[14] Patients in the sequential treatment group were treated with CXL 6 months prior to topography-guided PRK. He concluded that by combining PRK and CXL on the same day, the Athens Protocol achieved a synergistic effect on corneal flattening in eyes with keratoconus. The procedure also avoids removal of any crosslinked tissue because CXL is performed after PRK.

Intrastromal corneal ring segments. Crosslinking treatments can also be combined with ICRSs to treat ectasia. The benefit to this combination is additional corneal flattening compared with use of ICRSs alone. The CXL treatment not only stabilizes the cornea but also contributes to the reversal of previous corneal steepening when combined with ICRSs.

ICRS implantation followed by transepithelial CXL has been shown to decrease the amount of corneal cylinder to a greater degree than ICRS implantation alone.[17,18] This treatment may also be performed in reverse, with CXL performed first and ICRS implantation at a later time. With this sequence, Coskunseven[19] achieved a greater increase in distance BCVA, spherical error, and mean K compared with CXL alone.

CONCLUSION

The true mechanism of CXL has not been clearly defined, but it appears to result in stabilization of corneal ectasia. Therefore, surgeons around the world are gravitating toward use of this treatment in patients with keratoconus and other corneal conditions associated with progressive stromal thinning. Thus far, it has provided surgeons with a method to strengthen the weakened corneal structure in an effort to avoid or delay the need for corneal transplantation. Additionally, the possibilities of combining CXL with therapeutic procedures hold promise for visual rehabilitation in this patient population.

Although more long-term studies are needed, it is safe to say that CXL is an exciting avenue of refractive surgery that deserves further exploration. In the meantime, I invite you to peruse the in-depth roundtable on the following pages. ■

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