Dual Benefits of CXL

Corneal collagen crosslinking show efficacy against both post-LASIK ectasia and keratoconus.

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CXL Benefits Postrefractive Surgery Patients With Ectasia
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Corneal collagen crosslinking (CXL) is a promising new treatment modality designed to stabilize or decrease the progression of keratoconus, as well as other corneal-thinning processes such as ectasia after LASIK or PRK. An increase in corneal biomechanical strength after CXL slows the progression of keratoconus and other forms of ectasia with few reported complications.

Underlying the efficacy of CXL is the production of covalent crosslinks within and between collagen molecules, leading to strengthening of the stromal tissue and mitigation of the progression of ectatic corneal disorders. Multiple studies suggest that CXL may have beneficial visual and optical effects by decreasing corneal steepness, improving topographic irregularity indices, and improving distance UCVA and BCVA.

POST-LASIK KERATECTASIA
LASIK is the most commonly performed refractive surgical procedure for ametropia correction. It causes less discomfort and offers faster visual recovery than surface ablation techniques. Like keratoconus, post-LASIK keratectasia is a noninflammatory process in which the cornea deforms in association with thinning and biomechanical weakening.

Since its first description by Seiler in 1998, iatrogenic post-LASIK ectasia has been recognized as the most severe and feared complication after refractive surgery, with a potentially devastating impact on patients’ quality of vision. The reported incidence is about one case for every 5,000 LASIK procedures. It is important to devote great vigilance in carrying out thorough preoperative examination of LASIK candidates. Exhaustive tomographic, pachymetric and biomechanical readings are mandatory in order to detect the potential for postoperative ectasia. At present, however, there are few safe prognostic tools to determine who is at risk for post-LASIK keratectasia. Major risk factors for this condition include high myopic corrections, thin corneas, low residual stromal thickness, retreatments, and preexisting abnormal corneal topography.

Patients with this complication present with increasing myopia and astigmatism, loss of distance UCVA, and often also loss of distance BCVA due to progressive steepening that occurs centrally or inferiorly. Ectatic changes can occur as early as 1 week after LASIK or can be delayed for several years after the initial procedure. Progressive distortion and bowing of the cornea results in irregular astigmatism, progressive myopia, and increased higher-order aberrations (HOAs) with consequent loss of visual function.

Iatrogenic keratectasia still remains an obscure subject. The underlying problem is far from well understood, making it very difficult to control this entity.

ALTERNATIVES FOR TREATMENT
Until recently, treatment options for post-LASIK ectasia were limited to the prescription of hard contact lenses or the insertion of intrastromal corneal ring segments (ICRSs) to help mechanically stabilize the cornea. However, many cases must still be treated with penetrating keratoplasty.

A combination of therapeutic strategies can be successful in preserving the patient’s quality of vision and delaying or even arresting the progression of the underlying pathology. The principal aims of treating post-LASIK ectasia are (1) visual rehabilitation, which is usually achieved with ICRSs and/or topography-guided PRK and (2) CXL with riboflavin to address the underlying condition.

RESULTS
The exact preoperative characteristics that may predict the effect of CXL therapy are not known. The clinical and optical outcomes of CXL for the treatment of keratoconus and corneal ectasia remain to be clearly elucidated.

To the best of our knowledge, Kohlhaas et al were the first to report a case of post-LASIK iatrogenic keratectasia successfully treated with CXL. A study in 10 patients with post-LASIK keratectasia showed that CXL induced by appli-
cation of riboflavin and ultraviolet-A (UV-A) light increased corneal biomechanical stability. This alternative therapy arrested or partially reversed the keratectasia through postoperative follow-up of 25 months, as demonstrated by corneal topography and keratometric readings.

In a prospective, nonrandomized study of 13 eyes that underwent CXL to treat ectasia following excimer laser refractive surgery (three PRK and 10 LASIK), Vinciguerra and colleagues reported that BCVA was significantly improved 6 months postoperatively. Mean refractive sphere was reduced, and mean cell counts, K readings, and Klyce and Ambrósio indexes for corneal curvature showed no deterioration at 1-year follow-up.

In a study of 22 eyes with post-LASIK corneal ectasia, Salgado et al showed that 1 month after CXL, UCVA and BCVA declined slightly, with a myopic shift and an increase in astigmatism. K readings also showed steepening of the cornea in the early months, which regressed over time. Visual acuity gradually improved after 3 months. Twelve months after CXL, the UCVA, BCVA, and maximum K readings were stabilized or improved in most patients. The authors speculated that the initial worsening after CXL may have been related to compression, structural changes, and remodeling of the corneal stromal collagen.

A preliminary study by Li et al showed long-term stability of post-LASIK corneal ectasia after CXL without relevant side effects. The authors concluded that CXL seems to be a safe and promising procedure to slow the progression of post-LASIK keratectasia, thereby avoiding or delaying keratoplasty.

Multiple studies by Greenstein, Hersh, and colleagues evaluated 1-year outcomes of CXL for treatment of keratoconus and iatrogenic corneal ectasia. CXL was effective in improving UCVA, BCVA, maximum K values, and average K values. Both BCVA and maximum K values worsened between baseline and 1 month, followed by improvement between 1 and 6 months, and stabilizing thereafter. Corneal haze was greatest at 1 month, leveled at 3 months, and then decreased to preoperative values by 12 months; changes in haze did not correlate with postoperative clinical outcomes. Patients with keratoconus had more improvement in haze did not correlate with postoperative clinical outcomes.

Although crosslinking is safe and has few complications, we must bear in mind that after LASIK, patients are always at risk for diffuse lamellar keratitis (DLK) because any cause of inflammation may result in accumulation of white blood cells in the interface. Kymions and colleagues reported a case of a patient with post-LASIK corneal ectasia who developed DLK after CXL.

CXL WITH OTHER PROCEDURES

According to Kanellopoulos and Binder, the long-term stability provided by CXL can be combined with customized corneal surface refractive ablation to improve and correct refractive error in patients with keratoconus. A pilot study by Celik et al suggests that a combination of LASIK and accelerated CXL may provide a promising method to reduce the risk for postoperative keratectasia in a population in which at-risk patients are difficult to discern. The combination of CXL with ICRSs can also be considered in patients with post-LASIK ectasia.

CONCLUSION

CXL is a promising alternative to keratoplasty for patients with post-LASIK keratectasia. It is necessary to wait for longer-term results with more patients in randomized controlled clinical trials to confirm the safety, efficacy, and stability of the procedure. Combination of crosslinking with other procedures such as customized PRK or LASIK, and even ICRS, is a promising field to be explored.

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CXL Strengthens Corneal Tissue in Keratoconus

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Corneal collagen crosslinking (CXL) with application of riboflavin and ultraviolet-A (UV-A) is a relatively new technique of corneal tissue strengthening using riboflavin as a photosensitizer and UV-A to increase the formation of intra- and interfibrillar covalent bonds by photosensitized oxidation.1

Using UV-A parameters of 360- to 370-nm wavelength with cumulative irradiance of 5.4 J/cm² ensures that exposure of all ocular structures is below harmful levels.1 Keratocyte cytotoxicity and apoptosis in the anterior segment of the corneal stroma to a depth of about 300 µm have been described,2,3 and a demarcation line between treated and untreated cornea is clearly shown (Figure 1).4 It is important to ensure that the cytotoxic threshold of the endothelium is not exceeded by strictly respecting the minimum recommended corneal thickness of 400 µm.5 Confocal microscopy studies show that repopulation of keracytes is already visible 1 month after treatment, reaching preoperative quantity and quality in terms of functional morphology within 6 months after treatment.6

There is a significant indirect effect of CXL during and after treatment due to a more compact and rigid cornea.7 A considerable decrease in corneal sensitivity has been demonstrated, intense in the first week after the procedure with progressive recovery up to 6 months.8 Since its clinical introduction a decade ago,9 CXL has been extensively evaluated as a method for stopping the progression of keratectasia in patients with keratoconus. It has been proposed as a way to reduce the need for penetrating keratoplasty in patients with keratoconus. Potential indications for CXL include keratoconus (including forme fruste keratoconus and pellucid marginal degeneration), iatrogenic keratectasia, corneal melting, and bullous keratopathy. This article concentrates on CXL for keratoconus and reviews some information we have learned about this procedure for this indication in the past 10 years.

WITH OR WITHOUT EPITHELIAL REMOVAL

CXL should be performed under sterile conditions in an operating room. The original treatment protocol included deep epithelialization to allow efficient penetration of riboflavin.9 Abrasion of the corneal epithelium out to 7 mm is performed under topical anesthesia. Riboflavin solution, 0.1% in 20% dextran, is then applied to the cornea every 3 minutes for 30 minutes. Riboflavin saturation ensures the formation of free radicals, and, at the same time, the riboflavin shields the deeper ocular structures such as the corneal endothelium from UV damage (Figure 2).

Irradiation is performed using a UV-A lamp for 30 minutes at 3 mW/cm², corresponding to a surface dose of 5.4 J/cm². During the procedure, riboflavin solution and balanced salt solution are applied every 2 to 3 minutes to maintain saturation of the cornea with riboflavin and provide corneal hydration.10 After the treatment, one drop of topical antibiotic is instilled, and a bandage contact lens is placed until complete reepithelialization. Patients instill topical antibiotic four times daily until contact lens removal. In most cases, the contact lens is removed on the third day after treatment. The patient then instills topical steroids four times daily, followed by tapering.

CXL without epithelial removal, rather than with the large-diameter epithelial removal described previously, would likely be less painful and would be ideal if it efficiently stabilized keratectasia. Several substances, including 20% alcohol;11 combination of tromethamine and sodium EDTA;12 combination of proparacaine and benzalkonium chloride (BAK);13 and combination of proparacaine, BAK, garamycin, and mechanical abrasion,14 have been used to loosen the tight junctions of the epithelial layer and increase the penetration of riboflavin. Epithelial removal by phototherapeutic keratectomy (PTK) has also been described,
providing the same results for subsequent CXL as complete mechanical removal.\textsuperscript{15}

Application of transepithelial CXL using riboflavin with substances added to enhance epithelial permeability has been reported to be safe and either not effective,\textsuperscript{16} moderately effective,\textsuperscript{12,13,17,18} or fully effective\textsuperscript{14,19,20} in keratoconic eyes. This approach could be reserved for patients with ultrathin corneas, and application of the procedure could be extended to patients with mild keratoconus in whom the full effect achievable with standard epithelium-off technique may not be necessary. Additional promising mechanisms of drug penetration without removing the epithelium, such as iontophoresis, are under investigation.

**CLINICAL RESULTS OF CXL FOR KERATOCONUS**

The first in vivo controlled clinical study of CXL, by Wollensak et al,\textsuperscript{9} showed that CXL was effective in halting the progression of keratoconus over a period of 4 years. This study included 23 eyes of 22 patients with moderate or advanced progressive keratoconus. Follow-up ranged from 3 to 47 months. Distance BCVA improved in 65\% of patients by an average of 1.26 lines. Spherical equivalent (SE) improved by an average of 1.14 D. In 70\% of patients, maximum keratometry (K) was flattened by an average of 2.01 D. K value remained stable in five patients and increased by 0.28 D in one patient. In 22\% of fellow control eyes, the maximum K value increased by an average of 1.48 D.

Numerous prospective comparative contralateral studies have since confirmed these findings: modest reduction in K values, small reduction in corneal astigmatism and SE, and small increase in distance UCVA and BCVA.\textsuperscript{21-28} Nontreated eyes showed progression of all corneal parameters under study. CXL was effective in reducing corneal and total wavefront aberrations 1 year postoperatively.\textsuperscript{26-28}

**COMBINED TREATMENTS**

Although CXL resulted in decreases of SE, astigmatism, and maximum K values in patients with keratoconus, most studies report only modest increases in distance UCVA and BCVA. If CXL can stop or slow progression of keratoconus, it may be logical to combine it with other procedures to reshape the cornea, such as intrastromal corneal ring segment (ICRS) implantation or topography-guided photoablation, in order to synergize their effects. In a combined approach, a pretreatment method would flatten and regularize corneal shape, followed by CXL to stabilize the cornea. Alternatively, the CXL procedure could be performed first, followed by reshaping.

**CXL combined with ICRS implantation.** The synergistic effect of ICRSs and CXL has been reported to be very powerful, addressing patients with preoperative SE as high as -14.50 D and keratometry of more than 55.00 D.\textsuperscript{29} In a study comparing inferior ICRS placement with or without CXL, eyes with CXL plus ICRS had significantly greater reduction in cylinder than ICRS-only eyes, and there was a significantly greater reduction in maximum K in the ICRS-with-CXL eyes.\textsuperscript{30}

The optimal sequence of treatments was investigated by Coskunsever et al.\textsuperscript{31} CXL with ICRS already in place showed an effect similar to CXL-only treatment. ICRS implantation had a greater effect when applied to an intact cornea than when the cornea was already treated with CXL, although improvement was seen in all corneal parameters with either treatment sequence.\textsuperscript{31}

Figure 2. Treatment in progress with the cornea soaked with riboflavin and irradiated by UV-A lamp. In the inset, the UV-A diodes within the UV lamp are seen from the patient’s perspective.

Considering the overall effect of combined treatments, patients who had ICRS implantation followed by CXL showed a greater overall increase in distance UCVA and BCVA and decrease in cylinder and SE, compared with patients with the inverse order of treatment.\textsuperscript{31} These findings suggest that although each treatment step has an improving effect on the cornea, a cornea already stiffened by CXL somewhat inhibits the flattening forces of ICRS, thus restricting the combined effect and decreasing the maximal flattening potential.\textsuperscript{31} In order to achieve maximum overall effect, ICRS should be applied first, allowing unrestricted reshaping of the cornea, after which CXL treatment should be applied to additionally flatten and biomechanically stabilize the cornea.\textsuperscript{31}

**CXL combined with limited topography-guided PRK.** One of the most promising uses of CXL is in combination with partial PRK. Investigators compared the results of CXL with topography-guided PRK performed either on the same day or 6 months later using the Allegretto (WaveLight) topography-guided laser platform.\textsuperscript{32,33} Statistically, the simultaneous treatment group performed better in all parameters evaluated, including distance UCVA and BCVA,
SE, and K, with less corneal haze. In a similar prospective study, favorable results were reported after customized topography-guided PRK with the Pulzar Z1 213-nm wavelength laser (CustomVis) immediately followed by CXL. Combined topography-guided transepithelial PRK with ICRS implantation and CXL in a three-step procedure has also been shown to be an effective, promising treatment sequence, offering patients functional visual acuity and stopping progression of the ectatic disorder.

It is important to emphasize that combined treatment with CXL and PRK is a specialized intervention with the goal of normalizing the cornea as much as possible to increase distance BCVA, rather than treating the refractive error itself as in purely refractive PRK (Figure 3). Therefore, the primary treatment target is cylinder, in order to improve irregular astigmatism, and the secondary target is to correct some of the sphere, while keeping the amount of ablated tissue within the recommended limit of 50 µm. The most important goal is avoiding the need for corneal transplantation.

COMPPLICATIONS AND CONSIDERATIONS

Although CXL is a minimally invasive procedure, reports have indicated possible adverse effects. Formation of corneal edema and haze, permanent scars, endothelial damage, treatment failure, sterile infiltrates, and herpes
reactive keratouveitis have been reported. An 18-year-old boy who underwent CXL for keratoconus developed keratouveitis with general-ized corneal edema 3 weeks after the procedure. Specular microscopy revealed mildly reduced density of endothelial cells, but by 6-month follow-up, corneal edema had increased, and epithelial bullae formed. Penetrating keratoplasty was performed.

NEW TRENDS

Lowering the age limit for CXL. Although CXL was initially performed only in patients older than 18 years, in recent reports the minimum age has decreased to as young as 10 years. Results of these studies indicate that CXL was as effective as in older subjects, with better and faster functional recovery. A modified surgical technique without epithelial removal has been proposed for pediatric patients, as this approach is less painful, provides similar effectiveness, and results in fewer complications than epithelium-off CXL.

Decreasing treatment time. Keeping total UV-A energy exposure equivalent at 5.4 ml/cm² facilitates effective CXL and is shown to be safe. UV-A exposure time for CXL can be reduced if energy is simultaneously increased. As standard treatment timing is 3.0 mW/cm² for 30 minutes, rapid treatment timing could be achieved with parameters such as 6.0 mW/cm² for 15 minutes, 10.0 mW/cm² for 9 minutes, or 15.0 mW/cm² for 6 minutes. There seems to be a sudden decrease in treatment effect with energy greater than 45.0 mW/cm² and time less than 2 minutes, with no cross-linking effect taking place in the cornea.

Using stress-strain measurements on porcine corneal strips, rapid CXL treatment was shown to be equivalent to the standard procedure in terms of increase in corneal stiffness. A rapid protocol could theoretically shorten treatment duration by more than two-thirds, from 30 to 9 minutes.

Clinical data have confirmed these theoretical and in vitro findings. CXL using 7 mW/cm² for 15 minutes compared with the standard 3 mW/cm² for 30 minutes (with 50-µm PTK for epithelial removal) showed identical clinical effect without additional complications.

Accelerated CXL may be applied prophylactically in high-risk LASIK cases. Higher-fluence 10 mW/cm² treatment applied for 3 minutes following an earlier single instillation of 0.1% riboflavin within the flap interface appears to be a safe and effective adjunctive treatment to prevent refractive regression and ectasia. This application may be viewed as prophylactic customization of the biomechanical behavior of corneal collagen.

CONCLUSION

CXL with riboflavin and UV-A is a safe and effective technique to strengthen corneal tissue in eyes with keratoconus. CXL can also be used in combination with another method to flatten and regularize the corneal shape, such as ICRS implantation or limited topography-guided photoablation. Early diagnosis and treatment of keratoconus increases the prospects for successful treatment.

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