

# CXL Indications and Patient Selection

Patients must be told that the goal of treatment is not a refractive endpoint.

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Collagen crosslinking (CXL) and bonding technology has been used in dentistry, orthopedics, and dermatology for many years. In 1998, a breakthrough for its use in ophthalmology occurred when Theo Seiler, MD, PhD, of Zurich, Switzerland, used CXL to treat severe keratoconus. Its potential benefit in ophthalmology is to improve the biomechanics of the cornea.

After significant research into the safety aspects of the procedure, Professor Seiler's technique has been tried and adopted by many surgeons worldwide. It involves application of UV-A light of a specific wavelength (370 nm) and fluence (3 mW/cm<sup>2</sup>), for a specific time period (30 minutes), to a cornea previously saturated with riboflavin (vitamin B2). Unstable oxygen-free radicals are liberated within the stroma during the process, creating bonding and bridging between adjacent collagen fibrils. This crosslinking reaction produces a stiffer, stronger cornea.

## TREATMENT OPTION

CXL is capable of becoming a popular addition or alternative to current management options for keratoconus. This bilateral, nonsymmetric, noninflammatory, progressive corneal degenerative condition has a recognized incidence of one per 2,000 in the general population.<sup>1</sup> It can occur monocularly in up to 15% of cases, and up to 20% may later require penetrating keratoplasty (PK) to maintain functional vision.<sup>2</sup>

Topography of a patient with forme fruste keratoconus is a red flag to the refractive surgeon and a definite contraindication to LASIK. It may, however, escape recognition. Despite a high alert to avoid treatment in suspect cases—and to leave an adequate residual stromal bed in routine LASIK—ectasia has been reported in up to 0.3% of eyes undergoing LASIK.<sup>3</sup> Post-LASIK ectasia is a great fear for the LASIK surgeon. This fear may be assuaged by maintaining a systematic and intuitive patient selection process. This article reviews the indications and contraindications for CXL and provides a general basis for patient selection.

## INDICATIONS

CXL is the only procedure available to inhibit progression of both keratoconus and ectasia by supplying inherent strength

to individual corneal collagen fibers. Corneal ring segments placed within the stroma and transplantation with donor tissue fail to prevent progression of ectasia in many cases.

CXL should herald a significant reduction in the demand for eye bank tissue for the treatment of keratoconus. In many countries, waiting lists for donor corneas may range from months to years. CXL will save rehabilitation time and lost working hours for patients undergoing PK. It also eliminates the problem of regression. In addition, for the LASIK surgeon, CXL is a useful method to treat post-LASIK ectasia.

At the Wellington Eye Clinic in Dublin, Ireland, we first performed CXL in 2007. To date, we have used the procedure in four cases of post-LASIK ectasia and in the following two specific indications for keratoconus: progressive keratoconus and established keratoconus intolerant to hard contact lenses.

Typical progressive keratoconus cases are found in (1) younger patients, (2) those with an early diagnosis, or (3) slightly older patients showing refractive instability and increasing astigmatism or myopia. Clear evidence of the progression of keratoconus is noted on topography and tomography (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany).

CXL arrests progression and stabilizes the shape of the cornea so that patients may be fitted with contact lenses after healing. CXL alone improves keratometry readings and astigmatism in up to 70% of cases and leads to significant improvements in UCVA and BCVA.<sup>4</sup> We have seen a flattening of up to 3.00 or 4.00 D at the cone apex (average, 2.10 D). Sometimes hard contacts are not required after treatment, and the patient's vision improves with spectacles or soft contact lenses. More important, such patients no longer progress to the need for keratoplasty. This group has much to gain from CXL technology.

Patients with established keratoconus and intolerance to hard contact lenses are difficult to treat. Previously, this group would have required PK; however, we may now use CXL to slow or inhibit progression. This treatment may improve the shape of the eye for better contact fitting, and PK may be delayed or postponed indefinitely if visual rehabilitation is achieved.

In both groups, we have used either CXL on its own or, in

some cases, combined with PRK to further improve the shape and refractive performance of the treated eye. Other centers have combined the use of CXL with Intacs (Addition Technology, Inc., Des Plaines, Illinois) or intrastromal corneal ring segments with varying degrees of success.

Other conditions that may benefit from CXL include pellucid marginal degeneration, recurrent keratoconus after PK, bullous keratopathy, and chronic corneal infections.

## PATIENT SELECTION

When discussing CXL with patients and their families before surgery, the surgeon must stress that the goal of treatment is not a refractive endpoint—even if CXL is combined with laser ablation. Especially younger patients are under the impression that treatment will cure their conditions permanently, allowing them to see clearly.

Explanations require additional chair time and patience with family members. Video demonstrations and animations allow patients to gain understanding of how the treatment limits further progression and improves and stabilizes the shape of the cornea to provide better functional vision. Patients must understand that spectacles and/or contact lenses (hard or soft) will still be required. The best news is that this minimally invasive procedure is safe and avoids the disruption that comes with corneal transplantation. With CXL, patients can continue their lifestyles and jobs with useful vision.

Full clinical history and ophthalmic examination is necessary to exclude patients who may be at risk of developing adverse reactions or suboptimal outcomes. Contraindications include the following conditions: (1) epithelial healing disorders, such as map dot dystrophy and rheumatic disorders, (2) refractive keratotomy, (3) previous herpes simplex virus keratitis (because the UV-A may induce herpes reactivation), (4) corneal melting disorders, and (5) pregnancy.

Certain corneal parameters must be satisfied prior to CXL treatment. Serial topography and Pentacam tomography supply data vital to the preoperative assessment. After riboflavin is applied to the cornea, the pachymetry must be at least 400  $\mu\text{m}$  at the thinnest point (without epithelium) to safeguard the integrity of the endothelium. Hypotonic riboflavin may be used to swell the stroma in thinner corneas. Additionally, it has been suggested that keratometry

(K) readings should be less than 60.00 D. Rigid contact lenses should be removed 2 weeks before surgery, and vitamin C, a potent antioxidant, should be discontinued 1 week before surgery patients with significant atopic eye disorders, ocular surface disorders, or poor tear function warrant caution.

All patients should be counseled regarding their postoperative course and potential for risks or complications, which include but are not limited to (1) haze, which is uncommon and easily managed with topical steroids, (2) delay in reepithelialization, (3) infection, (4) sterile infiltrates, (5) potential for induction of herpes simplex virus and dendritic ulcer, and (6) ocular surface disorder and tear dysfunction.

Although the full effect of CXL occurs within the first 30 minutes of application, corneal changes in shape and steepness will evolve over several months. It may take 3 to 6 months before a patient is ready to be fitted for contact lenses. Interestingly, patients will often note a loss in UCVA; they are no longer able to mold their astigmatic corneas by squeezing or squinting now that the stiffening effect has occurred.

## DURING TREATMENT

The treatment should be performed under aseptic conditions. The cornea must be presaturated with a solution of 0.1% riboflavin and 20% dextrose, and anterior chamber flare must be demonstrated prior to commencing UV-A illumination. There is ongoing debate on whether the epithelium should be removed prior to riboflavin application. At the Wellington Clinic, we remove the epithelium to the 9-mm zone, leaving a ring of epithelium at the limbus to protect the stem cells. UV-A irradiation, supplied by the UV-X illumination system (IROC Medical, Zurich, Switzerland; distributed by Peschke Meditrade GmbH, Nuremberg, Germany), is applied for 30 minutes to the cornea but not to the limbal area or sclera. During UV-A illumination, all members of the surgical team and attendants should wear protective eyewear.

Regular application of riboflavin (every 2 minutes) to the cornea enhances safety, providing the source of polymerization and crosslinking and protecting the deeper endothelium, lens, and retina by absorbing the UV-A light source. It also lubricates the eye. Local anesthetic drops keep the patient comfortable.

## POSTOPERATIVE MANAGEMENT

A bandage contact lens is applied for 5 days, and the patient is instructed to use topical Maxitrol (neomycin sulfate, polymyxin B sulfate, and dexamethasone; Alcon Laboratories, Inc., Fort Worth, Texas) drops and lubricants tapered over 4 weeks. As with PRK, patients often experience significant discomfort and distress. Individual tolerance to pain and light sensitivity is highly variable; this should be rein-

### TAKE-HOME MESSAGE

- In ophthalmology, the benefit of CXL is its ability to improve corneal biomechanics by producing stiffer, stronger corneas.
- The procedure inhibits progression of keratoconus and ectasia by strengthening individual corneal collagen fibers.

forced during preoperative counseling, along with use of appropriate analgesics and sedation after surgery, and accounting for days off work. A sympathetic surgeon is always available on the phone to reassure the anxious patient.

Patients should be seen on the first postoperative day and again at day 5 to remove the contact lens. Visual rehabilitation with contacts and glasses can begin 6 weeks postoperatively. Serial topography and Pentacam tomography is important to chart progress or recognize postop regression if and when it should occur.

CXL is an innovative and exciting technology to combat progressive keratoconus and iatrogenic forms of corneal ectasia. Our reports to date confirm effectiveness in stabilizing corneal biomechanics and rehabilitating patients without the need for more invasive procedures.

The debate about CXL is prominent in refractive surgery: Will it play a role in prophylactic therapy prior to LASIK in patients with thinner corneas or a suggestion of forme fruste keratoconus? Further studies and research are necessary to optimize indications and monitor unwanted side effects and negative outcomes, particularly in the long term. I believe we are looking only at the tip of the iceberg of CXL; its further application in ophthalmology will become well established with time. ■

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