# Therapeutic Options to Delay the Need for Corneal Transplant

If positive results with ICRSs and CXL continue, the number of patients requiring transplant procedures may decline.

BY YARON S. RABINOWITZ, MD

Until quite recently, the only option for a keratoconus patient who was contact lens intolerant was a corneal transplant (lamellar or full-thickness). With approximately 20% of keratoconus patients needing corneal transplants during their lifetimes, this degenerative disorder is one of the most common indications for corneal transplants in the young.[1] However, pioneering work by the late Joseph Colin, MD, in France, and a group in Dresden, Germany, under the direction of Theo Seiler, MD, PhD, has provided two new treatment options to significantly delay or prevent the need for transplants in these patients.[2,3] These two treatment modalities, intrastromal corneal ring segments (ICRSs) and corneal collagen crosslinking (CXL), can be used together or separately, depending on the clinical situation. Additionally, they can be augmented with excimer laser treatments to enhance visual outcomes.

## ICRSs

Professor Colin was the first to demonstrate that inserting ICRSs in patients with moderately advanced keratoconus and contact lens intolerance flattened the cornea; improved UCVA, BCVA, and contact lens tolerance; and, in some instances, allowed patients to transition from rigid to soft contact lenses.[2,4]

In our experience, this procedure has about a 70% success rate in carefully selected cases. Ideal candidates are contact lens intolerant, have a maximum keratometry (K) not exceeding 58.00 D, have no central or paracentral scarring, have corneas at least 450 µm thick at the 7-mm optical zone, and have nonprogressive keratoconus. Most important, patients must have realistic expectations, as they will still need glasses or contact lenses for optimal distance visual acuity postoperatively.

We use a femtosecond laser to create channels for ICRS implantation, typically placing them at a depth of 400 µm. We have found that the laser creates a more reliable channel at this intended depth, with better visual outcomes and less chance of erosion, than a mechanical technique. This is important, as erosion can occur if the rings are placed too superficially. Additionally, we use optical coherence tomography (OCT) to plan surgery, and we try to transect the thinnest part of the cornea with the ring to restore physiological normality.

When the cone is located inferiorly or inferotemporally and the refractive error includes a large amount of regular astigmatism—in addition to the irregular astigmatism found in keratoconus—we use a single inferior ICRS. If the refractive error is mild and we think vision will improve by changing the eye's spherical equivalent, we use two asymmetric rings (0.45 and 0.25 µm) typically placed inferiorly and superiorly, respectively. Visual improvement is usually due to reduction in the irregular astigmatism, as demonstrated by a decrease in higher-order aberrations on wavefront analysis.[5,6]

As previously mentioned, the key to success with ICRS implantation is adequate patient selection. Patients with realistic expectations will be happy after surgery, but those who expect to see well without contact lenses or glasses may be disappointed. Improving patient selection comes with experience and requires the practice of the art as well as the science of medicine.

## CXL

When Professor Seiler originally introduced CXL as a therapeutic option to delay or prevent the progression

| TABLE 1. CORNEA EYE INSTITUTE PEDIATRIC STUDY (AGES 10-18; 54 EYES) | | | | |
|---|---|---|---|---|
| | Preoperative | Postoperative (6 months) | Change | *P* value (6 months) |
| UCVA (logMAR) | 0.71 | 0.41 | 0.30 | .009 |
| BCVA (logMAR) | 0.28 | 0.20 | 0.08 | .06 |
| Mean K | 49.30 D | 46.40 D | 2.90 D | .007 |
| Mean Pach | 444 µm | 427 µm | 17 µm | .07 |
| K = keratometry; Pach = pachymetry | | | | |

of keratoconus, we viewed this with a healthy degree of skepticism. However, preclinical experiments and a large body of literature supporting its efficacy have since convinced me that this is a good treatment modality.[7-10]

Approximately 4 years ago, we obtained permission from the US Food and Drug Administration (FDA) to conduct a physician-sponsored clinical trial using the Dresden technique with an ultraviolet-A lamp (IROC Lamp; Peschke Medical) to produce the irradiation. Of the approximately 300 cases we have done to date with 3-year follow-up, we have noted minimal progression in only 2% of patients.

We have also treated 43 patients less than 18 years of age using CXL. In these 51 eyes, even though keratoconus progression was rapid preoperatively, we have not seen any progression to date (Table 1).

Based in part on Seiler's recommendations,[11] we have adopted the following inclusion criteria for CXL:

- Patient at least 12 years of age;
- Progression of myopia and/or cylinder by refractions of at least 1.00 D and confirmed by topographic evidence of keratoconus in the year preceding treatment;
- Pachymetry, as measured by corneal OCT, of no less than 400 µm;
- Central K readings not exceeding 58.00 D; and
- No central or paracentral corneal scarring.

In selected eyes in which corneal thickness is between 350 and 400 µm, we have started performing CXL after using hypotonic solution or balanced saline solution for 15 minutes to swell the cornea.

If we believe that outcomes will be less than optimal because of severe central corneal irregularity, we recommend penetrating keratoplasty or deep anterior lamellar keratoplasty instead of CXL to avoid performing an additional procedure prior to proceeding to a transplant. However, recent discussions with colleagues suggest that my approach in these instances might be incorrect. Their reasoning is that, even if a patient subsequently requires corneal transplant, crosslinking the peripheral cornea potentially avoids recurrent keratoconus and induced astigmatism. Using this logic, we have repaired astigmatism in the grafts of keratoconic patients and supplemented this with targeted CXL in the host tissue only. This concept warrants further careful investigation.

## COMBINATION PROCEDURES

I am often confronted with the question of which procedure or procedures to perform in a single session. Whether to do CXL only, ICRSs only, or both simultaneously depends on the clinical situation. There is no blanket rule, but there are provisional guidelines (Table 2). Generally I tell patients that CXL is performed to halt keratoconus progression and ICRSs are implanted to improve vision or contact lens tolerance. In some instances, the two procedures can be combined to achieve better postoperative outcomes. Although CXL improves vision in more than 60% of cases, I do not like to promise improved vision from CXL only.

If the patient wants both to improve vision and to stop the progression of the disease, I combine treatments in the same session; however, I do not encourage this and tell patients that a more conservative approach would be to do the procedures 3 months

### TAKE-HOME MESSAGE

- Ideal candidates for ICRS placement are contact lens intolerant, have a maximum K not exceeding 58.00 D, have no central or paracentral scarring, have a cornea at least 450 µm thick at the 7-mm optical zone, and have nonprogressive keratoconus.
- Seiler et al recommend the following conservative inclusion criteria for CXL treatments: at least 12 years of age; progression of myopia and/or cylinder by refractions of at least 1.00 D and confirmed by topographic evidence of keratoconus in the year preceding treatment; pachymetry, as measured by corneal OCT, of no less than 400 µm; central K readings not exceeding 58.00 D; and no central or paracentral corneal scarring.
- CXL and ICRS implantation can be combined in one session; however, a more conservative approach would be to do the procedures 3 months apart.

| TABLE 2. DECISION TREE FOR CXL VS ICRS | | |
|---|---|---|
| **Diagnosis** | **CXL** | **ICRS** |
| Post-LASIK ectasia | Yes | Only to reduce anisometropia or improve CL tolerance |
| Pellucid Marginal Degeneration | Yes | To improve CL tolerance |
| Keratoconus under age 18 years | Yes | No |
| Keratoconus age 18 to 35 years | Yes, if progressive (more than 1.00 D) | No, only to improve CL tolerance or vision combined with CXL |
| Keratoconus age more than 35 years | No if stable; only if documented progression | Yes, to improve vision or CL tolerance |
| CXL= corneal collagen crosslinking; ICRS= intrastromal corneal ring segment; CL = contact lens | | |

| TABLE 3. CXL WITH PTK VS MECHANICAL EPITHELIAL REMOVAL (6 MONTHS) | | | |
|---|---|---|---|
| | **PTK (n=24)** | **Mechanical (n=63)** | ***P* value** |
| UCVA increase | 1.62 | 1.35 | 0.4 |
| BCVA increase | 0.83 | 0.59 | 0.2 |
| K decrease (D) | 1.81 | 0.83 | 0.1 |
| SRI | 0.04 | -0.07 | 0.3 |
| CXL = corneal collagen crosslinking; PTK = phototherapeutic keratectomy; K = keratometry; SRI = surface regularity index | | | |

apart. Preliminary analysis of our long-term outcome data suggests that it does not matter whether CXL and ICRS implantation are done simultaneously or 3 months apart. If I do the two procedures simultaneously, I make the tunnels with the femtosecond laser first, perform CXL second, and then insert the ICRSs last.

## EPITHELIUM ON OR OFF?

There is some debate as to whether to remove the epithelium during CXL (ie, epi-off treatment) or to leave it on (ie, epi-on) to improve patient comfort. Reports in the literature yield conflicting data.[12,13] Wollensak et al[14] reported that epi-on, even with disruption at the epithelial junctions to allow riboflavin penetration, is only 20% as effective as complete epithelium removal. Protagonists of the epi-on method maintain that increasing riboflavin soaking time—in some instances to more than 1 hour—allows the riboflavin to enter the stroma. However, to the best of my knowledge, no published data scientifically support these claims. Additionally, we have seen many patients whose keratoconus has progressed following an epi-on procedure and whom we subsequently treated with the epi-off technique.

We use excimer laser phototherapeutic keratectomy (PTK) to remove the epithelium, setting the treatment at 50 µm and expanding the PTK circle to 8.5 mm with the Visx excimer laser (Abbott Medical Optics Inc). This results in better UCVA and BCVA after treatment due to the smoothing of irregularities at the corneal apex. Additional flattening in the steepest K also occurs after treatment, which is important for contact lens fitting following CXL because the steep part of the cornea rubbing against the contact lens can contribute to contact lens intolerance.

Our approach makes the epi-on versus epi-off argument moot, and by removing the epithelium with PTK we can use the epi-off technique to our advantage. This concept was first suggested by Kymionis et al[15,16] and subsequently confirmed by Kapasi et al.[17] We recently presented our 6-month data at the American Society of Cataract and Refractive Surgery (ASCRS) meeting in San Francisco (Table 3), and a video on Eyetube summarizes our results (eyetube.net/?v=saraq).[18]


If this technique stands the test of time and does not demonstrate any long-term adverse effects, I foresee that we will be able to use it in combination with excimer laser ablation to reduce regular astigmatism. Removing a small amount of tissue with the excimer laser may significantly enhance contact lens tolerance and, thus, avoid the need for a corneal transplant. This technique has already been done with significant success in patients who have had prior treatments with Intacs ICRSs (Addition Technology, Inc.).[19]

## GENETIC EFFECT

While CXL results are promising, it is difficult to explain the huge variability in effect in different patients.

This might be explained by genetic variability in patients undergoing treatment. Our group recently described variations in the lysyl oxidase gene associated with keratoconus.[20] We plan to test patients undergoing treatments for variability in this gene to see if we can predict or titrate the effect of treatment in individual patients.

Our group is also working on stem cell therapy that may one day be used in conjunction with CXL to stop progression and possibly replace corneal tissue to avoid the need for corneal transplantation.

## CONCLUSION

The future for keratoconus patients looks good, and hopefully in the not-too-distant future the need for corneal transplantation will be significantly reduced. ■

*Yaron S. Rabinowitz, MD, is the Director of the Cornea Eye Institute, Director of Research at Cedars-Sinai Medical Center, Clinical Professor of Ophthalmology at UCLA School of Medicine, and the principal investigator of a CXL study to treat progressive keratoconus. Dr. Rabinowitz may be reached at tel: +1 310 423 9640; e-mail: rabinowitzy@cshs.org.*

1. Zare M, Javadi MA, Einollahi B, et al. Changing indications and surgical techniques for corneal transplantation between 2004 and 2009 at a tertiary referral center. *Middle East Afr J Ophthalmol.* 2012;19(3):323-329.
2. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. *J Cataract Refract Surg.* 2000;26(8):1117-1122.
3. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135(5):620-627.
4. Colin J, Cochener B, Savary G, Malet F, Holmes-Higgin D. Intacs inserts for treating keratoconus: one-year results. *Ophthalmology.* 2001;108(8):1409-1414.
5. Rabinowitz YS, Li X, Ignacio TS, Maguen E. Intacs inserts using the femtosecond laser compared to the mechanical spreader in the treatment of keratoconus. *J Refract Surg.* 2006;22(8):764-771.
6. Rabinowitz YS. Intacs for keratoconus and ectasia after LASIK. *Int Ophthalmol Clin.* 2013;53(1):27-39.
7. Koller T, Pajic B, Vinciguerra P, Seiler T. Flattening of the cornea after collagen crosslinking for keratoconus. *J Cataract Refract Surg.* 2011;37(8):1488-1492.
8. Iseli HP, Popp M, Seiler T, Spoerl E, Mrochen M. Laboratory measurement of the absorption coefficient of riboflavin for ultraviolet light (365 nm). *J Refract Surg.* 2011;27(3):195-201.
9. Spoerl E, Wollensak G, Dittert DD, Seiler T. Thermomechanical behavior of collagen-cross-linked porcine cornea. *Ophthalmologica.* 2004;218(2):136-140.
10. Wollensak G, Spoerl E, Wilsch M, Seiler T. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. *J Cataract Refract Surg.* 2003;29(9):1786-1790.
11. Gaster RN, Caiado Canedo AL, Rabinowitz YS. Corneal collagen cross-linking for keratoconus and post-LASIK ectasia. *Int Ophthalmol Clin.* 2013;53(1):79-90.
12. Boxer Wachler BS, Pinelli R, Ertan A, Chan S. Safety and efficacy of transepithelial crosslinking (C3-R/CXL). *J Cataract Refract Surg*. 2010;36(1):186.
13. Koppen C, Wouters K, Mathysen D, Rozema J, Tassignon MJ. Refractive and topographic results of benzalkonium chloride-assisted transepithelial crosslinking. *J Cataract Refract Surg.* 2012;38(6):1000-1005.
14. Wollensak G, Iomdina E. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement. *J Cataract Refract Surg.* 2009;35(3):540-546.
15. Kymionis GD, Grentzelos MA, Karavitaki AE, et al. Transepithelial phototherapeutic keratectomy using a 213-nm solid-state laser system followed by corneal collagen cross-linking with riboflavin and UVA irradiation. *Ophthalmology*. 2010;146543.
16. Kymionis GD, Grentzelos MA, Kounis GA, Diakonis VF, Limnopoulou AN, Panagopoulou SI. Combined transepithelial phototherapeutic keratectomy and corneal collagen cross-linking for progressive keratoconus. *Ophthalmology*. 2012;119(9):1777-1784.
17. Kapasi M, Baath J, Mintsioulis G, Jackson WB, Baig K. Phototherapeutic keratectomy versus mechanical epithelial removal followed by corneal collagen crosslinking for keratoconus. *Can J Ophthalmol.* 2012;47(4):344-347.
18. Rabinowitz Y. Comparison of mechanical vs PTK laser removal of the epithelium for collagen cross linking in patients with keratoconus: 6 month data. Paper presented at: the 2013 Annual Meeting of the ASCRS; April 19-23, 2013; San Francisco.
19. Tan BU, Purcell TL, Nalgirkar A, Ehrenhaus MP, Torres LF, Schanzlin DJ. Photorefractive keratectomy for the correction of residual refractive error with Intacs intrastromal corneal ring segments in place. *J Cataract Refract Surg.* 2008;34(6):909-915.
20. Bykhovskaya Y, Li X, Epifantseva I, et al. Variation in the lysyl oxidase (LOX) gene is associated with keratoconus in family-based and case-control studies. *Invest Ophthalmol Vis Sci.* 2012;53(7):4152-4157.