CXL IN 2015: WHAT DO WE KNOW?

An update on treatment for keratoconus and other corneal ectatic conditions.

BY WILLIAM B. TRATTLER, MD

It is now common knowledge that CXL effectively stops the progression of keratoconus and other ectatic corneal conditions and also enhances quality of vision and corneal shape, with improvement continuing for years after the procedure. Research is ongoing, however, regarding optimal treatment parameters as well as whether CXL should be performed initially as a standalone procedure or in combination with surgical modalities such as Intacs (Addition Technology), topography-guided PRK, or conductive keratoplasty.

A study examining long-term results (10 years) of epithelium-off (epi-off) CXL confirmed that improvements in corneal shape and vision seen during the first few years after the procedure continue over a decade.[1] Not only did patients' ectasia stabilize, but their corneal shape and BCVA also improved. This study gives clinicians the confidence to tell patients that a single CXL treatment will, in most cases, result in long-term improvement.

Although the initial treatment parameters of a decade ago were effective, numerous innovations have further improved the results of CXL. For example, surgeons now understand that, although treatment can be centered on the middle of the corneal apex in keratoconic eyes, results are better in eyes with peripheral corneal weakness from pellucid marginal degeneration (PMD) when the UV light is centered over the thinner part of the cornea located inferiorly. The concern with peripheral UV light treatments was the risk of damage to conjunctival goblet cells. A paper by Hafezi et al, however, has confirmed that the conjunctiva is not damaged by UV light during CXL.[2]

DATA AND DEBATE

Epi-off CXL is currently being studied by Avedro with hopes of FDA approval either in the near term or within a few years. Developed in 1998 by Theo Seiler, MD, PhD, the procedure was initially designed as a 30-minute treatment. Recent research has suggested, however, that exposure times can be shortened when the UV light energy is proportionally increased.[3] Many clinical trials, including a phase 3 multicenter randomized trial sponsored by the American-European Congress of Ophthalmic Surgery (AECOS) and Avedro, are evaluating whether the results of higher-energy UV light treatment of shorter duration are the same, better, or worse than those of the traditional 3-mW treatment for 30 minutes (see *Under Investigation: Accelerated CXL*). More data should become available during the next year to help clinicians optimize treatment parameters.

Whether epithelium-on (epi-on, also known as *transepithelial CXL*) can be as effective as epi-off has been the subject of controversy. Studies comparing the efficacy of the two approaches have had mixed outcomes; one demonstrated reduced efficacy with epi-on and another equal effect.[4,5] Because each study used different formulations of riboflavin and methods, differences in efficacy could be related to the methods rather than to epi-on treatment itself. Some keys to improving the efficacy of epi-on therapy are using a riboflavin formula without dextran, placing a corneal protector sponge to maximize riboflavin exposure, and evaluating the cornea at the slit lamp to confirm that sufficient riboflavin is present prior to initiating UV light treatment (Figure 1A).

For the past 5 years, the prospective, nonrandomized, multicenter CXL-USA study has enrolled patients with keratoconus, PMD, post-LASIK ectasia, post-RK fluctuations in vision, and Terrien marginal degeneration. In this study, epi-on has been effective, with less than 1% of eyes needing a second treatment.[6] Additionally, patients have often experienced an improvement in corneal shape and in UCVA and/or BCVA, which can continue for many years (Figure 1B).[6]

ADDITIONAL TREATMENT

After CXL, patients have a variety of choices. Most choose to continue using their current methods of vision correction, either glasses or contact lenses. Many wearing contact lenses switch to scleral designs, which can provide excellent visual acuity and are friendly to the ocular surface. A small percentage of patients may choose to undergo additional surgery such as topography-guided PRK or the placement of Intacs. These procedures can be performed from 6 months to many years after CXL.

An area of intensive research concerns whether combining CXL with other surgical procedures is a more effective approach than performing CXL alone. A popular combination is topography-guided PRK with CXL.[7] Other possible pairings

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AT A GLANCE

- Research is ongoing regarding optimal treatment parameters for CXL, as well as whether it should be performed initially as a standalone procedure or in combination with other surgical modalities.
- Innovations that have further improved the results of CXL include adjustments to the time and energy parameters of UV light exposure, optimization of the location where light is delivered to the cornea, and combinations of CXL with other procedures.

UNDER INVESTIGATION: ACCELERATED CXL

By Callan Navitsky, Senior Editor

The use of accelerated CXL is currently being investigated at approximately 83 clinical sites in the United States as part of a study sponsored by the American-European Congress of Ophthalmic Surgery (AECOS) and conducted by Avedro.

The phase 3, multicenter, randomized controlled ACOS-KXL-001 study is designed to evaluate the safety and efficacy of the KXL System with VibeX (riboflavin ophthalmic solution; both by Avedro) for impeding the progression of and/or reducing maximum corneal curvature in keratoconus or corneal ecastia after refractive surgery. Three doses of irradiation are being evaluated in the study: 15 mW/cm^2 for 8 minutes, 30 mW/cm^2 for 4 minutes, and 45 mW/cm^2 for 2 minutes and 40 seconds. All treatments are being performed with the epithelium removed.

The study was designed to enroll up to 2,000 study eyes with keratoconus and up to 2,000 study eyes with corneal ectasia following refractive surgery. Patients aged 12 years and older are being randomized to one of the three treatment groups by active treatment condition. All study eyes are being treated, and all fellow eyes that meet the criteria have access to treatment.

The primary outcome measure of the study is the mean change in maximum corneal curvature (Kmax) from baseline. The secondary outcome measure is a comparison of treatment groups within each treatment indication.

At the 2015 AECOS Summer Symposium in Deer Valley, Utah, John A. Vukich, MD, principal investigator of ACOS-KXL-001, presented an intermediate analysis of the study data. Dr. Vukich reported that the diagnostic-specific results showed larger effects for keratoconus than for ectasia. In patients with keratoconus, all three treatment groups have shown improvement.

"We are seeing the maximum effect at the longer treatment and lower intensity," Dr. Vukich said, adding that the investigators are looking to determine if CXL may be not only dose-dependent but also time-dependent.

A similar trend in improvement was seen in patients with ectasia, although the results are not yet statistically significant. "If we could at least seek stability, that in itself is a very desirable outcome in these very challenging patients," Dr. Vukich said.

The study, which began in July 2012, has an estimated primary completion date of January 2016.

ADDITIONAL STUDIES ON ACCELERATED CXL

For more on the safety and efficacy of this approach, see:

- Alnawaiseh M, Rosentreter A, Bohm MR, et al. Accelerated (18 mW/cm2) corneal collagen cross-linking for progressive keratoconus [published online ahead of print September 9, 2015]. Cornea.
- Hashemi H, Miraftab M, Seyedian MA, et al. Long-term results of an accelerated corneal cross-linking protocol (18 mw/cm^2) for the treatment of progressive keratoconus [published online ahead of print August 24, 2015]. *Am J Ophthalmol.* doi:10.1016/j.ajo.2015.08.027.
- Ng AL, Chan TC, Cheng AC. Conventional versus accelerated corneal collagen cross-linking in the treatment of keratoconus [published online ahead of print July 3, 2015]. *Clin Experiment Ophthalmol.* doi:10.1111/ceo.12571.
- Chan TC, Chow VW, Jhanji V, Wong VW. Different topographic response between mild to moderate and advanced keratoconus after accelerated collagen cross-linking. *Cornea.* 2015;34(8):922-927.
- Ozgurhan EB, Akcay BI, Kurt T, et al. Accelerated corneal collagen cross-linking in thin keratoconic corneas. *J Refract Surg.* 2015;31(6):386-390.
- Marino GK, Torricelli AA, Giacomin N, et al. Accelerated corneal collagen cross-linking for postoperative LASIK ectasia: two-year outcomes. *J Refract Surg.* 2015;31(6):380-384.
- Shetty R, Pahuja NK, Nuijts RM, et al. Current protocols of corneal collagen cross-linking: visual, refractive, and tomographic outcomes. *Am J Ophthalmol.* 2015;160(2):243-249.
- Hashemi H. Fotouhi A, Miraftab M, et al. Short-term comparison of accelerated and standard methods of corneal collagen crosslinking. *J Cataract Refract Surg.* 2015;41(3):533-540.
- Waszczykowska A, Jurowski P. Two-year accelerated corneal cross-linking outcome in patients with progressive keratoconus. *Biomed Res Int.* 2015;2015:325157.
- Konstantopoulos A, Mehta JS. Conventional versus accelerated collagen cross-linking for keratoconus. *Eye Contact Lens.* 2015;41(2):65-71.

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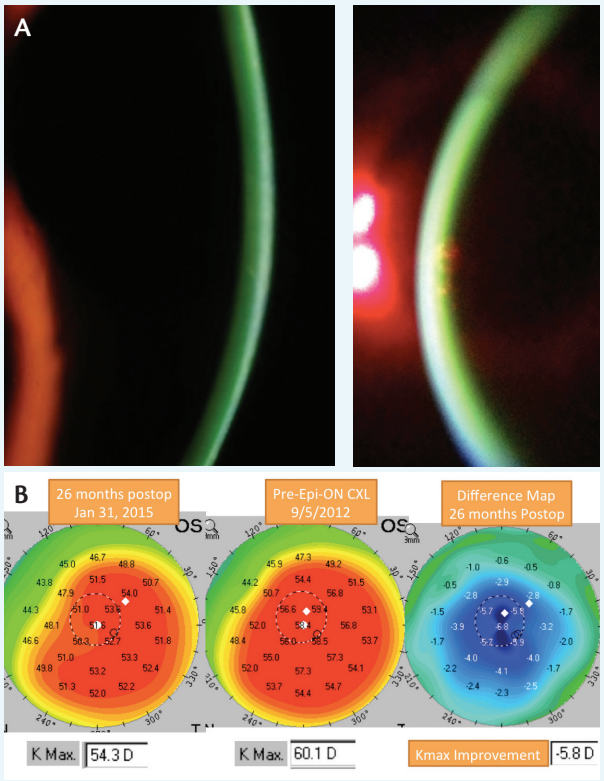

Figure 1. Slit-lamp view confirms sufficient riboflavin in the cornea to proceed with UV light therapy for epi-on CXL (A). A 35-year-old woman underwent epi-on CXL in 2012. Twenty-six months later, the cornea had flattened significantly (B).

include Intacs with CXL[8] and performing CXL 1 day after conductive keratoplasty (S. Shetty, MD, and R. Rubinfeld, MD, unpublished data, 2015). Although these combined procedures may quicken improvement in corneal shape and visual acuity compared with CXL alone, they potentially carry higher levels of risk because multiple procedures are being performed. ■

1. Raiskup F, Theuring A, Pilunat LE, et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. 2015;41(1):41-46.
2. Hafezi F, Mrochen M, Koller T, Seiler T. Current state of CXL (corneal collagen cross-linking): controversies and recommendations. Instructional course presented at: XXXI Congress of the ESCRS; October 7, 2013; Amsterdam, The Netherlands.
3. Mazzotta C, Traversi C, Pardiso A, et al. Pulsed light accelerated crosslinking versus continuous light accelerated crosslinking: one-year results. *J Ophthalmol*. 2014;2014:604731.
4. Leccisotti A, Islam T. Transepithelial corneal collagen cross-linking in keratoconus. *J Refract Surg*. 2010;25:1-7.
5. Filippello M, Stagni E, Buccoliero D, et al. Transepithelial cross-linking in keratoconus patients: confocal analysis. *Optom Vis Sci*. 2012;89(10):e1-7.
6. Trattler W, Rubinfeld R, Correa R, et al. Evaluation of epi-on corneal collagen cross-linking (CXL) at 6 months and 1 year follow-up in patients diagnosed with keratoconus and post-LASIK ectasia. E-poster presented at: XXXII Congress of the ESCRS; September 13-17, 2014; London, England.
7. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. *J Refract Surg*. 2009;25(9):S812-S818.
8. Vicente LL, Boxer Wachler BS. Factors that correlate with improvement in vision after combined Intacs and trans-epithelial corneal crosslinking. *Br J Ophthalmol*. 2010;94(12):1597-1601.

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