

## Transepithelial CXL Is Gaining Ground

By Roy S. Rubinfeld, MD, and the CXL-USA Study Group

At its simplest, corneal collagen cross-linking (CXL) is a unique technique for the treatment of keratoconus and ectasia that was introduced in the late 1990s. The procedure involves loading riboflavin into the corneal stroma and then exposing the cornea to ultraviolet A (UVA) light. The riboflavin combined with UVA light strengthens the cornea by cross-linking it, which halts the progression of keratoconus.<sup>1</sup>

In Europe, CXL technology received CE Mark approval in 2006, but it is still undergoing evaluation in the United States. Among surgeons familiar with the procedure, its popularity is rising rapidly because of its positive safety profile and its unique efficacy in stopping progressive vision loss by addressing the root cause of ectasia: pathological corneal weakness. The standard technique involves partial or complete removal of the central epithelium followed by the topical administration of riboflavin 0.1% solution to achieve intrastromal penetration.<sup>2</sup> In ongoing studies, however, investigators are leaving the epithelium intact or performing “epi-on” or transepithelial CXL. As one of the researchers evaluat-

ing the epi-on technique, it has been my experience and belief that patients endure less pain, heal faster, and are at a lower risk for adverse events with epi-on compared with the epithelium-off or epi-off technique. Although rare, corneal ulcers can occur after the epi-off procedure, but none has been reported to date with epi-on CXL. It also makes logical sense that the risk of infection would be lower in eyes that do not have a large epithelial defect compared with eyes that do.

### How epi-on differs from epi-off

Using the standard epi-off technique, surgeons remove the epithelium, apply riboflavin drops to the cornea for 30 minutes, expose the riboflavin-laden cornea to UVA light for 30 minutes, place a bandage contact lens, and provide postoperative care similar to after PRK.

The CXL-USA Study Group ([www.cxlusa.com](http://www.cxlusa.com) and [www.clinicaltrials.gov](http://www.clinicaltrials.gov); identifiers NCT01189864, NCT01024322, and NCT01097447) is a physician sponsored, prospective research effort underway at 13 US sites. We began evaluating outcomes using the

traditional epi-off Dresden technique. It rapidly became apparent to us, however, that epi-on CXL was providing patients with equivalent or superior outcomes and a much faster return to normal activities while causing significantly less pain. Current and future patients in our study are generally treated with the epi-on technique, although each case is evaluated individually. We are also actively enrolling older patients, because preliminary studies have indicated that older patients benefit to the same extent as younger patients from the CXL procedure.<sup>3</sup>

The CXL-USA investigational protocols use an FDAcleared medical UV light source off label (approved by investigational review boards). The epi-on technique was originally described by Brian Boxer Wachler, MD, in 2004 and then by Roberto Pinelli, MD. In some cases, the epi-on procedure can take up to 40 to 60 minutes longer than epi-off CXL, because the surgeon must ensure that the corneal stroma has properly absorbed the riboflavin. Epi-on CXL cannot be combined with topography-guided PRK, because the

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epithelium is debrided before PRK and cross-linking.

The reported rates of stromal and corneal haze after epi-off CXL have ranged from 7% to 90%.<sup>4-7</sup> In one study of epi-off, Greenstein found that postoperative haze cleared faster in patients being treated for ectasia than with keratoconus.<sup>7</sup> Almost no significant haze has been reported to date with the epi-on technique.

### The CXL-USA Study

The CXL-USA Study is a prospective, nonrandomized, multicenter investigation evaluating CXL. Hundreds of eyes have undergone treatment and have been followed for 6 to 12 months. Additionally, the study now has investigational review board approval for the treatment of infectious keratitis with CXL. Enrollment criteria for the CXL-USA Study include keratoconus, forme fruste keratoconus, post-LASIK ectasia and other ectatic conditions, or previous RK with diurnal fluctuations in vision. The protocol allows for treatment in children as young as 9 years of age, but corneal thickness has to be at least 300  $\mu\text{m}$  (thinner corneas in some publications have been considered possibly at higher risk for complications). Patients as young as 9 have been treated in Europe, so we opted to follow that lead. We have also found that patients older than 35 benefit significantly from the procedure, and most patients are pleased that additional options such as Intacs (Addition Technology, Inc.) or corneal transplants are not prohibited down the road.

Preliminary data comparing the epi-off (n = 45) to the epi-on (n = 128) groups

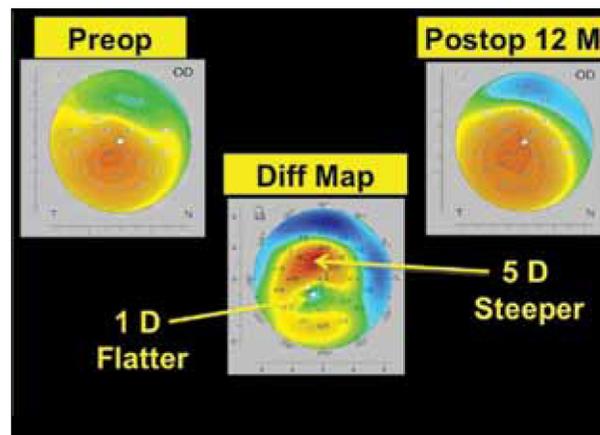


Figure 1. Pre- and postoperative topography is compared to yield the difference map in patients with keratoconus who have undergone CXL.

found that vision improved for 50% of the patients in the latter group at 3 months versus only 31.1% of former. At 6 months, the improvement was doubled in the epi-on group compared to the epi-off group (52% vs 24%, respectively). We evaluate changes in the corneal shape after crosslinking by studying difference maps (Figure 1).

These maps provide a point-by-point comparison of the eye and can demonstrate areas of flattening and steepening. Figures 2 and 3 are case studies from the CXL-USA group illustrating how we use difference maps to verify the corneal flattening after CXL treatment for keratoconus or ectasia.

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Figure 2. Examples of patients who underwent epi-on CXL for ectasia; the difference map represents the corneal flattening 3 months after the transepithelial procedure.

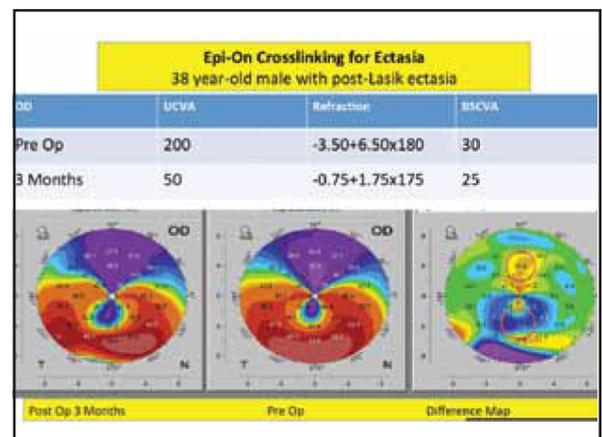
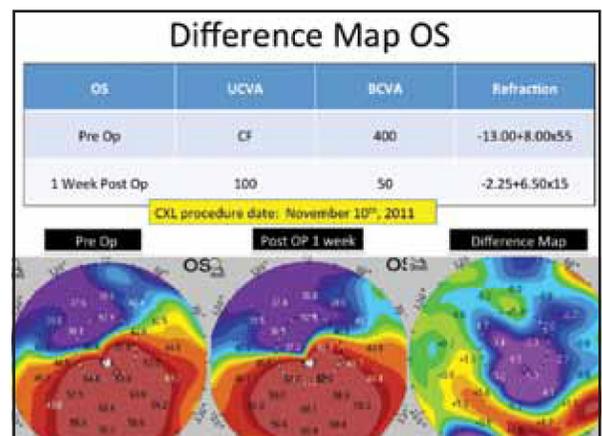


Figure 3. In this difference map, 1 week after transepithelial CXL, the topography clearly shows substantial flattening of the cornea.



Our early results add to the growing body of research worldwide suggesting that CXL can prevent further vision loss in more than 95% of patients and improve vision in up to 80%.<sup>8-13</sup>

## What the future holds

In the Athens protocol, Kanellopoulos combines laser treatment with CXL. To date, no cases of breakthrough ectasia have been reported in significantly more than 400 cases.<sup>2,14-16</sup> In fact, his results show a benefit regardless of whether the CXL is performed before topography-guided PRK or if the procedures are performed concurrently on the same day. His data suggest limiting the PRK treatment to no more than 3.00 to 4.00 D. Debate continues on the benefit of using mitomycin C after PRK plus cross-linking and, if the agent is used, the amount necessary.

Others have commented from the podium about topographical changes that continue even 5 or 6 years after the original treatment. In the US studies, 1-year follow-up suggests that patients with keratectasia continue to show improvements on corneal topography when analyzed with the Pentacam Comprehensive Eye Scanner (Oculus Optikgeräte GmbH),<sup>17</sup> reflecting what our European counterparts found with Scheimpflug photography.<sup>18</sup>

## Conclusion

There is no doubt in my mind that CXL will become the procedure of choice for treating keratoconus once longer-term data confirm what we and others have seen initially. Halting the progression of this often vision-threatening disease is highly gratifying.



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He has proprietary interests in the CXL space. Dr. Rubinfeld may be reached at (301) 657-5711; rubinkr1@aol.com.

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