

CXL With the Epithelium on or off: Which Is Better?

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.¹

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.² In ongoing studies, however, investigators are leaving the epithelium intact or performing “epi-on” or transepithelial CXL. As one of the researchers evaluating 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.

(Continued on page 46)

Why I Prefer Epithelium-off Cross-Linking



By Yaron S. Rabinowitz, MD

The use of corneal collagen cross-linking (CXL) to arrest progressive keratoconus was first introduced by Wollensak, Spoerl, and Seiler in 2003. In their initial description of the procedure, they removed the epithelium (epi-off) prior to administering riboflavin.¹ These investigators have the most experience with the procedure, have experimented with different ways of preparing the cornea prior to the cross-linking step, and have conducted many studies demonstrating its safety and efficacy. Interestingly, they recently reported their 6-year results, and they are still using the same technique.²

EXPERIMENTS WITH EPI-ON

Wollensak experimented with the epithelium-on (epi-on) technique in the laboratory and found that it was only 20% as effective at stiffening the cornea as the epi-off procedure. Therefore, he has recommended that epi-on should only be considered in instances where corneas are not thick enough for the standard epi-off procedure.³

It is tempting to wish to perform a procedure in which the epithelium is retained for several compelling reasons: there is less postoperative pain, there is less risk of infection, and patients can return more quickly to wearing rigid contact lenses. Is it worth doing epi-on CXL, however, in the absence of solid scientific data demonstrating its safety and at the expense of efficacy?

WHERE ARE THE DATA?

Two studies with very short-term data suggest that the epi-on technique is as efficacious as epi-off. The number of eyes included is small, and the data are not very convincing.^{4,5} In the United States, a group con-

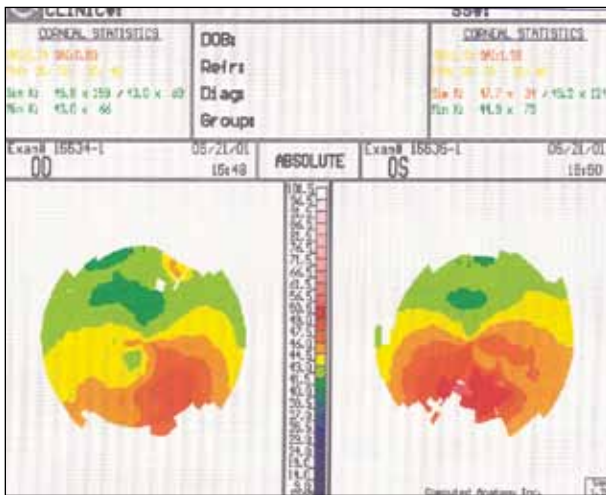


Figure 1. Preoperative topography of the right eye of a patient with mild keratoconus. The surface regularity index is 1.14.

ducting a study with the epi-on approach cites excellent results, but none of the data is published. The lamp and riboflavin these investigators use are “proprietary,” so thus far, no other researchers are able to reproduce the technique. In addition, there are no long-term data showing that this technique is safe.

During the past 5 years, my colleagues and I have seen more than 20 patients in our office who have undergone an epi-on procedure called C3R (a technique not described in the literature in any detail or approved by the FDA). As far as I know, this technique is not being performed under a study protocol. All 20 patients experienced progression of their disease or were unhappy with

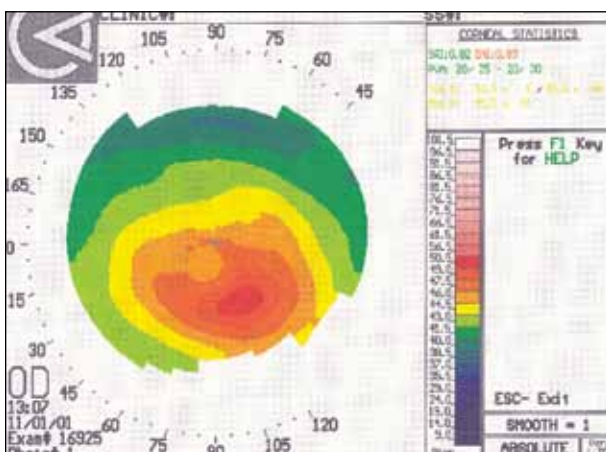


Figure 2. Postoperative topography of the same patient 6 weeks after the PTX procedure. Note the smoother surface and improvement in surface regularity index from 1.14 to 0.82. This change was accompanied by a 2-line gain in BCVA.

their outcomes and had to be re-treated in our clinic. None of the patients we re-treated using the epi-off technique has demonstrable progression to date.

OUR PROTOCOL

In 2009, my fellow researchers and I received an investigational device exemption from the FDA to perform a clinical study comparing the use of CXL with CXL plus Intacs (Addition Technology, Inc.) to determine which technique is more efficacious. We use the original lamp made by IROC Innocross AG (subsequently purchased by Avedro, Inc.) and riboflavin formulated by Medio Cross, which we import from Europe. We use the standard Dresden epi-off protocol initially described by Wollensak et al.

We have treated more than 150 eyes to date, and the outcomes have been quite impressive and surprising. Our data reflect those published by many other groups for this technique. Although we have only 2-year follow-up, just two patients have demonstrated mild evidence of progression (approximately 0.50 D). Considering we have treated only patients with progressive disease, our study suggests that epi-off CXL may be very effective. Interestingly, more than 60% of our patients have also noticed improved vision (1 or 2 lines), although this was not the reason for their treatment. The improved vision, in most instances, is not accompanied by any significant changes in topography or refractive error.

PAIN

Our patients do have postoperative pain. It is not a major problem, however, because it is well controlled with a combination of cyclopentolate hydrochloric acid (Cyclogel; Alcon Laboratories, Inc.), diluted anesthetic drops, and nepafenac (Nevanac; Alcon Laboratories, Inc.) (To see patients' experiences and the live procedure, visit www.youtube.com/watch?v=k9g63v73iiq.) We also give our patients a prescription for acetaminophen-hydrocodone (Vicodin; Abbott Laboratories) if they should need it. One patient developed an infection, which we treated and which has not resulted in a permanent decrease in vision.

ADDITIONAL RESULTS

Recently, Kymionis et al from Greece published an article in which they used a laser in the phototherapeutic keratectomy (PTK) mode to remove the epithelium prior to cross-linking. They demonstrated a 2-line improvement in both corrected and uncorrected visual acuity using this technique.⁶ Approximately 13 years ago, our group studied patients with mild keratoconus that was stable and upon whom we performed a combination of PTK

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and PRK. We used the PTK technique first described by Vinciguerra in Italy and used Refresh Celluvisc (Allergan, Inc.) as a smoothing agent.⁷ We were impressed that we were able to improve the surface irregularity in these eyes and, at the same time, demonstrate improved BCVA (Figures 1-2).

Based on Kymionis’ and our experiences, we decided to use our PTK technique to remove the epithelium prior to performing cross-linking on our patients. We have treated approximately 25 eyes so far and have noticed a 2- to 3-line improvement in visual acuity compared with a 1- to 2-line improvement in patients whose epithelium we removed manually. We will be presenting our data at this year’s ARVO meeting.⁸

CONCLUSION

Now there is another excellent reason to remove the epithelium prior to cross-linking: better visual acuity is achieved, which is a secondary benefit of this procedure. Although epi-on CXL may have limited applications depending on the riboflavin formulation used, I believe that the epi-off technique using the PTK mode is a superior treatment in patients with progressive keratoconus. ■

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1. 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.
2. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg.* 2008;34(5):796-801.
3. Wollensak G, Iomdina E. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement. *J Cataract Refract Surg.* 2009;35:540-546.
4. Pinelli R, El Beltagi T. C3-R: the present and the future. October 1, 2008. *Ophthalmology Times Europe.* www.oteurope.com/ophthalmologytimeseurope/Cornea/C3-R-the-present-and-the-future/ArticleStandard/Article/detail/556880. Accessed April 11, 2012.
5. Lecicisotti A, Islam T. Trans epithelial corneal collagen cross-linking in keratoconus. *J Refract Surg.* 2010;26:942-948.
6. Kymionis GD, Grentzelos MA, Karavitaki AE, et al. Trans epithelial phototherapeutic keratectomy using a 213-nm solid-state laser system followed by corneal collagen cross-linking with riboflavin and UVA irradiation. *J Ophthalmol.* 2010;20(10):1465-43.
7. Vinciguerra P, Albe E, Trazza S. Refractive, topographic, tomographic and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. *Ophthalmology.* 2009;116:369-378.
8. Rabinowitz YS, Gaster R. Early results of laser-assisted collagen cross-linking (laser CXL) suggest that patients achieve better-uncorrected acuity at 6 months compared to mechanical debridement of the epithelium in patients with progressive keratoconus. Paper presented at: The 2012 ARVO Annual Meeting; May 10, 2012; Fort Lauderdale, FL.

(Continued from page 44)

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 and 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.³

The CXL-USA investigational protocols use an FDA-cleared 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 epithelium is debrided before PRK and cross-linking.

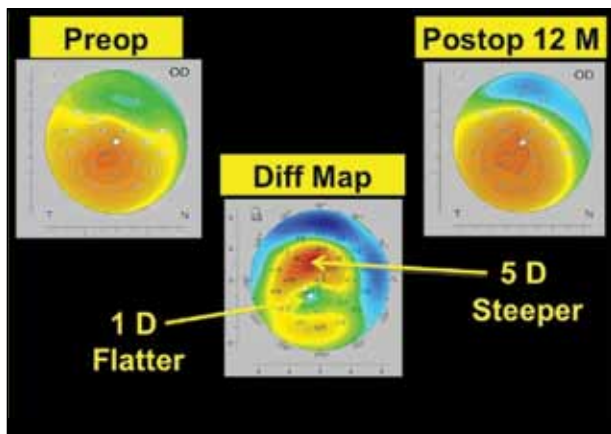


Figure 1. Pre- and postoperative topography is compared to yield the difference map in patients with keratoconus who have undergone CXL.

“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.”

The reported rates of stromal and corneal haze after epi-off CXL have ranged from 7% to 90%.⁴⁻⁷ In one study of epi-off, Greenstein found that postoperative haze cleared faster in patients being treated for ectasia than with keratoconus.⁷ 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 ectactic 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 μm (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 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 cross-linking 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.

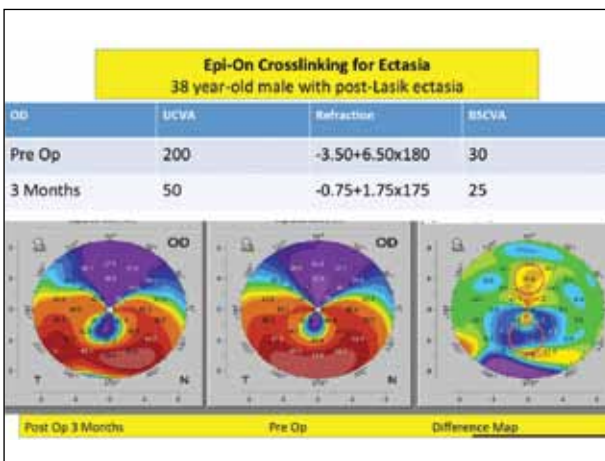
Our early results add to the growing body of research worldwide suggesting that CXL can prevent further vision loss in more than 95% of patients and improve vision in up to 80%.⁸⁻¹³

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.^{2,14-16} 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

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

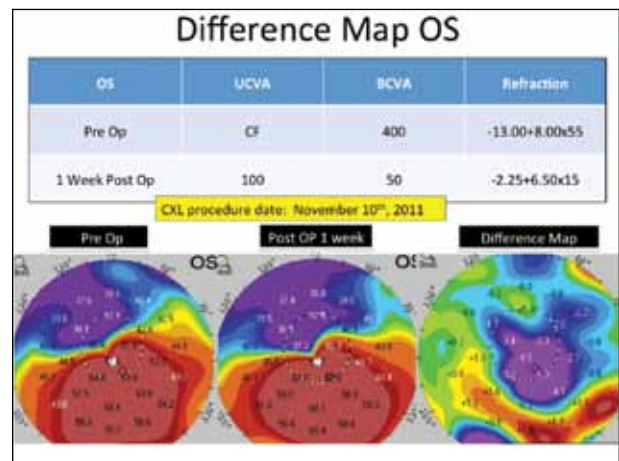


Figure 3. In this difference map, 1 week after transepithelial CXL, the topography clearly shows substantial flattening of the cornea.

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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 keratoectasia continue to show improvements on corneal topography when analyzed with the Pentacam Comprehensive Eye Scanner (Oculus Optikgeräte GmbH),¹⁷ reflecting what our European counterparts found with Scheimpflug photography.¹⁸

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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1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620-627.
2. Kanellopoulos AJ. Collagen cross-linking in early keratoconus with riboflavin in a femtosecond laser-created pocket: initial clinical results. *J Refract Surg.* 2009;25:1034-1037.
3. Majmudar P, Rubinfeld R, McCall T, et al. Evaluation of epithelial-on corneal collagen crosslinking in patients ages 35 or older. Poster presented at: ISRS Annual Meeting, October 21-22, 2011; Orlando, FL.
4. Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. *J Refract Surg.* 2009;25:S824-828.
5. Lim LS, Beuerman R, Lim L, Tan DT. Late-onset deep stromal scarring after riboflavin-UV-A corneal collagen cross-linking for mild keratoconus. *Arch Ophthalmol.* 2011;129:360-362.
6. Mazzotta C, Balestrazzi A, Baiocchi S, et al. Stromal haze after combined riboflavin-UVA corneal collagen cross-linking in keratoconus: in vivo confocal microscopic evaluation. *Clin Experiment Ophthalmol.* 2007;35:580-582.
7. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *J Cataract Refract Surg.* 2010;36:2105-2114.
8. Bikbov MM, Bikbova GM, Khabibullin AF. Corneal collagen cross-linking in keratoconus management [in Russian]. *Vestnik Oftalmologii.* 2011;127:21-25.
9. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol.* 2010;149:585-593.
10. Coskunseven E, Jankov MR, Znd, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. *J Refract Surg.* 2009;25:371-376.
11. Grewal DS, Brar GS, Jain R, et al. Corneal collagen crosslinking using riboflavin and ultraviolet-A light for keratoconus: one-year analysis using Scheimpflug imaging. *J Cataract Refract Surg.* 2009;35:425-432.
12. Raiskup-Wolff F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg.* 2008;34:796-801.
13. Vinciguerra P, Albe E, Traza S, et al. Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus. *Arch Ophthalmol.* 2009;127:1258-1265.
14. 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:S812-818.
15. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. *Cornea.* 2007;26:891-895.
16. Kanellopoulos AJ, Binder PS. Management of corneal ectasia after LASIK with combined, same-day, topography-guided partial transepithelial PRK and collagen cross-linking: the Athens protocol. *J Refract Surg.* 2011;27:323-331.
17. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg.* 2011;37:1282-1290.
18. Koller T, Iseli HP, Hafezi F, et al. Scheimpflug imaging of corneas after collagen cross-linking. *Cornea.* 2009;28:510-515.