CASE REPORT

Transepithelial crosslinking retreatment of progressive corneal ectasia unresponsive to classic crosslinking

Roy S. Rubinfeld, MD, Rachel H. Epstein, MD, Parag A. Majmudar, MD, Deborah Kim, OD, Michael Choi, BS, Randy J. Epstein, MD

A 41-year-old man presented 10 years after uneventful laser in situ keratomileusis (LASIK) with symptomatic post-LASIK ectasia. He had treatment with the classic Dresden epithelium-off technique and presented 4 years later with progression of the ectasia. He was subsequently retreated with conductive keratoplasty (CK) followed by a new proprietary epithelium-on corneal collagen crosslinking (CXL) procedure using a proprietary transepithelial riboflavin formulation and delivery system on the following day. One year after retreatment, the patient noted stable vision in the treated eye with a corrected distance visual acuity (CDVA) of 20/60^{+}. Thus, epithelium-on CXL, if performed with appropriate formulations and delivery technology as well as careful attention to appropriate riboflavin loading of the stroma, can stabilize an ectatic cornea. In addition, when performed prior to CXL, CK can induce a significant, lasting improvement in corneal shape and CDVA. This technique merits further study.

J Cataract Refract Surg 2017; 43:131–135 © 2017 ASCRS and ESCRS

Corneal collagen crosslinking (CXL) has become a standard treatment for progressive keratoconus and post-laser in situ keratomileusis (LASIK) ectasia in most of the world. The incidence of progression after CXL has been reported to be between 7.6%[1] and 3.2%.[2] Substantial controversy has existed as to whether the classic Dresden epithelium-off (epi-off) or the newer epithelium-on (epi-on) technique is preferable. Although the classic technique has a well-established track record, it is associated with a longer healing period, more discomfort, and a greater potential for infection, scarring, and chronic ocular surface disease, among other risks. Although commercially available epi-on approaches have been reported to yield less efficacy than classic epi-off CXL,[1–3] recent modifications involving a unique riboflavin formulation, delivery system, and ultraviolet-A (UVA) pulsed treatment have improved the safety and efficacy of this procedure.[A–C]

Conductive keratoplasty (CK), initially developed as a treatment for hyperopia and presbyopia, has been used as a potential adjuvant for corneal remodeling in conjunction with CXL.[4] Early reports of combined application of CK and CXL to improve the corneal shape in patients with advanced keratoconus showed only a temporary effect.[5] A more recent nonrandomized prospective noncomparative case series of 209 eyes of 149 patients with ectasia had CK followed by a same-day or next-day proprietary epi-on CXL found improvement in CDVA 10 to 15 months after the procedure.[D] However, the efficacy of CK followed by epi-on CXL in the management of post-LASIK ectasia refractory to epi-off CXL has not previously been reported.

We describe a patient with post-LASIK ectasia with additional progression after standard epi-off CXL. He was successfully retreated using a combination of a proprietary epi-on CXL system to stabilize the ectasia and CK to improve vision.

CASE REPORT

A 41-year-old white man presented with a chief complaint of poor vision in both eyes. His medical history was noncontributory. His ocular history was significant for what was reportedly an uneventful bilateral LASIK procedure performed 10 years before presentation. Preoperative, intraoperative, and postoperative data were not available; however, the patient stated that he had a satisfactory visual outcome from that procedure. Our initial examination showed an uncorrected distance visual acuity (UDVA) in the right eye of 20/30^{-2} and a corrected distance visual acuity (CDVA) of 20/20^{+2} with a manifest refraction of $-2.00 + 0.75 \times 27$. The UDVA in the left eye was 20/400 and the CDVA was 20/30^{-2} with a manifest refraction of $-3.00 + 5.75 \times 47$.

Submitted: August 30, 2016 | Final revision submitted: September 26, 2016 | Accepted: November 7, 2016

From Georgetown University Medical Center (Rubinfeld) and Washington Hospital Center (Rubinfeld), Washington, DC, Re: Vision (Rubinfeld, Kim, Choi), Rockville, Maryland, and Fairfax, Virginia, the Cornea Service (R.H. Epstein, Majmudar, R.J. Epstein), Department of Ophthalmology, and Rush University Medical Center, and Chicago Cornea Consultants, Ltd. (Majmudar, R.J. Epstein), Chicago, Illinois, USA.

Corresponding author: Randy J. Epstein, MD, 806 Central Avenue, Suite 300, Highland Park, Illinois 60035, USA. E-mail: repstein@chicagocornea.com.

0886-3350/$ - see frontmatter
http://dx.doi.org/10.1016/j.jcrs.2016.11.038

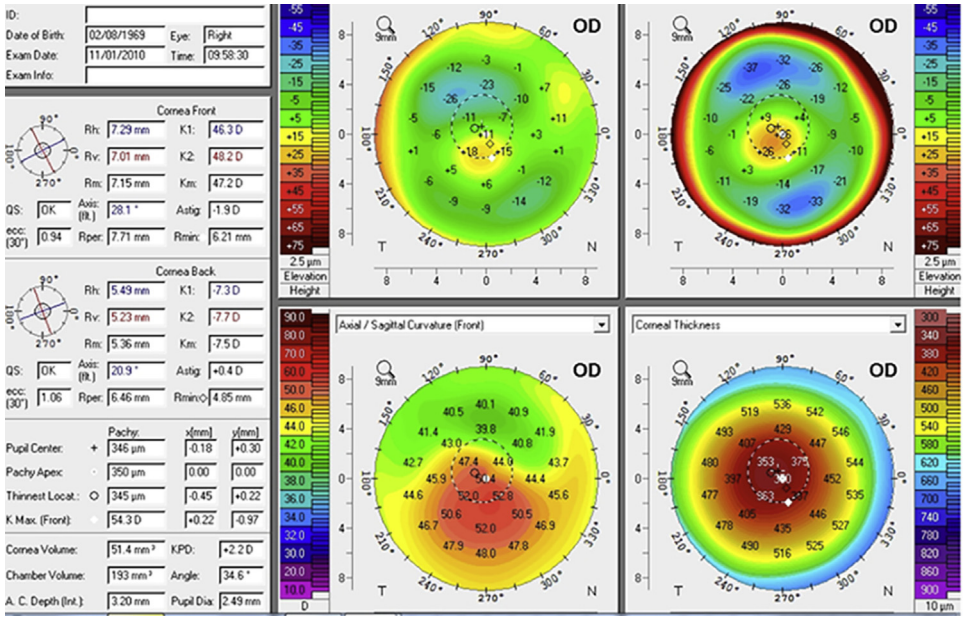

Figure 1. Scheimpflug-derived anterior segment tomography shows ectasia in the right cornea, characterized by central and inferior steepening.

Scheimpflug-derived anterior segment tomography (Pentacam, Oculus Optikgeräte GmbH) evaluation (Figures 1 and 2) showed definite corneal ectasia in both eyes, with thinnest pachymetry measurements of 345 µm in the right cornea and 312 µm in the left. Our institutional review board (IRB)–approved CXL protocol at that time mandated a minimum pachymetry of 375 µm before UVA application. Thus, it was determined that the eye with the worst acuity (left eye) required treatment with classic epi-off CXL with the hopes that it would "swell" the cornea with hypotonic riboflavin before CXL was performed. Successful swelling of the left cornea was accomplished after debridement by instilling sterile hypoosmolar riboflavin drops until the left cornea achieved a pretreatment thickness of 381 µm. The surgeon, at the slitlamp using white and cobalt blue tangential slit beams, confirmed adequate stromal riboflavin penetration. The patient did well postoperatively, with a UDVA of 20/400 and CDVA of $20/60^{+}$ with a manifest refraction of −19.00 + 6.00 × 096 at 12 months.

One year later, the right eye, which had less advanced ectasia, had proprietary epi-on CXL under an IRB-approved study protocol on December 28, 2011, using the same pulsed UVA device. At that time, our research protocol had been modified to permit UVA application if the corneal pachymetry was at least 300 µm, and epi-on treatments became the preferred treatment of choice in our study. Twelve months postoperatively, the patient's UDVA was 20/400 and his CDVA was $20/30^{+3}$ with a manifest refraction of −11.25 + 5.25 × 101.

Four years after the epi-off CXL procedure in the left eye, the patient presented with markedly reduced subjective and objective visual acuity in the left eye. Examination of the left eye showed a UDVA of 20/400 at 1 foot and a CDVA of 20/200 with a manifest refraction of −13.00 + 1.50 × 175. In the right eye, the UDVA was 20/400 at 1 foot and the CDVA was 20/50 with a manifest refraction −13.25 + 3.75 × 116. Scheimpflug-derived anterior segment

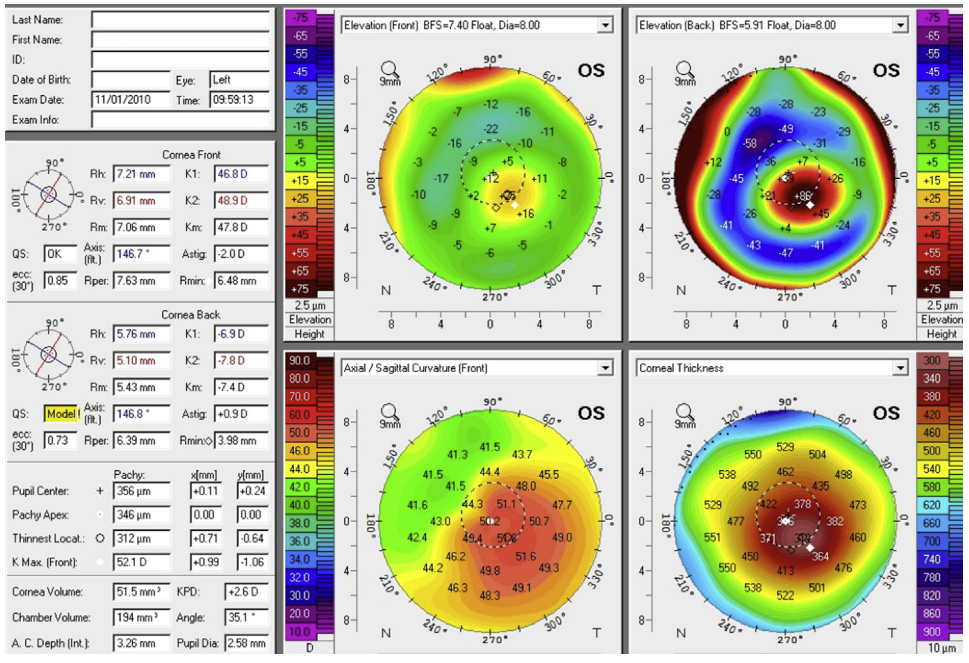

Figure 2. Scheimpflug-derived anterior segment tomography shows even more marked ectasia in the left cornea, characterized by greater central and inferior steepening and significant posterior elevation.

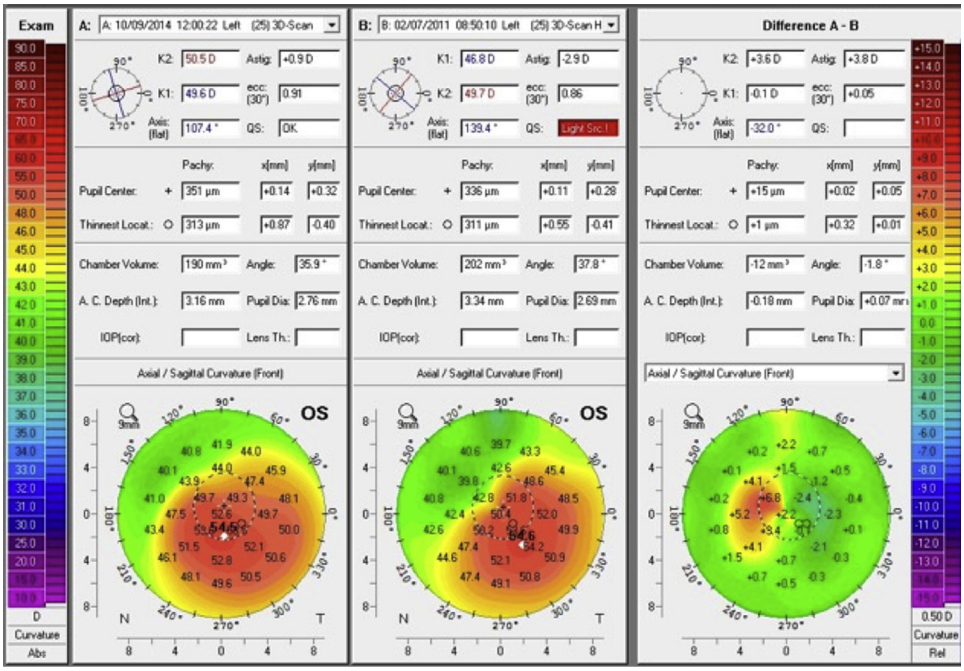

Figure 3. Scheimpflug-derived anterior segment tomography after epi-off CXL performed on the left cornea shows progression of the ectatic changes, as evidenced by the high positive values on anterior sagittal curvature difference map.

tomography, Snellen acuity, and refractions showed what appeared to be an inadequate therapeutic effect from the crosslinking, with a significant increase in irregular myopic astigmatism and corneal curvature. The right eye, which had been previously treated with epi-on CXL, remained stable when compared with findings at the previous examination (Figures 3 and 4), and the patient was very satisfied with the improvement in CDVA with a soft contact lens.

This patient then had retreatment in the left eye on February 25, 2015, with CK (Refractec View Point CK) followed by epi-on CXL using a proprietary transepithelial riboflavin formulation and delivery system and the same pulsed UVA device performed on the following day.

Printouts of the patient's Scheimpflug-derived anterior segment tomography scans were placed near the operating microscope and placed upside down to align them with the surgeon's view of the patient's eye. The initial 1 to 3 CK spots were placed at approximately the 3.0 mm optical zone (~1.5 mm from the corneal center) in the steepest meridian corresponding to the steepest area of the cone on the scan under real-time intraoperative keratometry. This permitted the surgeon to monitor the effects of the CK spots on corneal curvature. Additional CK spots were added as needed after assessing the effect with intraoperative keratometry or serial Scheimpflug-derived anterior segment tomography scans, including subtraction difference maps. Because significant regression is known to occur in the first 24 hours after thermokeratoplasty, the objective was to achieve an immediate overcorrection of approximately 4.0 to 6.0 diopters (D) after CK spot placement. The next day, proprietary transepithelial CXL was performed as per our IRB-approved protocol.

The patient had a significant improvement postoperatively. Three months after CK with CXL, the UDVA in the left eye was

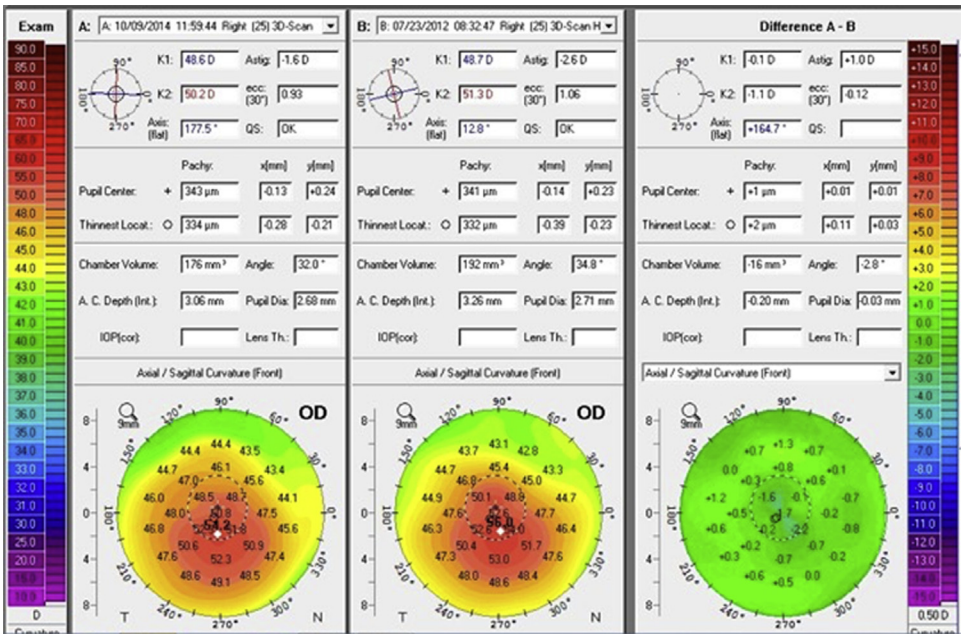

Figure 4. Scheimpflug-derived anterior segment tomography difference map after epi-on CXL retreatment in the right eye shows no further progression of the ectatic changes, as evidenced by the "0" values on the anterior sagittal curvature difference map.

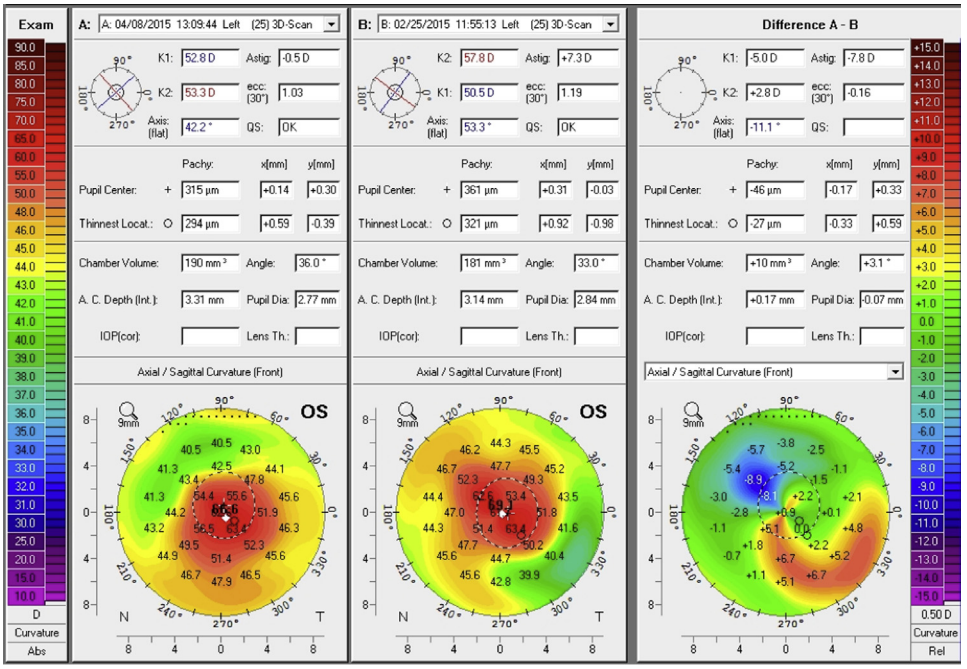

Figure 5. Scheimpflug-derived anterior segment tomography difference map of the left cornea after CK and epi-on CXL shows a significant reduction in keratometric astigmatism (from 7.3 D to 0.5 D) with significant overall flattening.

20/400 at 1 foot and the CDVA was $20/80^{+}$ with a manifest refraction of $-9.25 + 4.00 \times 174$. Scheimpflug-derived anterior segment tomography studies of the left eye after retreatment showed improvement in overall corneal shape, especially anterior sagittal curvature, as seen in Figure 5. One year after this retreatment, the patient had stable vision in that eye; the UDVA remained 20/400 at 1 foot and the CDVA was $20/60^{+2}$ with a manifest refraction of $-9.25 + 2.50 \times 25$.

DISCUSSION

This patient's post-LASIK ectasia and loss of vision continued to progress despite treatment with epi-off CXL (classic Dresden technique). In this case, further progression was halted by the use of epi-on CXL as well as CK. Conductive keratoplasty has been reported to be a useful adjunct to CXL.[4,5,D–F] Although this single case report is insufficient to establish the best method to use for performing CXL, several salient observations can be made. We believe the key issue should not be whether the epithelium is or is not removed but whether the corneal stroma is or is not adequately loaded with riboflavin. Our protocol requires the surgeon to document adequate riboflavin stromal loading before the UVA-light exposure is administered, which is shown in Figure 6. Because epi-on CXL eliminates most morbidity associated with traditional CXL, it is our preferred technique unless precluded by an inadequate corneal thickness, such as was the case with the patient's left eye at the time of initial presentation.

Opponents of the epi-on technique have cited early literature[3,6,7] that shows its efficacy to be inferior to the standard epi-off Dresden protocol. However, in many of these studies, the formulation of riboflavin was inadequate for transepithelial delivery or loading of riboflavin was not adequately documented. In addition, this proprietary transepithelial riboflavin does not accumulate in the epithelium and therefore appears to not block transmission of UVA light or result in unnecessary consumption of oxygen by riboflavin in the epithelium, as seen in Figure 6. Recently, studies[8,9] have shown that 1 unique epi-on CXL technology might be effective. Certainly, longer follow-up with optimized riboflavin formulations and loading systems will be required to validate epi-on CXL as a first-line treatment. Recent independent ex vivo rabbit studies[8] compared the efficacy of optimized transepithelial riboflavin solutions. By analyzing stromal loading through intact epithelium using chromatography, the proprietary solution used in this patient has been shown to effectively load the corneal stroma; however, another commercial transepithelial formulation used in previous studies did not effectively load.

There have been other published reports of the progression of keratoconus after epi-off CXL.[1,2] This report highlights that epi-on CXL, if performed with attention to appropriate riboflavin loading of the stroma, might be able to stabilize an ectatic cornea. As previously described,[4,5,D–F] when CK

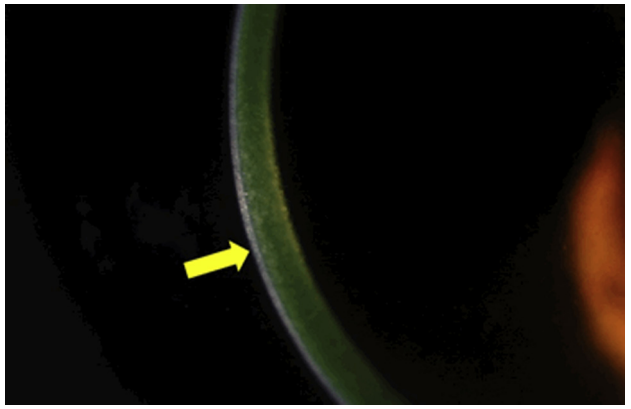

Figure 6. Slitlamp examination after the administration of riboflavin using the proprietary epi-on technique shows uniform stromal loading yet almost no epithelial fluorescence (*solid yellow arrow*).

is performed sequentially (ie, 1 day before CXL), it can yield more significant improvement in the overall corneal shape and CDVA and merits further study.

REFERENCES

1. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009; 35:1358–1362
2. Antoun J, Slim E, el Hachem R, Chelala E, Jabbour E, Cherfan G, Jarade EF. Rate of corneal collagen crosslinking redo in private practice: risk factors and safety. J Ophthalmol 2015 article ID690961. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4383466/pdf/JOPH2015-690961.pdf. Accessed December 2, 2016
3. Caporossi A, Mazzotta C, Paradiso AL, Baiocchi S, Marigliani D, Caporossi T. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results. J Cataract Refract Surg 2013; 39:1157–1163
4. Cummings AB, Sinjab MM, Hatch KM, Talamo J, Randleman B, Kanellopoulos AJ, Asimellis G, Sakla H, Altroudi W, Rabinowitz YS, Kõlõç A, Rubinfeld RS, Ambrósio R Jr, El-Kateb M, DeVore DP, Ross MA, De Woolfson BH, Dryjski O, Stulting RD. Combined corneal cross linking and other procedures: indications and application models. In: Sinjab MM, Cummings AB, eds, Corneal Collagen Cross Linking. Cham, Switzerland, Springer International Publishing AG, 2017; 87–165
5. Kymionis GD, Kontadakis GA, Naoumidi TL, Kazakos DC, Giapitzakis I, Pallikaris IG. Conductive keratoplasty followed by collagen cross-linking with riboflavin-UV-A in patients with keratoconus. Cornea 2010; 29:239–243. Available at: http://www.ivo.gr/files/items/2/257/ck_plus_cxl.pdf. Accessed December 2, 2016
6. Wollensak G, Iomdina E. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement. J Cataract Refract Surg 2009; 35:540–546
7. Baiocchi S, Mazzotta C, Cerretani D, Caporossi T, Caporossi A. Corneal crosslinking: Riboflavin concentration in corneal stroma exposed with and without epithelium. J Cataract Refract Surg 2009; 35:893–899
8. Filippello M, Stagni E, O'Brart D. Transepithelial corneal collagen crosslinking: Bilateral study. J Cataract Refract Surg 2012; 38:283–291; erratum, 1515
9. Rossi S, Orrico A, Santamaria C, Romano V, De Rosa L, Simonelli F, De Rosa G. Standard versus trans-epithelial collagen cross-linking in keratoconus patients suitable for standard collagen cross-linking. Clin Ophthalmol 2015; 9:503–509. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4370945/pdf/opth-9-503.pdf. Accessed December 2, 2016

OTHER CITED MATERIAL

A. Stulting RD, "Predicting and Treating Corneal Ectasia," the Binkhorst Lecture presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, New Orleans, Louisiana, USA, May 2016
B. Rubinfeld R, Mrochen M, Perez G, Person P, Kaiser C, Trattler W, "Evaluation of transepithelial corneal collagen cross-linking (CXL) at 6 months and 1 year follow-up in patients with different proprietary transepithelial riboflavin solutions," presented at the XXXI Congress of the European Society of Cataract and Refractive Surgeons, Amsterdam, the Netherlands, October 2013. Abstract available at: http://www.escrs.org/abstracts/details.asp?confid=16&sessid=411&type=free&paperid=16023. Accessed December 2, 2016
C. Rubinfeld R, Talamo J, Stulting D, "Quantitative Analyses of Trans-Epithelial Corneal Stroma Riboflavin Loading Comparing Commercial Epithelium On Formulation With A Novel Proprietary Formulation and Delivery System," presented at the 11th International Congress of Corneal Cross-Linking, Boston, Massachusetts, USA, December 2015
D. Dryjski O, Rubinfeld R, Lindstrom R, Kim D, Choi M, Shetty S, Ambrosio R, Cummings A, "Same Day vs Sequential CK+CXL in the Treatment of ectasia," poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Seattle, Washington, USA, May 2016. Abstract available at: http://www.arvo.org/webs/am2016/sectionpdf/CO/Session_311.pdf. Accessed December 2, 2016
E. Cummings AB, "Factors Affecting the Stability of Keraflex Treatments for Keratoconus," poster presented at the annual meeting of the American Academy of Ophthalmology, Chicago, Illinois, USA, October 2012
F. Shetty SR, Rubinfeld RS, Littner R, McFadden BE, Kolchak M, Trattler WB, Lindstrom RL, "Conductive Keratoplasty With Corneal CXL for Keratoconus and Corneal Ectasia," poster presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, April 2015. Abstract available at: https://ascrs.confex.com/ascrs/15am/webprogram/Paper14023.html. Accessed December 2, 2016

DISCLOSURES

Dr. Rubinfeld has equity in and is a managing member of CXL Ophthalmics LLC, he is a managing member of Curveright, and is president of CXL USA, LLC. Dr. Epstein is a consultant to Abbott Medical Optics Inc., Alcon Laboratories, Inc., and Shire International GmbH. Dr. Majmudar is an owner of CXL Ophthalmics, LLC, and Rapid Pathogen Screening; he is a consultant to Alcon Laboratories, Inc., Allergan, Inc., Shire International GmbH, and Valeant Pharmaceuticals International, Inc. None of the other authors has a financial or proprietary interest in any material or method mentioned.

First author:
Roy S. Rubinfeld, MD

Georgetown University Medical Center, Washington, DC, USA