

# Transepithelial Corneal Crosslinking Using a Novel Ultraviolet Light-Emitting Contact Lens Device: A Pilot Study

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**Received:** October 31, 2020

**Accepted:** March 17, 2021

**Published:** April 29, 2021

**Keywords:** keratoconus; corneal crosslinking; riboflavin; ultraviolet light; contact lenses

**Citation:** Dackowski EK, Logroño JB, Rivera C, Taylor N, Lopath PD, Chuck RS. Transepithelial corneal crosslinking using a novel ultraviolet light-emitting contact lens device: A pilot study. *Transl Vis Sci Technol.* 2021;10(5):5. <https://doi.org/10.1167/tvst.10.5.5>

**Purpose:** To evaluate the feasibility of a novel, on-eye UVA light-emitting contact lens device driven by fiber optics for the corneal crosslinking (CXL) of patients with keratoconus.

**Methods:** In nine corneal transplant candidates with advanced keratoconus a scleral contact lens reservoir containing 0.007% benzalkonium chloride preserved with 0.25% riboflavin-monophosphate was placed on the eye for 30 minutes. The reservoir lens was removed and replaced with the CXLens UVA light-emitting contact lens. A 375-nm UVA light at 4 mW/cm<sup>2</sup> intensity was delivered for 30 minutes for a dose of 7.2 J/cm<sup>2</sup>. A one-sided paired *t*-test was used to evaluate mean differences in maximum keratometry, thinnest corneal thickness, and endothelial cell density between screening and 6 months after CXL. A two-sided paired *t*-test was used to evaluate differences in best-corrected distance visual acuity between screening and 6 months after CXL.

**Results:** All patients received the treatment as per protocol and adhered to follow-up testing. At 6 months after CXL, treated eyes had an average  $-1.0 \pm 1.6$  diopters decrease in the maximum keratometry ( $P = 0.049$ ), a nonsignificant  $2.3 \pm 7.5$  letter improvement in best-corrected distance visual acuity ( $P = 0.19$ ), a nonsignificant  $-17 \pm 14 \mu\text{m}$  decrease in thinnest corneal thickness ( $P < 0.01$ ), and a nonsignificant  $-86 \pm 266$  cells/mm<sup>2</sup> decrease in endothelial cell density ( $P = 0.20$ ).

**Conclusions:** Our pilot study demonstrated the feasibility of the novel CXL device for the treatment of keratoconus and indicates the device is ready for larger scale studies with longer follow-up periods.

**Translational Relevance:** The novel CXLens on-eye UVA light-emitting contact lens device offers the potential for efficient, high-throughput transepithelial corneal CXL.

## Introduction

Keratoconus is a corneal degeneration caused by an underlying biomechanical weakness in the collagen structure that leads to progressive steepening and thinning over time.<sup>1</sup> Corneal crosslinking (CXL) was first introduced by Wollensak et al.<sup>2</sup> in 2003. The technique uses riboflavin (vitamin B<sub>2</sub>) and UVA light to form additional covalent bonds between stromal collagen molecules to increase biomechanical stability and halt the progression of the disease.<sup>1,3</sup> Con-

ventional CXL, or the “Dresden protocol,” requires epithelial debridement to allow stromal penetration of the riboflavin.<sup>4</sup> Unfortunately, epithelial debridement causes significant pain during the first postoperative days and poses a risk for epithelial healing problems<sup>5–7</sup> and infection.<sup>8</sup> Although there are limited studies of transepithelial techniques showing substantial efficacy,<sup>9,10</sup> transepithelial CXL, which uses various penetrating agents to increase corneal epithelial permeability to riboflavin was developed to circumvent the postoperative discomfort and infection risk caused by epithelium-off CXL.<sup>11</sup>

Although widely practiced today, both transepithelial and epithelium-off methods of CXL have several drawbacks. Most current CXL procedures require an uncomfortable eyelid speculum and extended patient immobility to avoid motion-induced UVA light targeting and dosing errors. A simple, comfortable device that could be worn on the eye instead of being held at a distance throughout the duration of the treatment may provide simultaneous, bilateral CXL capability. The purpose of this pilot study was to evaluate the feasibility of a novel CXL contact lens device for the treatment of keratoconus over a 6-month follow-up period.

## Methods

This pilot study of a novel CXL device was designed to assess full trial feasibility and to gather preliminary data. It was not intended to be a trial evaluating efficacy of the device. Because CXL is already an accepted treatment for keratoconus, the study did not have a true sham control group.

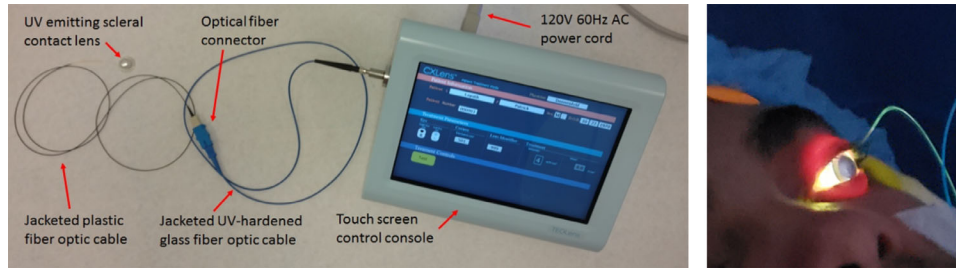
This prospective, nonmasked, nonrandomized pilot study was performed at the Cornea and Refractive Surgery Laser Center, Santo Domingo, Dominican Republic. Ethical approval was granted by the Comité de Ética de la Investigación, Hospital General Plaza de la Salud, Santo Domingo, Dominican Republic. All procedures complied with the Declaration of Helsinki and local laws pertaining to research on human subjects. Study approval was obtained by the Consejo Nacional de Bioética en Salud (CONABIOS). Informed consent for the procedure and subsequent examination was obtained from all patients. This pilot study enrolled a total of 10 patients. Initially, two patients were treated and evaluated at 1 day, 1 week, and 1 month after treatment to assess any acute safety issues. After clearing this patient safety assessment, the remaining eight patients were enrolled and treated. One patient was later lost to follow-up owing to an international move.

Inclusion criteria included patients with an age of 18 years or older, a study eye with a diagnosis of keratoconus that was an imminent candidate for corneal transplantation, a corneal cone centered within the calibrated UV beam pattern of the treatment device, and a minimum required time without the use of contact lenses (no studied eyes wore contact lenses). All patients were selected by a single surgeon. Eyes that were found suitable for CXL with the CXLens qualified for either anterior lamellar, penetrating keratoplasty, or intrastromal ring segments with or without CXL based on topographic or tomographic evidence

of advanced keratoconus, which was a maximum keratometry ( $K_{\max}$ ) of greater than 57 diopters (D) (one patient had a  $K_{\max}$  below this threshold at 55.9 D), often with a thinnest corneal thickness (TCT) of less than 450  $\mu\text{m}$ . Exclusion criteria consisted of patients with a corneal ultrasound pachymetry of less than 375  $\mu\text{m}$ , a history of corneal surgery such as intracorneal ring segments, chemical injury, or previously documented delayed epithelial healing; corneal scarring or opacities in the CXL treatment zone; pregnant or lactating patients or patients who planned to become pregnant; a known sensitivity to study medications; conditions that would prevent cooperation during the procedure or testing (nystagmus or inability to maintain steady gaze); or the presence or history of any other condition that in the opinion of the investigator would confound the outcome of the study.

Calibration of the treatment lens was performed to ensure beam uniformity and proper incident intensity (4  $\text{mW}/\text{cm}^2$  in central cornea) on the cornea. The beam pattern was assessed with a WinCamD Tapercam beam profiling camera (DataRay, Redding, CA) fitted with a fiber optic coherent imaging bundle (Schott, Elmsford, NY) custom ground to 12.0 mm in diameter with an 8.0 mm radius of curvature to simulate the cornea (Pioneer Precision Optics, Florence, MA). The UV-emitting aperture of the treatment lens was positioned appropriately above the simulated cornea to capture the beam pattern on the Tapercam as it would fall on the cornea. The UV emission from the TECLens treatment lens is approximately Lambertian,<sup>12</sup> meaning no correction for the difference in reflection coefficient from air to glass (as opposed to from air to cornea) was needed, as would be necessary with a collimated beam, to ensure that the measured relative intensity map accurately depicted the light intensity pattern transmitted into the cornea. However, because the curved image bundle propagates the incident light down onto a flat charged coupled device array in the Tapercam, a geometric adjustment to the relative intensity as a function of distance from the optical axis was necessary to create an accurate relative intensity map on the corneal surface.

To calibrate each treatment lens to deliver the required 4  $\text{mW}/\text{cm}^2$  to the central region of the cornea, the percent of the total power in the beam above the 80% intensity contour on the surface intensity map was calculated ( $47.1 \pm 1.9\%$ ), along with the diameter of this region ( $5.6 \pm 0.13$  mm). The total output power from each lens was measured with an S120VC photodiode power sensor coupled to a PM200 power meter (Thorlabs, Newton, NJ), and the source optical power from the internal 375 nm laser in the TECLens system was adjusted to provide the total power needed



**Figure 1.** The TECLens 'CXLens' corneal collagen CXL system (left) and the UVA light-emitting contact lens delivering treatment to a patient (right).

for the surface intensity to average  $4.0 \text{ mW/cm}^2$  in the central region (all treated cones were centered at least 1.0 mm inside the periphery of the central region of the beam of the selected treatment lens). The calibrations were stored electronically in the system, recallable by the unique number assigned to each device.

To perform the CXL procedure, and in a manner similar to a previously published epithelium-off study<sup>13</sup> a scleral contact lens reservoir containing riboflavin (vitamin B<sub>2</sub>) 0.25%, 1.2% hydroxypropyl methylcellulose, benzalkonium chloride 0.007% (Peschke TE, Peschke Meditrade GmbH, Huenenberg, Switzerland) was placed on the eye for 30 minutes. Owing to concerns of benzalkonium chloride toxicity to the corneal epithelium, the first patient was examined after 20 minutes of riboflavin installation. Slit-lamp examination showed an intact epithelium and stromal riboflavin penetration, but no yellow flare in the anterior chamber. The riboflavin-filled scleral contact lens was reapplied for 10 minutes and then the patient was reexamined to find an intact epithelium with a yellow flare in the anterior chamber. All other patients received a slit-lamp examination after the 30-minute riboflavin soak to confirm presence of a yellow flare in the anterior chamber. After the riboflavin soak, the reservoir lens was removed, corneal saturation was confirmed with slit-lamp examination, and a drop of proparacaine 0.5% (ANESTEARS, Lansier, Lima, Peru) was placed on the eye. A single drop of balanced salt solution (Alcon Laboratories, Inc., Fort Worth, TX) was placed on the scleral haptic surface of the treatment lens to ensure 100% humidity under the lens throughout the 30-minute irradiation. The CXLens UVA light-emitting contact lens device (TECLens LLC, Stamford, CT) shown in Figure 1 was installed on the eye. The 375-nm UVA light at  $4 \text{ mW/cm}^2$  intensity was delivered for 30 minutes for a total dose of  $7.2 \text{ J/cm}^2$  to the central region of cornea containing the cone. After placement of the device, patients were allowed to close their eyelids if they

desired and find a comfortable position for the remainder of the procedure. Riboflavin was not reapplied during the procedure. About halfway through the 30-minute treatment period, an additional drop of proparacaine was applied over the lens. The post-CXL medication regimen consisted of prednisolone acetate 1% (Pred Forte, Allergan, Bucks, UK), topical moxifloxacin 0.5% (VIGAMOX, Alcon Laboratories, Inc.), and topical lubricating drops (Systane Ultra, Alcon Laboratories Inc.). All medications were given every 2 hours on day 0, every 4 hours on day 1, and then tapered over 4 weeks.

Patients were evaluated at screening, 0 days (treatment day), 1 day, 1 week, and 1, 3, and 6 months after treatment. Corneal tomography measured by the Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany), manifest refraction, optical coherence tomography, endothelial cell density (ECD), and measurements of distance visual acuity (uncorrected distance visual acuity [UCDVA] and best-corrected distance visual acuity [BCDVA]), and intraocular pressure were obtained at baseline and at appropriate times after treatment. Corneal pachymetry measurements were obtained on each patient before and after treatment. The untreated contralateral eyes were also assessed in patients with no prior keratoconus-related interventions (e.g., corneal transplantation) or ocular conditions that would prevent accurate comparisons. Safety monitoring throughout the study included observations for subjective complaints, complications, adverse events, clinically significant findings on ophthalmic examination, dilated fundus examination, and slit-lamp examination.

Although this study was not intended to formally evaluate the treatment effect owing to its small sample size and pilot nature, statistical analysis using a one-sided paired Student *t*-test was used to examine screening versus 6-month differences in  $K_{\text{max}}$ , TCT, and ECD in treated eyes. A two-sided paired Student *t*-test was used to examine

screening versus 6-month differences in UCDVA and BCDVA in treated eyes. In a subset analysis, the sign test and a linear mixed effect model were used to evaluate  $K_{max}$ , UCDVA, and ECD between the treated and contralateral untreated eyes without previous surgical intervention ( $n = 4$ ).

## Results

A total of 9 of the 10 patients completed the 6-month follow-up period after receiving CXL treatment and were included in the final analysis (one patient was lost to follow-up after moving to another country). Of all the contralateral eyes, four eyes were keratoconic with no prior surgical treatments and were compared with the corresponding treated eye in a subset analysis.

The 10 patients who started the study were enrolled over a period of 5 months at a single refractive surgery center. All patients underwent CXL treatment delivered as per protocol by a single corneal surgeon. With the exception of one patient who moved to Spain and who was unable to return to the Dominican Republic owing to the global 2019 novel coronavirus pandemic, all patients returned to all screening and follow-up appointments.

The mean  $\pm$  standard deviation baseline  $K_{max}$  of treated eyes was  $61.8 \pm 5.1$  D (range, 55.9–71.6 D) and mean baseline of the contralateral untreated eyes was  $55.8 \pm 8.8$  D (range, 47.3–67.8 D). Figure 2 illustrates the mean change from baseline in  $K_{max}$  over the 6-month post-CXL observation period. At 6 months after CXL, the mean change from baseline in treated eyes was  $-1.0 \pm 1.6$  D ( $P = 0.049$ ). In a subset analysis, when the mean change from baseline of  $K_{max}$  of the

four treated eyes was compared with the mean change from baseline in the corresponding untreated contralateral eyes, the treated eyes had a nonsignificant relative decrease in the  $K_{max}$  of  $-1.9 \pm 1.7$  D at 6 months after CXL ( $P = 0.36$ ).

Figure 3 shows changes in the mean UCDVA. On average, treated eyes improved from  $19.8 \pm 12.2$  letters at screening to  $23.9 \pm 9.7$  letters at 6 months after CXL (mean difference =  $4.1 \pm 4.4$  letters;  $P = 0.02$ ). In the subset analysis of treated eyes (mean letter gain of  $3.5 \pm 3.7$  letters) subtracted from the corresponding contralateral unoperated eyes (mean letter gain of  $0.25 \pm 3.4$  letters), there was a nonsignificant mean letter gain of  $3.3 \pm 2.6$  letters ( $P = 0.68$ ). Figure 4 shows changes in mean BCDVA. On average, treated eyes nonsignificantly improved from  $35.7 \pm 10.4$  letters at screening to  $38.0 \pm 8.3$  letters at 6 months after CXL (mean difference =  $2.3 \pm 4.4$  letters;  $P = 0.19$ ). In the subset analysis of treated eyes (mean letter gain of  $1.5 \pm 8.7$  letters) compared with corresponding contralateral untreated eyes (mean letter change of  $-6.3 \pm 5.7$  letters), there was a nonsignificant mean letter gain of  $7.6 \pm 5.12$  letters ( $P = 0.41$ ). As shown in Figure 5, the mean TCT in treated eyes decreased from  $445 \pm 33.2$   $\mu\text{m}$  to  $429 \mu\text{m} \pm 42.4$  (mean difference =  $-17 \pm 14$   $\mu\text{m}$ ;  $P < 0.01$ ). The subset of contralateral untreated eyes had a nonsignificant mean decrease of  $-15 \pm 5.0$   $\mu\text{m}$  ( $P = 0.30$ ) at 6 months. At the end of the follow-up period, nearly all patients showed signs of TCT stabilization through trends toward a decreased thinning rate or even toward an increased TCT.

The mean ECD counts nonsignificantly decreased from  $2400 \pm 366$  cells/ $\text{mm}^2$  to  $2314 \pm 579$  cells/ $\text{mm}^2$  (mean difference =  $-86 \pm 266$  cells/ $\text{mm}^2$ ;  $P = 0.20$ ). ECD counts for patient 7 were excluded owing to

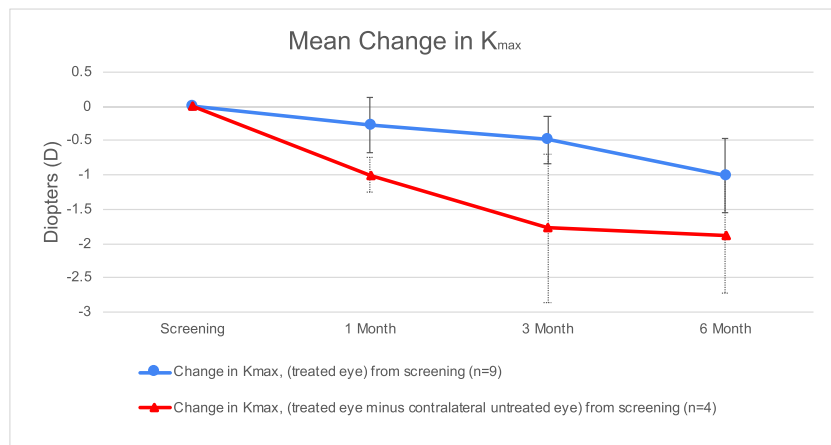
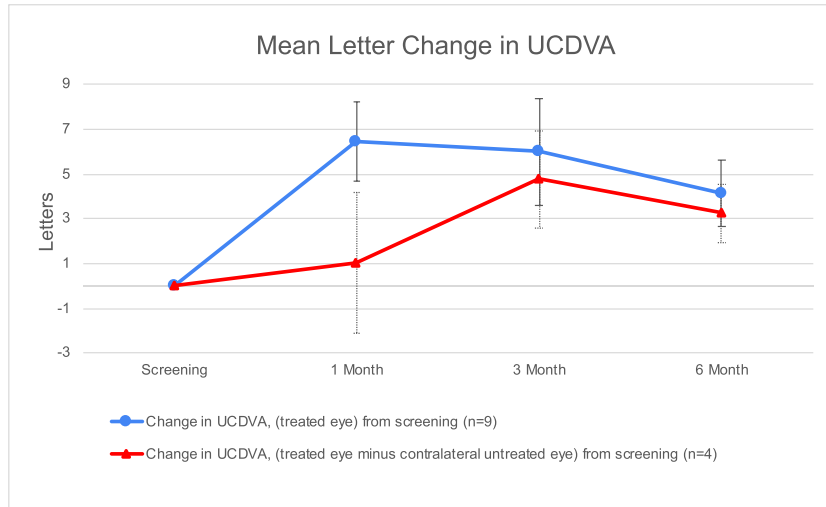
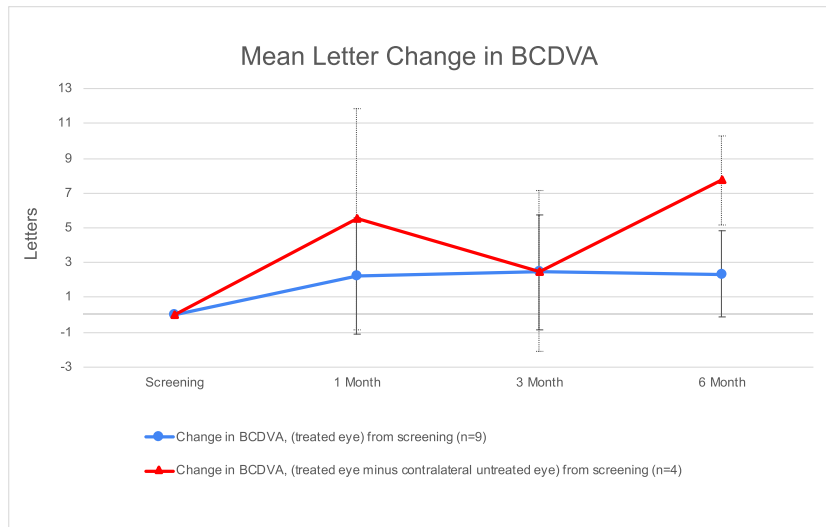


Figure 2. Mean change in  $K_{max}$  from screening to 6 months post-CXL treatment. Blue circles represent change in  $K_{max}$  from screening in all treated eyes ( $n = 9$ ) and red triangles represent change in  $K_{max}$  from screening in treated eyes minus contralateral untreated eyes ( $n = 4$ ). Error bars represent the standard error.





**Figure 3.** Mean letter change in UCDVA from screening to 6 months post-CXL treatment. Blue data points represent change in UCDVA from screening in all treated eyes ( $n = 9$ ) and red data points represent change in UCDVA from screening in treated eyes minus contralateral untreated eyes ( $n = 4$ ). Error bars represent the standard error.



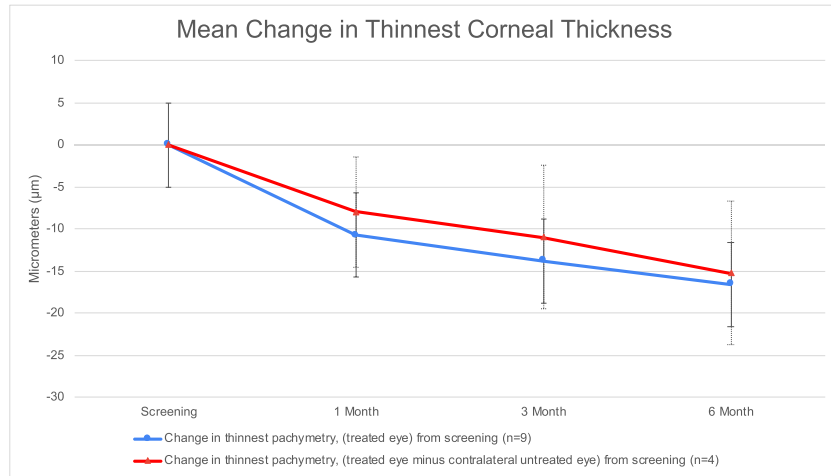
**Figure 4.** Mean letter change in BCDVA from screening to 6 months post-CXL treatment. Blue data points represent change in BCDVA from screening in all treated eyes ( $n = 9$ ) and red data points represent change in BCDVA from screening in treated eyes minus contralateral untreated eyes ( $n = 4$ ). Error bars represent the standard error.

operator error when taking the measurements. Despite this, the patient who was excluded and all others did not demonstrate any clinical evidence of corneal decompensation throughout the study follow-up period.

Pain associated with epithelial erosions and/or abrasions likely associated with exposure to the benzalkonium chloride was mild and resolved within 24 to 48 hours. Two eyes developed late-onset paracentral midstromal haze of less than 1 mm in width at

the 6-month follow-up visit, both of which resolved completely on tapered topical steroid therapy. These two eyes had no significant decrease in visual acuity as compared with baseline. The lens, retina, and intraocular pressure remained within normal limits after the procedure in all eyes.

At 1-month after CXL, clear demarcation lines were observed in all patients. The average demarcation line depth was  $322 \pm 47.0 \mu\text{m}$ . Figure 6 shows the demarcation line seen in patient 10 at 1-month after CXL.



**Figure 5.** The mean change in TCT. Blue circles represent change in TCT from screening in all treated eyes and red triangles represent change in TCT from screening in treated eyes minus contralateral untreated eyes. Error bars represent the standard error.



**Figure 6.** The demarcation line (blue arrows) seen in patient 10 at the 1 month post-CXL visit.

## Discussion

Invasive and uncomfortable epithelium-off CXL treatment is currently the gold standard procedure to halt the progression of keratoconus.<sup>14</sup> The most commonly practiced Dresden protocol requires painful epithelial debridement and is performed unilaterally with external eyelid retraction throughout the procedure, leading to patient discomfort both during and after the treatment, as well as a prolonged visual recovery period.<sup>14</sup> Emerging epithelium-on methods still require eyelid retraction and are performed unilaterally. This prospective, nonmasked, nonrandomized pilot study of nine corneal transplant candidates evaluated the feasibility of a novel, fiber optic-based UVA light-emitting scleral contact lens device that could offer high-throughput, bilateral, transepithelial corneal CXL in a much more patient- and physician-friendly procedure.

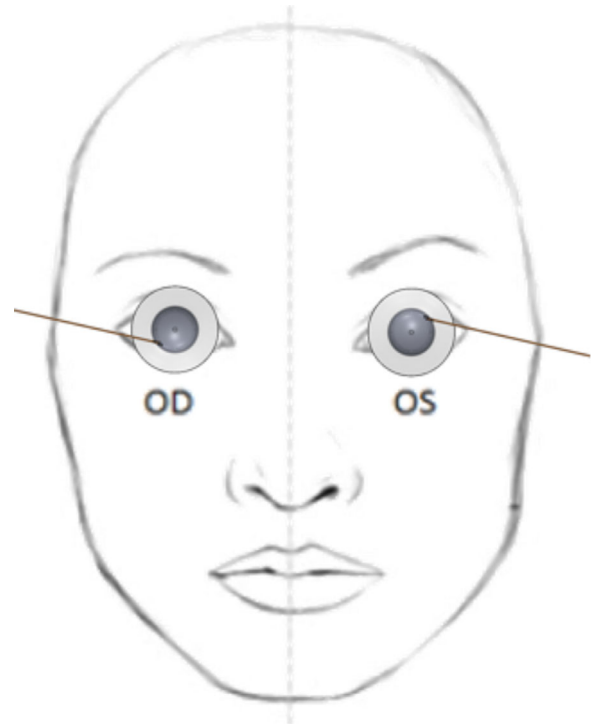
This study was conducted under corporate sponsorship as a first experience with the TECLens CXLens device. As a new approach to CXL, care was taken to minimize any unforeseen risks. The study popula-

tion was chosen to be very advanced keratoconus patients who, in the opinion of the surgical center’s ophthalmologists, were likely headed for surgical intervention. Furthermore, to ensure that there were no acute safety issues, a 30-day hold was built into the protocol after the first two patients were treated. After a safety evaluation by the principal investigator and the medical monitor, the enrollment was opened for the remaining eight patients (in all, 10 patients were scheduled for treatment; 1 patient was lost to follow-up because of an international move after 3 months). Given that this procedure encompassed a new type of CXL including an approach to riboflavin loading that had been reported only once before in the literature,<sup>13</sup> some flexibility was built into the protocol to allow procedural adjustments to be made under the guidance of the investigator. The goals of this pilot study were to develop a more patient- and practice-friendly CXL procedure without jeopardizing safety or efficacy. Although admittedly too few patients were treated to draw conclusions about either safety or efficacy, the study format did allow the logistics of this first-in-human procedure to be worked out in a manner that minimized risk to the patients and provided some evidence that the ‘on-eye’ approach to CXL is worth pursuing, with an “epithelium-on” procedure that could result in a safe and effective treatment for keratoconus.

The current literature suggests that although transepithelial CXL has better outcomes in corrected distance visual acuity and postoperative complications, standard epithelium-off methods may have better outcomes in halting the progression of  $K_{max}$ .<sup>11,15</sup> This finding may be explained partially by insufficient

riboflavin penetration in many epithelium-on protocols. Additionally, an intact 50  $\mu\text{m}$  to 60  $\mu\text{m}$  epithelial layer also absorbs UVA radiation and limits the effective stromal CXL UVA dose.<sup>16,17</sup> Although new methods have been introduced to increase epithelial permeability to riboflavin, the majority of studies comparing transepithelial CXL with standard protocols use the same total UVA dose of 5.4  $\text{J}/\text{cm}^2$ <sup>15</sup> with an applied riboflavin concentration of 0.10% to 0.15%. To account for the CXL-impeding properties of the riboflavin-loaded epithelium and the additional UV absorption from the 0.25% riboflavin used in this study, 4  $\text{mW}/\text{cm}^2$  for 30 minutes to deliver a total dose of 7.2  $\text{J}/\text{cm}^2$  was used. To verify that these settings would result in an endothelial dose below the Wollensak toxicity threshold of 0.65  $\text{J}/\text{cm}^2$ , a Fick diffusion model was created to calculate the riboflavin gradient in the cornea after a 30-minute riboflavin soak. Then, a Lambert–Beer attenuation calculation was performed integrating over that concentration gradient to verify that the (fully photobleached) UVA intensity at the minimum corneal thickness allowed in the study (375  $\mu\text{m}$ ) was below Wollensak’s limit. The cumulative dose was then calculated by summing the UVA intensity over the 30 minutes. Dynamic attenuation of the UVA as a result of photobleaching was included in the simulation based on previous in vitro experimental work using 375 nm light at 4  $\text{mW}/\text{cm}^2$  incident on 0.25% riboflavin. With these assumptions, the simulation showed an endothelial dose (at 375  $\mu\text{m}$ ) of 0.42  $\text{J}/\text{cm}^2$ . This model abstracts somewhat from the clinical case because the riboflavin gradient must change to some extent during the course of the treatment because the high anterior concentration continues to diffuse posteriorly and some is lost to the anterior chamber. However, given the large margin between the calculated endothelial dose and the Wollensak limit, this expectedly small change in the riboflavin gradient was deemed negligible.

The scleral UV delivery lens is large in diameter (21 mm), which is necessary to carry the optics required to diffuse the UV laser energy from the 250  $\mu\text{m}$  fiber into an approximately 8.5-mm beam. To ensure these large, rigid lenses fit appropriately to track with the patients’ eye and head movements, the lens was made with 0.4 mm of toricity to account for typical scleral astigmatism out at 10.5 mm from the central cornea. Fitting was done during screening using a scleral lens of the same configuration that carries the fiber optics package in the UV delivery lens. As is typical with the PROSE device (BostonSight, Needham, MA), the steep axis of the fitting lens was marked with a dot. The lens was installed and the patient was asked to blink a few times to allow the lens to rotate into a



**Figure 7.** Fiber optic leads exit at lateral canthus on either side.

stable position. The location of the dot in the coronal plane was noted relative to the vertical. In patients that exhibited “with-the-rule” scleral astigmatism, the dots remained close to the vertical axis. In patients with “against-the-rule” astigmatism, the dots oriented horizontally. This determination allowed the selection of a properly toric treatment lens for each patient.

Establishing the correct toricity allowed the fiber optic supplied UV delivery treatment lens to be designed so that the fiber optic exited at the lateral canthus without impeding the eyelid closure regardless of treated eye (left or right). The internal optics design of the lens required the fiber to exit roughly tangential to the eyelid facing surface. This tangential exit position was at a fixed position relative to the vertical axis of that particular eye (against-the-rule or with-the-rule astigmatism). The tangential direction of exit was arbitrarily chosen so that the fiber exited in a clockwise manner from the perspective of the physician, meaning that on the right eye, the fiber exited at approximately the 8:00 o’clock position and extended slightly superiorly, and on the left eye, the fiber exited at approximately the 2:00 o’clock position and extended somewhat inferiorly (Fig. 7).

Because not all scleral astigmatisms are precisely aligned with the ‘with-the-rule/against-the-rule’ paradigm, the fiber exit point was not perfectly consistent for each patient; however, it was observed that the fiber exit point was generally more appropriate

(relative for a lateral canthus exit) on the right eye cases. With a symmetrical UV beam, this difference had no bearing on the therapy. This pilot study helped us to conclude that, because the particular rotational direction of the fiber exit is not critical to the operation of the lens, for a larger trial, a symmetric (nontoric) lens will be used so the fiber exit point can be rotated to the most comfortable position for each patient. To ensure a good fit that prevents relative motion with respect to the cornea, the periphery of the lens will be medical grade silicone to conform to each patients' scleral astigmatism. Additionally, instead of with-the-rule and against-the-rule versions, both clockwise and counter-clockwise fiber exit rotational directions will be fabricated for true right and left versions of the treatment lens.

Riboflavin application in this procedure was achieved with the use of a scleral reservoir lens. The goal of this approach was three-fold: Eliminate the need for an eyelid speculum during riboflavin loading to make the procedure more comfortable for the patient, eliminate the need for a technician to remain with the patient for 30 minutes before UV application, and sustain a fixed concentration of riboflavin in contact with the cornea during the loading.

During the first two treatments, riboflavin loading was done using a corneal shield sponge that rested on the cornea in a manner similar to Stulting et al.,<sup>9</sup> covered with a custom-made fenestrated scleral lens (BostonSight). The sponge was used to minimize riboflavin leakage that was likely to occur without it, because the scleral reservoirs were not individually fit. The scleral lens was applied to eliminate the need for the speculum used in Stulting's study, enabling the patient to close the treated eye during loading, opening the lid only to add a few drops of riboflavin to the sponge through the fenestrations as was needed. However, owing to the steep corneas of these patients, the sponge did not stay in place over the center of the cornea, and attempts to maneuver it into position through the fenestrations were challenging. This approach was abandoned for a full scleral lens in the manner of Soares et al.<sup>13</sup> for the remaining patients, with minor riboflavin leakage in some patients. The leakage highlighted the need to move to a silicone one-size-fits-all reservoir for a larger trial.

Riboflavin was not reapplied after the initial one-time scleral reservoir soak for several reasons. First, as noted by Kamaev et al.<sup>18</sup> and confirmed through several unpublished trials administering a 30-minute UVA dose to riboflavin-containing wells at varying thicknesses, the magnitude of photobleaching is not enough to necessitate reapplication of riboflavin. In these trials, the transmitted light from the 375-nm light

source through the riboflavin samples was measured using a  $375 \pm 36$ -nm bandpass filter (to eliminate the fluorescent light) and a calibrated photodiode and optical power meter (Thorlabs). For an administered dose of  $7.2 \text{ J/cm}^2$  ( $4 \text{ mW/cm}^2$  intensity), riboflavin concentrations between 0.125% and 0.500% photobleached at most 13% within a 50- $\mu\text{m}$  well. Second, because the majority of the photobleaching and CXL occurs in the anterior stroma,<sup>19</sup> where the concentration of riboflavin is greatest, reapplication of riboflavin, which would replenish the anterior stromal riboflavin concentration, would result in decreased UVA penetration to the posterior corneal segments and a shallow depth of CXL.<sup>20</sup> Finally, given the CXLens is a contact lens device, the reapplication of riboflavin could cause the accumulation of a riboflavin film between the corneal epithelium and the device, ultimately blocking the UVA light and decreasing the efficacy of the CXL treatment.<sup>20</sup>

Typical indicators of efficacious CXL include flattened keratometry, visible demarcation line, and decreased pachymetry.<sup>21,22</sup> The US Food and Drug Administration requires a  $-1.0 \text{ D}$  differential between the mean change in  $K_{\text{max}}$  of treated eyes minus the control eyes. Without a true control group, our study approximated this measurement by comparing the four contralateral eyes without prior surgery against the corresponding treated eye. Our results from nine patients who completed the 6-month post-CXL follow-up showed a mean decrease in the  $K_{\text{max}}$  of  $-1.0 \pm 1.6 \text{ D}$  ( $P = 0.049$ ). In the four treated eyes that were compared with the contralateral untreated eye, the nonsignificant differential was  $-1.9 \pm 1.7 \text{ D}$  ( $P = 0.36$ ) because the untreated eyes progressed. The lack of significance found in this subset analysis (as well as the subset analyses for the other outcomes) comparing treated eyes with the corresponding contralateral untreated eyes is likely due to an insufficient in sample size ( $n = 4$ ) in this pilot study. The  $K_{\text{max}}$  findings also correlated with a mean UCDVA change of  $4.1 \pm 4.4$  letters ( $P = 0.02$ ) and a nonsignificant mean BCDVA change of  $2.3 \pm 7.5$  letters ( $P = 0.19$ ) at 6 months after CXL, although these improvements could be due to the patients undergoing repeated visual acuity assessments.<sup>23</sup> These preliminary results, while early, are promising given that optimal corneal healing and remodeling occurs 6 to 12 months after the CXL procedure.<sup>24</sup>

The mean TCT progressively decreased through the 6-month follow-up period ( $P < 0.01$ ). Although the TCT is known to decrease after CXL, some studies show thickness starts to increase after 3 months after CXL and reaches baseline values at 1 year.<sup>25,26</sup> Other studies show that the thickening process takes longer



and that treated corneas may not reach baseline thickness values, even years after treatment.<sup>27,28</sup> In nearly all patients, we saw a plateauing trend evident at month 6, indicating a trend toward stabilization of the TCT. Ultimately, a longer follow-up period would be required to make firm conclusions about the corneal pachymetry and to adequately monitor stabilization in this study. However, the early thinning effects and trends toward stabilization correlated with reductions in  $K_{max}$  and consistently deep demarcation lines are encouraging.

Two eyes developed a late-onset paracentral midstromal haze, a finding that has been reported previously.<sup>29</sup> The haze resolved completely in both eyes without significant impact on the final visual acuity. Although this pilot study did not formally grade perioperative pain, there was one patient who complained of significant pain lasting up to the night after the procedure. All other cases had less pain, and had mostly moderate to diffuse punctate epithelial erosions on the examination the same day of the procedure, which resolved within 24 to 48 hours after the time of treatment. All future studies will adequately grade perioperative pain, because decreased patient pain is a major motivation for implementation of transepithelial CXL. The mean ECD counts had a small, nonsignificant decrease at 6 months after CXL compared with baseline ( $2400 \pm 366$  cells/mm<sup>2</sup> vs  $2314 \pm 579$  cells/mm<sup>2</sup>;  $P = 0.20$ ). This result could be partially explained by the sampling of different areas within a cohort of steep and unstable keratoconic eyes, because some eyes experienced a gain in ECD at 6 months, whereas others experienced a loss. Ultimately, these findings suggest that the CXLens device and corresponding procedure were well-tolerated.

Overall, this pilot study demonstrated the feasibility of the novel CXLens UVA-emitting contact lens device. Although the trends reported from the preliminary data are encouraging, an adequately powered study of greater magnitude is required to make firm conclusions on treatment effect and safety. The CXLens device offers many improvements to current standard protocols of CXL. With a UVA-emitting scleral lens that tracks with the patient's eye and head movements, these lenses can be placed into a patient's eyes after appropriate corneal riboflavin instillation and left untouched for the entire 30-minute procedure. The operator does not need to monitor as closely for proper centering of the UV light with respect to the corneoscleral limbus. Nor does the operator have to regulate the UV light source height to ensure that the light is focused on the corneal surface rather than deeper corneal lamellae or within the eye. This process translates to greatly

increased patient comfort, because the patient can sit upright with their eyes closed throughout the treatment. Such a design also opens the possibility for one operator to simultaneously manage the CXL treatments for multiple patients at one time, further optimizing a corneal surgeon's practice efficiency. Moreover, CXL with the CXLens system can be performed bilaterally, with unique dosing specifications programmed for each eye, resulting in a more efficient treatment for bilateral disease.

In conclusion, our pilot study demonstrated the feasibility of a novel CXL device. Further larger scale studies with a 1-year follow-up are planned to make robust conclusions on treatment effect. Transepithelial CXL with the CXLens device has the potential to increase patient comfort and procedure efficiency compared with standard CXL treatments.

## Acknowledgments

Disclosure: **E.K. Dackowski**, None; **J.B. Logroño**, None; **C. Rivera**, None; **N. Taylor**, TECLens (E); **P.D. Lopath**, TECLens (E); **R.S. Chuck**, TECLens (C)

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