

# Epithelial-disruption collagen crosslinking for keratoconus: One-year results

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**PURPOSE:** To evaluate the efficacy of epithelial-disruption collagen crosslinking (CXL) for progressive keratoconus using a corneal disruptor device and a riboflavin solution designed for a transepithelial technique.

**SETTING:** Magna Graecia University Eye Clinic, Catanzaro, Italy.

**DESIGN:** Prospective comparative case series.

**METHODS:** The most severely affected eye of patients with bilateral progressive keratoconus was treated. The fellow eye served as a control. Follow-up was 12 months. A corneal disruptor device was used to create pockmarks in the epithelium. Riboflavin solution was applied for 30 minutes and irradiation for 30 minutes. Three days postoperatively, patients were asked to assess the level of pain.

**RESULTS:** The study comprised 28 patients (mean age 28 years). The mean postoperative pain score was 4.3, 2.6, and 2.1 at 1 day, 2 days, and 3 days. The mean preoperative uncorrected (UDVA) and corrected (CDVA) distance visual acuities improved from  $0.73 \log\text{MAR} \pm 0.21$  (SD) and  $0.30 \pm 0.11 \log\text{MAR}$  to  $0.48 \pm 0.15 \log\text{MAR}$  and  $0.25 \pm 0.1 \log\text{MAR}$ , respectively, at 12 months ( $P=.02$ ). The mean spherical equivalent refraction decreased 0.96 diopter (D). The mean baseline apical keratometry, apical gradient curvature, average pupillary power, inferior–superior index, and cone area were 59.21 D, 8.91 D, 47.9 D, 11.49 mm<sup>2</sup>, and 10.32 mm<sup>2</sup>, respectively. At 12 months, these values were 56.18 D, 7.32 D, 41.34 D, 9.65 mm<sup>2</sup>, and 7.75 mm<sup>2</sup>, respectively. No adverse effects were observed.

**CONCLUSIONS:** Corneal epithelial-disruption CXL was safe and effective in medium-term stabilization of keratoconus with an improvement in topographic and refractive parameters and less patient discomfort.

**Financial Disclosure:** No author has a financial or proprietary interest in any material or method mentioned.

*J Cataract Refract Surg* 2013; 39:1171–1178 © 2013 ASCRS and ESCRS

 Online Video

Corneal collagen crosslinking (CXL) is a therapeutic technique that requires stromal absorption of riboflavin followed by irradiation with ultraviolet-A (UVA) light.<sup>1–3</sup> The goal of the treatment is to increase the mechanical strength of the cornea by up to 300%,<sup>4</sup> halting the progression of keratoconus and corneal ectasia from laser refractive surgery.<sup>5–9</sup> In the classic technique, CXL is performed after complete removal of the corneal epithelium (epithelium-off [epi-off] technique). This procedure allows better penetration of riboflavin; however, it often results in severe pain and poor vision for 5 to 7 days after the procedure. Other complications, such as stromal haze,<sup>10</sup> can persist for

months and compromise visual acuity. Topographic and aberrometric indices normally start to improve 6 to 12 months after treatment.<sup>11,12</sup>

The epithelium-on (epi-on) transepithelial CXL technique was developed to reduce postoperative pain and discomfort as well as to restore vision more rapidly. To help penetration of riboflavin while leaving the corneal epithelium intact, 2 enhancers (trometamol and ethylenediaminetetraacetic acid [EDTA] sodium) were added to the riboflavin solution. These agents enhance the penetration of riboflavin through intact epithelium by temporarily impairing the tight junctions between corneal epithelial cells. This technique has

been shown to be safe and effective.<sup>13</sup> Corneal ocular coherence tomography (OCT) in patients having treatment with the modified riboflavin found a hyperreflective line between 90  $\mu\text{m}$  and 110  $\mu\text{m}$  posterior to the epithelium, showing involvement of the upper third of corneal stroma.

In this study, we evaluated the refractive, topographic, tomographic, and aberrometric outcomes 12 months after a modified transepithelial technique combining the use of the transepithelial riboflavin solution with epithelial disruption to further enhance stromal penetration of riboflavin. The technique involves pockmarking and disrupting the corneal epithelium using a disruptive device. The aim of the study was to prospectively evaluate the efficacy of epithelial-disruption CXL.

## PATIENTS AND METHODS

This prospective nonrandomized single-center study comprised consecutive patients with bilateral keratoconus who were enrolled at the Cornea Service of the Ophthalmology Department of Magna Graecia University, Catanzaro, Italy, from March to September 2010. The study was reviewed and approved by the department's ethical committee and performed in accordance with the ethical standards described in the 2000 revision of the 1964 Declaration of Helsinki. All patients signed an informed consent form.

Inclusion criteria were documented progression of keratoconus in both eyes by changes in serial topography and optical pachymetric maps<sup>14,15</sup> and a minimum corneal thickness of 400  $\mu\text{m}$  or more.<sup>16,17</sup> Progression was defined as fulfilling 1 or more of the following criteria: (1) an increase in central corneal astigmatism of 1.00 diopter (D) or more, (2) an increase in mean central keratometry of 1.50 D or more, and (3) a reduction in tomographic central corneal thickness (CCT) of 2% or more at 2 consecutive evaluations. Exclusion criteria were severe dry eye, pregnancy, anterior and posterior segment pathology, corneal scarring, and previous corneal surgery.

Patients were counseled about the investigational nature of the procedure and had a complete ophthalmic examination preoperatively and 1, 3, 6, and 12 months postoperatively. Evaluation included a basal Schirmer test, slitlamp biomicroscopy of the anterior segment, fundus examination,

and applanation tonometry (Goldmann). The uncorrected (UDVA) and corrected (CDVA) distance visual acuities were measured using the logMAR Early Treatment Diabetic Retinopathy chart at 4 m after noncycloplegic refraction, as suggested by Bailey and Love<sup>18</sup> and described by Ferris et al.<sup>19</sup> Corneal topography was performed under photopic conditions with a Placido-disk topographer (Eyedrop, Costruzione Strumenti Oftalmici) that analyzes 6144 points spread over a 9.5 mm<sup>2</sup> corneal surface area. The sensitivity of the technique for keratoconus detection is 98.5%, and the repeatability is  $\pm 0.03$  mm for axial and instantaneous maps and  $\pm 0.5$  mm for elevation maps.<sup>20</sup> Corneal higher-order aberrations (HOAs) for a 5.0 mm pupil were measured with the topographer's corneal aberrometry program. Pachymetric maps were obtained by Fourier-domain anterior segment OCT (RTVue, Optovue, Inc.) using a wide-angle corneal adaptor module that provides a scan width of 6.0 mm and a transverse resolution of 15.0  $\mu\text{m}$ . Each eye was scanned 3 times. A pupil-centered scan was taken using real-time video imagery of the eye and a circular overlay. The pachymetry scan pattern used to map the cornea consists of 8 high-definition meridional scans (1024 axial scans per meridian). A 6.0 mm diameter pachymetry map is then constructed by interpolating the thickness profiles in the 8 meridians. The map is divided into zones by octants and annular rings (2.0 mm, 5.0 mm, and 6.0 mm). The mean pachymetry in each zone is shown in the sector map. The CCT and thinnest corneal thickness are automatically detected and shown in a summary table.<sup>21</sup>

One month postoperatively, a high-resolution horizontal corneal OCT scan was taken to identify the stromal demarcation line. All patients were asked to look at the optical target in the system, and the demarcation line depth was measured using the flap tool provided by the instrument's software. The depth of the demarcation line was measured centrally and 2.0 mm nasally and temporally.

Endothelial cell counts (ECCs) (Cell Check Specular Microscope, Konan Medical, Inc.) were performed; 50 contiguous cells were counted manually as described by Prinz et al.<sup>22</sup>

## Surgical Technique

All procedures were performed by the same surgeon (M.R.). The worst eye, judged to be the one with the highest average keratometry (K) value (simulated average K), was treated. The riboflavin (Ricrolin TE, Sooft Italia SpA) used was a transepithelial preparation; this hypotonic ophthalmic solution contains riboflavin 0.1% and the enhancers trometamol (tris-hydroxymethyl aminomethane) and sodium EDTA to improve epithelial penetration. Ultraviolet-A irradiation was applied using the CBM Vega X-Linker device (Costruzione Strumenti Oftalmici). Preoperatively, the irradiance was checked using a UVA meter to ensure a fluence within the range of 2.9 to 3.1 mW/cm<sup>2</sup>. The irradiance spot diameter was set at 8.0 mm.

Two days before the epithelial-disruption CXL procedure, patients were treated with netilmycin (Nettacin monodose) single-dose eyedrops, 2 drops 3 times a day. Thirty minutes before the procedure, single-dose oxybuprocaine hydrochloride 0.4% drops were administered every 5 minutes. Pilocarpine 2.0% was instilled twice at 10-minute intervals to promote miosis and reduce UVA exposure to the lens and retina. The eye was draped with a sterile dressing and a lid speculum applied. The cornea was rinsed with a sterile physiologic balanced salt solution. Repeated epithelial puncturing was performed using a corneal disruptor (Daya,

Submitted: December 17, 2012.

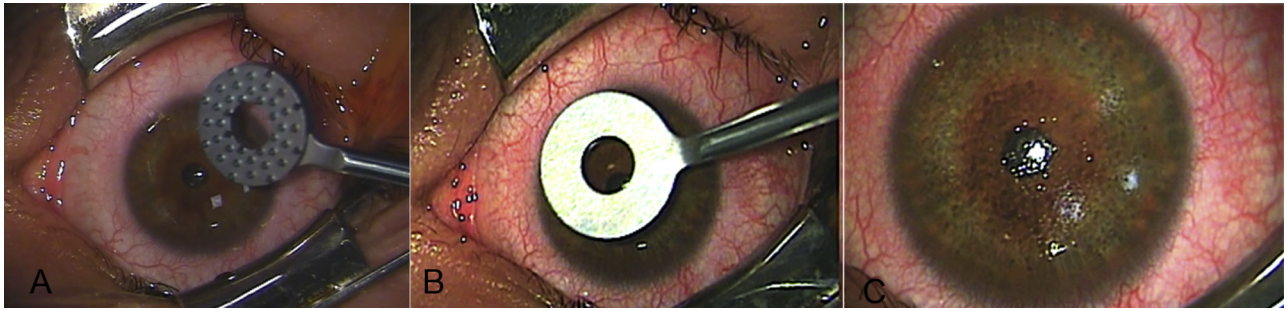
Final revision submitted: May 7, 2013.

Accepted: May 8, 2013.

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Presented in part as a poster at 8th International Crosslinking Congress, Geneva, Switzerland, December 2012, and at the 92nd Congress of the Italian Society of Ophthalmology, Rome, Italy, November 2012.

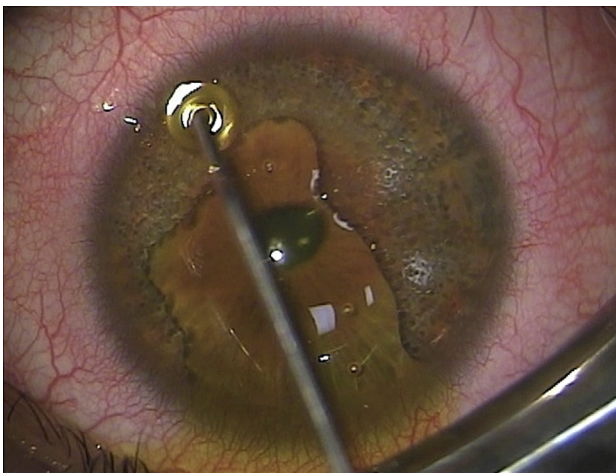
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**Figure 1.** A: Treatment side of disruptor device. B: Use of the corneal epithelial disruptor. C: Corneal surface after disruption before application of riboflavin.

Duckworth & Kent, Ltd.). **Figure 1** and the [video](http://jcrsjournal.org) (available at <http://jcrsjournal.org>) show the device and technique as well as the desired effect of disruption on the cornea. The disruptor device is titanium and has 40 fine, sharp points radially spaced on a 9.0 mm base with a central opening. It is attached at 45 degrees to a round handle with a length of 125 mm. The fine sharp points are sharp enough to penetrate through the corneal epithelium without damage to Bowman layer. The device is used to disrupt the epithelium by multiple contact with the sharp points, creating numerous perforations. Disruption is satisfactory when the whole epithelium from limbus to limbus is evenly disrupted with narrowly spaced perforations (**Figure 1**).

The primary goal is to maintain as much live epithelium as possible with enough epithelial perforations to promote riboflavin penetration. A ring-shaped silicone container designed by Filippello et al.<sup>13</sup> was placed on the cornea for 30 minutes and filled repeatedly with riboflavin to ensure a constant, homogeneous layer of enhanced riboflavin above the epithelium. This corneal ring improves penetration and reduces dispersion of the solution. The epithelial-disrupted cornea visibly retained riboflavin on its surface as a result of increased surface tension (microvilli-like action) (**Figure 2**). After this imbibition phase, the corneal ring was removed and the patient was instructed to follow the pulsating green reference light on the CXL device. Then, UVA irradiation to the central 8.0 mm of the cornea was applied for 30 minutes



**Figure 2.** Riboflavin drops applied on the disrupted cornea. Note the tendency of the drops to remain attached to the corneal surface as a result of increased surface tension of the disrupted irregular epithelium.

divided into 6 steps of 5 minutes each. Riboflavin drops were regularly administered (2 drops every 5 minutes) during the process by the surgeon to maintain a homogeneous riboflavin layer over the epithelium. Centration of treatment was continuously checked to ensure good corneal exposure and avoidance of limbal irradiation. At the end of the procedure, the eye was rinsed with a balanced salt solution and a soft bandage contact lens was applied to promote reepithelialization and improve patient comfort. At the end of the procedure, patients received cyclopentolate (Ciclolux) and netilmicin drops.

Postoperative medications included topical netilmicin 4 times daily for 7 days, sodium hyaluronate 0.15% with amino acid drops (Aminoftal) 5 times daily for 45 days, and dexamethasone 21-phosphate 0.15% drops (Etacortilen) twice daily for 5 days after contact lens removal. Oral therapy included oral amino acid supplements (Aminoftal cps), 3 capsules daily for 15 days.<sup>23</sup> Postoperatively, patients were seen after 3 days for contact lens removal. At this first visit, patients were asked to rate their perceived pain 1, 2, and 3 days postoperatively in each eye using an 11-point verbal numerical rating scale of 0 to 10 (0 = no pain; 10 = the most excruciating pain imaginable).

### Statistical Analysis

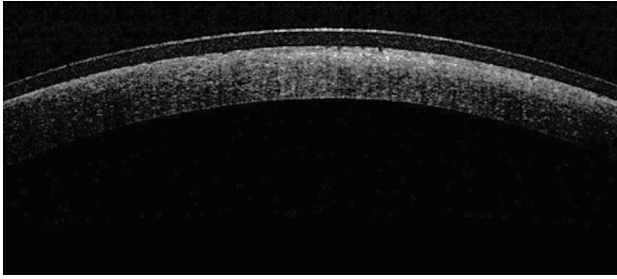
Statistical analysis was performed using Statistica software (version 8, Statsoft, Inc.). The Mann-Whitney *U* test was used for nonparametric data (UDVA, CDVA) and the paired *t* test for parametric data (refraction, mean curvature power, central CCT, macular thickness). The paired 2-tailed Student *t* test was used to verify the level of statistical significance. A *P* value less than .05 was considered significant. All results are reported as the mean  $\pm$  SD.

### RESULTS

The study comprised 28 eyes (16 right, 12 left) of 28 consecutive patients (12 men, 16 women) with a mean age of 28.8 years (range 18 to 41 years). All 28 patients completed the 12-month follow-up.

The treatment was well tolerated by patients. Three days postoperatively, the mean pain score was  $2.42 \pm 0.9$ . **Figure 3** shows the corneal OCT section at the end of the epithelial-disruption CXL treatment under a contact lens. The epithelial pockmarks were not visible on fluorescein staining 3 days postoperatively. Twenty patients (71%) reported a foreign-body



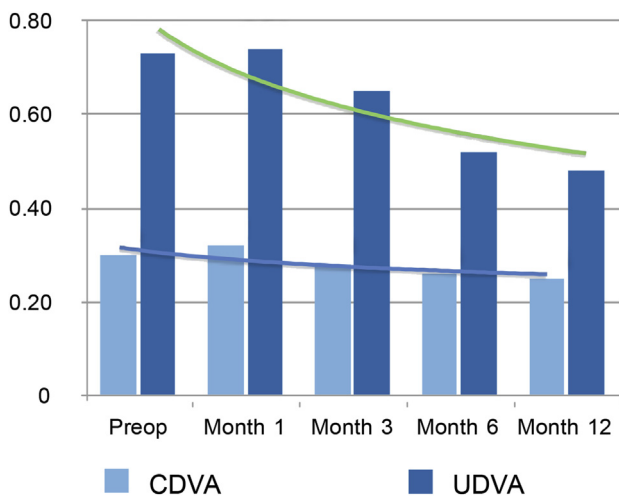


**Figure 3.** Corneal OCT immediately postoperatively. Discrete epithelial fissures demonstrating epithelial disruption are seen over an area of anterior stromal hyperreflectivity.

sensation, and 12 patients (43%) reported photophobia; in all cases, the symptoms resolved 2 days postoperatively. There were no instances of delayed reepithelialization or endothelial damage, and no adverse events were reported.

### Visual Acuity

Figure 4 shows the UDVA and CDVA data. The mean preoperative UDVA was  $0.73 \pm 0.21$  logMAR. Postoperatively, the mean UDVA was  $0.74 \pm 19$  logMAR at 1 month,  $0.65 \pm 0.2$  logMAR at 3 months,  $0.52 \pm 0.19$  logMAR at 6 months, and  $0.48 \pm 0.15$  logMAR at 1 year. The mean preoperative CDVA was  $0.30 \pm 0.1$  logMAR. Postoperatively, the mean UDVA was  $0.30 \pm 0.15$  logMAR at 1 month,  $0.28 \pm 0.11$  logMAR at 3 months,  $0.26 \pm 0.11$  logMAR at 6 months, and  $0.25 \pm 0.1$  logMAR at 1 year. There was a statistically significant improvement in UDVA and CDVA by 3 months and 6 months postoperatively ( $P < .05$ ). Visual improvement continued throughout the 12-month follow-up. The untreated fellow control eyes showed progressive worsening of UDVA and CDVA during the same follow-up period.



**Figure 4.** Visual acuity trend over time (CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity).

### Topography and Corneal Wavefront Analysis

Table 1 shows the visual acuity, topography, aberrometry, and pachymetry data over the 12-month follow-up. There was a significant difference in the mean preoperative 3.0 mm average simulated keratometry (K), steepest simulated K, and simulated corneal cylinder ( $P < .05$ ), but not in the flattest simulated K, between preoperatively and 12 months postoperatively. Improvements in all keratoconus indices (apical K, apical gradient curvature, average pupillary power, keratoconus symmetry index, cone area) were significant at 6 months. The improvement continued, and at the 12-month follow-up, treated eyes showed further flattening (Figure 5). In treated eyes, the root mean square (RMS), coma, and spherical aberration improved. This was statistically significant at 6 months for RMS and at 3 months for coma and spherical aberration, with continuing improvement up to 12 months. In contrast, the keratoconus indices and HOAs in control eyes worsened over the 12-month follow-up.

### Stromal Demarcation Line

Corneal OCT 1 month after treatment showed a dense linear zone of hyperreflectivity in the corneal stroma that was not present before treatment in 27 of 28 eyes (96.4%). The mean stromal demarcation line depth measured at the central, nasal, and temporal locations was  $250.41 \pm 21.89$   $\mu$ m,  $249.48 \pm 23.06$   $\mu$ m, and  $251.74 \pm 23.17$   $\mu$ m, respectively. Demarcation lines were still partially visible at 3 months in 2 eyes (7.14%); the lines were not visible at 6 months.

### Corneal Thickness

Preoperatively, the mean CCT was  $444 \pm 28$   $\mu$ m and the mean corneal thickness at the thinnest location was  $415 \pm 30$   $\mu$ m. In control eyes, the mean CCT was  $442.38 \pm 27.5$   $\mu$ m and the mean thinnest point of the cornea was  $418 \pm 29$   $\mu$ m. At 12 months, the treated eyes had a mean CCT of  $432.88 \pm 28$   $\mu$ m and a mean thinnest point of the cornea of  $407 \pm 26$   $\mu$ m. In control eyes, the mean CCT was  $430.77 \pm 27.49$   $\mu$ m and the mean thinnest point of the cornea was  $406 \pm 31$   $\mu$ m. A reduction in corneal thickness occurred in both groups in the first 3 months. This was followed by a trend toward stabilization of pachymetry in treated eyes compared with control eyes, which was statistically significant after 6 months.

### Endothelial Cell Count

Table 1 also shows the mean ECC over time. There was no statistically significant difference between treated eyes and control eyes at any time.

**Table 1.** Mean visual acuity, topography, aberrometry, pachymetry, and ECC over time.

Parameter	CXL-Treated Eyes					Untreated Control Eyes				
	Preop	Postop				Preop	Postop			
		1 Mo	3 Mo	6 Mo	12 Mo		1 Mo	3 Mo	6 Mo	12 Mo
CDVA (logMAR)	0.30	0.32	0.28 <sup>†</sup>	0.26 <sup>†</sup>	0.25 <sup>†</sup>	0.29	0.30	0.33	0.31	0.37
UDVA (logMAR)	0.73	0.74	0.65	0.52 <sup>†</sup>	0.48 <sup>†</sup>	0.75	0.75	0.78	0.80	0.85
SimK avg (D)	48.88	48.95	48.64 <sup>†</sup>	48.60 <sup>†</sup>	48.49 <sup>†</sup>	48.79	49.00	49.23	49.57	49.77
SimKs (D)	51.39	51.44	50.94	50.70	50.50 <sup>†</sup>	51.29	51.55	51.83	52.19	52.43
Sim Kf (D)	46.37	46.46	46.34	46.49	46.48	46.30	46.46	46.50	46.96	47.11
AK (D)	59.21	59.32	57.94	56.22	56.18	59.11	59.56	60.12	60.34	60.52
AGC (D)	8.91	9.12	7.94 <sup>†</sup>	7.75 <sup>†</sup>	7.32 <sup>†</sup>	8.99	9.06	9.25	9.32	9.44
Avg PP (D)	47.90	48.23	45.90 <sup>†</sup>	43.54 <sup>†</sup>	41.34 <sup>†</sup>	47.82	47.90	49.20	49.80	50.20
Kc SI	11.49	11.22	10.85 <sup>†</sup>	9.92 <sup>†</sup>	9.65 <sup>†</sup>	11.43	11.53	11.82	11.85	11.92
Kc area (mm <sup>2</sup> )	10.32	10.42	9.40 <sup>†</sup>	8.23 <sup>†</sup>	7.75 <sup>†</sup>	10.25	10.31	11.12	11.21	12.13
SE (D)	-4.24	-4.36	-4.18	-3.69	-3.28 <sup>†</sup>	-4.20	-4.17	-4.20	-4.48	-4.51
Sim KCyl (D)	5.01	4.98	4.61	4.20 <sup>†</sup>	4.02 <sup>†</sup>	4.99	5.09	5.19	5.24	5.31
RMS 5.0 mm (μm)	4.91	4.89	4.78	4.73 <sup>†</sup>	4.58 <sup>†</sup>	4.66	4.90	4.98	5.04	5.10
Coma (μm)	2.21	2.31	2.19 <sup>†</sup>	1.96 <sup>†</sup>	1.84 <sup>†</sup>	2.19	2.20	2.42	2.56	2.70
SA (μm)	1.10	1.21	0.95 <sup>†</sup>	0.91 <sup>†</sup>	0.89 <sup>†</sup>	1.18	1.22	1.31	1.38	1.42
ECC (cells/μm <sup>2</sup> *)	2501 ± 26	2502 ± 30	2497 ± 28	2497 ± 32	2499 ± 30	2491 ± 25	2493 ± 28	2489 ± 25	2490 ± 24	2487 ± 26
Pachymetry (μm)	442.00	430.00	431.00	429.00	427.00	442.38	440.50	437.77	434.54	427.50

AGC = apical gradient curvature; AK = apical keratometry; Avg PP = average pupillary power; CDVA = corrected distance visual acuity; CXL = collagen crosslinking; ECC = endothelial cell count; Kc area = keratoconus area; Kc SI = keratoconus symmetry index; RMS = root mean square; SA = spherical aberration; SE = spherical equivalent; Sim KCyl = simulated keratometry cylinder; Sim Kf = simulated keratometry flat axis; SimK avg = average simulated keratometry; SimKs = simulated keratometry steep axis; UDVA = uncorrected distance visual acuity

\*Mean ± SD

<sup>†</sup>Statistically significant

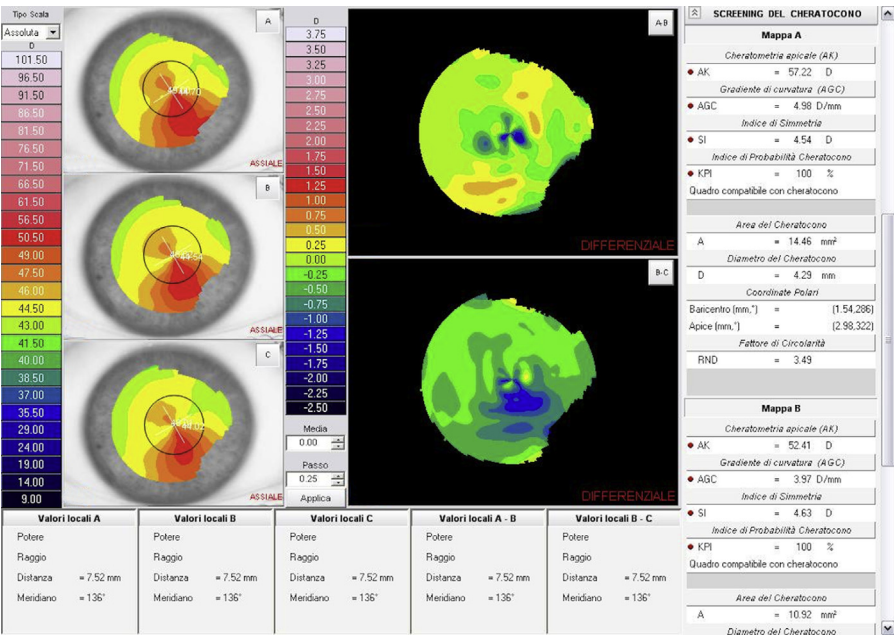
## DISCUSSION

Collagen crosslinking with total epithelium removal can be extremely uncomfortable for patients for several days until the epithelium heals. Also, with the epithelial debridement technique, in addition to pain, there is a risk for bacterial keratitis as well as for sterile infiltrates. These can prolong recovery and in the case of bacterial keratitis, can lead to decreased vision from corneal scarring. For these reasons and to promote rapid recovery, other techniques, such as transepithelial<sup>13</sup> and epithelial disruption,<sup>A</sup> have been developed. To promote penetration of riboflavin, agents have been added to solutions to help riboflavin penetrate corneal epithelial tight junctions. This prospective study evaluated the benefit of combining an epithelial disruptive technique with an enhanced riboflavin solution recommended for a transepithelial procedure. This prospective study used the fellow eye as a control, with the more severely affected eye treated

with epithelial-disruption CXL. We found CXL to be safe and efficacious, leading to better results in treated eyes than in untreated control eyes.

After an initial worsening in the first month, statistically significant improvements were observed at 6 months in all refractive and topographic indices. Keratoconus indices on the topographic device (apical K, apical gradient curvature, average pupillary power, keratoconus symmetry index, cone area) showed objective evidence of corneal flattening that was comparable to the results in a study by Vinciguerra et al.<sup>11</sup> in which the epithelial removal (epi-off) technique was used. The slight worsening in visual and topographic parameters at 1 month was possibly a result of early anterior haze and corneal epithelial remodeling.

Epithelial-disruption CXL was effective not only in halting the progression of keratoconus compared with that in control eyes but also in improving visual acuity. All keratoconus parameters worsened in



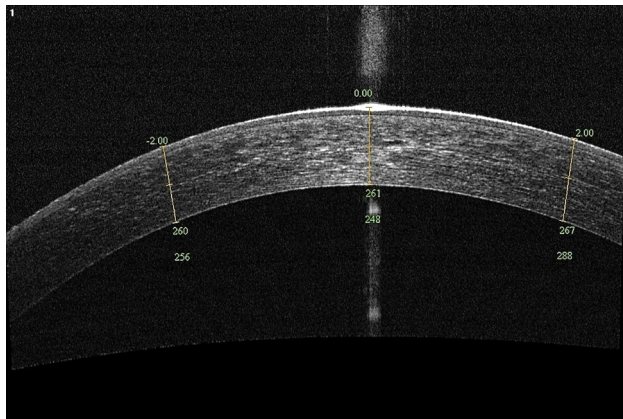
**Figure 5.** Corneal topographic axial map of keratoconus-affected eye treated with epithelial-disruption CXL. **A:** Topographic axial map before epithelial-disruption CXL. **B:** Topographic axial map 3 months after epithelial-disruption CXL. **C:** Topographic axial map 12 months after epithelial-disruption CXL. Note the reduction of apical K values from 57.22 to 51.37 D and average K from 46.8 to 46.07 D.

untreated contralateral control eyes. Similar findings have been described by others<sup>1,11-13,24-31</sup> with the epi-on CXL procedure and with the epi-off CXL procedure. The endothelial cell layer was unaffected by this technique, with no significant change in sequential mean ECCs and no difference between treated eyes and control eyes.

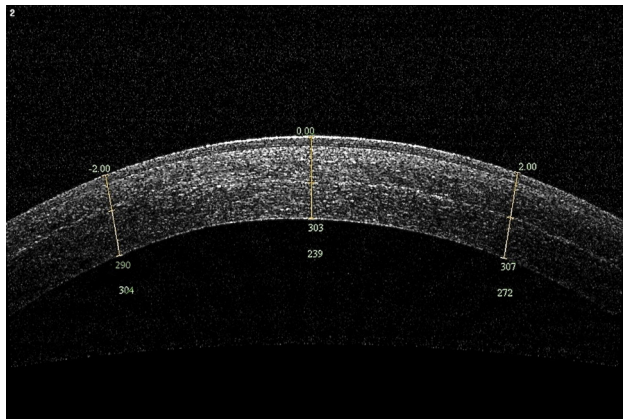
The corneal thickness in treated eyes measured by tomography decreased initially, with a reduction in CCT and minimum corneal thickness of 11  $\mu$ m and 8  $\mu$ m, respectively, at 1 month; this remained stable until from 6 to 12 months. The magnitude of the reduction in corneal thickness is less than that reported by Vinciguerra et al.,<sup>11</sup> who found a 21  $\mu$ m CCT reduction

measured by a rotating Scheimpflug camera (Pentacam, Oculus Inc.) 12 months after CXL; this may be because of the epithelial retention in the epithelial-disruption technique. The greatest CCT reduction (24  $\mu$ m) was observed at 12 months in 1 patient with a preoperative CCT of 409  $\mu$ m.

The corneal demarcation line measured by corneal OCT was visible in almost all eyes 1 month after treatment at a mean depth of  $250.41 \pm 21.89$   $\mu$ m centrally. A previous study<sup>25</sup> hypothesized that this line represents keratocyte activation and new collagen synthesis, while Seiler and Hafezi<sup>26</sup> report that its presence depends on the concentration of riboflavin solution and the intensity of the UVA-light exposure. A



**Figure 6.** High-resolution corneal OCT scan showing the stromal demarcation line 1 month after epithelial-disruption CXL in a patient with progressive keratoconus with central, nasal, and temporal depths of 260  $\mu$ m, 261  $\mu$ m, and 267  $\mu$ m, respectively.



**Figure 7.** High-resolution corneal OCT scan showing the stromal demarcation line 1 month after CXL in a patient with progressive keratoconus with central, nasal, and temporal depths of 303  $\mu$ m, 290  $\mu$ m, and 307  $\mu$ m, respectively.



shallower demarcation line (100  $\mu\text{m}$  from the epithelial surface) has been reported in transepithelial CXL,<sup>13</sup> and a deeper demarcation line (280 to 330  $\mu\text{m}$ ) has been reported using the classic (epi-off) procedure<sup>26–28</sup> (Figures 6 and 7). The demarcation line in our study was approximately 250  $\mu\text{m}$ , which is comparable to that reported for the epi-off technique. The significance of the demarcation line and its relationship to the efficacy of CXL are unknown. One assumption is that the demarcation line represents the effect of CXL, with most of the effect being in the anterior stroma, where the density of collagen fibers is higher.<sup>30,31</sup> Under this assumption, the deeper the line, the greater the involvement of corneal stroma.

Longer term follow-up of patients having epithelial-disruption CXL would be useful in understanding the long-term efficacy of the technique. However, this 1-year study comparing epithelial-disruption CXL performed in the more severely affected keratoconic eye with results in the contralateral control eye found an early and beneficial effect. The technique reduced discomfort, provided rapid recovery, and reduced or eliminated complications. Long-term prospective randomized comparative studies using a variety of available techniques (epi-off CXL, transepithelial CXL, epithelial-disruption CXL) would be useful to determine whether one procedure is better than the others over the long term.

Based on relatively short-term data, we believe that the combination of epithelial disruption and transepithelial preparation of riboflavin for enhanced penetration of riboflavin is a safe alternative to epithelial removal with demonstrable efficacy in arresting the progress of keratoconus compared with the progression in contralateral control eyes.

#### WHAT WAS KNOWN

- Epithelial removal CXL with riboflavin is considered the gold standard to ensure good penetration of riboflavin as well as sufficiently deep UVA penetration.

#### WHAT THIS PAPER ADDS

- This intraindividual study using a combination of epithelial disruption and a transepithelial preparation of riboflavin found an arrest in the progression of keratoconus compared with that in the more mildly affected untreated fellow eye.
- Using this method, the outcomes were similar to those in previous studies using the epithelial-removal CXL method.
- Epithelial-disruption CXL resulted in more rapid recovery with a lower risk for complications.

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