Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results

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PURPOSE: To evaluate 1-year outcomes of corneal collagen crosslinking (CXL) for treatment of keratoconus and corneal ectasia.

SETTING: Cornea and refractive surgery subspecialty practice.

DESIGN: Prospective randomized controlled clinical trial.

METHODS: Collagen crosslinking was performed in eyes with keratoconus or ectasia. The treatment group received standard CXL and the sham control group received riboflavin alone. Principal outcomes included uncorrected (UDVA) and corrected (CDVA) distance visual acuities, refraction, astigmatism, and topography-derived outcomes of maximum and average keratometry (K) value.

RESULTS: The UDVA improved significantly from 0.84 logMAR ± 0.34 (SD) (20/137) to 0.77 ± 0.37 logMAR (20/117) (P = .04) and the CDVA, from 0.35 ± 0.24 logMAR (20/45) to 0.23 ± 0.21 logMAR (20/34) (P < .001). Fifteen patients (21.1%) gained and 1 patient lost (1.4%) 2 or more Snellen lines of CDVA. The maximum K value decreased from baseline by 1.7 ± 3.9 diopters (D) (P < .001), 2.0 ± 4.4 D (P = .002), and 1.0 ± 2.5 D (P = .08) in the entire cohort, keratoconus subgroup, and ectasia subgroup, respectively. The maximum K value decreased by 2.0 D or more in 22 patients (31.0%) and increased by 2.0 D or more in 3 patients (4.2%).

CONCLUSIONS: Collagen crosslinking was effective in improving UDVA, CDVA, the maximum K value, and the average K value. Keratoconus patients had more improvement in topographic measurements than patients with ectasia. Both CDVA and maximum K value worsened between baseline and 1 month, followed by improvement between 1, 3, and 6 months and stabilization thereafter.

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Keratoconus and corneal ectasia occurring after laser in situ keratomileusis (LASIK) are noninflammatory processes in which the cornea deforms in association with thinning and biomechanical weakening. The incidence of keratoconus is approximately 1 in 2000, and the literature contains hundreds of cases of post-LASIK ectasia. Both diseases can result in irregular astigmatism, progressive myopia, or visual impairment secondary to stromal scarring. Because of optical aberrations caused by this progressive distortion and bowing of the cornea in keratoconus and ectasia, patients usually require rigid or complex curvature contact lenses to achieve good functional vision; spectacle correction frequently does not result in acceptable quality of vision. Furthermore, keratoconus tends to progress over the second to fifth decades of life and, ultimately, the need for corneal transplantation in 10% to 20% of cases. New treatments available to patients with keratoconus and ectasia include intrastromal corneal ring segment implantation, conductive keratoplasty, and corneal collagen crosslinking (CXL).

Collagen crosslinking has emerged as a promising technique to slow or stop the progression of keratoconus as well as post-LASIK ectasia. In this procedure, riboflavin (vitamin B2) is administered in conjunction with ultraviolet A (UVA, 365 nm). The interaction of riboflavin and UVA causes the formation of reactive oxygen species, leading to the formation of additional covalent bonds between collagen molecules, with consequent biomechanical stiffening of the cornea. In this study, we analyzed primary visual acuity, refractive, and topographic outcomes in...
patients with keratoconus and post-LASIK ectasia over a 1-year postoperative period. In addition, we compared the treatment groups to sham and fellow-eye control groups.

PATIENTS AND METHODS

Patients were enrolled as part of multicenter prospective randomized controlled clinical trials performed under guidelines of the U.S. Food and Drug Administration and approved and monitored by an investigational review board. This study was compliant with the U.S. Health Insurance Portability and Accountability Act. All patients provided informed consent. Randomization was computer generated and, on the procedure day, a sealed envelope was opened revealing whether the eye would be in the sham or treatment group. Patients were aware of their randomly assigned group.

The inclusion criteria included patients 14 years of age or older, axial topography pattern consistent with keratoconus or corneal ectasia, an inferior–superior ratio greater than 1.5 on topography mapping, a corrected distance visual acuity (CDVA) worse than 20/20, and a diagnosis of progressive keratoconus or LASIK-induced or photorefractive keratectomy (PRK)-induced ectasia. Progressive keratoconus or ectasia was defined as 1 or more of the following changes over a period of 24 months: an increase of 1.0 diopter (D) or more in the steepest keratometry (K) measurement, an increase of 1.00 D or more in manifest cylinder, an increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE). Exclusion criteria included patients with a history of corneal surgery, corneal pachymetry less than 300 μm, history of chemical injury or delayed epithelial healing, and pregnancy or lactation during the course of the study.

Treatment Group

Contact lens wearers were instructed to discontinue spherical soft lenses for a minimum of 3 days and soft toric rigid-gas permeable and hard lenses for a minimum of 2 weeks before the preoperative eye examination. Contact lens wearers required confirmation of a stable refraction at 2 examinations that were at least 7 days apart. A stable refraction was determined as one in which the MRSE and keratometry measurements at the first visit did not differ by more than 0.75 D from the respective measurements at the second visit.

Patients were initially randomized into a treatment or control group. The treatment group received standard UVA–riboflavin 0.1% CXL treatment. Corneal CXL was performed according to the methodology described by Wollensak et al. Initially, a topical anesthetic agent was administered and the central 9.0 mm epithelium removed by mechanical debridement. Riboflavin (0.1% in 20% dextran T500 solution) was then administered topically every 2 minutes for 30 minutes. Riboflavin absorption throughout the corneal stroma and anterior chamber was confirmed by slitlamp examination. Ultrasound (US) pachymetry was performed and if the cornea was thinner than 400 μm, hypotonic riboflavin (0.1% in sterile water) was administered, 1 drop every 10 seconds for 2-minute sessions, after which US pachymetry was performed to ascertain that the stroma had swollen to more than 400 μm. This was repeated until adequate corneal thickness was obtained. The cornea was aligned and exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm² (UV-X system, IROC AG). During UVA exposure, isotonic riboflavin administration was continued every 2 minutes. Postoperatively, antibiotic and corticosteroid drops were administered, a soft contact lens bandage was placed, and the eye was reexamined at the slitlamp. The contact lens was removed after the epithelial defect had closed. Antibiotics and corticosteroid drops were continued 4 times daily for 1 week and 2 weeks, respectively. Patients were followed for 12 months postoperatively and had complete examinations at 1, 3, 6, and 12 months.

Sham Control Group

The sham control group received riboflavin 0.1% ophthalmic solution alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for 30 minutes. Next, the cornea was exposed to a sham treatment in which the UVA light was not turned on, during which time riboflavin was administered topically every 2 minutes for an additional 30 minutes. The sham control patients were followed for 3 months postoperatively, at which point the study eye crossed over to the treatment group and received full CXL treatment.

Fellow-Eye Control Group

In addition to the sham control group, a fellow-eye control group was analyzed. The fellow eyes of patients who did not have CXL treatment bilaterally were included in this group. This group consisted of eyes with frank keratoconus or ectasia that did not have CXL, eyes with evidence of disease that did not meet the inclusion criteria of this study, and eyes with no evidence of disease. Visual acuity and topography measurements were analyzed at baseline and 12 months and compared with the postoperative measurements in the treatment group at the same time points.

Outcome Measures

Visual Acuity and Refraction The uncorrected distance visual acuity (UDVA) and CDVA were measured...
preoperatively and postoperatively at 1, 3, 6, and 12 months. Visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment of Diabetic Retinopathy Study visual acuity test (2nd edition) with Sloan letters. Patients were tested 4 m from the visual acuity chart. If patients could not read any letters at 4 m, they were tested at 2 m. Visual acuity was recorded and analyzed as the logMAR value.15 Manifest refraction was performed preoperatively and 1, 3, 6, and 12 months postoperatively, and the MRSE and manifest astigmatism were analyzed. In the astigmatism analysis, vector analysis was performed as described by Holladay et al.16 In this study, the mean surgically induced astigmatism (SIA) and the vectorial magnitude of the SIA were analyzed using methodology similar to that in a previous analysis of PRK and LASIK.17 For a graphic representation of these results, data points were converted to Cartesian coordinates and the axis of cylinder values were doubled to give a doubled-angle plot.16 Thus, when plotted on an x-y graph, steepening toward 90 degrees (induced with the rule) is represented by points on the negative x-axis and steepening toward 180 degrees (induced against the rule) is represented by points on the positive x-axis. To better ascertain the directionality of the induced astigmatism change, right eyes and left eyes were assessed separately because the astigmatism axis between eyes in keratoconus may exhibit mirror-image symmetry.

Topography  Topography measurements were obtained using a rotating Scheimpflug camera (Pentacam, Oculus, Inc.). The Scheimpflug system generates a 3-dimensional model of the cornea and anterior segment. Topographic data were obtained preoperatively and 1, 3, 6, and 12 months postoperatively. Maximum K values, average K values, flat K values, and steep K values as well as corneal astigmatism (simulated K) were recorded from the topography data generated by the Scheimpflug system.

Statistical Analysis  Statistical analysis was performed using PASW Statistics software (version 18, SPSS, Inc.). Three groups were analyzed: the entire cohort, the individual keratoconus subgroup, and the ectasia subgroup. A paired 2-tailed Student t test was performed to analyze the postoperative outcome changes compared with baseline values and to analyze the postoperative outcome changes over time. An independent t test was performed to compare outcome data 12 months postoperatively between the keratoconus subgroup and ectasia subgroup and between the treatment group and control group. A P value less than 0.05 was used to determine statistical significance.

RESULTS  Seventy-one eyes of 58 patients had CXL and were followed for 1 year. Of the eyes, 49 were in the keratoconus subgroup and 22 in the post-LASIK ectasia subgroup. The sham control group comprised 41 eyes (28 keratoconus, 13 ectasia), and the fellow-eye control group comprised 30 eyes (21 keratoconus, 9 ectasia).

Visual Acuity Changes after Corneal Collagen Crosslinking  Uncorrected Distance  Table 1 and Figure 1, top, show the UDVA over time. The changes in UDVA compared with baseline failed to reach statistical significance at 1 month, 3 months, or 6 months (P = .21, P = .47, and P = .35, respectively). At 12 months, the change in UDVA compared with baseline was statistically significant (P = .04). However, when the keratoconus and ectasia subgroups were analyzed individually, changes in UDVA compared with baseline were not statistically significant at any time point.

The UDVA improved by 2 or more Snellen lines in 18 eyes (25.4%); 6 eyes (8.5%) lost 2 or more Snellen lines of UDVA (Figure 1, bottom).

Corrected Distance  Table 1 and Figure 2, top, show the CDVA over time. The mean CDVA remained unchanged at month 1 (mean change 0.02 ± 0.18 logMAR; P = .33). The mean CDVA improved significantly between 1 month and 3 months (mean change −0.07 ± 0.15 logMAR; P < .001) and between 3 months and 6 months (mean change −0.05 ± 0.12 logMAR; P < .001). There was no statistically significant change between 6 months and 12 months (mean change −0.02 ± 0.13, P = .27). At 12 months, the change in CDVA compared to baseline was statistically significant (P < .001).

Similar to the entire cohort, the mean CDVA improved significantly in the keratoconus subgroup (mean change −0.13 ± 0.21 logMAR; P < .001) and in the ectasia subgroup (mean change −0.07 ± 0.11 logMAR; P = .02) over 1 year. The mean CDVA in the keratoconus subgroup remained unchanged at 1 month (mean change 0.006 ± 0.18 logMAR; P = .81), improved between 1 month and 3 months (mean change −0.07 ± 0.14 logMAR; P = .001) and between 3 months and 6 months (mean change −0.06 ± 0.12 logMAR; P < .001), and plateaued between 6 months and 12 months postoperatively (mean change −0.01 ± 0.11 logMAR; P = .70). In contrast, in the ectasia subgroup, interval changes in CDVA failed to reach statistical significance (0 to 1 month, P = .20; 1 to 3 months, P = .08; 3 to 6 months, P = .32; 6 to 12 months, P = .21).

The CDVA improved by 2 or more Snellen lines in 15 eyes (21.1%); 1 eye (1.4%) in a patient with ectasia lost 2 Snellen lines of CDVA (Figure 2, bottom).

Refractive Changes after Corneal Collagen Crosslinking  Refraction  There was a mean improvement of 0.86 D in the MRSE from preoperatively to 12 months postoperatively; however, the improvement was not statistically significant (P = .07). There was a statistically
significant improvement in MRSE between preoperatively and 1 month postoperatively (mean change \( +0.76 \pm 2.13 \text{D} \); \( P = .004 \)) but not between 1 month and 3 months (mean change \( +0.38 \pm 2.73 \text{D} \); \( P = .25 \)), between 3 months and 6 months (mean change \( -0.26 \pm 1.58 \); \( P = .18 \)), or between 6 months and 12 months (mean change \( -0.03 \pm 2.58 \); \( P = .92 \)) (Table 2 and Figure 3).

### Table 1. Postoperative visual acuity in all eyes, the keratoconus subgroup, and the ectasia subgroup.

<table>
<thead>
<tr>
<th>Acuity/Group</th>
<th>Preop</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>Preop</th>
<th>Change from Baseline to 12 Months</th>
</tr>
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<tbody>
<tr>
<td>UDVA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All eyes</td>
<td>0.84 ± 0.34</td>
<td>0.87 ± 0.31</td>
<td>0.82 ± 0.37†</td>
<td>0.81 ± 0.37</td>
<td>0.77 ± 0.37*</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Keratoconus</td>
<td>0.87 ± 0.35</td>
<td>0.91 ± 0.31</td>
<td>0.85 ± 0.37</td>
<td>0.86 ± 0.40</td>
<td>0.82 ± 0.39</td>
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<tr>
<td>Ectasia</td>
<td>0.75 ± 0.30</td>
<td>0.78 ± 0.30</td>
<td>0.74 ± 0.36†</td>
<td>0.70 ± 0.29</td>
<td>0.65 ± 0.31</td>
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<tr>
<td>CDVA</td>
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<tr>
<td>All eyes</td>
<td>0.35 ± 0.24</td>
<td>0.37 ± 0.29</td>
<td>0.30 ± 0.22;*</td>
<td>0.25 ± 0.21;*</td>
<td>0.23 ± 0.21*</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Keratoconus</td>
<td>0.39 ± 0.27</td>
<td>0.39 ± 0.30</td>
<td>0.32 ± 0.24;*</td>
<td>0.26 ± 0.23;*</td>
<td>0.25 ± 0.23*</td>
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<td></td>
</tr>
<tr>
<td>Ectasia</td>
<td>0.26 ± 0.16</td>
<td>0.32 ± 0.25</td>
<td>0.25 ± 0.17</td>
<td>0.22 ± 0.17</td>
<td>0.19 ± 0.14*</td>
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</tbody>
</table>

CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity

*Significant change compared with baseline measurements
†Significant change compared with previous visit measurement

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Figure 1. **Top:** Change in UDVA over time. Numbers reported are Snellen visual acuity (20/×). **Bottom:** Change in UDVA Snellen lines between baseline and 12 months postoperatively (KC = keratoconus).

Figure 2. **Top:** Change in CDVA over time. Numbers reported are Snellen visual acuity (20/×). **Bottom:** Change in CDVA Snellen lines between baseline and 12 months postoperatively.
Manifest Astigmatism

Absolute In the entire study cohort, all changes in the mean absolute manifest astigmatism between preoperatively and each postoperative visit failed to reach statistical significance (1 month, \( P = .39 \); 3 months, \( P = .24 \); 6 months, \( P = .97 \); 12 months, \( P = .84 \)). Similarly, absolute astigmatism in the keratoconus and ectasia subgroups remained unchanged at 1 year (Table 2). The manifest astigmatism improved by 1.00 D or more in 24 eyes (33.8%) (17 keratoconus, 7 ectasia), changed between –1.00 D and 1.00 D in 29 eyes (34.7%) (19 keratoconus, 10 ectasia), and worsened by 1.00 D or more in 18 eyes (25.4%) (13 keratoconus, 5 ectasia).

Vector Analysis of Surgically Induced Astigmatism The mean SIA at 12 months was 0.61 D × 73.4 degrees, 1.12 D × 75.2 degrees, and 0.53 D × 81.7 degrees in the entire cohort, the keratoconus subgroup, and the ectasia subgroup, respectively. In the entire cohort, the mean induced astigmatism was 0.99 D × 88.8 degrees and 0.65 D × 44.7 degrees in right eyes and left eyes, respectively (Figure 4). In the keratoconus subgroup, the mean induced astigmatism was 1.75 D × 87.9 degrees and 1.01 D × 49.8 degrees in the right eyes and left eyes, respectively. In the ectasia subgroup, the mean induced astigmatism was 0.65 × 83.3 degrees and 0.42 × 79.0 degrees in the right eyes and left eyes, respectively. Regarding the induced magnitude of astigmatism, the mean vectorial magnitude of SIA at 12 months was 2.99 D × 2.55 degrees, 3.16 D × 2.72 degrees, and 2.61 D × 2.15 degrees, in the entire cohort, the keratoconus subgroup, and the ectasia subgroup, respectively.

Postoperative Topography Table 3 shows the postoperative topographic measurements.

Maximum Keratometry There was a significant decrease in the mean maximum K value (–1.7 ± 3.9 D) between preoperatively and 12 months postoperatively (\( P < .001 \)). There was a significant increase between baseline and 1 month (mean 1.39 ± 2.80 D; \( P < .001 \)) and then a significant decrease between 1 month and 3 months (mean –1.69 ± 2.55 D; \( P < .001 \)) and between 3 months and 6 months (mean –0.93 ± 3.02; \( P = .01 \)). There was no significant change in maximum K between 6 months and 12 months (mean –0.48 ± 3.20; \( P = .21 \)) (Figure 5, A).

In the keratoconus subgroup, there was a 2.00 D decrease in the mean maximum K value between preoperatively and 12 months postoperatively (\( P = .002 \)).

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Table 2. Postoperative refractive measurements by group.

<table>
<thead>
<tr>
<th>Parameter/Group</th>
<th>Preop</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>Change from Baseline to 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSE All eyes</td>
<td>–8.63 ± 5.30</td>
<td>–7.86 ± 4.61*</td>
<td>–7.48 ± 4.73*</td>
<td>–7.74 ± 4.74*</td>
<td>–7.77 ± 5.40</td>
<td>.10</td>
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<tr>
<td>Keratoconus</td>
<td>–9.32 ± 5.65</td>
<td>–8.34 ± 4.95*</td>
<td>–8.05 ± 5.08*</td>
<td>–8.20 ± 5.04*</td>
<td>–8.47 ± 5.50</td>
<td>.10</td>
</tr>
<tr>
<td>Ectasia</td>
<td>–7.08 ± 4.10</td>
<td>–6.80 ± 3.62</td>
<td>–6.23 ± 3.63</td>
<td>–6.73 ± 3.91</td>
<td>–6.22 ± 4.93</td>
<td>.10</td>
</tr>
<tr>
<td>Manifest astigmatism All eyes</td>
<td>4.76 ± 2.52</td>
<td>4.62 ± 2.30</td>
<td>4.51 ± 2.78</td>
<td>4.76 ± 2.50</td>
<td>4.81 ± 2.51</td>
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</tr>
<tr>
<td>Keratoconus</td>
<td>5.09 ± 2.54</td>
<td>4.95 ± 2.21</td>
<td>5.01 ± 2.53</td>
<td>5.08 ± 2.53</td>
<td>5.01 ± 2.43</td>
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<tr>
<td>Ectasia</td>
<td>4.05 ± 2.36</td>
<td>3.90 ± 2.39</td>
<td>3.41 ± 3.05</td>
<td>4.05 ± 2.34</td>
<td>4.39 ± 2.69</td>
<td>.10</td>
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</table>

MRSE = manifest refraction spherical equivalent
*Significant change compared with baseline measurements
†Significant change compared with previous visit measurement

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**Figure 3.** Postoperative MRSE measurements. Box-and-whisker plots (upper bar = 4th quartile; lower bar = 1st quartile).
Figure 4. Double-angle plot of vector change in astigmatism 1 year after CXL. Left: Right eyes. Right: Left eyes.

Table 3. Postoperative topographic measurements by Scheimpflug imaging.

<table>
<thead>
<tr>
<th>Parameter/Group</th>
<th>Preop</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>Postop (Keratoconus Vs Ectasia)</th>
<th>Change from Baseline to 12 Months</th>
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<tr>
<td>Maximum K</td>
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<tr>
<td>All eyes</td>
<td>58.6 ± 9.62</td>
<td>60.0 ± 9.80&lt;sup&gt;•&lt;/sup&gt;</td>
<td>58.3 ± 9.09&lt;sup&gt;†&lt;/sup&gt;</td>
<td>57.4 ± 8.54&lt;sup&gt;••&lt;/sup&gt;</td>
<td>56.9 ± 8.62&lt;sup&gt;•&lt;/sup&gt;</td>
<td>0.02</td>
<td>0.22</td>
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<td>Keratoconus</td>
<td>60.4 ± 9.99</td>
<td>61.7 ± 10.2&lt;sup&gt;•&lt;/sup&gt;</td>
<td>60.0 ± 9.87&lt;sup&gt;†&lt;/sup&gt;</td>
<td>59.1 ± 8.96&lt;sup&gt;••&lt;/sup&gt;</td>
<td>58.4 ± 8.41&lt;sup&gt;•&lt;/sup&gt;</td>
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<tr>
<td>Ectasia</td>
<td>54.7 ± 7.52</td>
<td>56.2 ± 7.78&lt;sup&gt;•&lt;/sup&gt;</td>
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<td>53.6 ± 6.18&lt;sup&gt;•&lt;/sup&gt;</td>
<td>53.7 ± 6.86&lt;sup&gt;•&lt;/sup&gt;</td>
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<tr>
<td>All eyes</td>
<td>48.2 ± 6.97</td>
<td>48.8 ± 7.11&lt;sup&gt;•&lt;/sup&gt;</td>
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<tr>
<td>Ectasia</td>
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<td>44.3 ± 3.90&lt;sup&gt;•&lt;/sup&gt;</td>
<td>43.1 ± 3.37&lt;sup&gt;†&lt;/sup&gt;</td>
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<tr>
<td>All eyes</td>
<td>45.8 ± 6.42</td>
<td>46.3 ± 6.79</td>
<td>45.2 ± 6.36&lt;sup&gt;••&lt;/sup&gt;</td>
<td>45.2 ± 6.32&lt;sup&gt;•&lt;/sup&gt;</td>
<td>44.9 ± 5.40&lt;sup&gt;•&lt;/sup&gt;</td>
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<td>0.18</td>
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<td>48.2 ± 7.09</td>
<td>47.2 ± 6.49&lt;sup&gt;••&lt;/sup&gt;</td>
<td>47.3 ± 6.32&lt;sup&gt;•&lt;/sup&gt;</td>
<td>46.7 ± 5.29&lt;sup&gt;••&lt;/sup&gt;</td>
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<tr>
<td>Ectasia</td>
<td>41.1 ± 3.32</td>
<td>42.0 ± 3.22</td>
<td>40.8 ± 2.92&lt;sup&gt;†&lt;/sup&gt;</td>
<td>40.5 ± 2.82&lt;sup&gt;•&lt;/sup&gt;</td>
<td>40.7 ± 2.63&lt;sup&gt;•&lt;/sup&gt;</td>
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<tr>
<td>All eyes</td>
<td>50.9 ± 7.33</td>
<td>51.7 ± 7.73&lt;sup&gt;•&lt;/sup&gt;</td>
<td>50.5 ± 7.53&lt;sup&gt;••&lt;/sup&gt;</td>
<td>50.2 ± 6.70&lt;sup&gt;•&lt;/sup&gt;</td>
<td>49.7 ± 6.08&lt;sup&gt;••&lt;/sup&gt;</td>
<td>0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>52.9 ± 7.45</td>
<td>53.8 ± 7.86&lt;sup&gt;•&lt;/sup&gt;</td>
<td>50.5 ± 7.53&lt;sup&gt;•&lt;/sup&gt;</td>
<td>52.1 ± 6.81&lt;sup&gt;•&lt;/sup&gt;</td>
<td>51.5 ± 5.94&lt;sup&gt;••&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectasia</td>
<td>46.51 ± 4.73</td>
<td>47.0 ± 4.98</td>
<td>45.82 ± 4.28&lt;sup&gt;••&lt;/sup&gt;</td>
<td>45.9 ± 3.96&lt;sup&gt;•&lt;/sup&gt;</td>
<td>45.7 ± 4.33&lt;sup&gt;•&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astigmatism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>4.94 ± 2.45</td>
<td>5.46 ± 2.82</td>
<td>5.37 ± 2.76</td>
<td>4.99 ± 2.46</td>
<td>4.76 ± 2.59</td>
<td>0.50</td>
<td>0.34</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>4.80 ± 2.42</td>
<td>5.64 ± 2.95&lt;sup&gt;•&lt;/sup&gt;</td>
<td>5.50 ± 2.87&lt;sup&gt;•&lt;/sup&gt;</td>
<td>4.87 ± 2.26&lt;sup&gt;•&lt;/sup&gt;</td>
<td>4.76 ± 2.26&lt;sup&gt;•&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectasia</td>
<td>5.24 ± 2.55</td>
<td>5.06 ± 2.54</td>
<td>5.06 ± 2.53</td>
<td>5.28 ± 2.89</td>
<td>4.76 ± 3.28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

K = keratometry
<sup>•</sup>Significant change compared with baseline measurements
<sup>†</sup>Significant change compared with previous visit measurement
There was a significant increase between baseline and 1 month (mean change 1.33 ± 3.03 D; \( P = .003 \)) and a significant decrease between 1 month and 3 months (mean change −1.70 ± 2.66 D; \( P < .001 \)) and 3 months and 6 months (mean change −0.94 ± 3.22 D; \( P = .046 \)). There was no significant change between 6 months and 12 months (mean change −0.72 ± 3.58 D; \( P = .17 \)).

In the ectasia subgroup, there was a 1.00 D decrease in the mean maximum K value between preoperatively and 12 months postoperatively; however, this failed to reach statistical significance (\( P = .08 \)). There was a significant increase between baseline and 1 month (mean change 1.51 ± 2.27 D; \( P = .005 \)) and a significant decrease between 1 month and 3 months (mean change −1.66 ± 2.35 D; \( P = .003 \)). There were no significant changes between 3 months and 6 months (mean change −0.91 ± 2.60 D; \( P = .12 \)) or between 6 months and 12 months (mean change 0.05 ± 2.08 D; \( P = .91 \)).

The maximum K value decreased by 2.00 D or more in 22 eyes (31.0%) patients and remained unchanged in 28 eyes (39.4%) patients. It increased by 2.00 D or more in 3 eyes (4.2%) (Figure 5, B).
Average Keratometry  In the entire cohort, there was a significant decrease in the mean average K value (−1.10 ± 2.39 D) between preoperatively and 12 months postoperatively (P < .001). There was a significant increase between baseline and 1 month (mean change 0.56 ± 1.87 D; P = .01) and significant decreases between 1 month and 3 months (mean change −1.11 ± 1.26 D; P < .001) and between 6 months and 12 months (mean change −0.41 ± 1.60 D; P = .03). There was no significant change between 3 months and 6 months mean change (−0.14 ± 1.99 D; P = .56) (Figure 5, C).

In the keratoconus subgroup, there was a 1.50 D decrease in the mean average K value between preoperatively and 12 months postoperatively (P < .001). There was a significant decrease between 1 month and 3 months (mean change −1.07 ± 1.38 D; P < .001) and between 6 months and 12 months (mean change −0.64 ± 1.79 D; P = .02). There were no significant changes in between baseline and 1 month (mean change 0.40 ± 2.07 D; P = .19) or between 3 months and 6 months (mean change −0.15 ± 2.27 D; P = .65).

In the ectasia subgroup, there was a 0.3 D decrease in the mean average K value between preoperatively and 12 months postoperatively; however, this failed to reach statistical significance (P = .22). There was a significant increase between baseline and 1 month (mean change 0.91 ± 1.28 D; P = .003) followed by a significant decrease between 1 month and 3 months (mean change −1.21 ± 0.99 D; P < .001). There were no significant changes between 3 months and 6 months (mean change −0.12 ± 1.16 D; P = .64) or between 6 months and 12 months (mean change 0.09 ± 0.92 D; P = .65).

Corneal Astigmatism (Simulated Keratometry)  In the entire cohort and the ectasia subgroup, all changes in corneal astigmatism, measured by Scheimpflug simulated K, failed to reach significance at all time points. In the keratoconus subgroup, there were significant increases in corneal astigmatism compared with baseline at 1 month (P = .01) and 3 months (P = .02). However, the simulated K value returned to baseline at 6 months; there were no significant changes in corneal astigmatism compared with baseline at 6 months (P = .76) or 12 months (P = .87).

Comparison Between Groups
Keratoconus Versus Ectasia  The baseline CDVA, maximum K value, average K value, flat K value, and steep K value in the keratoconus subgroup were significantly different from the same baseline measurements in the ectasia subgroup (CDVA, P = .02; maximum K, P = .02; average K, P < .001; flat K value, P < .001; steep K, P < .001). However, there were no significant differences between the keratoconus subgroup and ectasia subgroup in changes in visual acuity (UDVA, CDVA), refraction (MRSE, manifest astigmatism), or topography (maximum K, average K, flat K, steep K, astigmatism) 12 months after CXL (Tables 1 to 3).

Control Groups
Sham  In the sham control group, there were no statistically significant changes in CDVA, manifest astigmatism, MRSE, maximum K value, average K value, steep K, or corneal astigmatism at the 1-month or 3-month follow-up visits. There was a statistically significant improvement in UDVA at 1 month (mean change −0.09 ± 0.26 logMAR; P = .03) and 3 months (mean change −0.08 ± 0.23 logMAR; P = .03) compared with baseline. There was also a statistically significant increase in flat K value from baseline to 3 months (mean change 0.54 ± 1.65 D; P = .04).

Fellow-Eye  In the fellow-eye control group, there were no changes in UDVA, CDVA, maximum K, average K, flat K, steep K, MRSE, or corneal astigmatism over the 12-month study. The mean change in UDVA was −0.04 ± 0.18 logMAR (P = .19); in CDVA, −0.04 ± 0.14 logMAR (P = .17), in the maximum K value, +0.29 ± 1.19 D (P = .19); and in the average K value, +0.20 ± 0.79 D (P = .18). There was a statistically significant increase in manifest astigmatism (mean change 0.34 ± 0.82 D; P = .03) at 1 year.

Treatment Versus Control Groups
At 3 months, there were no significant differences between the treatment and sham control group in changes from baseline in UDVA, CDVA, maximum K, or average K value (P = .13, P = .44, P = .25, and P = .89, respectively). At 1 year, all of the outcomes were significantly better in the treatment group than in the fellow-eye control group (P = .02, P < .001, P < .001, and P < .001, respectively) (Figure 6).

DISCUSSION
Corneal collagen crosslinking is a promising new treatment for keratoconus12 and corneal ectasia.13 Crosslinking is thought to biomechanically strengthen the corneal stroma and, consequently, slow the progression of keratoconus and ectasia. In many cases, moreover, CXL improves the patient’s visual, refractive, and topographic outcomes18 with few reported complications.19 In this controlled clinical trial, visual acuity, refraction, and topography outcomes were analyzed in patients diagnosed with keratoconus and in those with post-LASIK corneal ectasia. This study represents one of the largest prospectively analyzed treatment groups to date. Unique to this investigation are...
the comparisons of the treatment group with a sham control group and a fellow-eye control group, an analysis of the postoperative time course of CXL-mediated clinical changes, as well as an analysis of these patients as an entire cohort and individually within their respective keratoconus or ectasia subgroup.

In our study, the mean UDVA was approximately 1 Snellen line better 12 months postoperatively. This improvement is somewhat less than previously reported. Vinciguerra et al.18 report a significant improvement in mean UDVA, from 0.77 logMAR preoperatively to 0.57 logMAR 12 months postoperatively. Caporossi et al.20 reported a significant improvement in mean UDVA of 2.41 Snellen lines.

In clinical practice, it is valuable to give the patient an idea of his or her possible outcomes as an individual, rather than as a population mean, to afford them proper expectations. Thus, it is helpful to look at the likelihood that an individual patient will improve or decline substantially. In this type of analysis, 18 eyes (25.4%) gained 2 or more lines of UDVA, and 6 eyes (8.5%) lost 2 or more lines of UDVA. The cause of UDVA loss in these patients is unclear and did not appear directly related to refractive error or change in corneal topography. Of the 6 eyes, 3 were in the keratoconus subgroup and 3 in the ectasia subgroup. The 3 keratoconus cases were stage I, stage III, and stage IV. The range of baseline UDVA in the 6 eyes was 20/40 to 20/100, and they lost between 2 lines and 4 lines of UDVA by 1 year postoperatively (Table 4).

Like UDVA, a significant improvement in postoperative CDVA has been reported in studies of CXL. In a study by Vinciguerra et al.,18,21 in patients with stage III keratoconus, the mean CDVA improved from 0.28 logMAR to 0.14 logMAR 12 months postoperatively, and in patients with ectasia, the CDVA improved significantly, from 0.16 logMAR to 0.06 logMAR. Similarly, at 1-year follow-up, Caporossi et al.20 and Raiskup-Wolf et al.22 found significant improvements in CDVA (0.08 logMAR and 1.34 Snellen lines, respectively), with continued improvement after 1 year. Hafezi et al.13 report that CDVA improved in 4 of 10 eyes with post-LASIK ectasia.

In our study, there was also a significant improvement of more than 1 line of mean CDVA 1 year postoperatively (mean change 0.12 ± 0.19 logMAR). This was in contrast to the fellow-eye control group, in which CDVA did not change significantly. In the entire study cohort, 15 eyes (21.1%) gained 2 or more Snellen lines of CDVA and only 1 (1.4%) lost 2 lines of CDVA. The latter case had post-LASIK ectasia, and both the CDVA and UDVA decreased from 20/100 to 20/160 at 1 year; the cause was unclear. We are currently performing further analysis to determine preoperative predictors of patients in whom outcomes significantly improve or worsen after CXL treatment.

Looking at the time course of CDVA change in the entire study cohort, the significant changes in CDVA appeared to occur between 1 month and 3 months and between 3 months and 6 months, with a plateau

Table 4. Visual acuity in the 6 eyes that lost 2 or more Snellen lines of UDVA 1 year after CXL.

<table>
<thead>
<tr>
<th>Eye</th>
<th>Subgroup</th>
<th>Stage of KC</th>
<th>Baseline</th>
<th>12 Mo Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Keratoconus</td>
<td>Stage I</td>
<td>20/80</td>
<td>20/160</td>
</tr>
<tr>
<td>2</td>
<td>Keratoconus</td>
<td>Stage III</td>
<td>20/80</td>
<td>20/125</td>
</tr>
<tr>
<td>3</td>
<td>Keratoconus</td>
<td>Stage IV</td>
<td>20/40</td>
<td>20/100</td>
</tr>
<tr>
<td>4</td>
<td>Ectasia</td>
<td>—</td>
<td>20/100</td>
<td>20/200</td>
</tr>
<tr>
<td>5</td>
<td>Ectasia</td>
<td>—</td>
<td>20/100</td>
<td>20/160</td>
</tr>
<tr>
<td>6</td>
<td>Ectasia</td>
<td>—</td>
<td>20/80</td>
<td>20/160</td>
</tr>
</tbody>
</table>

UDVA = uncorrected distance visual acuity
in improvement thereafter. In the keratoconus subgroup, the change in CDVA over time followed a pattern similar to that in the entire cohort. The ectasia subgroup did not have any significant changes between time points; however, there was a significant change in CDVA from baseline to 12 months postoperatively.

Previous studies report changes in the MRSE of 0.40 D, 1.43 D, and 2.20 D. In our study, the mean improvement in the MRSE at 12 months was 0.86 D. However, this change failed to reach statistical significance. Similarly, there were no significant changes in the MRSE in the keratoconus and ectasia subgroups. Poor reproducibility of subjective refraction in these patients with irregular corneal topographies might account for the lack of a significant difference in postoperative refraction after CXL.

Previous studies reported significant changes in manifest astigmatism of 0.93 D and 0.26 D respectively. In our study, the mean manifest astigmatism at 12 months was 2.01 D, 1.90 D, 1.46 D, and 1.42 D in keratoconic patients. Hafezi et al. report a decrease in maximum K value in patients with ectasia after LASIK. Our current study corroborates findings in these previous studies; we found a significant decrease in maximum K value of 1.70 D at 1 year, compared with no significant change in the fellow-eye control group. The largest change was in the keratoconus subgroup, which showed a 2.0 D flattening effect, whereas a smaller change of 1.0 D, which failed to reach statistical significance, was found in the ectasia subgroup.

In all groups, there was a significant increase in maximum K value at 1 month, followed by the largest decrease in maximum K value between 1 month and 3 months. In all groups, there was no significant change in the maximum K value between 6 months and 12 months. This contrasts with the findings of Caporossi et al. and Raiskup-Wolf et al., who reported a continued decrease in maximum K values after the 1-year follow-up. Further follow-up is required to determine whether the maximum K value will continue to decrease after 12 months in patients with keratoconus or ectasia.

Individually, the maximum K value decreased by 2.0 D or more in 22 eyes (31.0%) (17 keratoconus, 5 ectasia) and increased by 2.0 D or more in 3 eyes (4.2%) (1 keratoconus, 2 ectasia). These latter 3 eyes would be considered treatment failures because cone progression was not stabilized. Similar to the results of Koller et al., the maximum K value increased by 1.00 D or more in 7 eyes (9.8%) (5 keratoconus, 2 ectasia). Curiously, none of the 7 eyes were among those that lost 2 or more lines of UDVA and CDVA.

Similar to maximum K value, the decrease in the average K value in the entire cohort at 12 months compared with baseline was significant. In the keratoconus subgroup, the average K value was significantly decreased at 12 months as well. However, in the ectasia subgroup, the average K value did not significantly change. Analogous to the maximum K value, all groups had the largest significant decrease in the average K value between 1 month and 3 months.

The flat K and steep K values showed improvements similar to those in the maximum K and average K values. It remains unclear whether the achieved flattening of the flat K value at 1 year is, in fact, a desirable outcome from the clinical viewpoint because it may mitigate irregularity of the corneal topography. Further study of corneal topography after CXL is needed to determine whether it is this general topographic flattening, or perhaps, more complex changes in the corneal optical contour, that result in the significant improvements in CDVA after CXL treatment.

In this study, there were significant differences between the baseline topographic measurements and CDVA in the keratoconus and ectasia subgroups. Therefore, it is difficult to accurately assess the differences in the changes in postoperative outcome measurements in these 2 groups. However, the data here and in previous studies suggest that there may be differences between the postoperative CXL outcomes in keratoconus patients and ectasia patients.

In the ectasia group, the only significant change in CDVA was when 1-year postoperative measurements were compared with baseline. In contrast to the keratoconus subgroup, the ectasia subgroup had no significant change in CDVA at any time interval between baseline and 12 months. This may suggest increased variability in the time course of CDVA changes in ectasia patients compared with changes in keratoconus patients.

Furthermore, although there was a trend toward improvement, there were no significant changes in maximum K, average K, or flat K in the ectasia subgroup; only steep K showed a statistically significant improvement at the 1-year follow-up. At baseline, the ectatic corneas in this study were flatter than those in the keratoconus subgroup and, therefore, the topographic...
changes caused by CXL in these corneas may be subtler. Notwithstanding, our data suggest that ectatic corneas may not have as robust a response to CXL as keratoconus corneas. Similar to our findings, Vinciguerra et al. 21 found no significant topographic changes (average K, flat K, steep K) in patients with post-LASIK ectasia.

The cause of a potential difference between keratoconic corneas and ectatic corneas is, as yet, unclear. Biomechanical differences caused by the LASIK flap; possible differences in the riboflavin diffusion rate in post-LASIK corneas, especially at the flap interface; and intrinsic pathophysiologic differences between keratoconus and ectasia may all contribute to the different responses to CXL between the 2 groups. Certainly, further study with a greater number of ectatic eyes is necessary to further elucidate differences in the response to CXL between eyes with keratoconus and eyes with ectasia.

Treatment patients were compared with a sham control group and a fellow-eye control group. In the study protocol, the sham control group received riboflavin alone and was placed under a UVA light that was turned off. Most notably, the epithelium was not removed in any of the control patients. Therefore, any contribution of deep epithelialization, rather than the UVA light treatment, to patient outcomes was not accounted for by this control group. In addition, these patients were only followed for 3 months, at which point they crossed over to the treatment group; therefore, our comparison with the treatment group was limited to 3 months.

These limitations of the sham control group suggested an additional comparison of the treatment group with a 12-month fellow-eye control group. Ideally, all fellow eyes would have been compared with treatment eyes. However, the protocol in this clinical trial allowed fellow-eye CXL 3 months after first-eye treatment. Therefore, in this study, the treatment group was compared only with the fellow eyes of patients who had unilateral treatment. Some fellow eyes in this study had no topographic or visual signs of keratoconus or ectasia. Thus, disease progression would be expected to be minimal.

The treatment group was compared with the 2 control groups. The changes in UDVA, CDVA, maximum K, and average K between baseline and 3 months in the sham control group were not significantly different than the changes in these measurements in the treatment group during the same 3-month period. However, treated eyes had significant improvement in UDVA, CDVA, maximum K, and average K compared with the fellow-eye controls. Thus, the efficacy of the CXL procedure in improving patient outcomes and stabilizing corneal ectatic progression over a 1-year period was clearly shown.

As seen, the basic clinical outcomes of CXL seem to follow a reproducible time course after treatment. In general, visual acuity and corneal steepness worsen somewhat at the 1-month time point. Resolution to baseline occurs by approximately 3 months, with improvement thereafter. This is similar to the clinical time course of CXL-associated corneal haze, which we reported elsewhere. 20 In these cases, the haze is greatest at 1 month, plateaus at 3 months, and decreases significantly between 3 months and 12 months postoperatively. Thus, stromal and epithelial healing responses to CXL appear to continue over months, concomitant with the changes in clinical outcomes, which we report here.

REFERENCES


OTHER CITED MATERIAL

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