Clinical and Corneal Biomechanical Changes After Collagen Cross-Linking With Riboflavin and UV Irradiation in Patients With Progressive Keratoconus: Results After 2 Years of Follow-up

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Purpose: To assess the biomechanical and keratometric effects and the safety of treatment of progressive keratoconus with UV–riboflavin collagen cross-linking (CXL).

Methods: This is a prospective clinical controlled study. Fourteen eyes of 14 patients with progressive keratoconus were treated with CXL after corneal deepithelization. Patients were assessed preoperatively, at week 1 and at months 1, 3, 6, 9, 12, and 24 after treatment. We measured uncorrected visual acuity (UCVA) and best spectacle–corrected visual acuity (BSCVA) (logarithm of the minimum angle of resolution), refraction, biomicroscopy and fundus examination, intraocular pressure, axial length, endothelial cell density, corneal topography, minimal corneal thickness, macular optical coherence tomography, and corneal biomechanics with the ocular response analyzer.

Results: Comparing the preoperative results with 24-month postoperative results, we observed significant improvement in BCVA (0.21 ± 0.1 to 0.14 ± 0.1, $P = 0.002$) and stability in UCVA (0.62 ± 0.5 and 0.81 ± 0.49, $P = 0.475$). We observed a significant decrease in steepest-meridian keratometry (diopters) (53.9 ± 5.9 to 51.5 ± 5.4, $P = 0.001$) and in mean cylinder (diopters) (10.2 ± 4.1 to 8.1 ± 3.4, $P = 0.001$). Significant elongation of the eyes was observed, from 24.39 ± 1.7 mm to 24.71 ± 1.9 mm ($P = 0.007$). No significant change was observed in mean simulated keratometry, minimal corneal thickness, endothelial cell density, corneal hysteresis, and corneal resistance factor or foveal thickness.

Conclusions: Two years after CXL, the observation of stable UCVA, improved BCVA, and reduced keratometry suggests stabilization in progression of keratoconus. Unchanged corneal thickness, endothelial cell density, and foveal thickness suggest the long-term safety of this procedure. The observed increase in axial length and stability in corneal biomechanical parameters measured with the ocular response analyzer require further study for verification and explanation.

Key Words: collagen cross-linking, riboflavin, UVA irradiation, progressive keratoconus

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Keratoconus is a progressive corneal degeneration resulting from noninflammatory thinning of the corneal stroma.[1] Visual impairment typically commences in adolescence and progresses thereafter.[2] Further increase in myopia, irregular astigmatism, and subepithelial scarring leads to visual impairment.[3] Current acceptable treatment modalities are based on refractive correction with spectacles and contact lenses to correct astigmatism and restore visual acuity.[4] Such modalities do not stop ectatic progression and further visual deterioration, which ultimately necessitates corneal transplantation in 10% to 20% of patients.[5]

Corneal collagen cross-linking (CXL) using UVA and riboflavin was introduced by Wollensak et al[6] as a method to halt the progression of keratoconus. This therapy aims to increase corneal biomechanical stability by inducing additional covalent binding between molecules of collagen. In vitro studies have shown increased corneal rigidity and increased corneal resistance to enzymatic degradation after CXL.[7–10] Recent clinical studies reported the efficacy and safety of this new treatment modality in reducing the progression of ectasia in keratoconus patients.[11–16] However, long-term analysis of corneal biomechanical changes and stability after CXL has not yet been reported. Corneal biomechanical properties may be assessed in vivo with the ocular response analyzer (ORA; Reichert, Inc, Buffalo, NY) and be presented by 2 parameters, corneal hysteresis (CH) and corneal resistance factor (CRF). The purpose of the current study was to evaluate long-term results, safety, and biomechanical effects of corneal CXL.

PATIENTS AND METHODS

Patients with keratoconus were prospectively recruited from the cornea outpatient clinic of the Assaf Harofeh Medical Center. Included were subjects with progressive keratoconus

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confirmed by an increase of at least 1.5 diopters (D) in astigmatic refraction and/or maximum curvature documented by corneal topography at 3 time points within the past 12 months. Other inclusion criteria were age more than 18 years, no previous ocular surgery, no corneal opacities, minimal corneal thickness (MCT) of 400 μm, and avoidance of contact lens wear for 1 month before initial evaluation and treatment. Patients were treated with UVA–riboflavin CXL under aseptic conditions using topical preoperative anesthesia with 0.4% oxybuprocaine hydrochloride drops (Localin; Fisher Pharmaceutical Labs). Treatment included 7-mm-diameter corneal deepithelization, instillation of 0.1% riboflavin in 20% dextran solution (Peschke Meditrade GmbH, Huenenberg, Switzerland) every 5 minutes for 40 minutes and corneal irradiation with 3 mW/cm^2 UVA (UV-X; Peschke Meditrade GmbH) for 30 minutes, 5 cm from the cornea with persistent application of 0.1% riboflavin in 20% dextran solution drops. After the procedure, patients were treated with a topical antibiotic (Oflox, 0.3% ofloxacin; Allergan) 4 times a day for 7 days and a topical corticosteroid (Sterodex, 0.1% dexamethasone; Fisher Pharmaceutical Labs) 4 times a day for 1 month, and the eye was dressed with a soft therapeutic contact lens (Ocular Sciences, Ltd, Southampton, United Kingdom) for 3 days. UV irradiance was checked preoperatively in each patient using a UV meter.

Patients were assessed preoperatively and at week 1 and at months 1, 3, 6, 12, and 24 after treatment. Each examination included measurement of uncorrected visual acuity (UCVA), best spectacle–corrected visual acuity (BCVA), and slit-lamp and dilated fundus examination. Corneal topography, pachymetry, endothelial cell density (ECD), intraocular pressure (IOP) by Goldmann applanation tonometry, central foveal thickness (CFT), and corneal biomechanical assessment using the ORA were assessed. Corneal topography and pachymetry were assessed preoperatively and at months 6, 9, 12, and 24 with Orbscan II (Bausch & Lomb, Claremont, CA). ECD was assessed preoperatively and at months 1, 6, 12, and 24 with the Konan Noncon Robo SP 6000 noncontact specular microscope (Konan Medical, Inc, Hyogo, Japan). CFT was assessed preoperatively and at months 3, 6, 9, 12, and 24 with Stratus optical coherence tomography (Zeiss Humphrey Instruments, Dublin, CA). Axial length (AL) was assessed preoperatively and at months 12 and 24 with IOL Master (Carl Zeiss Meditec AG, Jena, Germany). Corneal biomechanical properties were assessed preoperatively and at months 3, 6, 9, 12, and 24 with the ORA and are presented by 2 parameters, CH and CRF. The contact lens users were asked to remove the lens 14 days before each follow-up examination.

The study was approved by the Institutional Ethics Committee of Assaf Harofeh Medical Center, and a written informed consent form was obtained from each subject after the nature and intent of the study had been fully explained. The study protocol was consistent with the tenets of the Declaration of Helsinki.

Statistical Analysis

The data are presented as frequency or mean ± SD. Two linear mixed models have been used to examine the influence of several effects on the dependent variables. Both the models used time as fixed effect and subject as random effect. Treating subject as random effect is necessary because of the repeated-measures structure of the research. Ignoring that structure means a violation of the classical assumption of independency between observations. Because of this, it would be wrong to perform ordinary *t* tests.

However, the models treat the time effect differently. In the first model, time functions as an ordinal effect. Thus, the coefficients of its dummy variables express the marginal change in the dependent variable because of the sequential change in time. However, in the second model, time functions as a nominal effect. Therefore, its dummy variables are indicators for each category of time, in comparison to the base category—which is the first one. Thus, the coefficients of its dummy variables express the marginal change in the dependent variable when changing to some category of time, with comparison to the base category. The distributions of values within each data set were evaluated graphically. Analyses were performed using JMP-8 statistical software (SAS Institute, Inc). A *P* value of 0.05 was selected for the threshold of statistical significance.

RESULTS

Fourteen eyes of 14 patients (8 men and 6 women) aged 28.2 ± 5.9 years were included. The UCVA, BCVA, and subjective spherical equivalent (SE) refraction data are summarized in Table 1. BCVA was statistically significantly better at 12 and 24 months compared with the preoperative data ($P = 0.002$ and 0.018, respectively). The difference in BCVA between 12 and 24 months was not statistically significant ($P = 0.485$) (Fig. 1). UCVA did not show a statistically significant change at 12 and 24 months compared with that at baseline ($P = 0.43$ and 0.48, respectively). Mean SE decreased

TABLE 1. Visual Acuity and Refractive Error Before and After CXL

Parameter	Before CXL, Mean ± SD	6 mo After CXL, Mean ± SD	12 mo After CXL, Mean ± SD	24 mo After CXL, Mean ± SD	*P*				
					6 mo vs. Before	12 mo vs. Before	24 mo vs. Before	12 mo vs. 6 mo	24 mo vs. 12 mo
BCVA, logMAR	0.21 ± 0.1	0.17 ± 0.1	0.11 ± 0.1	0.14 ± 0.1	0.631	0.002	0.018	0.009	0.485
UCVA, logMAR	0.62 ± 0.5	1.02 ± 0.6	0.78 ± 0.6	0.81 ± 0.49	0.229	0.430	0.475	0.512	0.941
SE, D	−5.3 ± 3.8	−5.2 ± 3.6	−4.0 ± 3.2	−4.0 ± 3.3	0.583	0.061	0.017	0.175	0.549

logMAR, logarithm of the minimum angle of resolution.

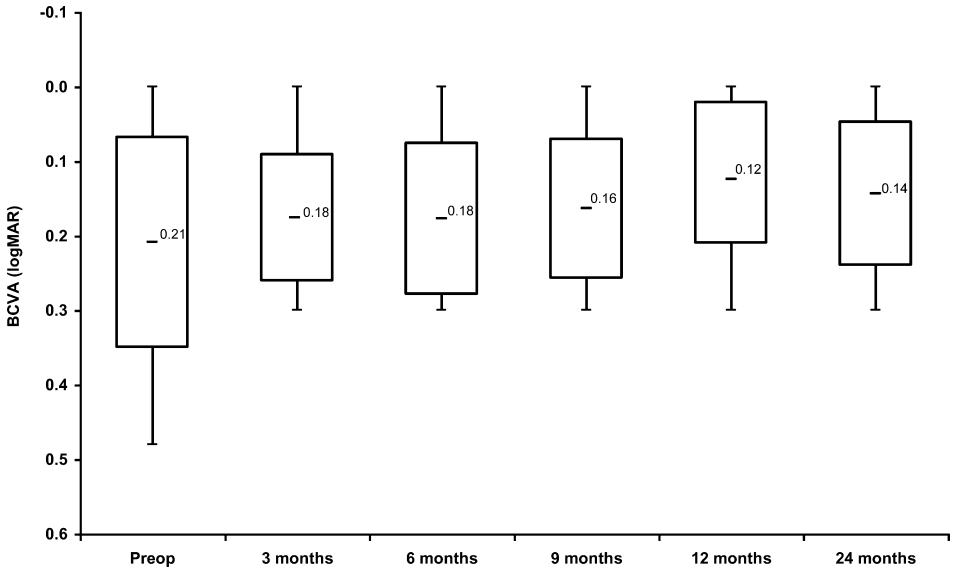

FIGURE 1. Box plots (mean ± SD) and whisker plots (smallest and largest values) showing BCVA (logarithm of the minimum angle of resolution) before treatment (Preop) and at 3, 6, 9, 12, and 24 months thereafter.

continuously during the 24-month follow-up, with the difference from baseline reaching borderline statistical significance at 12 months ($P = 0.061$) and definite significance at 24 months ($P = 0.017$). In 2 patients, SE was increased (−0.8 to −3.0 D and −2.6 to −3.8 D, respectively).

The steepest meridian keratometry (Kmax), flattest meridian keratometry (Kmin), mean cylinder (Kcyl = Kmax − Kmin), and average simulated keratometry (mean SimK), all showed a tendency to decrease continuously over the 24-month follow-up as shown in Table 2. Only changes from baseline in Kmax and Kcyl were statistically significant (Figs. 2, 3). In 1 patient, Kmax was increased (51.9–52.45 D), and in 13 patients (92.8%), Kmax was decreased at 24 months as compared with that at baseline. In 1 patient, Kcyl was increased from 5.35 to 6.47 D, and in 13 patients (92.8%), Kcyl was decreased at 24 months as compared with that at baseline. Changes in these 2 parameters between 6 and 24 months were not statistically significant. Both the measured biomechanical parameters, CH and CRF, did not show statistically significant changes throughout the study period (Table 2, Fig. 4).

AL was measured statistically significantly longer, 2 years after CXL treatment (Table 2). Mean IOP by Goldmann applanation tonometry was 10.14 ± 1.5 mm Hg before cross-linking, 11.08 ± 0.9 mm Hg 1 year after treatment ($P = 0.105$), and 10.82 ± 0.8 mm Hg 2 years after treatment ($P = 0.281$). There were no statistically significant differences between preoperative and postoperative values of ECD, MCT, and CFT at any time point during the follow-up (Table 2).

DISCUSSION

Our results suggest that treating progressive keratoconus with CXL leads to progressive corneal flattening with a slow but significant BCVA improvement during the subsequent 24 months. In this cohort, we did not observe significant improvement in UCVA or significant measurable change in corneal biomechanical parameters. Although treatment with CXL aims mainly to stop progression of ectasia, recent long-term studies have also reported decrease of the corneal curvature.[6,12,14] In this study, we observed significant flattening

TABLE 2. Study Parameters and Their Mean Change After CXL

Parameter	Before CXL, Mean ± SD	6 mo After CXL, Mean ± SD	12 mo After CXL, Mean ± SD	24 mo After CXL, Mean ± SD	*P* 6 mo vs. Before	*P* 12 mo vs. Before	*P* 24 mo vs. Before	*P* 12 mo vs. 6 mo	*P* 24 mo vs. 12 mo
CH, mm Hg	8.24 ± 1.8	7.94 ± 1.4	7.61 ± 1.8	7.34 ± 1.6	0.534	0.100	0.157	0.291	0.856
CRF, mm Hg	7.0 ± 1.7	7.38 ± 1.3	6.44 ± 1.4	6.58 ± 0.8	0.276	0.067	0.915	0.006	0.095
CFT, μm	203 ± 21	203 ± 17	205 ± 22	202 ± 19	0.436	0.839	0.157	0.563	0.221
ECD, cells/mm^2	2730 ± 261	2793 ± 290	2640 ± 266	2541 ± 344	0.352	0.497	0.209	0.139	0.487
MCT, μm	461 ± 38	441 ± 47	478 ± 52	466 ± 46	0.057	0.484	0.704	0.021	0.357
AL, mm	24.39 ± 1.7	—	24.42 ± 1.8	24.71 ± 1.9	—	0.095	0.007	—	0.206
Kmax, D	53.9 ± 5.9	53.1 ± 5.5	52.1 ± 5.0	51.5 ± 5.4	0.045	0.009	0.001	0.568	0.265
Kmin, D	44.3 ± 2.6	44.2 ± 3.3	43.7 ± 2.8	43.6 ± 3.5	0.215	0.150	0.088	0.918	0.737
Kcyl, D	10.2 ± 4.1	9.0 ± 3.6	8.3 ± 3.2	8.1 ± 3.4	0.030	0.012	0.001	0.834	0.211
Mean SimK, D	46.2 ± 2.8	46.3 ± 3.3	45.6 ± 2.9	45.5 ± 3.6	0.732	0.195	0.112	0.342	0.722

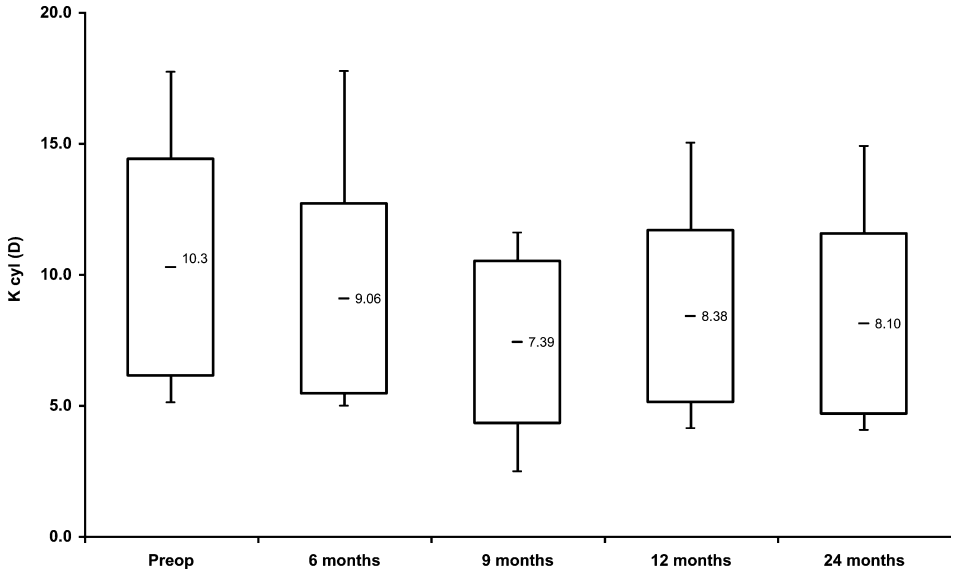

FIGURE 2. Box plots (mean ± SD) and whisker plots (smallest and largest values) showing mean cylinder (diopters) before treatment (Preop) and at 6, 9, 12, and 24 months thereafter.

of the steepest meridian by 2.4 D, on average. This is similar to previous published results. Wollensak et al[6] reported reduction of the maximal keratometry readings by 2.01 D, Vinciguerra et al[12] reported a mean 1.3 D reduction of the maximal keratometry after 2 years of follow-up, and Raiskup-Wolf et al[14] reported a 1.9 D decrease in steepest meridian after 2 years of follow-up. The mechanism underlying the observation by us and others that corneal flattening seems to continue even up to 2 years after CXL remains unclear.

CXL of collagen supposedly halts progression of keratoconus by increasing the stiffness of the cornea,[6] so some change in corneal biomechanical properties is intuitively expected. Several in vitro studies described physical changes in the cornea after cross-linking.[8,9] Wollensak et al[8] used stress–strain measurements to evaluate the effect of riboflavin–UVA CXL on corneal rigidity in human and porcine corneas. Using a microcomputer-controlled biomaterial tester, they showed a significant increase in rigidity in both human and porcine corneas. Dupps et al[9] used an ultrasonic device to evaluate the effect of human and porcine corneal cross-linking with glutaraldehyde. Through measuring sonic wave propagation time between 2 transducers positioned on the corneal surface, they found increased corneal stiffening after the procedure. Mattson et al[17] measured the tissue mechanical response to elevated IOP using photography of rabbit eyes. They reported that both riboflavin–UVA and glyceraldehyde cross-linking treatments reduced corneal expansion, implying increased mechanical stability.[17] In contrast to these in vitro studies, in our study, we did not observe significant changes in biomechanical properties of the cornea after CXL for keratoconus as measured in vivo by ORA. We previously published similar results after 6 months of follow-up.[18]

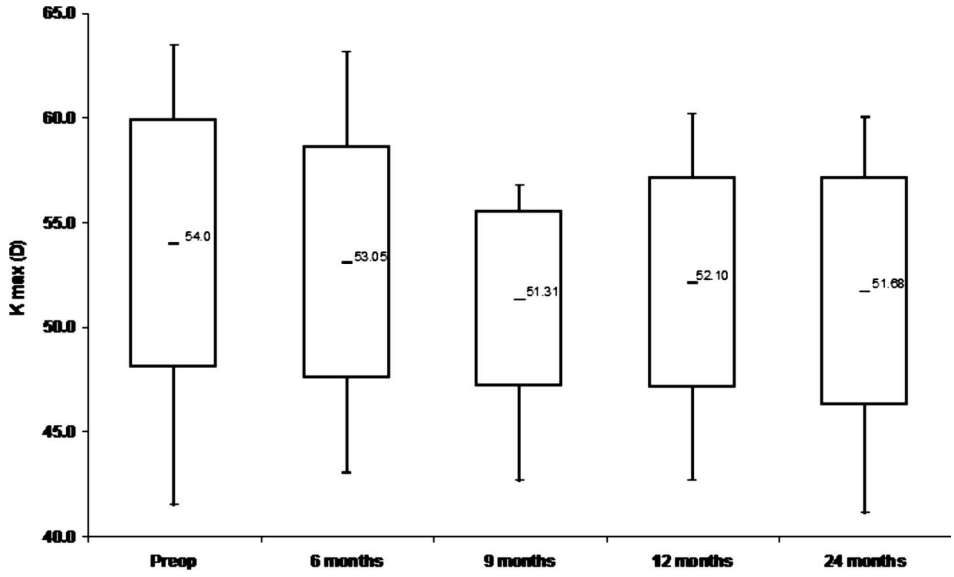

FIGURE 3. Box plots (mean ± SD) and whisker plots (smallest and largest values) showing steepest meridian keratometry (diopters) before treatment (Preop) and at 6, 9, 12, and 24 months thereafter.

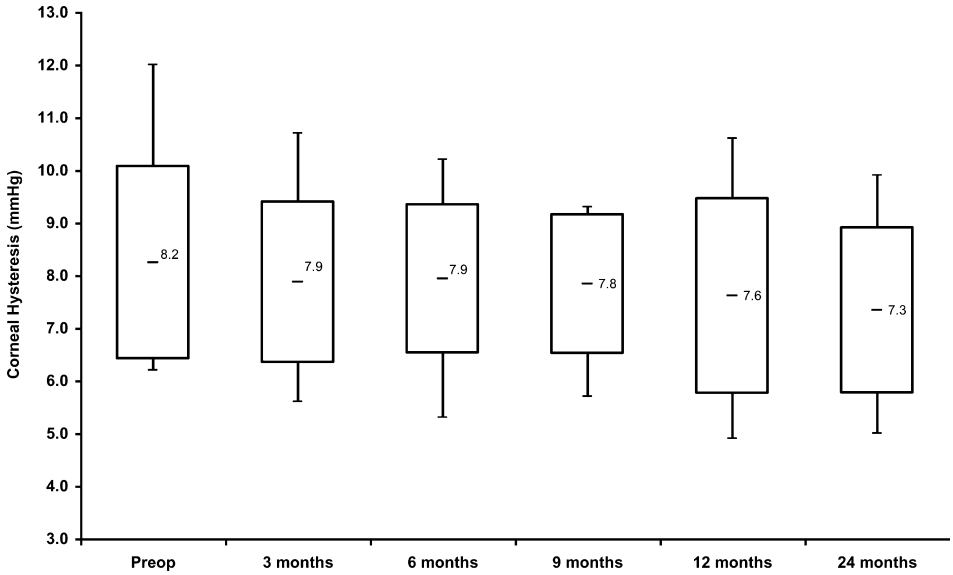

FIGURE 4. Box plots (mean ± SD) and whisker plots (smallest and largest values) showing CH (millimeters of mercury) before treatment (Preop) and at 3, 6, 9, 12, and 24 months thereafter.

Spörl et al[19] did not observe a significant difference in the CH or the CRF before and after CXL. Similarly, Vinciguerra et al[20] reported stability in biomechanical parameters measured by ORA 1 year after CXL. The possibility that biomechanical changes induced by CXL are too subtle to be measured by ORA or have characteristics not measured well by ORA remains unclear and requires further study.

We did not observe any change in the mean UCVA at 1 year and 2 years after CXL. The mean BCVA at 12 and 24 months was significantly improved from baseline (Table 1), but the change between 12 and 24 months was not statistically significant ($P = 0.485$). A decrease in BCVA was observed in 1 patient (0–0.1 logarithm of the minimum angle of resolution). Although CXL primarily aims to reduce progression of keratoconus and thus stabilize visual acuity, other short- and long-term studies have reported significant continuous improvement in visual acuity after CXL. Caporossi et al[13] reported significant improvement in both UCVA and BCVA after 6 months of follow-up, Wittig-Silva et al[16] after 1 year, and Vinciguerra et al[12] 2 years after CXL. Grewal et al[15] reported stable BCVA after the 1-year follow-up. Considering the proposed mechanism of cross-linking between collagen fibers induced by UVA–riboflavin, we anticipated only stabilization of progressive keratoconic changes; the reported significant improvements in VA as well as decreased keratometric indices remain unclear. Caporossi et al[13] suggested that the improvement in BCVA is secondary to an increase in morphologic symmetry with consequent reduction in coma aberrations.

Using subjective refraction to monitor changes after treatment in patients with keratoconus is problematic, as the cornea is highly irregular and asymmetric and so the measurement is variable. This may explain some of the differences in visual acuity results reported by different observers, as well as differences in reported changes in subjective refraction. In the present study we observed a decrease in manifest SE, similar to reports by Caporossi et al,[13] Wollensak et al,[6] and Vinciguerra et al.[12] However, stability of SE was observed by Wittig-Silva et al[16] and Grewal et al.[15] Another explanation for these differences may be the unmasked nature of the studies.

We did not observe a significant change in ECD throughout the 2-year study period. This finding is important when considering the long term safety of this novel procedure. We used a multi-diode array CXL lamp system, which emits the UV light via a special optical system (Koehler optics) that makes the unit much less responsive to slight variations in illumination distance. This way, the risk of focal overexposure is minimized due to a very smooth distribution of light over the cornea. Stability of ECD using a similar irradiation system was also reported by Witting-Silva et al[16] and Vinciguerra et al.[12] During our study we followed the safety criteria recommended by Wollensak et al[21]: we included patients with MCT of at least 400 μm and kept the cornea constantly saturated with riboflavin solution before and during UV irradiation to provide a shielding effect.

Lack of any retinal change is another important parameter when the safety of ocular UVA irradiation is considered. Using optical coherence tomography we observed stable foveal thickness during 2 years after CXL. A similar observation was reported by Grewal et al[15] after the 1-year follow-up. Importantly, both the reports show only anatomical stability, and so additional studies are needed to assess functional retinal safety.

We noted prolonged mild corneal haze in 2 patients, with complete resolution in 1 patient after 9 months. Recently, Koller et al[22] reported a persistent corneal scar in 3 eyes (2.9% of treated patients) after 1 year.

The role of AL in the progressive myopic shift in keratoconic patients is unknown. No study has been conducted to evaluate the progressive change of AL in keratoconus and its contribution to the myopic shift. In our study, using the IOLMaster, we noticed an increase in AL 2 years after CXL. This change, from 24.39 ± 1.7 mm to 24.71 ± 1.9 mm, was statistically significant ($P = 0.007$). Measurement of AL with IOLMaster has been shown to be highly repeatable, and

therefore, we think it is unlikely that the measured difference derived from measurement variability.[23] Theoretically, progressive elongation of the study eyes, mainly the posterior segment, that is unrelated to the treatment, could have taken place. Whether peculiar properties of scleral collagen in keratoconic eyes are responsible for this observation is unclear, and additional studies may be needed in this regard. Although being statistically significant, the clinical significance of this observation also remains unclear because despite the increase in AL, the mean SE decreased, probably resulting from the observed corneal flattening.

In conclusion, 2 years after CXL for progressive keratoconus, we observed stabilization of visual acuity and keratometric indices in most subjects. The underlying biomechanical processes that take place in the corneal stroma after CXL remain unclear. The long-term effect and safety of this procedure require further study.

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