

# Two-Year Corneal Cross-Linking Results in Patients Younger Than 18 Years With Documented Progressive Keratoconus

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- **PURPOSE:** To report refractive, topographic, aberrometric, and tomographic outcomes 24 months after corneal cross-linking (CXL) in patients up to 18 years of age with progressive keratoconus.
- **DESIGN:** Prospective, interventional case series.
- **METHODS:** Forty eyes underwent riboflavin-ultraviolet A-induced CXL. Uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), sphere and cylinder, topography, aberrometry, tomography, and endothelial cell counts were evaluated at baseline and at 1, 3, 6, 12, and 24 months.
- **RESULTS:** Mean logarithm of the minimum angle of resolution baseline UCVA and BSCVA were  $0.79 \pm 0.21$  and  $0.39 \pm 0.10$ , respectively. Mean UCVA and BSCVA at 2 years were  $0.58 \pm 0.18$  and  $0.20 \pm 0.09$ , respectively. The improvement in UCVA and BSCVA was significant throughout the postoperative follow-up ( $P < .05$ ). Mean spherical equivalent refraction showed a significant decrease of 1.57 diopters (D) at 24 months ( $P = .02$ ). Mean baseline simulated keratometry was 46.32 D in the flattest meridian and 51.48 D in the steepest meridian; at 2 years, the values were 45.30 D ( $P = .04$ ) and 50.21 D ( $P = .07$ ), respectively. For a 3-mm pupil, there was a significant reduction ( $P < .05$ ) in whole eye (total), corneal, higher-order, and astigmatic wavefront aberrations at 24 months. A significant difference ( $P < .05$ ) in total coma and total spherical aberration 2 years after CXL also was observed. Mean baseline pupil center pachymetry decreased significantly ( $P = .04$ ) at 6 months, but recovered by 12 months and remained stable thereafter through the 2-year follow-up. Endothelial cell counts did not change significantly ( $P = .32$ ).
- **CONCLUSIONS:** CXL improved UCVA and BSCVA in the study patients, most likely by significantly reducing corneal asymmetry and corneal as well as total wavefront aberrations. (Am J Ophthalmol 2012;154:520–526. © 2012 by Elsevier Inc. All rights reserved.)

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**K**ERATOCONUS IS A SLOWLY PROGRESSIVE, NONINflammatory corneal dystrophy characterized by changes in corneal collagen structure and organization.<sup>1–3</sup> A reduced number of collagen cross-links and a pepsin digestion higher than normal have been suggested as possible explanations for an overall structural weakness of the corneal tissue in keratoconus, resulting in a stiffness that is only 60% of the normal cornea.<sup>4</sup> Decreased mechanical corneal stability plays an important role in the progressive ectasia of the keratoconic cornea, resulting in mild to marked impairment of visual acuity resulting from irregular astigmatism, progressive myopia, corneal thinning, and central corneal scarring.<sup>5</sup>

Progression of the disease can be dramatically faster in children, with increasing visual impairment, inability to obtain satisfactory correction with spectacles or soft contact lenses, and intolerance to rigid gas permeable contact lenses. Intracorneal ring segments implantation improves uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) in patients with mild to moderate keratoconus and contact lens intolerance.<sup>6–8</sup> However, long-term follow-up has shown that intracorneal ring segment implantation fails to provide a permanent flattening of the cornea. A significant progression of K-values in intracorneal ring segment-treated corneas has been observed,<sup>7</sup> demonstrating that this procedure has only a temporary effect.

Collagen cross-linking (CXL) was introduced by Wollensak and associates to stabilize progressive keratoconus, to prevent some of the underlying pathophysiologic mechanisms of the disease, and to avoid the need for penetrating keratoplasty, which is usually required in advanced cases.<sup>9–15</sup> The peer-reviewed literature, as well as our own experience with adult eyes that underwent CXL for progressive keratoconus and iatrogenic ectasia, demonstrated that the procedure was able to arrest progression. Further, no endothelial cell loss, no cataract development, and no permanent side effects were observed in the adults.<sup>16–19</sup>

Accordingly, we initiated a CXL study in patients younger than 18 years with progressive stage II keratoconus (Amsler-Krumeich classification). In this cohort, we examined the refractive, topographic, aberrometric, and tomographic outcomes at 24 months after CXL.

## METHODS

• **POPULATION:** Forty eyes of 40 consecutive white patients (9 females, 31 males) in which keratoconus progression was observed in the preceding 3 months were enrolled at the Departments of Ophthalmology, Istituto Clinico Humanitas, Rozzano-Milano, Italy, and Inselspital University Hospital, Bern, Switzerland, in 2008 in this prospective, nonrandomized, study.

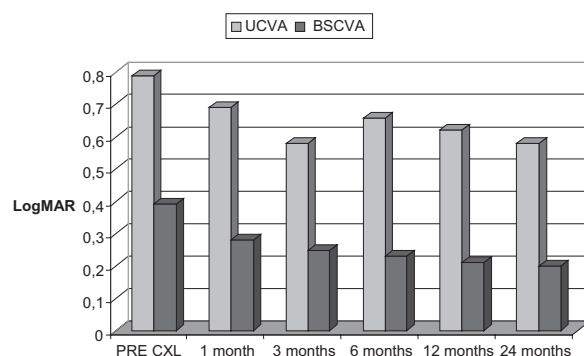
Preoperative keratoconus progression was confirmed by serial differential corneal topographies and by differential optical pachymetry analyses in all eyes included in the study.<sup>20</sup> Keratoconus progression was defined as a change in either myopia or astigmatism of at least 3.0 diopters (D) in the previous 3 months, or a mean central K reading change of at least 1.5 D observed in 2 consecutive topographies during the preceding 3 months, or a mean central corneal thickness decrease of at least 5% in 3 consecutive tomographies performed in the previous 3 months. The Amsler-Krumeich classification was used for keratoconus grading.<sup>21</sup> The corneal higher-order aberrations scale could not be used as a measure of progression because many ophthalmologists who referred patients for keratoconus progression did not provide aberration data.<sup>22,23</sup>

Inclusion criteria were a documented keratoconus progression in the previous 3 months, corneal thickness of at least 400  $\mu\text{m}$  at the thinnest point, and age up to 18 years. The age of the patients included in the study ranged from 9 to 18 years (mean,  $14.2 \pm 1.7$  years). All treated eyes were graded stage II according to the Amsler-Krumeich classification.

Exclusion criteria included corneal thickness less than 400  $\mu\text{m}$  at the thinnest point,<sup>12-14,16</sup> a history of herpetic keratitis, severe dry eye, concurrent corneal infections, concomitant autoimmune diseases, and any previous ocular surgery. Also excluded were patients with central or paracentral corneal opacities, patients with poor compliance, and patients wearing rigid gas permeable lenses for at least 4 weeks before baseline examination.

At baseline and at each of the postoperative follow-up examinations (1, 3, 6, 12, and 24 months), all patients underwent UCVA and BSCVA assessment; slit-lamp biomicroscopy; basal Schirmer testing; Goldmann tonometry; dilated fundus examination; endothelial biomicroscopy (Konan Specular Microscope; Konan Medical Inc, Hyogo, Japan); corneal topography; corneal, internal, and total aberrometry with the Optical Path Difference Platform (OPD; NIDEK, Gamagori, Japan); and central pachymetry and optical tomography with the Pentacam HR (Oculus Inc, Lynnwood, Washington, USA).

• **VISUAL ACUITY ASSESSMENT:** Visual acuity was assessed with the Early Treatment Diabetic Retinopathy Study logarithm of the minimal angle of resolution charts (Lighthouse International, New York, New York, USA) based on the design suggested by Bailey and Lovie and incorporating the recommendations of the U.S. National



	PRE CXL	1 month	3 months	6 months	12 months	24 months
UCVA	0.79±0.21	0.69±0.16	0.58±0.20	0.66±0.17	0.62±0.19	0.58±0.18
BSCVA	0.39±0.10	0.28±0.13	0.25±0.09	0.23±0.11	0.21±0.11	0.20±0.09

FIGURE 1. Bar graph showing cross-linking (CXL) uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) results in the 40 treated pediatric patients with progressive keratoconus before and after CXL.

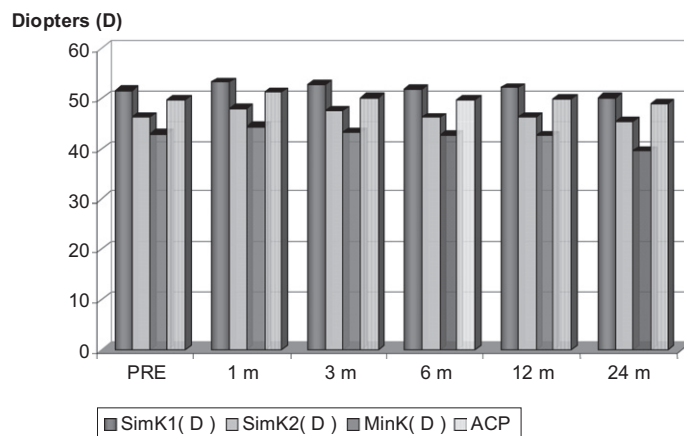
Academy of Sciences–National Research Council.<sup>24,25</sup> The chart was described in detail by Ferris and associates.<sup>26</sup> Measurements were made with best correction after a noncycloplegic refraction at 4 m.

• **CORNEAL TOPOGRAPHY:** Topography was analyzed with the OPD unit. The OPD documented the 21 Klyce indices provided by the Corneal Navigator Topo-Classifer Map (OPD; NIDEK, Gamagori, Japan). In keratoconus diagnosis, the Navigator was found to be more specific and sensitive than the Rabinowitz-McDonnell test and also more specific and sensitive than central corneal power of more than 47.2 D or inferosuperior asymmetry of more than 1.4 D.<sup>27-30</sup>

• **WAVEFRONT ANALYSIS:** Total (corneal and internal) wavefront analysis was performed with the OPD-Scan, which provides an aberrometric analysis of the eye, decomposing whole eye (total) aberrations into corneal aberrations resulting from the anterior corneal surface and internal aberrations because of the posterior corneal surface, the anterior chamber, the lens, the vitreous body, and the retina.

• **ANTERIOR CHAMBER ANALYSIS:** Anterior chamber analysis was performed with the Oculus Pentacam HR, which uses a rotating Scheimpflug camera.<sup>31-34</sup> The analyses performed with the Pentacam included pupil center pachymetry and the pachymetry of the thinnest point of the cornea. The Pentacam also measured total and partial corneal volume, anterior chamber volume, and anterior chamber depth. Anterior and posterior elevation maps are derived by using a toric reference body, with calculations based on the central radii and the eccentricity of the keratometry measurements. The advantage of the toric reference shape is its good approximation to astigmatic corneas.

## TOPOGRAPHIC RESULTS



	PRE CXL	1 month	3 months	6 months	12 months	24 months	<i>P</i> PRE CXL-24 m
Sim K1 (D)	51.48±3.4	53.12±3.5	52.78±3.3	51.81±3.4	52.16±3.5	50.21±3.2	0.07
Sim K2 (D)	46.32±3.0	47.98±3.1	47.52±3.2	46.19±2.9	46.26±2.5	45.30±2.7	0.04
Min K (D)	42.95±1.9	44.34±2.8	43.22±2.7	42.73±2.0	42.61±2.2	39.47±1.7	0.01
ACP	49.69±3.2	51.22±3.4	50.12±3.3	49.57±2.9	49.95±3.0	48.90±2.8	0.03

Sim K1 = Simulated keratometry in the steepest meridian  
 Sim K2 = Simulated keratometry in the flattest meridian  
 Min K = Minimum keratometry  
 ACP = average corneal power

FIGURE 2. Bar graph showing cross-linking (CXL) results in pediatric patients with progressive keratoconus. Topographic findings illustrating changes in keratoconus indices (before versus after cross-linking) as measured with the optical path difference scan. ACP = average corneal power; m = months; PRE = before treatment.

- **ENDOTHELIAL CELL COUNT:** Endothelial cell count was performed according to the method described by Prinz and associates.<sup>35</sup>

- **CROSS-LINKING PROCEDURE:** Thirty minutes before the procedure, systemic pain medication was administered and pilocarpine 2% drops were instilled in the eye to be treated. CXL was performed under sterile conditions in the surgical suite. Children younger than 15 years of age had 1 parent attend the procedure.

After topical anesthesia with 2 applications of lidocaine 4% and oxybuprocaine hydrochloride 0.2% drops, the patient was draped, the ocular surface was rinsed with balanced salt solution, and a lid speculum was applied. The corneal epithelium was abraded in a central, 9-mm diameter area with the aid of an Amoils brush (Vision Technology Co Ltd, Seoul, Korea).

Before beginning ultraviolet A irradiation, Ricrolin (SOOFT, Montegiorgio, Italy), a photosensitizing riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran-T-500) was applied onto the cornea every minute for 30 minutes to achieve adequate penetration of the solution. Using a slit lamp with the blue filter, the surgeon confirmed the presence of riboflavin in the anterior chamber before ultraviolet irradiation was started. The cornea was exposed to a ultraviolet source emanating from a

solid-state device (CSO-VEGA X-linker; Scandicci, Firenze, Italy) that emits light at a wavelength of  $370 \pm 5$  nm and an irradiance of  $3 \text{ mW/cm}^2$  or  $5.4 \text{ J/cm}^2$ . Exposure lasted for 30 minutes, during which time riboflavin solution again was applied, this time once every 5 minutes. The cropped light beam has a 7.5-mm diameter. A calibrated ultraviolet A meter (LaserMate-Q; Laser 2000, Wessling, Germany) was used before treatment to check the irradiance at a 1.0-cm distance. The CSO-VEGA laser emission probe has only 1 central light-emitting diode radiation source to be held 54 mm from the treated eye. Intraoperative pachymetry was performed throughout the procedure. Fixation during irradiation was achieved by instructing the patient to focus on the central LED of the probe. During the procedure, the surgeon also controlled for centration of treatment. Both topical anesthetics were added as needed during irradiation.

After surgery, patients received cyclopentolate (Ciclolux; Allergan, Roma, Italy) and levofloxacin drops (Ofaquix; Tubilux Pharma, Pomezia, Italy). A soft bandage contact lens was applied until re-epithelialization was complete. Topical levofloxacin was given 4 times daily for 7 days, dexamethasone 21-phosphate 0.15% drops (Etacortilen; Sifi, Laviniaio, Italy) were administered 3 times daily for 20 days, and sodium hyaluronate 0.15% drops (BluYal; SOOFT) were applied 6 times daily for 45 days. In addition, patients received oral

**TABLE 1.** Cross-Linking Results in Pediatric Patients with Progressive Keratoconus: Changes in Klyce Indices as Measured with the Optical Path Difference Scan

	Before Cross-Linking	1 Year after Cross-Linking	2 Years after Cross-Linking
Simulated keratometry in the steepest meridian (D)	51.48	52.16	50.21
Simulated keratometry in the flattest meridian (D)	46.32	46.26	<b>45.30</b>
Minimum keratometry (D)	42.95	42.61	<b>39.47</b>
Average corneal power (D)	49.69	49.95	<b>48.90</b>
Simulated keratometry cylinder (D)	6.05	6.05	<b>5.57</b>
Coefficient of variation of corneal power <sup>a</sup>	100.99	99.04	<b>99.37</b>
Standard deviation of corneal power <sup>a</sup>	4.97	4.78	<b>4.8</b>
Corneal eccentricity index <sup>a</sup>	1.05	0.9	<b>0.84</b>
Logarithm of the minimal angle of resolution <sup>a</sup>	0.29	0.28	<b>0.27</b>
Differential sector index <sup>a</sup>	11.10	11.20	12.05
Surface regularity index <sup>a</sup>	1.66	1.67	<b>1.58</b>
Area compensated surface regularity index <sup>a</sup>	1.46	1.48	<b>1.44</b>
Surface asymmetry index <sup>a</sup>	2.61	2.58	2.68
Irregular astigmatism index <sup>a</sup>	0.63	0.63	<b>0.62</b>
Opposite sector index <sup>a</sup>	8.87	8.81	9.41
Center surround index <sup>a</sup>	3.21	2.68	<b>2.45</b>
Keratoconus index <sup>a</sup>	0.79	0.75	<b>0.74</b>
Keratoconus prediction index <sup>a</sup>	0.41	0.39	<b>0.40</b>
Elevation/depression power (D)	3.69	3.88	<b>3.64</b>
Elevation/depression diameter (mm)	14.88	13.59	14.49

D = diopters.

Statistically significant differences between preoperative and postoperative data ( $P < .05$ ) are shown in boldface.

<sup>a</sup>Absolute index.

amino-acid supplements (Trium; SOOFT) for 7 days.<sup>36</sup> Patients were examined daily until the epithelium healed.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed with the Statistica computer package (StatSoft Inc, Tulsa, Oklahoma, USA). All data are reported as mean  $\pm$  standard deviation. Normality of the data was tested using the Wilcoxon test and was chi-square corrected with the Fisher test, when necessary. Comparisons were performed using the Student t test. The level of statistical significance was set at  $P < .05$ .

## RESULTS

• **VISUAL ACUITY:** UCVA and BSCVA data, expressed in logarithm of the minimal angle of resolution units and covering the entire follow-up period, are summarized in Figure 1. Mean  $\pm$  standard deviation (SD) baseline UCVA was  $0.79 \pm 0.21$ . Mean  $\pm$  SD UCVA readings after CXL were as follows: 1 month after CXL,  $0.69 \pm 0.16$ ; 3 months after CXL,  $0.58 \pm 0.20$ ; 6 months after CXL, was  $0.66 \pm 0.17$ ; 12 months after CXL,  $0.62 \pm 0.19$ ; and at 24 months after CXL,  $0.58 \pm 0.18$ . Mean  $\pm$  SD baseline BSCVA was  $0.39 \pm 0.10$ . Mean  $\pm$  SD BSCVA readings after CXL were as follows: 1 month after CXL,  $0.28 \pm 0.13$ ; 3 months after CXL,

$0.25 \pm 0.09$ ; 6 months after CXL,  $0.23 \pm 0.11$ ; 12 months after CXL,  $0.21 \pm 0.11$ ; and 24 months after CXL,  $0.20 \pm 0.09$ .

UCVA and BSCVA improvements were statistically significant ( $P < .05$ ) throughout the entire postoperative period when compared with the preoperative values. Both UCVA and BSCVA improved significantly during the first 6 months after CXL and remained unchanged between 6 and 24 months after surgery.

• **REFRACTIVE RESULTS:** The mean  $\pm$  SD preoperative spherical equivalent was  $-3.63 \pm 3.45$  D, with a mean  $\pm$  SD sphere of  $-2.32 \pm 2.87$  D and a mean  $\pm$  SD cylinder of  $-2.87 \pm 1.12$  D. Two years after CXL, mean  $\pm$  SD spherical equivalent was  $-2.06 \pm 2.21$  D, mean  $\pm$  SD sphere was  $-1.38 \pm 1.64$  D, and mean  $\pm$  SD cylinder was  $-1.56 \pm 1.38$  D. The difference in mean spherical equivalent was 1.57 D, a statistically significant reduction ( $P = .02$ ) because of a statistically significant decrease of both sphere ( $P = .01$ ) and cylinder ( $P = .02$ ). Vector analysis showed an axis shift from  $100.72 \pm 32.16$  degrees to  $110 \pm 41.29$  degrees after CXL, a difference that was not statistically significant ( $P = .15$ ).

• **TOPOGRAPHIC RESULTS:** Topographic astigmatism measured with the OPD-Scan during follow-up is shown in Figure 2. Mean baseline simulated keratometry 2, simu-

**TABLE 2.** Cross-Linking Results in Pediatric Patients with Progressive Keratoconus: Changes in Corneal Geometry as Measured with the Pentacam Scheimpflug Unit (before versus after Cross-Linking)

	Before Cross-Linking	After Cross-Linking (mos)			
		3	6	12	24
Pupil center pachymetry ( $\mu\text{m}$ )	489	415	471	480	522
Thinnest point ( $\mu\text{m}$ )	467	420	452	462	481
Chamber volume ( $\text{mm}^3$ )	222	225	214	217	220
Anterior chamber depth (mm)	3.50	3.58	3.41	3.46	3.56
Posterior best fit sphere (D)	5.39	5.19	5.47	5.54	5.54
Anterior best fit sphere (D)	6.77	6.63	6.91	6.41	7.36
Total corneal volume ( $\text{mm}^3$ )	57	55	57	57	65

D = diopters.

The differences between these parameters were not statistically significant ( $P > .05$ ).

lated keratometry 1, and minimum keratometry were 46.32 D, 51.48 D, and 42.95 D, respectively. At 24 months, these readings were 45.30 D, 50.21 D, and 39.47 D, respectively, a difference that was statistically significant for simulated keratometry 2 ( $P = .04$ ) and minimum keratometry ( $P = .01$ ). Mean average corneal power was 49.69 D at baseline and 48.90 D at 24 months, a difference that was statistically significant ( $P = .03$ ). These results demonstrate a flattening effect of CXL on the keratoconic cornea. The Klyce indices<sup>27</sup> obtained with the OPD platform were analyzed at baseline and at 24 months (Table 1).

• **ABERROMETRIC RESULTS:** Wavefront analysis performed with the OPD-Scan showed mean  $\pm$  SD baseline total (corneal and internal) aberrations for a 3-mm pupil at  $1.98 \pm 0.32 \mu\text{m}$ . By 24 months, they had decreased to  $1.15 \pm 0.24 \mu\text{m}$ . Mean  $\pm$  SD baseline total higher-order aberrations were  $0.38 \pm 0.09 \mu\text{m}$ , decreasing to  $0.26 \pm 0.07 \mu\text{m}$  by 24 months. Mean  $\pm$  SD baseline total astigmatism decreased from  $0.09 \pm 0.03 \mu\text{m}$  to  $0.06 \pm 0.02 \mu\text{m}$ . Mean baseline total coma was down from  $0.57 \pm 0.15 \mu\text{m}$  to  $0.44 \pm 0.09 \mu\text{m}$ , and mean baseline total spherical aberrations decreased from  $0.14 \pm 0.05 \mu\text{m}$  to  $0.10 \pm 0.02 \mu\text{m}$ . All of the above differences were statistically significant ( $P < .05$ ).

Mean  $\pm$  SD baseline corneal aberrations for a 3-mm pupil decreased from  $1.63 \pm 0.35 \mu\text{m}$  to  $1.45 \pm 0.32 \mu\text{m}$ , mean  $\pm$  SD baseline corneal higher-order aberrations decreased from  $0.56 \pm 0.11 \mu\text{m}$  to  $0.43 \pm 0.12 \mu\text{m}$ , and mean  $\pm$  SD baseline corneal astigmatism decreased from  $0.98 \pm 0.12 \mu\text{m}$  to  $0.86 \pm 0.13 \mu\text{m}$ . All differences were statistically significant ( $P < .05$ ) at 24 months. No statistically significant changes in corneal coma and corneal spherical aberration were observed.

• **TOMOGRAPHIC RESULTS:** Mean  $\pm$  SD pupil center pachymetry and corneal pachymetry at the thinnest point measured, by means of Pentacam optical pachymetry at baseline, were  $489 \pm 25 \mu\text{m}$  and  $467 \pm 23 \mu\text{m}$ , respectively. At 6 months, they decreased to  $471 \pm 15 \mu\text{m}$  and

$452 \pm 12 \mu\text{m}$ , respectively, a difference that was statistically significant ( $P = .04$ ). Compared with the preoperative data, there was no statistically significant difference in pupil center pachymetry and thinnest point at 12 or at 24 months. Mean  $\pm$  SD total corneal volume increased from  $57 \pm 5 \text{mm}^3$  to  $65 \pm 4 \text{mm}^3$  by 24 months, anterior chamber volume and anterior chamber depth remained stable, and anterior as well as posterior elevation had increased by 24 months, as seen in Table 2. Despite these measurable changes, the differences between these parameters were not statistically significant ( $P > .05$ ).

• **ENDOTHELIAL RESULTS:** Mean  $\pm$  SD baseline endothelial cell count was  $3221 \pm 212 \text{cells/mm}^2$ . One month after CXL, it was  $2876 \pm 456 \text{cells/mm}^2$ ; at 3 months after CXL, it was  $2912 \pm 433 \text{cells/mm}^2$ ; at 6 months after CXL,  $3018 \pm 361 \text{cells/mm}^2$ ; at 12 months after CXL, it was  $3189 \pm 342 \text{cells/mm}^2$ ; and at 24 months after CXL, the count was  $3209 \pm 178 \text{cells/mm}^2$ . The difference between baseline and 24 months was not statistically significant ( $P = .25$ ), indicating that CXL did not induce endothelial cell damage in the 2-year follow-up period.

• **OTHER FINDINGS:** Abrasion-related discomfort was reported by most patients in the immediate postoperative period. No ocular or systemic adverse events were noted, apart from a 5% incidence of blepharitis and 3% of the patients reporting mild photophobia at 4 months. No significant intraocular pressure change was seen. In 62% of eyes, CXL-specific golden striae<sup>9</sup> developed, and 6.9% of the eyes had a 1+ haze (Hanna scale). The haze regressed after 1 month with the topical steroids regimen.

## DISCUSSION

WE EVALUATED THE 2-YEAR POSTOPERATIVE REFRACTIVE, topographic, aberrometric, and tomographic results in a group of young patients with a mean  $\pm$  SD age of  $14.2 \pm 1.7$  years

who had been treated with corneal CXL for progressive keratoconus.

After an initial worsening of all keratoconus indices, probably because of the epithelial debridement,<sup>37-39</sup> refractive and topographic outcomes showed a slow but continuous improvement of most of the indices up to 24 months after surgery. The significant reduction of simulated keratometry, apical corneal power, total and corneal aberrations, and the Klyce indices all document the progressive flattening of the ectatic cornea. These findings also explain both the significant decrease in sphere and cylinder ( $P < .05$ ) and the significant improvement of UCVA and BSCVA observed during the first 6 postoperative months. Similar results were found in adult keratoconus stage III eyes reported by our group, by Caporossi and associates, and by Wollensak and associates.<sup>9,17,19,40</sup>

Analysis of total (whole eye) aberrations showed a significant reduction in astigmatism, coma, and spherical aberrations. However, corneal surface aberrometric analysis did not show an improvement in coma, suggesting that there may be a change in the posterior surface of the cornea, which is masked by the total aberration status. The Klyce topographic indices showed better sensitivity and specificity in detecting keratoconus regression after CXL than the corneal aberrometry grading system.

No significant variation of anterior and posterior best-fit sphere has been observed, indicating that the effectiveness of treatment was not limited to the anterior stroma, but extended to the middle and posterior stroma. Central corneal thickness had a faster recovery in our mostly pediatric population as compared with adult eyes,<sup>17,19</sup> suggesting a faster and more

effective healing process in the young eyes. No major complications were seen. There was no decrease in endothelial cell count, a finding supported by Wollensak and associates.<sup>41</sup>

Clinical experience has shown that the progression of keratoconus in children can be dramatic, with a significant visual impairment accompanying the rapidly developing corneal ectasia. Our pediatric patients (only 3 in the cohort were older than 16 years) also exhibited a faster and more dramatic progression than adults. In this context, the arrest of progression after treatment with CXL seen in this study underscores the importance of early diagnosis in children and of a tight follow-up schedule to identify those eyes that deteriorate rapidly. (Our patients were seen at 3-month intervals before surgery to identify early progression.) Serial differential corneal topographies and optical pachymetry are essential components of such a follow-up. The recognition of early progression is a key aspect. A progression of 1.0 D in 3 months, for example, would be an indication for CXL. The procedure, performed early enough, may eliminate the need for penetrating keratoplasty.

If the CXL effect turns out to be stable over a longer period, the procedure could be combined with intracorneal ring segments or customized excimer surface ablation to correct partially the refractive error of the CXL-treated keratoconus patients.<sup>42</sup>

Further follow-up is required to ascertain whether CXL in children will be as effective as in adults in the longer term.<sup>43</sup> The higher viscosity and lower resistance of younger corneas may make a difference in the end result.<sup>44,45</sup> It remains unclear how pediatric corneas would react to possible retreatments.

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ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were reported. Dr Vinciguerra is consultant for Oculus. Involved in Design of study (P.V., E.A., B.E.F.); Data collection (E.A., S.T.); Provision of materials, patients, or resources (P.V., E.A., B.E.F.); Statistical analysis (E.A.); Literature search (E.A.); Administrative, technical, or logistic support (E.A., S.T.); Analysis and interpretation of data (P.V., E.A., B.E.F., D.E.); Manuscript preparation (E.A., B.E.F., D.E.); Critical revision of manuscript (P.V., E.A., B.E.F., D.E.); and Final approval of manuscript (P.V., E.A., B.E.F., D.E.). The study received a prospective institutional review board approval by the ethical committees of Istituto Clinico Humanitas and the Canton of Bern and was conducted according to the ethical standards set in the 1964 Declaration of Helsinki, as revised in 2000. Informed consent forms for participation in this research were signed by the parents.

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