Corneal Collagen Cross-linking for Ectasia After Excimer Laser Refractive Surgery: 1-year Results

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ABSTRACT

PURPOSE: To evaluate the 1-year results of corneal collagen cross-linking (CXL) in eyes with postoperative excimer laser refractive surgery corneal ectasia.

METHODS: Thirteen eyes of 9 consecutive patients who had undergone excimer laser refractive surgery (photorefractive keratectomy [n=3], LASIK [n=10]) with resultant unstable corneal ectasia underwent CXL with photosensitizing riboflavin 0.1% solution and subsequent exposure to ultraviolet radiation. Study eyes underwent complete ophthalmologic examination, endothelial specular microscopy, corneal topography, and aberrometry as well as central pachymetry and Scheimpflug-based topo/tomography preoperatively and at 3-, 6-, and 12-month intervals.

RESULTS: Best spectacle-corrected visual acuity (BSCVA) improvement was statistically significant ($P<.05$) beyond 6 months after surgery (improvement of 0.1 logMAR at 1 year). Mean spherical equivalent refraction and mean refractive sphere reduction (improvement of 1.40 and 1.44 diopters [D], respectively) were statistically significant ($P<.05$) at 6 months postoperatively. At 1 year after CXL, mean endothelial cell count and keratometry (average SimK decrease of 2.02 D) as well as Klyce and Ambrósio indices did not deteriorate. Coma and spherical aberration did not change significantly. Mean pupil center pachymetry and corneal thickness at 0 and 2 mm from the thinnest corneal point decreased significantly.

CONCLUSIONS: One year after surgery, CXL appears to stabilize eyes with ectasia consequent to excimer laser refractive surgery and improve BSCVA. [*J Refract Surg*. 2010;26(7):486-497.]

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Identification of eyes at risk for ectasia after excimer laser refractive surgery remains difficult and controversial, and ectasia after excimer laser corneal refractive surgery involves more often postoperative LASIK eyes, but it may also occur after photorefractive keratectomy (PRK).[1-3] The occurrence of ectasia is dramatic for both the patient and the physician, and eventually penetrating keratoplasty may be required.[1]

The successful introduction of corneal collagen cross-linking (CXL) in the armamentarium for the treatment of keratoconus-related ectasia provided a new tool for the management of ectasia consequent to excimer laser refractive surgery. The limited invasiveness as well as the potential for repeatability of CXL make it an ideal treatment for these refractive surgery patients who, after looking for a solution to an unpleasant situation such as a significant myopic refractive defect, find themselves in an optically worse situation, with apparently endless instability and progression.

We present our experience with CXL in the treatment of postoperative excimer laser refractive surgery corneal ectasia.

PATIENTS AND METHODS

Study Population

Thirteen eyes of nine consecutive patients (six women, three men) in whom postoperative excimer laser refractive surgery ectasia progression was detected in the preceding 6 months were enrolled at the Cornea Service of the Ophthalmology Department of Istituto Clinico Humanitas (Rozzano, Milan, Italy) from September 2007 to September 2008 in this prospective, nonrandomized, single-center study, representing an interim analysis of a subpopulation.

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The authors have no commercial or proprietary interest in the materials presented herein.

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Mean patient age was 42 years (range: 30 to 59 years). Of the treated eyes, six were right eyes and seven were left eyes.

Inclusion criteria were previous excimer laser refractive surgery, a documented ectasia progression in the previous 6 months, corneal thickness of at least 350 µm at the thinnest point, and age (as specified by our institution's ethical committee) 18 to 60 years.

Preoperative ectasia progression was confirmed by serial differential corneal topography and by differential optical pachymetry analysis in all eyes included in the study.[4] Ectasia progression was defined as a change in either myopia and/or astigmatism of at least 3.00 diopters (D) total over the previous 6 months, or a mean change in central and/or pupillary keratometry (K) reading of a total of at least 1.50 D observed in three consecutive topographies over the preceding 6 months, or a total mean central corneal thickness decrease of at least 5% in three consecutive tomographies performed over the previous 6 months.

Exclusion criteria were corneal thickness <350 µm at the thinnest point, a history of herpetic keratitis, severe dry eye, concurrent corneal infections, corneal opacities, concomitant autoimmune diseases, and any previous non-excimer laser refractive ocular surgery.[5-9] Pregnant or nursing women, patients with poor compliance, and patients wearing rigid gas permeable lenses for at least 4 weeks before baseline examination were also excluded.

Criteria for aborting the study itself included a reduction in endothelial cell density of more than 50% in >2 eyes, the development of corneal haze grade 3-4 (Hanna scale) in >5% of eyes, a loss of >2 lines of best spectacle-corrected visual acuity (BSCVA) in >5% of eyes, and the detection of lens opacities in >1% of treated eyes when compared to untreated eyes (LOCS II classification).

The study received institutional review board approval by the ethical committee of Istituto Clinico Humanitas and was conducted according to the ethical standards set in the 1964 Declaration of Helsinki, as revised in 2000. All patients signed a specific informed consent form.

At baseline and at each postoperative follow-up examination (3, 6, and 12 months), all patients underwent uncorrected visual acuity (UCVA) and BSCVA assessment, slit-lamp microscopy, basal Schirmer test, Goldmann tonometry, dilated fundus examination, endothelial biomicroscopy (Konan Specular Microscope; Konan Medical Inc, Hyogo, Japan), and corneal topography as well as corneal, internal, and total aberrometry with the Optical Path Difference Scan platform (OPD-Scan; NIDEK, Gamagori, Japan) and Pentacam optical pachymetry and Scheimpflug-based topo/tomography (Oculus Inc, Lynnwood, Washington).

All patients previously had excimer laser refractive surgery, either PRK (n=3 eyes) or LASIK (n=10 eyes), and were referred from other centers. The reasons for biomechanical instability after excimer laser refractive surgery was due to formerly undiagnosed forme fruste keratoconus in 5 eyes and high correction with reduced residual corneal thickness in 3 eyes. The cause could not be identified in the remaining 4 eyes.

Visual Acuity Assessment

Visual acuity was assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR charts (Lighthouse International, New York, New York) based on the design suggested by Bailey and Lovie[10] and incorporating the recommendations of the US National Academy of Sciences–National Research Council.[11] The chart has been described in detail by Ferris et al.[12] Measurements were made with best correction after a non-cycloplegic refraction at 4 m.

Corneal Topography

Corneal topography was performed with the topographer feature of the OPD-Scan, analyzed with a Placido disk 6480 points over an 11-mm diameter, a 94.98 mm^2 corneal surface area. The examination was performed in photopic conditions.

The OPD-Scan was also used to study the 21 Klyce indices provided by the Corneal Navigator Topo-Classifier Map.[13-16]

Oculus Pentacam HR (Oculus Optikgeräte, Wetzlar, Germany) provided analysis of the seven Ambrósio keratoconus indices.[17]

Wavefront Analysis

Corneal wavefront analysis was performed with the OPD-Scan. The device was also used to objectively analyze mean refraction. The OPD-Scan further provides an aberrometric analysis of the eye, decomposing whole eye (total) aberrations into corneal aberrations and internal aberrations. For the purpose of this study, only corneal aberrations for a 6-mm pupil were considered.

Corneal and Anterior Chamber Analysis

Anterior chamber analysis was performed with the Pentacam HR.[18-22] The analyses performed with the Pentacam included pupil center pachymetry and the pachymetry of the thinnest point of the cornea. The distance of these two points from the corneal apex is shown by x and y coordinates.

Total and partial corneal volume is calculated in a

ring around the apex, using diameters of 3, 5, 7, and 10 mm. Anterior chamber volume is calculated by measuring the distances between the back surface of the cornea and the iris-lens plane over a 12-mm diameter.

Anterior chamber depth is measured from the endothelium of the corneal apex to the iris-lens plane. Anterior and posterior elevation maps use a toric reference body, with calculations based on the central radii and the eccentricity of the keratometry measurements.

Endothelial Cell Count

Endothelial biomicroscopy was performed manually according to the method described by Prinz et al.[23] Cell centers of at least 50 contiguous cells were identified by aligning a cursor on the cell apices and endothelial cell density was recorded. The Konan Noncon Robo (Konan Medical Inc, Nishinomiya, Hyogo, Japan) device was used.

Cross-linking Procedure

The surgical technique has been described elsewhere.[24] All patients underwent CXL on a day-surgery basis. Thirty minutes before the procedure pain medication was administered and 2% pilocarpine drops were instilled in the eye to be treated. Pupil diameter reduction was planned to protect the retina from ultraviolet A (UVA) radiation (amount of radiation is proportional to the square value of pupil diameter).

The procedure was conducted under sterile conditions in the operating suite. After topical anesthesia with two applications of 4% lidocaine drops and oxybuprocaine hydrochloride 0.2%, the patient was draped, the ocular surface was rinsed with sterile physiological balanced salt solution, and a lid speculum was applied. The corneal epithelium was manually abraded cautiously in a central 9-mm diameter area. No lifting of the flap margin was observed.

Before beginning UVA irradiation, photosensitizing riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran-T-500 10 mL solution) (Ricrolin; SOOFT italia S.p.A., Montegiorgio [AP], Italy) was applied to the cornea every minute for 30 minutes to achieve adequate penetration of the solution. This treatment was performed only when corneal thickness, including the epithelium, was ⩾400 µm.

In three eyes, corneal thickness ranged between the minimum usually accepted for CXL, 350 to 450 µm, thus before irradiation, corneal thickness expansion by swelling was performed as follows. Photosensitizing riboflavin 0.1% solution was applied to the cornea every minute for 20 minutes as described above. Then, hypotonic riboflavin-5-phosphate solution without dextran-T-500 (Vitamin B2 Streuli; Streuli Pharma AG, Uznach, Switzerland) was applied on the corneal surface for 5 minutes, and intraoperative pachymetry was performed. If corneal thickness was <400 µm, this procedure was repeated. Usually, 15 minutes of riboflavin-5-phosphate solution application was necessary to properly expand corneal thickness. Once 400 µm was reached, the procedure went on to the following step.

Using a slit lamp with the blue filter, the surgeon confirmed the presence of riboflavin in the anterior chamber before UVA irradiation was started. The cornea was exposed to a UVA source emanating from a solid-state device (UV-X System; Peschke Meditrade GmbH, Huenenberg, Switzerland), which emits light at a wavelength of 370±5 nm and an irradiance of 3 mW/cm^2 or 5.4 J/cm^2. Exposure lasted for 30 minutes, during which time the 0.1% riboflavin solution was again applied, this time once every 5 minutes. The cropped light beam has a 7.5-mm diameter. A calibrated UVA meter (LaserMate-Q; Laser 2000, Wessling, Germany) was used before treatment to check the irradiance at a 1.0-cm distance. The Peschke laser emission probe has one central and six peripheral light emitting diodes (LED). Fixation during irradiation was achieved by instructing the patient to focus on the central LED of the probe. During the procedure, the surgeon also checked for centration of treatment. Both topical anesthetics were added as needed during irradiation.

Postoperatively, patients received cyclopentolate (Ciclolux; Allergan, Rome, Italy) and levofloxacin 0.5% drops (Oftaquix; Tubilux Pharma, Pomezia, Rome, Italy). A soft bandage contact lens was applied until re-epithelialization was complete. Topical levofloxacin was given four times daily for 7 days, dexamethasone 21-phosphate 0.15% drops (Etacortilen; Sifi, Lavinaio [CT] Italy) three times daily for 20 days, and 0.15% sodium hyaluronate drops (BluYal; SOOFT italia S.p.A.) six times daily for 45 days. In addition, all patients received oral amino acid supplements (Aminoftal, SOOFT italia S.p.A.) for 7 days.[25]

Patients were examined every day until re-epithelialization was complete and then at 1, 3, 6, and 12 months.

Data Analysis

Statistical analyses were performed with the Statistica (StatSoft Inc, Tulsa, Oklahoma) computer package. All data are reported as mean±standard deviation. Normality of the data was tested using the Kolmogorov-Smirnov test and the normal probability plot. The level of statistical significance was set at $P<.05$.

RESULTS

Mean re-epithelialization time was 48±15 hours (range: 21 to 75 hours). All eyes attained at least

TABLE 1

Uncorrected Visual Acuity and Best Spectacle-corrected Visual Acuity in 13 Eyes Before and After Cross-linking

	Mean±Standard Deviation (Range)			
	Before CXL	3 Months	6 Months	12 Months
No. of eyes	13	13	11	7
UCVA	1.08±0.43 (0.40 to 1.70)	1.05±0.43 (0.05 to 1.70)	0.94±0.37 (0.10 to 1.30)	0.94±0.46 (0.10 to 1.30)
BSCVA	0.16±0.14 (0.00 to 0.40)	0.14±0.12 (0.00 to 0.40)	0.09±0.10 (0.00 to 0.30)	0.06±0.08 (0.00 to 0.22)
SE (D)	−4.16±2.90 (−10.00 to −0.13)	−3.24±3.49 (−7.00 to 3.00)	−2.56±2.61 (−6.00 to 2.75)	−3.25±2.05 (−6.50 to −0.50)
Sphere (D)	−2.96±2.63 (−9.00 to +0.25)	−2.06±3.15 (−5.50 to 4.50)	−1.52±2.47 (−6.00 to 3.75)	−2.25±1.39 (−5.00 to −0.50)
Cylinder (D)	−2.40±2.06 (−6.00 to 0.00)	−2.37±2.13 (−5.50 to 0.00)	−2.07±2.10 (−6.00 to 0.00)	−2.00±2.00 (−5.00 to 0.00)

CXL = cross-linking, UCVA = uncorrected visual acuity, BSCVA = best spectacle-corrected visual acuity, SE = spherical equivalent refraction

3-month follow-up; maximum follow-up was 12 months for 7 eyes (mean: 11 months, range: 3 to 17 months).

Visual Acuity and Refractive Results

Uncorrected visual acuity and BSCVA data, expressed in logMAR, throughout the entire follow-up period are summarized in Table 1.

Uncorrected visual acuity did not change significantly during follow-up. Best spectacle-corrected visual acuity improvement was statistically significant beyond 6 months postoperatively (20/25) when compared to preoperative levels (20/35).

Refractive results are also presented in Table 1. The reductions in spherical equivalent refraction and mean sphere value were statistically significant at 6 months, but not at 12 months.

Topographic Results

Topographic astigmatism measured with the OPD-Scan during follow-up is shown in Table 2. Mean baseline flattest meridian keratometry, steepest meridian keratometry, and mean keratometry change over 12 months was not statistically significant.

The Klyce indices[16] obtained with the Nidek OPD-Scan were analyzed in treated and untreated eyes at baseline and at 3, 6, and 12 months (Table 3). At 3 months postoperative, the Klyce indices coefficient of variation of corneal power, logMAR, and area compensated surface regularity index had significantly increased, whereas the index standard deviation of corneal power had significantly decreased.

Figure 1 shows case 13 who underwent LASIK in the left eye for −4.00 −0.50 @ 125. Best spectacle-corrected visual acuity was 20/35 with −1.50 −3.25 @ 110 and initial ectasia is visible. Figure 2 shows the same case, 3 years later, immediately before CXL; BSCVA is 20/50 with −2.75 −6.00 @ 95. Note the worsening of ectasia. Figure 3 presents the same eye, 6 months after treatment, with BSCVA 20/30 with −2.50 −6.00 @ 105. Central flattening is noted. Figure 4 presents the differential map between Figures 1 and 2, and Figure 5 the differential map between Figures 2 and 3.

TABLE 2

Topographic Astigmatism Measured With the NIDEK OPD-Scan in Eyes Before and After Cross-linking

	Mean±Standard Deviation (Range)	
	Before CXL	12 Months
No. of eyes	13	7
SIMK_Kf	43.05±5.06 (37.01 to 53.23)	40.44±3.57 (35.60 to 45.12)
SIMK_Ks	45.93±6.03 (37.42 to 57.01)	42.49±4.88 (35.79 to 49.13)
SIMK AVG	44.49±5.48 (37.22 to 54.75)	41.47±4.21 (35.70 to 47.13)

CXL = cross-linking, SIMK_Kf = simulated keratometry flattest meridian, SIMK_Ks = simulated keratometry steepest meridian, SIMK AVG = average simulated keratometry

The Ambrósio indices obtained with the Oculus Pentacam HR were analyzed in treated and untreated eyes at baseline and 3, 6, and 12 months (Table 4). At 6 months postoperative, the Ambrósio index of vertical

TABLE 3

Changes in Klyce Indices Measured With the NIDEK OPD-Scan in Eyes That Underwent CXL

	Mean±Standard Deviation (Range)						
	Before CXL	3 Months	*P* Value	6 Months	*P* Value	12 Months	*P* Value
No. of eyes	13	11		7		7	
Average corneal power (D)	44.67±6.09 (37.47 to 57.08)	43.68±5.78 (34.98 to 54.13)	NS	44.15±6.43 (37.87 to 54.53)	NS	41.50±4.94 (34.98 to 48.84)	NS
Simulated keratometry cylinder (D)	2.88±1.94 (0.10 to 6.43)	2.14±1.65 (0.19 to 4.55)	NS	2.57±1.61 (0.46 to 4.55)	NS	2.04±1.49 (0.19 to 4.01)	NS
Coefficient of variation of corneal power	69.72±29.11 (21.56 to 126.89)	71.30± 25.68 (23.66 to 100.36)	.006*	77.17±26.09 (28.43 to 104.50)	NS	67.59±23.21 (21.60 to 92.48)	NS
Standard deviation of corneal power	3.15±1.52 (0.88 to 6.56)	3.13±1.19 (0.98 to 4.16)	.007†	3.46±1.34 (1.17 to 5.29)	NS	2.85±1.02 (0.92 to 3.86)	NS
Analyzed area (%)	85.27±4.43 (76.85 to 90.60)	82.54±3.08 (77.00 to 87.20)	NS	83.10±5.44 (74.43 to 89.74)	NS	84.60±3.62 (79.96 to 88.36)	NS
Corneal eccentricity index	0.32±0.95 (−1.22 to 1.47)	0.12±1.05 (−1.25 to 1.37)	NS	0.14±1.14 (−1.20 to 1.33)	NS	−0.41±1.02 (−1.21 to 1.29)	NS
LogMAR	0.14±0.13 (−0.12 to 0.32)	0.15±0.11 (−0.05 to 0.25)	.01*	0.16±0.11 (−0.03 to 0.25)	NS	0.12±0.09 (−0.03 to 0.21)	NS
Differential sector index	8.02±3.56 (2.90 to 12.89)	8.15±3.82 (1.92 to 12.76)	NS	9.03±3.55 (3.80 to 12.62)	NS	7.12±3.70 (1.92 to 12.37)	NS
Surface regularity index	1.31±0.46 (0.44 to 2.04)	1.29±0.34 (0.71 to 1.71)	NS	1.39±0.43 (0.85 to 2.05)	NS	1.27±0.31 (0.68 to 1.57)	NS
Area compensated surface regularity index	1.17±0.37 (0.37 to 1.62)	1.22±0.25 (0.69 to 1.43)	.05*	1.26±0.26 (0.77 to 1.53)	NS	1.18±0.22 (0.71 to 1.37)	NS
Surface asymmetry index	1.76±0.94 (0.58 to 3.78)	1.71±0.78 (0.64 to 2.99)	NS	1.95±0.95 (0.78 to 3.15)	NS	1.55±0.73 (0.64 to 2.57)	NS
Irregular astigmatism index	0.52±0.16 (0.04 to 0.64)	0.58±0.06 (0.42 to 0.64)	NS	0.58±0.08 (0.40 to 0.65)	NS	0.58±0.06 (0.46 to 0.64)	NS
Opposite sector index	6.46±3.36 (1.89 to 10.98)	6.54±3.39 (1.00 to 10.86)	NS	7.57±3.14 (2.95 to 10.74)	NS	5.80±3.37 (1.00 to 10.52)	NS
Center surround index	0.87±2.50 (−2.82 to 6.33)	0.24±2.23 (−2.84 to 3.92)	NS	0.56±2.78 (−2.68 to 4.50)	NS	−0.65±2.19 (−2.63 to 3.46)	NS
Klyce keratoconus index	0.46±0.46 (0.00 to 1.00)	0.34±0.44 (0.00 to 1.00)	NS	0.51±0.44 (0.00 to 1.00)	NS	0.20±0.33 (0.00 to 0.69)	NS
Keratoconus prediction index	0.31±0.10 (0.19 to 0.55)	0.29±0.08 (0.00 to 1.00)	NS	0.32±0.10 (0.19 to 0.48)	NS	0.26±0.08 (0.13 to 0.34)	NS
Elevation/depression power	2.70±1.23 (1.03 to 5.65)	2.65±1.06 (1.19 to 4.66)	NS	2.91±1.03 (1.62 to 4.16)	NS	2.50±0.76 (1.46 to 3.39)	NS
Elevation/depression diameter	8.92±6.24 (0.02 to 19.68)	7.78±5.93 (0.54 to 17.23)	NS	10.44±6.71 (1.47 to 18.98)	NS	8.12±5.56 (1.27 to 14.09)	NS

CXL = cross-linking, NS = not statistically significant
**Significantly decreased values.*
†Significantly increased values.

asymmetry had significantly increased and the keratoconus center index had significantly decreased.[17]

Aberrometric Results

Aberrometric results are shown in Table 5. Mean corneal coma, spherical aberration, and high order astigmatism had decreased by 1-year follow-up, but the difference was not statistically significant when compared with preoperative data.

Tomographic Results

Table 6 presents changes in corneal and anterior

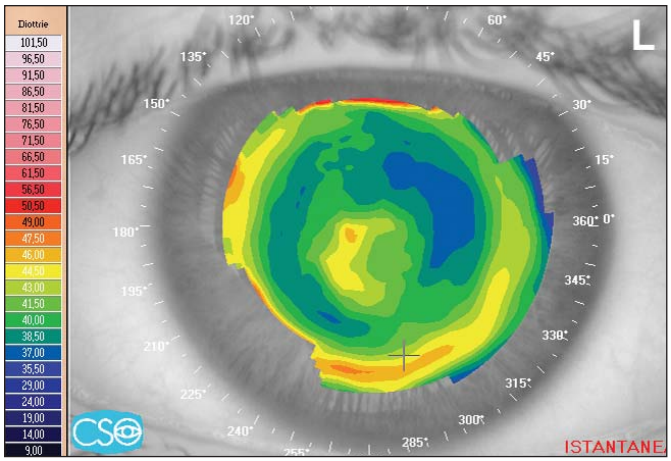

Figure 1. *Case 13.* This patient underwent LASIK in the left eye for −4.00 −0.50 @ 125. In April 2005, 4 years after LASIK, BSCVA is 20/35 with −1.50 −3.25 @ 110. Ectasia within the ablated zone is apparent.

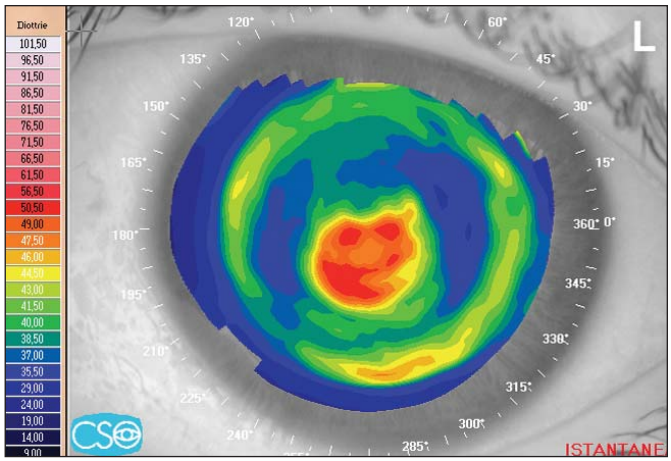

Figure 2. *Case 13.* Left eye of the same patient in Figure 1 in September 2008, immediately before cross-linking. Best spectacle-corrected visual acuity is 20/50 with −2.75 −6.00 @ 95. Note the worsening of ectasia.

chamber morphological values measured by means of Pentacam optical pachymetry. Pupil center pachymetry and corneal pachymetry at the thinnest point total corneal showed a statistically significant decrease over the entire follow-up period.

Anterior chamber volume did not change significantly, anterior chamber depth showed a statistically significant increase at 3 months, and anterior and posterior elevation values did not show a significant change. Total corneal volume showed significant decrease at 3 months. Mean baseline, 3-, 6-, and 12-month corneal thickness values at 0, 2, 4, 6, and 8 mm from the thinnest corneal point are presented in Table 6. A limited (−9.0%) but statistically significant decrease in corneal thickness was found at 0 mm and 2 mm after 3-month follow-up. This decrease remained stable over the entire follow-up period. A similar significant decrease at 4 mm was observed only at 12-month follow-up.

Endothelial Results

Mean baseline endothelial cell count was 2555±470 cells/mm^2 (range: 1515 to 2994 cells/mm^2). At 12 months postoperative, endothelial cell count was 2120±517 cells/mm^2 (range: 1547 to 2857 cells/mm^2). The difference between baseline and 12 months was not statistically significant, indicating that CXL did not induce endothelial damage in the 1-year follow-up period.

No ocular or systemic adverse events were observed, as well as no epithelial ingrowth or diffuse lamellar keratitis, and no significant intraocular pressure changes were noted. Subjectively, patients perceived improvement of UCVA during the first 6 postoperative months. Between 6 and 12 months, they reported a continuing increase in BSCVA.

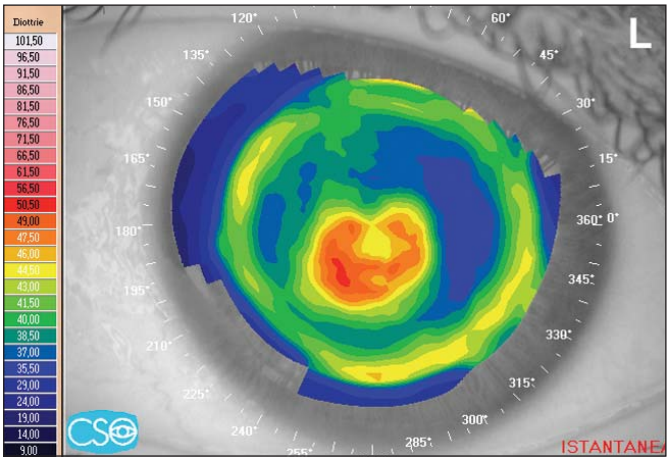

Figure 3. *Case 13.* Left eye of same patient in Figures 1 and 2 in April 2009, 6 months after cross-linking. Best spectacle-corrected visual acuity is 20/30 with −2.50 −6.00 @ 105. Central flattening is noted.

DISCUSSION

Ectasia after LASIK and, generally, excimer laser refractive surgery, is receiving increasing interest due to its dramatic negative effect on visual quality and potential for litigation.[2,26,27] Traditional treatment for ectasia after excimer laser refractive surgery follows the keratoconus scheme, including rigid gas permeable contact lenses and intracorneal ring segments, but the most frequent choice remains corneal transplantation.[3,28] Recently, after the success observed with keratoconus, several studies reported CXL treatment for postoperative LASIK ectasia.

The first case report of CXL in postoperative LASIK keratectasia was published in 2005 by Kohlhaas et al.[29] A similar case report by Kanellopoulos[30] was published in 2007, with PRK applied after CXL. In the same year, Hafezi et al[31] reported 10 contact lens–intolerant eyes, with 1-year follow-up, observing stabilization in 5 eyes

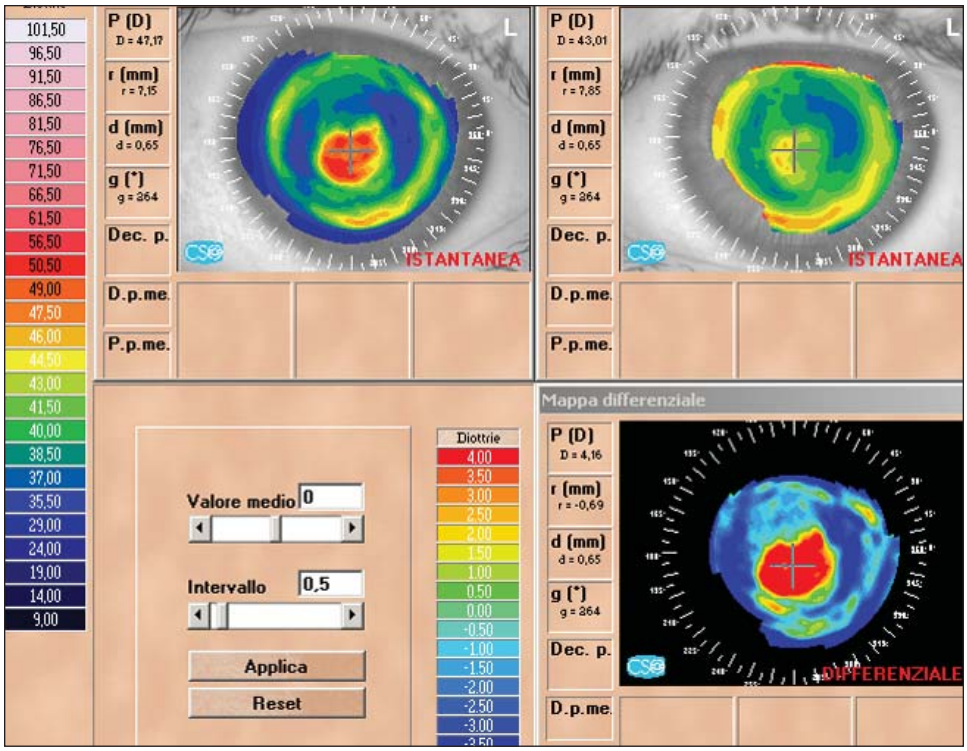

Figure 4. Differential map between Figures 1 and 2. **Upper right)** Left eye in April 2005. The cross indicates a central point with 43.01 D of curvature. **Upper left)** Left eye in September 2008 immediately before cross-linking. The same cross-marked point now has 47.17 D of curvature. **Bottom right)** Differential map showing that the progression of ectasia is of 4.15 D.

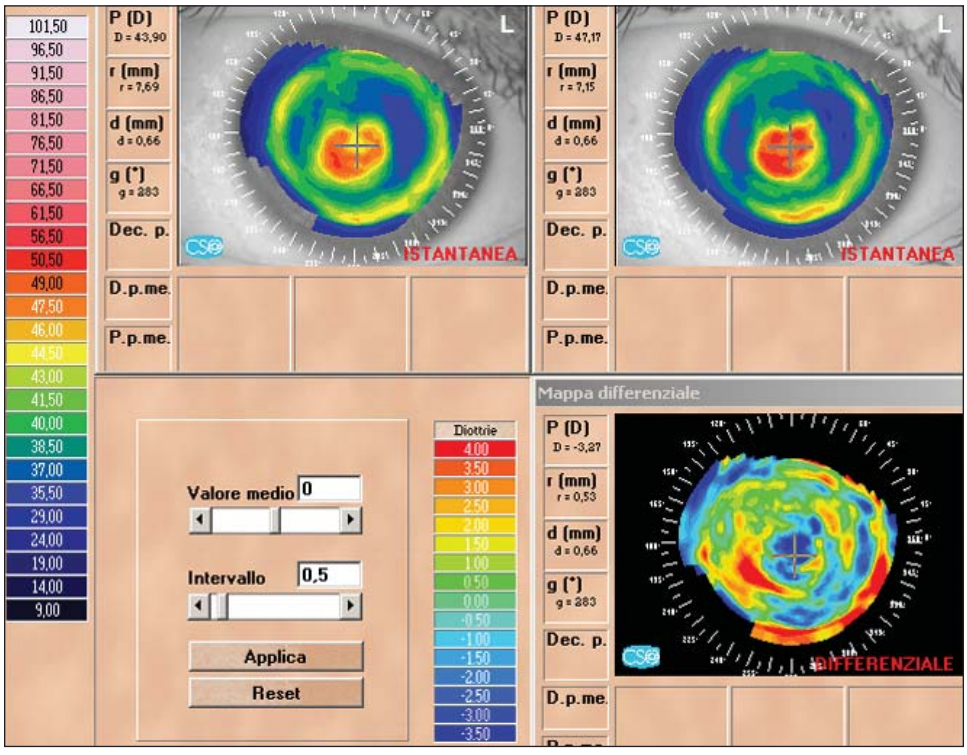

Figure 5. Differential map between Figures 2 and 3. **Upper right)** Left eye in September 2008 immediately before cross-linking (CXL). The cross is on the central point with 47.17 D of curvature (see Fig 4). **Upper left)** Left eye in April 2009, 6 months after CXL. The same cross-marked point now has 43.90 D of curvature. **Bottom right)** Differential map. Ectasia regressed 3.27 D.

and regression of keratectasia in the other 5 eyes. In 2008, Mackool[32] commented on this treatment, suggesting that flap suture placement induced elimination of ectasia in postoperative LASIK eyes before CXL.

Kymionis et al[33] recently reported a case series of five eyes of five patients with postoperative LASIK keratectasia. Patients were followed for 1 year with confocal microscopy after corneal collagen CXL. Corneal alterations, such as keratocyte disappearance in the anterior and intermediate corneal stroma for the first 3 months after CXL, were similar in eyes with both keratoconus and postoperative LASIK corneal ectasia.

TABLE 4

Changes in the Ambrósio Indices as Measured With the Oculus Pentacam HR

	Mean±Standard Deviation (Range)						
	Before CXL	3 Months	*P* Value	6 Months	*P* Value	12 Months	*P* Value
No. of eyes	13	9		6		4	
Index surface variance	71.31±33.22 (15.00 to 126.00)	77.00±36.05 (18.00 to 128.00)	NS	88.00±35.62 (21.00 to 123.00)	NS	75.00±31.22 (22.00 to 115.00)	NS
Index of vertical asymmetry	0.81±0.45 (0.17 to 1.75)	0.83±0.51 (0.20 to 1.81)	NS	1.10±0.47 (0.29 to 1.74)	.04*	0.90±0.47 (0.19 to 1.61)	NS
Keratoconus index	1.14±0.13 (0.93 to 1.37)	1.15±0.17 (0.85 to 1.37)	NS	1.18±0.13 (1.03 to 1.34)	NS	1.15±0.12 (0.98 to 1.33)	NS
Center keratoconus index	1.01±0.06 (0.90 to 1.10)	1.01±0.07 (0.90 to 1.09)	NS	0.99±0.07 (0.90 to 1.12)	.04†	0.98±0.07 (0.91 to 1.08)	NS
Index of height asymmetry	17.51±15.47 (0.50 to 46.40)	19.27±14.37 (4.00 to 43.40)	NS	19.46±16.66 (9.70 to 49.10)	NS	12.82±11.48 (1.90 to 31.80)	NS
Index of height decentration	0.06±0.04 (0.01 to 0.12)	0.06±0.03 (0.02 to 0.12)	NS	0.07±0.04 (0.02 to 0.11)	NS	0.06±0.03 (0.01 to 0.11)	NS
Minimum sagittal curvature in 8-mm zone	6.67±0.77 (5.56 to 8.07)	6.68±0.92 (5.50 to 8.07)	NS	6.71±0.84 (5.63 to 8.01)	NS	6.88±0.44 (6.44 to 7.54)	NS

CXL = cross-linking, NS = not statistically significant
**Significantly decreased values.*
†Significantly increased values.

TABLE 5

Changes in Higher Order Corneal Aberrations as Measured With the NIDEK OPD-Scan for a 6-mm Pupil

	Mean±Standard Deviation (Range) (μm)						
	Before CXL	3 Months	*P* Value	6 Months	*P* Value	12 Months	*P* Value
No. of eyes	11	7		9		7	
Coma	2.232±1.290 (0.594 to 3.805)	2.438±1.401 (0.694 to 3.831)	NS	2.152± 1.279 (0.541 to 3.831)	NS	1.849±1.324 (0.482 to 3.596)	NS
SA	0.717±0.677 (0.088 to 2.165)	0.951±0.721 (0.069 to 2.203)	NS	0.762±0.540 (0.129 to 1.450)	NS	0.584±0.519 (0.044 to 1.450)	NS
HOA	0.380±0.282 (0.075 to 0.975)	0.449±0.337 (0.069 to 1.065)	NS	0.363±0.283 (0.048 to 0.981)	NS	0.273±0.207 (0.083 to 0.546)	NS

CXL = cross-linking, NS = not statistically significant, SA = spherical aberration, HOA = higher order astigmatism

The implantation of Intacs SK (Addition Technology Inc, Des Plaines, Illinois) has also been considered an adjunct to CXL.[34]

Regarding the success of CXL in the treatment of postoperative LASIK ectasia, Hafezi and Iseli[35] reported a case of bilateral iatrogenic keratectasia that occurred during a patient's first pregnancy 26 months after LASIK. Cross-linking was performed in both eyes, leading to stabilization and even to improvement in keratometric steepness over 22 months. However, during a second pregnancy, exacerbation of postoperative LASIK keratectasia occurred, despite previous CXL. For this reason, pregnant women were not included in the present study.

From a psychological point of view, refractive surgery patients with corneal ectasia may be profoundly different from keratoconus patients, in that they are used to having complete refractive correction with good visual acuity and thus may complain immediately when visual disturbances occur due to early ectatic changes. Moreover, when postoperative LASIK eyes—the most frequent victims of iatrogenic ectasia—are considered, the amount of residual corneal thickness may be limited. After a 140-μm flap and 130-μm ablation, a normal

TABLE 6

Changes in Corneal and Anterior Chamber Morphological Values as Measured With Oculus Pentacam HR Optical Pachymetry

	Mean±Standard Deviation (Range)						
	Before CXL	**3 Months**	***P* Value**	**6 Months**	***P* Value**	**12 Months**	***P* Value**
No. of eyes	13	11		4		6	
Pachymetry at the pupil center (μm)	436.92±45.28 (377 to 515)	404.36±64.69 (276 to 476)	.001*	426.33±64.25 (320 to 476)	.012*	431.83±37.51 (395 to 494)	.027*
Pachymetry thinnest point (μm)	427.55±47.33 (360 to 512)	388.91±66.42 (275 to 469)	.001*	413.33±66.01 (299 to 473)	.15*	422.17±43.61 (377 to 492)	.003*
AC volume (mm^3)	223.27±38.31 (156 to 266)	222.27±34.76 (161 to 272)	NS	216.17±46.33 (151 to 271)	NS	237.33±32.70 (184 to 271)	NS
Anterior chamber depth (mm)	3.46±0.26 (2.87 to 3.77)	3.48±0.25 (2.91 to 3.76)	.04†	3.43±0.32 (2.84 to 3.78)	NS	3.51±0.15 (3.24 to 3.66)	NS
Posterior BFS (mm)	5.63±0.65 (4.39 to 6.28)	5.56±0.71 (4.20 to 6.27)	NS	5.72±0.49 (4.86 to 6.19)	NS	5.67±0.59 (4.75 to 6.33)	NS
Anterior BFS (mm)	7.47±1.00 (6.02 to 8.95)	7.61±1.14 (6.11 to 9.79)	NS	7.79±0.96 (6.36 to 8.87)	NS	7.44±0.77 (6.67 to 8.89)	NS
Total corneal volume (mm^3)	57.44±2.58 (53.40 to 61.50)	56.22±3.18 (51.60 to 60.20)	.006*	58.34±1.91 (55.10 to 60.10)	NS	56.80±3.25 (51.70 to 60.50)	.059
Corneal thickness‡ (μm)							
0 mm	427.55±47.33 (360 to 512)	388.91±66.42 (275 to 469)	.001*	436.40±39.09 (372 to 473)	.036*	422.17±43.61 (377 to 492)	.003*
2 mm	449.82±42.76 (393 to 531)	414.55±57.15 (315 to 488)	.000*	460.00±30.95 (411 to491)	.031*	445.33±40.75 (407 to 510)	.005*
4 mm	503.45±43.25 (418 to 577)	488.18±35.38 (427 to 539)	NS	523.40±16.32 (502 to 541)	NS	504.00±38.30 (460 to 560)	.001*
6 mm	586.18±31.09 (546 to 633)	579.45±35.53 (530 to 616)	NS	608.80±5.93 (602 to 616)	NS	596.00±40.29 (543 to 648)	NS
8 mm	684.95±34.15 (637 to 744)	672.80±35.94 (621 to 721)	NS	695.00±15.38 (681 to 712)	NS	685.17±46.83 (624 to 763)	NS

CXL = cross-linking, BFS = best-fit sphere, NS = not statistically significant
**Significantly decreased values.*
†Significantly increased values.
‡Corneal thickness values at 0, 2, 4, 6, and 8 mm from the thinnest corneal point.

530-µm cornea has limited residual central thickness, and an ectatic one may have even less.

Thus, we considered the selection criteria for CXL adopted for keratoconic eyes only partially valid for eyes with ectasia consequent to excimer laser refractive surgery. A proven corneal curvature instability as well as no endothelial cell reduction were mandatory, but we did not accept minimal corneal thickness of 400 µm as an absolute limit. Because progressing ectasia may lead to penetrating keratoplasty, we chose to apply a corneal expansion procedure with riboflavin-5-phosphate solution application in corneas thinner than 400 µm.[36] To date, the three eyes treated in this way have not shown any complications and behaved similarly to the other eyes with thicker corneas.

We followed the inclusion criteria specified by the ethical committee of our institution for non-pediatric CXL, and this included an age limitation (18 to 60 years). However, no patient with ectasia after excimer laser refractive surgery outside this age range was encountered.

In this study, we observed corneal changes similar but less marked than those observed after CXL in keratoconic eyes.[24,37] As in keratoconus, the situation remained stable up to 6 months. At the 6-month interval, we noticed improvement in refraction and BSCVA. Traditional topographic indices indicate that corneal curvature remained stable at the 1-year interval. Because simulated keratometry values do not consider the entire corneal surface, we analyzed the Klyce and Ambrósio indices for keratoconus. Four Klyce indices showed significant variation at 3 months, but were stable with respect to preoperative values after 6 months. One Ambrósio index, index of vertical asymmetry, increased at 6 months, whereas another, center keratoconus index, decreased at 6 months. The index of vertical asymmetry is an index that is elevated in cases of oblique astigmatism, in keratoconus, or in ectasia. The center keratoconus index decreases with decreasing severity of central keratoconus. This improvement may be consistent with the fact that an ectatic cornea following excimer laser refractive surgery may show the most prominent curvature variation almost centrally and CXL may lead to improvement in this central corneal portion. Thus, there was apparent corneal curvature stabilization and also a tendency towards central flattening, with improvement of the refractive situation. This is in accordance with the study by Hafezi and Iseli.[35] In summary, the Klyce and Ambrósio indices did not deteriorate at 1 year.

The following concept is important for understanding visual improvement in these patients. After myopic refractive ablation, the postoperative LASIK cornea is an oblate surface, with a centrally flattened optical zone. In its initial phases, ectasia consequent to excimer laser refractive surgery appears topographically as a steepened, hypercurved area inside this flattened optical zone. It is our impression that this steepened area reduces the extension of the flattened optical zone, inducing a topographic pattern that resembles optical zone decentration. If treatment with CXL reduces the curvature of this area, the optical zone should partially regain its initial aspect. The aberrometric result of ectasia induced by excimer laser refractive surgery is the induction of coma, and the CXL-induced reduction of ectasia should lead to coma reduction.

Corneal CXL appeared to stabilize these iatrogenically ectatic eyes. Reduction in sphere, increase in BSCVA, apparent central corneal flattening, and tendency to decrease coma at the 6-month interval may indicate a tendency towards improvement of the ectatic situation, with possible partial recentration of the optical zone.

The decrease in corneal thickness, on the other side, is consistent with what is observed in eyes with keratoconus, where linkage and stiffening of corneal stromal fibers lead to corneal volume reduction.[24,37]

Effective duration of CXL effect remains to be ascertained. In our long-term keratoconus cohort, we did not have to retreat any eye.[37] Confocal microscopy studies document recolonization of anterior and intermediate stroma as well as no endothelial damage, thus suggesting that CXL treatment may be safely repeated in time.

Among complications of CXL in postoperative LASIK corneal ectasia, diffuse lamellar keratitis has been reported.[38] We did not observe any complications, such as epithelial ingrowth, diffuse lamellar keratitis (sands of the Sahara), or elevations of the flap margin.

Finally, the psychological effect of corneal CXL in postoperative LASIK eyes must be considered. A patient who underwent refractive surgery to reduce the daily burden of a refractive defect, and, after a few years, experiences highly ectasia-related unstable refraction, as well as a new and more dramatic ocular surgery such as penetrating keratoplasty, ends up again with a marked, lifestyle-limiting refractive defect. In our experience, patients with ectatic corneas after LASIK who had to undergo penetrating keratoplasty often developed resentment towards their surgeon, leading to medical malpractice cases.

Corneal collagen CXL intervenes in this process as a surgical procedure of limited invasiveness. Patients in this cohort perceived this treatment as an important and positive evolution in their situation, after a period of progressive worsening.

Limitations of this study are the interim analysis of a subpopulation, the number of eyes considered, and

the incomplete follow-up for some patients. A larger group with longer follow-up will produce more enlightening information on the long-term behavior of eyes with corneal ectasia consequent to excimer laser refractive surgery after treatment with CXL.

Corneal collagen CXL appears to improve BSCVA in eyes with ectasia after excimer laser refractive surgery. No deterioration of the Klyce and Ambrósio indices or permanent side effects were observed.

AUTHOR CONTRIBUTIONS

Study concept and design (P.V., F.I.C.); data collection (F.I.C., E.A., S.T.); analysis and interpretation of data (F.I.C., E.A.); drafting of the manuscript (F.I.C., S.T.); critical revision of the manuscript (P.V., F.I.C., E.A.); statistical expertise (F.I.C., E.A.); supervision (P.V.)

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