

Photorefractive Keratectomy Followed by Cross-linking versus Cross-linking Alone for Management of Progressive Keratoconus: Two-Year Follow-up

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- PURPOSE: To compare visual, refractive, topographic, and corneal higher-order aberration outcome at the 2-year follow-up after customized photorefractive keratectomy (PRK) followed by cross-linking (CXL) as a single procedure versus CXL alone in eyes with progressive keratoconus.
- DESIGN: Prospective, interventional, nonrandomized clinical trial.
- METHODS: Seventeen patients (34 eyes) with progressive keratoconus were assigned to 2 groups: the worse eye (17 eyes) was assigned to the PRK plus CXL group and the better eye (17 fellow eyes) was assigned to the CXL group.
- RESULTS: In the PRK plus CXL group, uncorrected distance acuity improved significantly, from a mean \pm standard deviation of 0.63 ± 0.36 logMAR units to 0.19 ± 0.17 logMAR units ($P < .05$) and best distance acuity from 0.06 ± 0.08 logMAR to 0.03 ± 0.06 logMAR ($P < .05$). Manifest refraction spherical equivalent and spherical and cylindrical power improved significantly ($P < .05$). Simulated keratometry, flattest, steepest, average, cylindrical, apex keratometry, and inferior-superior value decreased significantly ($P < .05$). Total and coma-like aberrations significantly decreased for all pupil diameters ($P < .05$). In the CXL group, uncorrected distance acuity improved, but not significantly, from 0.59 ± 0.29 logMAR units to 0.52 ± 0.29 logMAR units, and best distance acuity improved from 0.06 ± 0.11 logMAR units to 0.04 ± 0.07 logMAR units ($P > .05$). Manifest refraction spherical equivalent and cylindrical power improvement was not significant ($P > .05$), unlike spherical power ($P < .05$). Steepest simulated keratometry, average simulated keratometry, and inferior-superior value significantly decreased ($P < .05$), unlike flattest simulated keratometry, cylindrical simulated keratometry, and apex keratometry ($P > .05$). Total and coma-like aberrations were not decreased

significantly for all pupil diameters ($P > .05$). No significant endothelial changes were observed in either group.

- CONCLUSIONS: The PRK plus CXL procedure may be a good option to reduce corneal aberrations and stabilize corneas with progressive keratoconus. (Am J Ophthalmol 2012; ■■■ © 2012 by Elsevier Inc. All rights reserved.)

C ORNEAL CROSS-LINKING (CXL) USING RIBOFLAVIN and ultraviolet A has been used to stabilize the cornea with progressive keratoconus or ectatic corneal disorders after corneal refractive procedures.¹ Further investigations are being conducted regarding its use for corneal melting and bullous keratopathy.^{2,3} Although the potential advantage of CXL over penetrating keratoplasty is well recognized in keratoconic corneas, the former procedure raises concerns about visual and topographic outcomes in treated eyes.⁴ Studies with a mean follow-up ranging from 10.69 to 36 months demonstrated that the simultaneous wavefront optimized approach of photorefractive keratectomy (PRK) plus CXL offers improvements in uncorrected distance acuity (UDA), best distance acuity (BDA), and topographic irregularity, even if the surgical goal is not a refractive end point.⁵⁻⁷

The aim of this prospective, nonrandomized, single-center study was to evaluate and compare the results obtained by topographic PRK with minimal ablation using the iVIS Suite platform (Ligi Tecnologie Medicali, Taranto, Italy) followed by CXL as a single procedure with those obtained by CXL treatment alone. Visual acuity, refractive, topographic, corneal higher-order aberration (HOA), and tomographic outcomes up to 24 months after surgery were analyzed.

METHODS

SEVENTEEN PATIENTS (4 WOMEN AND 13 MEN) WITH PROGRESSIVE KERATOCONUS IN BOTH EYES WERE ENROLLED IN THIS STUDY. MEAN AGE WAS 31.17 ± 8.12 YEARS (RANGE, 21 TO 46 YEARS). INCLUSION CRITERIA WERE A DOCUMENTED PROGRESSION OF KERATOCONUS IN THE PREVIOUS 12 MONTHS, A CORNEAL THICKNESS OF AT LEAST 450 μm AT THE THINNEST POINT IN THE WORSE EYE, HARD CONTACT LENS AND FULL SPECTACLE CORRECTION

Accepted for publication Jul 11, 2012.

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intolerance because of blurred or distorted vision or subjective perception of comet-like asymmetric starbursts, and age older than 18 years. The diagnosis of keratoconus was made based on corneal topography results (Orbscan IIz; Bausch & Lomb, Rochester, New York, USA) as an asymmetric bowtie pattern, with or without skewed axes,⁸ and a paracentral inferior–superior dioptric difference of more than 1.4 diopters (D).⁹ Progression of keratoconus was defined, based on serial differential topography, as an increase in the apex keratometry by more than 1.0 to 1.5 D and a corresponding change (> 1.0 to 1.5 D) in the refractive cylinder in the previous 6 months. Exclusion criteria were a corneal thickness of less than 450 µm at the thinnest point in the worse eye, corneal scarring or Vogt striae, any history of other ocular disease or eye surgery, any systemic disease, and pregnancy. Patients who failed to attend the follow-up visits also were excluded.

Based on the treatment received, the 34 eyes were assigned to 1 of 2 groups: all patients underwent the combined procedure, namely PRK immediately followed by CXL as a single procedure (17 eyes) in the worse eye, and CXL alone in the fellow eye (17 eyes). At least 3 months elapsed between surgery on the first and then the fellow eye. The 34 eyes were graded as stage I to III according to the Aliò and Shabayek classification,¹⁰ using the C.S.O. EyeTop Topographer Corneal Aberrometry Program (Compagnia Strumenti Oftalmici, Firenze, Italy) for 6-mm pupil diameter; grade I keratoconus is characterized by a mean keratometry value of less than 48.00 D and a coma-like root mean square (RMS) value of between 1.50 and 2.50 µm for a 6.0-mm simulated pupil. Grade II keratoconus is characterized by a mean keratometry value of less than 53.00 D and a coma-like RMS value of between 2.5 and 3.5 µm. Grade III keratoconus is characterized by a mean keratometry value of less than 55.00 D and a coma-like RMS value of between 3.5 and 4.5 µm. In the PRK plus CXL group, 9 eyes had keratoconus stage I, 5 eyes had keratoconus stage II, and 3 eyes had keratoconus stage III. In the CXL alone group, 10 eyes had keratoconus stage I, 4 eyes had keratoconus stage II, and 3 eyes had keratoconus stage III.

- **PATIENT ASSESSMENT:** At baseline and at each follow-up (1, 3, 6, 12, 18, and 24 months), a full ophthalmic examination was performed, including assessment of UDA and BDA (JANG vision tester; Sifi Diagnostic, Treviso, Italy), slit-lamp microscopy examination, optical and Scheimpflug-based topography and tomography (Orbscan II; Orbtec, Bausch & Lomb; Precisio; Ligi Tecnologie Medicali, Taranto, Italy; respectively), measurement of corneal HOA (C.S.O. EyeTop Topographer; Compagnia Strumenti Oftalmici, Firenze, Italy), pachymetry using optical coherence tomography (OCT; Carl Zeiss Meditec Inc, Dublin, California, USA), and confocal microscopy (Corneal Confocal Microscope CS4; NIDEK Technologies, Erlangen, Germany). To improve the reliability of

topographic, tomographic, aberrometric, and interferometric measurements, at least 3 consecutive scans were performed by the same examiner for each eye, and the mean values of all scans were used for data analysis.

- **SURGICAL TECHNIQUE:** All treatments were performed with the iVIS Suite platform by the same experienced surgeon (G.A.) at the Department of Ophthalmology of Bari University Hospital from June 26, 2008, through July 8, 2009. The iVIS Suite custom ablation system combines the Scheimpflug-based topographer and tomographer Precisio, the dynamic pupillometer pMetrics, the topography-based ablation Corneal Interactive Programmed Topographic Ablation (CIPTA) planning software, and the high-resolution 1-KHz flying spot laser iRES. The steps of both topographic-guided PRK plus CXL as a single procedure (worse eye) and the CXL procedure alone (better eye) are reported below briefly.

The first part of the PRK plus CXL treatment consisted of acquisition of the corneal shape by means of the Precisio tomographer, which uses a rotating Scheimpflug camera to generate a 3-dimensional model of the cornea and anterior segment, with a repeatability of less than 3 µm. The elevation data from 50 high-resolution images with 39 000 measurement points on the anterior and posterior corneal surface from all captured images were combined with the patient's subjective refraction and were imported into the CIPTA planning software. Variations in pupil size were not taken into consideration.

Transepithelial topography-guided custom ablation with CIPTA software has been described elsewhere.^{11,12} This is a single-step, no-touch ablation technique involving the corneal epithelium and stroma; the uninterrupted, customized ablation procedure was planned to remove the corneal epithelium and the stroma. To minimize the tissue consumption and to assure the smoothness of the transition zone toward the untreated area, the CIPTA software provides the option of the Restored Morphological Axis strategy. The goal is to achieve an aspherical surface with a basic curvature corresponding to the flattest meridian, defined by the Precisio tomographer elevation map. The center of this surface is fitted to the corneal morphologic axis, which is not the visual axis, but rather a computer-generated axis of the restored corneal optical symmetry that approximates the best match between the axis of the ideal shape and that of the true shape of the cornea.¹³ In this way, the postoperative corneal surface is symmetrical with respect to the preoperative morphologic features and the change of corneal curvature allows the maximum reduction of irregularities with the minimum tissue consumption. The center of the planned ablation was the corneal apex in all treated eyes. The optical zone ranged between 2.16 and 5.45 mm; the diameter of the transition zone ranged between 6.00 and 8.75 mm. Ablation stromal depth was planned between 18 and 49 µm (mean, 31.1 ± 9.5 µm). Because of the

TABLE 1. Visual and Refractive Outcomes at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus.

| | PRK plus CXL Group | | | CXL Group | | | | <i>P</i> Value ^a | <i>P</i> Value ^b | <i>P</i> Value ^c |
|------------------------------------|--|--|-----------------------------|--|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | Baseline | 24-Month Follow-up | <i>P</i> Value ^a | Baseline | 24-Month Follow-up | <i>P</i> Value ^a | <i>P</i> Value ^a | | | |
| UDA (logMAR) | 0.63 ± 0.36 (1.6 to 0.18) | 0.19 ± 0.17 (0.5 to 0.00) | 4.77 × 10 ⁻⁴ | 0.59 ± 0.29 (1.18 to 0.18) | 0.52 ± 0.29 (1.00 to 0.00) | .07 | .72 | 4.03 × 10 ⁻⁴ | | |
| BDA (logMAR) | 0.06 ± 0.08 (0.3 to 0.00) | 0.03 ± 0.06 (0.18 to 0.00) | .198 | 0.06 ± 0.11 (0.3 to 0.00) | 0.04 ± 0.07 (0.18 to 0.00) | .05 | 1.00 | .019 | | |
| MRSE (D) | -1.94 ± 1.30 ^d (-3.25 to +2.00) | -0.19 ± 0.65 ^d (-1.75 to +1.25) | 9.15 × 10 ⁻⁶ | -1.54 ± 1.37 ^e (-3.25 to +0.75) | -1.09 ± 0.87 ^e (-2.75 to +0.50) | .148 | .38 | .003 | | |
| Spherical power (D) | 0.95 ± 1.49 (-2.00 to +4.00) | +0.11 ± 0.46 (-0.75 to +1.25) | .02 | -0.13 ± 1.02 (-1.5 to +2.00) | +0.32 ± 0.65 (-1.00 to +1.50) | .03 | .07 | .285 | | |
| Cylindrical power ^f (D) | -2.48 ± 1.01 (-0.75 to -4.50) | -0.88 ± 0.79 (0.00 to -2.50) | 8.18 × 10 ⁻⁵ | -2.78 ± 1.27 (-0.50 to -4.00) | -2.34 ± 1.25 (0.00 to -4.00) | .059 | .45 | 1.73 × 10 ⁻⁴ | | |

BDA = best distance acuity; CXL = cross-linking; D = diopters; logMAR = logarithm of the minimal angle of resolution; MRSE = manifest refraction spherical equivalent; PRK = photorefractive keratectomy; UDA = uncorrected distance acuity.

Data are presented as mean ± standard deviation (range) unless otherwise indicated. In all cases, the level of statistical significance was set at *P* < .05.

^aDifferences between preoperative and last postoperative values.

^bDifferences between PRK plus CXL and CXL alone values before surgery.

^cDifferences between PRK plus CXL alone values 24 months after surgery.

^dIn the PRK plus CXL group, preoperative MRSE was positive in 4 cases, negative in 11 cases, and 0 in 2 cases; 24-month postoperative MRSE was positive in 2 cases, negative in 10 cases, and 0 in 5 cases.

^eIn the CXL alone group, preoperative MRSE was positive in 1 case, negative in 14 cases, and 0 in 2 cases; 24-month postoperative MRSE was positive in 1 case, negative in 13 cases, and 0 in 3 cases.

^fCylindrical power was intended as refractive cylinder.

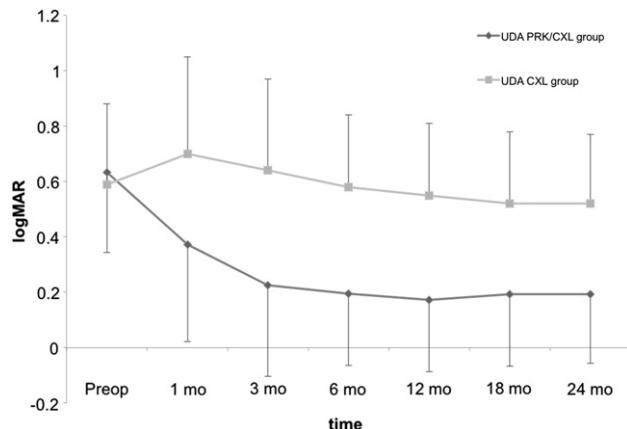


FIGURE 1. Graph showing change in uncorrected distance visual acuity (UDA) in logarithm of the minimal angle of resolution units (logMAR) during postoperative follow-up in eyes treated by photorefractive keratectomy with cross-linking (PRK/CXL group; deep gray line; $n = 17$) and in eyes treated by CXL alone (CXL group; light gray line; $n = 17$) for progressive keratoconus.

transepithelial treatment, a supplementary depth of the ablation for the epithelium was added, but in keratoconus eyes, the epithelial thickness profile was altered, so the value was selected arbitrarily as 50- μm in all cases by the surgeon. The corneal epithelium was removed by laser within a 9-mm diameter in all cases. Because of variations in the epithelial thickness map in keratoconic corneas,¹⁴ at the end of the photoablative procedure, possible remaining cells at the base of the cone were removed mechanically by the surgeon using a blunt spatula. The ablation plan was transferred to the iRES excimer laser, which is a 193-nm dual flying-spot laser, with the fluence adjusted to 250 mJ/cm², a maximum frequency of delivery of 1 KHz, and an infrared active-passive eye tracker for x, y, and cyclotorsional tracking. After topical anesthesia with 4% lidocaine drops, the laser beam, generated within the iRES laser, was delivered to the corneal surface. Within the selected optical zone, the aim was to normalize the anterior corneal surface as much as possible, rather than treating the refractive error itself.

After PRK, 2% pilocarpine drops were instilled to induce myosis of the pupil, and a CXL procedure was performed, according to the methodology described by Wollensak and associates.¹⁵ Riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran T500 solution; Ricrolin; SOOFT Italia S.p.A., Montegiorgio, Italy) was applied to the cornea every 2 minutes for 20 minutes. Using a slit lamp with blue filter inserted, the surgeon confirmed the presence of a yellow flare in the anterior chamber before the cornea was exposed to the ultraviolet A emitter Vega CBM X-linker (SOOFT Italia S.p.A.) for 30 minutes. During ultraviolet A exposure, riboflavin drops were applied again every 2 minutes.

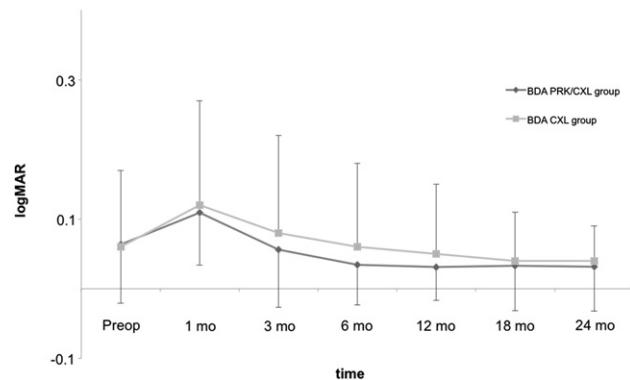


FIGURE 2. Graph showing change in best-corrected distance visual acuity (BDA) logarithm of the minimal angle of resolution units (logMAR) during postoperative follow-up in eyes treated by photorefractive keratectomy with cross-linking (PRK/CXL group; dark gray line; $n = 17$) and in eyes treated by CXL alone (CXL group; light gray line; $n = 17$) for progressive keratoconus.

The eye with lesser keratoconus staging received only CXL treatment. After removing the central 9.0 mm epithelium by mechanical debridement, using a blunt spatula (Desmarre corneal knife; John Weiss & Son Ltd, Milton Keynes, UK), the procedure was performed according to the steps described above. Before every CXL treatment, the intended irradiance (3 mW/cm^2 at 3 cm) of the VEGA CBM X-linker was checked with a LaserMate Q ultraviolet A meter (Laser 2000, Wessling, Germany).

The postoperative medical treatment was the same for both groups of eyes. After surgery, a soft bandage contact lens was applied until re-epithelialization was complete and patients were instructed to use 0.3% ofloxacin (Exocin; Allergan, Roma, Italy) and 0.1% indomethacin (Indocolilirio; Bausch+Lomb, Vimodrone, Milano, Italy) eye drops for the first 5 days, then, after complete re-epithelialization and removal of contact lens, patients received 0.1% topical fluorometholone (Flumetol; Thea Farma, Settimo Milanese, Italy) 4 times daily for the first month. The dosage was tapered by 1 drop monthly over the next 3 months. Postoperative follow-up was scheduled at 1, 3, 6, 12, 18, and 24 months after each eye surgery. Follow-up was 24 months for all eyes of both groups included in the study. All data were collected in an Excel spreadsheet (Microsoft, Redmond, Washington, USA) and were reported as mean \pm standard deviation. The 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. The unpaired *t* test was performed to compare outcome data at the last follow-up visit between the PRK plus CXL group and the CXL alone group. The level of statistical significance was set at $P < .05$.

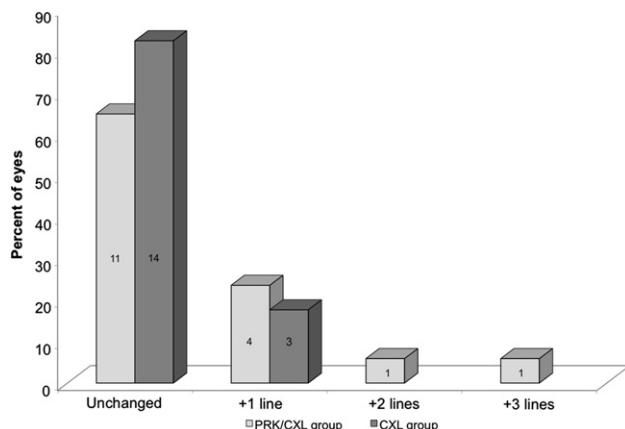


FIGURE 3. Bar graph showing change in best-corrected distance visual acuity (Snellen) at the last postoperative follow-up for eyes treated by photorefractive keratectomy with cross-linking (PRK/CXL group; light gray bars; n = 17) and for eyes treated by CXL alone (CXL group; deep gray bars; n = 17) for progressive keratoconus. The number of eyes for each change appears within each bar.

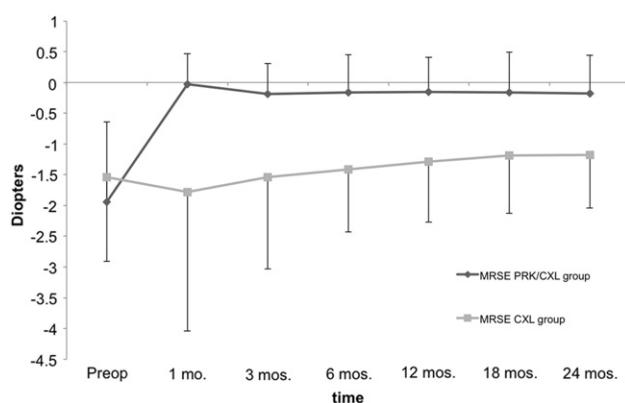


FIGURE 4. Graph showing change in manifest refraction spherical equivalent (MRSE) during postoperative follow-up in eyes treated by photorefractive keratectomy with cross-linking (PRK/CXL group; deep gray line; n = 17) and in eyes treated by CXL alone (CXL group; light gray line; n = 17) for progressive keratoconus. Diopters (D) ± standard deviation. mo(s) = month(s); Preop = before surgery.

RESULTS

- VISUAL ACUITY AND REFRACTIVE OUTCOME:** Table 1 summarizes preoperative and postoperative visual and refractive data for both groups: PRK plus CXL and CXL alone. UDA and BDA changes over time are shown in Figures 1 and 2. In the PRK plus CXL group, the eyes with UDA of 20/40 or better increased from 3 (17.6%) before surgery to 14 (82.3%) at the last follow-up examination; in the CXL only group, the eyes with

TABLE 2. Analysis of Refractive Astigmatic Vectors in eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | PRK plus CXL Group | CXL Group |
|---------------------------------|--------------------|--------------|
| Targeted induced astigmatism | 2.53 ± 1.1 | 2.68 ± 1.2 |
| Surgically induced astigmatism | 2.13 ± 1.1 | 1.61 ± 1.1 |
| Difference vector | 0.63 ± 0.67 | 1.69 ± 2.27 |
| Angle of error | 6.8 ± 17 | 7.76 ± 30.5 |
| Magnitude of error ^a | -0.4 ± 0.6 | -1.17 ± 1.39 |
| Index of success ^b | 0.3 | 0.7 |

CXL = cross-linking; PRK = photorefractive keratectomy.

Data are presented as mean ± standard deviation unless otherwise indicated.

^aThe negative value of the magnitude of error indicates an undercorrection.

^bThe index of success is directly proportional to the difference vector and inverse to the targeted induced astigmatism vector; the ideal result is 0, implying that the targeted astigmatism correction has been achieved.

UDA of 20/40 or better were 3 (17.6%) before surgery, and these remained unchanged at the last postoperative visit.

The stability of UDA, defined as 1-line (Snellen) difference in UDA between follow-up visits, was analyzed at different time points after treatment for both groups. In the PRK plus CXL group, from the 1-month to the 3-month examination, 6 (35.3%) eyes gained more than 1 Snellen line of UDA, and 11 (64.7%) eyes remained stable. From the 3-month to the 6-month examination, 7 (41.2%) eyes gained 1 or more than 1 Snellen line of UDA and 10 (58.8%) eyes remained stable. From the 6-month to the 12-month examination, 6 (35.2%) eyes gained 1 Snellen line of UDA and 11 (64.7%) eyes remained stable. From the 12-month to the 18-month examination, 2 (11.7%) eyes gained 1 Snellen line of UDA, and 13 (76.4%) eyes remained stable. From the 18-month to the 24-month examination, all the eyes (100%) were stable. No eye lost Snellen lines of UDA.

In the CXL only group, from the 1-month to the 3-month examination, 3 (17.6%) eyes gained 1 or more than 1 Snellen line of UDA, and 14 (82.3%) eyes remained stable. From the 3-month to the 6-month examination, 3 (17.6%) eyes gained 1 or more than 1 Snellen line of UDA, and 14 (82.3%) eyes remained stable. From the 6-month to the 12-month examination, from the 12-month to the 18-month examination, and from the 18-month to the 24-month examination, all the eyes (100%) were stable. No eye lost Snellen lines of UDA.

At the last postoperative examination, in the PRK plus CXL group, no eye lost lines of BDA and 6 eyes (35.2%) gained 1 to 3 lines of BDA, as compared with preoperative data; in the CXL only group, no eye lost lines of BDA and 3

TABLE 3. Topographic and Keratoconus Indices Obtained with the C.S.O. EyeTop Topographer (Costruzione Strumenti Oftalmici, Florence, Italy) at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | PRK plus CXL Group | | | CXL Group | | | | |
|----------|--------------------|--------------------|-------------------------|--------------|--------------------|-------------------------|----------------------|----------------------|
| | Baseline | 24-Month Follow-up | P Value ^a | Baseline | 24-Month Follow-up | P Value ^a | P Value ^b | P Value ^c |
| SimK-1 | 44.83 ± 11.67 | 43.17 ± 2.97 | 6.23 × 10 ⁻⁸ | 44.92 ± 2.76 | 43.85 ± 1.38 | .23 | .97 | .39 |
| SimK-2 | 47.41 ± 12.44 | 44.94 ± 3.33 | 3.33 × 10 ⁻⁹ | 47.17 ± 3.74 | 46.08 ± 3.21 | 1.3 × 10 ⁻³ | .94 | .31 |
| SimK-AVG | 46.12 ± 12.04 | 44.05 ± 3.11 | 6.66 × 10 ⁻⁸ | 46.01 ± 3.18 | 44.86 ± 1.92 | .04 | .97 | .36 |
| SimK-Cyl | 2.70 ± 1.56 | 1.58 ± 1.29 | 3.9 × 10 ⁻³ | 2.29 ± 1.00 | 2.25 ± 0.94 | .76 | .36 | .09 |
| AK | 54.46 ± 14.3 | 50.00 ± 4.60 | 3.68 × 10 ⁻⁷ | 54.14 ± 2.79 | 52.79 ± 3.36 | .07 | .92 | .05 |
| IS | 6.31 ± 3.34 | 3.28 ± 2.72 | 6.46 × 10 ⁻⁶ | 5.86 ± 1.40 | 5.08 ± 1.46 | 1.28 × 10 ⁻⁶ | .61 | .02 |

AK = apex keratometry; CXL = cross-linking; D = diopters; IS = inferior-superior index; PRK = photorefractive keratectomy; SimK-AVG = simulated keratometry average; SimK-Cyl = simulated keratometric cylinder; SimK-1 = flattest simulated meridian keratometry; SimK-2 = steepest simulated meridian keratometry.

Data are presented as mean ± standard deviation unless otherwise indicated. In all cases, the level of statistical significance was set at $P < .05$.

^aDifferences between preoperative and last postoperative values.

^bDifference between the PRK plus CXL and CXL alone groups before surgery. The baseline 6 CSO indices in the PRK plus CXL group were not significantly different from the same baseline measurements in the CXL alone group.

^cDifference between the PRK plus CXL and CXL alone groups 24 months after surgery. All 6 CSO indices were decreased, but the difference between the 2 groups was not significant for SimK-1, SimK-2, SimK-AVG, and SimK-Cyl, whereas the difference was significant for AK and IS values.

TABLE 4. Mean Maximum Anterior Corneal Elevation above the Best Fit Sphere within the Central 3-mm Diameter, Obtained by Precisio Tomographer (Ligi Tecnologie Medicali, Taranto, Italy) at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | PRK plus CXL Group | | | CXL Group | | | P Value ^a | P Value ^b | P Value ^c |
|-------------------------|-----------------------------|-------------------------|---------------------------|---------------------------|--------------------|----------------------|-------------------------|----------------------|----------------------|
| | Baseline | 24-Month Follow-up | P Value ^a | Baseline | 24-Month Follow-up | P Value ^a | | | |
| 39.47 ± 18.07 (5 to 88) | 3.21 ± 29.90 (-48 to 64) | 4.18 × 10 ⁻⁷ | 38.98 ± 16.5 (6 to 57) | 32.52 ± 11.4 (3 to 35) | .76 | .87 | 4.32 × 10 ⁻⁵ | | |

CXL = cross-linking; PRK = photorefractive keratectomy.

Data are presented as mean ± standard deviation (range) unless otherwise indicated. In all cases, the level of statistical significance was set at $P < .05$.

^aDifferences between preoperative and last postoperative values.

^bDifferences between the PRK plus CXL and CXL alone groups before surgery. The preoperative maximum anterior corneal elevation was not significantly different between the 2 groups.

^cDifferences between the PRK plus CXL and CXL alone groups 24 months after surgery. Maximum anterior corneal elevation was significantly different between the 2 groups.

eyes (17.6%) gained 1 line of BDA, as compared with preoperative data (Figure 3).

Spherical error was present before surgery in 15 (88.2%) eyes in the PRK plus CXL group and in 13 (76.4%) eyes in the CXL only group. All patients had astigmatic error. At the last follow-up visit, spherical error was present in 7 (41.1%) eyes in the PRK plus CXL group and in 10 (58.8%) eyes in the CXL group.

In both groups, at different time points after surgery, mean manifest refraction spherical equivalent was stable

within a 1.00-D difference (Figure 4). Also, vector analysis of astigmatic correction according to the Alpin method, based on refractive data, was performed in both groups (Table 2).

- **TOPOGRAPHIC RESULTS:** Table 3 summarizes topographic and keratoconus indices as measured with the C.S.O. Topographer at baseline and 24 months after surgery for both groups. In the entire cohort, the following anterior corneal surface parameter was evaluated with the

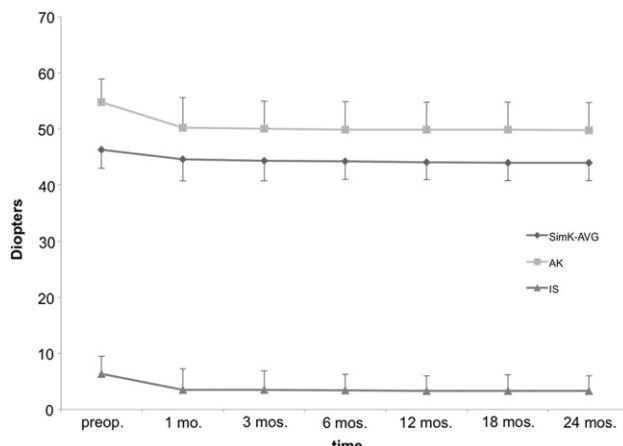


FIGURE 5. Graph showing change in topographic indices obtained with C.S.O. EyeTop Topographer (Costruzione Strumenti Oftalmici, Florence, Italy) in eyes treated by photorefractive keratectomy with cross-linking for progressive keratoconus, throughout the postoperative period. AK = apex keratometry; IS = inferior-superior index; mo(s) = month(s); preop = before surgery; SimK-AVG = average simulated keratometry.

Precisio tomographer: maximum anterior corneal elevation above the best fit sphere in the central 3-mm diameter area before surgery and at last follow-up time. After surgery, in each case, the sphere reference was fitted to the preoperative best fit sphere value. The results are reported in Table 4.

The topographic stability was analyzed at different time points after treatment for both groups, stability being defined as a 1.00-D difference in average simulated keratometry, apex keratometry, and inferior-superior value⁸ indices between follow-up visits. In both groups, mean average simulated keratometry, mean apex keratometry, and mean inferior-superior values were stable within a 1.00-D difference (Figures 5 and 6).

• **ABERROMETRIC RESULTS:** For both groups, the corneal HOA values, defined as total and coma-like aberrations, were measured for 3-mm, 5-mm, and 7-mm pupil diameters by means of the C.S.O. EyeTop Corneal Aberrometry Program. The results are shown in Tables 5 and 6. Examples of HOA changes after PRK plus CXL are shown in Figure 7.

• **TOMOGRAPHIC RESULTS:** Before surgery and at the last postoperative examination, the pachymetry map obtained by means of the anterior segment OCT Visante system (Carl Zeiss Meditec Inc)¹⁶ was used to evaluate central corneal thickness (CCT; that is, the corneal thickness at the center of the scan) and thinnest corneal thickness (that is, the corneal thickness at the thinnest location) in both groups (Table 7).

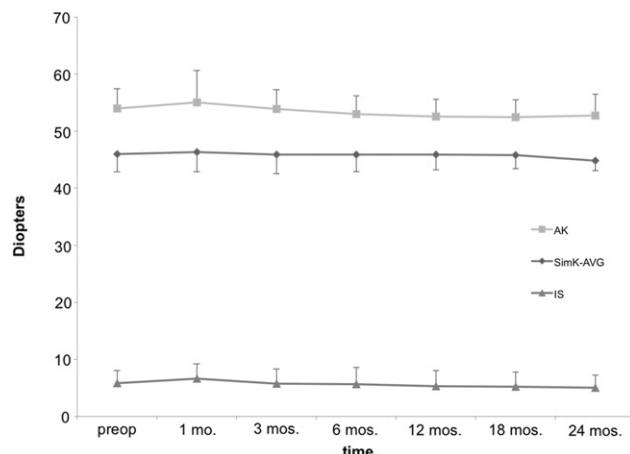


FIGURE 6. Graph showing change in topographic indices obtained with C.S.O. EyeTop Topographer (Costruzione Strumenti Oftalmici, Florence, Italy) in eyes treated by cross-linking alone for progressive keratoconus, throughout the postoperative period. AK = apex keratometry; IS = inferior-superior index; mo(s) = month(s); preop = before surgery; SimK-AVG = average simulated keratometry.

• **ENDOTHELIAL RESULTS:** Data regarding endothelial cell density before and after surgery are reported in Table 8. A detailed description of the endothelial changes, revealed by confocal microscopy in both groups of eyes, will be the focus of a separate report.

• **COMPLICATIONS:** All patients reported some degree of pain during the first day after treatment. Re-epithelialization occurred within 5 days in all patients. Of the 34 treated eyes, 23 (67.64%) demonstrated a CXL-specific demarcation line (14 eyes in the PRK plus CXL group and 9 eyes in the CXL group) and 11 (32.35%) had central subepithelial haze formation (grades 0.5 to 1; 7 eyes in the PRK plus CXL group and 4 eyes in the CXL group) by 12 months after treatment. Because of haze formation, no eye lost Snellen lines of UDA related to the last postoperative examination before the haze developed. The haze disappeared with a topical steroids regimen tapered within 1 month. No ocular or systemic adverse events were observed after treatment.

DISCUSSION

THIS PROSPECTIVE STUDY INVESTIGATED THE VISUAL ACUITY, refractive, topographic, and HOA outcomes of the PRK plus CXL procedure performed using the iVIS suite platform compared with the CXL only procedure in eyes diagnosed with progressive keratoconus over a follow-up of 24 months. Although the goal of the PRK plus CXL procedure was not emmetropia, the results showed that at the

TABLE 5. Total and Coma-like Aberrations (Root Mean Square) for 3-mm, 5-mm, and 7-mm Pupil Diameter Measured Using the C.S.O. EyeTop Corneal Aberrometry Program (EyeTop Topographer; Costruzione Strumenti Oftalmici, Florence, Italy) at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | Total Aberrations (μm) | | | Coma-like Aberrations (μm) | | |
|----------------------|-------------------------------------|--------------------------------|--------------------------------|---|--------------------------------|--------------------------------|
| PRK plus CXL group | | | | | | |
| Pupil diameter (mm) | 3.00 | 5.00 | 7.00 | 3.00 | 5.00 | 7.00 |
| Baseline | 1.94 \pm 0.62 | 5.57 \pm 1.90 | 10.66 \pm 3.82 | 1.45 \pm 0.60 | 4.76 \pm 2.00 | 9.27 \pm 3.90 |
| 24-month follow-up | 1.14 \pm 0.60 | 3.44 \pm 1.76 | 7.19 \pm 3.75 | 0.81 \pm 0.51 | 2.75 \pm 1.64 | 5.60 \pm 3.82 |
| P value ^a | 9.07 \times 10 ⁻⁷ | 1.69 \times 10 ⁻⁷ | 7.37 \times 10 ⁻⁶ | 5.29 \times 10 ⁻⁶ | 5.98 \times 10 ⁻⁶ | 9.11 \times 10 ⁻⁵ |
| CXL group | | | | | | |
| Pupil diameter (mm) | 3.00 | 5.00 | 7.00 | 3.00 | 5.00 | 7.00 |
| Baseline | 1.79 \pm 0.81 | 5.76 \pm 1.99 | 11.18 \pm 3.83 | 1.42 \pm 0.56 | 4.70 \pm 1.66 | 9.41 \pm 3.73 |
| 24-month follow-up | 1.68 \pm 0.86 | 5.12 \pm 1.97 | 10.50 \pm 3.70 | 1.30 \pm 0.50 | 4.41 \pm 1.57 | 9.20 \pm 4.03 |
| P value ^a | .325 | .093 | .141 | .052 | .073 | .355 |

CXL = cross-linking; PRK = photorefractive keratectomy.

Data are presented as mean \pm standard deviation unless otherwise indicated.

^aDifferences between preoperative and 24-month postoperative values. The level of statistical significance was set at $P < .05$.

TABLE 6. Statistical Comparison (Unpaired t Test) of Total and Coma-like Aberrations for 3-mm, 5-mm, and 7-mm Pupil Diameter at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | Total Aberrations | | | Coma-like Aberrations | | |
|--|-------------------|------|------|-----------------------|------|------|
| Pupil diameter (mm) | 3.00 | 5.00 | 7.00 | 3.00 | 5.00 | 7.00 |
| P value between 2 groups at baseline | .549 | .778 | .694 | .881 | .925 | .915 |
| P value between 2 groups at 24-month follow-up | .042 | .013 | .014 | .008 | .005 | .012 |

The total and coma-like aberrations data were obtained by C.S.O. EyeTop Topographer Aberrometry Program (Costruzione Strumenti Oftalmici, Florence, Italy). The level of statistical significance was set at $P < .05$.

last postoperative examination, the PRK plus CXL procedure provided better UDA, lower manifest refraction spherical equivalent, mean spherical and cylindrical power, and lower keratometric values than the CXL only procedure. Furthermore, corneal astigmatic changes were analyzed using the Alpin vectorial method after both surgical approaches: the eyes treated by the CXL only procedure showed, on average, a greater magnitude of error and lower index of success compared with eyes treated by the PRK plus CXL procedure, despite the planned undercorrection in the PRK plus CXL treatment adopted to take into account the long-term flattening effect resulting from CXL.¹⁷

To estimate the degree of changes in the elevation of the anterior corneal surface induced by surgery, the maximum anterior corneal elevation in the central 3-mm diameter area obtained by the Precisio tomographer was evaluated at the last postoperative visit relative to the preoperative best-fit sphere. The PRK plus CXL procedure induced greater changes in maximum anterior central corneal

elevation above the best fit sphere compared with preoperative data.

Corneal HOA analysis for 3-mm, 5-mm, and 7-mm of pupil diameter showed a greater reduction in RMS values after the PRK plus CXL procedure than after the CXL only procedure. In the PRK plus CXL group, the reduction in RMS values was consistent with the better visual performance and should be attributed to the quality of the ablation plan. By conforming to the topography height map, the PRK plus CXL treatment leads to a correction of irregular astigmatism, resulting in improved third-order aberrations and enhanced visual acuity.

Previous studies also assessed HOA using the C.S.O. Eye Top topographer corneal aberrometry program after the CXL procedure, but conflicting findings were reported. In a study by Vinciguerra and associates, the mean spherical and mean astigmatic aberrations were significantly lower 12 months after treatment, but the mean coma aberration did not show a statistically significant decrease.¹⁸ In another study with longer follow-up, Vinciguerra and

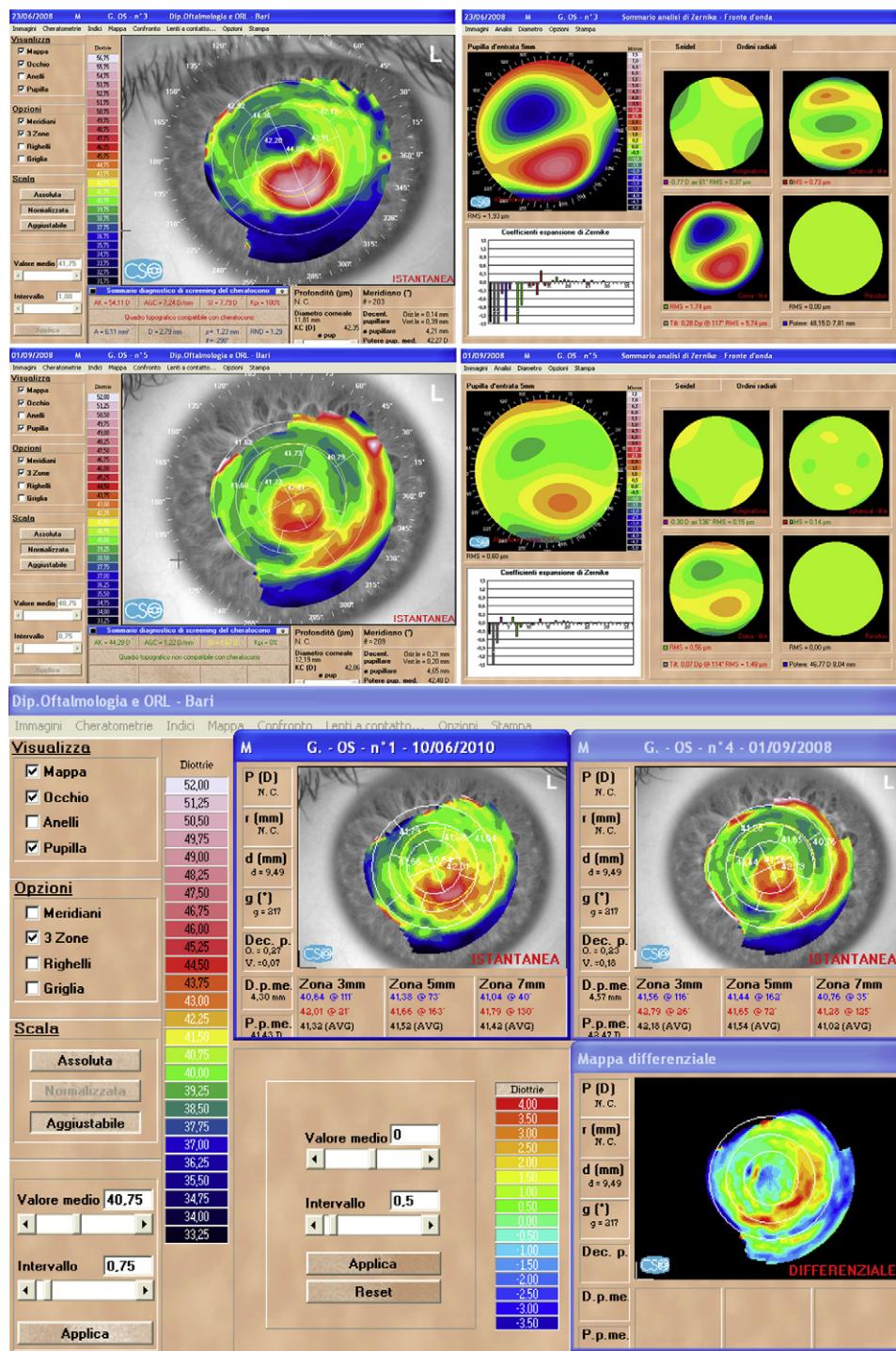


FIGURE 7. Topographic and corneal higher-order aberration maps of a keratoconic eye obtained before and after the topographic-guided photorefractive keratectomy followed by cross-linking in a single procedure. The maps were obtained with the C.S.O. EyeTop Topographer (Costruzione Strumenti Oftalmici, Florence, Italy). (Top left) Tangential map obtained before treatment; (Top right) higher-order aberration map of the first corneal surface before treatment for 5-mm pupil diameter; (Middle left) tangential map obtained 65 days after surgery; (Middle right) higher-order aberration map of the first corneal surface 65 days after treatment for 5-mm pupil diameter; (Bottom) differential map, derived by subtracting the image collected 24 months after treatment from the image obtained 65 days after surgery, showing further flattening of the cone in the central area associated with steepening in the paracentral nasal area; the map appearance was nearly the same at 24 months as at 65 days of follow-up.

TABLE 7. Central Corneal Thickness and Thinnest Corneal Thickness Measured by Anterior Segment Optical Coherence Tomography at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | PRK plus CXL Group | | | CXL group | | | | P Value ^b | P Value ^c |
|-----------------------|--------------------|--------------------|-----------------------|-----------------|--------------------|-----------------------|------|----------------------|----------------------|
| | Baseline | 24-Month Follow-up | P Value ^a | Baseline | 24-Month Follow-up | P Value ^a | | | |
| CCT (μm) | 516 \pm 26.50 | 486.8 \pm 28.3 | 8.20×10^{-5} | 513 \pm 32.01 | 501.1 \pm 27.1 | 1 | .309 | .107 | |
| TCT (μm) | 489.3 \pm 23.64 | 441.8 \pm 29.77 | 2.66×10^{-5} | 491 \pm 16.50 | 472.2 \pm 17.1 | 5.22×10^{-5} | .722 | .008 | |

CCT = central corneal thickness; CXL = cross-linking; PRK = photorefractive keratectomy; TCT = thinnest corneal thickness.

Data are presented as mean \pm standard deviation unless otherwise indicated. In all cases, the level of statistical significance was set at $P < .05$.

^aDifferences between preoperative and 24-month postoperative values.

^bDifferences between the PRK plus CXL and CXL alone values before surgery.

^cDifferences between the PRK plus CXL and CXL alone values 24 months after surgery.

TABLE 8. Endothelial Cell Density at Baseline and 24 Months after Surgery in Eyes Treated by Photorefractive Keratectomy with Cross-linking and in Eyes Treated by Cross-linking Alone for Progressive Keratoconus

| | PRK plus CXL Group | | | CXL Group | | | P Value ^a |
|------------------------------|----------------------------------|----------------------------------|----------------------|----------------------------------|----------------------------------|----------------------|----------------------|
| | Baseline | 24-Month Follow-up | P Value ^a | Baseline | 24-Month Follow-up | P Value ^a | |
| ECD (cells/mm ²) | 2945 \pm 115 (2731 to 3012) | 2824 \pm 119 (2650 to 3001) | .56 | 2899 \pm 168 (2691 to 3101) | 2651 \pm 135 (2513 to 2986) | .59 | |

CXL = cross-linking; ECD = endothelial cell density; PRK = photorefractive keratectomy.

Data are presented as mean \pm standard deviation (range) unless otherwise indicated.

^aDifferences between the PRK plus CXL and CXL alone values before surgery and 24 months after surgery. The level of statistical significance was set at $P < .05$.

associates found a significant reduction in total RMS and in some high order aberrations (piston, defocus, and coma) for the 7-mm pupil diameter.¹⁹ Caporossi and associates found a statistically significant reduction in coma and total wave-front HOAs in 44 keratoconic eyes 24 months after CXL, but it is difficult to interpret the data in this study because aberrometric outcomes were not coupled with pupil diameter.²⁰

In the current study, the combined PRK plus CXL approach has the potential to enhance visual rehabilitation of eyes with progressive keratoconus. The rationale for this surgical approach is to halt the progression of keratoconus and to provide better refractive, topographic, and HOA results than with CXL treatment alone by reshaping the cornea and flattening and regularizing the anterior corneal surface, while ensuring stable outcomes over time in terms of nonprogression of the disease.

To the best of our knowledge, the results of the PRK plus CXL procedure have not been compared with those of CXL alone in prospective clinical trials. Case series reported a PRK procedure followed by CXL for keratoconus. In one study, 325 keratoconic eyes were assigned to 2 groups.⁶ The first group ($n = 127$ eyes) underwent CXL with subsequent topography-guided PRK performed 6 months later

(sequential group) and the second group ($n = 198$ eyes) underwent CXL and PRK in a combined procedure on the same day (simultaneous group) using the Allegretto (WaveLight, Erlangen, Germany) topography-guided laser platform. This system incorporates the Allegretto Wave Topolyzer with T-CAT software for treatment. The Topolyzer is a Placid disc-based topographer that produces an elevation map with measurements aligned to the line-of-sight passing through the pupil center. The T-CAT software bases ablation planning on the same axis on which the topographic measurements were acquired, that is, the visual axis; no tilt correction was chosen in all cases. In this procedure, corneal epithelium was removed after debridement by a 20% alcohol solution. Statistically, the simultaneous group achieved better results ($P < .05$) in all parameters evaluated, including UDA and BDA, spherical equivalent refraction and keratometry, and less corneal haze. In a similar prospective study, Kymionis and associates reported favorable results in 14 eyes with progressive keratoconus treated with customized topography-guided PRK with the Pulzar Z1 (wavelength 213 nm, CustomVis) solid-state laser, immediately followed by CXL.⁵ In these eyes, the corneal epithelium was removed mechanically, and the software adjusted the percentage of customization

according to corneal HOAs, not exceeding 50 µm of maximum ablation depth. In these surgical approaches, the effects of epithelial remodeling, characteristic of the keratoconic cornea, were not taken into consideration, and the influence of centration and orientation of the ablation profile was not considered in the ablation planning strategy. Several studies showed that, in the keratoconic cornea, the epithelium is thicker over the depressed stroma and thinner over the cone, so topography-guided ablation, applied to the stroma, can correct only the irregularity that has not been compensated by the epithelium.^{14,21} Some authors included a preliminary step, namely a phototherapeutic keratectomy procedure, performed to remove the corneal epithelium, followed by PRK.^{22,23} One step toward the goal of correcting epithelial and stromal irregularities is the development of software that allows epithelial removal together with stromal ablation in a single, uninterrupted ablation. The CIPTA software allows epithelial removal with the excimer laser as part of the ablation plan and definition of the restored morphologic axis based on the elevation map of the corneal surface, independently of the fixation axis along which the measurements must be obtained. Improvements in mean UDA, mean BDA, mean astigmatism, and keratometric asymmetry were achieved after PRK plus CXL treatment with the iVIS suite platform for periods of up to 12 months in a study of Stojanovic and associates.⁷ In this case series, the Precisio tomographer was used to investigate changes that occurred not only in the anterior corneal surface, but also in the posterior corneal surface. Sheimplug system devices lead to highly repeatable measurements of the anterior segment in normal eyes as well as in eyes with previous refractive surgery or keratoconus, but concern remains about the accuracy of posterior corneal surface measurements by the Precisio device, especially in corneas with haze, so in the current study, we decided not to use the Precisio tomographer to characterize posterior changes.^{24,25}

Because the anterior segment OCT Visante system proved to be unaffected by changes in the reflectivity of the corneal stroma induced by the CXL procedure before surgery and at the last postoperative follow-up, pachymetry maps were obtained to measure differences in CCT and thinnest corneal thickness between the 2 groups.²⁶ The thinnest corneal thickness parameter is included among preoperative inclusion criteria for enrollment to plan the ablation profile and provides a reliable tool for accurately

monitoring corneal thickness after the CXL procedure. Eyes subjected to the combined PRK plus CXL surgical procedure had a significantly lower postoperative CCT that was consistent partly with the ablation profile reduction. In fact, there was not a precise correspondence between expected and current postoperative central pachymetry, investigated with the anterior segment OCT Visante system: current CCT was higher than the expected pachymetry as planned with CIPTA software. This pachymetric mismatch could be ascribed to the epithelial doughnut pattern demonstrated in keratoconic eyes and to an epithelial compensatory mechanism, suggested after CXL treatment, as shown in some studies conducted with a very high-frequency digital ultrasound arc scanning.^{14,21,27} The customized transepithelial PRK plus CXL procedure, aimed to regularize the anterior corneal surface, promotes an epithelial profile change, suggesting a more uniform arrangement of epithelium resulting from a progressive improvement in the shape of the anterior corneal surface.

In our study, we found that both procedures were safe, specifically because changes in the endothelial cell density, as compared with those obtained before surgery, were not statistically significant over time, and these results were consistent with those of several authors.^{18,20,28} A detailed description of the changes revealed by confocal microscopy in both groups of eyes will be the focus of a separate report.

In conclusion, this nonrandomized trial demonstrated that the PRK plus CXL procedure is an effective treatment option for progressive keratoconus, and stable refractive, topographic, and HOA outcomes over time were found to be associated with the treatment. A potential limitation of this study seems to be that the eyes were not randomized into the PRK plus CXL or CXL groups. Nevertheless the worse eye, treated in the first group, showed the greatest improvement in all cases. The main limitation of this study is that it was based on topographic and HOA data as indirect clinical measures of the stability of the PRK plus CXL treatment over time, rather than on the knowledge of individual biomechanical corneal properties, but for obvious reasons, this is not feasible at this stage of the technology.

In the future, ideally we would customize the surgical PRK plus CXL procedure on the basis of the biomechanical properties of the cornea. This potentially would improve visual outcomes even further, with no fear of unstable results over time.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. Involved in design of study (G.A., M.L., C.S., M.G.L.T.); Conception and design of study (G.A.); Data collection and literature search (M.L.); Analysis and interpretation of data (M.G.L.T., M.L.); Preparation and writing of article (M.L.); Critical revision of article (G.A., M.G.L.T.); Final revision of article (M.G.L.T., M.L.); and Final approval of article (C.S.). The Local Ethics Committee of Azienda Ospedaliera Policlinico di Bari gave approval for this prospective study (protocol no. 839/C.E.). Clinical trial registration is available at: <http://www.controlled-trials.com/ISRCTN57262986>. Informed consent was obtained from the participating patients of the study. All procedures consistently adhered to the tenets of the Declaration of Helsinki.

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Biosketch

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Photorefractive keratectomy followed by cross-linking versus cross-linking alone for management of progressive keratoconus: two-year follow-up. Giovanni Alessio, Milena L'Abbate, Carlo Sborgia, and Maria Gabriella La Tegola

This clinical trial compared refractive, topographic, and corneal higher-order aberrations outcomes after topographic photorefractive keratectomy (PRK) with minimal ablation followed by cross-linking (CXL) in single procedure versus CXL alone in 17 patients (34 eyes) with progressive keratoconus. In all patients, the worse eye received PRK plus CXL and the better eye received CXL alone. The results were better in the PRK plus CXL group.