Collagen copolymer toric phakic intraocular lens for residual myopic astigmatism after intrastromal corneal ring segment implantation and corneal collagen crosslinking in a 3-stage procedure for keratoconus

Efekan Coşkunseven, MD, Daya Papalkar Sharma, MB BS, FRANZCO, Mirko R. Jankov II, MD, PhD,
George D. Kymionis, MD, PhD, Olivier Richoz, MD, Farhad Hafezi, MD, PhD

PURPOSE: To evaluate staged combined treatment for keratoconus with intrastromal corneal ring segment (ICRS) implantation followed by corneal collagen crosslinking (CXL) with riboflavin–ultraviolet-A (UVA) and then toric implantable collagen copolymer phakic intraocular lens (pIOL) implantation.

SETTING: Large private ophthalmic hospital system.

DESIGN: Case series.

METHODS: Eyes with progressive keratoconus had ICRS implantation, then CXL, and then pIOL implantation (minimum 6 months between procedures).

RESULTS: The study enrolled 14 eyes (9 patients). After the combined treatments, the mean decimal uncorrected distance visual acuity (UDVA) and mean decimal corrected distance visual acuity (CDVA) were significantly improved from 0.01 and 0.14, respectively, preoperatively to 0.44 and 0.57, respectively ($P<.0001$). The mean manifest refraction spherical equivalent decreased from -16.40 diopters (D) $\pm$ 3.56 (SD) (range -11.50 to -22.50 D) to -0.80 ± 1.02 D (range -2.00 to $+2.00$ D) after the combined treatments ($P<.0001$). The mean refractive astigmatism decreased from -4.73 ± 1.32 D (range -3.00 to -7.00 D) to -0.96 ± 0.35 D (range -0.50 to -1.50 D) ($P<.0001$). The mean steep and mean flat keratometry values reduced from 60.57 D and 56.16 D, respectively, to 54.48 D and 53.57 D ($P<.0001$), respectively. No intraoperative or postoperative complications occurred.

CONCLUSIONS: A combined 3-stage-approach keratoconus treatment comprising ICRS implantation followed by CXL and then toric pIOL implantation was effective in improving functional vision and reducing disease progression. Longer term studies are required for further evaluation and comparison with other methods.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2013; ■:■–■ © 2013 ASCRS and ESCRS

Keratoconus is a corneal ectatic disorder characterized by corneal thinning and bulging, leading to irregular astigmatism and reduced vision.[1] It presents 2 key management issues: rehabilitating vision and halting the disease progression. For keratoconic patients who no longer have acceptable spectacle-corrected vision, rigid gas-permeable (RGP) lenses or hybrid contact lenses are usually the preferred option. However, deep anterior lamellar keratoplasty (DALK) or penetrating keratoplasty (PKP) may be required in advanced cases.[2] Contact lens intolerance has been reported to be a major cause (83%) of keratoconic patients requiring PKP, whereas poor vision despite a good contact lens fit is a much less frequent reason

(8.5%) for progressing to PKP.[3] High post-keratoplasty astigmatism remains a common occurrence, with many patients having more than 3.0 diopters (D) of residual astigmatism after suture removal.[4] For patients with contact lens intolerance but good contact lens–corrected vision, surgical management has evolved. The multiple alternative options include stabilizing the cornea with corneal collagen crosslinking (CXL),[5] regularizing the cornea with intracorneal ring segment (ICRS) implantation[6,7] and performing topography-guided excimer laser ablation,[8] and treating myopic astigmatism with toric phakic intraocular lens (pIOL) implantation.[9] Unlike keratoplasty, these techniques do not require the use of donor corneal tissue; hence, there is no risk for endothelial rejection (PKP) or stromal rejection (DALK and PKP).

Corneal CXL is a safe and effective treatment to reduce or halt the progression of keratoconus[10–14] with long-term results showing it has a prolonged effect in most cases.[10,13] In some patients, induced mild flattening and regularization of the cornea lead to modest improvements in vision that rarely improve functional vision. For successful visual rehabilitation, other management options are usually required. For the irregular astigmatism component of reduced vision, corneal regularization can be achieved using ICRS implantation[6] or limited topography-guided excimer laser custom ablation treatment.[8,15,16] Intrastromal corneal ring segment implantation adds structure to the cornea and is a reversible technique; the segments can be explanted or exchanged with segments of different thicknesses or arc lengths. Topography-guided ablation can also effectively reduce irregular astigmatism and can be performed after ICRS implantation.[17] The toric Visian Implantable Collamer Lens (Staar Surgical Co.) can be used to treat high residual myopic astigmatism (up to −20.0 D of sphere and 6.0 D of astigmatism),[18,19] in particular after treatment of the irregular component of astigmatism. Because these techniques are still

evolving, the best strategy for their use is being determined, in particular in terms of simultaneous or staged procedures and how to best combine treatment modalities.

The purpose of this study was to assess the efficacy and safety of a 3-stage approach to improve vision and stop progression in keratoconic eyes with extreme myopia and irregular astigmatism. The first stage was ICRS (Keraring, Mediphacos Ltda.) implantation using a femtosecond laser to reduce irregular astigmatism. This was followed by corneal CXL to stabilize the cornea. The final stage was posterior chamber toric pIOL (Visian Implantable Collamer Lens) implantation to treat the residual high myopic astigmatism.

PATIENTS AND METHODS

Eyes with progressive keratoconus were included in this prospective case series, which comprised all patients treated with the 3-stage approach who had at least 1 year of follow-up. Progressive keratoconus was defined as an increase in the topographic keratometry (K) readings of 0.75 D over at least 6 months. Before their participation in the study, all patients were appropriately informed about the possible outcomes and the current clinical experience. All provided written informed consent in accordance with institutional guidelines and the Declaration of Helsinki.

Inclusion criteria for the study were clear central corneas with at least 400 μm of corneal thickness at the thinnest point, poor spectacle-corrected vision, and contact lens intolerance. Exclusion criteria were no improvement in visual acuity with a diagnostic RGP or hybrid contact lens trial, anterior chamber depth (ACD) from endothelium of less than 2.8 mm (after ICRS implantation, which is expected to decrease the ACD), history of herpetic eye disease, keratitis, corneal dystrophies, diagnosed autoimmune disease, systemic connective tissue disease, severe atopy, acute or grade IV keratoconus, and endothelial cell density less than 2500 cells/mm^2.[20]

The preoperative and postoperative examination included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, topographic findings, and slitlamp evaluation. Visual acuities were measured in decimal notation, converted to logMAR equivalent for statistical evaluation, and then converted back to decimal notation for reporting.

Corresponding author: Efekan Coşkunseven, MD, Refractive Surgery Department, Dunya Eye Hospital, Etiler, Istanbul, Turkey. E-mail: efekan.coskunseven@dunyagoz.com.

Surgical Technique

All procedures were performed by the same surgeon (E.C.) at Dunya Eye Hospital, Istanbul, Turkey. All patients had 3-stage treatment in the following order: ICRS implantation, CXL, toric pIOL implantation.

Intrastromal Corneal Ring Segment Implantation   Keraring Si5 segments were used in this study. They are poly (methyl methacrylate) segments with a triangular cross-section, an apical diameter of 5.0 mm, and a flat base width of 0.6 mm. The thickness varies from 0.15 to 0.35 mm in 0.05 mm steps, with arc lengths of 90, 120, 160, and 210 degrees. The segments provide a 5.0 mm diameter optical zone.

The surgical procedure was performed under sterile conditions using topical anesthesia. The Purkinje reflex

was chosen as the central point and was marked under an Allegretto biomicroscope (Wavelight). A 5.0 mm marker was used to locate the exact ring channel. Intraoperative ultrasound pachymetry (Sonogage, Inc.) was performed along the ring location markings. A 60 kHz femtosecond laser (Intralase) was used to create the ring channels using an inner diameter of 4.4 mm and an outer diameter of 5.6 mm (600 μm tunnel width). The tunnel depth was set at 80% of the thinnest corneal thickness on the tunnel location in the femtosecond laser. The tunnel incision was made on the steepest topographic axis, with an entry cut length of 1.1 mm and thickness of 1.0 μm. One or 2 segments were implanted according to the distribution of the ectatic area on the corneal surface; the location of the segment was decided according to the distribution of the ectatic area as determined by the Orbscan device (Bausch & Lomb); coma was not used for planning. Because toric pIOL implantation was planned for later spherocylindrical correction, ICRS implantation was performed with the primary treatment aim of reducing corneal irregularity rather than of correcting the spherical equivalent (SE). The ICRS were inserted with a Keraring forceps while bubbles from the channel creation were still visible, revealing the tunnel location.

Postoperatively, a bandage contact lens (Air Optix, Ciba Vision) was applied until the 1-day postoperative visit and tobramycin–dexamethasone (Tobradex) was used 4 times daily for 2 weeks. Patients were encouraged to use artificial tears for 3 months postoperatively.

Corneal CXL with Riboflavin and Ultraviolet A   The treatment was performed under sterile conditions in an operating room. Topical oxybuprocaine 0.4% drops were applied. After debridement of 7.0 mm of corneal epithelium, 0.1% riboflavin solution in 20% dextran was applied on the cornea every 3 minutes for 30 minutes. No cases were treated with an epithelium-on technique. The saturation of the cornea with riboflavin and its presence in the anterior chamber were monitored closely by slitlamp inspection before treatment. Riboflavin saturation ensures the formation of free radicals, whereas riboflavin shielding ensures the protection of deeper ocular structures, such as the corneal endothelium.

Before treatment, ultrasound pachymetry was performed over the deepithelialized cornea at the thinnest point to ensure a minimum thickness of 400 μm. For corneas thinner than the safety limit, hypotonic riboflavin 0.1% without dextran was applied every 30 seconds until the corneal thickness reached at least 400 μm. Ultraviolet-A (UVA) irradiation was performed after the pachymetry reached 400 μm. The UVA irradiation was performed with a UV-X illumination system (version 1000, Peschke Meditrade GmbH) with 3 mW/cm^2 surface irradiance for 30 minutes (5.4 J/cm^2). Before each procedure, the unit was calibrated with a UVA meter (Lasermate-Q, Laser 2000) at a working distance of 6 cm. During UVA irradiation, riboflavin drops were applied every 2 to 3 minutes to saturate and moisten the cornea. Topical anesthesia was reapplied as needed every 2 to 3 minutes. Sponges were used to protect the limbal epithelium, and focusing was monitored during the procedure. After 15 minutes of irradiation, ultrasound pachymetry was repeated. Hypotonic riboflavin solution was reapplied if the corneal thickness was below 400 μm.

Postoperatively, a bandage contact lens was applied until reepithelialization; tobramycin drops (Tobrex) were given 4 times daily. After bandage contact lens removal, patients used a tapering course of fluorometholone 0.1% drops

(FML) over the subsequent 3 weeks and were encouraged to use artificial tears for 3 months postoperatively.

Toric Phakic Intraocular Lens Implantation   The pIOL selection was made a minimum of 6 months after CXL treatment; the axis of alignment was calculated using the refractive astigmatism at that time point. To control for potential cyclotorsion when the patient was supine, the zero horizontal axis was marked at a slitlamp while the patient was sitting upright. Each patient received 2 neodymium:YAG laser peripheral iridotomies 1 week before surgery. The pIOLs were sized according to the corneal white-to-white and ACD measurements using the Orbscan II device. The pIOL was inserted through a temporal clear corneal incision and rotated to the correct axis with a Mendez axis marker (Asico LLC) as indicated by markings. Postoperatively, patients were given tobramycin–dexamethasone (Tobradex) 4 times daily for 2 weeks followed by loteprednol etabontate 0.5% (Lotemax) 2 times daily for 2 weeks.

Statistical Analysis

Normality was tested using the D'Agostino-Pearson normality test. Repeated-measures analysis of variance with Bonferroni posttest analysis was used for normally distributed data values. The Friedman test with the Dunn multiple comparison test was used for nonparametric data values.

RESULTS

The study enrolled 14 eyes of 9 patients (6 eyes of 3 men, 8 eyes of 6 women). The mean patient age was 25.21 years ± 1.76 (SD) (range 22 to 28 years). The mean interval between ICRS and CXL was 7.0 months, and the mean interval between CXL and toric pIOL implantation was 8.4 months. All patients were followed for at least 1 year after pIOL implantation.

The manifest refraction spherical equivalent (MRSE) decreased from a mean of −16.40 ± 3.56 D (range −11.50 to −22.50 D) to −9.81 ± 2.71 D 6 months after ICRS implantation ($P < .0001$, Bonferroni test). Six months after CXL treatment, the mean MRSE was −9.67 ± 2.79 D; the difference was not statistically significant. One year after toric pIOL implantation, the MRSE decreased to a mean of −0.80 ± 1.02 D (range −2.00 to +2.00 D) ($P < .0001$).

The refractive astigmatism decreased from −4.73 ± 1.32 D (range −3.00 to −7.00 D) to −2.36 ± 0.58 D 6 months after ICRS implantation ($P < .0001$, Bonferroni test). Six months after CXL treatment, it decreased to −2.09 ± 1.31 D; the difference was not statistically significant. One year after toric pIOL implantation, the refractive astigmatism decreased to −0.93 ± 0.31 D (range −0.50 to −1.50 D) ($P < .01$).

The mean flat K value decreased from 56.16 ± 2.40 D to 54.78 ± 2.20 D 6 months after ICRS implantation and to 53.54 ± 2.24 D 6 months after CXL treatment (Figure 1); the reduction after each step was statistically significant ($P < .0001$, Bonferroni test). All but 1 patient had a decrease in the flat K value after ICRS
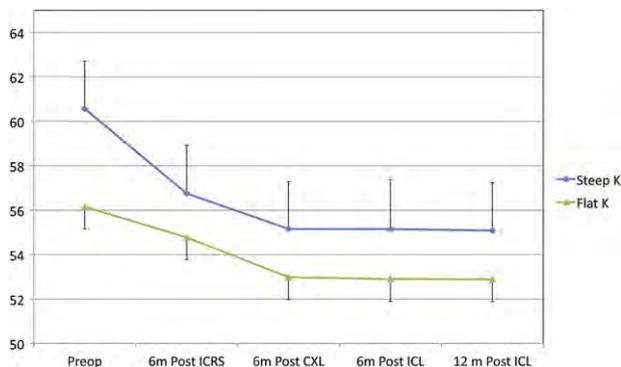
Figure 1. Change in steep and flat K at different time points. Error bars indicate standard deviation.

implantation, and every patient had a reduction in the flat K value after CXL.

The mean steep K value decreased from 60.57 ± 2.14 D to 56.76 ± 2.17 D ($P < .0001$) 6 months after ICRS implantation and to 54.61 ± 2.74 D 6 months after CXL ($P < .05$) (Figure 1). After the first 2 stages of treatment, the mean reduction in the steep K value was 5.96 ± 2.88 D; however, the mean reduction in the flat K value was 2.62 ± 0.73 D, resulting in similar mean steep and mean flat K values (54.61 D and 54.78 D, respectively). This shows the regularization of and reduction in corneal astigmatism, which is underestimated when considering the reduction in refractive astigmatism in isolation (a mean reduction in refractive astigmatism of 2.64 ± 1.43 D).

The mean of the mean K value decreased from 58.36 ± 2.18 D to 55.77 ± 2.17 D 6 months after ICRS implantation and to 54.07 ± 2.12 D 6 months after CXL ($P < .0001$, Bonferroni test for each comparison).

Toric pIOL implantation had a minimal effect on K values after 1 year, with the mean flat K value stable at 53.57 ± 2.28 D, the mean steep K value stable at 54.48 ± 3.07 D, and the mean of the mean K value stable at 54.03 ± 2.19 D; none of the differences was statistically significant. Hence, the wound construction for pIOL implantation had a negligible effect on corneal astigmatism and no progression of keratoconus was detected.

The 3-stage procedure resulted in a highly significant improvement in the mean UDVA ($P < .0001$, Friedman test, used because of nonparametric data set for preoperative and post-ICRS UDVA). The mean UDVA increased from 0.01 ± 1.3 lines to 0.03 ± 5 lines 6 months after ICRS implantation and to 0.06 ± 4.3 lines 6 months after CXL treatment; the difference was not statistically significant at either time point. One year after toric pIOL implantation, the mean UDVA increased to 0.45 ± 1.1 lines ($P < .01$, Dunn multiple comparison test).

The mean CDVA increased from 0.14 ± 2.4 lines to 0.40 ± 1.3 lines 6 months after ICRS implantation ($P < .0001$) and to 0.47 ± 1.0 lines 6 months after CXL treatment; the difference was not statistically significant. One year after toric pIOL implantation, the CDVA increased to 0.57 ± 0.7 lines, and the improvement in the mean CDVA with the 3-stage treatment was highly significant ($P < .0001$). After pIOL implantation, the CDVA was significantly better than after ICRS implantation ($P < .05$) but not statistically significantly better than after CXL.

Refractive Outcomes

Efficacy (Figure 2, _A_) All eyes in this series achieved a contact lens–corrected preoperative visual acuity of 0.6 or better because the patients were selected on the basis of good contact lens–corrected visual acuity combined with contact lens intolerance and reduced (spectacle) CDVA. With the 3-stage procedure, there was a significant improvement in functional vision in all cases, with all but 1 eye having significantly better postoperative UDVA than the preoperative (spectacle) CDVA. In the remaining eye, the postoperative UDVA was the same as preoperative CDVA (0.4). Although 7 eyes (50%) had a preoperative (spectacle) CDVA of worse than 0.1, 9 eyes (64%) had a final UDVA of better than 0.5. In all eyes, the postoperative UDVA did not achieve the preoperative contact lens–corrected acuity, with 5 eyes (36%) being 1 line worse, 5 eyes (36%) 2 lines worse, and 4 eyes (29%) 3 lines worse. Postoperative (spectacle) CDVA was the same as the preoperative contact lens–corrected acuity in 1 eye (7%), was 1 line worse in 10 eyes (71%), and was 2 lines worse in 3 eyes (21%).

Safety (Figure 2, _B_) Because all eyes had poor (spectacle) CDVA preoperatively, there was a significant improvement in CDVA after the 3-stage procedure, with all eyes gaining at least 1 line of CDVA and 12 eyes (86%) gaining 3 or more lines of CDVA. Postoperative contact lens vision was not measured; however, the (spectacle) CDVA results suggest that it is unlikely that any eye lost contact lens CDVA.

Predictability (Figure 2, _C_) The attempted correction in all eyes was greater than -10.0 D of MRSE. One eye (7%) had a significant overcorrection.

Accuracy (Figure 2, _D_) All eyes were within ± 2.00 D of target, 12 eyes (86%) were between plano and -2.00 D, and 7 eyes (50%) were within 1.00 D of target.

Refractive Astigmatism (Figure 2, _E_) The combined 3-stage treatment resulted in a significant improvement in refractive astigmatism. Preoperatively, 13 eyes (93%) had more than 3.00 D of astigmatism.
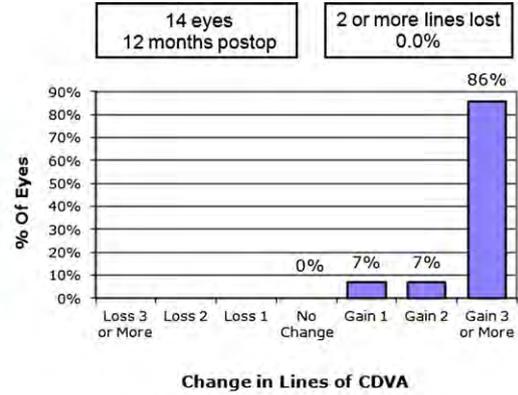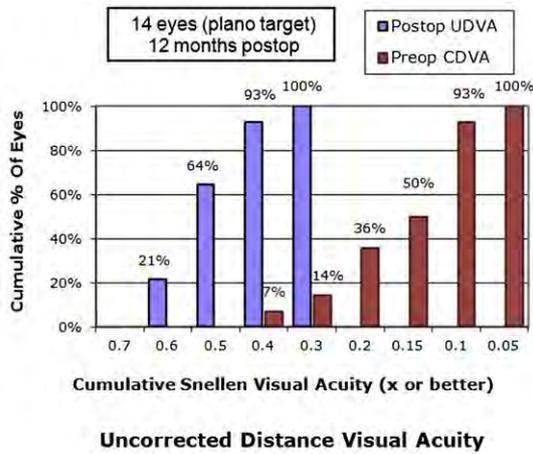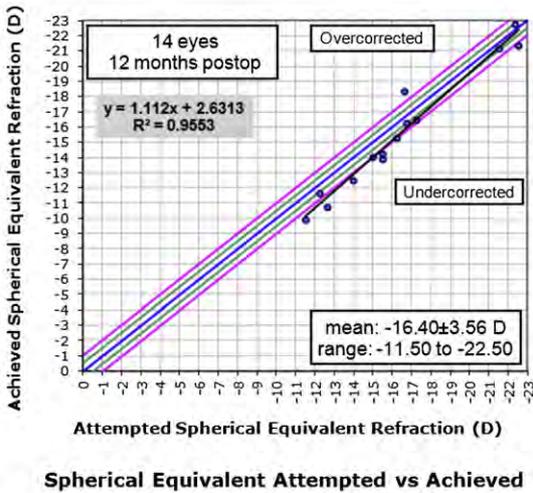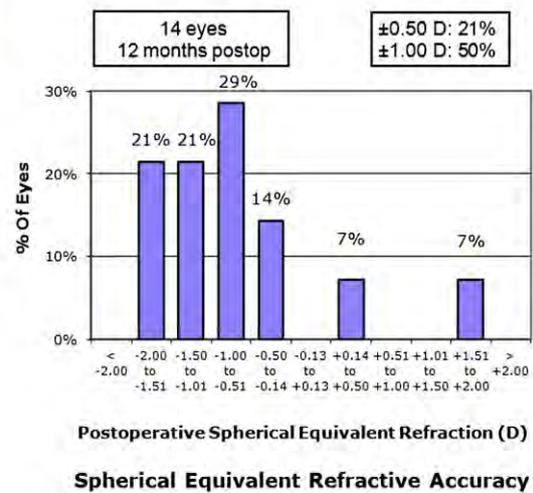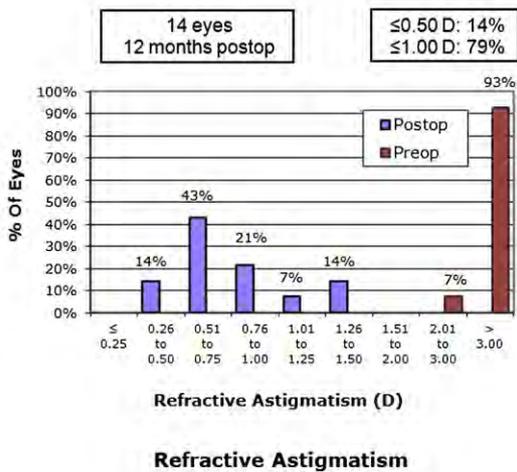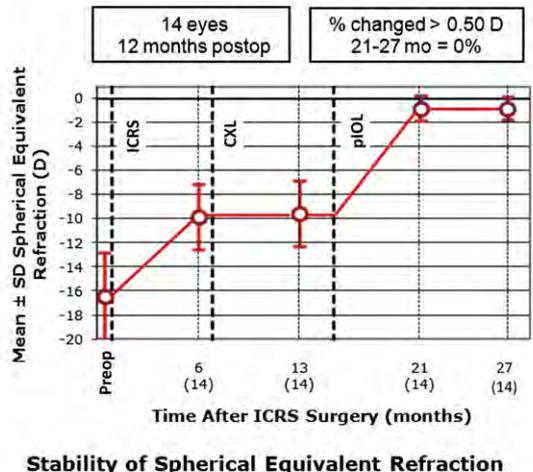
Figure 2. Standard refractive graphs showing the outcomes of the combined 3-stage treatment of ICRS, CXL, and toric pIOL implantation for keratoconus. *A*: Efficacy. *B*: Safety. *C*: Predictability. *D*: Accuracy. *E*: Refractive astigmatism. *F*: Stability.

Postoperatively, no eye had more than 1.50 D of astigmatism and 8 eyes (57%) had less than 0.75 D of astigmatism.

Stability (Figure 2, F) The combined 3-stage treatment resulted in stable refractive results in all eyes 1 year after pIOL implantation. No eye had a change in MRSE of more than 0.50 D.

DISCUSSION

The treatment goals of keratoconus management involve improved visual acuity and a reduction in or halting of disease progression. For contact lens–intolerant patients, the ideal sequence and staging of combined treatments, which may include ICRS implantation, CXL, toric pIOL implantation, and topography-guided ablation, remains to be fully elucidated.

Corneal CXL is primarily a treatment to increase the biomechanical stability of the cornea. It has been shown to be effective in halting the progression of keratoconus over a period of years,[10,13] and it could continue to induce longer term corneal flattening with a resulting reduction in myopia. A previous report[10] showed a reduction in maximum K readings by more than 2.0 D, while the postoperative SE was reduced by an mean of more than 1.0 D and refractive cylinder decreased by approximately 1.0 D. Corneal CXL treatment is also effective in reducing corneal wavefront aberrations.[10] Published cases show a regression in K values after CXL treatment of more than 9.0 D.[21] Therefore, the potential for an ongoing hyperopic shift after CXL should be taken into account when planning staged procedures. Corneal CXL followed by toric pIOL implantation as a 2-stage procedure has been reported.[18,22] Although the toric pIOL can correct high spherocylindrical refractive error, the pIOL cannot effectively treat the irregular component of astigmatism and the expected effect of CXL would be a maximum of a 2.0 D decrease in irregularity of the cornea. Hence, this treatment strategy will not be ideal for some patients, in particular those with marked irregular astigmatism.

The effectiveness of the 5.0 mm optical zone Keraring ICRS is limited to corneal regularization of astigmatism of approximately 7.0 D, depending on the corneal thickness. It is still unclear what effect ICRS implantation has on keratoconus progression and on long-term changes in refraction after CXL. Our previous study[23] found that ICRS followed by CXL in a combined treatment was safe and effective for visual correction and in reducing progression in keratoconic patients. However, in patients with residual myopic astigmatism after ICRS implantation and CXL, the current study shows that the residual spherocylindrical refractive

error can be effectively treated with a toric pIOL. Also, the combined treatment allows ICRS to be used primarily to regularize the corneal astigmatism because the residual spherical error (and regular astigmatism) after CXL can be corrected with the pIOL.

The combined 3-stage treatment of ICRS implantation, CXL, and toric pIOL implantation appears to be effective for a maximum additive effect of approximately 7.0 D from the ICRS implantation, 2.0 D of reduction in corneal irregularity from CXL treatment, and up to −20.0 D in spherical correction and 6.0 D in astigmatic correction with the toric pIOL. No intraoperative or postoperative complications (eg, cataract, glaucoma, pIOL sizing problems) were observed in this small case series, whereas an improvement in UDVA and (spectacle) CDVA with a significant reduction in manifest refraction were observed. All steps were uneventful in all eyes, with toric pIOL implantation not causing problems in these keratoconic eyes, (in which the anterior chamber is deeper). Also, having an ICRS in situ did not produce difficulties during toric pIOL implantation.

The mean interval between ICRS implantation and CXL was more than 6 months. These procedures can be performed simultaneously (with CXL performed immediately after ICRS implantation). However, an incision site that is completely epithelialized helps prevent migration and other ICRS complications. Another reason to wait is to monitor progression after ICRS implantation. A recent study comparing ICRS before and after CXL[24] found that femtosecond-laser channel creation required more energy after CXL and increased the tendency toward haze formation. The authors therefore suggested that ICRS implantation should precede CXL or be performed concurrently. We previously reported that treatment results were better with this sequence (ICRS then CXL) in a study comparing 2 sequences: ICRS then CXL and CXL then ICRS.[23] The mean interval between CXL and toric pIOL implantation was more than 6 months to ensure topographic and refractive stabilization after CXL treatment, allowing the most appropriate pIOL to be chosen. Although it is possible to have progression of keratoconus or progressive flattening after CXL, both of which would affect the refractive correction with the toric pIOL, in this small series the refraction was stable up to 1 year after pIOL implantation. Toric pIOL implantation was an important functional step in visual rehabilitation because these eyes still had high myopic astigmatism after the first 2 steps of treatment. Although toric pIOL rotation could be a potential problem in eyes with severe keratoconus, this complication was not encountered in our series.

In conclusion, a 3-stage approach of Keraring ICRS implantation followed by corneal CXL and then

posterior chamber toric implantable collagen copolymer pIOL implantation was an effective treatment in keratoconic eyes with high myopic astigmatism and resulted in significant improvements in UDVA and CDVA ($P < .0001$). In particular, ICRS implantation improved CDVA ($P < .0001$), and pIOL implantation improved UDVA ($P < .01$). Although CXL resulted in no significant changes in MRSE, refractive astigmatism, UDVA, or CDVA, it significantly improved the flat, steep, and mean K values and the K values remained stable after pIOL implantation. This treatment approach appears to stop progression and improve visual and refractive results in keratoconic eyes with high myopic astigmatism. However, this was a relatively small series with a relatively short follow-up; therefore, long-term follow-up of a larger population study is required to validate these findings.

WHAT WAS KNOWN

- Combined refractive surgery for keratoconus using various modalities (eg, ICRS and CXL, CXL and toric pIOL, topography-guided PRK and CXL) has been studied. These treatments have inherent limitations; pIOL implantation cannot treat irregularity, while CXL has a limited capacity for this. Topographic-guided PRK can treat irregularity, but treatment of high myopic astigmatism is limited by safe ablation depths.

WHAT THIS PAPER ADDS

- The combination of 3 surgical modalities (ICRS, CXL, and toric pIOL) improved functional uncorrected vision in keratoconic eyes with a high refractive error and reduced keratoconus progression.

- This approach takes advantage of the benefits of each modality: ICRS to treat irregular astigmatism, CXL to reduce progression, and toric pIOL to treat the high residual myopic astigmatism.

REFERENCES

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998; 42:297–319. Available at: http://www.keratoconus.com/resources/Major+Review-Keratoconus.pdf. Accessed December 11, 2012
2. Pramanik S, Musch DC, Sutphin JE, Farjo AA. Extended long-term outcomes of penetrating keratoplasty for keratoconus. Ophthalmology 2006; 113:1633–1638
3. Lim N, Vogt U. Characteristics and functional outcomes of 130 patients with keratoconus attending a specialist contact lens clinic. Eye 2002; 16:54–59. Available at: http://www.nature.com/eye/journal/v16/n1/pdf/6700061a.pdf. Accessed December 11, 2012
4. Kelly T-L, Williams KA, Coster DJ. Corneal transplantation for keratoconus; a registry study. Arch Ophthalmol 2011; 129:691–697. Available at: http://archopht.jamanetwork.com/data/Journals/OPHTH/10243/ecs05112_691_697.pdf. Accessed December 11, 2012
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135:620–627
6. Coşkunseven E, Kymionis GD, Tsiklis NS, Atun S, Arslan E, Jankov MR, Pallikaris IG. One-year results of intrastromal corneal ring segment implantation (KeraRing) using femtosecond laser in patients with keratoconus. Am J Ophthalmol 2008; 145:775–779
7. Kymionis GD, Siganos CS, Tsiklis NS, Anastasakis A, Yoo SH, Pallikaris AI, Astyrakakis N, Pallikaris IG. Long-term follow-up of Intacs in keratoconus. Am J Ophthalmol 2007; 143:236–244
8. Kymionis GD, Kontadakis GA, Kounis GA, Portaliou DM, Karavitaki AE, Magarakis M, Yoo S, Pallikaris IG. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. J Refract Surg 2009; 25:S807–S811
9. Coşkunseven E, Onder M, Kymionis GD, Diakonis VF, Arslan E, Tsiklis N, Bouzoukis DI, Pallikaris I. Combined Intacs and posterior chamber toric implantable Collamer lens implantation for keratoconic patients with extreme myopia. Am J Ophthalmol 2007; 144:387–389
10. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet A corneal collagen cross-linking for keratoconus in Italy: the Siena Eye Cross Study. Am J Ophthalmol 2010; 149:585–593
11. Hafezi F, Mrochen M, Iseli HP, Seiler T. Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas. J Cataract Refract Surg 2009; 35:621–624
12. Jankov MR II, Jovanovic V, Delevic S, Coşkunseven E. Corneal collagen cross-linking outcomes: review. Open Ophthalmol J 2011; 5:19–20. Available at: http://www.benthamscience.com/open/toophtj/articles/V005/SI0010TOOPHTJ/19TOOPHTJ.pdf. Accessed December 11, 2012
13. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg 2008; 34:796–801
14. Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. J Refract Surg 2008; 24:S720–S725
15. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg 2009; 25:S812–S818
16. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK; a temporizing alternative for keratoconus to penetrating keratoplasty. Cornea 2007; 26:891–895
17. Coşkunseven E, Jankov MR II, Grentzelos MA, Plaka AD, Limnopoulou AN, Kymionis GD. Topography-guided transepithelial PRK after intracorneal ring segments implantation and corneal collagen CXL in a three-step procedure for keratoconus. In press, J Refract Surg 2013
18. Kymionis GD, Grentzelos MA, Karavitaki AE, Paraskevi Z, Yoo SH, Pallikaris IG. Combined corneal collagen cross-linking and posterior chamber toric implantable collamer lens implantation for keratoconus. Ophthalmic Surg Lasers Imaging 2011; 42 Online:e22–e25
19. Kamiya K, Shimizu K, Kobashi H, Komatsu M, Nakamura A, Nakamura T, Ichikawa K. Clinical outcomes of posterior chamber toric phakic intraocular lens implantation for the correction of high myopic astigmatism in eyes with keratoconus: 6-month follow-up. Graefes Arch Clin Exp Ophthalmol 2011; 249:1073–1080

20. Edelhauser HF, Sanders DR, Azar R, Lamielle H. ICL in Treatment of Myopia Study Group. Corneal endothelial assessment after ICL implantation. J Cataract Refract Surg 2004; 30:576–583

21. Hafezi F, Koller T, Vinciguerra P, Seiler T. Marked remodelling of the anterior corneal surface following collagen cross-linking with riboflavin and UVA [letter]. Br J Ophthalmol 2011; 95:1171–1172

22. Güell JL, Morral M, Malecaze F, Gris O, Elies D, Manero F. Collagen crosslinking and toric iris-claw phakic intraocular lens for myopic astigmatism in progressive mild to moderate keratoconus. J Cataract Refract Surg 2012; 38:475–484

23. Coşkunseven E, Jankov MR II, Hafezi F, Atun S, Arslan E, Kymionis GD. Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus. J Cataract Refract Surg 2009; 35:2084–2091

24. El-Raggal TM. Effect of corneal collagen crosslinking on femtosecond laser channel creation for intrastromal corneal ring segment implantation in keratoconus. J Cataract Refract Surg 2011; 37:701–705

First author:
Efekan Coşkunseven, MD

World Eye Hospital, Istanbul, Turkey