UNIVERSITÉ DE GENÈVE

Archive ouverte UNIGE
https://archive-ouverte.unige.ch

Article professionnel | Article | 2009

Published version | Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus

Coskunseven, Efekan; Jankov, Mirko R (2nd); Hafezi, Farhad; Atun, Serife; Arslan, Ebru; Kymionis, George D

How to cite

COSKUNSEVEN, Efekan et al. Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus. In: Journal of cataract and refractive surgery, 2009, vol. 35, n° 12, p. 2084–2091. doi: 10.1016/j.jcrs.2009.07.008

This publication URL: https://archive-ouverte.unige.ch/unige:22461
Publication DOI: 10.1016/j.jcrs.2009.07.008

© This document is protected by copyright. Please refer to copyright holder(s) for terms of use.

Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus

Efekan Coskunseven, MD, Mirko R. Jankov II, MD, PhD, Farhad Hafezi, MD, PhD, Serife Atun, MD, Ebru Arslan, George D. Kymionis, MD, PhD

PURPOSE: To compare 2 sequences of combined intrastromal corneal ring segment (ICRS) implantation and ultraviolet/riboflavin–mediated corneal collagen crosslinking (CXL) in progressive keratoconus.

SETTING: Dunya Eye Hospital, Istanbul, Turkey.

METHODS: In this prospective comparative randomized consecutive study, CXL was followed by ICRS implantation (Group 1) or ICRS implantation was followed by CXL (Group 2). Uncorrected (UDVA) and corrected (CDVA) distance visual acuities, spherical equivalent (SE), manifest cylinder (cylinder), and mean keratometry (K) were compared preoperatively and postoperatively.

RESULTS: The mean interval between treatments was 7 months ± 2 (SD) (mean follow-up, 13 ± 1 months). The mean UDVA and CDVA improved in both groups (UDVA: 0.07 ± 0.09 to 0.25 ± 0.12, Group 1, and 0.11 ± 0.09 to 0.32 ± 0.21, Group 2; CDVA: 0.24 ± 0.11 to 0.41 ± 0.20 and 0.22 ± 0.16 to 0.55 ± 0.2, respectively). The mean SE, cylinder, and mean K values decreased in both groups (SE: −7.13 ± 3.34 D to −2.98 ± 2.33 D, Group 1, and −7.05 ± 5.54 D to −2.81 ± 4.08 D, Group 2; cylinder: −4.38 ± 2.03 D to −2.62 ± 1.93 D and −4.68 ± 2.60 D to −2.20 ± 1.67 D, respectively; mean K: 52.47 ± 4.01 D to 48.31 ± 3.65 D and 52.06 ± 4.93 D to 48.08 ± 4.13 D, respectively). Overall, there was more improvement in CDVA, SE, and mean K in Group 2 than in Group 1.

CONCLUSION: Implantation of ICRS followed by CXL resulted in greater improvement of keratoconus.

J Cataract Refract Surg 2009; 35:2084–2091 © 2009 ASCRS and ESCRS

Keratoconus is a relatively rare disease of the cornea, with a reported frequency in the general population of approximately 1 in 2000.[1] It is an asymmetric, bilateral, progressive, and noninflammatory ectasia of the cornea caused by gradual biomechanical instability of the cornea. Usually, the condition starts at puberty and progresses until the mid-30s; in up to 20% of patients, the cornea is affected to an extent that the corrected distance visual acuity (CDVA) is significantly decreased and cannot be improved by optical means.[1]

Once the patient is not able to use rigid contact lenses, there are few surgical alternatives for correction in eyes with keratoconus. Expectations are limited, and the anatomic and functional results can be unpredictable.[1] In addition to lamellar and penetrating keratoplasty procedures, the introduction of intrastromal corneal ring segments (ICRS) has provided another way to manage keratoconus.[2–5] These vision-correcting methods attempt to regularize the front surface of the cornea while maintaining the existing biomechanical status in the underlying stroma. In cases in which irregular astigmatism is progressive (eg, keratoconus, pellucid marginal degeneration, laser-induced iatrogenic ectasia), the corneal stroma is structurally weakened and some cases may worsen over time.

Corneal collagen crosslinking (CXL) with riboflavin and ultraviolet A (UVA) is a new technique to strengthen corneal tissue using riboflavin as a photosensitizer and UVA to increase the formation of intrafibrillar and interfibrillar covalent bonds by photosensitized oxidation.[6] This technique is similar to photopolymerization of polymers and stabilizes the cornea's biomechanics. To correct the irregular astigmatism caused by a biomechanically unstable cornea, a primary

 © 2009 ASCRS and ESCRS
Published by Elsevier Inc.

0886-3350/09/$—see front matter
doi:10.1016/j.jcrs.2009.07.008

intervention, such as CXL, should be considered to stabilize the cornea.

To our knowledge, this is the first comparative study of the role of the sequence of 2 treatments—ICRS implantation and UV/riboflavin–mediated CXL—in patients with progressive keratoconus. We compared the preoperative and postoperative results of the 2 sequences.

PATIENTS AND METHODS

This prospective consecutive comparative study comprised patients with progressive keratoconus confirmed by an increase in maximum curvature of at least 1.00 diopter (D) in the previous 6 months as assessed by computerized corneal topography. Surgeries were performed between March 2007 and March 2008 at Dunya Eye Hospital, Istanbul, Turkey. The study followed the principles of the Declaration of Helsinki. In adherence with institutional guidelines, all patients provided informed consent after being informed of the possible complications.

Inclusion criteria were keratoconus grade I to III according to the Amsler-Krumeich classification,[7] age older than 14 years, contact lens intolerance, proof of keratoconus evolution, and corneal thickness at the thinnest point of at least 400 µm. Exclusion criteria were grade IV keratoconus; hydrops; corneal opacity; severe atopy; recurrent corneal erosion syndrome; herpetic keratitis; corneal dystrophy; endothelial cell count (ECC) less than 1000 cells/mm^2; collagen, vascular, autoimmune, or other systemic disease; and pregnancy or breast feeding.

The patients were randomly divided into 2 groups. In Group 1, CXL was performed first followed by ICRS implantation. In Group 2, ICRS implantation was performed first followed by CXL.

In all cases, the following examinations were performed before and after surgery: uncorrected distance visual acuity (UDVA) and CDVA with manifest refraction in a bright environment, corneal topography (Orbscan IIz, Bausch & Lomb; WaveLight Allegretto Topolyzer, WaveLight Laser Technologie), slitlamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP) by tonometry, and endothelial cell density measurement by specular microscopy (SP 9000 Noncon Robo Pachy, Konan Medical, Inc.).

Surgical Technique

All operations were performed by the same surgeon (E.C.). Corneal crosslinking was performed with a UVA light lamp (UV-X, Peschke Meditrade GmbH) and ICRS implantation (KeraRing, Mediphacos Ltda), with a femtosecond laser (IntraLase, Abbott Medical Optics, Inc., formerly Advanced Medical Optics, Inc.) for tunnel creation.

Crosslinking The CXL procedure was performed in an operating room under sterile conditions. Topical anesthetic eyedrops were applied. After manual abrasion of the corneal epithelium of at least 7.0 mm, riboflavin 0.1% solution in 20% dextran was applied to the cornea every 3 minutes for 30 minutes. Saturation of the cornea with riboflavin and its presence in the anterior chamber were monitored closely at the slitlamp before treatment began. Riboflavin saturation causes the formation of free radicals, whereas riboflavin shielding protects 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 corneal thickness of 400 µm. Ultraviolet-A irradiation was performed using an optical system (Koehler illumination) consisting of an array of 7 UVA diodes with a potentiometer to allow regulation of voltage. Before treatment, the intended surface irradiance of 3 mW/cm^2 (5.4 J/cm^2 surface dose) was calibrated using a UVA meter (LaserMate-Q, Laser 2000) at a working distance of 6 cm. Irradiance was performed for 30 minutes using 3 mW/cm^2, corresponding to a surface dose of 5.4 J/cm^2. During treatment, riboflavin solution and a topical anesthetic agent (oxybuprocaine 0.4%) were applied every 2 to 3 minutes to saturate the cornea with riboflavin and moisten the cornea.

After the treatment, ofloxacin 0.3% was applied and a bandage contact lens fitted to the corneal surface; the latter was left in place until reepithelialization. Patients were given topical dexamethasone phosphate 0.1% 4 times daily, with gradual tapering over the following 2 months.

Intrastromal Corneal Ring Segment Implantation Intrastromal corneal ring segment (Keraring, Mediphacos) implantation was performed in an operating room under sterile conditions using topical anesthetic drops. The Purkinje reflex was chosen as the central point and marked under a biomicroscope (Allegretto, WaveLight Laser Technologie). A 5.0 mm marker was used to locate the exact ring channel. Intraoperatively, corneal thickness was measured along the ring location markings using ultrasonic pachymetry (Sonogage). Tunnel depth was set at 80% of the thinnest corneal thickness on the tunnel location.

The arc length and thickness were chosen according to the manufacturer's nomogram. A 60 kHz femtosecond laser was used to create the ring channels. The channel's inner diameter was set to 4.4 mm and the outer diameter, to 5.6 mm. The entry-cut thickness was 1 µm and the ring energy for channel creation, 1.30 µJ. The entry-cut energy was 1.30 µJ and channel creation timing with the femtosecond laser, 15 seconds. The ICRS was implanted immediately after the channel was created and before the bubbles disappeared; the bubbles showed the exact tunnel location. To avoid injury to the incision area, the ICRS was directly implanted with the accompanying forceps.

Submitted: February 1, 2009.
Final revision submitted: July 6, 2009.
Accepted: July 8, 2009.

From Dunya Eye Hospital (Coskunseven, Atun, Arslan) Istanbul, Turkey; a private surgical center (Jankov), Belgrade, Serbia; IROC, Institute for Refractive and Ophthalmic Surgery (Hafezi), Zurich, Switzerland; Institute of Vision and Optics (Kymionis), University of Crete, Greece.

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

Presented in part at the XXVI Congress of the European Society of Cataract & Refractive Surgeons, Berlin, Germany, September 2008.

Corresponding author: Mirko R. Jankov II, MD, PhD, LaserFocus, 25, Cara Nikolaja II, 11000 Belgrade, Serbia. E-mail: visioncare@mac.com.

Postoperatively, antibiotic–steroid eyedrops were taken 4 times a day for 2 weeks. The patients were instructed to avoid rubbing the eye and to use preservative-free artificial tears frequently.

On the first postoperative day, a slitlamp biomicroscopic examination was performed. Corneal wound healing and migration of the segment were evaluated. At the last follow-up visit, manifest refraction, UDVA, CDVA, slitlamp, and topographic examinations were performed.

Statistical Analysis

The paired Student *t* test was used for statistical analysis of within-group comparisons for different time points and for between-group comparisons at the last follow-up. A *P* value less than 0.05 was considered statistically significant.

RESULTS

The study evaluated 48 eyes of 43 patients (25 men, 18 women) with a mean age of 21 years ± 5 (SD) (range 14 to 34 years). The mean interval between the treatment steps was 7 months and the mean follow-up after the second step, 6 months. Table 1 shows the preoperative and postoperative data in by treatment-sequence group.

All treatments were uneventful; the bandage contact lens was removed between the third and the fourth day after CXL and on first day after ICRS implantation. All corneas had a deep demarcation line between the superficial (treated) and the deep (untreated) portions of the cornea; 8 eyes (18.6%) also had slight subepithelial and stromal edema with cotton-like, ring-shaped stromal opacities 1 month after the CXL treatment (Figure 1). These signs disappeared within 3 months after the treatment.

Group 1

After CXL and before ICRS implantation in Group 1, there was a statistically significant decrease (0.88 D) in the mean K value and a statistically significant increase (2 mm Hg) in mean IOP (both $P<.01$). There was also a statistically significant decrease (1.39 D) in SE and a statistically significant increase (>0.5 line) in UDVA (both $P<.05$). The increase in CDVA (0.5 line) and decreases in manifest cylinder (0.44 D), mean pachymetry (6 µm), and ECC (39 cells/mm^2) were not statistically significant ($P>.05$) (Table 1).

After additional treatment with ICRS implantation, there was a statistically significant increase in UDVA and CDVA (both 1 line) and a statistically significant decrease in SE (2.76 D), manifest cylinder (1.32 D), and the mean K value (3.28 D) (all $P<.01$). There was also a statistically significant decrease (28 µm) in mean pachymetry ($P<.05$). The marginal change in IOP and the increase in ECC (15 cells/mm^2) were not statistically significant ($P>.05$).

Group 2

After ICRS implantation and before CXL in group 2, there was a statistically significant increase in UDVA (2 lines) and CDVA (3 lines) and a statistically significant decrease in SE (3.31 D), manifest cylinder (2.05 D), and the mean K value (2.94 D) (all $P<.01$). The decrease in pachymetry (6 µm) and in IOP (1 mm Hg) and the increase in ECC (1 cell/mm^2) were not statistically significant ($P>.05$).

After additional treatment with CXL, there was a statistically significant decrease in SE (0.93 D) and in mean K (1.08 D) (both $P<.01$). There was also a statistically significant increase in UDVA (1 line) and pachymetry (5 µm) and a statistically significant decrease in ECC (15 cell/mm^2) (all $P<.05$). The increase in CDVA (0.5 line) and IOP (1 mm Hg) and the decrease in manifest cylinder (0.43 D) were not statistically significant ($P>.05$).

Both Groups

All measured parameters in both groups showed a highly statistically significant difference between the preoperative values and final postoperative values except for pachymetry, IOP, and ECC.

Evaluation of the final results showed that Group 2 had a statistically significantly overall higher increase in CDVA than Group (3 lines versus 2 lines) and a statistically significantly greater decrease in manifest cylinder (2.48 D versus 1.76 D) ($P<.01$ and $P<.05$, respectively). The differences between groups in pachymetry, IOP, and ECC were also statistically significant ($P<.05$). There was no statistical difference between the 2 groups in UDVA, SE, or mean K ($P>.05$).

DISCUSSION

The key indication for CXL is to inhibit the progression of corneal ectasia, such as in cases of keratoconus and pellucid marginal degeneration.[8] On the other hand, ICRS implantation is a minimally invasive surgical procedure that can be used to treat keratoconic corneas.[9,10] Although CXL stops or slows the progression of the ectatic process without significantly changing its shape, ICRS implantation significantly flattens and regularizes the cornea without affecting the biomechanical properties of the cornea as the underlying cause of the ectasia.

This led us to the following hypothesis: If the result of the CXL were solely to stop or slow the progression of keratoconus and that of ICRS implantation to reshape the cornea, a logical solution would be to combine the 2 methods to gain the benefits of both. Pretreatment with ICRS implantation would significantly reshape the cornea by flattening and

Table 1. Preoperative and postoperative data by groups.

Parameter	Group 1 (CXL Followed by ICRS)			*P* Value*
	Preop	After CXL	After CXL + ICRS	
UDVA				<.001
Mean ± SD	0.07 ± 0.09	0.14 ± 0.12	0.25 ± 0.12	
Range	0.01 to 0.40	0.02 to 0.60†	0.05 to 0.40‡	
P value	—	.019	.001	
CDVA				<.001
Mean ± SD	0.24 ± 0.11	0.29 ± 0.16	0.41 ± 0.20	
Range	0.05 to 0.50	0.05 to 0.70	0.10 to 1.0‡	
P value	—	.138	.008	
SE (D)				<.001
Mean ± SD	−7.13 ± 3.34	−5.74 ± 2.84	−2.98 ± 2.33	
Range	−15.50 to +0.25	−12.00 to +1.25†	−8.13 to +1.75‡	
P value	—	.021	<.001	
Cylinder (D)				<.001
Mean ± SD	−4.38 ± 2.03	−3.94 ± 2.30	−2.62 ± 1.93	
Range	−9.25 to −0.25	−7.50 to −0.50	−5.75 to −0.00‡	
P value	—	.241	<.001	
Mean K (D)				<.001
Mean ± SD	52.47 ± 4.01	51.59 ± 4.01	48.31 ± 3.65	
Range	45.65 to 59.85	45.25 to 59.90‡	42.05 to 58.50‡	
P value	—	<.001	<.001	
Pachymetry (μm)				.003
Mean ± SD	451 ± 26	445 ± 31	416 ± 55	
Range	405 to 525	348 to 520	299 to 516†	
P value	—	.407	.017	
IOP (mm Hg)				.002
Mean ± SD	9 ± 3	12 ± 4	12 ± 3	
Range	5 to 19	5 to 20‡	5 to 17	
P value	—	.004	.688	
ECC (cells/mm^2)				.363
Mean ± SD	2583 ± 153	2545 ± 154	2559 ± 133	
Range	2247 to 2924	2200 to 2817	2235 to 2770	
P value	—	.082	.311	

CDVA = corrected distance visual acuity; CXL = crosslinking; ECC = endothelial cell count; ICRS = intrastromal corneal ring segment; IOP = intraocular pressure; K = keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity
*Final versus preoperative
† <.05
‡ <.01

regularizing it, and subsequent CXL would stabilize the newly shaped cornea. Alternatively, the CXL could be performed first and the reshaping later.

Questions arose about the correct treatment sequence. Would a cornea pretreated with CXL react to the ICRS implantation in the expected way, or would its effect be lessened by it application over a stiffer cornea? Alternatively, would CXL have the same effect on a cornea with an ICRS in place?

The first in vivo controlled clinical study of CXL alone[8] included 23 eyes with moderate or advanced progressive keratoconus. The study found that CXL effectively halted the progression of keratoconus for up to 4 years. Postoperatively, the maximum K value decreased by a mean of 2.01 D and the SE, by a mean of 1.14 D. These findings were confirmed in other studies,[11–13] in which the groups treated with CXL had a similar mean decrease in the maximum K value and SE and an increase in UDVA and CDVA.

In our study, the group in which CXL was applied on an intact cornea (Group 1) had an increase in UDVA (approximately 1.0 line) and CDVA (approximately 0.5 line) and a decrease in SE (1.39 D), manifest cylinder (0.44 D), and the mean K value (0.88 D). In the group in which CXL was performed with ICRS in place (Group 2), there was an increase in UDVA and CDVA and a decrease in manifest cylinder similar to those in Group 1. There was a smaller decrease in SE

Table 1. Continued.

Group 2 (ICRS Followed by CXL)				Group 1 Vs Group 2
Preop	After ICRS	After ICRS + CXL	*P* Value*	*P* Value
			<.001	.510
0.11 ± 0.09	0.26 ± 0.21	0.32 ± 0.21		
0.01 to 0.40	0.01 to 0.70‡	0.01 to 0.80†		
—	.004	.018		
			<.001	.009‡
0.22 ± 0.16	0.50 ± 0.24	0.55 ± 0.23		
0.05 to 0.70	0.30 to 1.00‡	0.05 to 1.00		
—	<.001	.155		
			<.001	.921
−7.05 ± 5.54	−3.74 ± 4.25	−2.81 ± 4.08		
−19.38 to −0.63	−14.38 to 1.25‡	−12.75 to 2.88‡		
—	<.001	.001		
			<.001	.029†
−4.68 ± 2.60	−2.63 ± 1.57	−2.20 ± 1.67		
−9.00 to −1.25	−6.00 to 0.00‡	−6.75 to 0.00		
—	.001	.052		
			<.001	.837
52.06 ± 4.93	49.12 ± 4.61	48.08 ± 4.13		
45.70 to 59.60	41.95 to 58.35‡	42.10 to 56.50‡		
—	<.001	<.001		
			.880	.011†
424 ± 37	418 ± 33	423 ± 29		
367 to 510	365 to 499	375 to 483‡		
—	.174	.004		
			.615	.019†
11 ± 4	10 ± 3	11 ± 3		
5 to 21	7 to 18	7 to 15.		
—	.186	138		
			.066	.730
2602 ± 50	2603 ± 49	2589 ± 41		
2525 to 2700	2538 to 2710	2519 to 2670†		
—	.671	.033		

and a larger decrease in the mean K value than in Group 1; however, neither was statistically significant. Therefore, CXL treatment had a similar effect with ICRS in place as with an intact cornea, producing a modest improvement in all corneal parameters. Longer follow-up is needed to determine whether the biomechanical effect continues, as has been described after CXL with intact corneas.

Although CXL can lead to a modest reduction in SE, manifest cylinder, and K values, other treatment methods for keratoconus (eg, ICRS implantation) yield more significant improvements in corneal parameters. In 2000, Colin et al.[14] reported 1-year results in 10 patients with keratoconus after implantation of Intacs ICRS (Addition Technologies). There was a significant improvement in CDVA (2 lines) and a significant reduction in SE (>2.00 D) and the maximum K value (>4.00 D).

Miranda et al.[5] report a reduction in SE (>2.50 D) and the maximum K value (6.00 D) after Ferrara ICRS (Ferrara Ophthalmics) implantation. The study included 26 eyes with grade 3 or 4 keratoconus. The ICRS flattened the central and peripheral cornea, thus displacing the corneal apex to its physiologic position in front of the pupil by reducing the paracentral ectasia commonly seen in keratoconic corneas.

Studies by Alió et al.,[15,16] Siganos et al.,[17] and Kymionis et al.[9] show similar improvement in

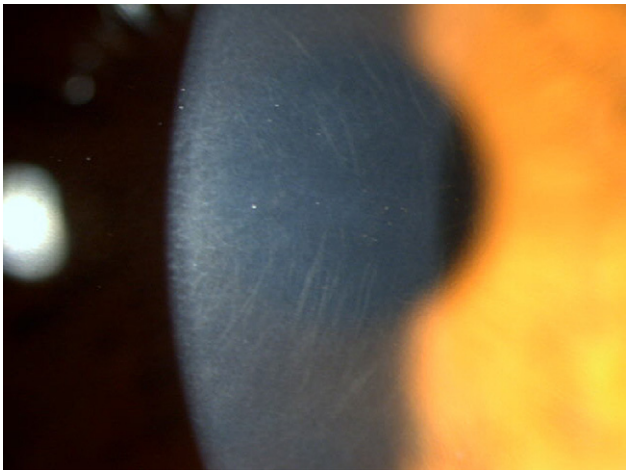

Figure 1. Slitlamp photograph 1 month after CXL treatment shows transient stromal and epithelial edema with a mild, cotton-like haze within the corneal stroma.

UDVA, with a small number of eyes losing lines of CDVA. A majority of patients in the study had an increase in CDVA (up to 6 lines) and a significant decrease in SE and manifest cylinder (>2.00 D).

In the only comparative study of Intacs ICRS implantation using a femtosecond laser or a mechanical spreader, Rabinowitz[4] found no significant differences between the 2 groups in UDVA, CDVA, SE, maximum K value, or the surface irregularity or surface asymmetry indices. However, the femtosecond group had fewer and less severe complications than the mechanical group.

In our Group 2, which had ICRS implantation in an intact cornea, there was an increase in UDVA (approximately 2.0 lines) and CDVA (approximately 3.0 lines) and a decrease in SE (3.31 D), manifest cylinder (2.05 D), and mean K (2.94 D), as described in the literature. Moreover, in Group 1, in which ICRS implantation was performed after previous CXL, the results were a similar; however, there was a slightly smaller increase in UDVA and mean K and a statistically significantly smaller increase in CDVA (1 line). There was also a statistically significantly smaller decrease in SE and manifest cylinder (2.76 D and 1.32 D, respectively). Therefore, ICRS implantation had a greater effect on an intact cornea than when it was performed after the cornea had been treated with CXL. However, there was improvement in all corneal parameters with both treatment sequences.

Long-term results and corneal stability after ICRS implantation are problematic because the procedure does not tackle the underlying condition (ie, a cornea that is not strong enough) but rather manages the consequence (ie, an irregular corneal surface resulting from a weaker cornea). Alió et al.[16] evaluated the stability in 13 eyes that had Intacs implantation for keratoconus. With a follow-up of up to 4 years, the mean decrease in inferior–superior (I–S) asymmetry was 2.81 D and in the average K value, 3.13 D. The mean difference between 6 months and 36 months (stability) showed no significant difference in CDVA and I–S asymmetry. However, there was a significant increase (1.67 D) in the average K value, which at 36 months did not reach the preoperative value.

Kamburoglu and Ertan[18] combined CXL and ICRS implantation to determine whether that approach improved long-term stability over that with ICRS implantation alone. They report sequential treatment of ICRS implantation followed by CXL in a case with ectasia after laser in situ keratomileusis. The preoperative SE was −14.50 D in the right eye and −10.50 D in the left eye and the mean K value, 56.20 D and 50.70 D, respectively. After bilateral ICRS implantation, CXL was performed after 1 day in the left eye and after 1 month in the right eye. Eight months postoperatively, the CDVA was 20/25 in the right eye and 20/25 in the left eye; the manifest refraction was -1.50×170 and -1.25×50, respectively; and the mean K value was 47.20 D and 44.20 D, respectively.

In a retrospective nonrandomized comparative case series by Chan et al.,[19] 12 eyes (9 patients) had inferior-segment Intacs placement without CXL and 13 eyes (12 patients) had inferior-segment Intacs placement followed by CXL with uv light and riboflavin. The combined surgery group had a significantly greater reduction in cylinder (2.73 D versus 1.48 D) and the maximum K value (1.94 D versus 0.89 D) than the group having ICRS implantation only. The authors concluded that the addition of CXL to the Intacs procedure resulted in greater improvement in keratoconus than ICRS implantation alone.

In terms of the overall effect of the combined treatment in our study, Group 2 (ICRS first, then CXL) had a statistically significantly higher overall increase in CDVA and decrease in manifest cylinder as well as a higher, but not statistically significant overall increase in UDVA and decrease in SE than Group 1 (CXL first, then ICRS). The decrease in manifest cylinder in Group (2.48 D) versus that in Group 1 (1.76 D) is similar to that in the group having ICRS with CXL versus the group having ICRS implantation alone in Chan et al.'s study[19] The difference in the overall effect in our 2 groups was smaller than the difference between the groups in Chan et al.'s study, confirming that the effect of combined CXL and ICRS implantation is always higher that of ICRS implantation alone, regardless treatment sequence.

These findings suggest that although each treatment step improves the cornea, a stiffer cornea that has been treated by CXL decreases the flattening effect of ICRS

implantation, thus restricting its effect and decreasing the maximum flattening potential. Thus, to achieve the maximum overall effect, ICRS implantation should be performed first so the segments can reshape the cornea without restriction. The CXL treatment then can be applied to further flatten the cornea and to stabilize corneal biomechanics.

The additional flattening after CXL with ICRS in place can be explained by the rearrangement of corneal lamellae and the surrounding matrix, just as occurs in an intact cornea with keratoconus.[6] Fibrils and lamellae are likely stiffer after CXL as a result of the increased number of crosslinking sites within the collagen molecule. This process rearranges the corneal lamellae and thus relocates the surrounding matrix, which reduces the central corneal curvature.[12,13]

Although we agree with Chan et al.[19] that additional stiffening of the cornea, especially around the channel of the ICRS, could cause an additive effect with sequential treatment, we disagree with the proposed mechanism; that is, there is a localized increase in riboflavin concentration that, in turn, might increase collagen crosslinking. Riboflavin that is pooled in one area more than in another area (eg, around or inside the channels) does not increase in concentration; therefore, the crosslinking effect is not increased. In fact, it may even be diminished because the pooled riboflavin may absorb more UV light, allowing less light to pass through the deeper layers of cornea, where it should exert its effect on the corneal collagen.

We could therefore conclude that the same crosslinking process that occurs in an intact cornea also occurs in a cornea with ICRS in place, and we could thus assume that the biomechanical effect would also be present in the later postoperative period, as described after CXL alone.[8] This highlights the main advantage of the combined approach presented in our study; that is, to ensure the best of both techniques (significant visual recovery with ICRS implantation and long-term stability with CXL).

Regarding the histologic effect of CXL, keratocyte apoptosis in the anterior segment of the corneal stroma has been described, and in vitro studies[20–22] show a clear demarcation line between the treated cornea and untreated cornea. In vivo confocal microscopy studies[11,23] show that repopulation of keratocytes is already visible 1 month after treatment, reaching the preoperative quantity and quality in the terms of functional morphology within 6 months after treatment. More detailed in vitro and in vivo studies of corneas treated with a combination of CXL and ICRS implantation would help determine the potential influence of the ICRS on the distribution of the UV light, the pharmacodynamics of the riboflavin, and the potential alteration in the crosslinking effect.

In summary, ICRS implantation followed by the UV/riboflavin–mediated corneal CXL resulted in greater improvement in keratoconus than CXL followed by ICRS implantation. Regarding safety, there was no significant change in central corneal pachymetry, ECC, or IOP in either group in our study.

REFERENCES

1. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol 1986; 101:267–273
2. Shimmura S, Tsubota K. Deep anterior lamellar keratoplasty. Curr Opin Ophthalmol 2006; 17:349–355
3. Tan BU, Purcell TL, Torres LF, Schanzlin DJ. New surgical approaches to the management of keratoconus and post-LASIK ectasia. Trans Am Ophthalmol Soc 2006; 104:212–218. discussion, 219–220. Available at: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1809910&blobtype=pdf. Accessed August 27, 2009
4. Rabinowitz YS. Intacs for keratoconus. Curr Opin Ophthalmol 2007; 18:279–283
5. Miranda D, Sartori M, Francesconi C, Allemann N, Ferrara P, Campos M. Ferrara Intrastromal corneal ring segments for severe keratoconus. J Refract Surg 2003; 19:645–653
6. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. Exp Eye Res 1998; 66:97–103
7. Alió JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. J Refract Surg 2006; 22:539–545
8. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A–induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135:620–627
9. 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
10. Coskunseven 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
11. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen; preliminary refractive results in an Italian study. J Refract Surg 2006; 32:837–845
12. Coskunseven E, Jankov MR, Hafezi F. Comparative study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. In press, J Cataract Refract Surg 2009
13. Jankov MR II, Hafezi F, Beko M, Ignjatovic Z, Djurovic B, Markovic V, Schor P. Ultra B2-promoção de ligações covalentes do colágeno cornea (corneal cross-linking) no tratamento de ceratocone: resultados preliminares. [Corneal cross-linking for the treatment of keratoconus: preliminary results]. Arq Bras Oftalmol 2008; 71:813–818. Available at: http://www.scielo.br/pdf/abo/v71n6/a09v71n6.pdf. Accessed August 27, 2009
14. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. J Cataract Refract Surg 2000; 26:1117–1122
15. Alió JL, Artola A, Hassanein A, Haroun H, Galal A. One or 2 Intacs segments for the correction of keratoconus. J Cataract Refract Surg 2005; 31:943–953

16. Alió JL, Shabayek MH, Artola A. Intracorneal ring segments for keratoconus correction: long-term follow-up. J Cataract Refract Surg 2006; 32:978–985
17. Siganos CS, Kymionis GD, Kartakis N, Theodorakis MA, Astyrakakis N, Pallikaris IG. Management of keratoconus with Intacs. Am J Ophthalmol 2003; 135:64–70
18. Kamburoglu G, Ertan A. Intacs implantation with sequential collagen cross-linking treatment in postoperative LASIK ectasia. J Refract Surg 2008; 24:S726–S729
19. Chan CCK, Sharma M, Boxer Wachler BS. Effect of inferior-segment Intacs with and without C3-R on keratoconus. J Cataract Refract Surg 2007; 33:75–80
20. Wollensak G, Spoerl E, Reber F, Seiler T. Keratocyte cytotoxicity of riboflavin/UVA- treatment in vitro. Eye 2004; 18:718–722
21. Wollensak G, Spoerl E, Wilsch M, Seiler T. Keratocyte apoptosis after corneal collagen cross-linking using riboflavin/UVA treatment. Cornea 2004; 23:43–49
22. Wollensak G, Spoerl E, Wilsch M, Seiler T. Endothelial cell damage after riboflavin–ultraviolet-A treatment in the rabbit. J Cataract Refract Surg 2003; 29:1786–1790
23. Mazzotta C, Balestrazzi A, Traversi C, Baiocchi S, Caporossi T, Tommasi C, Caporossi A. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. Cornea 2007; 26:390–397

First author:
Efekan Coskunseven, MD

Dunya Eye Hospital,
Istanbul, Turkey