

# Point/Counterpoint: My Ideal Ablation Pattern for Combined CXL Treatments

Surgeons share their preferred methods to combine laser and CXL.

BY A. JOHN KANELLOPOULOS, MD; AND LEOPOLDO SPADEA, MD



## The Athens Protocol: Topography-Guided Partial PRK With CXL

*An effective way to stabilize and visually rehabilitate patients with keratoconus and post-LASIK ectasia.*

By A. John Kanelopoulos, MD

Our investigative team at the Laser Vision Eye Institute has studied the clinical application of corneal collagen crosslinking (CXL) in patients with keratoconus and post-LASIK ectasia for more than 10 years and in more than 2,000 eyes.<sup>1-29</sup> We introduced the use of CXL through a femtosecond laser-created intrastromal corneal pocket,<sup>3,6</sup> the use of higher-fluence CXL,<sup>3,5-12,14,15,21,26</sup> and the use of CXL prophylactically in myopic LASIK and as an efficacy booster in hyperopic LASIK.<sup>14,21</sup> Most recently, we introduced the use of high-fluence CXL in femtosecond laser-assisted astigmatic keratotomy procedures in order to enhance the effect and/or reduce the incision arc.<sup>30</sup>

Our biggest contribution to the global ophthalmic community, however, may be the introduction of topography-guided normalizing surface ablation plus CXL as a visual rehabilitation tool.<sup>2</sup> The concept of ablating a thin, ectatic cornea usually generates fear in surgeons and patients alike. Nevertheless, we have found that the apparent disadvantage of thinning the cornea is accompanied by remarkable vision-rehabilitating improvement and synergy from the CXL component.

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## The Ideal Ablation Pattern for Combined Treatments: CXL Plus PRK

*Customized ablation and crosslinking can stabilize the cornea after lamellar surgery.*

By Leopoldo Spadea, MD

Conventional excimer laser surface ablation has shown efficacy in visual rehabilitation of eyes with very irregular corneas after lamellar keratoplasty. However, postoperative complications such as unpredictable refractive outcome, refractive regression, and corneal haze are commonly seen, limiting the use of noncustomized PRK in these eyes.<sup>1</sup> Excimer laser customized ablation shows promise to be a powerful technique to treat such corneal irregularities.

Corneal ectasia after lamellar keratoplasty has occasionally been reported, but its incidence has not been assessed. Corneal collagen crosslinking (CXL) induced by application of riboflavin and ultraviolet-A (UV-A) light has been shown to increase the biomechanical stability of corneas with lamellar flaps, arresting and even partially reversing iatrogenic keratectasia after LASIK.<sup>2</sup>

Keratoconus is a degenerative disorder in which the cornea thins and steepens, affecting vision. For many years, full-thickness keratoplasty was the principal surgical treatment for patients with advanced keratoconus, but, more recently, lamellar corneal approaches have been advocated as less invasive surgical alternatives. One of these, excimer-laser-assisted lamellar keratoplasty (ELLK), has been proposed to augment thin corneas in keratoconus

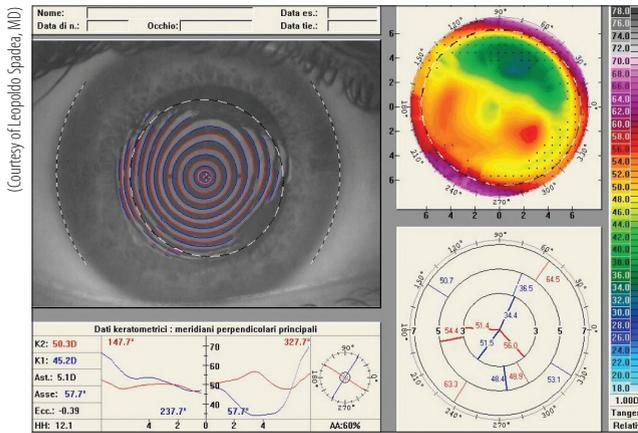


Figure 1. Videokeratographic map of a right eye before the treatment. The topographic pattern highlights irregular astigmatism (relative scale, tangential algorithm).

and keratectasia after LASIK.<sup>3</sup>

Some time ago, we saw one patient who developed corneal ectasia after ELLK for keratoconus and a secondary PRK for residual refractive correction.<sup>4</sup> In this 33-year-old woman, CXL resulted in improvement of visual acuity and preservation of a clear lamellar graft with 2 years' follow-up.

To further assess this therapeutic combination of CXL and PRK as a prophylaxis against ectasia after lamellar keratoplasty, we conducted a larger study.<sup>5</sup> This study evaluated the efficacy, predictability, safety, and stability of the combined treatment of customized excimer laser PRK and prophylactic CXL for residual refractive error in 14 patients previously treated with ELLK for keratoconus (Figure 1). The aim was for customized PRK to regularize the central cornea and CXL to strengthen and stabilize the cornea in these eyes.

**SURGICAL TECHNOLOGY**

The iVis Suite integrated platform (iVis Technologies) was used to perform custom excimer laser PRK. The platform consists of surgical planning software (Central Corneal Regularization [CCR]), a corneal morphology data source (Precisio), and a high-frequency excimer laser (iRES; all by iVis Technologies).

Treatment began with acquisition of reliable corneal topography. Excimer laser photoablation was performed using the high-frequency excimer laser with the following parameters: gaussian flying-spot size, 650 μm; frequency, 1,000 Hz; and wavelength, 193 nm. All ablation profiles were calculated with corneal apex as the ablation center. This choice creates a postoperative corneal surface symmetrical with respect to the preoperative morphology of the cornea, which will likely be more physiologically accepted by the patient.



Figure 2. Pattern of transepithelial customized ablation.

as the difference, within the optical zone, between the ideal postoperative surface and the preoperative corneal shape, with the aims of minimizing corneal ablation and regularizing a small central cornea area. Epithelial ablation was enlarged to 9 mm to perform subsequent standard CXL. This transepithelial custom refractive treatment standardizes the technique, making it no-touch surgery.

The maximum net mean ablation depth was 100.0 μm (range, 80–135), and the minimum mean estimated residual stromal thickness was set at 463 μm (range, 411–569; Figure 2).

Ablation procedures were performed under topical anesthesia. At the end of ablation, after application of topical pilocarpine 1%, riboflavin solution (Ricrolin; Sooft Italia Spa) was applied for corneal soaking for 15 minutes. UV-A illumination was then applied with the solid-state

The postoperative curvature of the cornea was obtained by combining two methods: (1) The corneal surface was standardized to the lowest preoperative keratometric reading by flattening the steepest axis, and (2) the spherical component of the manifest refraction was added with a positive or negative sign to the standardized keratometric value to obtain the desired (ideal) postoperative surface. The system calculated the ablation profile

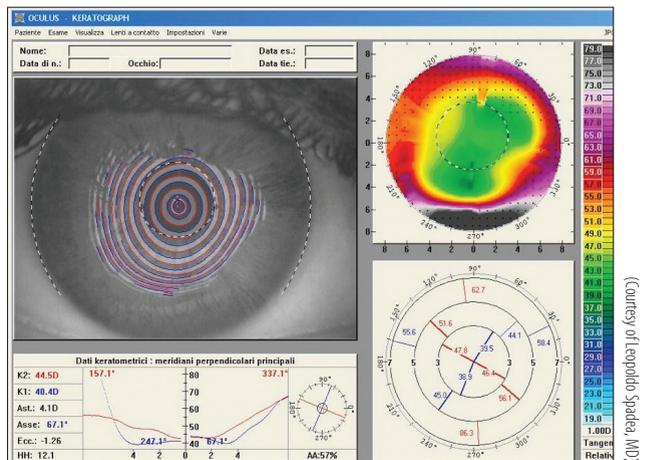


Figure 3. Videokeratographic map of the same eye shown in Figure 1 at 2 years after customized PRK and CXL. The topographic pattern shows an improvement in corneal profile with central flattening (relative scale, tangential algorithm).

Vega (Ofta high-tech Innovazione Tenico Chirurgica) UV-A light source for 30 minutes, irradiating an area 9 mm in diameter and applying the riboflavin solution every 2.5 minutes. Energy was delivered at 3 mW/cm<sup>2</sup>.

At the end of the treatment, a therapeutic bandage soft contact lens was applied, and ofloxacin drops were ordered at three times a day for 2 weeks. Topical corticosteroid (butyrate clobetasone 0.1%) drops were also prescribed three times a day for 1 month and then subsequently tapered and titrated.

## RESULTS

The study included 14 eyes of 14 patients who had initially undergone ELLK for keratoconus and subsequently presented with ametropia ( $-6.11 \text{ D} \pm 2.48$  standard deviation [SD]; range,  $-2.50$  to  $-9.50$ ). The combination customized PRK and CXL procedures were performed in these 14 eyes a mean  $40.1 \pm 12.4$  SD months after ELLK.

At a mean  $15 \pm 6.5$  SD (range, 6–24) months after customized PRK plus CXL, all eyes gained at least 1 line of Snellen distance UCVA (range, 1–10) from preoperative levels, no patient lost lines of distance BCVA, and four patients gained 3 lines of BCVA. The mean post-operative manifest refraction spherical equivalent was  $-0.79 \text{ D} \pm 2.09$  SD (range, +1 to -3). The mean topographic keratometric astigmatism was  $5.02 \text{ D} \pm 2.93$  SD (range, 0.8–8.9; Figure 3). All corneas remained clear, with haze less than grade 1.

## CONCLUSION

The combination of customized PRK and CXL provided safe and effective results in these eyes with residual ametropia after ELLK for keratoconus. The combined procedure provided corneal regularization and refractive improvement in these difficult-to-treat eyes. ■

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(Continued from page 49)

We initially performed topography-guided partial PRK in patients who showed stabilization after CXL but had poor visual rehabilitation due to remaining significant corneal irregularity. Soon, however, we began to perform both treatments on the same day, with topography-guided PRK applied first, followed immediately by high-fluence CXL. With 1 to 3 years of follow-up in many cases, the BCVA gains achieved by most patients were impressive. Hundreds of cases followed, and we reported the results and complications in large groups of patients treated with this protocol for keratoconus and post-LASIK ectasia.<sup>26</sup> Several esteemed colleagues have also presented similar approaches of combined PRK and CXL.

Our findings suggest that simultaneous topography-guided partial PRK with CXL offers a safe and effective approach for normalizing the cornea and enhancing visual function in eyes with ectatic conditions. The core importance of CXL in this technique is to address highly irregular astigmatism in eyes with keratoconus and post-LASIK ectasia. Our theoretical and clinical evidence supports the use of this technique, dubbed the *Athens Protocol*, in which CXL and topography-guided surface ablation are performed in the same session rather than sequentially (Figure 4).

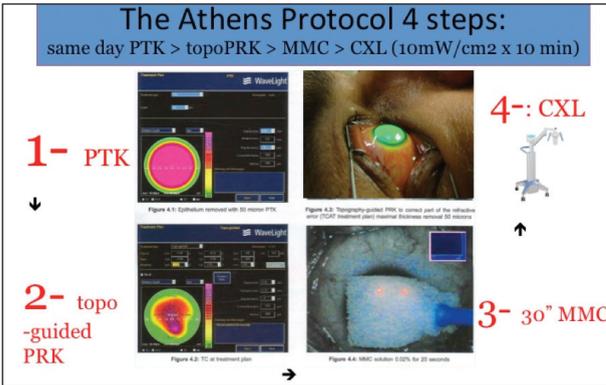
In our experience, surface ablation using a topography-guided excimer laser platform (Allegretto Wave 200-Hz and 400-Hz models and recently the WaveLight EX500; all by Alcon Laboratories, Inc.) effectively and predictably normalizes the corneal surface and improves functional vision. We have documented a synergistic effect when this procedure is performed simultaneously with CXL. Safety with this combination approach has been favorable as well. The minor complications of postoperative haze and delayed epithelial healing have occurred in a small number of eyes in our large series.<sup>26</sup>

## MEETING VISUAL REHABILITATION NEEDS

Although the efficacy of CXL for stabilizing keratectasia is well established and the procedure causes some corneal flattening, significant residual astigmatism that limits effective soft contact lens or spectacle wear may be a persistent problem for patients who are unable to wear rigid gas-permeable contact lenses. This situation creates an indication to perform subsequent topography-guided partial PRK or to implant intrastromal corneal ring segments (ICRSs). The latter option is used by some colleagues, but in our hands has very variable efficacy and may be counterintuitive, as the main mechanism of action of the ICRS relies on high elasticity of the cornea. The stiffening effect of CXL may make these eyes poor responders to subsequent ICRS implantation.

Surface ablation of a keratoconic eye may sound unorthodox, but the goal of using topography-guided software is to normalize the corneal surface and improve BCVA. This is a

(Courtesy of A. John Kanellopoulos, MD)



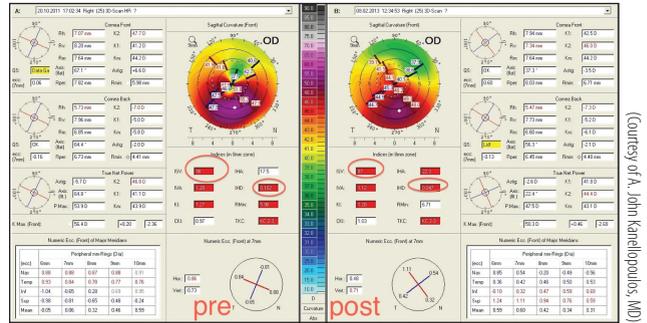
**Figure 4.** The basic steps of the Athens Protocol. (1) The PTK treatment plan on the Alcon WaveLight platform; (2) following PTK, areas of Bowman membrane have been ablated, confirming that the epithelium over the cone is thinner; (3) mitomycin C is applied prior to (4) the riboflavin and CXL.

therapeutic procedure in our opinion, not a refractive one; in fact, some eyes become more myopic postoperatively but have significantly better corneal regularity and improvement in BCVA. We have chosen to remove no more than 50  $\mu\text{m}$  of stroma, which at most usually treats 2.00 to 2.50 D of astigmatism and up to 1.00 D of myopia.

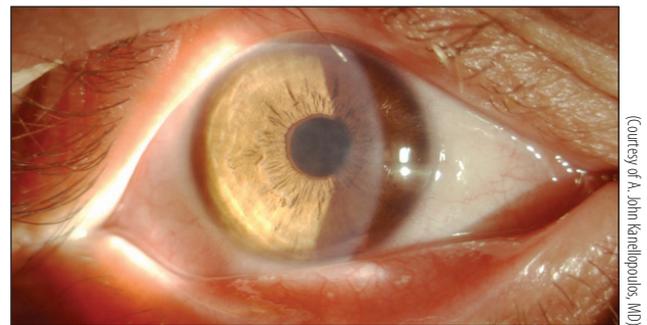
The pivotal element in this technique is the proprietary topography-guided platform of WaveLight that utilizes Placido disc images and/or Pentacam (Oculus Optikgeräte GmbH) tomographic maps to calculate a treatment consisting of combined myopic and hyperopic subsegments to normalize the irregular corneal surface. We are currently reviewing long-term results of a very large case series (more than 500 cases) to determine which modality is more effective, and the preliminary data suggest the Pentacam-driven platform. Experience has taught us that visual function in these cases correlates closely with two main topometric corneal indices, the index of high decentration (IHD) and the index of surface variance (ISV). The aim of these treatments is improve these two indices of ectasia-related topometric irregularity (Figure 5).

**ATHENS PROTOCOL**

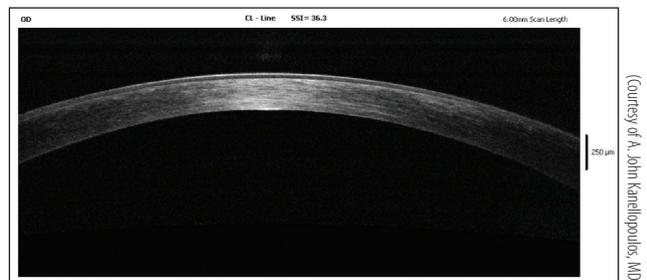
The Athens Protocol begins with a 6.5-mm phototherapeutic keratectomy (PTK) to remove 50  $\mu\text{m}$  of epithelium. Then topography-guided partial PRK is performed. The topography reference image for this application is generated by the Oculyzer II (a Pentacam HR-based tomographic capture device; Alcon Laboratories, Inc.). The excimer laser ablation resembles part of a hyperopic treatment combined with part of an eccentric myopic treatment over the cone. It is performed using a 5.5-mm effective optical zone and targets steepening of the area adjacent to the cone in an attempt to regularize the corneal surface.



**Figure 5.** Improvement of topometric indices before and after treatment with the Athens Protocol.

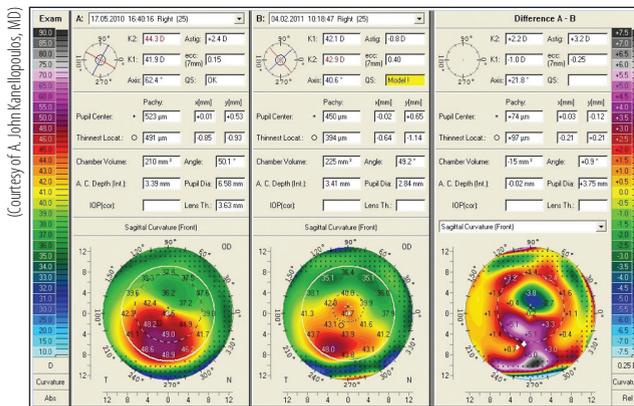


**Figure 6.** The right eye of a 27-year-old man with advanced keratoconus. Preoperative BCVA was 20/50 with refraction of -2.50 -5.00 X 80. After application of the Athens Protocol, the patient achieved a UCVA of 20/30 and BCVA of 20/20 with -1.00 -1.50 X 85. The slit-lamp photo shows the corneal clarity and ground-glass appearance typical of CXL-treated eyes.



**Figure 7.** Anterior segment OCT of the same eye 7 months after the Athens Protocol. One can appreciate the anterior cornea hyperreflectivity consistent with CXL and the demarcation line at about 300  $\mu\text{m}$  depth depicting the depth of effective CXL. Clinicians familiar with these findings following CXL alone may appreciate the enhanced depth and wider diameter of the CXL effect noted on the OCT images following the Athens Protocol.

Mitomycin C (0.002 mg/mL) is applied for 30 seconds, followed by our version of the CXL procedure. Ultraviolet-A (UV-A) light is applied at 5 mW fluence for 18 minutes with our own riboflavin solution formulated with 0.1%



**Figure 8.** Pentacam images preoperatively (left) and 7 months postoperatively, showing significant normalization of the cone, keratometric flattening, and improved symmetry. Difference map is at right.

sodium phosphate, slightly hypotonic (prepared in the United States by Leiter's Pharmacy). This part of our technique was designed with CXL expert Satish Herekar, MS, a science fellow with Avedro. For a video of the surgical technique, visit [youtube.com/watch?v=ZrOaFknL88Q&list=UU SFLzt\\_qEuOwTKlnqhwLPmg&index=30&feature=plcp](http://youtube.com/watch?v=ZrOaFknL88Q&list=UU SFLzt_qEuOwTKlnqhwLPmg&index=30&feature=plcp).

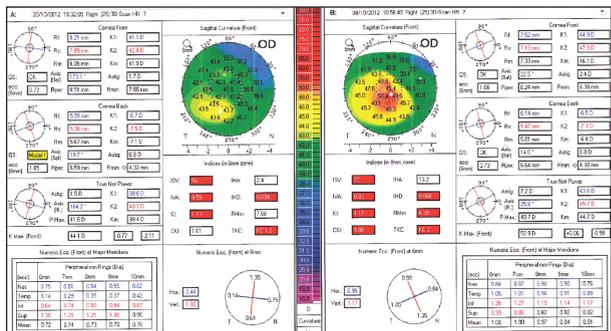
The corneal epithelium and Bowman membrane can act as barriers to UV-A light penetration into the stroma. Because these tissues are removed in the PTK and/or PRK procedure, it seems intuitive that the efficacy of CXL would increase; our clinical findings support this theory. For example, in a patient who had CXL alone in one eye and the Athens Protocol in the other, OCT hyperreflectivity maps show that the area of crosslinking is much broader and denser in the eye that received the combination treatment (Figures 6 and 7). We recently described these OCT maps as a sign of the extent of CXL.<sup>24</sup>

We also theorized that a PRK-treated eye represents a better biomechanical model for performing CXL (Figure 8). In theory, an eye with a regularized surface, as opposed to one in which there is ongoing strain from intraocular pressure and eye rubbing localized over the cone peak, would be better strengthened by CXL and more likely to remain stable after the procedure.

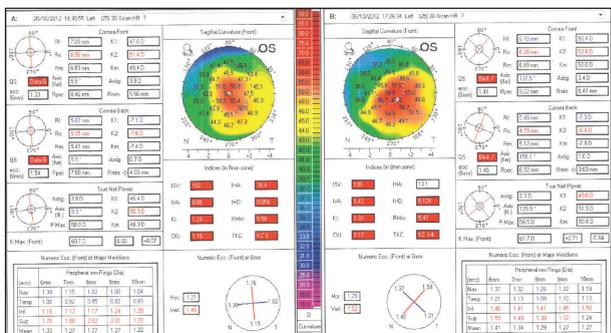
We believe redistribution of corneal strain by remodeling of the cornea with surface ablation is a significant factor in the synergistic effect achieved when performing PRK and CXL together. The order of treatment in the Athens Protocol also avoids removing crosslinked cornea, as would occur if CXL were performed first followed by PRK.<sup>22</sup>

### CLINICAL DATA

In a comparison of two large, consecutive series of eyes treated either with PRK and CXL at the same session or



**Figure 9.** Topometric comparison of postoperative (left) and preoperative (right) tomographic maps of an eye with keratoconus treated with the Athens Protocol by Dr. Baddar.



**Figure 10.** Similar images of the left fellow eye of the same keratoconus patient treated with Ferrara Rings and CXL by Dr. Baddar's team. Note improvements in the IHD and ISV. Nevertheless, this patient and most of the 25 patients enrolled in this comparison study preferred their Athens Protocol-treated eye due to better quality of vision and less discomfort. Eyes treated with ICRS and CXL recovered much faster.

with CXL first followed by topography-guided surface ablation 1 year later, statistically significant differences in several outcome parameters favored the same-day procedure. The study included 127 eyes in the sequential group and 198 eyes treated with the Athens Protocol.<sup>5</sup>

In the sequential group, mean logMAR UCVA improved from 0.90 to 0.49, and mean logMAR BCVA improved from 0.41 to 0.16. Mean keratometry (K) reading decreased by 2.75 D, and mean manifest refraction spherical equivalent (MRSE) by 2.50 D. The mean postoperative haze score was 1.2. For eyes in the simultaneous group, there was a significantly greater improvement in mean logMAR UCVA (from 0.96 to 0.30) and mean logMAR BCVA (from 0.39 to 0.11), as well as a significantly greater mean reduction in MRSE (-3.20 D) and keratometry (-3.50 D). The mean haze score in the simultaneous group was 0.5, which was significantly lower than the control group score. Central corneal thickness decreased by 70  $\mu$ m after both procedures, and there was no significant change in

## CXL PLUS TORIC PHAKIC IOL IMPLANTATION

The combination of CXL and toric phakic IOL implantation may be used to correct myopic astigmatism in patients with progressive mild to moderate keratoconus. In a video on eyetube.net, Jose L. Güell, MD, PhD, presents a case in which this combination treatment was successfully employed.

As described in the video, a 21-year-old man presented with keratoconus. The referring ophthalmologist reported that the patient's refraction and topography had been progressively changing during the past 3 years. CXL was performed in both eyes with application of riboflavin solution and ultraviolet-A light. Three months later, a Toric Artiflex (Ophtec BV) foldable iris-supported phakic IOL was implanted in the patient's amblyopic (high anisometropia) right eye. At 14 months postoperative, in the right eye his UCVA was 0.6 and BCVA was 0.6 with a refraction of plano -0.25 X 30 and 0.6 with rigid gas permeable contact lens (RGPCL) over-refraction. In the left eye, UCVA was 0.8 and BCVA was 0.9+ with refraction of +0.50 -1.00 X 105 and 1.00 with RGPCL.

In this case, CXL stabilized the patient's keratoconus, while the toric IOL corrected his ametropia. If the degree of irregular astigmatism is clinically nonsignificant, the ametropia is high, and the patient desires spectacle independence, the implantation of a phakic IOL (in the absence of standard contraindications) might be considered an option for patients with early keratoconus. If the degree of irregular astigmatism is clinically significant, we could have first considered the implantation of intracorneal ring segments.



endothelial cell count in either group.

These findings show that performing the two procedures in the same session offers the advantages of less PRK-associated scarring and better riboflavin and UV-A penetration to achieve a wider and deeper CXL effect with greater corneal flattening.

### ATHENS PROTOCOL VS ICRS

Sherif Baddar, MD, of Cairo, Egypt, is conducting an interesting study as a postdoctoral thesis, evaluating the outcomes of patients with keratoconus who are treated with the Athens Protocol in one eye and ICRS implantation (Ferrara Rings, Ferrara Ophthalmics) and CXL in the fellow eye. Preliminary results show improvements in both groups, although BCVA and the index of height decentration improvement appear to be significantly better in the Athens Protocol group (Figures 9 and 10).

### CONCLUSION

In our experience, same-day, simultaneous topography-guided PRK and CXL is a safe and effective therapeutic

intervention in highly irregular corneas with keratoconus and progressive post-LASIK ectasia. The Athens Protocol appears to be superior to sequential CXL and PRK.

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