

# Collagen Cross-Linking (CCL) With Sequential Topography-Guided PRK

## *A Temporizing Alternative for Keratoconus to Penetrating Keratoplasty*

*A. John Kanellopoulos, MD\*†‡ and Perry S. Binder, MS, MD§*

**Purpose:** To assess the effectiveness of ultraviolet A (UVA) irradiation-induced collagen cross-linking (CCL) on keratoconus (KC) progression.

**Methods:** A patient with bilateral, progressive KC underwent UVA irradiation (3 mW/cm<sup>2</sup> for 30 minutes) after topical 0.1% riboflavin drops over a deepithelialized cornea. Twelve months later, a topography-guided penetrating keratoplasty (PRK; wavelight 400 Hz Eye-Q excimer) was performed in 1 eye for a refractive error of  $-3.50 -4.00 \times 155$  by using an attempted treatment of  $-2.50 -3.00 \times 155$ . At all postoperative follow-up visits to 18 months, uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), pachymetry, and topography were performed.

**Results:** In the treated left eye, the UCVA after the UVA CCL improved from 20/100 to 20/80, and the BSCVA improved from 20/50 to 20/40. Eighteen months after the topography-guided PRK, the UCVA was 20/20, and the BSCVA was 20/15, with a refractive error of Plano  $-0.50 \times 150$ . The cornea was clear, and the endothelial cell count remained unchanged. The untreated right mate eye continued to progress during the same period.

**Conclusions:** The significant clinical improvement and the apparent stability of more than a year after UVA CCL, and subsequent PRK compared with the untreated mate eye, seems to validate this treatment approach for KC. An adjusted nomogram may be considered in the ablation of cross-linked cornea tissue to avoid overcorrections.

**Key Words:** keratoconus, cornea ectasia, surgical management, collagen cross-linking, ultraviolet A, riboflavin, customized topography-guided cornea ablation, visual rehabilitation

(*Cornea* 2007;26:891–895)

Received for publication June 19, 2006; revision received April 6, 2007; accepted April 15, 2007.

From the \*Laservision.gr Institute, Athens, Greece; the †New York University Medical College, New York, NY; the ‡Manhattan Eye, Ear and Throat Hospital, New York, NY; and the §Gordon Binder & Weiss Vision Institute, San Diego, CA.

Reprints: A. John Kanellopoulos, Laservision.gr Institute, 2 Mesogeion Avenue, Athens 11527, Greece (e-mail: laservision@internet.gr).

Copyright © 2007 by Lippincott Williams & Wilkins

Keratoconus is a bilateral, nonsymmetric, and noninflammatory progressive corneal degeneration. Its incidence has been thought to be 1 in 2000 in the general population,<sup>1</sup> but the increased number of eyes undergoing screening for laser refractive surgery suggests the prevalence may be higher. It can be diagnosed at puberty, with up to 20% of the eyes progressing to the extent that penetrating keratoplasty is indicated.<sup>2</sup> Although spectacles and contact lenses can provide useful vision in many cases, there are several surgical options for those cases that can no longer benefit from them: implantation of intracorneal ring segments (Intacs or Ferrera rings),<sup>3</sup> lamellar keratoplasty,<sup>4</sup> or penetrating keratoplasty.<sup>2</sup> Other ectatic corneal disorders such as Pellucid marginal degeneration<sup>5</sup> and post-LASIK ectasia<sup>6</sup> require similar treatment approaches. Although penetrating keratoplasty for ectatic corneal disorders is highly successful, many eyes require contact lenses to correct the unpredictable topographic changes that are associated with sutures and postsuture abnormal corneal shapes, and sometimes the contact lens is not successful.<sup>7</sup>

In recent years, basic laboratory studies and subsequent clinical studies have suggested that by increasing the collagen cross-linking (CCL) of the corneal stromal collagen, one is able to increase the stiffness (biomechanics?) of the cornea with attendant stabilization of the normally progressive corneal disorder.<sup>8–16</sup> We present a case of bilateral progressive keratoconus that underwent unilateral CCL followed by PRK with an excellent outcome.

### CASE REPORT

A 26-year-old male patient had been treated with gas-permeable contact lenses for 8 years before his presentation. Because of debilitating giant papillary conjunctivitis he was no longer able to wear the contact lens; spectacles were unable to provide functional vision because of poor vision and asthenopia. At the time of his examination, his uncorrected visual acuity (UCVA) was 20/40 in the right eye and 20/100 in the left eye, and his best spectacle-corrected visual acuity (BSCVA) was 20/15 OD (manifest refraction  $-0.75 -0.75 \times 165$ ) and 20/50 OS (manifest refraction  $-3.75 -4.50 \times 155$ ). The keratometry readings were as follows: OD,  $43.25 \times 10/44.25 \times 100$ ; OS,  $45.50 \times 05/48.50 \times 95$  (Topolyzer; Wavelight, Erlangen, Germany).

Slit-lamp examination of the right eye failed to show clinical findings associated with keratoconus such as a Fleischer ring, Vogt striae, or a noticeable excessive thinning of the central or paracentral cornea. The central pachymetry was 520  $\mu\text{m}$  (Orbscan II; Bausch and

Lomb, Rochester, NY; ultrasound; Echoscan US-1800; NIDEK, Gamamory, Aichi, Japan). The left cornea had significant central corneal thinning of 440  $\mu\text{m}$  and a Fleischer ring and Vogt lines without apical scarring. The endothelial cell density was 2800 cells/ $\text{mm}^2$  OD and 2750 cells/ $\text{mm}^2$  OS (Konan Medical, Boston, MA). Corneal topography (Topolyzer; Wavelight) in the OS (Fig. 1A) clearly showed a steep "island" in the infero-temporal cornea consistent with the cone apex. Figures 1A–F show the storyline of our treatment in the OS eye. Figures 1G and H show the fellow untreated OD at the beginning and at the end of our treatment to the OS. The OD (Fig. 1G) revealed with-the-rule cylinder that seems irregular. The lower component of the cornea cylinder is steeper than the upper and does not continue in a straight diametric line in respect to the center of the cornea. It is obvious from the topographies of the 2 eyes that, at the beginning of our treatment, the left eye was significantly more affected by keratoconus. This made the patient and us decide to treat the OS first and observe the less affected OD.

Intracorneal ring segments as a means of visual rehabilitation for the OS were discussed, but because of our experiences with this modality,<sup>17</sup> we presented the risks, benefits, and alternatives of penetrating keratoplasty. The patient asked if there were any other alternatives to penetrating keratoplasty. Because of our preliminary success with CCL in a case of post-LASIK ectasia,<sup>18</sup> we counseled him about CCL, which he elected to undergo knowing that a subsequent penetrating keratoplasty might be needed.

### CCL Procedure

Two weeks after the initial examination, a Keracure prototype device was used (Priavision, Menlo Park, CA). The epithelium was removed in a 9-mm diameter by using 20% alcohol applied to the surface for 20 seconds. For the next 30 minutes, 0.1% riboflavin ophthalmic solution was applied topically every 2 minutes. Riboflavin was used to facilitate CLL while protecting the iris, crystalline lens, and retina.<sup>12</sup> After the riboflavin drops, 4 light-emitting diodes, ultraviolet light of 370-nm wavelength and 3-mW/ $\text{cm}^2$  radiance, was projected onto the surface for 30 minutes, after which a bandage contact lens was inserted. The device has a built-in beeper that resets at the beginning of the treatment and alerts clinicians every 2 minutes during the 30 minutes of treatment to instill the riboflavin solution.

After CCL, topical Ofloxacin (Allergan, Irvine, CA) and prednisolone acetate 1% (Pred Forte; Allergan) were used 4 times a day for 10 days. The contact lens was removed at day 4 after reepithelialization.

### Clinical Course

Three months after the CCL procedure, the UCVA had improved to 20/80 and the BSCVA improved to 20/40, with the refraction improving to  $-3.50 -4.00 \times 165$ . These parameters (UCVA, BSCVA, and refraction) remained stable for the next 12 months. At this 12-month period, the thinnest part of the cornea measured 450  $\mu\text{m}$  by Orbscan and ultrasonic pachymetry. The topography at the 12-month follow-up for the CCL procedure in the treated OS is depicted in Figure 1B. There is some reduction in the cone steepness in the treated left eye, better shown in the difference map (Fig. 1C). The difference map clearly shows that the CCL treatment in the left eye resulted in cone flattening and improvement of the keratoconus. This was evident clinically as well, by the improvement in UCVA, BSCVA, and refraction as noted above.

The patient remained unable to wear contact lenses because of the giant papillary conjunctivitis and it was difficult to wear spectacles because of the anisometropia. In our attempt to visually rehabilitate the eye and taking into account the 12-month stability after the CCL, we proceeded with a limited topography-guided PRK in an attempt to reduce the irregular astigmatism, and we hope that it will facilitate visual rehabilitation. We decreased the effective optical zone diameter

to 5.5 mm from our standard routine of 6.5 mm and partially treated the sphere to not exceed 50  $\mu\text{m}$  in planned stromal removal. The attempted myopic sphere was  $-2.50$  D and the planned astigmatism treatment was  $-3.00$  D by using the Allegretto-Wave topography-guided customized program (T-CAT).<sup>19</sup> This proprietary software uses topographic data from the linked topography device (Topolyzer; Wavelight). By default, it permits the consideration of 8 topographies (of predetermined threshold accuracy), averages the data, and enables the surgeon to adjust the desired postoperative cornea asphericity; the inclusion, or not, of tilt correction; and the adjustment of sphere, cylinder, axis, and treatment zone. The image of the planned surgery generated by the laser software is displayed in Figure 1D.

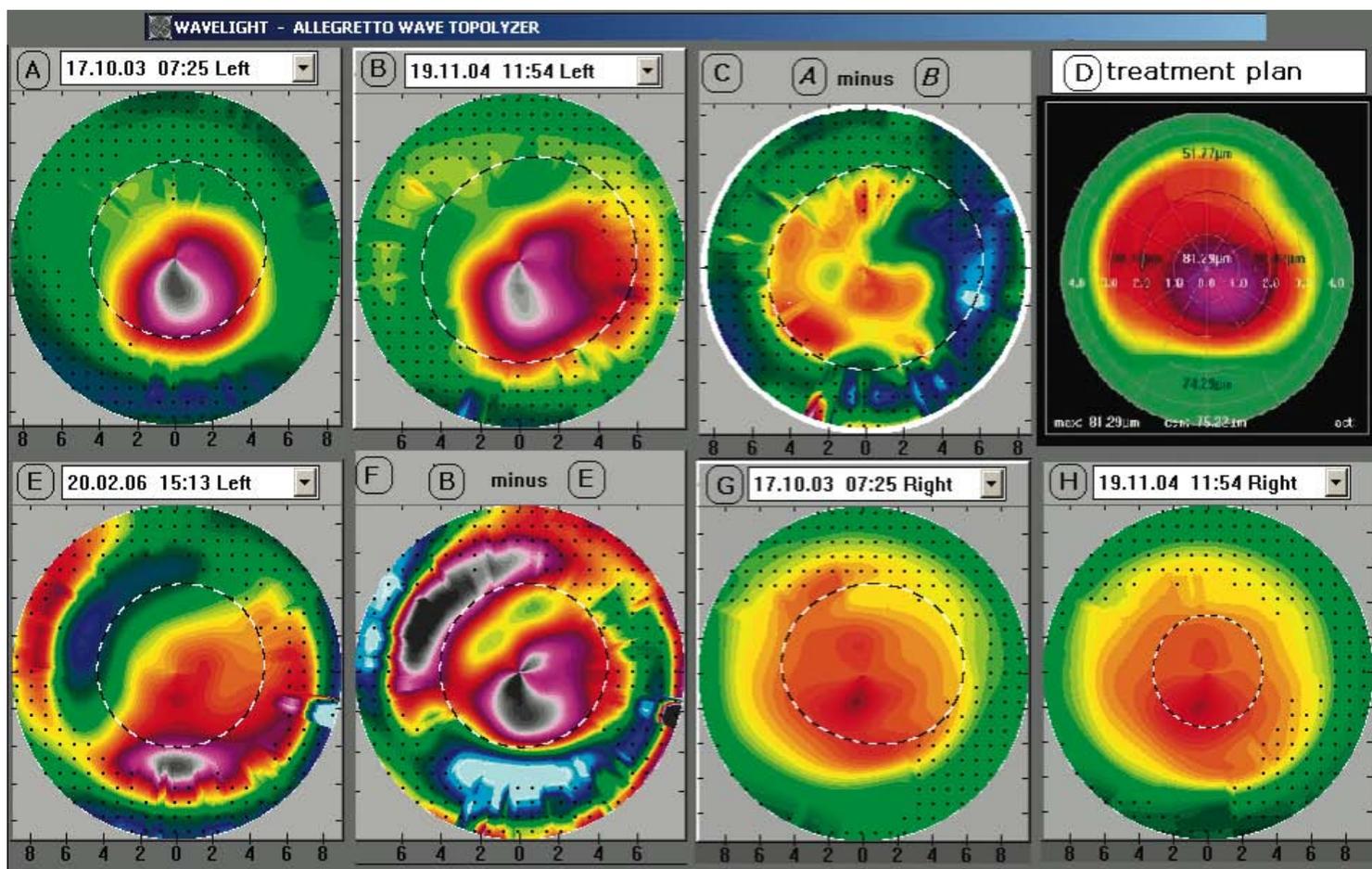
For the PRK procedure, the epithelium was removed by using 20% alcohol placed on the surface for 20 seconds, after which the laser treatment was performed. A cellulose sponge soaked in mitomycin-C 0.02% solution was applied over the ablated tissue for 30 seconds, followed by irrigation with 10 mL of chilled balanced salt solution. Finally, a bandage lens was placed onto the cornea. Ofloxacin and prednisolone acetate 1% were used topically 4 times a day for 10 days. Prednisolone acetate 1% was used 4 times a day for 3 more weeks and twice a day for an additional 4 weeks. Protection from all natural light with sunglasses was encouraged, along with oral 1000 mg of vitamin C daily for 60 days, which is our standard PRK treatment. The bandage contact lens was removed at day 5 after complete reepithelialization.

One month after the laser treatment, the UCVA improved to 20/20, with subjective good nighttime vision. Thirty months after the UVA CCL treatment and 18 months after the laser treatment, the UCVA remained 20/20 and the BSCVA was 20/15, with a manifest refraction of Plano  $-0.50 \times 150$ . The cornea was clear and compact, and by biomicroscopy, the Vogt striae were removed by the PRK, but the Fleischer ring was still present. No haze was noted over the healed area of the PRK treatment. The endothelial cell density remained stable at 2750 cells/ $\text{mm}^2$ , which was the same 1 month after the UVA CCL treatment, as well as at months 1 and 12 after the PRK. The post-PRK topography for the operated left eye is displayed in Figure 1E. The difference map for the left eye, from before the PRK (Fig. 1B) to final measurement 18 months after the PRK (Fig. 1E), is depicted in Figure 1F.

Meanwhile the untreated mate eye had worsened because of the natural progression of the keratoconus. The patient was discouraged from eye rubbing. During the 30 months after the beginning of the treatment of the OS, the UCVA in the OD deteriorated to 20/70 and a BSCVA to 20/25 with a refractive error of  $-1.25 -1.75 \times 160$ .

The keratometry readings had increased to  $43.75 \times 05/44.75 \times 95$ . The topography 30 months after treatment of the fellow eye is shown for the untreated OD (Fig. 1H).

In Figure 1D, the reader can evaluate the topography-guided PRK treatment plan. There seems to be a "deeper" ablation over the steep cone area and evidence of peripheral "flattening" effect of the cornea 180 degrees opposite of the cone center. The flattening of this part of the peripheral cornea will result in steepening the middle cornea just away from the cone apex. The combined action on cone apex flattening while the rest of the central cornea is steepened is the unique modality that the topography-guided treatment offers. It resembles a part-myopic and part-hyperopic treatment blended together. Because we combined this flattening on the cone apex with steepening of the rest of the central cornea, little stroma tissue is removed from the cone apex area in relation to the normalization achieved. It is remarkable how similar Figures 1D and F are. They represent the topography-guided PRK treatment plan and the actual achieved topographic difference just before and 18 months after this treatment, respectively. The similarity of Figures 1D and F establishes the accuracy of ablation delivery and achieved effect with this novel PRK treatment.



**FIGURE 1.** This is a sequence of topographic maps for both the left treated eye and the right untreated eye. A–F, Storyline through our treatment to the OS. G and H, Fellow untreated OD at the beginning and at the end of our treatment to the OS. A, Pretreatment topography of the left, most affected eye. The OS clearly shows a steep “island” in the infero-temporal cornea consistent with the cone apex. At the time of his examination, his UCVA was 20/100 in the left eye, and his BSCVA was 20/50 OS (manifest refraction, 23.75 24.50 3 155). The keratometry readings were 45.50 3 05/48.50 3 95. B, Left, treated eye 12 months after UVA CCL. The central steepening is still present, although reduced. At this point, the UCVA was 20/80, the BSCVA was 20/40, and the manifest refraction was 23.50 24.00 3 115. This image serves also as the pre-PRK topography for the same eye. C, This is the difference of the initial topography for the OS (A) minus the 12-month post-UVA CCL treatment topography of the same eye (B). It clearly showed that the UVA CCL treatment in the left eye resulted in cone flattening and improvement of the keratoconus also evident clinically by the improvement in UCVA, BSCVA, and refraction as noted above. It seems that the CCL effect resulted in some cone flattening, shown by this comparison topography. D, This is the topography-guided PRK treatment plan. There seems to be a “deeper” ablation over the steep cone area and evidence of peripheral “flattening” effect of the cornea 180 degrees opposite of the cone center. The flattening of this part of the peripheral cornea will result in steepening the middle cornea just away from the cone apex. The combined action on cone apex flattening while the rest of the central cornea is steepened is the unique modality that the topography-guided treatment offers. It resembles a part-myopic and part-hyperopic treatment blended together. Because we combined this flattening on the cone apex with steepening of the rest of the central cornea, little stroma tissue is removed from the cone apex area in relation to the normalization achieved. E, Left eye 18 months after topography-guided PRK. The central cornea seems more regular and much flatter than the pre-PRK topography (B) and the initial topography just before initial UVA CCL treatment (A). There is no topographic evidence of keratoconus progression 18 months after the topography-guided PRK and a total of 30 months of the stabilizing UVA CCL treatment in the same eye. F, The difference between B and E of the left treated eye. It is the difference of the topography before and 18 months after the topography-guided PRK in the left cornea. The reader can appreciate a “deeper” ablation over the steep cone area and evidence of peripheral “flattening” effect of the cornea 180 degrees opposite to the cone center. The flattening of this part of the peripheral cornea resulted in steepening the middle cornea just away from the cone apex. The combined action on cone apex flattening while the rest of the central cornea is steepened is the unique modality that the topography-guided treatment offers. It resembles a part-myopic and part-hyperopic treatment blended together. Because we combined this flattening on the cone apex with steepening of the rest of the central cornea, little stroma tissue is removed from the cone apex area in relation to the normalization achieved. It is remarkable how similar D and F look. G, This is the topography of the right, less affected eye at the beginning of this study. The topography reveals with-the-rule cylinder that appears irregular. The keratometry readings had increased to 43.75 3 05/44.75 3 95. Comparing this topography with G, which depicts the same untreated right eye at the beginning of this study, is important. There is topographic evidence of deterioration of the cone compared to the previous topography G.

## DISCUSSION

The technique of CCL by the photosensitizer, similar to photopolymerization in polymers, has been previously described.<sup>10,20</sup> Experimental studies in rabbit and porcine eyes have shown an approximate increase in corneal rigidity by 70% after CCL.<sup>11</sup> A clinical study of 22 cases showed the stabilization of keratoconus with 4-year follow-up. In that study, there was a 70% mean keratometry regression of 2 D at the corneal plane and a regression of 1.14 D of the manifest spherical equivalent refractive error. Corneal and lens transparency, as well as endothelial cell density and intraocular pressure, remained unchanged, whereas visual acuity improved slightly in 65% of the eyes.<sup>8,11–14</sup>

Although multiple approaches have been used to treat ectatic corneal disorders, in cases of progressive disease, the “gold standard” treatment has become penetrating keratoplasty,<sup>2</sup> with its established attendant risks. As an alternative to penetrating keratoplasty, riboflavin/UVA CCL to decrease the progression of keratoconus<sup>8,9,16</sup> and progressive iatrogenic ectasia<sup>15,18</sup> has been studied.

We present 1 case that had bilateral keratoconus that underwent CCL and subsequent PRK on 1 eye with an excellent and stable outcome for 12 months after UVA CCL and 18 months after a subsequent PRK, whereas the mate eye underwent progression of the keratoconus. The first step of our treatment was used to stabilize the keratoconus. The PRK was attempted to improve the post-CCL refractive error. Figures 1E and H display the latest topography for both eyes. Figures 1B and E demonstrate the original and final topography of the left (treated) cornea. One can appreciate the difference map (Fig. 1C) between pre- (Fig. 1A) and post-UVA CCL (Fig. 1B) for the operative eye and the difference map (Fig. 1F) between pre- (Fig. 1B) and post-topography-guided treatment (Fig. 1E).

In contrast, the topography map (Fig. 1G) of the untreated mate eye before and at the conclusion of the treatment in the left (Fig. 1H) documents progression of the keratoconus. In the PRK treatment plan (Fig. 1D), as well as the difference map before PRK to 1 year after PRK (Fig. 1F), there seems to be a deeper ablation over the steep cone area and evidence of a midperipheral “steepening” effect of the cornea 180 degrees opposite of the cone center. This was achieved by flattening just peripheral to the cornea the area that is planned to be “steepened.” It almost looks like a 90-degree part in circumference of a hyperopic treatment.

The CCL procedure used riboflavin solution over the deepithelialized cornea to protect the crystalline lens, endothelium, and possibly the retina from UVA radiance and to enhance UVA absorption in the anterior stroma and facilitate the cross-linking process.<sup>8,10–14,16</sup>

Clinically, it has been reported that one can see the depth of the protective effect of the riboflavin in the cornea,<sup>9</sup> but we did not see this in our case; at the end of the UVA CCL treatment, the entire cornea seemed to be “soaked” with yellow-tinted riboflavin by slit-lamp evaluation and in the anterior chamber. We did not detect a “line” in the stroma at the last visit.

We subsequently performed a topographic-guided PRK procedure<sup>19</sup> in hopes of prolonging the need for a corneal

transplant. The clinical results have been rewarding during a post-PRK follow-up of 18 months. The visual and topographic results document the improvement.

We concluded that the spherical outcome was achieved by both flattening the cone apex combined with steepening the opposite side of the cone, which results in a “steepening” of the central part of the cornea opposite of the cone with respect to the center of the cornea. This treatment offers the clinically significant advantage of reduced need for tissue removal that would be required with a wavefront-guided treatment<sup>19</sup> from the cone apex, which corresponds to the thinnest part of the cornea. If a wavefront-guided approach was attempted in a similar case, and we assume that the wavefront analyzer would be able to image such an irregular eye, the wavefront-guided software would “read” and attempt to flatten the steep cone irregularity to the reference point of more peripheral and equally flatter cornea. This would require significant ablation thickness specifically in stroma underlying the cone apex. This customized approach that uses topography addresses and measures effectively the extreme cornea irregularity that these cases may have. It is a significant tool in enhancing visual rehabilitation. In cases where the refractive error will not permit full correction, we propose the correction of only the irregular astigmatism to improve the BSCVA but not necessarily the UCVA, without risking significant cornea thinning.

Corneal stabilization, followed by full visual rehabilitation, leads us to believe that this combined approach may have wider applications and may become a temporizing alternative to cornea transplantation. Special emphasis should be taken preoperatively in cases with a minimal corneal thickness <400  $\mu\text{m}$  because of potential cytotoxic effects of UVA on corneal endothelial cells.<sup>12</sup> In addition, the laser treatment must be applied with caution because the more rigid cornea may have an ablation rate different from that of a normal cornea. For this reason, we elected to attempt an undercorrection of the sphere and cylinder by 25%; we obtained a 100% effect. We therefore recommend attempting 75%–80% of the measured sphere and cylinder as a correction parameter when planning the Excimer ablation with T-CAT software or other wavefront-guided software until we can more accurately determine the new ablation rate of CCL stroma. Larger, comparative studies establishing the safety and efficacy of this treatment and longer follow-up are necessary to further validate these results and potentially make this treatment available for ectatic corneal disorders.

## REFERENCES

1. Rabinowitz Y. Keratoconus. *Surv Ophthalmol.* 1998;42:297–319.
2. Pramanik S, Musch DC, Sutphin JE, et al. Extended long-term outcomes of penetrating keratoplasty for keratoconus. *Ophthalmology.* 2006;113:1633–1638.
3. Rabinowitz YS, Li X, Ignacio TS, et al. Intacs inserts using the femtosecond laser compared to the mechanical spreader in the treatment of keratoconus. *J Refract Surg.* 2006;22:764–771.
4. Amayem AF, Anwar M. Fluid lamellar keratoplasty in keratoconus. *Ophthalmology.* 2000;107:76–80.
5. Ertan A, Bahadir M. Management of superior pellucid marginal degeneration with a single intracorneal ring segment using femtosecond laser. *J Refract Surg.* 2006;23:205–208.

6. Binder PS. Ectasia after laser in situ keratomileusis. *J Cataract Refract Surg.* 2003;29:2419–2429.
7. Gordon M, Steger-May K, Szczotka-Flynn L, et al. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. *Am J Ophthalmol.* 2006;142:923–930.
8. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet -a-induced collagen cross linking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620–627.
9. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea.* 2006;25:1057–1059.
10. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res.* 1998;66:97–103.
11. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg.* 2003;29:1780–1785.
12. Wollensak G, Spoerl E, Wilsch M, et al. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. *J Cataract Refract Surg.* 2003;29:1786–1790.
13. Wollensak G, Spoerl E, Reber F, et al. Keratocyte cytotoxicity of riboflavin/UVA-treatment in vitro. *Eye.* 2004;18:718–722.
14. Wollensak G, Spoerl E, Wilsch M, et al. Keratocyte apoptosis after corneal collagen cross-linking using riboflavin/UVA treatment. *Cornea.* 2004;23:43–49.
15. Hafezi F, Mrochen M, Jankov M, et al. Corneal collagen crosslinking with riboflavin/UVA for the treatment of induced kerectasia after laser in situ keratomileusis. 2007; (in press).
16. Spoerl E, Seiler T. Techniques for stiffening the cornea. *J Refract Surg.* 1999;15:711–713.
17. Kanellopoulos A, Pe L, Perry H, et al. Modified intracorneal ring segment implantations (Intacs) for the management of moderate to advanced keratoconus: efficacy and complications. *Cornea.* 2006;25:29–33.
18. Kanellopoulos A. Management of post-LASIK ectasia with UVA collagen-cross linking followed by customized topography-guided PRK—an efficient approach to avoid corneal transplantation. *J Ophthalmol.* 2007; (in press).
19. Kanellopoulos A, Pe L. Wavefront-guided enhancements using the wavelight excimer laser in symptomatic eyes previously treated with LASIK. *J Refract Surg.* 2006;22:345–349.
20. Hettlick H, Lucke K, Kreiner C. Light induced endocapsular polymerization of injectable lens refilling materials. *Ger J Ophthalmol.* 1992;1:346–349.