Handout

Complications of Collagen Cross-Linking: Indications, Applications, results, complications and evolving technology

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Synopsis: Didactic approach to the management of progressive cornea ectasia associated with keratoconus and refractive surgery. Several surgical treatment modalities utilized internationally will be presented, including: collagen cross-linking with ultraviolet radiation A in order to halt ectasia, combined in some cases with a customised excimer laser ablation to facilitate visual rehabilitation (as presented in previous ESCRS meetings by the author), these alternatives to Intracornea ring segment implantation, lamellar grafts as well as penetrating graft techniques will be analyzed. Surgical and medical treatment technique, indications, potential complications and their management as well as clinical experience pearls will be presented.

Objective:
The participants will share our vast experience in managing progressive keratoconus and post-LASIK ectasia in order to visually rehabilitate these patients. Pearls on indications, patient selection, surgical technique and complication management for safe and effective results will be presented and discussed with the participants.
Dear Editor:

I report a patient who had post-LASIK ectasia and was managed in a novel fashion, without keratoplasty. A 29-year-old male underwent uniconical LASIK 38 months ago. Little detail was available from the patient and the surgeon. His original uncorrected visual acuity (UCVA) before LASIK was 20/80, and his spectacle-corrected visual acuity (BSCVA) was 20/20 with refraction of sphere being −2.00−175×85. Initially after the LASIK procedure, the patient reported that vision was good. During the following months, vision in that eye deteriorated. The original LASIK surgeon diagnosed ectasia and recommended the placement of Intacs (Addition Technology, Des Plaines, IL). After Intacs placement, his vision did not improve, and the patient developed severe night vision halos.

The treating LASIK surgeon then recommended penetrating keratoplasty (PK) as the next step, and the patient came for a second opinion for PK. 11 months after the original LASIK procedure and 3 months after Intacs implantation. Corneal topography is shown in Figure 1 (available at http://aaojournal.org); the central corneal thickness was 410 μm, and the endothelial cell count was 2750 cells/mm² (Conan, Boston, MA). I discussed with the patient the following:

1. The poor long-term experience with Intacs in post-LASIK ectasia that I have reported.1
2. The benefits and risks of PK.
3. Combined ultraviolet radiation and riboflavin treatment to achieve collagen cross-linking and biomechanical stabilization of the ectasia.

After informed consent was given, I removed the Intacs. Two weeks later, I treated the ectatic cornea with a single application of combined ultraviolet radiation and riboflavin treatment to achieve collagen cross-linking at 3 mW/cm² for 30 minutes (KeraCure, Priavision, Menlo Park, CA) combined with the use of 0.1% riboflavin ophthalmic solution in 20% dextran T-500.

The treatment was performed after 20% alcohol-assisted epithelial removal. The riboflavin solution was then applied for approximately 2 minutes to soak the stromal bed and protect the iris, crystalline lens, and retina from the ultraviolet A irradiation, and then I drop every 2 minutes for a total of 30 minutes. A bandage contact lens was placed onto the cornea for 5 days and the patient treated with topical ofloxacin 1% (Ocuflox, Allergan, Irvine, CA) and prednisolone acetate 1% (Predforte, Allergan) 4 times a day for 10 days.

At 3 months, his UCVA improved from 20/400 to 20/70 and his BSCVA from 20/200 to 20/40. Refraction changed from −4.50−4.50×120 to −4.00−3.50×115, and corneal topography changed as seen in Figure 1. The stability of these parameters and the corneal topography between months 1 and 3 of this treatment encouraged me to proceed with topography-guided photorefractive keratectomy (PRK) to reduce the irregular astigmatism and try to provide the patient with a visual acuity not requiring the use of spectacles or a soft contact lens.

The corneal thickness at that point of 420 μm enabled a PRK of his full spectacle correction with a topography-guided customized ablation on top of the LASIK flap (T-CAT software, Wavelight excimer laser, Wavelight, Erlangen, Germany). At the first post-PRK month, UCVA was 20/20 and BSCVA 20/20, with a refraction of +0.50−0.50×160. There was no corneal endothelium count change. It is now 24 months after the operation and the patient enjoys UCVA of 20/20, although there are some mild night vision problems. Postoperative corneal topography is shown on Figure 1.

The most frequent management for post-LASIK ectasia has been PK.2 Previous reports of the use of combined ultraviolet radiation and riboflavin treatment to achieve collagen cross-linking mention a slowing down of keratoconus.3 We have reported the management of extreme cornea irregularity with topography-guided ablations.4 This is the first report of management of post-LASIK ectasia with combined ultraviolet radiation and riboflavin treatment to achieve collagen cross-linking followed by customized PRK for visual rehabilitation. The apparent corneal stabilization, along with the successful visual rehabilitation, suggests that this approach may have a wider application as an alternative to therapeutic PK.5

Larger comparative studies and longer follow-up are obviously necessary to validate the long-term efficacy of this combined ultraviolet radiation and riboflavin treatment followed by a surface excimer laser treatment. Nevertheless, the refractive and topographic stability for 2 years appears to validate this minimally invasive treatment of iatrogenic keratectasia and leads me to believe that it may have an even wider application in the near future.

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References
Figure 1. Display of topographies. 1. Corneal topography of this case when first seen by the authors, with central cornea ectasia and midperiphery flattening as an effect of the Intacs that were present. At this point, best spectacle-corrected visual acuity (BSCVA) is 20/200. 2. Corneal topography 2 months after the removal of Intacs and 1 month after combined ultraviolet radiation and riboflavin treatment to achieve collagen cross-linking. The central steepening is still present, and the effect of the Intacs removal relative to the previous image is appreciated mostly at the midperiphery, which appears steeper now. At this point, BSCVA is 20/200. Bottom center. An estimated corneal topographic ablation pattern as a laser treatment plan of the topography-guided procedure. It is notable that this ablation pattern is highly irregular, with a deeper ablation plan just inferior to and right of the center, which matches, however, the central corneal irregularity in the previous topographies. 4. Corneal topography 6 months after topography-guided photorefractive keratectomy. The central cornea appears more regular and much flatter. At this point, BSCVA and UCVA are 20/200. Bottom left. Comparison map depicting the result of subtraction of corneal topography 4 (final result) from corneal topography 1 (state of the complication when we encountered it). Impressively, the difference resembles the topography-guided ablation pattern (bottom center), demonstrating effectively the specificity of this treatment in reducing the pathogenic cornea irregularity, which, we theorize, contributed to the drastic improvement in BSCVA.
Collagen Cross-Linking (CCL) With Sequential Topography-Guided PRK
A Temporizing Alternative for Keratoconus to Penetrating Keratoplasty

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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/cm² for 30 minutes) after topical 0.1% riboflavin drops over a deep epithelialized cornea. Twelve months later, a topography-guided penetrating keratoplasty (PRK; wavefront 400 Hz Eye-Q excimer) was performed in 1 eye for a refractive error of −3.50 −4.00 × 155 by using an attempted treatment of −2.50 −3.00 × 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 × 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

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Keratoconus is a bilateral, nonsymmetric, and noninflammatory progressive corneal degeneration. Its incidence has been thought to be 1 in 2000 in the general population, 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. 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), lamellar keratoplasty, or penetrating keratoplasty. Other ectatic corneal disorders such as Pellucid marginal degeneration and post-LASIK ectasia 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 posttransplant abnormal corneal shapes, and sometimes the contact lens is not successful.

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. 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 × 165) and 20/50 OS (manifest refraction −3.75 −4.50 × 155). The keratometry readings were as follows: OD, 43.25 × 10/44.25 × 100; OS, 45.50 × 05/48.50 × 95 (Topolyzer; Wavelight, Erlangen, Germany).

Slit-lamp examination of the 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 μm (Orbscan II; Bausch and...
Lomb, Rochester, NY; ultrasonic; Echocan US-1800; NIDEK, Gamamory, Aichi, Japan). The left cornea had significant central corneal thinning of 440 μm and a Fleischer ring and Vogt lines without apical scarring. The endothelial cell density was 2800 cells/mm² OD and 2750 cells/mm² 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,17 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,18 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 CCL while protecting the iris, crystalline lens, and retina.12 After the riboflavin drops, 4 light-emitting diodes, ultraviolet light of 370-nm wavelength and 3-mW/cm² radiation, 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 install 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 × 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 μm 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 μm in planned stromal removal. The attempted myopic sphere was −2.50 D and the planned astigmatism treatment was −3.00 D by using the Allegra–Wave topography-guided customized program (T-CAT).19 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 Planos −0.50 × 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/mm², 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 × 160.

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

In Figure 1D, the surgeon evaluated 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, small 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.

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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, BSCA, 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 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.

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DISCUSSION

The technique of CCL by the photosensitizer, similar to photopolymerization in polymers, has been previously described.10,20 Experimental studies in rabbit and porcine eyes have shown an approximate increase in corneal rigidity by 70% after CCL.11 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.

Although multiple approaches have been used to treat ectatic corneal disorders, in cases of progressive disease, the “gold standard” treatment has become penetrating keratoplasty,9 with its established attendant risks. As an alternative to penetrating keratoplasty, riboflavin/UVA CCL to decrease the progression of keratoconus9,16 and progressive iatrogenic ectasia15,18 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 topography map before 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.7,10–14,16

 Clinically, it has been reported that one can see the depth of the protective effect of the riboflavin in the cornea,9 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-tinged 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 procedure19 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 treatment19 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 μm because of potential cytotoxic effects of UVA on corneal endothelial cells.12 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


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Comparison of Sequential vs Same-day Simultaneous Collagen Cross-linking and Topography-guided PRK for Treatment of Keratoconus

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ABSTRACT

PURPOSE: The safety and efficacy of corneal collagen cross-linking (CXL) and topography-guided photorefractive keratectomy (PRK) using a different sequence and timing were evaluated in consecutive keratoconus cases.

METHODS: This study included a total of 325 eyes with keratoconus. Eyes were divided into two groups. The first group (n=127 eyes) underwent CXL with subsequent topography-guided PRK performed 6 months later (sequential group) and the second group (n=198 eyes) underwent CXL and PRK in a combined procedure on the same day (simultaneous group). Statistical differences were examined for pre- to postoperative changes in uncorrected (UCVA, logMAR) and best-spectacle-corrected visual acuity (BSCVA, logMAR), manifest refraction spherical equivalent (MRSE), keratometry (K), topography, central corneal thickness, endothelial cell count, corneal haze, and ectatic progression. Mean follow-up was 36±18 months (range: 24 to 68 months).

RESULTS: At last follow-up in the sequential group, the mean UCVA improved from 0.9±0.3 logMAR to 0.49±0.25 logMAR, and mean BSCVA from 0.41±0.25 logMAR to 0.16±0.22 logMAR. Mean reduction in spherical equivalent refraction was 2.50±1.20 diopters (D), mean haze score was 1.2±0.5, and mean reduction in K was 2.75±1.30 D. In the simultaneous group, mean UCVA improved from 0.96±0.2 logMAR to 0.3±0.2 logMAR, and mean BSCVA from 0.39±0.3 logMAR to 0.11±0.16 logMAR. Mean reduction in spherical equivalent refraction was 3.20±1.40 D, mean haze score was 0.5±0.3, and mean reduction in K was 3.50±1.3 D. Endothelial cell count preoperatively and at last follow-up was unchanged (P<.05) in both groups. Statistically, the simultaneous group did better (P<.05) in all fields evaluated, with improvement in UCVA and BSCVA, a greater mean reduction in spherical equivalent refraction and keratometry, and less corneal haze.

CONCLUSIONS: Same-day simultaneous topography-guided PRK and CXL appears to be superior to sequential CXL with later PRK in the visual rehabilitation of progressing keratoconus. [J Refract Surg. 2009;25:S812-S818.] doi:10.3928/1081597X-20090813-10

Keratoconus is a bilateral, nonsymmetric, noninflammatory progressive corneal degeneration that frequently manifests in post-pubescent young adults as progressive steepening attributed to biomechanical stromal collagen weakening. Its incidence has been reported to be 1 in 2000 in the general population. The increased number among eyes undergoing screening for laser refractive surgery suggests the prevalence may be higher. Current surgical/non-surgical interventions such as spectacles and contact lenses, intracorneal ring segment implantation, lamellar keratoplasty, and, the gold standard, penetrating keratoplasty, although popular, have limitations.

In recent years, basic laboratory studies and subsequent clinical studies have demonstrated stiffening of the cornea with use of ultraviolet A (UVA) light and riboflavin solution as a photosensitizer-initiated corneal collagen cross-linking (CXL) with no loss in corneal transparency. The CXL procedure has demonstrated the revolutionary potential for retarding or eliminating the progression of keratoconus and postoperative LASIK ectasia.

We have performed over 1000 CXL treatments in our facility over the past 7 years both after LASIK and keratoconus with satisfactory outcomes. We have also demonstrated that topography-guided ablation of the cross-linked corneal stroma can "normalize" the highly irregular corneal surface in these eyes by reducing irregular astigmatism and often reducing the refractive error as well, providing patients with improved visual outcomes.

The clinical results of a novel, same-day, simultaneous approach of topography-guided photorefractive keratectomy (PRK) and CXL for keratoconus are presented and retrospec-
Sequential vs Simultaneous Topography-guided PRK and CXL/Kanellopoulos

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Effectively compared to the data from our previous experience of performing CXL first and PRK at least 6 months later. The outcomes of these two groups are compared in a retrospective case series with follow-up of 2 to 5 years.

PATIENTS AND METHODS

PATIENT SELECTION
All patients were enrolled in our Athens clinical facility. Once a diagnosis of keratoconus was confirmed (see below), patients were informed of various popular options, including CXL. Being neither FDA-approved nor CE Marked (in cases treated prior to December 2006), informed consent was obtained from all patients and the surgery was performed in the following sequence: CXL first with topography-guided PRK at least 6 months later in eyes treated from August 2003 to May 2005 (sequential group). After gaining significant experience, we shifted our approach to same-day simultaneous customized topography-guided PRK and CXL in eyes treated from June 2005 to May 2008 (simultaneous group).

DIAGNOSIS OF KERATOCONUS
A diagnosis of progressive keratoconus was made in all patients (all aged <30 years), who developed progressive corneal steepening of at least 1.00 diopter (D) in keratometry, associated with a documented progression of increasing myopia and/or astigmatism over a period of 3 or more months. These findings were in parallel with increasing inferior corneal steepening and thinning to no less than 350 µm after PRK, based on videokeratography and pachymetry. Preoperative clinical data and topography were used as a baseline. Progression of the myopic refractive error with or without progression of the manifest astigmatism, decreasing uncorrected visual acuity (UCVA), loss of best spectacle-corrected visual acuity (BSCVA), progressive inferior corneal steepening on topography, and/or decreasing inferior corneal thickness were findings in all cases.

CLINICAL EXAMINATION
Each patient underwent manifest refraction before and 30 minutes after administration of one drop of 1% tropicamide solution (Akorn Inc, Lake Forest, Ill), as well as measurement of UCVA and BSCVA that was recorded in a 20-foot lane using high contrast Snellen visual acuity testing and then converted to logMAR scale values. A slit-lamp microscopic examination performed by the author confirmed invariably in all cases the presence of keratoconus either by the presence of a Fleischer ring, central or paracentral corneal thickening with prominent cornea nerves, and/or Vogt’s striae. Keratometry readings were obtained by videokeratography (Topolyzer; WaveLight Laser Technologie AG, Erlangen, Germany) and by two tomography-based topography devices—Orbscan II (Bausch & Lomb, Rochester, NY) and Pentacam (Oculus Optikgeräte, Wetzlar, Germany). Pachymetry was performed using all of the following instruments: Pentacam, Orbscan II, and ultrasonic EchoScan US-1800 (NIDEK Co Ltd, Gamagori, Japan). The minimal measurement in each case was used as the cornea thickness value, due to the importance of referencing the thinnest point. Specular microscopy was performed using the Konan specular microscope (Konan Medical, Boston, Mass).

Our technique of sequential CXL followed by topography-guided PRK at a later date has been reported previously.20,21 Both procedures have received a CE Mark for clinical use (CXL in 2006, topography-guided PRK in 2003) within the countries of the European Union, including Greece. Topography-guided ablations with the WaveLight platform and CXL have not received FDA approval to date. As this is a novel approach and may be unfamiliar to most readers, the same-day simultaneous approach of topography-guided PRK and then CXL is described.

STEP 1: PARTIAL, SPHERICALLY CORRECTED TOPOGRAPHY-GUIDED PRK
We have devised this technique based on the proprietary WaveLight customized platform (Topolyzer). Use of the topography-guided platform with this device to normalize irregular corneas, including those with ectasia, has been reported previously.23-25 This proprietary software utilizes topographic data from the linked topography device (Topolyzer). By default, it permits the consideration of eight topographies (of predetermined threshold accuracy), averages the data, and enables the surgeon to adjust the desired postoperative cornea asphericity (chosen as zero in all cases), the inclusion, or not, of tilt correction (no tilt was chosen in all cases), as well as the adjustment of sphere, cylinder, axis, and treatment zone (an optical zone of 5.5 mm was chosen in all cases). The image of the planned surgery is generated by the laser software.20,21

We used topography-guided PRK to normalize the cornea, by reducing irregular astigmatism and also treating part of the refractive error. To ensure minimal tissue removal, the effective optical zone diameter was decreased to 5.5 mm (compared to our usual treatment diameter in routine PRK and LASIK cases of at least 6.5 mm). The transition zone was 1.5 mm. We also planned ~70% treatment of cylinder and whatever level of sphere (up to 70%), so as not to exceed 50 µm in planned stromal removal. The value of 50 µm was...
chosen arbitrarily by the author, based on experience with this platform in irregular corneas.

Following the placement of an aspiring lid speculum (Rumex, St Petersburg, Fla), 20% alcohol solution was placed within a 9-mm titanium LASEK trephine (Rumex) for 20 seconds after which the epithelium was wiped with a dry Weck-cell sponge. The laser treatment was then applied. A cellulose sponge soaked in mitomycin C 0.02% solution was applied over the ablated tissue for 20 seconds followed by irrigation with 10 mL of chilled balanced salt solution.

**STEP 2: COLLAGEN CROSS-LINKING**

For the next 10 minutes, 0.1% riboflavin sodium phosphate ophthalmic solution (PriaVision Inc, Menlo Park, Calif) was applied topically every 2 minutes. The solution appeared to “soak” into the corneal stroma rapidly, as it was centrally devoid of Bowman’s layer. Following the initial riboflavin administration, four diodes, emitting UVA light of approximately 370 nm wavelength (365 to 375 nm) and 3 mW/cm² radiance at 2.5 cm was projected onto the surface of the cornea for 30 minutes. A “Keracure” prototype device was used (PriaVision). The Keracure device has a built-in beeper that alerts the clinician every 2 minutes during the 30-minute treatment to install the riboflavin solution in a timely fashion. A bandage contact lens was placed on the cornea at the completion of the procedure.

After CXL, topical ofloxacin (Allergan Inc, Irvine, Calif) was used four times a day for the first 10 days and prednisolone acetate 1% (Pred Forte, Allergan) was used four times a day for 60 days. Protection from all natural light with sunglasses was encouraged along with oral Vitamin C 1000 mg daily for 60 days postoperatively (our standard postoperative management following PRK). The bandage contact lens was removed at approximately day 5 following complete reepithelialization.

All cases were evaluated before and after both treatments for age, sex, UCVA, BSCVA, refraction, kerometry (K), topography, central corneal thickness (CCT), endothelial cell count, corneal haze on a scale 0 to 4 (0=clear cornea, 1=mild haze, 2=moderate haze, 3=severe haze, and 4=reticular haze [obstructing iris anatomy]), and ectasia stability. These parameters were retrospectively collected and then statistically analyzed using paired t test.

**RESULTS**

Approximately 40% of patients complained of significant pain during the first postoperative night after both CXL alone or when combined with simultaneous topography-guided PRK the same day, whereas others reported minimal discomfort. Reepithelialization occurred by postoperative day 4 in 90% of patients.

Specifically, 127 consecutive eyes (sequential group) had topography-guided PRK at least 6 months following CXL, whereas 198 eyes (simultaneous group) underwent topography-guided PRK followed immediately by CXL as a single procedure. Mean follow-up was 36 months (range: 24 to 68 months) from the time of the last procedure performed.

Mean endothelial cell count and morphology were unchanged in both groups (2650±150 cells/mm² preoperatively and 2700±140 cells/mm² postoperatively).

Mean patient age in the sequential group was 21.5 years (range: 17 and 29 years) and comprised 44 males and 32 females. At last follow-up, preoperative UCVA of 0.9±0.3 logMAR improved to 0.49±0.25 logMAR postoperatively, and BSCVA improved from 0.41±0.25 logMAR preoperatively to 0.16±0.22 logMAR postoperatively. Mean reduction in spherical equivalent refraction was 2.50±1.2 D, and mean reduction in K was 2.75±1.3 D. Mean haze score was 1.2±0.5. Mean CCT decreased from 465±45 µm preoperatively to 395±25 µm postoperatively.

Mean patient age in the simultaneous group was 20.5 years (range: 16 to 29 years) and comprised 53 males and 42 females. Mean UCVA improved from 0.96±0.2 logMAR preoperatively to 0.3±0.2 logMAR postoperatively, and BSCVA from 0.39±0.3 logMAR to 0.11±0.16 logMAR. Mean reduction in spherical equivalent refraction was 3.20±1.4 D, and mean reduction in K was 3.50±1.3 D. Mean haze score was 0.5±0.3, and CCT decreased from 475±55 µm preoperatively to 405±35 µm postoperatively.

Statistical comparison using paired t test revealed that the simultaneous group performed superiorly with a better BSCVA (P<.001), spherical equivalent reduction (P<.005), mean K reduction (P<.005), and corneal haze score (P<.002) at final follow-up. No eye lost lines of UCVA or BSCVA.

Figure 1 shows representative corneal topographies from sequential Pentacam examinations in a 29-year-old patient from the simultaneous group (same-day simultaneous topography-guided PRK and CXL). The keratometric data changes ~3.50 D from 49.0 and 44.3 @ 60.9° preoperatively to 44.0 and 41.8 @ 46° postoperatively, whereas the visual and refraction data changed from UCVA of 20/100 to 20/25 and −2.75 −3.50 @ 65 (20/30) to +0.50 −1.00 @ 35 (20/20) at 2-year follow-up.

**DISCUSSION**

The technique of collagen CXL via a photosensitizing agent is similar to photopolymerization in polymers...
and has found a broad international application for keratoconus in recent years. Although multiple approaches have been used to treat ectatic corneal disorders, in cases of progressive disease, the gold standard treatment in many countries is penetrating keratoplasty with its established costs, morbidity, and attendant risks.

The mechanism of topography-guided ablation is the fitting of an ideal cornea shape (usually a sphere) under the present topography map with the ablation of tissue in between.

We have been able to use topography-guided treatments in highly irregular corneas that are beyond the limits of wavefront measuring devices, making this approach more efficient in treating highly irregular astigmatism, such as in keratoconus. It may also be applied in cases with some media opacity, such as in keratoconus eyes with corneal scars, as its measurements are based solely on the corneal surface reflection.

Topography-guided PRK flattens not only some of the cone “peak” but also an arculate, broader area of the cornea away from the cone, usually in the superior nasal periphery; this ablation pattern will resemble part of a hyperopic treatment and thus will cause some amount of steepening, or elevation adjacent to the cone, effectively normalizing the cornea. It is this core concept in the topography-guided PRK treatment that makes it, in our opinion, more therapeutic than refractive. We theorize additionally that the new, “flatter” and less irregular cornea shape may perform better biomechanically in keratoconus. Specifically, as the cornea cone gives way to a flatter and “broader” cone, this may redistribute the biomechanical strain from the eye’s intraocular pressure and other factors (such as eye rubbing). This effect may be further enhanced with the CXL adjunct.

We have converted to same-day simultaneous topography-guided PRK and CXL in our clinical practice, represented herein by the cases in the simultaneous group, for three reasons: 1) the combination reduces the patient’s time away from work, 2) performing both procedures at the same time with topography-guided PRK first appeared to minimize the potential superficial stromal scarring resulting from PRK, and 3) when topography-guided PRK is performed after the CXL procedure, some of the cross-linked anterior cornea is removed, minimizing the potential benefit of CXL.

Regarding the second reason, our initial experience with the cases in the sequential group suggested that if the practitioner waited between procedures, the damaged keratocytes would replenish and may become activated as fibroblasts after PRK, causing scarring even with the use of mitomycin C (MMC). In these cases, we performed topography-guided PRK at least 6 months after CXL and encountered significant haze in 17 eyes, despite using MMC. When we employed CXL immediately after topography-guided PRK, we encountered minimal haze formation (2 cases with significant haze). The CXL procedure has been shown to “kill” keratocytes as deep as 300 µm, which may explain why this late haze formation was prevented when CXL was performed the same day after topography-guided PRK in the eyes in the simultaneous group.

Regarding the final reason, we believe it is counter-intuitive to remove the cross-linked tissue with topography-guided PRK at a later time, as we are potentially removing a beneficial layer of the stiffer, cross-linked
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cornea, which helps maintain the normalized corneal shape.

Although a patient with keratoconus can have an improved visual result with the addition of the topography-guided PRK procedure, completely removing a high level of refraction was not our goal. We have placed an arbitrary “ceiling” of 50 µm to the amount of tissue that we safely remove centrally, anticipating that further thinning might destabilize the cornea’s biomechanical integrity, even with the effect of CXL.

Special attention should be given to eyes with a preoperative minimal corneal thickness <350 µm because of potential cytotoxic effects of UVA light on corneal endothelial cells. It should be noted that the proprietary riboflavin solution used was a slightly hypotonic (340 mOsm) formulation, resulting in slight “swelling” of the cornea intraoperatively (during CXL). This restored the corneal thickness to ~400 µm to protect the corneal endothelium, and may be the reason we did not encounter any corneal endothelial decompensation in any of the eyes studied.

In addition, the laser treatment was applied with caution, as the refractive effect of the CXL (cornea flattening), had to be anticipated. For this reason, we elected to always attempt a significant undercorrection of both the sphere and cylinder by at least 30%. As described previously, we suggest attempting at most 70% of the measured sphere and cylinder when planning the excimer ablation with T-CAT software (WaveLight Laser Technologie AG) or other wavefront-guided software after CXL. In the future, we hope to more accurately determine the new ablation rate of CXL stroma.

Simultaneous topography-guided PRK and CXL appeared in this study to be superior to sequential treatment in the rehabilitation of keratoconus. A possible reason for the difference may be an “enhanced” CXL in the former group, either due to better penetration of the riboflavin solution through the ablated stroma or to the absence of Bowman’s layer. In addition, cross-linking the more “normal” corneal shape in the laser pre-treated keratoconus eyes (simultaneous group) makes them more “resistant” to factors affecting ectasia progression.

Why bother with topography-guided PRK in the first place? Our long-term follow-up of CXL alone in keratoconus appears to halt ectasia progression, but it often leaves the patient with difficulty in visual rehabilitation, as most cases had contact lens intolerance. In the patient population we encountered, the great majority fell into this category even when CXL had successfully halted the progression of ectasia.

The reality of the efficacy of topography-guided PRK and CXL has been the reduction of penetrating keratoplasty cases performed for the indication of keratoconus in our clinical practice over the past 4 years. The same-day, simultaneous topography-guided PRK/CXL procedure was easy to perform, but in some cases the central epithelial surface took up to 1 month to smoothen and become lucent. It took from 1 to 4 weeks for us to detect stable changes in the K and topography, which seemed to match the visual and refractive changes.

A specific demarcation line of separation was noted between the suspected cross-linked collagen and the deeper cornea both clinically as well as with corneal optical coherence tomography (Optivue, Freemont, Calif) (Fig 2). The cross-linking effect in the stroma was clinically assessed at the slit lamp following the procedure by the “ground-glass” appearance of the anterior stroma, and in most cases, by the presence of ultra-thin, curved, whitish fine lines in the anterior and mid-stroma (Fig 3). These lines do not appear to affect vision and tend to fade away by postoperative month 12. In our clinical assessment, the presence of this finding over the anterior half of the stroma confirms sufficient CXL treatment has occurred. As we perform more CXL procedures, we hope to learn which candidates might best benefit from the procedure.

Questions such as “How much ectasia?” and “What types of ectasia can we safely and predictably correct?”

Figure 2. Corneal optical coherence tomography demonstrates hyper-reflective intracorneal stromal “lines” at 2/3 depth (arrows) corresponding with the clinical presence of the corneal collagen cross-linking (CXL) demarcation line in a patient from the simultaneous group 3 years following the combined topography-guided photorefractive keratectomy and CXL procedure.
as well as “Is there a minimum preoperative CXL corneal thickness that will not respond to the procedure?” require further investigation. Strategies need to be developed to determine the attempted correction and ablation depth for the topography-guided PRK portion of this process. The proper concentration of riboflavin, its delivery within the corneal stroma, and the proper UVA light exposure and duration will need to be adjusted as we move from animal model studies into clinical procedures. Perhaps CXL will have a wider application as prophylaxis in laser refractive surgery, as we reported procedures. Perhaps CXL will have a wider application as prophylaxis in laser refractive surgery, as we reported in PRK and LASIK.

Our findings suggest better results with same-day, simultaneous topography-guided PRK and collagen CXL, as a therapeutic intervention in highly irregular corneas with progressive keratoconus. Our goal was to stabilize the ectasia (with CXL) and rehabilitate the vision (with topography-guided PRK) in young adults with advancing keratoconus to delay or even avoid corneal transplantation. Larger, prospective and randomized, comparative studies, establishing the safety and efficacy of this treatment, and longer follow-up, are necessary to further validate these results.

REFERENCES

| Sequential vs Simultaneous Topography-guided PRK and CXL/Kanellopoulos |
|-------------------------|-------------------------|
Stability of Simultaneous Topography-guided Photorefractive Keratectomy and Riboflavin/UVA Cross-linking for Progressive Keratoconus: Case Reports

Ronald R. Krueger, MD, MSE; A. John Kanellopoulos, MD

**ABSTRACT**

**PURPOSE:** To follow the stability of a simultaneously delivered therapy that corrects aberrations and stiffens the corneal collagen of eyes with progressive keratoconus.

**METHODS:** Two patients with progressive keratoconus underwent partial treatment (70% cylinder and sphere up to 50-µm central depth) with topographic customized photorefractive keratectomy (PRK) using the T-CAT module of the ALLEGRETTO WAVE Eye-Q excimer laser (Alcon Laboratories Inc), and then immediate corneal collagen cross-linking (CXL) with riboflavin 0.1% drops every 2 minutes while exposed to mean 365-nm ultraviolet A (UVA) light at 3.0 mW/cm² for 30 minutes (the Athens Protocol). Pre- and postoperative evaluations included manifest and cycloplegic refraction, Scheimpflug corneal tomography and pachymetry, and slit-lamp examination of corneal clarity with a minimum follow-up of 30 months.

**RESULTS:** Both treated eyes experienced rapid healing of the epithelial surface within 5 days and progressive improvement of vision. In the first case, partial treatment reduced the astigmatism and aberrations, allowing for successful soft contact lens wear at 3 months. Follow-up at 13, 19, 30, and 36 months showed progressive reduction of refractive myopia and keratometric power. In the second case, laser treatment led to a near emmetropic refraction with an uncorrected visual acuity of 20/20 at 3 months, which remained unchanged at 21 and 30 months postoperative.

**CONCLUSIONS:** Partial topography-guided PRK followed by riboflavin/UVA CXL is a safe and effective therapy that halts the progression of keratoconus and reduces the spherocylindrical refraction and aberrations to improve the visual function of patients with progressive keratoconus. Stability and progressive improvement over time is observed, although limitations may exist for steeper and thinner corneas. [J Refract Surg. 2010;26(10):S827-S832. doi:10.3928/1081597X-20100921-11]

Keratoconus is a disease of corneal collagen that leads to progressive and irregular steepening of the corneal shape with a loss of corrected vision. When advanced, the irregular corneal shape can no longer be fit with a contact lens, and keratoplasty must be considered to rehabilitate visual function. Riboflavin/ultraviolet A (UVA) corneal collagen cross-linking (CXL) has been shown to effectively halt the progression of keratoconus, and in some cases, gradually reduce the refractive and keratometric irregularity. When exposed to UVA light, the riboflavin absorbed within the cornea is photoactivated in the presence of oxygen to create a reactive singlet oxygen species, which interacts with collagen to form the cross-links within the exposed tissue. Although CXL halts the progression of keratoconus, it does not improve or restore the irregularity in corneal shape sufficiently to rehabilitate the visual function of the patient. Hence, the need for further refractive correction is required after CXL, which may be problematic if the patient remains contact lens intolerant. As one alternative, intrastromal corneal ring segments (Intacs; Addition Technology Inc, Des Plaines, Illinois) have been proposed as a method of regularizing the corneal shape in association with riboflavin/UVA CXL. Although effective in many patients, some eyes still have sufficient irregularity limiting the full potential return of corrected vision, and must undergo keratoplasty.

Topography-guided photorefractive keratectomy (PRK) has been proposed as a palliative method for correcting irregular astigmatism in keratoconus. However, in the absence of cross-linking, the weakened corneal structure is still vulnerable to progression, so that the ectasia may worsen. Herein, we evaluate the stability of simultaneous topography-guided PRK with riboflavin/UVA CXL, as a method for both regular-
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SURGICAL TECHNIQUE AND EVALUATION

THE ATHENS PROTOCOL

This technique was recently reported for the management of keratoconus.8-12

Step 1: The (Partial, Spherically Corrected) Topography-guided Transepithelial PRK Technique. We devised this technique based on the proprietary WaveLight ALLEGROTT WAVE Eye-Q laser (Alcon Laboratories Inc, Ft Worth, Texas) customized platform. As noted above, we previously described the use of the topography-guided platform with this device to normalize irregular corneas as well as ectasia.

This customized excimer laser treatment is guided by topographic images and is different from wavefront-guided treatments. It received CE Mark approval for clinical use in the European Union in 2003; however, it has yet to receive US Food and Drug Administration (FDA) approval.

This proprietary software utilizes topographic data from the linked topography device (Topolyzer; WaveLight GmbH, Erlangen, Germany). By default, it permits the consideration of eight topographies (of pre-determined threshold accuracy), averages the data and enables the surgeon to adjust the desired postoperative cornea asphericity (chosen as zero in all cases), provides the option of including tilt correction (no tilt was chosen in all cases), as well as adjustment of sphere, cylinder, axis, and treatment zone (optical zone of 5.5 mm was chosen in all cases). The image of the planned surgery is generated by the laser software.

We used topography-guided PRK to normalize the cornea by reducing irregular astigmatism while treating part of the refractive error. To remove the minimum possible tissue, we decreased the effective optical zone diameter to 5.5 mm in all cases (compared to our usual treatment diameter of at least 6.5 mm in routine PRK and LASIK). We also planned ~70% treatment of cylinder and sphere (up to 70%), so as not to exceed 50 µm in planned stromal removal. We chose the value of 50 µm as the maximum ablation depth, based on our experience of treating irregular corneas with this platform.7-10

Following the placement of an aspirating lid speculum (Rumex, St Petersburg, Florida), a 6.5-mm, 50-µm phototherapeutic keratectomy (PTK) was performed to remove the corneal epithelium. Partial topography-guided PRK laser treatment was applied. A cellulose sponge soaked in mitomycin C (MMC) 0.02% solution was applied over the ablated tissue for 20 seconds followed by irrigation with 10 mL of chilled balanced salt solution.

Step 2: Collagen CXL Procedure. For the next 10 minutes, the proprietary 0.1% riboflavin sodium phosphate ophthalmic solution (Priavision, Menlo Park, California) was applied topically every 2 minutes. The solution appeared to “soak” in the corneal stroma rapidly, as it was centrally devoid of Bowman layer. Following the initial riboflavin administration, 4 diodes, emitting UVA light of mean 370-nm wavelength (range: 365 to 375 nm) and 3 mW/cm² radiance at 2.5 cm was projected onto the surface of the cornea for 30 minutes (Keracure prototype device, Priavision). The Keracure device, which has a built-in beeper, alerts clinicians every 2 minutes during the 30-minute treatment to install the riboflavin solution in a timely fashion. A bandage contact lens was placed on the cornea upon completion of the combined procedures.

Postoperatively, topical ofloxacin (Ocufl ox 0.3%; Allergan Inc, Irvine, California) was used four times a day for the first 10 days and prednisolone acetate 1% (Pred Forte, Allergan) was used four times a day for 60 days. Protection from all natural light with sunglasses was encouraged, with administration of oral 1000 mg Vitamin C daily for 60 days postoperative. The bandage contact lens was removed at or around day 5 following complete re-epithelialization.

EVALUATION

The following evaluations were completed before and after both treatments: age, sex, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), refraction, keratometry (K), tomography, pachymetry, endothelial cell count, corneal haze on a scale of 0 to 4 (0=clear cornea, 1=mild haze, 2=moderate haze, 3=severe haze, and 4=reticulat haze [obstructing iris anatomy]), and ectasia stability as defined by stability in mean keratometry and tomography.

Both cases reported were performed at Laservision.gr Institute, Athens, Greece.

CASE REPORTS

CASE 1

A 24-year-old man with advanced keratoconus and contact lens intolerance was recruited for sequential therapy using the Athens Protocol instead of undergoing corneal transplantation. Manifest refraction was −14.00 +3.50 × 80 in the right eye with a corrected distance visual acuity (CDVA) of 20/50. Scheimpflug corneal tomography (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany) revealed a steep inferocentral cone with a central keratometry...
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(K) reading of 58.30 diopters (D) and a maximum K reading of 59.70 D at a distance of 1 mm inferior to the center (Fig 1A), where the thinnest corneal thickness was 421 µm.

On June 13, 2007, topographic-guided PRK was performed by the first author (R.R.K.) with the WaveLight ALLEGRETTO WAVE Eye-Q laser using the T-CAT module with 70% correction of the cylinder and partial correction of the sphere (up to 70% with maximum ablation of 50 µm). The modified T-CAT laser setting was −0.75 − 2.50 × 170 for a maximum ablation depth of 56 µm. Photorefractive keratectomy was performed after the epithelium was removed by 6.5-mm diameter and 50-µm deep PTK, after which the tracker was engaged for topographic-guided PRK treatment. After PRK, mitomycin C (0.02%) was applied with a sponge for 30 seconds and then irrigated. Following the conclusion of the MMC application, topical riboflavin sodium phosphate 0.1% drops were placed on the cornea every 2 minutes, and with the second application of riboflavin, the surface was exposed to 370-nm UVA light with a 10-nm bandwidth at 3.0 mW/cm² for 30 minutes. A soft contact lens was placed on the eye with topical antibiotic (0.3% ofloxacin) and steroid (1.0% prednisolone acetate) drops administered four times daily until re-epithelialization, after which the topical steroid was tapered over several weeks.

Following uneventful epithelial closure, uncorrected distance visual acuity (UDVA) returned to 20/400 at 3 months postoperative with a manifest refraction of −10.50 + 1.50 × 80, yielding 20/25 CDVA. Pentacam corneal tomography showed a maximum steep K reading of 60.80 D centrally with a reduced inferocentral reading of 54.80 D, revealing a more central and symmetric shape compared to preoperatively (Fig 1B). Although the steepest K reading was slightly increased, the cornea was now 93 µm thinner, based on the laser ablation depth and collagen compaction due to CXL. With reduced astigmatism and asymmetry, the eye was easily rehabilitated with a −7.00-D soft contact lens.

At 13 months postoperative, the refraction improved to −6.50 D (20/25) with a reduced K reading of 56.30 D centrally and 56.20 D at the 1-mm inferocentral location. At 19 months, UDVA and refraction improved to 20/40 and −3.25 + 0.75 × 05 (20/20), respectfully, and the corneal tomography revealed a central K reading of 54.30 D and inferocentral reading of 57.90 D (Fig 1C). At 30 months, corneal tomography revealed a central K reading of 51.50 D and inferocentral reading of 59.30 D (Fig 1D) with UDVA of 20/30 and refraction of −2.25 + 0.50 × 05 (20/20). Although the inferior steepening of the cornea

Figure 1. Case 1. A) Preoperative Pentacam tomography reveals inferocentral steep cone (maximum keratometry [K] 59.70 D) (refraction: −14.00 − 3.50 × 80; corrected distance visual acuity [CDVA]: 20/50). B) Three months following simultaneous topography-guided photorefractive keratectomy and riboflavin/ultraviolet A cross-linking, the tomography reveals greater symmetry and centrality of steep shape (central K of 60.80 D and inferocentral K of 54.80 D) (refraction: −10.50 − 1.50 × 80; CDVA: 20/25). C) At 19 months postoperative, the central corneal power is reduced (54.30 D), while the inferocentral power increased (57.90 D) (refraction: −3.25 + 0.75 × 05; CDVA: 20/25). D) This trend continues at 30 months (central K, 51.50 D; inferocentral K, 59.30 D) although both uncorrected and corrected distance visual acuity progressively improved (refraction: −2.25 + 0.50 × 05; CDVA: 20/20).
neal shape progressively returned between 3 and 30 months (from 54.80 to 59.30 D), with progressive thickening of the central corneal thickness (~44 µm), a progressive reduction in the magnitude of the central K reading (~8.00 D) was also noted with marked improvement in UDVA and CDVA. At 36-month follow-up, the progressive inferior steepening seemed to be stabilizing, as both the central K reading at 49.10 D and inferocentral reading at 56.40 D improved.

The fellow eye had milder keratoconus with a refraction of -6.00 - 1.50 × 90; corrected distance visual acuity (CDVA): 20/20. Scheimpflug corneal tomography (Pentacam) revealed a steep inferocentral cone with a maximum K reading of 53.10 D (Fig 2A) and thinnest corneal thickness of 496 µm. On June 13, 2007, topography-guided PRK with the WaveLight Allegretto WAVE Eye-Q laser using the T-CAT module with a partial correction of sphere and 75% correction of cylinder for a maximum depth of 50 µm was performed as in case 1, and topical riboflavin sodium phosphate 1% drops and UVA light were applied in the same manner with the same postoperative antibiotic and steroid drop regimen as the Athens Protocol.

The epithelium closed uneventfully within 5 days, and at 3 months postoperative, CDVA was 20/20 with a manifest refraction of -1.00 +0.75 × 125. Pentacam tomography revealed a maximum steep K reading of 45.70 D (Fig 2B) and thinner apical corneal thickness, being reduced by 113 µm. The patient did not return for follow-up at 6, 12, or 18 months. At 21-month follow-up, examination revealed a stable UDVA of 20/20 with a manifest refraction of -0.25 +0.50 × 125 (20/20). Pentacam corneal tomography revealed a maximally steep K reading of 45.60 D (Fig 2C), with a nearly identical appearance to the map.
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taken 18 months earlier. This same appearance was once again seen at 30 months with a steep K reading of 45.70 D (Fig 2D) and CDVA of 20/15 and manifest refraction of −0.75 +0.75 × 125. The thinnest Pentacam corneal thickness was 387 µm at 21 months and 385 µm at 30 months, which was identical to the 385-µm reading taken at 3 months postoperative.

The fellow eye had a greater degree of myopia, −11.25 +1.25 × 82 (20/30), with a steepest inferior K reading of 57.00 D and a thinnest corneal thickness of 459 µm. This eye was previously treated with simultaneous topography-guided PRK and CXL in September 2006 (A.J.K.). On last examination at 3 years postoperative, refraction and CDVA were −5.50 D (20/25), and steepest K reading was reduced to 52.90 D centrally and thinnest corneal thickness was 363 µm.

**DISCUSSION**

Simultaneous topography-guided PRK and riboflavin/UVA CXL—the Athens Protocol—is a new combined therapy that takes into account both the irregular corneal shape and structural collagen weakening of progressive keratoconus. At the time of this writing, neither topographic-guided PRK nor riboflavin/UVA CXL have been approved for clinical use by the FDA, although each of these therapies is commonly used internationally. The success of each of these two modalities in the management of irregular corneal astigmatism and ectasia makes their combined clinical use worthy of consideration for progressive keratoconus. The combined use of both modalities during the same surgical setting has been reported recently. To properly evaluate the full merit of simultaneous therapy, one should first consider the pros and cons of one therapy without the other, as well as sequential CXL followed by topography-guided PRK, to access the validity of the simultaneous strategy.

First, the concept of riboflavin/UVA CXL for progressive keratoconus has become an internationally accepted therapy over the past 2 years with more than 1000 procedures being performed worldwide each month (personal communication, Michael Mrochen, PhD; February 16, 2008). Although the effectiveness of this therapy in halting the progression of keratoconus has been important in stabilizing the condition, it does not address the residual refractive error with marked irregular astigmatism. Many of these patients who were dependent on contact lenses prior to the therapy still require contact lens wear. Some, however, have become contact lens intolerant based on progressive steepening, and remain so after CXL therapy. Even if the therapy makes it possible to once again wear contact lenses, its investigational nature (especially within the US FDA clinical trial) makes it necessary for the patient to cease wearing contact lenses during the investigation, which for many patients is functionally unacceptable. The positive side of riboflavin/UVA CXL is the stability of progressive keratometric steepening, whereas the negative side is the lack of refractive rehabilitation, which fails to address the visual dysfunction of the disease.

Second, the irregular astigmatism of keratoconus, as with other highly aberrated eyes, can be effectively minimized with customized laser ablation procedures. Topography-guided PRK has been proposed as a reasonable intervention for symptomatic, highly aberrated corneas, including those with keratoconus. Although effective in regularizing the aberrated corneal shape, the structural weakening of this ectatic disease leaves the cornea vulnerable to progressive change and inadequately addresses the fundamental problem. Yet myopic astigmatic PRK and topography-guided PRK are still being proposed by some for cases of early keratoconus. Although correcting the irregularity of keratoconus with customized PRK is in itself functionally beneficial, the long-term progressive instability without CXL makes this therapy controversial at best.

Combining these two procedures sequentially offers a solution to both the structural weakening and irregular corneal shape. Riboflavin/UVA CXL followed at least 6 months later by topography-guided PRK has been proposed previously by one of the authors (A.J.K.), and has been successfully implemented in an unpublished study of 27 progressive keratoconic eyes. In this evaluation, 22 of the 27 eyes experienced a mean improvement of 2.00 D in the steepest K and 2.40 D of the spherical equivalent refraction at 6 months after CXL. One year following topography-guided PRK with MMC as a second step further revealed a reduction of the overall mean spherical equivalent refraction by another 6.40 D and the steepest K from a mean of 54.00 to 47.00 D. These refractive changes were met by a mean reduction in UDVA from 20/400 to 20/60 and CDVA from 20/100 to 20/40. Although impressive, some of these sequentially treated eyes also had a mild to moderate amount of corneal haze, which was not observed in the two patients reported herein, or in the larger series of simultaneously treated eyes reported by Kanellopoulos. With simultaneous topography-guided PRK and CXL, the initial step of epithelial removal is utilized by both PRK and CXL, making the simultaneous process more efficient and less traumatic. Overall, the concept of both strengthening and reshaping the cornea in keratoconus is a revolutionary idea that appears to work well in corneas that are not too steep or too thin. In our second case, with a steepest K reading of 53.10 D
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and thinnest pachymetric reading of 496 µm, moderate myopia and astigmatism were fully corrected with the modified T-CAT laser settings, in addition to the irregular astigmatism. Excellent stability in this example over 3 to 30 months demonstrates keratometry of 53.00 D and thinnest corneal thickness of 496 µm as being acceptable when considering simultaneous treatment. In our first case, with a steepest K reading of 59.70 D and thinnest pachymetric reading of 421 µm, the correction of both regular and irregular astigmatism was possible with the modified T-CAT laser settings, resulting in greater corneal symmetry and the fitting of a soft contact lens. However, the residual myopia at 3 months underwent a progressive reduction in magnitude over the next 27 months, demonstrating a lack of stability, even though the progression was desirable. Topographically, the improved corneal symmetry at 3 months gradually regressed to a pattern of inferior steepening, with the central keratometric values being reduced by ~8.00 D in magnitude, but the inferocentral keratometry being increased by ~4.50 D. This change together with the progressive increase in central corneal thickness of ~44 µm suggests a possible loss of CXL effect, yet with progressive reduction of central K reading and improvement in UDVA and CDVA.

The progressive reduction of keratometric power over time following corneal CXL is a poorly understood process, but has been documented in several studies. This likely explains the progressive re-stabilization process, but has been documented in several studies.1,8,16 This likely explains the progressive regression of keratoconus. These results are further validated by the larger comparative series of simultaneous versus sequential CXL with topography-guided PRK published previously. The detailed analysis of these two individuals and the longer follow-up have demonstrated a satisfactory outcome in both cases, making this therapy worthy of consideration in advancing keratoconus.

AUTHOR CONTRIBUTIONS

Study concept and design (R.R.K., A.J.K.); data collection (A.J.K.); analysis and interpretation of data (R.R.K., A.J.K.); drafting of the manuscript (R.R.K.); critical revision of the manuscript (A.J.K.); administrative, technical, or material support (A.J.K.); supervision (R.R.K.)

REFERENCES

Management of Corneal Ectasia After LASIK With Combined, Same-day, Topography-guided Partial Transepithelial PRK and Collagen Cross-linking: The Athens Protocol

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ABSTRACT

PURPOSE: To evaluate a series of patients with corneal ectasia after LASIK that underwent the Athens Protocol: combined topography-guided photorefractive keratectomy (PRK) to reduce or eliminate induced myopia and astigmatism followed by sequential, same-day ultraviolet A (UVA) corneal collagen cross-linking (CXL).

METHODS: Thirty-two consecutive corneal ectasia cases underwent transepithelial PRK (WaveLight ALLEGRETTO) immediately followed by CXL (3 mW/cm²) for 30 minutes using 0.1% topical riboflavin sodium phosphate. Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction spherical equivalent, keratometry, central ultrasonic pachymetry, corneal tomography (Oculus Pentacam), and endothelial cell counts were analyzed. Mean follow-up was 27 months (range: 6 to 59 months).

RESULTS: Twenty-seven of 32 eyes had an improvement in UDVA and CDVA of 20/45 or better (2.25 logMAR) at last follow-up. Four eyes showed some topographic improvement but no improvement in CDVA. One of the treated eyes required a subsequent penetrating keratoplasty. Corneal haze grade 2 was present in 2 eyes.

CONCLUSIONS: Same-day, combined topography-guided PRK and CXL appeared to offer tomographic stability, even after long-term follow-up. Only 2 of 32 eyes had corneal ectasia progression after the intervention. Seventeen of 32 eyes appeared to have improvement in UDVA and CDVA with follow-up >1.5 years. This technique may offer an alternative in the management of iatrogenic corneal ectasia. [J Refract Surg. 2010;xx(x):xxx-xxx.] doi:10.3928/1081597X-20101105-01

Progressive, asymmetrical corneal steepening associated with an increase in myopic and astigmatic refractive errors, combined with midperipheral and/or peripheral corneal thinning, represents a constellation of findings in ectatic corneal disorders, such as keratoconus and pellucid marginal degeneration. Asymmetry in presentation and unpredictability of progression associated with a myriad of abnormal topographic findings describe these entities. Similar findings following LASIK have been described as corneal ectasia. Analysis of different series of eyes developing corneal ectasia after LASIK has suggested that certain preoperative and/or operative features may be associated with this adverse outcome of LASIK or photorefractive keratectomy (PRK). The fact that corneal ectasia can occur in the absence of these features, or that it does not occur despite the presence of these features, has confounded our understanding of this entity. Nevertheless, corneal ectasia after LASIK is a visually disabling complication with an ultimate surgical treatment of penetrating keratoplasty when spectacles or contact lenses can no longer provide patients with the quality of vision to permit activities of daily living.

Over the past 10 years, the use of topical riboflavin combined with ultraviolet A (UVA) irradiation to increase collagen cross-linking (CXL) has demonstrated the potential for retarding or eliminating the progression of keratoconus and corneal ectasia after LASIK. We have previously reported the application of CXL in corneal ectasia after LASIK. Once the
progression has stabilized, it is possible to treat the
surface of the eye with customized PRK to normalize
the corneal surface by reducing irregular astigmatism
and potentially reducing the refractive error as well
as providing improved visual outcomes in addition to
stabilizing the disease process. We have subsequently
introduced the combined, same-day use of these two
intervention modalities in the management of kerato-
conus.8–11

We present a series of patients with corneal ectasia
after LASIK who have undergone combined, same-day
topography-guided PRK and subsequent UVA colla-
gen CXL to achieve stabilization of corneal ectasia and
enhance visual rehabilitation.

**PATIENTS AND METHODS**

**PATIENT SELECTION**

Patients entered into this study were seen by one
of the authors (A.J.K.) in his private practice, either
through individual patient referral, referral from other
eye care practitioners, or were his own patients. Once a
diagnosis of corneal ectasia after LASIK was confirmed
(see below), patients were presented with the options
of contact lens fitting, intracorneal ring segment im-
plantation, or, in advanced cases, penetrating kerato-
plasty. If these modalities did not serve the needs of
the patient, he/she was then presented with the option
of undergoing topography-guided PRK and UVA colla-
gen CXL as a possible technique to prolong or prevent
the need for penetrating keratoplasty. Patients provided
verbal and written consent prior to undergoing the
combined topography-guided PRK/CXL procedure.

A diagnosis of corneal ectasia was made when patients
developed progressive corneal steepening associated
with an increasing myopic and/or astigma-

tic refractive error 2 or more months after LASIK
surgery. These findings were combined with increas-
ing inferior corneal steepening and thinning based on
video keratography and ultrasound pachymetry. Preop-
erative LASIK clinical data and topography were re-
quested from the referring physician or primary LASIK
surgeon for analysis. Progression of the myopic refrac-
tive error with or without progression of the manifest
astigmatism, decreasing uncorrected distance visual
acuity (UDVA), loss of corrected distance visual acu-
ity (CDVA), progressive inferior corneal steepening on
topography, and/or decreasing inferior corneal thick-
ness were findings in all cases.

**CLINICAL EXAMINATION**

Each patient underwent manifest refraction as well
as measurement of UDVA and CDVA, which was re-
corded in a 20-foot lane using high-contrast Snellen
visual acuity testing. Cycloplegic refractions were
performed using 1% tropicamide solution (Alcon
Laboratories Inc, Fort Worth, Texas). Slit-lamp micros-
copy confirmed the presence of a LASIK fl ap. Kerato-
tomy readings were obtained by videokeratography
(Topolyzer; WaveLight AG, Erlangen, Germany) and/or
manual keratometry (model 71-21-35; Bausch & Lomb,
Rochester, New York). Pachymetry was performed us-
ing at least one of the following devices/instruments:
Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany),
Orbscan II (Bausch & Lomb), or EchoScan US-1800
(NIDEK Co Ltd, Gamagori, Japan). Specular microscopy
was performed using the Konan specular microscope
(Konan Medical, Boston, Massachusetts). Topography
was performed using the Orbscan II or Pentacam.

**SURGICAL TECHNIQUE—THE ATHENS PROTOCOL**

We have reported this technique in the management
of keratoconus.8–11

**Step 1. The (Partial, Spherically Corrected)**

Topography-guided Transepithelial PRK Technique.

We devised this technique based on the proprietary
WaveLight customized platform. As noted above, we
previously described the use of the topography-guided
platform with this device to normalize irregular cor-
neas as well as corneal ectasia.

This customized excimer laser treatment is guided
by topographic images and is different from wavefront-
guided treatments. It received CE mark for clinical use
in the European Union in 2003; however, it has yet to
receive US Food and Drug Administration approval.

This proprietary software utilizes topographic data
from the linked topography device (Topolyzer). By
default, it permits the consideration of eight topogra-
phies (of predetermined threshold accuracy), averages
the data and enables the surgeon to adjust the desired
postoperative cornea asphericity (chosen as zero in all
cases), provides the option of including tilt correction
(no tilt was chosen in all cases), as well as the adjust-
ment of sphere, cylinder, axis, and treatment zone (opti-
cal zone of 5.5 mm was chosen in all cases). The image
of the planned surgery is generated by the laser software.

We used topography-guided PRK to normalize the
cornea by reducing irregular astigmatism while treat-
ing part of the refractive error. To remove the minimum
possible tissue, we decreased the effective optical zone
diameter to 5.5 mm in all cases (compared to our usual
treatment diameter of at least 6.5 mm in routine PRK
and LASIK). We also planned ~70% treatment of cyl-
inder and sphere (up to 70%) so as not to exceed 50 µm
in planned stromal removal. We chose the value of
50 µm as the maximum ablation depth effected, based
on our experience of treating irregular corneas with this platform.7-10

Following the placement of an aspirating lid speculum (Rumex, St Petersburg, Florida), a 6.5-mm, 50-µm phototherapeutic keratectomy (PTK) was performed to remove the corneal epithelium. Partial topography-guided PRK laser treatment was applied. A cellulose sponge soaked in mitomycin C (MMC) 0.02% solution was applied over the ablated tissue for 20 seconds followed by irrigation with 10 mL of chilled balanced salt solution.

Step 2. Collagen CXL Procedure. For the next 10 minutes, the proprietary 0.1% riboflavin sodium phosphate ophthalmic solution (Priavision, Menlo Park, California) was applied topically every 2 minutes. The solution appeared to “soak” into the corneal stroma rapidly, as it was centrally devoid of Bowman layer. Following the initial riboflavin administration, 4 diodes emitting UVA light of mean 370-nm wavelength (range: 368 to 375 nm) and 3 mW/cm² radiance at 2.5 cm were projected onto the surface of the cornea for 30 minutes (Keracure prototype device, Priavision). The Keracure device, which has a built-in beeper, alerts clinicians every 2 minutes during the 30-minute treatment to install the riboflavin solution in a timely fashion. A bandage contact lens was placed on the cornea at the completion of the combined procedures.

Postoperatively, topical ofloxacin (Ocufl ox 0.3%; Allergan Inc, Irvine, California) was used four times a day for the first 10 days and prednisolone acetate 1% (Pred Forte, Allergan Inc) was used four times a day for 60 days. Protection from all natural light with sunglasses was encouraged, with administration of oral 1000 mg Vitamin C daily for 60 days postoperative. The bandage contact lens was removed at or around day 5 following complete re-epithelialization.

EVALUATION

The following evaluations were completed before and after both treatments: age, sex, UDVA, CDVA, refraction, keratometry, tomography, pachymetry, endothelial cell count, corneal haze on a scale of 0 to 4: (0=clear cornea, 1=mild haze, 2=moderate haze, 3=severe haze, and 4=reticular haze [obstructing iris anatomy]), and corneal ectasia stability as defined by stability in mean keratometry and tomography.

CASE REPORTS

CASE 1

A 39-year-old man had undergone LASIK in May 2004 at another institution. At that time, according to patient history, UDVA was counting fingers in both eyes. Manifest refraction was $-6.50 - 0.50 \times 020$ (20/20) in the right eye and $-6.00 - 0.50 \times 165$ (20/20) in the left eye. Preoperative keratometry and corneal thickness readings were not available. No surgical data were available. The patient achieved UDVA of 20/20 in each eye, and reportedly plano refraction in both. In October 2005, he complained of progressively decreasing vision in both eyes. At that time, UDVA was 20/50 in the right eye and 20/40 in the left eye and he was told that “astigmatism was developing.”

The patient presented in March 2006, 26 months after LASIK, with a manifest refraction of $+2.25 - 1.75 \times 090$ (20/20) in the right eye and $-1.25 - 0.75 \times 010$ (20/20) in the left eye. Uncorrected distance visual acuity was 20/40 in the right eye and 20/30 in the left eye. Keratometry was 38.75@690/35.62@180 in the right eye and 40.65@05/39.55@95 in the left eye. Central corneal thickness (measured with Pentacam and ultrasound) was 495 µm in the right eye and 505 µm in the left eye, respectively. A diagnosis of bilateral corneal ectasia was made.

Because of the decrease in UDVA and the presence of corneal ectasia, the patient was informed of the risks, benefits, and alternatives of the combined topography-guided PRK/CXL technique. This procedure was performed on both eyes in January 2007, 32 months after LASIK. Based on the clinical manifest refraction of right ($+2.25 - 1.75 \times 90$ [20/20]) and left ($-1.25 - 0.50 \times 005$ [20/20]) eyes, the attempted correction was reduced to $+1.75 - 1.50 \times 90$ and $-0.75 - 0.50 \times 005$ for the right and left eyes, respectively. (The goal in the treatment was modified to anticipate the possible long-term flattening effect that CXL may have on these corneas.)

In February 2010, 37 months after topography-guided PRK/CXL, UDVA improved to 20/40 in the right eye and 20/20 in the left eye with a manifest refraction of $-0.75$ (20/20) in the right eye and $+0.25 - 0.25 \times 95$ (20/20) in the left eye. Keratometry was 37.50@85/36.62@175 in the right eye and 37.75@79/37.87@169 in the left eye. Ultrasound pachymetry was 440 µm and 414 µm in the right and left eyes, respectively. Figure 1 demonstrates the pre- and postoperative topographies of the right eye as well as the difference map after treatment with the Athens Protocol.

CASE 2

A 33-year-old woman reportedly had a manifest refraction of $-4.00 - 2.50 \times 90$ (20/20) in the right eye and $-1.50 - 2.00 \times 100$ (20/20) in the left eye. No other preoperative data were available. The patient had a history of eye rubbing.

Sometime in 2002, the patient underwent bilateral...
LASIK (the exact date is unknown and the surgical data were unavailable). Initially, the patient recovered excellent UDVA, but in December 2005, approximately 3 years postoperatively, she presented with slowly decreasing vision in both eyes. At that time, UDVA was 20/800 in each eye. Manifest refraction was −10.50 −6.00 × 105 (20/40) in the right eye and −7.75 −2.50 × 110 (20/30) in the left eye. Central corneal thickness measured by ultrasound was 395 µm in the right eye and 410 µm in the left eye. Keratometry was 52.87@103/46.12@13 in the right eye and 47.12@111/45.00@021 in the left eye. Corneal topography revealed bilateral corneal ectasia after LASIK, which was more pronounced in the right eye.

On December 19, 2005, >3 years after LASIK, the patient underwent topography-guided PRK/CXL in the right eye only, with no treatment in the left eye. At this time, manifest refraction was −10.50 −6.00 × 105 (20/30) in the right eye and −7.75 −4.50 × 130 (20/40) in the left eye. In June 2007, 18 months after topography-guided PRK/CXL, UDVA was 20/800 in each eye. Manifest refraction in the treated right eye had worsened to −12.00 −2.50 × 100 (20/40). Keratometry was 48.00@29/47.3@119 in the right eye and 47.87@20/46.20@110 in the left eye, and ultrasound pachymetry was 424 µm in the right eye and 388 µm in the left eye. Corneal topography revealed flattening in the difference map in the right eye (Fig 2). The patient was unhappy with this result and is currently uncomfortable with her anisometropia. She decided not to proceed with treatment in the fellow eye because she was unconvinced she had benefited from the topography-guided PRK/CXL procedure. She is currently wearing rigid gas permeable contact lenses in both eyes.

**CASE 3**

A 26-year-old male helicopter pilot underwent LASIK in both eyes in June 2004. No operative data were available. The only data available from the initial LASIK procedure was that he had “about” −3.00 diopters (D) of myopia in both eyes prior to LASIK. Uncorrected distance visual acuity during the initial 2 years after LASIK was “good” but then deteriorated in his right eye. He was subsequently diagnosed with corneal...
ectasia and was offered Intacs (Addition Technology Inc, Des Plaines, Illinois) or a corneal transplant.

He presented to our institution in September 2007, 3 years after LASIK. Uncorrected distance visual acuity was 20/40 the right eye and 20/15 in the left eye. Manifest refraction was +1.50 – 2.00 × 65 (20/20) in the right eye and plano (20/15) in the left eye. Kera-
tometry was 41.62@65/43.62@155 in the right eye and 41.75/42.12@10 in the left eye. Central ultrasound pachymetry was 476 µm in the right eye and 490 µm in the left eye.

On September 13, 2007, 39 months after LASIK,
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Combined topography-guided PRK and immediate CXL was performed in the right eye for +0.50 –1.50 × 60. The planned laser resection was 35 µm. Prior to treatment, manifest refraction was +1.50 –2.00 × 65; we reduced the attempted sphere and cylinder, anticipating a subsequent flattening effect of the sequential CXL procedure. Within 6 months, UDVA improved to 20/25 and 24 months later in September 2009, UDVA improved to 20/15 and the manifest refraction improved to plano +0.25 (20/10). Keratometry in the right eye was 43.00@97/43.25@07 and ultrasound pachymetry was 441 µm. The difference maps (Pentacam) before topography-guided PRK/CXL and 2 years postoperative are shown in Figure 3. At 3-year follow-up, UDVA remains at 20/10.

As a result of the improvement and stability in visual function, this patient has joined the United States Air Force as a fighter pilot and is currently serving in active duty.

**CASE 4**

A 32-year-old woman underwent LASIK in both eyes in December 2006 for a refractive error of −3.75 D in the right eye and −4.00 D in the left eye. No other data were available in regard to the surgery. Her vision was good for 2 years and then started to deteriorate. The treating surgeon made the diagnosis of corneal ectasia after LASIK in December 2008.

The patient presented to our institution in January 2009. Uncorrected distance visual acuity was 20/100 in the right eye and 20/20 × 2 in the left eye. Corrected distance visual acuity was 20/30 with manifest refraction of −3.25 −3.25 × 45 in the right eye and 20/15 with +0.50 −1.25 × 100 in the left eye. Keratometry was 46.7@156/44.1@66 and 39.75@155/41.75@65 in the right and left eyes, respectively. Pachymetry readings were 419 µm and 460 µm in the right and left eyes, respectively. The diagnosis of corneal ectasia after LASIK was confirmed by Pentacam in the right eye (Fig 4, left image). The patient was contact lens–intolerant and opted to undergo topography-guided PRK/CXL despite the informed consent that the estimated residual corneal thickness would be 360 µm. This procedure was performed in February 2009 in the right eye.

The planned correction was −2.50 −2.50 × 45 after 6-mm diameter, 50-µm depth PTK. After ablation, 0.02% MMC in a moistened weck-cell sponge was used on the stroma for 20 seconds. In January 2010 (11 months...
following treatment), UDVA was 20/30, CDVA was 20/20§ with manifest refraction of −0.50 −0.75 × 141. Keratometry was 43.3 and 42.7°103. Central corneal thickness was 330 µm. The pre- and postoperative difference map is shown in Figure 4. Endothelial cell count was unchanged at 20 months (2600 from 2650 prior to application of the Athen’s protocol).

Optical coherence tomography (OCT) of the central cornea in the right eye at 11 months postoperative shows hyper-reflectivity of the anterior 2/3 of the cornea (Fig 5) demonstrating the CXL effect, which we reported previously when applying similar treatment in cases of keratoconus.10,11 The hyper-reflective demarcation in the middle of the cornea in this case suggests a thick LASIK flap calculated to >200 µm by corneal OCT prior to application of the Athen’s protocol.

**SUMMARY OF ALL CASES**

A total of 32 eyes in 22 patients with corneal ectasia occurring 1 to 4 years after LASIK were treated. Preoperative LASIK data were not available in most cases. In the 5 patients who had available data, no irregularity on topography or tomography was noted and no other factor of the LASIK procedure was evaluated to be high risk (eg, thick flap, residual stromal bed <250 µm).

All patients had documented progression of inferior steepening in topography and/or tomography maps. Patient age ranged from 23 to 66 years (mean: 32 years) with gender divided (women:men=11:11). The mean measurements representing values after corneal ectasia were confirmed and preoperative to our technique were as follows. Mean sphere was −7.50 D and mean preoperative astigmatism was −2.40 D in the 32 eyes. Mean preoperative to the original LASIK central corneal thickness was ≥525 µm in 25 of 32 eyes. The original LASIK laser resection data were unavailable in 27 eyes, and flap thickness was assumed or calculated using corneal OCT (Optovue, Fremont, California). The mean residual stromal thickness was 285 µm (range: 210 to 355 µm). Of all 32 ectasia cases, 15 were thought to have resulted from thicker than planned flaps (mean residual stromal bed 230 µm), 10 showed signs of corneal irregularity on preoperative LASIK topography, and 7 had no recognizable risk factor for the development of corneal ectasia.

All topography-guided PRK procedures were planned to reduce corneal thickness by a maximum of 50 µm, despite the existing refractive error, to avoid exacerbation of the ectasia. Most patients (19 patients, 25 eyes) complained of significant pain the first postoperative night whereas others reported minimal discomfort. Mean follow-up after the procedure was 27 months.

Uncorrected distance visual acuity improved in 27 eyes, was unchanged in 4 eyes, and worsened in 1 eye; it was 20/30 or better (+0.18 logMAR) in 11 of 32 eyes and 20/60 or worse (+0.47 logMAR) in 2 eyes. Corrected distance visual acuity was 20/40 or better (+0.30 logMAR) in 27 of 32 eyes and 20/25 or better (+0.10 logMAR) in 14 eyes.

Mean refractive error decreased by more than 2.50 D in 27 of 32 eyes, appeared to increase by 0.75 D in 3 eyes, and remained stable in 2 eyes. Mean final spherical equivalent refraction was −1.75 D, indicating the reduction of corneal irregularity was the target and not emmetropia.

**DISCUSSION**

Topography-guided PRK flattens some of the cone apex (in a fashion similar to an eccentric partial myopic PRK) but simultaneously flattens an arcuate, broader area of the cornea away from the cone, usually in the superior nasal periphery; this ablation pattern (see Fig 3C) resembles part of a hyperopic treatment and thus will cause some amount of steepening or elevation adjacent to the cone, effectively normalizing the cornea.

We have introduced this concept as an effective tissue-sparing ablation pattern in highly irregular corneas such as ectasia in keratoconus.12 It is this core concept in the topography-guided PRK treatment that makes it, in our opinion, more therapeutic than refractive. We have reported7-10 that in theory, the new “flatter” and less irregular corneal shape may perform better biome-
chanically in eyes with corneal ectasia. Specifically, as the corneal apex becomes a flatter and “broader” cone (see Figs 3A and 3B), this may redistribute the biomechanical strain from the eye’s intraocular pressure and other external factors (eg, eye rubbing, blinking, etc). This effect may be further enhanced with additional collagen CXL strengthening.

Same-day simultaneous topography-guided PRK and CXL has several advantages: 1) the combination reduces the patient’s time away from work, 2) performing both procedures at the same time with topography-guided PRK appears to minimize the potential superficial stromal scarring resulting from topography-guided PRK (unpublished observations, December 2005), and 3) when topography-guided PRK is performed following the CXL procedure, some of the cross-linked anterior cornea is removed, minimizing the potential benefit of CXL (unpublished observations, December 2005). We believe it may be counterintuitive to remove the cross-linked tissue with topography-guided PRK at a later time, as we are potentially removing a beneficial layer of the stiffer, cross-linked cornea, which helps maintain the normalized corneal shape. Lastly, 4) by removing the Bowman layer with topography-guided PRK, this may facilitate riboflavin solution penetration in the corneal stroma and less “shielding” of UVA light in its passage through the cornea, resulting in more effective CXL.

Although a patient with corneal ectasia can have an improved visual result with the addition of the topography-guided PRK, completely removing significant refractive errors was not our goal. We have placed an arbitrary “ceiling” of 50 µm to the amount of tissue that we safely removed centrally, anticipating that further thinning might destabilize the cornea’s biomechanical integrity, even following the “stiffening” effect of CXL.

It should be noted that the proprietary riboflavin solution used was a slightly hypotonic (340 mOsm) formulation, resulting in slight “swelling” of the cornea intraoperatively (during CXL). This restored the corneal thickness to approximately 400 µm during CXL to protect the corneal endothelium; we did not encounter any corneal endothelial decompensation in any of the eyes studied herein despite treating cases with corneal thickness less than the theoretical limit of 400 µm before CXL (case 4).

In addition, the laser treatment was applied with caution, as the refractive effect of CXL (corneal flattening) had to be anticipated. For this reason, we elected to always attempt a significant undercorrection of both sphere and cylinder by at least 30%. At a later time, we hope to more accurately determine the new ablation rate of CXL stroma.

Simultaneous topography-guided PRK and CXL appears to be effective in the rehabilitation of corneal ectasia after LASIK. The reality of the efficacy of this treatment has been the reduction of penetrating keratoplasty cases performed for the indication of keratoconus and corneal ectasia after LASIK in our practice over the past 4 years. The same-day, simultaneous topography-guided PRK and CXL procedure was easy to perform, but in some cases, the central epithelial surface took up to 1 month to regularize and become lucent. It took from 1 to 4 weeks for us to detect stable changes in keratometry and topography, which seemed to match the visual and refractive changes.

The main goal for all refractive surgeons is to try to eliminate or at least significantly reduce the number of eyes developing corneal ectasia after PRK and LASIK. In some eyes, a pre-existing condition that may lead to corneal ectasia with either PRK or LASIK may not be able to be detected, but by eliminating eyes with abnormal preoperative topography and leaving corneas with the maximum clinically acceptable residual stromal thickness, we will be able to reduce the number of eyes that develop corneal ectasia.

Our findings suggest potentially promising results with same-day, simultaneous topography-guided PRK and collagen CXL as a therapeutic intervention in highly irregular corneas with progressive corneal ectasia after LASIK. We have reported herein effective CXL treatment in cases with minimal corneal thickness <350 µm. Our study demonstrates that we now have another means of improving the visual and refractive results of a devastating complication while avoiding or delaying penetrating keratoplasty.

**AUTHOR CONTRIBUTIONS**

Study concept and design (A.J.K.); data collection (A.J.K., P.S.B.); analysis and interpretation of data (A.J.K., P.S.B.); drafting of the manuscript (A.J.K., P.S.B.); critical revision of the manuscript (A.J.K., P.S.B.); administrative, technical, or material support (A.J.K., P.S.B.); supervision (A.J.K.)

**REFERENCES**


INTRODUCTION

The different modalities of epithelium on, epithelium off, epithelium on with special agents in the riboflavin solution to dissolve hemidesmosomes and potentially increase and enhance riboflavin solution penetration to the corneal stroma, as well as the amount of cross linking that is achieved with any and all of the above techniques, as well as the newly described techniques, such as the Athens Protocol (where a partial topography-guided PRK is combined with collagen cross-linking), combining CXL with Intracorneal rings (combined, before, after?).

We have seen several breakout sessions in these last few year's meetings (ESCRS, ISRS, AAO, ASCRS), on heated discussions of several “hot” issues: Are cross-linking too much of corneal tissue in order to treat ectasia?, can we “focus” on cross-linking a certain area of the cornea?, a certain thickness of the cornea?, at a certain level of the cornea?, and whether newer applications of collagen cross-linking will be able to increase safety and the potential disadvantages of the classic technique of collagen cross-linking described over ten years ago?.

All these very interesting subjects, as well as potential means of assessing quantitatively and qualitatively, collagen cross-linking within corneal tissue will be discussed in this special session.
It has been over ten years that the University of Dresden started experimenting with collagen cross-linking, as a means of increasing corneal rigidity and potentially treating ectasia, such as keratoconus and post refractive surgery ectasia, mainly post-LASIK ectasia.

Becoming involved with CXL in 2002 in Greece, an endemic area for KCNa and ...ectasia, we have seen this procedure spread in dramatic numbers internationally, especially after the 2006 CE mark approval.

The procedure is currently in several FDA trials, and in several investigative device exception (IDE) trials in the US. Several US colleagues will join us in this special collagen cross-linking session with fresh experiences! It has been almost alongside with CXL, that over the last decade, tremendous technology dedicated to corneal imaging (Cornea topography and tomography, OCT, confocal microscopy etc) that can elucidate or “confuse” us more in regard to early diagnosis and criteria for suspicious cases for ectasia or keratoconus.

So, it has been my goal for this meeting, to bring together some of the expert minds in corneal refractive surgery and keratoconus ectasia management, from all over the world, at the American Academy meeting in Chicago, Illinois. The ISRS was been gracious to host this special collagen cross-linking session.

It will start at 6:30 in the morning on Friday, October the 15th, to precede the subspecialty day of refractive surgery of Friday and Saturday, October 15th and 16th respectively.

The areas that are quite interesting to discuss within this session, are:

1- Innovations in collagen cross-linking, (several manufacturers and investigators with new technologies are invited to present new modalities and new techniques), as well as

2- Presentations by clinicians on complications encountered and potential combinations of these techniques with other technologies and techniques.
I think that one of the fruitful areas of discussion would be to share and discuss, and debate maybe:

3- Updated Definitions for keratoconus, Forme Fruste keratoconus, Pellucid Marginal Degeneration; how do we define ectasia in 2010, in means and modes that we can help our colleagues that perform refractive surgery through the world, to avoid treating cases of ectasia or be aware of early signs of ectasia, and when to intervene if a case that has had refractive surgery is starting to develop worrisome signs of corneal change.

We will therefore devise a schedule that will include:

a) Presentation of new technologies of collagen cross-linking scheduled from 6:30 am – 7:00 am. These will be five-minute presentations (presentation time will be strictly enforced in order to allow several speakers to present within these 30 minutes, at least six different new cross-linking modalities or combination modalities).

b) From 7:00 to 7:30 we will try and define the main four entities that I described before: 1) Forme Fruste keratoconus, 2) Clinical keratoconus, 3) Pellucid Marginal Degeneration, and 4) what do we consider today, in 2010, progressive ectasia in any of the above cases.

c) And last, from 7:30 – 8:00, the floor will be open for discussion of any of the above issues, comment on potential complications that fellow clinicians have encountered and their suggestion for management, as well as comments for a new form of collagen cross linking and all the satellite entities involved with that.

It will be my pleasure to chair this meeting and I am very excited in seeing everyone of you. I have invited, and I am very happy to announce to everyone Professor Seiler, has accepted to be my co-chair in this special session. I nevertheless think that all of YOU, will enhance the scientific level and the scientific argument and discussion that we will put together.

I hope for this session to be of informal form and everyone can be heard through their questions.
I look forward to this session and the participation of all of you.

Sincerely,
John

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