Stability of Simultaneous Topography-guided Photorefractive Keratectomy and Riboflavin/UVA Cross-linking for Progressive Keratoconus: Case Reports

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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/cm^2 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 keratoectasia 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.]

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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.[1] 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.[2]

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.[3,4] 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.[5-7] 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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izing the cornea and strengthening the weakened collagen of keratoconus over time.

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 ALLEGRETTO 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 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" 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/cm^2 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 (Ocuflox 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=reticular 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 $-14.00 +3.50 \times 80$ 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

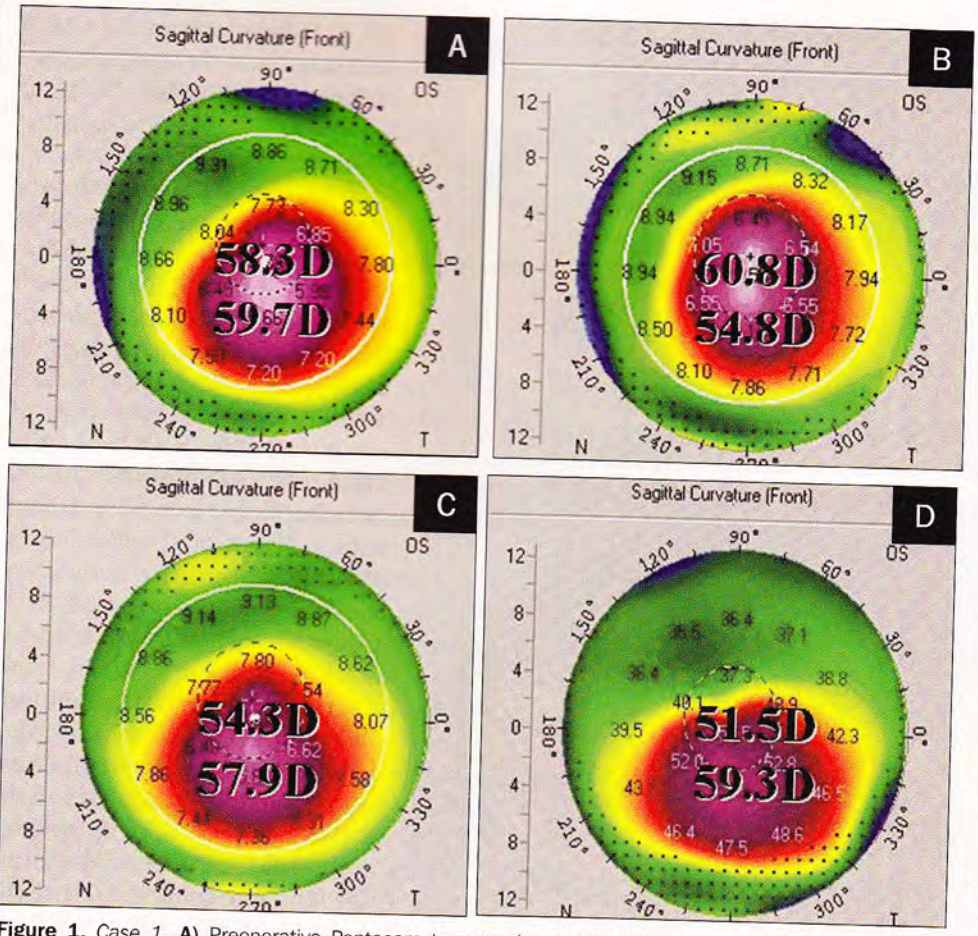

Figure 1. *Case 1.* **A)** Preoperative Pentacam tomography reveals inferocentral steep cone (maximum keratometry [K] 59.70 D) (refraction: −14.00 −3.50 × 80; corrected distance visual acuity [CDVA]: 20/50). **B)** Three months following simultaneous topography-guided photorefractive keratectomy and 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).

(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 (20/30), 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 cor-

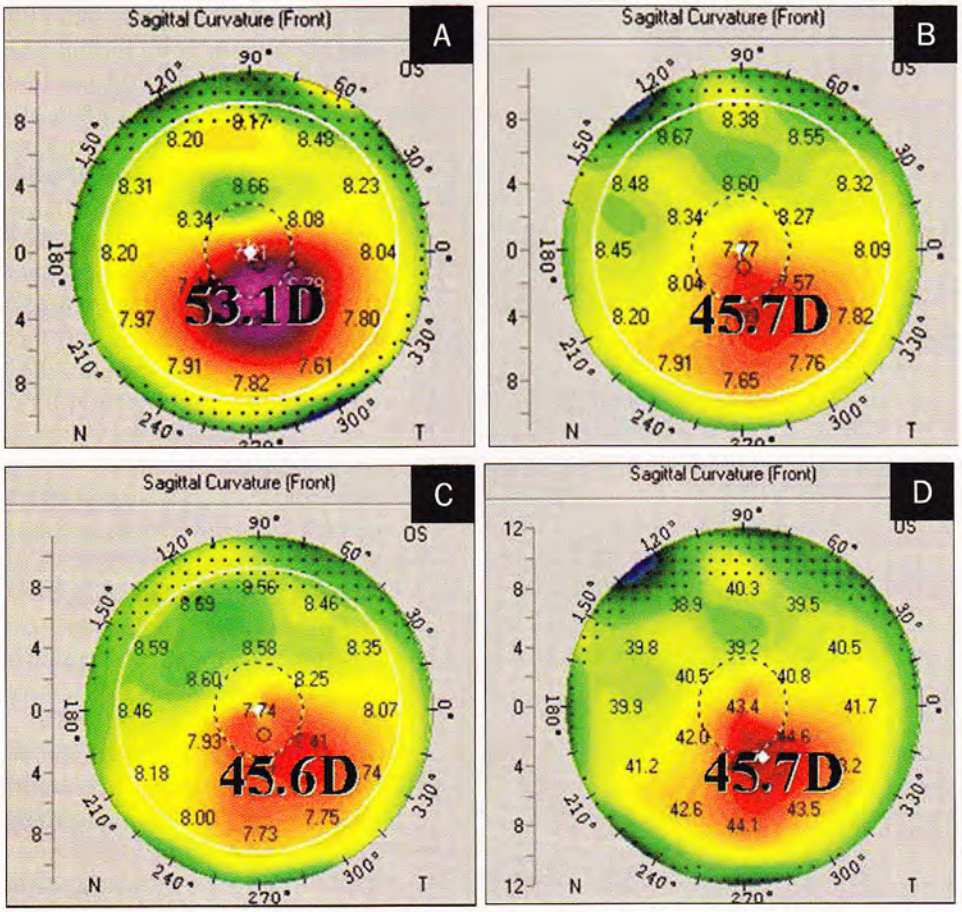

Figure 2. *Case 2.* **A)** Preoperative Pentacam tomography reveals inferocentral steep cone (maximum keratometry [K] 53.10 D) (refraction: −6.00 −1.50 × 90; corrected distance visual acuity [CDVA]: 20/30). **B)** Three months following simultaneous topography-guided photorefractive keratectomy and riboflavin/ultraviolet A cross-linking, the tomography reveals greater symmetry and reduced steepness of corneal shape (maximum K 45.70 D) (refraction: −1.00 +0.75 × 124; CDVA: 20/20). **C)** At 21 months postoperative, the keratometric power and shape is stable (maximum K 45.60 D) (refraction: −0.25 +0.50 × 125; CDVA: 20/20). **D)** Keratometric power and shape remain unchanged at 30 months postoperative (refraction: −0.75 +0.75 × 125; CDVA: 20/15).

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 −4.00 +4.00 × 140 (20/30), steepest K reading of 51.20 D inferiorly and 47.60 D centrally, and thinnest corneal thickness of 461 µm. The eye was treated 3 months after the first eye with only CXL (A.J.K.). Now, 3 years later, manifest refraction is −3.25 +1.50 × 175 (20/20) with a steepest K of 52.10 D inferiorly and 44.80 D centrally, and thinnest corneal thickness of 469 µm.

Case 2

A 21-year-old man with progressive keratoconus was also recruited for sequential therapy using the Athens Protocol prior to corneal transplantation. Uncorrected distance visual acuity was 20/200 and, with a manifest refraction of −6.00 +1.50 × 90 in the right eye, CDVA was 20/30. 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 by the first author (R.R.K.). The modified T-CAT laser setting was −2.25 −1.50 × 80 (the topography calculated a refraction of −1.00 −3.00 × 80) for a maximum depth of 48 µm. Photorefractive keratectomy 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 × 124. 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

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.[13] 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.[6,7] 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.),[8] and has been successfully implemented in an unpublished study of 27 progressive keratoconic eyes.[14,15] 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.[13]

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

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.[1,8,16] This likely explains the progressive reduction of corneal power and myopic refraction in our first case, although the relative inferocentral steepening at 19 and 30 months suggests the degree of CDVA improvement may not have been enough. Despite the keratometric findings, the visual outcome of this patient was more than satisfactory.

Simultaneous topography-guided PRK using the T-CAT module of the ALLEGRETTO WAVE Eye-Q excimer laser with corneal CXL appears to be an acceptable alternative for the management of progressive keratoconus. These results are further validated by the larger comparative series of simultaneous versus sequential CXL with topography-guided PRK published previously.[13] 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.)

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