

Riboflavin Ultraviolet Crosslinking With Topography-Based PRK

An update on this experimental treatment for ectasia.

BY A. JOHN KANELLOPOULOS, MD

Corneal ectasia has been a serious anterior segment problem for several years. As ophthalmic surgeons, we have managed this pathological issue with techniques such as penetrating keratoplasty (PKP), epikeratophakia, and Intacs (Addition Technology, Inc., Des Plaines, IL) after the use of contact lenses has failed.

Collagen cross-linking utilizing riboflavin and ultraviolet light is a new modality that has been shown in laboratory and preliminary human studies to change the cornea's biomechanical properties and to help in the stabilization of keratoconus and ectasia following refractive surgery.

CASE REPORT

A 29-year-old male underwent unioocular LASIK in his eye 6 years ago. He presented to my clinic with few details about his medical history. The UCVA in his treated eye was 20/80, and his BSCVA was 20/20 with a refraction of -2.00 -1.75 @ 85° prior to his LASIK procedure. The patient was initially pleased with his visual outcome, but his visual acuity deteriorated over the ensuing months. The original surgeon diagnosed ectasia and implanted Intacs in the eye that underwent LASIK. The procedure failed to improve the patient's vision, and he developed severe nighttime halos. The original surgeon recommended PKP.

At this point, the patient consulted me for a second opinion. Eleven months had elapsed since his original LASIK procedure, and 3 months had passed after the implantation of Intacs (Figure 1).

Corneal topography measured a central corneal thickness of 410 μm , and the endothelial cell count was 2,750 cells per mm^2 . I discussed with the patient my poor long-term experience with Intacs in cases of post-LASIK ectasia. I had been using Intacs to treat keratoconus for more than 10 years, and my patients were thrilled with the change in their visual function. I had found, however, that keratoconic corneas were much "softer" than normal ones in their long-term stability with Intacs. More than half of the segments migrated through the cornea and surfaced.¹ I had been forced to remove some segments because of the risk of infection.

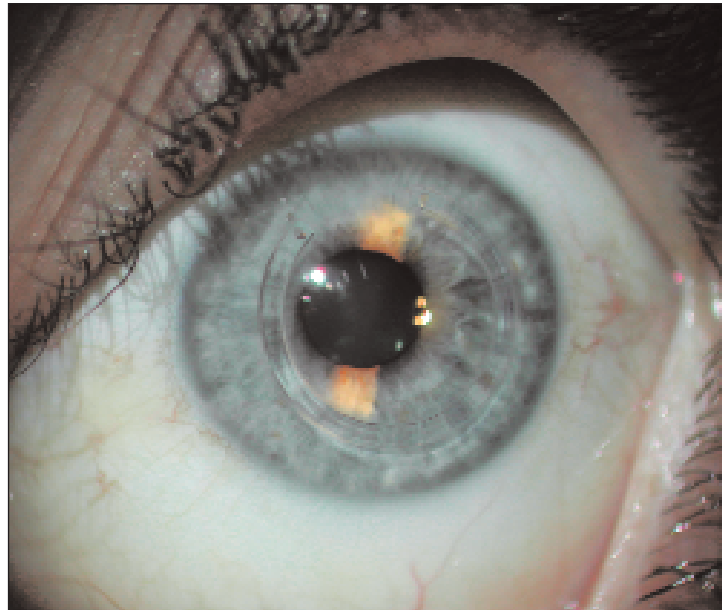


Figure 1. A clinical picture of the cornea at the first consultation after implantation of Intacs.

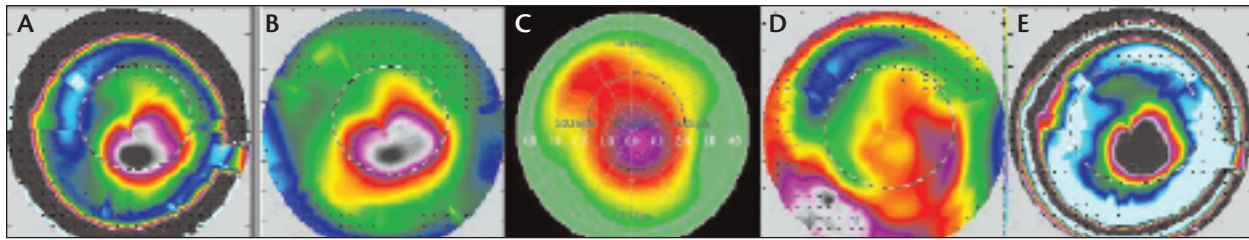
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Figure 2. Corneal topography showed central corneal ectasia and midperipheral flattening as an effect from Intacs. BSCVA was 20/200 (A). The corneal topography 2 months following the removal of the Intacs and 1 month after UVA collagen cross-linking showed central steepening and the effect of the removal of Intacs is seen at the midperiphery. BSCVA was 20/200 (B). An estimated corneal topographic ablation pattern showed a laser treatment plan for a topography-guided procedure that took place in the case. Noteworthy is that this ablation pattern was highly irregular with a “deeper” ablation plan inferiorly and right to the center that matches the central corneal irregularity in the aforementioned topographies (C). The central cornea appeared more regular and much flatter 6 months following topography-guided PRK. At this point BSCVA and UCVA was 20/20- (D). The comparison map (E) depicts the difference of subtracting the corneal topography of D from the corneal topography of A. The difference resembles the topography-guided ablation pattern and demonstrated effectively the specificity of the treatment in reducing the pathogenic corneal irregularity, which the author theorized contributed to the drastic improvement in BSCVA.

Nevertheless, other studies have reported more favorable results.² I also informed the patient of combined ultraviolet radiation and riboflavin treatment in order to achieve collagen crosslinking (UVA CCL) and biomechanical stabilization of the ectasia.

CROSSLINKING TECHNIQUE AND PRK IN THE SAME PATIENT

Avoiding Corneal Transplantation

After becoming familiar with the crosslinking technique, I performed it on this post-LASIK patient who was scheduled for a corneal transplant. He had severe ectasia, and his vision could not be rehabilitated with contact lenses or Intacs. Not only did the crosslinking procedure freeze the ectasia for approximately a year, the process/procedure also appeared to reverse the pathologic condition somewhat.

A year after the crosslinking procedure, I performed a partial, topography-guided PRK with the Allegretto Wave topography-guided laser platform (Advanced Medical Optics, Inc., Santa Ana, CA). My goal was to decrease corneal abnormality and enhance the patient’s BSCVA. Rather than a straightforward PRK, the procedure combined myopic PRK over the apex of the cone with hyperopic PRK at the opposite side of the cornea. The mixed procedure flattened the ectatic portion of the cornea and steepened the flat part of the cornea. The technique removes little tissue centrally but smoothes the cornea. Four years postoperatively, the eye has a UCVA of 20/20.

Although one aim of topography-guided PRK can be treating refractive error, the real goal of the interven-

tion is to normalize the cornea as much as possible. Transforming a cornea with -4.00 D of irregular cylinder and a spherical equivalent of -4.00 D at the 70° axis into one with -3.50 D of cylinder and a spherical equivalent of -0.50 D is, in my opinion, a positive intervention. Postoperatively, the patient will be able to see nearly 20/20 with a -3.50 D soft contact lens or glasses. More importantly, in the case of crosslinking and topography-guided PRK, the patient may have avoided a corneal transplant.

Wavefront-Guided Technology

Some surgeons might argue that this customized treatment could be performed with wavefront-guided technology. I would agree when the ectasia is mild. In general, however, a wavefront-guided system attempts to ablate tissue until all of it is of equal elevation.³ In highly irregular ectatic corneas, that could mean removing more tissue, which is a concern despite the current lack of data on how much tissue should be reserved in these eyes.

Perfecting the Procedure

During the first years (2002 and 2004), my colleagues and I performed UVA CCL followed by topography-guided PRK. We crosslinked corneas first, and performed partial PRK as a secondary procedure later, when it was deemed necessary. Once it was clear that the combination was safe and effective, however, we decided to perform them at the same time and analyze our results.

Crosslinking occurs more vigorously in the surface layers of the cornea than the deep stroma. It therefore

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seemed reasonable to perform a partial PRK first, which would produce a more regular cornea.

In the last 3 years, my colleagues and I have treated 80% of our patients (more than 500 eyes) with this one-stop/two-part procedure, and only 10% of them may be potential candidates for a second enhancement. The preceding PRK facilitates the rapid diffusion of riboflavin solution in the exposed stroma.

We do not know how much tissue may be safely ablated in these eyes. We have settled on an arbitrary limit that seems to provide a sufficient margin of safety. The average keratoconic eye we treat has a stromal bed thickness of about 450 μm at the thinnest point; 50 μm is the maximum amount of tissue we remove centrally.

Special Considerations

A surprising effect of the crosslinking treatment has been that the corneal tissue reacts more strongly to laser ablation, so overcorrections are more likely than with virgin corneas. Performing PRK before UVA CCL negates this problem but raises a related one. How can we predict how much tissue to remove? I find this concern to be a nonissue, because the topography-guided ablation we have employed has been partial for both cylinder (up to 70% of refractive cylinder) and sphere.

Even when possible, regarding the cornea thickness standpoint, I have never treated for the full correction.

I have not regretted any of the crosslinking procedures we have performed, although we admittedly started in an uncharted territory, but a few patients have gone on to require a corneal graft nonetheless. In these cases, the ectasia was so advanced that UVA CCL did not work.

We achieved stabilization, but this alone was insufficient to restore normal visual function. A possible benefit of UVA CCL in these eyes, however, was that I feel it strengthened the host cornea, which may have increased the stability of the graft and decreased the amount of postoperative astigmatism.

WHAT'S NEXT?

UVA CCL, in my opinion, is the most impressive advance in corneal interventions since the excimer laser. In the future, the procedure may have applications for high myopes undergoing LASIK and for post-LASIK regression.

To prevent potential toxicity from UV light exposure in the presence of riboflavin requires a strict adherence to the established treatment parameters. As a transplant surgeon, I have happily seen my PKP cases for keratoconus drop by an impressive 80% during the

last 5 years. Most of my patients' vision has stabilized, and they are functioning satisfactorily.

Many questions, however, remain to be answered. What is the ideal fluence of ultraviolet light (my colleagues and I have introduced the fluence of 7nW/cm² for a 15 minute treatment, which we will present at this year's Annual AAO Meeting in Atlanta)? What is the best amount of riboflavin to use and at what corneal depth (we have introduced the intrastromal application of riboflavin solution via an IntraLase-created pocket⁴)? What is the correct duration of corneal ultraviolet light exposure?

Within the next few years and following the FDA approval of this technique, I believe that clinicians will move toward a more specific intracorneal application of riboflavin and utilize ultraviolet light of a higher fluence in a pulsed fashion. This process would theoretically attain the same crosslinking effect with less danger for host cytotoxicity. Our initially experimental, unpublished data support this.

Follow-up data for the procedure have been gathered out to 6 years at my center in Athens, Greece, and to 8 years by German researchers.^{5,6}

The procedure received CE Marking in December 2006, and it is currently in FDA trials. ■

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1. Kanellopoulos AJ, Pe LH, Perry HD, Donnenfeld ED. Modified intracorneal ring segment implantations (Intacs) for the management of moderate to advanced keratoconus: efficacy and complications. *Cornea*. 2006;25:29-33.
2. Kymopnisi GD, Tsiklis NS, Pallikaris AI, et al. Long-term follow-up of Intacs for post-LASIK corneal ectasia. *Ophthalmology*. 2006;113:1909-1917.
3. Kanellopoulos AJ, Pe LH. Wavefront-guided enhancements using the Wavelight Excimer Laser in symptomatic eyes previously treated with LASIK. *J Refract Surg*. 2006;22:345-349.
4. Kanellopoulos AJ. Cornea collagen crosslinking with IntraLase assisted intracorneal riboflavin administration. Paper presented at: The annual AAO Meeting: Refractive Surgery Subspecialty Day; November 10, 2007; New Orleans, LA.
5. Kanellopoulos AJ. Collagen cross-linking (CCL) with ultraviolet A light (UVA) and riboflavin in keratoconus, followed by customized topography-guided PRK. A case report of a temporizing alternative to penetrating keratoplasty. *Cornea*. 2007;26:891-895.
6. Hafezi F, Kanellopoulos AJ, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2007;33:2035-2040.