

# C3-Riboflavin Treatments: Where Did We Come From? Where Are We Now?

In this virtual roundtable, key leaders share their points of view on this revolutionary treatment for keratoconus.

## PARTICIPANTS



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**Pinelli:** Corneal collagen cross-linking with riboflavin (ie, C3-riboflavin) as a treatment for keratoconus is a topic that has been discussed quite often in the past 2 years. One substantial issue regarding C3-riboflavin seems to be the technique (ie, transepithelial treatment vs treatment with deepithelization). Recently, safety issues have been resolved.<sup>1</sup> In detail, the endothelium, lens, and retina are not involved in any potential or real damage after the treatment.

I would like to first thank our panel of surgeons for participating in this virtual roundtable. Let us start with the discussion now and find out just how long everyone has been involved in treating patients with C3-riboflavin. I will go first. In my practice, we have been performing C3-riboflavin treatments for keratoconus for 2 years. We have treated more than 100 corneas.

**Spörl:** In 1980, Troels T. Andreassen, MD, of Denmark, found a reduction in corneal stiffness among patients with keratoconus.<sup>2</sup> Many other investigations found keratoconic corneal changes in proteoglycans and cells, however, no one found a way to change this situation. In 1994, Theo Seiler, MD, PhD, the then-director of the University Eye Clinic in Dresden, Germany, and now of Zürich, Switzerland, began searching for methods to stiffen the cornea. Professor Seiler knew that dentists took advantage of the stiffening effect of UV in plastic materials, and he looked for a similar tactic for the treatment of keratoconus.

We tested several possibilities for cross-linking: aldehyde sugars, chemical cross-linkers, and irradiation. We tested the parameter in enucleated porcine eyes and in rabbit eyes. Then, in 1998 in Dresden, we treated the first patient with riboflavin and UVA. During follow-up, the patient experienced no side effects, and we started a pilot study with 23 eyes. I was responsible for the irradiation technique and for incorporating the correct treatment parameters. Now, more than 400 corneas have been cross-linked in Dresden.

**Trokel:** As an American clinician, I anxiously await US Food and Drug Administration (FDA) approval so that clinical studies may begin.

**Boxer Wachler:** I performed my first treatment 3.5 years ago.

**Ertan:** I have been performing this treatment for 6 months.

**Kanellopoulos:** I started using this modality 4 years ago to treat post-LASIK ectasia. So far, I have treated more than 200 cases (120 patients) and have presented

and published our results, which are encouraging.

**Pinelli:** What was your initial opinion of C3-riboflavin treatments, and what is your opinion now that you are using it?

**Trokel:** The entire concept of altering the macromolecular construction of the eye's collagen structure is a revolutionary alteration of our previous ideas about ocular structure. We had considered the collagen within the cornea and sclera to be an inert and unalterable structural element. This work with C3-riboflavin, as conceived by Professor Seiler, has revolutionized our entire way of thinking. We are now considering all the collagen elements of the eye as subject to biochemical manipulation for therapeutic purposes.

**C3-riboflavin makes contact lens-intolerant patients contact lens-tolerant patients who wear their lenses for longer periods during the day.**  
— Aylin Ertan, MD

**Ertan:** Before performing any C3-riboflavin treatments, I expected it to significantly improve both refraction and corneal topography. Talking about the first short-term results, the topographic improvement was not as impressive as I had expected. But, the change in visual acuity was far more than I had expected, and it was not parallel to changes in topographic variables. I must admit that I was surprised to observe such an improvement in visual acuity, especially after seeing the topographic change. This may be due to remodeling of the collagen fibers following C3-riboflavin treatment, which provides clear vision but has little effect on topography and refraction. This contrasts with Intacs (Addition Technology, Inc., Des Plaines, Illinois) treatment, because the topographic improvement is dramatic, but subjective complaints about vision—due to halo, glare, irregular astigmatism, or monocular diplopia—persist.

Another point about C3-riboflavin is that it makes contact lens-intolerant patients contact lens-tolerant patients who begin to wear their lenses for longer periods during the day. So, their visual acuity improves.

This treatment is less invasive and easy to perform. The C3-riboflavin treatment seems more suitable as a first choice for forme fruste keratoconus. I also recommend this procedure to patients with Intacs.

**Boxer Wachler:** C3-riboflavin may also be combined with Intacs to provide greater topographic improve-

Courtesy of A. John Kanellopoulos



**Figure 1.** UVA: 300 mW/cm<sup>2</sup> for 30 minutes.

ments than Intacs alone provide.<sup>3</sup> C3-riboflavin has also been shown to be effective for stabilizing keratoconus as well as most LASIK-induced ectasias. There are preliminary data that C3-riboflavin may be able to help stabilize postradial keratotomy hyperopic changes.

**Spörl:** We knew the physical parameters at the beginning of the treatment. We then investigated the changes in (1) corneal stiffness, (2) shrinking temperature, and (3) resistance against enzymatic degradation as well as the safety parameters to protect the endothelium and the lens. This basic research was necessary, but it did not give the guarantee that the treatment would provide an improvement for patients.

Scientifically, we had a good theoretical and experimental basis for the treatment. Now, after we have performed C3-riboflavin treatments, it is safe to say that patients benefit from it. The best evidence for me is that those who receive treatment in one eye want to treat the other eye. This showed me—regardless of the basic inves-

tigations—that the treatment is useful for the patient.

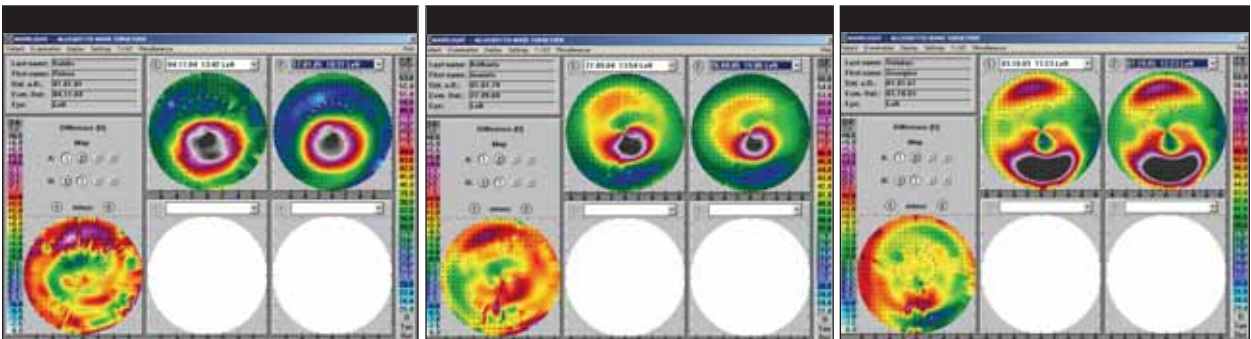
**Kanellopoulos:** As a transplant surgeon of 15 years, I consider C3-riboflavin treatment as a milestone in cornea surgery. I have reduced the number of penetrating keratoplasties I perform for ectatic disorders over the last 4 years by approximately 50%. The cross-linking has a definite stabilization effect in all cases. It is difficult to judge the topographic effect in the first 6 months, because the reepithelialized cornea is now thicker over the apex of the cone. (It is usually much thinner over the cone [eg, 20-30 μm], as nature or contact lens use thins that portion of corneal epithelium). It is, therefore, difficult to compare topographies from preoperative and early postoperative. We have, however, seen a significant reduction of ectasia, especially in post-LASIK cases and in keratoconus with significant ectasia (eg, over 52 K). We are in the process of publishing a series of 30 post-LASIK cases (Figure 1).

I am a strong believer in combining C3-riboflavin treatment with a conservative topography-guided treatment to better visually rehabilitate these patients. I do not wait to do this after the C3-riboflavin treatment. Instead, I perform a conservative topography-guided PRK followed by C3-riboflavin for 30 minutes (Figure 2) and mitomycin C 0.02% for 1 minute. I often deal with some postoperative haze, but it resolves with conservative treatment. The reward is that the refraction remains stable for years.

I have recently used C3-riboflavin in late high myopia LASIK regressions and have shown that the C3-riboflavin treatment clearly changes the posterior cornea curvature by changing the biomechanics of the operated cornea.

**Pinelli:** I have been interested in this treatment since its conception, and I studied the findings of Professors Seiler and Spörl to learn more. I also had the opportunity to visit Dr. Boxer Wachler's institution and see his patients.

Courtesy of A. John Kanellopoulos



**Figure 2.** Results UVA: At 6 months, keratoconus and ectasia appeared stabilized, although longer follow-up is necessary. In 22 eyes, there was a reduction of steep K by at least 2.00 D. In 22 eyes, there was a reduction of spherical equivalent of at least 2.40 D. There was no endothelial cell count change, and in most monocular cases, the other eye's ectasia progressed.

Now, my opinion is that C3-riboflavin represents a completely new planet in ophthalmology. I think that many new surgical options will soon be available thanks to this treatment, which will continually be developed and improved by surgeons worldwide.

Can everyone describe their technique of C3-riboflavin treatments and how they developed this method? It would be interesting to hear who keeps the epithelium and who removes it before irradiation of the cornea with UVA.

**Spörl:** We use the riboflavin-UVA method. We remove the epithelium and then drop riboflavin, which needs approximately 20 minutes to 30 minutes to diffuse into the stroma. We then irradiate with an irradiance of 3 mW/cm<sup>2</sup> for 30 minutes. The epithelium is removed, because riboflavin does not penetrate well through it. Not enough riboflavin is enriched in the stroma to produce high absorption or to prevent the endothelium and lens from UV irradiance.

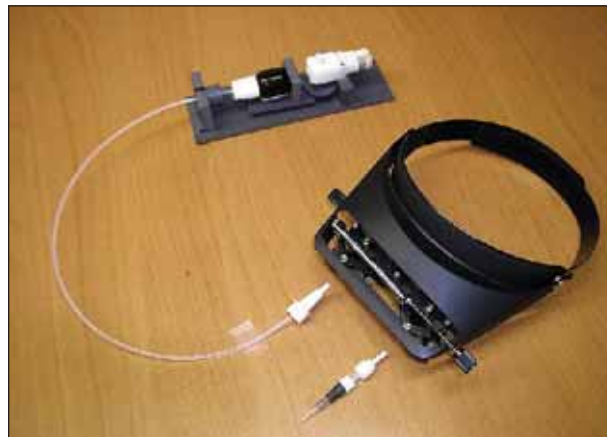
Recently, other variations of riboflavin application were developed to keep the epithelium. In these treatments, the epithelium was partially removed, or benzalkonium chloride was used to increase the permeability of the epithelium. Basic investigations are still necessary for these new techniques. Some interesting questions should be investigated. For instance: (1) What is the stiffening effect? (2) How does the endothelium or the lens react?

**Ertan:** I also do not remove the epithelium before irradiation of the cornea. I am using Pilosed 2% (Bilim Pharmaceuticals, Istanbul, Turkey) five times with 10-minute intervals before riboflavin dropping. Riboflavin is dropped two times every 3 minutes for 30 minutes.

In some patients, it may be difficult to observe riboflavin in the anterior chamber because of epithelial staining and edema. I use a fundus fluorescein camera to show riboflavin in the anterior chamber, and therefore, the riboflavin penetration in the epithelium is obvious. The weak point is accurately determining the anterior chamber riboflavin concentration, as there is no study reporting that all eyes with epithelium removal have the same riboflavin concentration in the anterior chamber. There are other factors (eg, corneal thickness) that influence riboflavin penetration.

**Pinelli:** We perform the technique bilaterally (Figure 3). The patient is in a pleasant and relaxing situation (Figure 4); there is no pain, and no steroid drops are needed after treatment. We do prescribe artificial tears postoperatively for 1 week.

We do not remove the epithelium before irradiation with UVA (ie, transepithelial technique). We chose this



Courtesy of Roberto Pinelli

**Figure 3.** This device (PriVision, Inc., Menlo Park, California) is used in C3-riboflavin treatments to provide a combined application of UVA and riboflavin.



Courtesy of Roberto Pinelli

**Figure 4.** A patient during the C3-riboflavin treatment.

technique because the epithelium represents a natural barrier against UVA. We have observed absences of corneal edema and pain, no damage to the corneal stroma, and patients have not needed steroid therapy. These are positive elements that influence us to continue our research with no epithelial removal, and we are proving two things in our institute. First, riboflavin plus tensoactive substances (under investigation) penetrate the stroma. Second, the cross-linking effect in the stroma does not necessarily mean that lines of demarcation are observed using the technique of epithelium removal.

**Boxer Wachler:** We favor the technique of not removing the epithelium, because we found equal efficacy in C3-riboflavin with and without epithelium removal. Without epithelial removal, it is important to use tetra-

caine (or a similar anesthetic) that loosens up the tight junctions of the epithelial cells and allow riboflavin to be absorbed. Slit-lamp photographs confirm riboflavin within the corneal stroma.

**Trokel:** It is essential that the proponents of transepithelial riboflavin saturation prove that adequate riboflavin enters the eye to produce a satisfactory substrate for the photochemical interactions to occur. Clinical efficacy must also be demonstrated.

**Pinelli:** Stephen, do you think that techniques for C3-riboflavin treatment will evolve in the future?

**Trokel:** It is clear that alternate technologies will allow cross-linking of corneal collagen. Some are being explored now.

**Spörl:** Furthermore, other indications for cross-linking of collagen and for the use of riboflavin and UVA will be developed. We already use UVA plus riboflavin to stop corneal melting processes in ulcers, and this technique may also be used for bacterial and fungal growth inhibition. In the field of tissue engineering, riboflavin plus UVA is used for the mechanical and enzymatical stabilization of collagen materi-

als, especially collagen membranes.

**Kanellopoulos:** As I mentioned, I invariably perform a limited topography-guided PRK and then C3-riboflavin for 30 minutes with epi-off. Most of these patients are transplantation candidates, and stabilizing the ectasia is not good enough, as contact lens use in the southern Mediterranean area of Greece can be uncomfortable due to the climate. In a few instances, I have complemented the PRK with a second treatment.

**Pinelli:** I agree that this technique will certainly evolve in the future. Our research and development team is investigating the possibility of using new tensoactive substances in place of or in combination with riboflavin to facilitate the penetration of riboflavin into the corneal stroma. We are also investigating the proper therapeutic range of parameters for the treatment (ie, UVA intensity and time of irradiation). Particularly, we are considering the possibility of using natural UVA irradiation. This is still under investigation, but in any case, a lot of new and exciting perspectives are on the horizon.

**Ertan:** In the future, this technique will be combined with other techniques.



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**Kanellopoulos:** I think that with proper follow-up and technique refinement, keratoconus may no longer be a surgical disease. With early diagnosis and cornea cross-linking, it may not progress to a surgical state. In the case of penetrating keratoplasty for ectatic disorders, cross-linking the host residual cornea may help reduce the postoperative astigmatism and future refractive stability.

**Pinelli:** Good point, which actually brings me to my next question. Do you think that this technique is complete by itself, or is it better in combination with other techniques (eg, Intacs)?

**Spörl:** Currently, C3-riboflavin techniques can only stabilize the cornea and stop the progression of kerato-

## UVA-RIBOFLAVIN CROSS-LINKING OF THE CORNEA

This treatment should trigger biomechanical corneal stabilization and discontinue disease progression.

**BY MICHAEL MROCHEN, PHD; EBERHARD SPÖRL, PHD; AND THEO SEILER, MD, PHD**

Cross-linking of the cornea is a new curative approach to increase the mechanical and biochemical stability of corneal tissue. Its aim is to create additional chemical bonds inside the corneal stroma by means of a highly localized photopolymerization as well as minimize exposure to surrounding eye structures. Current indications for corneal cross-linking are corneal ectasia disorders such as keratoconus, pellucid marginal degeneration, iatrogenic keratectasia after refractive lamellar surgery, and corneal melting that is unresponsive to conventional therapy.<sup>1,2</sup>

The most promising technique is photopolymerization with a 0.1% aqueous solution of riboflavin-phosphate (ie, vitamin B2) and homogeneous illumination to produce enough free radicals to achieve a reproducible increase in biomechanical strength.<sup>3</sup> This novel treatment consists of instilling riboflavin drops onto the cornea every 3 minutes for 30 minutes after a partial abrasion of the corneal epithelium. Using a slit-lamp inspection with blue light, the surgeon may ensure that riboflavin has reached the anterior chamber before the UV irradiation is initiated. Within a circular diameter of 9 mm, the cornea is exposed to UV light (wavelength, 365 nm) and an irradiance of 3 mW/cm<sup>2</sup> for 30 minutes,<sup>4,5</sup> corresponding to a total dose of 3.4 J (total dose density, 5.4 J/cm<sup>2</sup>) to the corneal surface (Figure 1).

Theo Seiler, MD, PhD, now of Zürich, Switzerland, conducted the first clinical applications of corneal cross-linking approximately 8 years ago. Since this time, several basic research studies and clinical trials have been performed worldwide.<sup>6</sup> Now, various future ophthalmic applications are under clinical investigation.

### ONE-DIMENSIONAL STRESS STRAIN

The key method to determine the stiffening effect on the cornea is the one-dimensional stress-strain measurement, which is performed in a micromaterial tester using corneal strips. In human cadaver corneas, corneal stiffness—measured with Young's Modulus—increased by a factor of 4.5 after cross-linking with UV radiation and riboflavin solution, as reported by Eberhard Spörl, PhD, of Dresden, Germany.

Wollensak and associates<sup>7-9</sup> studied the cytotoxicity of riboflavin/UVA on keratocytes and endothelium cells. Twenty-four hours after treatment in rabbit corneas, keratocyte apoptosis was found 300 μm deep. Therefore, the standard riboflavin/UVA technique requires a mandatory 400-μm preoperative minimal corneal thickness to avoid corneal endothelium damage and to preserve a fair amount of keratocytes to repopulate the cross-linked corneal stroma.

Should the corneas fall below this limit, a treatment option is still avail-



**Figure 1. Illumination of the cornea with the UV-X (IROC AG, Zürich, Switzerland) illumination system.**

conus. In the future, this technique should be combined with other vision-improving methods including Intacs as well as contact lenses or PRK.

**Trokel:** I agree. Extensive investigations will be required to learn the clinical applications and how they may be most efficiently applied. The potential ability to stabilize keratoconus when first diagnosed is a compelling application.

**Boxer Wachler:** We published a study in the *Journal of Cataract and Refractive Surgery* that compared Intacs alone with Intacs plus C3-riboflavin.<sup>3</sup> We found significantly better results with combined Intacs and C3-riboflavin use.

**Ertan:** The use of Intacs is statistically successful, but in some eyes, patient satisfaction is low due to glare, halos,

able. In this case, riboflavin solution may be used in the soak pretreatment phase to provoke corneal swelling into surpassing the safety limit of 400  $\mu\text{m}$ .

A clinical study performed at the University Eye Clinic of Dresden included a total of 418 eyes with progressive keratoconus and a maximum follow-up of 5 years.<sup>10</sup> In 86.8% of eyes, visual acuity increased by an average factor of 1.4. Astigmatism was reduced by 80%, and the maximum K-value was reduced in 86% of eyes. The average reduction in the maximum K-value was -2.86 D. The investigators did not find any changes in intraocular pressure measurement after UV cross-linking.

Tobias Koller, MD, and associates from the Institute of Ophthalmic and Refractive Surgery, in Zurich, Switzerland, compared 33 eyes before and after cross-linking. He reported that the human cornea undergoes a process of optical regularization, determined by Scheimpflug imaging, after cross-linking.<sup>11</sup>

As with any new technology, the introduction of corneal cross-linking to the broader public brings many questions. One of the most discussed topics is the administration of riboflavin B2. With its tight junctions, epithelium serves as a barrier for the penetration of riboflavin molecules, indicating at minimum a partial epithelium removal. Yellow flare in the anterior chamber is an indication that riboflavin penetrated through the cornea, however, this is only observed when the epithelium is partially removed and the cornea was soaked for at least 30 minutes with riboflavin solution. UV light exposure should only be initiated after a clear fluorescence is observed with a blue light slit lamp in the anterior chamber.

The goal of UV corneal cross-linking is biomechanical stabilization of the cornea and the discontinuation of disease progression altogether. Once this is achieved, patients may resume their preoperative contact lens program as soon as reepithelialization and healing are complete. The (1) likely change in corneal curvature after corneal cross-linking and (2) uncertainty about the length of time for stabilization suggest that a window of at least 2 months is necessary until a new contact lens fitting is advised.

New applications of this exciting technology—coupled

with possible limitations or complications—are likely to emerge following the broader use of corneal cross-linking by an increasing number of ophthalmologists. New frontiers are likely to be confronted in the near future. We will discuss many at the Third International Cross-Linking Congress, held December 7 to 8, in Zurich. For more information, visit [www.ccl-congress.ch](http://www.ccl-congress.ch). ■

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## CORNEAL ELASTICITY AND CROSS-LINKING

Cross-linking may be used to treat post-LASIK keratectasia and keratoconus.

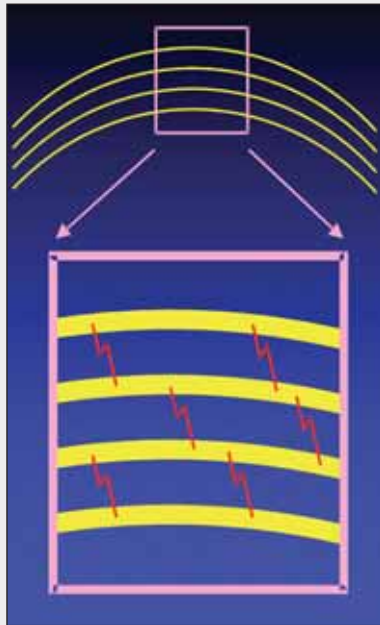
BY FRANZ FANKHAUSER, MD, PhD

Corneal cross-linking with riboflavin (C3-riboflavin) may be an effective treatment for post-LASIK keratectasia and keratoconus, while simultaneously improving corneal topography.

To better understand how C3-riboflavin treatment works, it is important to first understand basic corneal architecture. The cornea is composed of (1) approximately 300 lamella, each defined by specific thicknesses and lengths, (2) fibrils, which are approximately 30 nm in diameter and separated in distance by 30 nm, and (3) naturally occurring cross-linked collagen molecules, with higher elasticity. The cornea and its components create a physical stress resistance behavior called *elastic modulus*.

When examining the corneal architecture, it is also important to note that mechanical stress resistance is not equally distributed across the cornea. Resistance is stronger in the periphery versus the center. Additionally, each area shows a different amount of elasticity. The variance of mechanical stress resistance manifests in the stroma, because the stronger anterior stroma is composed of thin tightly interlaced lamellae, whereas the weaker posterior stroma has a thicker lamella, with a more hydrated structure.

The elastic behavior in the cornea plays an important role in a patient's susceptibility to keratoconus and keratectasia. Corneal elasticity is demonstrated in several ways: (1) Linear elasticity is a mechanical deformation with both increasing and decreasing force; it is linear and identical. (2) Nonlinear elasticity has no linear relationship between different forces and the mechanical deformation. Both decreasing and increasing deformation paths, however, are still identical. (3) Nonlinear viscoelastic behaves differently when there is mechanical deformation



**Figure 1. Cross-linking is the introduction of covalent chemical bonds between corneal lamellae, perpendicular to tangential tension.**

(eg, when the cornea is at tension vs at relaxation). This effect is called *hysteresis*. Over a short period, this nonlinear viscoelastic stays constant. Over a longer period, (ie, several weeks), however, relaxation and slow changes modify the elastic modulus. This concept of slow-acting modification may be used to address the elastic modulus when it reaches dangerously low levels.

When corneal thickness and elastic modulus are significantly lower than normal, patients are more likely to develop keratoconus or keratectasia. We have learned that cross-linking by means of C3-riboflavin plus UV radiation may prevent this from occurring.

Corneal cross-linking is the introduction of covalent chemical bonds between corneal lamellae, perpendicular to tangential tension (Figure 1). In cross-linking treatment outcomes at my clinic, we calculated a 1.3-time increase in stress resistance in the

treated cornea (eg, a cornea with a 190- $\mu$ m thickness behaved like a 250- $\mu$ m thick cornea).

We now know that when performed correctly, corneal cross-linking may result in mechanical stiffening and improved corneal topography. We also believe it may prevent the progression of keratoconus—although this needs further study. Additionally, the treatment may promote a change in corneal hysteresis, improve contact lens tolerance, or even be used in preparation before automatic lamellar keratoplasty—all without damaging the endothelium. ■

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chronic pain, and monocular diplopia. These visual complaints may continue following Intacs treatment, because the central cornea structure may be irregular. Intacs treatment does nothing to correct it, and patients are not always happy after treatment, even if they had improved refractions and topographic data.

I have performed C3-riboflavin treatments in some patients whom I had previously implanted Intacs. Seventy percent of these patients are now free of visual symptoms and have better vision. I observed that on post-operative day 1, patients felt that they had clearer vision, even if they had no significant change in refraction.

I think combined treatment with Intacs is necessary in moderate or advanced keratoconus patients. I prefer to implant Intacs first. The C3-riboflavin treatment is done as a second procedure, because C3-riboflavin stiffens the cornea, and Intacs implantation following C3-riboflavin may be ineffective.

**Kanellopoulos:** I do not believe Intacs for keratoconus are the best method for my patient population, because a significant amount of them admit to eye rubbing. This, of course, predisposes them to postoperative problems with Intacs. I am already using a limited topography-guided PRK with the C3-riboflavin to normalize the corneal surface and reduce irregular astigmatism. When the refraction is small enough, the total refractive error may be reduced. When the refraction is not reduced, BSCVA or use of soft contact lenses may be possible. I always compare these eyes with one after a penetrating keratoplasty. I am very encouraged by the results.

**Pinelli:** From what I have seen from my colleagues' experiences, it seems that the combination of C3-riboflavin plus Intacs is a successful procedure. In our experience, the procedure seems to be complete by itself, as we

# katena Glaucoma Punches

## Fukasaku Micro Punch

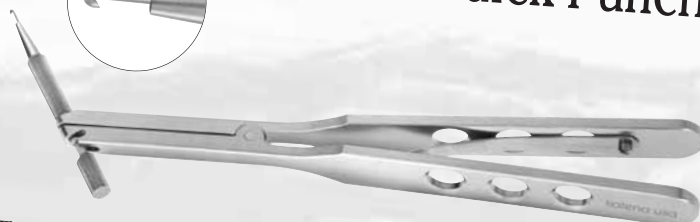
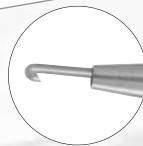


K2-9512

This punch is designed for the Fukasaku Micro Incision Trabeculectomy (MIT) technique which is performed through an incision as small as 1mm. The micro punch features a titanium squeeze handle mechanism for meticulous control and a micro bullet-shaped tip for easy insertion. The angled cutting edge removes 0.3mm of tissue with each bite. Multiple bites can be taken to obtain the ideal reduction in intraocular pressure.

Designed by Hideharu Fukasaku, MD of Yokohama, Japan

## Luntz-Dodick Punch



K2-9505

The Luntz-Dodick Punch features a bullet-shaped tip for easy insertion. Its angled cutting edge is designed to engage the scleral lip at the base and cut 0.5mm bites of tissue. The tip may be preset to cut in one of four directions and is easily disassembled for cleaning after each use.

## Kelly Descemet's Punch



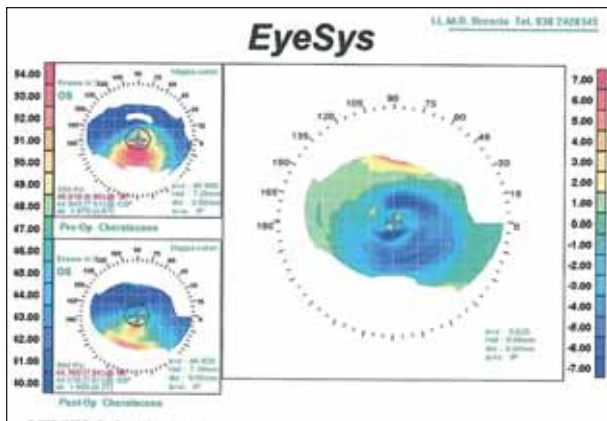
K2-9510

The Kelly Punch has been a favorite of glaucoma surgeons for many years. It features a 1mm diameter head which excises 0.75mm of tissue with each bite. The serrated flat handle has a mid-point pivot design for easy and precise actuation of the cutting edge by the surgeon.



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**Figure 5.** Six months postoperative difference map of a patient. Note the biomechanical response of the cornea 6 months postoperatively.

have had no complications and no damage to the cornea (Figure 5). Theoretically, we may repeat the treatment at regular time intervals.

We have come a long way in the treatment of keratoconus. What will happen in the next 5 years with C3-riboflavin treatments?

**Boxer Wachler:** I think we will start to see customized treatments.

**Trokel:** When keratoconus is first recognized, collagen cross-linking may well become the standard of care. It is also likely that it will play a role in management of post-LASIK ectasia, which may reflect a condition that occurs in patients with underlying and unrecognized keratoconus. Other corneal disorders that may be treated with this technique are pellucid marginal degeneration and a variety of corneal melting syndromes, as Professor Spörl already mentioned. Alternative technologies for the creation of collagen cross-linking will also be explored.

**Ertan:** This treatment may be performed using substances other than riboflavin, and it may be performed in a different spectrum of disorders.

**Spörl:** Keratoconus is one of the most probable indications for corneal transplantation. With this treatment, the number of corneal transplants may be reduced. Over the next few years, C3-riboflavin will be a normal method for the treatment of keratoconus progression. Because this technique can only stop the progression of keratoconus, it is important to treat it in an early state. That means that the keratoconus should be diagnosed as early

as possible, and the patient must not have complicated vision-improving procedures.

The riboflavin plus UVA cross-linking treatment stabilizes the cornea. We now have a good method to stabilize the cornea, but we must also search for the cause and releasing factors behind the development of keratoconus.

Is it possible to develop a genetic test to find the patients who are at risk for keratoconus? A promising method is to measure the biomechanical stiffness in patients with the Ocular Response Analyzer (Reichert, Inc., Depew, New York). We can control the cross-linking effect over several years, and we can use this device for diagnosis of weak corneas. With the cross-linking treatment, we have reached a new step in the field of keratoconus—but much research is still needed to reveal its mystery.

**Kanellopoulos:** I agree with C3-riboflavin applications for keratoconus. It is an inexpensive and easy treatment that may eliminate the need for PK in keratoconus. In the future, we may decide to cross-link corneas of high myopes to have LASIK.

I would also like to draw this group's attention to the potential applications of C3-riboflavin in keratitis (excluding herpetic). Cross-linking the collagen may reduce cornea proteolysis, which is the driving force behind corneal melt and pathogen dissemination in bacterial, fungal, and *Acanthamoeba* keratitis. UVA will probably make the herpes simplex virus worse—so this may be an absolute contraindication. As a cornea surgeon, I also foresee the pre-treatment of donor cornea tissue to wipe out stroma keratocytes, and specifically, Langhans cells—one of the driving forces in allograft recognition and rejection.

**Pinelli:** Great point. I think that a new era has begun. My hope is that keratoconus will soon not be considered a progressive disease, but a degenerative process that we can stop in its evolution, and that fewer patients will be candidates for corneal transplantation. I want to thank our roundtable panel for their participation and for this great discussion on C3-riboflavin treatments. We all look forward to seeing how this procedure continues to play out in the future. Until then, I think it is safe to say that we are all happy with our current C3-riboflavin results. ■

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