The Future of Corneal Collagen Crosslinking

Key opinion leaders address benefits of this state-of-the-art treatment during a roundtable discussion held at the 2010 ESCRS meeting in Paris.

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Trattler: Gathered here are some of the leaders in corneal collagen crosslinking (CXL). The purpose of our discussion is to recap the history of CXL and explore how it is being used in refractive surgery today. By the conclusion of this roundtable, we will have highlighted our preferred techniques; overviewed the indications, contraindications, and complications; and provided rationales for the use of CXL as both standalone and combined treatment modalities. The effects of CXL continue month after month, with results improving and changing over time. Why do the effects persist?

Kanellopoulos: The secret is found by looking at sequential anterior segment optical coherence topography (OCT) to determine corneal pachymetry. Postoperative pachymetry maps of these patients show that at 6, 12, and 18 months, the corneal periphery continues to thicken; the center does as well, but not as much. The difference in expansion between the periphery and the center produces a flattening effect.

Rubinfeld: John, can you describe what happens to the central and peripheral corneal thicknesses in a good CXL procedure and at what point these things happen?

Kanellopoulos: Let me start by clarifying the way we measure corneal thickness. Measurements with ultrasound or the Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) indicate approximately a 30% reduction in thickness with CXL; however, I think some of this is artifact.

Rubinfeld: Is this with epithelium off?

Kanellopoulos: Yes. There is immediate steepening of the cornea once the epithelium has healed, perhaps because the epithelium heals at its normal depth of 50 µm over the cone. There is also hyperplasia and other activity on the cornea. In my opinion, the turning point for these corneal changes is at 3 months, when significant corneal changes are visible on topography. However, it takes about 1 year before the thickness maps are reliable.

DID YOU KNOW?

A healthy cornea retains its shape due to strong crosslinks between the collagen fibers. In corneas with signs of keratoconus, these crosslinks are diminished, and the cornea weakens and bulges.[1] Corneal collagen crosslinking (CXL) wih riboflavin strengthens the weakened structure by adding crosslinks to the cornea, potentially stopping the progression of keratoconus.[2] The treatment involves applying riboflavin to the eye and projecting ultraviolet-A (UV-A) light at 3 mW/cm^2 of radiance onto the corneal surface to activate the riboflavin and produce the crosslinking effect.[3]

1. Corneal Collagen Cross-Linking (CXL) FAQs. LASIK of Boston Web site. http://www.lasikofboston.com/pdfs/CXL_FAQ.pdf. Accessed December 20, 2010.
2. Wollensak G, Spoerl E, Seiler T. Riboflavin/Ultravioled-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620-627.
3. Spoerl E, Wollensak G, Seiler T. Increased resistance of riboflavin/UVA-treated cornea against enzymatic digestion. *Curr Eye Res*. 2004;29:35-40.

Cummings: We must remember that the refractive index of the corneal tissue changes. Therefore, the more types of measurements we have—whether with OCT, biometry, or something else—the better. We should not rely on pachymetry alone.

Daya: Often, with raw images, what appears to be the corneal posterior is not actually the posterior. When a hazy cornea is imaged with the Orbscan (Bausch + Lomb, Rochester, New York), the posterior is not visible. So it is partly refractive index and partly other factors that introduce these measurement errors.

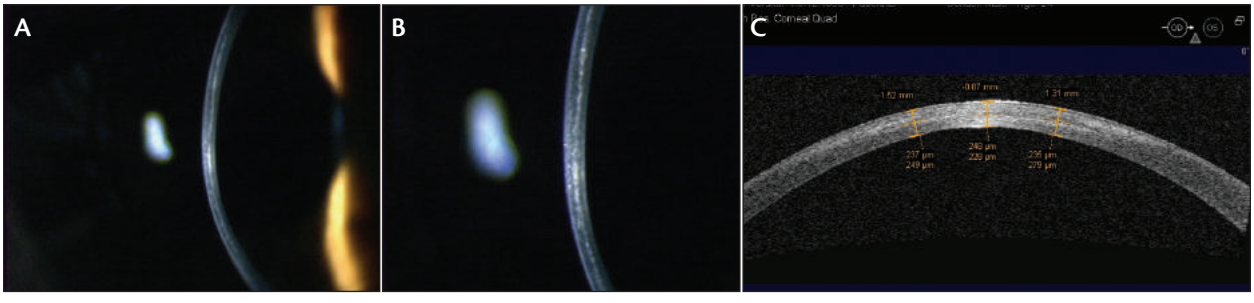
Kanellopoulos: But the original pachymetry is also off.

Daya: Yes, but we have not found it to be a 30% decrease. We have found that it is approximately 5%, if that.

THE EPITHELIUM

Rubinfeld: Let's be sure we are all speaking the same language. Are you doing CXL with the epithelium on or off?

Daya: Epithelium on, but I use a disruptive device (the Daya Disruptor; Duckworth & Kent, Hertfordshire, England) to create pockmarks in the epithelium. The primary goal is to



Courtesy of Sheraz M. Daya, MD, FACP, FACS, FRCS(Ed), FRCOphth

Figure 1. (A, B) The demarcation line is visible in these clinical images. (C) Visante OCT confirms the depth of the demarcation line.

DID YOU KNOW?

CXL can be performed as either an epithelium-off or epithelium-on treatment. When the epithelium is removed, this is done prior to the application of riboflavin[1,2] and corneal exposure to UV-A light. The healing process is similar to that of PRK, including the option to place a bandage contact lens to promote healing. Some surgeons argue that epithelium-off treatments are riskier, in part due to the possibilities of corneal infection associated with the lengthy healing process (4 to 6 days) and corneal haze.

An alternative[3,4] is to apply the riboflavin over the intact corneal epithelium. This is followed by corneal exposure to UV-A light. Visual recovery is faster with this approach, and there are lower risks for infection and haze. However, the treatment takes longer, because the cornea does not absorb the riboflavin as quickly as when the epithelium is removed.

Both techniques are effective; however, surgeons are still assessing which provides the greater degree of crosslinking.

1. Baiocchi S,Mazzotta C,Cerretani D,et al.Corneal crosslinking:riboflavin concentration in corneal stroma exposed with and without epithelium.*J Cataract Refract Surg.*2009;35(5):893-899.
2. Hayes S,O'Brart DP,Lamdin LS,et al.Effect of complete epithelial debridement before riboflavin-ultraviolet-A corneal collagen crosslinking therapy.*J Cataract Refract Surg.*2008;34(4):657-661.
3. Pinelli R.Corneal collagen cross-linking with riboflavin (C3-R) treatment opens new frontiers for keratoconus and corneal ectasia.*EyeWorld.*May 2007.http://www.eyeworld.org/article-corneal-collagen-cross-linking-withriboflavin— c3-r—treatment-opens-new-frontiers-for-keratoconus-and.Accessed November 15,2010.
4. Chan CC,Sharma M,Boxer BS.Effect of inferior segment Intacs with and without C3R on keratoconus.*J Cataract Refract Surg.*2007:33(1):75-80.

maintain as much live epithelium as possible but also promote riboflavin penetration—and it does penetrate. The secondary goal is to reduce inflammation in the eye and to get the patient out of the contact lens within 24 to 48 hours.

Some surgeons have noticed increased astigmatism and refractive change following CXL when the epithelium is removed, but in my experience this is not the case when the epithelium is left intact. With our epithelium-on method using the disruptive device, demarcation lines signify where the riboflavin penetrates the anterior chamber (Figure 1). The great thing is that patients do not have a huge refractive change for the worse; it either stays the same or improves. Sometimes they get a bit of induced astigmatism, but only for 1 to 3 months.

Trattler: How long do you saturate the eye with riboflavin?

Daya: Approximately 30 to 45 minutes.

Trattler: Roy and I are working together on a multicenter CXL outcomes study in the United States. About 4 months ago, we both converted from 100% epithelium-off to epithelium-on (ie, transepithelial) treatments. We leave the riboflavin drops in the eye for approximately 60 to 90 minutes, gauging when there is enough riboflavin penetration. We have seen some very nice early results.

Seiler: It must be said that 4 months is not long enough to establish solid evidence. Ideally, 1-year data from a controlled study would be preferable.

Kanellopoulos: I would like to stay on the topic of controlled studies. What Theo says is valid. The problem is, however, when we do a controlled study, what are we measuring? One of the most painstaking things for us, clinically, is to find a measurement aside from corneal curvature to assess the effects of CXL.

Seiler: I fully agree. In the early days, we thought that we were stuck with the experimental set-up of crosslinking in strips and measuring whether the strip became stiffer. As long as there are no data, I am not willing to accept that as solid proof that a CXL protocol works. One surgeon may crosslink only 55% of the cornea effectively, but he or she happens to be treating patients who do not require 100% crosslinking. The same protocol will not work for the surgeon who is treating advanced keratoconus with CXL. The bottom line is that each surgeon must provide data and be honest as a scientist.

Roberto Pinelli, MD, of Brescia, Italy, uses an epithelium-on approach. When we used his treatment protocol, we found that not one single keratocyte was killed. This means that not one single cell membrane of the keratocytes was crosslinked, and that means the treatment was ineffective. Nevertheless, patients could not perceive any difference, except that they did not feel pain. We now use a different epithelium-on approach, and this seems to work for us.

Trattler: One of the reasons that Antonio is with us today is because he does epithelium-on treatments, too. Can you explain your technique?

Leccisotti: My technique is based on the fact that, in 2009, Wollensak compared CXL in rabbits with the epithelium on and epithelium off.[1] Epithelium-on treatments, performed with benzalkonium chloride and oxybuprocaine, had one-fourth the effect of epithelium-off treatments.

But the question remained: How much effect do we need? Therefore, I performed an intraindividual study comparing results in 52 crosslinked eyes with the long-term outcome in the contralateral nontreated control eye (control), which was the better eye.[2] When we ruled out subjective data, which are completely unreliable measurements, mean spherical equivalent decreased by 0.35 D (less myopic) after CXL and increased by 0.83 D in the controls ($P<.05$). Mean apex curvature on tangential videokeratography increased by 0.51 D after CXL and by 1.61 D in the controls ($P=.16$). Mean average simK decreased by 0.10 D after CXL and increased by 0.88 D in the controls ($P<.05$). Mean index of

surface variance increased (worsened) by 0.9 after CXL and by 5.3 in the controls ($P<.05$). Mean endothelial cell density was unchanged (Figure 2).

Daya: Were these contact lens wearers?

Leccisotti: No, they never wore contacts.

Daya: I ask because contact lens wearers can experience changes to the corneal contour and height due to the contacts. Did they get demarcation lines?

Leccisotti: No. Perhaps the effect was too little to cause a demarcation line. Additionally, you cannot always see the fluorescence of the anterior chamber because it is very weak. Our technique is to treat the cornea with ethylenediaminetetraacetic acid and gentamicin, which in combination with benzalkonium chloride and oxybuprocaine increases the effects of the treatment on the epithelium. You get a very ugly epithelium after this.

Daya: Can I show you an ugly epithelium (Figure 3)? This is a patient who has been treated with CXL in whom I used the disruptor—you can see a very visible demarcation line. *(Editor's note: To see the Daya Disruptor in action, visit http://eyetube.net/?v=rohee.)*

Cummings: Riboflavin in the anterior chamber is one issue, but the other is the penetration of ultraviolet-A (UV-A) light afterward.

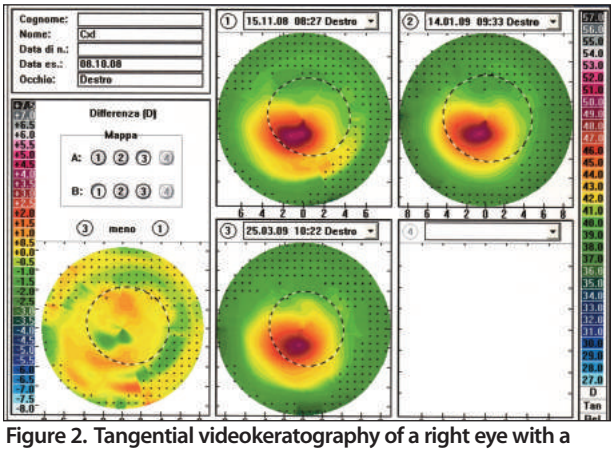
Rubinfeld: Is the demarcation line haze?

Seiler: No. In those places where we could find it, the demarcation line was the border between dead and living keratocytes.

Daya: Haze occurs because there is some degree of lamellar disruption, but this settles down and clears.

Rubinfeld: Is apoptosis required for crosslinking?

Seiler: That is exactly the crucial point. It might well be, and that was our previous approach. But with our current approach of epithelium on, we are just doing an overkill when we crosslink 100%. The best approach is to target 20% to 50%. Two years ago, we determined that the failure rate after CXL was 3% as long as we stayed away from eyes with keratoconus and treated only eyes with a maximum keratometry (K) reading of less than 58.00 D. I assumed the failures were because of measurement errors, and so I did a full treatment. But when crosslinking was reduced by 50%,



Courtesy of Antonio Leccisotti, MD, PhD

Figure 2. Tangential videokeratography of a right eye with a paracentral keratoconus, treated by transepithelial crosslinking. The difference map (bottom left) reveals a 3.00 D flattening of the apex at 4 months.

results were similar. Maybe what we need to do next is reduce the time, for example, to see what that would do to the failure rate. Then we would know whether we are at the upper limit for crosslinking and whether we can reduce it.

Then I would follow your logic, Antonio. If you can show that we do not need that much crosslinking, it should be reduced. But I would like to first see this approach evaluated in corneal strips or pig or rabbit eyes.

Daya: You just described the standard model of how to measure the changes in tensile strength. Maybe that should be used as a methodology.

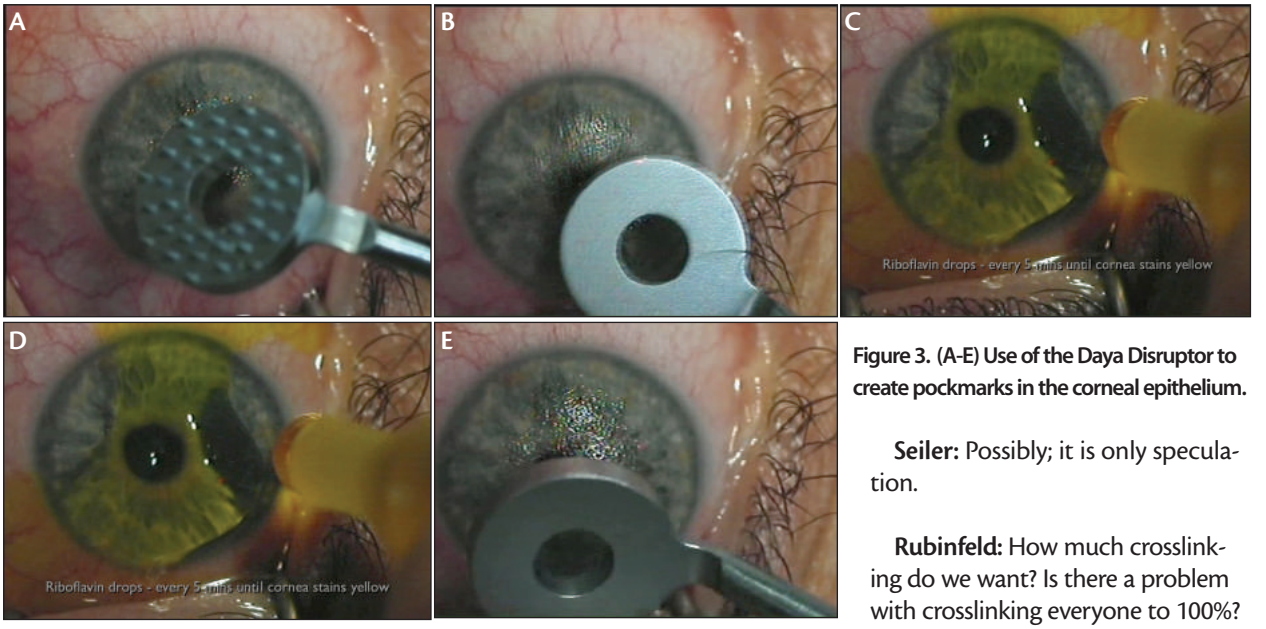
Kanellopoulos: We have proposed two ways to titrate the crosslinking effect, one of which is to study the amount of tissue shrinkage on cadaver corneas.[3-14] We have studied several fluences, time, and riboflavin mixtures using 1-month-old cadaver corneas that are approximately 900 µm thick. If the tissue has not been crosslinked, it does not shrink. We have looked at this with controls using the riboflavin and exposure to see how much that would shrink the tissue just by dehydration.

Daya: Riboflavin is hypertonic and will shrink the tissue. Therefore, your controls dehydrated at a normal rate.

Seiler: Dehydration is avoided if the experiment is done under mineral oil.

Kanellopoulos: The second clinical finding that we have proposed and published looks at OCT corneal noise.[3-14] Noise on OCT measures hyperrefractivity, not actually the presence of dead keratocytes.

In my experience, by looking at the noise in the



Courtesy of Sheraz M. Daya, MD, FACP, FACS, FRCS (Ed), FRCOphth

Figure 3. (A-E) Use of the Daya Disruptor to create pockmarks in the corneal epithelium.

cornea on OCT, I can determine the density, depth, and diameter of the CXL. When we look at corneas after epithelium-on treatment, there is a dramatic difference.

Trattler: Do you think that the act of taking the epithelium off helps the CXL process?

Kanellopoulos: The epithelium blocks approximately 45% of light going into the cornea. A study by Kolozsvári[15] showed the absorbance of UV-A light in the cornea. Bowman's membrane absorbs 35%, which is why we currently remove it when we do CXL. The epithelium and Bowman's membrane are big filters of UV-A light. Therefore, it is not only bioavailability of riboflavin in the cornea that matters but also the availability of UV-A light.

Seiler: Especially if there is riboflavin in both epithelium and Bowman's; then it is really shady. We believed we were clever when we used the strip-like pattern for epithelial removal, because healing occurred after approximately 1 day. At 1-month follow-up, however, we saw stromal haze under the strips but none under the epithelial islands.

Daya: We do not get focal haze under the pockmarks on the corneas with our technique, though, or any pockets of haze. It works much like epithelium-off with diffuse anterior haze.

HOW MUCH CXL?

Rubinfeld: I'd like to go back to Theo's question. If you need only 50% crosslinking, can you still get good results with not as much crosslinking?

Seiler: Possibly; it is only speculation.

Rubinfeld: How much crosslinking do we want? Is there a problem with crosslinking everyone to 100%?

Mrochen: But first, what do we mean by 100%?

Rubinfeld: I don't know. Biochemically, what happens? I know that crosslinking links two entities; however, can we link them all, and do we want to?

Kanellopoulos: We are unsure. It may be that CXL just shrinks collagen but does not interlink the collagen fibers.

Seiler: We originally thought we were creating interfibril crosslinks, but we are no longer sure. We know with certainty that crosslinks are induced inside the fibrils. It might be that proteoglycans induce some interfibril crosslinks, but that is not proven.

Daya: The fibers are too far apart to produce a chemical crosslink between them.

Seiler: Some proteoglycans overlap, and therefore they could crosslink.

Daya: I agree with that. The proteoglycans between the fibers have chemical properties that could crosslink and perhaps make the circle of fibroblasts more rigid. But it does not happen fiber to fiber, because they are physically too far apart.

Seiler: Establishing a bridge between fibers wouldn't work.

Kanellopoulos: But that is the proposed mechanism. That is what has been published.[16]

Daya: It may be proposed, but it is incorrect.

Cummings: John Marshall, PhD, FRCPath, FRCOphth (Hon), of London, describes it nicely for the layperson. He says the keratoconic corneal fiber is like a piece of licorice, quite stringy and floppy. CXL is compared with dipping the licorice in sugar; the sugar coating makes the licorice more rigid. This rigidity is what scientists believe produces the crosslinking affect, not interfibril bonds.

Daya: The fibers get shorter as well.

Mrochen: We recently measured the strain on corneal strips, adding a certain load to one of the strips and illuminating it with UV-A light. The control strip was not illuminated. Within 1 ng of accuracy, there was no measurable amount of shrinkage. If shrinking did occur, there would have been increased stress, which means the loads were practically nothing.

Daya: But what makes them thicker?

Seiler: We have no idea. Transmission and scanning electron microscopy show clearly that the collagen fiber is thicker by 13% in the crosslinked eye.[17] We do not know much about the morphology and the real reasons for increasing stiffness after crosslinking.

Corneal clarity should not change after CXL, but the refractive index does because the collagen changes. Additionally, the ultrasonic speed changes because it correlates with the elastic modulus in the sclera. Therefore, increasing the elastic modulus produces a higher speed. I would suggest that corneas after treatment are often thinner than our thickness measurements because of that effect.

Rubinfeld: Would OCT be more accurate?

Seiler: Nobody knows because the refractive index may change.

Kanellopoulos: But OCT uses a much smaller wavelength, and as such it should be affected less.

Daya: How much would the refractive index measurement change—1%, 5%, 10%?

Seiler: That depends on how much the stiffness and the modulus increase.

Mrochen: A rabbit study we performed[18] showed that the increase of the modulus after 3 months produces an increase in Young's module by a factor of 1.3 to 1.5.

Kanellopoulos: Those are the numbers we have also seen.

Rubinfeld: If I can ask my question again, even less intelligently than the last time: Whatever crosslinking is….

Seiler: Very well said.

Rubinfeld: …do we want a lot of it, or do we want some of it?

Seiler: That is a question we would all like the answer to.

Daya: I think it varies based on other variables, such as how severe the keratoconus is, how elastic the cornea is, and the age of the patient.

Seiler: It also depends on the diagnosis. For example, these patients must be screened for ectasia.

Rubinfeld: Is there harm in doing as much CXL as possible?

Mrochen: We did animal studies together with the University of Belgrade (Schumacher S, Jankov M, Bueeler M, Simon D, unpublished data, 2010) in which we looked at the intensities and concentrations of CXL. We believe that there is a certain limit over which the result is a lot of scarring that appears as large whitish spots. We call this over-crosslinking.

Seiler: You can also get agglomerations of collagen when you reach the upper limit of crosslinking. If you do too much it comes at a certain expense.

Rubinfeld: Is there a limit of UV-A exposure?

Mrochen: We must be sure that there is always a correlation between UV-A intensity, time (which gives us the amount of energy to be applied and the number of photons), and the concentration of the riboflavin.

LOCALIZED TREATMENT

Kanellopoulos: It is not only a matter of how much crosslinking is needed but also where in the cornea it is needed. This varies for different corneal models. For a thicker, more normal cornea, which is a better biological model, much less crosslinking is needed. For an advanced keratoconus model, where everything is focused at one part of the cornea, more crosslinking is needed.

Therefore, when I perform CXL I focus on where the

crosslinking is needed rather than how much, because that can be titrated. Theoretically, you can do three CXL procedures in the same patient, performing the second session 1 month after the first, and a third later if needed. The question is: What part of the cornea do we want to crosslink?

Rubinfeld: So you are suggesting selective crosslinking.

Seiler: Do we crosslink or not? This is not a yes-or-no question. We certainly know that strengthening the cornea is important, and we know that some corneas need more strengthening and others need less. We have to learn to titrate this effect over the long term to produce any answers.

Stojanovic: John, can you further comment on your ideas for localized treatment?

Kanellopoulos: One method is to add riboflavin within a corneal pocket created by a femtosecond laser or in Intacs channels (Addition Technology, Inc., Sunnyvale, California), localizing treatment in the mid-periphery. We proposed this mechanism, but the procedure was first done in Turkey.[5,7]

Stojanovic: How about masking the area where treatment is not wanted?

Kanellopoulos: I'm not sure about the efficacy of that, because crosslinking also occurs outside the area that is irradiated. Crosslinking apparently does not strictly follow the light path, and also free radicals are created. Adjacent crosslinking can occur, especially if there is no oxygen where the light is hitting but there is oxygen nearby.

Stojanovic: Yes, but treatments probably do not need to have sharp corners.

Kanellopoulos: There would be an annular projection from the treated area.

Mrochen: We have done some experiments (Schumacher S, Jankov M, Bueeler M, Simon D, unpublished data, 2010) where we asked the same questions that John raised. Is CXL localized? Is it defined by light? We shielded half of the treated corneas. You can directly see the cutoff, defined by the area of UV-A light exposure.

Seiler: Free radicals live on the order of nanoseconds, sometimes microseconds. Their travel distance is microns; they cannot travel millimeters.

DID YOU KNOW?

According to the literature, CXL prevents further vision loss in more than 95% of patients and improves vision in 60% to 81% of patients.[1-9]

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Rubinfeld: So light does delineate where the CXL occurs?

Seiler: More or less, yes. Of course there is diffraction at the edges.

Stojanovic: But that is not unwanted.

Rubinfeld: When performing selective CXL, do you treat the existing degree of ectasia or the degree of ectasia to be expected 2 years from now?

Leccisotti: There are many variables, including age and rate of progression.

Rubinfeld: If I had keratoconus, I would want you to treat as much as you could without hurting me.

Seiler: On the other hand, you are hurting the patient just by doing the treatment. It is painful.

COMBINED TREATMENTS

Kanellopoulos: Our Athens Protocol combines laser with CXL. We have not had any cases of breakthrough ectasia in a series of more than 400 cases. We compared 127 eyes treated with CXL first and topography-guided PRK later versus 198 that had the combined same-day treatment.[3,4,6] None of the patients had breakthrough ectasia in more than 5 years' follow-up. We concluded that crosslinking works no matter what the sequence.

Leccisotti: Is it OK to ablate a crosslinked cornea?

Kanellopoulos: That was the argument of the study. The answer is yes, it is OK.

Seiler: Strategically, it would be better to do PRK first and CXL afterward, because you can be sure that it is a fully crosslinked cornea. This will alleviate the possibility of removing what was the strongest part.

Cummings: Corneas that have been crosslinked are better-shaped corneas.

Seiler: On the other hand, some surgeons have argued that if PRK is done first in a weak cornea, the result is an immediate elastic response, steepening the periphery and flattening the center (or vice versa). They believe that this freezes the wrong shape with the CXL; however, John showed that is not the case.

Kanellopoulos: They actually have a synergistic effect when you do the procedures together.

Trattler: How do you know how much PRK to do?

Kanellopoulos: You can only treat 3.00 or at most 4.00 D. You have to choose between cylinder and sphere.

Daya: You get a lot of power effect by taking away 50 µm at a small 3- or 4-mm zone.

Seiler: Yes, but John homogenized the cornea because he wanted to preserve BCVA, which can then be corrected with phakic IOLs. In essence, the strategy was to correct irregular astigmatism.

Rubinfeld: Arthur has experience with this. Will you share with us?

Cummings: I have done 18 cases with good follow-up at 3 years. My strategy differs from John's; I do topography-guided PRK without any refractive input. A portion of the cone is ablated, but the majority of the treatment is in the steep superior aspect to reshape the cornea. Even though you put in zero refraction, the ablation makes the patient more myopic.

I do not think of this as a refractive procedure. These patients have a diseased cornea, and my goal is to rehabilitate them and get them into contact lenses as quickly as possible. We try to get them in the most comfortable contact lens, avoiding rigid contact lenses whenever possible. I do not perform CXL in patients who are 6/12 or 6/9; I do it for patients who have poor preoperative UCVA, and if their refraction is -6.00 or -9.00 D after the treatment, they do not care. All they know is the new contact lens is more comfortable, and it makes them see better.

Leccisotti: Why do you think the patients get more myopic?

Cummings: The treatment flattens the cornea over the pupil. As the cone moves centrally, the power of the cornea shifts centrally. It is more symmetrical and therefore a better shape. My contact lens practitioner sees more success with this strategy.

Trattler: Could you create more myopia, say in someone who has keratoconus but a 500-µm cornea?

Cummings: That is a great question, but I don't have an answer. John has used this approach with good results.

Kanellopoulos: I have treated more than 1,200 cases with this technique, and I do add refractive power.

Seiler: Do you stay within 50 µm?

Kanellopoulos: Yes, although if the cornea is more than 500 µm thick I will ablate more than 50 µm—maybe up to 70 µm. Believe it or not, I have treated a keratoconic cornea that was 580 µm at its thinnest point. I treated at 75 µm on that cornea.

Cummings: What is the highest refraction you can treat with this technique?

Kanellopoulos: This treatment is done with WaveLight's topography-guided platform (Alcon Laboratories, Inc., Fort Worth, Texas). Even if cylinder or myopia are not treated, 50 µm is removed from the central cornea. Within those 50 µm, using a 5-mm optical zone, I can typically treat approximately 2.00 D of myopia and 3.00 D of astigmatism. The biggest difficulty in these patients is axis, because refraction (autorefraction and cycloplegic) often indicates a different axis from topography. We have two mechanisms, the Pentacam and Placido-disc topography. My staff still does not understand why I treat the topographic cylinder. It is engraved in their minds to use the cycloplegic correction for the cylinder axis.

Seiler: We have to keep in mind that the refractive cylinder is only a subjective number that reduces coma. Cylindric glasses can compensate in part for this.

Trattler: Aleks, you use a different laser, correct?

Stojanovic: Yes, I use the iVis (iVis Technologies S.R.L, Taranto, Italy). I do not treat sphere or cylinder. Recently, I started to decrease the optical zone to 2 mm when the ablation depth is limited to only 30 or 40 µm. Patients are grateful for this correction, because their BCVA was poor, and their only alternative is transplantation. I initially did 12 eyes that now have 2 years' follow-up. Outcomes are stable, with no major developments after the initial results at 1 year. But at that time I used closer to a 5-mm zone, and now I am trying to shrink that. I am also trying to regularize the cornea as much as possible using as little corneal tissue as possible, compromising on sphere, cylinder, and optical zone—in that order.

Seiler: If the patient's keratoconus is so bad that you need a 50-µm ablation just to recenter it within 3 mm, wouldn't it be better to put an intrastromal corneal ring segment (ICRS) in first and do PRK and CXL later? You can reduce corneal asymmetry with an ICRS.

Kanellopoulos: I want to go on the record saying that, in these eyes, PRK is a therapeutic procedure. Perhaps the most important way that it works is not for refractive correction but for producing a better biomechanical model of the cornea. Ectasia is spread over a wider area, bringing balance to the cornea. It might help to do a hyperopic treatment to thin some of the peripheral cornea and redistribute the strain from blinking or intraocular pressure. This is one of the ways that the Athens Protocol works. However, I do not want to give surgeons the wrong impression; this is not a refractive procedure. We aim for 20/40 BCVA, but we also discuss the options of ICRS and corneal grafts with patients.

MITOMYCIN C

Leccisotti: Is there any place for mitomycin C? You are joining two procedures that are likely to induce haze.

Kanellopoulos: In our protocol, we use mitomycin C 0.02% for 20 seconds in between the ablation and CXL.

Seiler: I do not.

Cummings: Nor do I.

Daya: Keratocytes undergo apoptosis as a result of CXL. Are you likely to get more or less haze?

Stojanovic: Less.

Daya: So then is there a need to use mitomycin C?

Trattler: Well, we see haze after CXL by itself.

Seiler: That is a different haze; that is stromal haze.

Trattler: But now you are combining CXL with PRK, and the treatment involves UV-A light, which is a known risk factor for late-onset haze in PRK. I know in Miami I see more UV-A–related haze than my colleagues in Chicago, and John is in Greece, so I am sure he sees more as well.

Seiler: But wait, we have to define haze. When we started with PRK in the old days, nobody called it haze; we called it scarring. It was eventually termed haze because someone defined it as transient. But in the past 25 years, we have learned that there are scars as well as haze. Haze disappears within 6 months, but scars remain for approximately 1 year.

Haze is the product of disruption and death of keratocytes within a depth of 60 µm. As soon as the keratocytes repopulate that area, the cornea becomes homogeneously clear. However, scarring is a deposit of amorphous collagen of keratocytes that has transformed into myofibroblasts. This amorphous collagen needs years to reconfigure before it becomes clear. The use of mitomycin C does not diminish deep haze after CXL because there are no living keratocytes to deposit the collagen.

Daya: That is why I do not use mitomycin C. Based on a little bit of science, it seems pointless to use mitomycin C when you are combining PRK with CXL.

Kanellopoulos: Our clinical data support the use of mitomycin C. With the Athens Protocol, I perform phototherapeutic keratectomy to remove the epithelium at a diameter of approximately 6.5 mm. Therefore, close to the edge of the epithelial removal, there is a big hyperopic arch after PRK. If I do not use mitomycin C, scarring occurs on that arch near the superior cornea.

Trattler: Is there a downside to using mitomycin C?

DID YOU KNOW?

The use of topical mitomycin C 0.02% reduces the risk of haze and may produce more accurate refractive outcomes.[1,2] It has also been shown to enhance UCVA and BCVA after PRK compared with surface ablation alone.[2] Mitomycin C is appropriate when required but some sources comment that it probably should to be avoided if possible.[1] Also, mitomycin C changes how much tissue the laser ablates with each pulse, so the surgeon should manually change the treatment plan. This requires additional expertise.

1. USA Eyes Web site. LASEK. http://www.usaeyes.org/lasik/faq/lasek.htm. Accessed December 20, 2010.
2. Carones F, Vigo L, Scandola E, et al. Evaluation of the prophylactic use of mitomycin-C to inhibit haze formation after photorefractive keratectomy. *J Ophthalmic Visual Research*. 2002;28(12): 2088–2095.

Daya: For starters, we still do not know if it is safe.

Seiler: In nearly all of the cases I have seen, mitomycin C has delayed healing for months, resulting in infectious keratitis.

Trattler: Many US surgeons I know use mitomycin C in all of their surface ablation cases, and they have not found delays in epithelial healing related to intraoperative mitomycin C use. I wonder if there are other medications or causes for these cases of delayed epithelial healing.

Seiler: Epithelial healing can be delayed by weeks.

Trattler: In the United States, we noticed that nepafenac ophthalmic suspension (Nevanac; Alcon Laboratories, Inc., Fort Worth, Texas) delayed healing when used prior to the bandage contact lens with PRK, but we have not noticed delays in healing with mitomycin C. I use mitomycin C in a lot of surface ablation procedures.

Seiler: I use mitomycin C in every surface ablation procedure.

Kanellopoulos: The concentration used is important.

Rubinfeld: John is right. In a study I performed on corneal melts due to mitomycin C,[19-21] the incidence was dependent on cumulative dose.

Daya: Can I restate my question: Do you get haze when you do PRK without mitomycin C when the patient has been crosslinked?

Seiler: So far I have not, but others have.

Cummings: Theo lives in Zurich, and John lives in Athens. There is a huge difference in UV-A light.

Trattler: Aleks has written a paper about this. In the winter, do you ever see haze?

Stojanovic: No. I saw haze only with my previous laser platform, and it was in the mid-periphery after a hyperopic treatment, especially hyperopic cylinder.[22]

Cummings: So John is right. Topography-guided procedures place a lot of concentration of laser spots in that superior hyperopic segment. I see a little bit of haze in Dublin, but not enough to make me use mitomycin C. I can imagine in Athens it has to be worse.

Kanellopoulos: To give you an idea, I do not do hyperopic PRK, even with mitomycin C, because my patients will get scarring, which is also associated with regression.

Stojanovic: Even in Norway I used to get scarring in eyes treated with hyperopic PRK.

Daya: We are making some general statements. What degree of hyperopia do you treat with PRK?

Stojanovic: I usually do not treat more than 3.00 D.

Daya: Is there haze or scarring with a 1.00 D hyperopic PRK?

Stojanovic: I don't usually do 1.00 D treatments, but I did see haze or scarring with 2.00 or 3.00 D treatments.

Daya: The only PRKs I have had to do are for low levels of correction after multifocal IOL implants. I only use 0.02% mitomycin C in therapeutic applications because, although I hope I am wrong, I believe that it is a hazardous drug. If I am not wrong, we are going to have a massive issue on our hands in the future. Once you take the epithelium off, the cornea is a sponge that absorbs everything.

When mitomycin C was first used in refractive surgery, surgeons were keeping it on the eye for as long as 2 minutes. In an animal model, we found that, 6 hours after treatment, mitomycin C was present in the aqueous.[23]

Trattler: Parag A. Majmudar, MD, and Randy J. Epstein, MD, both of Chicago, have looked at this carefully; in multiple studies,[24-26] they have found no sign of toxicity.

Daya: Wait 10 more years.

Cummings: Two years ago, Jorge L. Alió, MD, PhD, of Alicante, Spain, presented 10-year results from 10,000 cases of PRK. Using mitomycin C in corneal dosages that were typically 0.02% for 20 seconds, he had not seen a single case of haze or scarring.

Trattler: If you do not use mitomycin C and your patient develops late-onset corneal haze following PRK, there will be vision loss and corneal damage.

Seiler: Twenty years ago, when we were still in Germany, we reported nearly no haze in corrections up to 6.00 D of myopia in PRK. But Tabara from Saudi Arabia saw it in nearly every case with 2.00 to 3.00 D corrections.[27] Tabara found that the amount of haze was seven times higher in Saudia Arabia compared with us in

Germany. So I have to agree that there may be local differences and racial differences. I think we should summarize this by saying that in some places in the world you need to use mitomycin C after PRK plus crosslinking, and in other places it is not necessary.

Trattler: I think we can all agree on that.

ONGOING CHANGES AFTER CXL

Rubinfeld: Why are clinical results better at 4 years than they were at 1 year if you do only CXL?

Kanellopoulos: The tissue and the cornea are reexpanding. The periphery of the cornea expands more than the center, and the result is flattening.

Rubinfeld: Is it flattening because of thickness differences induced by CXL?

Kanellopoulos: No, it is flattening because there is a differential between how much the periphery is expanding compared with the center.

Daya: It was that way to begin with in the periphery and in the center. Crosslinking may have thinned out the area, but it eventually returns to its original thickness.

We have seen changes in topography in some cases. There are also changes due to corneal and epithelial remodeling, because changes to vector forces cause changes in corneal shape. When we look at topography from cases that are now 5 or 6 years old, we see changes that take place. Even the elevation maps change. Is it the epithelium? We don't know.

Rubinfeld: What if the epithelium was not removed?

Daya: The epithelium turns over constantly, and it will therefore fill in the gaps. If the cornea changes, so does the epithelium.

Kanellopoulos: But can you get a 3.00 D change from epithelial remodeling?

Daya: At a 6.0- or 6.5-mm optical zone, 18 µm in the periphery will change 1.00 D of cylinder; 18 µm is three epithelial cells, so refraction will change.

Cummings: I would like to offer a simple suggestion. I see many patients with keratoconus referred from another ophthalmologist who has not told them not to rub their eyes. When you see these patients, you must immediately tell them to stop rubbing.

Mrochen: Some participants here have said that there is ongoing change with CXL over years. Where does this information come from?

Cummings: Topography.

Seiler: We have patients in Zurich with 5-year follow-up who have shown constant change. Some patients we treated had extreme thinning of the superior cornea close to the limbus. Over the course of 2 years, the cornea continued to get thicker; we believe that the collagen is in equilibrium between synthesis and catalysis. These changes are not only biomechanical, they are also biochemical.

Cummings: Crosslinking may be a drug after all.

Daya: Keep in mind that this is all speculative.

Seiler: The augmentation has been documented, however.

Daya: Absolutely. But the reason why the cornea keeps changing, whether it be biomechanical or biochemical synthesis and degradation, is yet to be proven. Bone takes about 30 years to turn over. Who knows how long it takes cornea to turn over?

CORNEAL PROTECTION

Rubinfeld: Do we need to protect limbal stem cells, based on what we know about UV-A light?

Seiler: The use of 3 mW/cm^2 of UV-A light has been tested several times, and it is safe. However, creation of free radicals close to the stem cells is dangerous.

Kanellopoulos: We have tested UV-A devices that have a very broad beam (14 mm), and those corneas took about 6 months to heal.

Mrochen: Ongoing reports from Switzerland (personal communication with several clinicians) showed that delayed epithelial healing is one of the major problems in CXL.

Daya: It may not be stem-cell related; it may be goblet-cell related. Alterations in the ocular surface may be affected by UV-A light on the conjunctiva. We forget the importance of conjunctiva. We think about the cornea and the stem cells, but we forget about this last piece. The whole environment is important.

Seiler: I try to avoid every injury to maximize the healing response, because delayed healing is the time when germs breed infections on the cornea.

DID YOU KNOW?

The wavelength of UV-A light is between 320 and 340 nm. In high surface doses (42.5 J/cm^2), it can induce corneal endothelial cell damage.[1,2] Therefore, the typical UV-A dose on the surface of the cornea is 5.4 J/cm,^{2} a similar dose to what the cornea would receive after 15 to 20 minutes of sun exposure on a summer day.[3] In CXL, UV-A light is projected at 3 mW/cm^2 of radiance onto the corneal surface. To prevent corneal endothelial damage, no more than 400 µm of stromal depth is treated.[4,5] The treatment produces the largest effect in the anterior 300 µm.[6]

1. Pitts DG, Gullen AP, Hacker PD. Ocular effects of ultraviolet radiation from 295 to 365 nm. *Invest Ophthalmol Visc Sci*. 1977;16:932-939.
2. Ringvold A, Davanger M, Olsen EG. Changes of the cornea endothelium after ultraviolet radiation. *Acta Ophthalmol*. 1982;60:41-53.
3. Kimlin MG, Parisi AV, Downs NJ. Human UVA exposures estimated from ambient UVA measurements. http://www.rsc.org/delivery/_ArticleLinking/DisplayArticleForFree.cfm?doi=b207953d&JournalCode=PP. Accessed December 20, 2010.
4. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea*. 2007;26:385-389.
5. Wollensak G, Spoerl E, Wilsch M, et al. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. *J Cataract Refract Surg*. 2003;29:1786-1790.
6. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A induced cross-linking. *J Cataract Refract Surg*. 2003;29:1781-1785.

Kanellopoulos: I protect the limbus with the Chayet sponge (Katena Products, Inc., Denville, New Jersey).

Leccisotti: I use a device that protects the limbus with a diaphragm (Vega X-Linker; Costruzione Strumenti Oftalmici, Florence, Italy).

Seiler: I do too.

Daya: I don't. I have devised a protector that is not yet manufactured.

Kanellopoulos: In addition to using the Chayet sponge, we put a diaphragm on the UV-A source so that only the central 8 mm of the cornea is illuminated.

Daya: The excimer laser causes dry eye when the conjunctiva is exposed to UV-A light. The bottom line is, if it is easy to protect, then protect it.

PROGRESSION AND RETREATMENT

Rubinfeld: Can CXL be repeated?

Daya: The only times we have done repeated CXL are in patients with post-LASIK ectasia. It seems to arrest development. The first CXL slowed progression, but the ectasia started to progress again. As a last-ditch effort before grafting, I performed CXL a second time.

Seiler: We and others have published results from cases of women who developed ectasia whenever they became pregnant.[28] We performed CXL after the first pregnancy, but during subsequent pregnancies they developed ectasia again due to hormonal changes. In each instance, results were stable for 5 years, but when these women became pregnant, suddenly the keratectasia recurred.

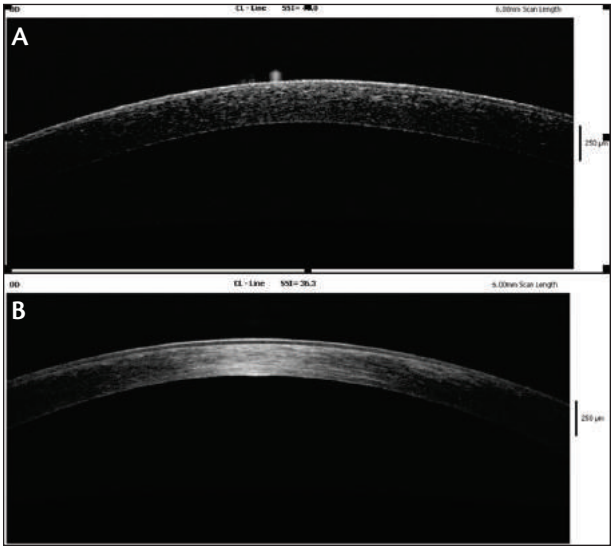
Kanellopoulos: We are submitting a series of seven cases of breakthrough ectasia after CXL; six of them were epithelium-on (Figure 4). These are patients whom I had seen and treated with CXL in New York from 2002 to 2004. Five have been retreated, and I recommended that they be retreated with epithelium off and laser. The OCTs show the difference between patients treated with the epithelium on and with the Athens Protocol.

Daya: They traveled to Athens for retreatment?

Kanellopoulos: That is the only way I could do it.

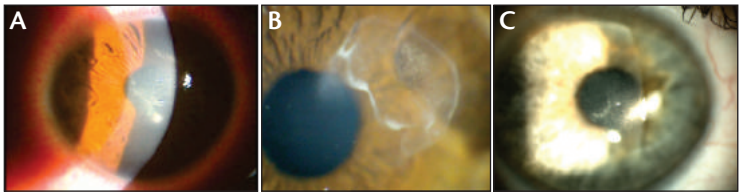
Rubinfeld: Sheraz, I am particularly interested in your technique because you leave the epithelium relatively intact. Have you treated any young patients with keratoconus who did not respond and then you treated again?

Daya: I have not identified any failed cases. We are looking through our data now to see if anyone has progressed. There are some progressions that are subtle. Theo recently presented at a symposium at the Royal



Courtesy of A. John Kanellopoulos, MD

Figure 4. (A) This cornea underwent CXL with the epithelium on. There is little hypereflectivity in the stroma, suggesting less CXL effect that is seen in Figure 4B. (B) A cornea that underwent the Athens Protocol. Note not only the vast hypereflectivity of the stroma in Figure 4A, up to 300 microns µm, but also the broad diameter at which this effect takes place.



Courtesy of A. John Kanellopoulos, MD

Figure 5. Three corneas that developed white scars. (A) Dense white spot after CXL. (B) Cornea melt and scar after CXL. (C) Salzman-like white spot in the healing process of CXL.

College of Ophthalmologists meeting in Liverpool. He has noticed that patients with steep corneas before surgery (K greater than 58.50 D) are the ones who do not respond to CXL.

Seiler: That is correct.

Daya: In my experience, the only two patients who underwent repeat CXL had post-LASIK ectasia.

Seiler: We have done retreatments in three patients, two of whom had neurodermatitis and were severe eye rubbers. The other developed infectious keratitis after CXL.

When these patients were initially treated, our procedure consisted of riboflavin placed on the eye for 10 minutes followed by 30 minutes of UV-A light exposure. Obviously that was too shallow. After the second treatment, these patients were stable.

Trattler: It sounds like there have been few retreatments among our panelists. If a patient had no change at 1 year, meaning keratoconus did not get worse but did not progress, would a second crosslinking procedure improve the result?

Kanellopoulos: That is a good question. I correspond with a lot of doctors, and I have seen a lot of significantly over-crosslinked corneas. The result is typically a white scar in the stroma. That is what I fear after crosslinking a cornea that has already been crosslinked.

Daya: Rapid crosslinking.

Kanellopoulos: That is another issue I am concerned about. But the bioavailability of riboflavin in those corneas acts as a safety net.

Daya: Have those patients who had scarring undergone repeated crosslinking?

Kanellopoulos: No.

Daya: How were they over-crosslinked?

Kanellopoulos: Correspondents have sent me about 12 pictures of corneas that have developed white scars after crosslinking (Figure 5). You have seen this too, haven't you Theo?

Seiler: Yes, and we hypothesize that it was white spots in the illumination.

DEFINING CONCENTRATIONS, DOSING

Kanellopoulos: I have tested different concentrations of riboflavin, and increasing the concentration from 0.01% to 0.02% increases tenfold the crosslinking reaction (unpublished results). Using 0.05% riboflavin and crosslinking with 7 mW/cm^2, you get a tremendous amount of crosslinking, but the corneas turn white. There must be some element in the procedure that increased the fluence of UV-A light or increased the effective concentration of riboflavin.

Seiler: I have found that when doubling the amount you must triple the intensity.

Trattler: If you apply drops for 15 minutes versus 30, then you change the amount of riboflavin in the cornea. Is the type of riboflavin and the dosing that you put in more important than the concentration? As I understand it, more riboflavin in the cornea produces more crosslinking.

Kanellopoulos: Not necessarily, because the additional riboflavin shields more UV-A light.

Seiler: Superiorly you get more.

Kanellopoulos: And less inferiorly.

Mrochen: If you increase the concentration and use the same energy dose, you get a small layer of crosslinks.

Seiler: The links are shallower with a higher concentration of riboflavin.

Mrochen: If you want to extend that to deeper stroma, you must increase the energy dose, which means either increasing the intensity or the treatment time. Both might have an impact on the damage thresholds of the endothelium.

Trattler: Could you use less riboflavin?

Mrochen: Yes, because with 0.3% riboflavin, the crosslinks will be generated in deeper layers when the amount of energy in the cornea is increased. However, energy is also increased across the superficial layer, and we are afraid of over-crosslinking and generation of white superficial scars. We must determine the optimal balance among concentration, intensity, and time with respect to the endothelium and possible scarring that might occur.

Seiler: That is how we decided the original protocol of 30 minutes and 3 mW/cm^2.

Trattler: Is there a standard way to figure out how much riboflavin to use? Everyone is dosing different frequencies of drops.

Mrochen: We must create a standard. R. Doyle Stulting, MD, PhD, of Atlanta, has performed UV-A measurements in rabbits.[29] The fusion time correlates with what we have observed experimentally. The riboflavin needs a certain amount of time to diffuse, and this defines the concentration distribution.

Seiler: The last 10 minutes of this 30 minutes produces only a little bit of flattening. I could imagine that the effect, decreasing the time to 10 or 15 minutes, might be not much different.

Stojanovic: It would be nice to put all of these variables into a software program.

Mrochen: We presented a computer model at the International Congress of Corneal Crosslinking in 2008.[30] The surgeon plugs in the time to diffusion, the concentration, and the quantity of time to determine the distribution for CXL. It might be a different number for thin corneas, where we want to have only a superficial layer, versus thick corneas, where we would like to have deeper penetration.

Seiler: It is also good for other applications such as antifungal treatments to kill fungus in the cornea. I like to have a high volume of tissue being crosslinked, and that is why I have transitioned to lower concentrations over a longer time.

Kanellopoulos: I am working with a UV-A device that can go up to 120 mW/cm^2. The light is pulsed to allow the tissue to reoxygenate. One of the self-limiting factors of crosslinking with continuous UV-A light is the lack of oxygen. Additionally, keratocytes are more resistant to higher doses of UV-A light, and therefore we use shorter duration and lower doses of UV-A light at a longer duration to reduce keratocyte apoptosis.

DID YOU KNOW?

Riboflavin is used during CXL because it increases the absorption of UV-A light by the cornea.[1,2] The more UV-A light that is absorbed, the greater the effect of crosslinking. An added benefit is that the riboflavin helps to protect the endothelium and intraocular tissues from UV-A exposure.

1. Michael R. Development and repair of cataract induced by ultraviolet radiation. Ophthalmic Res. 2000;32(Suppl).
2. Spoerl E, Schreiber J, Hellmund K. Untersuchungen zur verfestigung der hornhaut am kaninchen. Ophthalmologe. 2000;97:203–206.

Right now with the Seiler Protocol, by definition, in order to crosslink tissue you have to kill keratocytes. The question is, how would it affect the eye if the cornea could be crosslinked in the same way and in the same amount but with more keratocytes kept viable?

Seiler: That would be better.

Kanellopoulos: Would it produce more scarring because there are keratocytes right next to the irradiated area?

Seiler: That is why we use mitomycin C.

MEASUREMENTS

Rubinfeld: We all crosslink and we all do it differently. What do we want to measure?

Trattler: Not vision.

Cummings: The metrics for CXL are just like everything else in my practice, and that is that they must meet expectations. We should have the same goal for every patient who comes in for CXL. We are trying to arrest the keratoconus—that is the No. 1 goal. In most patients, perhaps close to 70%, the corneal topography improves slightly, but that is just a bonus. It is not about what we think is going on; it is about how our patients do afterward. If you can increase the success of patients and avoid corneal transplants, then we have achieved something. Corneal transplants work, but no one wants one.

Seiler: And they surely do not work in close to 70% of patients.

Cummings: That's exactly right. So if we can rehabilitate patients and they can feel confident in the success of the procedure—that is the metric that counts.

Rubinfeld: This has already been accomplished for several years in Europe.

Cummings: That is the first point. But the second point is providing good BCVA, and most of the time this is accomplished with a contact lens. It is interesting how many crosslinking facilities do not have a contact lens expert on site. If the patient is comfortable wearing a lens and sees well, this is better than any procedure you can do. If a keratoconic patient comes into my practice saying, "My definition of success is seeing without glasses afterward," I tell the patient that I cannot help him or her.

Trattler: But how about seeing with glasses? There is going to be a period when these patients cannot wear contacts because of risk of infection.

Cummings: That is where other modalities come in, such as ICRSs to improve corneal shape. But the objectives of CXL are to improve BCVA and stop the progression of keratoconus.

Seiler: Crosslinking is just the predisposition for remodeling the cornea.

Kanellopoulos: We have found that crosslinking makes patients' UCVA worse in the early period after surgery. After CXL in a 20-year-old, the topography improves but UCVA declines.

Seiler: I agree. We are not talking about 6 months, but 1 or 2 years.

Courtesy of A. John Kanellopoulos, MD

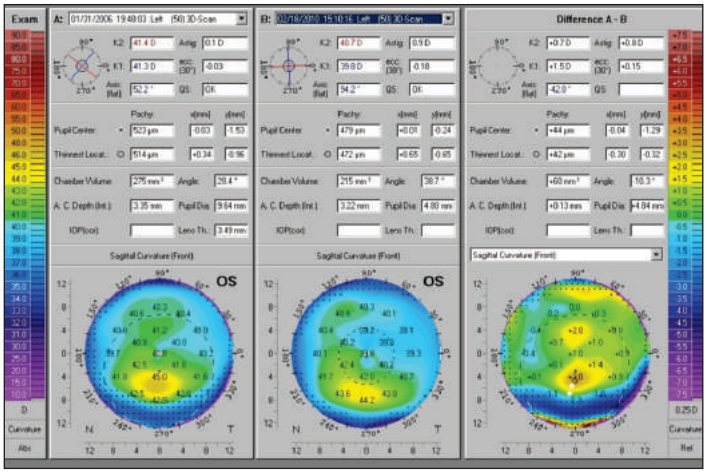


Figure 6. This 24-year-old Greek man had CXL with epithelium off in 2006 as a prophylaxis for early keratoconus. His refraction was as follows: UCVA=20/25; BCVA=20/15; -0.50 -1.50 X 85º. Four years later, his refraction is UCVA=20/40; BCVA=20/20; +2.00 -0.50 X 90º. There is clear improvement of the ectasia in Pentacam images before (left) and after (center), as well as significant before-after diffrences (right). Nevertheless, he is very unhappy with the hyperopic shift of his prescription.

Cummings: What do you think the cause is?

Seiler: They are getting more myopic.

Kanellopoulos: I think they lose the multifocality of the cornea because it is more rigid.

Cummings: Yes. Most patients with keratoconus squeeze, and what is their vision like when they squeeze?

Kanellopoulos: So therefore, whether a patient does well with glasses is relative. A 20-year-old patient with keratoconus may be 20/20 uncorrected before CXL but 20/40 uncorrected afterward. First, you must inform patients of the possibility of this before treatment, and, second, if it occurs, some therapeutic refractive intervention may be necessary.

I have an example, which happens to be my most unhappy CXL patient (Figure 6). This patient came to me 4.5 years ago and was plano with 20/20 vision. Now, he is +2.00 D. His cornea is thickening since the original shrinkage, and it is progressively flattening. He is extremely unhappy.

Seiler: I have had a different outcome. The patient was -2.00, and 5 years later he is plano.

Rubinfeld: What are some objective metrics, ways for us to be sure there is no progression and is perhaps improvement?

Cummings: What has given me the most objective measurement is a calculation called the upper-lower ratios. It compares the five points in the pupillary zone that are steepest versus the five points that are flattest. It is taking five steep K values and subtracting five flat K values.

Seiler: That is similar to the keratoconus index.

Rubinfeld: Arthur, which device are you using?

Cummings: I use Pentacam and Placido-disk topography, because the flattest points can sometimes change.

Trattler: Stephen D. Klyce, PhD, of Louisiana, uses similar software. I send him my Pentacam images. But he is measuring the raw data, so you don't get the difference in the points that show progression.

Seiler: Right now, I am still using K max on the Pentacam as my metrics, because its other

keratoconus indices are not highly statistically effective or as significant as the K max.

Daya: There are quite a few parameters on the Pentacam, but they cannot be taken in isolation. The question is how do we weigh each one, and how do we gauge whether the patient has keratoconus progression?

Seiler: That is true, and I am very sorry that we do not have appropriate means to describe success or failure right now.

Leccisotti: What do you do right now when you see a patient? Do you just compare maps in your mind?

Rubinfeld: I think we all do that. But it would be nice if we could be a little more scientific about it.

Seiler: I did an analysis, and only K max showed success or any difference at all. That does not mean that there are not better indices.

Kanellopoulos: What outcome measures are being used in the United States?

Trattler: K max is one of them, as well as progression.

Seiler: In the US study,[31] regression or progression was decided based on Pentacam. Anything more than three times the standard deviation was considered regressive or progressive.

PATIENT SELECTION

Trattler: What population is appropriate for CXL? What are the limits for age, K readings, and corneal thickness?

Leccisotti: In Italy, our parameters are dictated by the National Health Service. It is reimbursed if the patient's age is between 12 and 39 years and if the disease is progressing.

Trattler: But does it work in 40-year-olds? Do you see improvement in patients who are 40 or even 50 years old?

Cummings: I think if you have good indications, yes. I have done CXL in a couple of 55-year-olds who have had fantastic results.

Daya: Why did you treat them?

Cummings: Because they were progressing. The greatest effect of CXL is to stop progression.

Seiler: I would like to tell you the story of little Ioannis. He rubbed his eyes a lot, and after therapeutic treatments there was still progression. Because he was a student, we decided to do CXL in the worst eye over his winter holiday and the fellow eye before the summer so he would not miss school. He came back in May with hydrops in the better eye. That has now made us suspicious about age limits and other variables.

Trattler: So age affects progression. That is useful information. Thank you all for participating in this roundtable discussion. CXL is an exciting treatment, and I have a feeling we will be seeing increased use over the next few years. ■

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