

OCULAR SURGERY NEWS®

A SLACK Incorporated® publication

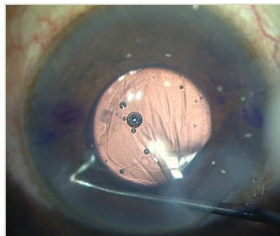
Volume 32 • Number 3

FEBRUARY 10, 2014

OSN EXCLUSIVES

COMPLICATIONS CONSULT

Endodiatheirmy marks useful in cases of



postoperative toric IOL rotation **33**

LINDSTROM'S PERSPECTIVE

Learning process ongoing for corneal collagen cross-linking **3**

NEWS YOU CAN USE FROM THE UPMC EYE CENTER

Large referral center explores efficacy of Trabectome-mediated ab interno trabeculectomy Good results were seen in challenging eyes, which should justify proceeding with a formal comparative trial of this MIGS system. **9**

IN THE JOURNALS

Cross-linking improves visual acuity, reduces higher-order aberrations at 2 years

Collagen cross-linking provided good long-term visual, refractive and topographic outcomes in eyes treated for progressive keratoconus, a study found. **19**

Meeting News Coverage
Macula 2014
January 11

Meeting coverage starts on page 13

COVER STORY

Cross-linking round table, part 1: Controversies, techniques and treatment decisions

At the 2013 European Society of Cataract and Refractive Surgeons meeting, OCULAR SURGERY NEWS convened a round table of international experts to discuss the current state of corneal cross-linking. The first part of that wide-ranging discussion, moderated by **Roy S. Rubinfeld, MD**, is featured in this issue of OSN.

Roy S. Rubinfeld, MD: At this moment, there is a lot of controversy in cross-linking. We are at a tipping point in terms of epithelium-on vs. epithelium-off methods. Multicenter U.S. clinical trials are ongoing to study both methods, and there has been a great deal of research and development as well as presentations that are significantly affecting clinical practice. We know much more now than we did just 1 to 2 years ago.

Originally epi-off cross-linking was developed in the 1990s because the riboflavin formulations, with high-molecular-weight dextran, would not penetrate the epithelium to get into the stroma well. At the time, it was an easy mental jump to think of PRK and remove the epithelium. However, there are newer proprietary riboflavin formulations and methods for performing highly effective epi-on cross-linking wherein the riboflavin loads the stroma well, UV light does penetrate, and cross-linking is achieved. Studies are showing best corrected visual acuity and maximum keratometry outcomes to be similar between methods.

Cover story continues on page 10



Image: Courtesy of photographer Donna Victor and Baptist Health South Florida

William B. Trattler, MD, has been performing epi-on cross-linking exclusively for more than 3 years.

Gene therapy may reduce treatment burden associated with AMD

PHILADELPHIA — Existing techniques enable the application of gene therapy for age-related macular degeneration, a clinician said here at Macula 2014.

“I think we’re in the most exciting period advancing forward with respect to biologics and the treatments of retinal diseases,” **Elias Reichel, MD**, said. “The idea is that this is going to last for a prolonged period of time. Hopefully, we’ll avoid some of the issues with the burden of treatment with multiple injections of either small molecules or biologics.”

The retina is easily accessible with existing

techniques such as intravitreal injection, sub-retinal injection, pars plana vitrectomy, internal limiting membrane removal and laser treatment, individually or in various combinations, he said.

“The key, though, is adequately infecting the retina to achieve therapeutic protein expression levels,” he said. “I believe that at least one of these approaches will work, if not several.”

Adeno-associated virus (AAV) is widely used for ocular gene therapy. Ongoing study is focused on AAV2. Phase 1 studies are being undertaken by Genzyme/Sanofi, Oxford Biomedica/Sanofi and Avalanche. Hemera Bio-

sciences and two groups at Cornell University are undertaking preclinical studies.

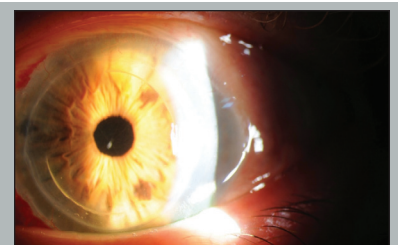
Reichel and colleagues at Hemera Biosciences are studying the use of the CD59 gene in preventing the development of wet AMD by blocking the last step of the complement cascade.

A retinal prosthesis being developed by Sheila Nirenberg, PhD, at Cornell involves light interacting with AAV2 injected into the vitreous, expressing channel rhodopsin-2 and activating the ganglion cells, Reichel said.

Disclosure: Reichel is a co-founder of Hemera Biosciences.

Surgical Maneuvers: Femtosecond laser astigmatic keratotomy

The correction of astigmatism resulted in significantly improved visual acuity and corneal cylinder. **4**



COVER STORY

Experts discuss the current state of corneal cross-linking

continued from cover

Any treatment that is completely effective is suspicious. We have identified now 31 eyes of about 2,200 eyes in our epi-on study that we believe are true treatment failures; that is 0.01%. In Michael Mrochen and colleagues' *Journal of Cataract and Refractive Surgery* article "Complications and failure rates after corneal cross-linking," the rate was about 5%.

William B. Trattler, MD: To the panel: What do you think your personal progression rate is with epi-off cross-linking? In Dr. Mrochen's paper, it was 5%. Is that about what you are observing now with epi-off? Do you ever see progression?

Arthur B. Cummings, FRCS: Using mean keratometry and maximum keratometry readings as the two parameters, I would say about 5% do not respond.

George O. Waring IV, MD: It is a good idea to separate out the complications from the failure rates because presumably the complication rate may be higher with epi-off but the progression rate might be lower. You have to separate those two variables when you look at this percentage.

Technique-dependent

Trattler: The success rate vs. failure rate depends on the epi-on technique. In the CXLUSA clinical trial, we do a more robust epi-on technique, and our rate of progression appears to be in the same range as that for epi-off, but I have not done enough epi-off cases personally to know for certain.

Rubinfeld: To use a phrase I have heard Dr. Trattler say, "Not all epi-on cross-linking is the same." I have observed procedures wherein, to standardize the treatment, a well is placed on the eye, a riboflavin solution is placed on the eye, and exactly 30 minutes later treatment starts, but no one has looked at the cornea to confirm the stroma is loaded with riboflavin.

Trattler: What you are describing has been published in a couple of papers that compared epi-on vs. epi-off and reported that epi-on was not as effective. The technique that they used for epi-on was exactly as you described: a timer technique in which the cornea is never evaluated to make sure there is sufficient riboflavin in the cornea for an effective cross-linking procedure. And that is why those papers showed inadequate

effect with epi-on; the issue was their technique.

Aleksandar Stojanovic, MD: In combination with laser, I now do phototherapeutic keratectomy first for slight topography-guided optical regularization of the corneal surface and then epi-off cross-linking, but I have done epi-on, too, for a couple of years. With epi-on, I wait quite a long time, maybe 45 to 50 minutes, to get saturation and to identify flare. I look for homogenous riboflavin staining of the stroma and anterior chamber flare — signs that the riboflavin has penetrated. I always wait quite a long time, so that is a disadvantage. After saturation I wash the epithelium, and then I use UV.

Rubinfeld: If you have too much riboflavin on the surface, how much UV goes through?

Trattler: In our experience with epi-on for the CXLUSA study group, we considered that the epithelium might be blocking some UV light, so we switched the riboflavin concentration and the UV power. We went from applying 3 mW for 30 minutes to applying 4 mW for 30 minutes and saw a nice jump in efficacy.

Jorge L. Alió, MD, PhD: I use the Dresden protocol or the one from Avedro. I never reduce the time.

Paolo Vinciguerra, MD: Twenty or 25 minutes could be enough. We get a demarcation line almost at the same depth, but flattening was much less with epi-on. That is our experience using 3 mW and 9 mW.

Rubinfeld: What metric should we use now to determine when to start UV light treatment?

Vinciguerra: First, always check the pachymetry because sometimes if you use the standard solution with dextran, you have a strong reduction in the pachymetry, and then you apply the UV light and have corneal burn and a deep opacity. So always check that you are within the Dresden protocol.

Round table participants



Roy S. Rubinfeld
Moderator



Jorge L. Alió



Arthur B. Cummings



Michael Mrochen



Karolinne Rocha



Aleksandar
Stojanovic



William B. Trattler



Paolo Vinciguerra



George O.
Waring IV

Rubinfeld: Looking at the cornea at the slit lamp, can you use the presence of a homogeneous green in the stroma to be a metric for loading the solution?

Vinciguerra: We published a paper in the *Journal of Refractive Surgery* that compares use of optical coherence tomography and electrophoresis to measure not only depth but also concentration against standard epi-off procedures. That is another metric that could be used.

Karolinne Rocha, MD, PhD: We published a paper in the *Journal of Refractive Surgery* last year showing significant irregularity, variability and alterations in regional epithelial thickness in keratoconus using spectral-domain OCT. Significant epithelial thinning is observed over areas in which the anterior stromal curvature is steep and the surface elevated, while thickening of the corneal epithelium is seen over areas of stromal thinning, especially in severe cases. When we talk about riboflavin and light distribution, is it possible to compensate for these areas of epithelial thickening and irregularity?

Michael Mrochen, PhD: Riboflavin, especially if you use it in high concentrations, absorbs that strong light. If you substantially reduce the concentration of riboflavin in the epithelium, then that affects the concentration in the stroma.

Energy distribution

Mrochen: There is a complete misunderstanding in the ophthalmic field about this 5.4 J/cm². If you look at the original data, the peak fluence we had was about 7.6 J/cm². In the periphery, we are actually going out to about 7 J/cm². Starting with 3 mW for 30 minutes is maybe too low. By increasing the numbers, you are in the range that is used in most devices. We started off with the original device in which we had something of a Gaussian profile, but we did not achieve enough effect in the periphery. Sheehan et al showed that about 30% more energy is needed in the periphery, 3 mm from the center, to have the same cross-linking effect. We applied an optical system that delivers much more light in the periphery, about 30% more. In 1-year data presented in Cambridge by Prof. Theo Seiler, 90% of patients had flattening of more than 1 D. In about 60% of cases, there was more than 2 D of flattening.

There is a lot of discussion about time. And there is a lot of discussion about whether we should leave on the epithelium. To optimize the outcome, in my opinion, we have to work on the energy distribution applied to the cornea to achieve the appropriate outcome because, at the end of the day, it is the

combination and not just the riboflavin. If you just put in riboflavin, nothing happens.

There is a complete misunderstanding about the energy distribution of the light on the cornea. The light distribution, the energy distribution, over time is the driver.

Developing a decision tree

Waring: Take a step back and look at it from a more global perspective: epi-on vs. epi-off. It is like a risk-benefit analysis. Even if epi-off is slightly more efficacious, it may still be OK to do epi-on in most cases if there is progression because you have the added safety profile and you can presumably re-treat more easily if needed. Potentially, there is a whole treatment algorithm that we could come up with for certain cases that may do better with epi-off, but the vast majority may do better with an optimized epi-on procedure. That may be the future of cross-linking.

Mrochen: I would envision a decision tree. Rather than saying, "This is the right way. This is the standard protocol," we develop a decision tree for surgeons based on evidence-based criteria so we can offer patients a solution.

Waring: It is a myopic view to think that you are just going to treat one way. A decision tree could reflect more than just a biomechanical outcome, but more of a truly refractive outcome as well.

Mrochen: Whatever we are achieving with cross-linking today is not really improving the vision of the patient. If someone comes in with bad vision, you might fix the problem and it does not get any worse, but that does not have a refractive solution.

Rubinfeld: As a standalone procedure, this is generally the case.

Trattler: We have found improvement in vision with epi-on cross-linking. About 50% of patients improve one line or more, and patients often report improvement in quality vision.

Thin vs. steep

Trattler: Question to the panel: About beam profiles, we have some patients with keratoconus and central thinning and other patients with pellucid marginal degeneration who have peripheral thinning. When using a 9-mm beam, is it best to treat the central cornea with UV light for every patient? Or should we alter the placement of the beam based on the thinnest portion of the cornea?

Mrochen: We advise surgeons to focus or center the beam on the thinnest part

POINT / COUNTER

What tool or method is best for diagnosing keratoconus?

POINT

Corneal topography in most cases

I think that computerized corneal topography analysis remains the primary tool for diagnosing keratoconus. I use corneal topography to look for early changes in the corneal shape and optics. When looking at these maps, one can either use Placido-based or elevation-based topography, and there are a number of factors to look for: We look at asymmetry of astigmatism, both with regard to inferior-superior differences in steepness and irregularity of the astigmatic bowtie, as well as corneal steepening. Traditionally, a keratometry reading of 47 D or above is one possible indicator for keratoconus.

Elevation topography is also of use. In particular, when using height maps, the posterior elevation map is of particular importance because this may be one of the early indicators for diagnosing keratoconus. This may be more sensitive than the anterior sagittal height map because the anterior irregularity might be masked by the epithelium, which can smooth the anterior keratoconic irregularity. In addition, this type of topographer can produce pachymetry maps. Corneas where the thinnest area is off axis or in which the central cornea is relatively thin in relation to the periphery may also suggest keratoconus.

I do think we need a tool to measure corneal biomechanics. Keratoconus is, inherently, a disease of corneal structure and strength; so, an instrument to directly measure corneal biomechanical properties would be an indispensable tool for early detection of keratoconus.

Peter S. Hersh, MD, is an OSN Refractive Surgery Board Member. Disclosure: Hersh is a consultant of Avedo Inc.



Peter S. Hersh

COUNTER

Multimodal approach most effective

I think it is important to begin by stipulating that no currently available tool for diagnosing keratoconus provides a complete view of the disease state. Rather, topography, tomography and biomechanical measurement principles all provide valuable but very distinct perspectives on a complex disease. Ultimately, I think the most effective screening tools will involve a multimodal approach that incorporates static corneal shape and dynamic corneal behavior. We still have much to learn about the early changes that lead to progressive corneal steepening, and the better we become at identifying and measuring the early disease drivers, the more sensitive our screening paradigms will become.

In most studies and throughout clinical practices today, anterior corneal curvature is still the de facto standard. I rely most heavily on Placido topography or Scheimpflug-based anterior surface curvature to determine my initial level of suspicion for disease, and I prefer a display that provides both axial and tangential curvature because the latter more accurately localizes and quantifies peripheral curvature features. I then refine that impression with corneal thickness and elevation maps, epithelial thickness maps, and Ocular Response Analyzer (Reichert) variables (including custom variables we have found to be more sensitive and specific for keratoconus). Emerging tools such as OCT elastography and Brillouin microscopy that can characterize the three-dimensional biomechanical properties of the cornea may support even earlier diagnosis by detecting areas of focal weakness that current devices cannot resolve.

One promising approach to wholistic screening is patient-specific computational modeling, which accounts for the totality of the 3-D corneal geometry and moves away from the confusion associated with parsing corneal shape into many partial representations of curvature and thickness. This structural approach also allows for simultaneous consideration of spatial material properties and simulation of the effects of surgery or further intrinsic weakening on corneal optics in a virtual representation of a patient's eye.

William J. Dupps Jr., MD, PhD, is Director, Ocular Biomechanics and Imaging Lab at Cleveland Clinic, Ohio. Disclosure: Dupps is a co-inventor on patents related to elastography and ocular computational modeling held by Cleveland Clinic Innovations, receives research support from NIH (R01 EY023381), a State of Ohio Third Frontier Innovation Platform Award, Avedo and Zeiss, and has served as a consultant for Zeimer.



William J. Dupps Jr.

Cover story continued from page 11

of the cornea to make sure they are not harming the endothelium. If you have a de-centered pellucid situation, we advise that surgeons protect the limbus area and de-center the beam. We basically have a profile around 8 mm or 9 mm, and we de-center the whole thing, so the upper part would not be cross-linked.

Waring: There is some really interesting finite element modeling data that suggest that if you do not treat the whole cornea, you may get improved shape. Presumably, there is a gradient of disease and the whole cornea is not equally ectatic. You have your super-threshold point where there is a thinnest point and the weakest part. We want to flatten one part but relatively steepen the other. If you cross-link the entire cornea, you may hold that back. You may achieve more effect by not cross-linking the entire cornea. That is what the model suggests and is something we should look at.

Rocha: The steepest corneal curvature may or may not correlate to the thinnest point in keratoconus. Finite element modeling data of the cornea and in vivo spectral-domain imaging studies suggest that the “stress” in corneal ectasia does not correlate to the steepest area but more likely to the thinnest point or the “weakest point.”

Mrochen: That is the reason why our beam profile has less of the center and goes more on the periphery.

Waring: The steepest area is not the thinnest area because of the epithelial hyperplasia.

Trattler: So we want to be on the thinnest spot, not the steepest.

Rubinfeld: If fibers are stretched thin beyond a certain point, whether or not you cross-link them, you are not going to stop the progression of disease, correct?

Cummings: Mrochen and Seiler published a paper 3 or 4 years ago suggesting that any cornea steeper than 58 D would probably not do well. I do not agree entirely. We have cross-linked corneas up to 65 D, sometimes even 70 D, that flatten by 3 D or 4 D, but in some, the cornea is so stretched and the fibers that you are trying to cross-link are so damaged that it is like trying to cross-link soup. There is no material there. It is all so destroyed that there is nothing you can really cross-link. We do not have hard and fast evidence, but I think for cross-linking to work, there needs to be collagen fibers that have some sort of structural integrity that can be strengthened. Otherwise, there will not be much effect.

Documenting progression

Rocha: Progression documentation prior to cross-linking treatment is important when we are comparing clinical trials. For example, I was involved in the U.S. Food and Drug Administration corneal collagen cross-linking clinical trial at Emory University for 1 year, and we needed to prove progression to enroll patients. This is a discussion among European and U.S. surgeons: “Do we need to prove progression to treat the patients?” For some studies, this is not a requirement. We definitely had eyes that were progressing, and then they were treated with epi-off cross-linking. We observed a stop in progression and even topographic improvement. I believe keratoconus patients should be treated upon the diagnosis despite significant clinical and/or topographic progression, especially in young patients. Cross-linking is a safe procedure if you follow the safety standards and guidelines, including the correct riboflavin concentration, UV light exposure, residual stromal bed and endothelial cell count.

Stojanovic: One point that has been made clear in the discussion whether to treat early disease is this: If you have a patient younger than 20 years with signs of keratoconus, then, go, treat.

Rubinfeld: This comes back to the idea of epi-on, epi-off, safety of the procedure and the development of an algorithm, as Dr. Waring suggested.

Trattler: I feel very comfortable treating early. We have a safe procedure in epi-on in which the risk is extremely low for all patients, young and old. Not only will epi-on stop progression, but often you will see improvement in corneal shape. I expect that over time we will see more people jump on the epi-on bandwagon.

Mrochen: In Europe, all of the systems are approved for progressive keratoconus. So if you do a treatment that is not shown to be progressive for the patient, you end up with off-label use.

Waring: Do you believe that progression needs to be documented before you treat?

Alió: I believe in treating case by case. With good vision and a stable condition in terms of evolution, I do not indicate immediately cross-linking as a dogmatic indication. We have a tool, but when should we use it? We use it when the patient is at risk for losing vision. Epi-off is badly tolerated in children, and infections frequently can happen. This is a tool that has a risk-benefit that you have to balance.

Trattler: I have been doing epi-on ex-

clusively for 3.5 years. The procedure itself is extremely safe. The downside is close to zero for patients, and I feel very comfortable recommending and treating right away. Even if the patient ends up seeing about the same on the Snellen chart, that is OK. There are still typically improvements in corneal shape and in quality of vision.

Patient's perspective

Cummings: The other point I want to make is this: At the end of the day, it is the patient's opinion that matters, so that has to be a part of our decision tree.

Typically, patients get some sort of psychological reassurance from the positive effects of cross-linking. That helps them a huge amount. They start rubbing their eyes less. They start chilling out a bit. They can wear lenses more readily, and so that makes them happier.

Trattler: If you ask a patient a month after cross-linking and he has received a new scleral contact lens, he may say that he sees better, but was it the cross-linking or just the fact that he got fitted with a new contact lens? That is what makes questionnaires such as the National Eye Institute Visual Function Questionnaire 25 so hard to decipher because cross-linking may not be the only reason the patient is seeing better. He has new contact lenses. If the physician has optimized the ocular surface with punctal plugs or topical cyclosporine, then his dry eye may be a little better as well — all factors that can help the patient see better.

One of the biggest innovations for our keratoconus patients has been the introduction of the scleral contact lens, which vaults over the center of the cornea but does not touch the cornea. Patients are more comfortable, and they achieve high-quality vision. Comparing rigid gas permeable lenses to scleral lenses, I do have one concern about rigid gas permeables. One of the biggest risk factors for progression of keratoconus is eye rubbing, which is essentially compression of the cornea. I wonder whether the compression of the cornea with each blink with a rigid gas permeable contact lens in any way affects the stability of the cornea.

Waring: There may be an orthokeratologic component to that as well, which we observed in some of our original studies. When we got the patients back into a rigid lens, not a scleral lens, early after treatment, we found that the lens may act almost like a cast as the cornea remodels. Even though it may not have a lasting effect, there may be some temporary effect, so that seemed to get a slightly improved benefit from an orthokeratologic standpoint. And, certainly, there is the idea that you get a more normal-

ized cornea so patients are more likely to be able to wear their contact lens in the first place. In our experience, we had the best luck with hybrid lenses.

Rubinfeld: If we are going to say that someone has had a cross-linking treatment failure, then that patient has subjective and objective vision loss?

Cummings: That makes sense. It is very subjective, and it depends on your contact lens expert. We have a fantastic contact lens person who tells us who is doing well and who is not.

Rubinfeld: Of seven cases in my clinic that were failures, all were associated with eye rubbing.

 OSN

Look for a discussion of epi-on vs. epi-off in part 2 of this round table in an upcoming issue of OSN.

References:

Koller T, et al. *J Cataract Refract Surg.* 2009;doi:10.1016/j.jcrs.2009.03.035.
 Rocha KM, et al. *J Refract Surg.* 2013;doi:10.3928/1081597X-20130129-08.
 Sheehan M, et al. *Optom Vis Sci.* 2011;doi:10.1097/OPX.0b013e31820f1585.
 Vinciguerra P, et al. *J Refract Surg.* 2013;doi:10.3928/1081597X-20130509-01.

Jorge L. Alió, MD, PhD, can be reached at Vissum, Instituto Oftalmológico de Alicante, Avda. de Denia, s/n, 03016 Alicante, Spain; 34-965-150-025; email: jlalio@vissum.com.

Arthur B. Cummings, FRCS, can be reached at Wellington Eye Clinic, Suite 36 Beacon Hall, Beacon Court, Sandyford, Dublin, Ireland; 353-1-2930470; email: abc@wellingtoneyeclinic.com.

Michael Mrochen, PhD, can be reached at IROC Science, Technoparkstrasse 1, 8005 Zurich, Switzerland; 41-43-5000850; email: michael.mrochen@irocscience.com

Karolinne Rocha, MD, PhD, can be reached at Cole Eye Institute, Cleveland Clinic Foundation, 2022 East 105th St., Cleveland, OH 44195; email: karolinnemaia@hotmail.com.

Roy S. Rubinfeld, MD, can be reached at Re:Vision, Roy Rubinfeld, MD, PO Box 30845, Bethesda, MD 20824; 301-908-8091; email: rsrubinfeld@gmail.com.

Aleksandar Stojanovic, MD, can be reached at SynsLaser Kirurgi, Oslo and Tromsø, Norway; email: aleks@online.no.

William B. Trattler, MD, can be reached at 8940 N. Kendall Drive, #400, Miami, FL 33176; 305-598-2020; email: wtrattler@gmail.com.

Paolo Vinciguerra, MD, can be reached Instituto Clinico Humanitas, Milan, Italy; 39-02-55-21-13-88; email: paolo.vinciguerra@humanitas.it.

George O. Waring IV, MD, can be reached MUSC Storm Eye Institute 167 Ashley Ave., Charleston, SC 29425; 843-792-1414; email: georgewaring@me.com.

Disclosures: Alió has no relevant financial disclosures. Cummings has no relevant financial disclosures. Mrochen is an IROC Innocross shareholder. Rocha is a consultant for CXL Ophthalmics LLC. Rubinfeld has financial interests in CXLUSA LLC, CXLO LLC and CurveRight LLC. Stojanovic has no relevant financial disclosures. Trattler has a financial interest in CXLO. Vinciguerra is a consultant to Schwind and Nidek. Waring is on the medical advisory board of CXLUSA.