

CXL:

The US Perspective

A *Cataract & Refractive Surgery Today* interview with Roy Rubinfeld, MD.

The area of corneal collagen cross-linking (CXL) is as "hot as it can be," Dr. Rubinfeld said during a recent chat with CRST.

CRST: How long have you been involved with CXL, and how are your studies organized?

DR. RUBINFELD: I have been performing and studying CXL since 2009. The research studies that I am involved with are very different than the ones being conducted by the FDA. That agency sets a protocol and then leaves it in place for several years as the data are gathered. Therefore, the studies are not iterative; that is, if something new is learned, for the most part, the study continues with the same protocol.

In the United States, researchers began looking at epithelium-off approaches, because that was what had been approved in Europe. By September 2006, all 25 European Union countries had approved CXL, and it was obvious that it worked. US corneal specialists found it frustrating that they did not have access to the technology, and these physicians felt badly that patients with keratoconus were continuing to lose their vision. Some of us got together and formed our own group and set up a physician-sponsored, Institutional Review Board-approved series of protocols under the auspices of the CXL-US Study Group (see *CXL Trials, Resource Guide, References*). There are 14 practices in the group, spread throughout the United States. In this manner, we can perform clinical studies of CXL and examine which techniques appear to be the most effective with the least risk.

Our group has moved from epi-off, which was the standard, to epi-on in 2010, and we have found greatly improved healing with that approach. Complications such as infections, haze, perforations, and melting are not common with epi-off, but one of any of these

serious cases is too many. We have developed better ways to do CXL by modifying, amending, and evaluating not just how to best perform epi-on CXL, but also ways to make it more like a refractive procedure.

DATA GATHERING: EPI-ON/EPI-OFF

CRST: Let us talk specifically about the data being gathered.

DR. RUBINFELD: The original studies were epi-off, as I mentioned. Early on, however, I observed some European surgeons who were proponents of an epi-on approach, and our group involved practitioners from photochemists to epidemiologists to evaluate the safest and best ways to do CXL.

In some of the studies, there was latitude in how the epithelium could be treated prior to the riboflavin's instillation. When we saw good results with certain techniques, the next step was to incorporate recent innovations and amend the protocols so that we could compare data among groups of patients.

One of the challenges in CXL is in measuring its effects. For example, the Pentacam Comprehensive Eye Scanner (Oculus Optikgeräte) is one of the best diagnostic technologies available for the diagnosis of keratoconus. It is not as useful, however, for measuring the postoperative effects of CXL. In essence, there is significant disagreement in the definition of success and the metrics used for outcomes analysis.

CRST: Do you have a sense of what metrics show the most promise?

DR. RUBINFELD: One metric being used is called *Kmax* for the maximum keratometry values. But, patients do not come to the office and say, "I'm worried about my *Kmax*." They report seeing multiple images, an inability to drive at night, and that spectacles do not help.

CXL TRIALS, RESOURCE GUIDE, REFERENCES

www.cxlusa.com/find-a-doctor-nearest-you.aspx

Visit the link and browse the map and the list below to find a CXL-USA Study Group surgeon or center nearest you. Centers outside of the United States are also included.

www.avedro.com/clinical-trials

Phase 3 studies of accelerated CXL in eyes with keratoconus or corneal ectasia after refractive surgery are currently being conducted in the United States using Avedro's KXL System and riboflavin.

www.keratoconuscenter.com/site/clinical-trials.htm

The Cornea and Laser Eye Institute, Hersh Vision Group/CLEI Center for Keratoconus is currently conducting clinical trials of CXL. The clinical trials are designed to study the benefits and safety of CXL in patients with either keratoconus or corneal ectasia after previous refractive surgery. The goal of CXL is to decrease the progression of these corneal thinning disorders.

www.nkcf.org/clinical-trials

National Keratoconus Foundation's information on clinical trials.

<http://mediacenter.ascrs.org/media/update-us-clinical-trials-cxl-usa>

The American Society of Cataract and Refractive Surgery Media Center's update on US CXL clinical trials.

Eyetube Videos

<http://eyetube.net/series/volume24issue4/corneal-cross-linking-for-keratoconus-and-post-laser-ectasia-safire/>

<http://eyetube.net/video/corneal-cross-linking-for-keratoconus-and-post-laser-ectasia-refodi/>

<http://eyetube.net/series/eyetube-tv-daily-coverage-orlando-2011/epi-on-vs-ep-off-cxl-for-keratoconus-post-lasik-ectasia/>

<http://eyetube.net/series/acos-dulaney-winter-meeting-2012-daily-coverage/acos-corneal-collagen-cross-linking-study-update/>

<http://eyetube.net/series/eyetube-tv-show-daily-sandiego-2011/corneal-collagen-crosslinking/>

<http://eyetube.net/video/topo-guided-lasik-xtra-for-hyperopia/>

<http://eyetube.net/series/daily-coverage-aspen-2014/state-of-the-art-techniques-for-cxl/>

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2. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg.* 2008;34(5):796-801.
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5. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea.* 2007;26(4):385-389.
6. Caporossi A, Mazzotta C, Baiocchi S, et al. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena Eye Study. *Am J Ophthalmol.* 2010;149:585-593.
7. Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cat Refract Surg.* 2008;34(5):796-801.
8. Vinciguerra P, Albè E, Trazza S, et al. Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus. *Arch Ophthalmol.* 2009;127(10):1258-1265.

SUGGESTED READING**CRST**

<http://bmctoday.net/crstoday/2013/04/article.aspx?corneal-collagen-cross-linking-in-children>

<http://bmctoday.net/crstoday/2013/04/article.aspx?point-counterpoint-my-ideal-ablation-pattern-for-combined-cx-1-treatments>

<http://bmctoday.net/crstoday/2013/02/article.aspx?post-lasik-ectasia>

<http://bmctoday.net/crstoday/2013/02/article.aspx?update-on-surface-ablation-procedures-part-two>

<http://bmctoday.net/crstoday/2012/10/article.aspx?strengthening-weak-corneas-with-cxl>

<http://bmctoday.net/crstoday/2012/10/article.aspx?topography-guided-laser-surgery>

<http://bmctoday.net/crstoday/2012/05/article.aspx?how-to-perform-cxl>

<http://bmctoday.net/crstoday/2012/05/article.aspx?illumination-lamps-for-cxl>

<http://bmctoday.net/crstoday/2012/05/article.aspx?cxl-with-the-epithelium-on-or-off-which-is-better>

<http://bmctoday.net/crstoday/2012/05/article.aspx?the-risks-of-cxl>

<http://bmctoday.net/crstoday/2012/05/article.aspx?preventing-ectasia-with-cross-linking-after-prk-or-lasik>

<http://bmctoday.net/crstoday/2012/05/article.aspx?update-on-the-us-status-of-cxl>

<http://bmctoday.net/crstoday/2012/03/article.aspx?cataract-surgery-after-refractive-surgery-and-cross-linking>

CRSTEurope

<http://bmctoday.net/crstodayeurope/2014/02/article.aspx?why-i-chose-to-perform-a-new-procedure-on-a-loved-one>

<http://bmctoday.net/crstodayeurope/2013/10/article.aspx?keratoconus-management-a-stepwise-approach>

<http://bmctoday.net/crstodayeurope/2013/06/article.aspx?therapeutic-options-to-delay-the-need-for-corneal-transplant>

<http://bmctoday.net/crstodayeurope/2011/01/article.aspx?the-case-for-cxl-is-it-a-standalone-or-a-combination-procedure>

<http://bmctoday.net/crstodayeurope/2011/01/article.aspx?the-future-of-corneal-collagen-crosslinking>

CRST's sister publication Advanced Ocular Care

<http://bmctoday.net/advancedoculercare/2013/09/article.aspx?are-you-the-missing-link-in-crosslinking>

<http://bmctoday.net/advancedoculercare/2012/06/article.aspx?cxl-with-the-epithelium-on-or-off-a-debate>

<http://bmctoday.net/advancedoculercare/2011/02/article.aspx?corneal-collagen-cross-linking>

<http://eyetubeod.com/2010/12/the-promise-of-corneal-collagen-cross-linking>

The real question, then, is how do we best measure the effects of CXL as a standalone procedure? In general, it is extremely effective at stopping the progression of keratoconus (> 90% with a single treatment). With an epi-on approach, nearly all of the risks are eliminated. Therefore, the risk-benefit ratio indicates that more patients will receive the treatment at younger ages and at earlier stages of the disease.

CRST: Your passion for this research really shines through, and it is refreshing.

DR. RUBINFELD: Our goal as a group is to find the safest, most effective, and most comfortable ways to prevent keratoconus from becoming a problem for patients: before they start to get irregular astigmatism. There is good evidence that epi-on CXL, just as a standalone procedure, can simply stop an overwhelming majority of patients from developing a problematic disease. For me, it is very rewarding to be involved in studies related to that.

THE SHORTCOMINGS OF EARLY EPI-ON STUDIES

CRST: What is the newest work that is being done?

DR. RUBINFELD: One area of focus today is in determining why some of the earlier studies of epi-on showed it not to be effective and why more recent studies show that it does work.

The success of CXL depends on a critical balance of three elements: riboflavin, ultraviolet (UV) light, and oxygen. The early studies employed dextran-containing riboflavin, which is a very large molecule, and it did not penetrate the epithelium well. It took researchers a while to figure this out.

Then, there was an attempt to standardize the amount of riboflavin in the early laboratory studies. Later, in clinical settings, researchers simply used riboflavin drops for X amount of time on intact epithelium. Some corneas are more permeable than others, some riboflavin formulations are much better at penetrating intact epithelium, and the delivery systems were different. For these reasons, the data obtained were not clear.

Using a slit lamp, surgeons now realize they can visualize how well the riboflavin has penetrated the stroma and whether it is prepared for the UV light application. This is to say, we have come to understand the critical role of observing the stromal riboflavin concentration before applying UVA.

Another question about epi-on CXL was if the UV light would go through the epithelium. With our inno-

ventions, it does, and there is more than enough UV light, even at 3 mW/cm², that this concern turned out not to be an issue.

CRST: So does this mean that more physicians are interested in performing epi-on CXL?

DR. RUBINFELD: Yes. The surgeons with experience performing epi-off want to find a way to reduce their patients' risk, discomfort, and long recovery process. Many of the treatments have been improved. My group uses a proprietary formulation of riboflavin that is capable of producing good stromal loading through epithelium in 15 to 20 minutes. Surgeons want reliable, consistent, efficient procedures that are safe and effective, and patients want quick healing and to be able see again the next day and wear their contact lenses within a week after their procedures. That is what we are aiming for.

CXL AS A REFRACTIVE PROCEDURE

CRST: Can you talk a little about CXL as a refractive procedure?

DR. RUBINFELD: CXL as a standalone procedure primarily stops the progression of keratoconus, and it is associated with mild improvement in some of the outcome metrics that we might measure, say Kmax. The real purpose of CXL today is to prevent a disease and not refractive improvement.

What if we turned our attention to CXL being performed in conjunction with other refractive procedures? For example, there have been efforts to combine CXL with microwaves to flatten overly steep keratoconic corneas. Unfortunately, like most heat-based procedures, the effect fades. Our group, however, is investigating other ways of doing this, and one in particular shows great promise.

The idea is to use CXL to improve and regularize the corneal shape, which is essentially a refractive procedure, for either a therapeutic effect or as an elective refractive procedure. The combination of CXL and the excimer laser, for example, is being pioneered by John Kanellopoulos, MD, in Athens; Arthur B. Cummings, MB ChB, FCS(SA), in Dublin; and David Lin, MD, FRCSC, in Vancouver. The excimer laser is used to sort of flatten some of the cone and steepen the other areas so that the cornea is not so irregular, shift it toward a more regular shape, and then cross-link it so that it is strengthened.

It is a promising approach, and it helps some patients. The problems with it are: (1) the surgeon must remove the epithelium because it is PRK; (2) the patient will likely never attain normal vision, just

improvement; (3) laser nomograms and technologies are in evolution; and (4) it is a subtractive procedure, and therefore further thins (weakens) the cornea.

CRST: What would be the approach in a patient who was seeking an elective, purely refractive procedure, as in to see well without glasses?

DR. RUBINFELD: CXL has been studied in this setting in several ways, one of which is CXL with LASIK. Minoru Tomita, MD, of the Shinagawa LASIK Center in Tokyo has done some work in this area. In this procedure, CXL could also prevent ectasia from developing in eyes undergoing LASIK.

Another idea being considered is what if CXL itself, so-called selective CXL, could be used to change the shape of the cornea in ways that adjusted the refractive status of the cornea? This concept is really in its infancy, but it is highly interesting because if we could accomplish this, we could potentially correct patients without a laser, no flap, no incisions, no PRK, no epithelial removal—the holy grail of refractive procedures!

CRST: Who is working on that?

DR. RUBINFELD: It is somewhat below the radar. Michael Mrochen, PhD, of IROC Science in Zurich is working on this. Michael has had a central role in other major innovations like excimer laser, the invention of CXL, and many others, so I am particularly interested in watching his work in this area.

CONCLUSION

DR. RUBINFELD: I see myself as if I were one of the Blues Brothers: I am on a “mission from God” to stamp out corneal transplant from keratoconus. ■

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