OCULAR SURGERY NEWS

Researchers attempt to progress cross-linking in the US

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U.S. surgeons lag behind their European colleagues when it comes to corneal collagen cross-linking, but attempts are being made to catch up because the potential benefits of the procedure are tantalizing.

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Researchers who are studying the combination of ultraviolet light and riboflavin in the cornea to strengthen collagen bonds cite promising outcomes in patients with keratoconus and ectasia as main reasons to press on with clinical trials, even if U.S. Food and Drug Administration approval and profitability in the marketplace may be in the distant future.

Even though FDA approval of the procedure is not expected for at least 2 years, experts said in telephone interviews, surgeons in the United States are exploring options through investigational new device exemptions and physician-sponsored investigational clinical trials.

“Cross-linking is a significant advance for ophthalmology,” **R. Doyle Stulting, MD, PhD,** who has conducted clinical trials with the technique, said. He said in a telephone interview that cross-linking can stabilize the cornea long before keratoconus would progress to the stage of requiring a corneal transplant.

Stulting, an OSN Cornea/External Disease Board Member, said he analyzed an Eye Bank Association of America statistical report that documents the indications for corneal transplantation in the U.S. and compared the data to reasonable assumptions of the effect of cross-linking based on its known efficacy in treating the conditions leading to corneal transplantation.

“[Cross-linking] has the potential of avoiding 50% of the corneal transplants in this country every year,” he said.

Keratoconus is widely underdiagnosed, **George O. Waring IV, MD,** said in a telephone interview. While the occurrence is about one in 2,000 cases in the literature, he said it may be closer to one in 500 in clinical practice.

David R. Hardten, MD, another cross-linking researcher and OSN Cornea/External Disease Section Editor, added, “There’s just a tremendous number of patients who have keratoconus, and there’s a tremendous burden on our patients.”

Combining cross-linking with other techniques may be an option for treating keratoconus, according to David R. Hardten, MD.

Image: Shari Fleming Photography

“There’s a fairly lengthy recovery from transplants; there’s a fair amount involved in the process” Hardten said. “If we can reduce the number of transplants, that would be a good thing for the patients that we take care of.”

In the pipeline

Rapid learning is at the heart of the second clinical trial, **Roy S. Rubinfeld, MD,** a clinical investigator for the CXLUSA clinical trials, said at the ASCRS meeting. He is one of nearly three dozen surgeons participating in a physician-sponsored, noncommercial, non-FDA, institutional review board-approved series of studies.

Roy S. Rubinfeld

The trial focuses primarily on evaluating and improving epithelium-on cross-linking.

The CXLUSA studies are different from the Avedro trial, which is designed for commercial approval and therefore must “freeze” protocols, Rubinfeld said.

“As we learn and incorporate new techniques and innovations, we are able to submit, amend and modify our protocols,” Rubinfeld said. “We learn quickly.”

For example, he said, when epithelium-off procedures were found efficacious in their early work in 2009 and other researchers were reporting some success with epithelium-on procedures, some of their protocols were changed to epithelium-on.

“We found the results to be similar to epi-off without the slow visual recovery, pain, and risks of haze, infection and the rare corneal melting,” he said.

In one CXLUSA sub-study, Rubinfeld said, short-duration cross-linking is performed in patients who have or who are suspected to possibly have forme fruste keratoconus and patients who are thought to be at potentially higher risk of developing ectasia and are scheduled to undergo laser vision correction. True keratoconus is an exclusion criterion for this study. Started in October 2011, the trial seeks to enroll 500 patients by December 2014.

Combination procedures

Hardten said that combining cross-linking with already established techniques could offer options for keratoconus patients who are not doing well in glasses or contact lenses. Cross-linking could halt progression, while a second method could improve corneal shape. Corneal implants or some form of keratoplasty might work, he said.

Waring called simultaneous cross-linking and LASIK an exciting indication, especially for patients with borderline cases who want a lamellar refractive procedure.

“We may be able to provide refractive surgical procedures to patients who are borderline, and we have evidence suggesting that combined cross-linking and LASIK may improve refractive stability,” he said.

A series of experiments in Canada and Europe combines cross-linking with limited topography-guided PRK. While it may not eliminate the need for glasses or contacts, it may greatly improve the overall visual functioning of patients with a highly aberrated eye, Waring said.

Eric D. Donnenfeld, MD, another cross-linking investigator and an OSN Cornea/External Disease Board Member, said wavefront-guided treatments offer about 80% of the patients a significant improvement in keratometry and visual acuity.


Eric D. Donnenfled

“Now we’re thinking about visually rehabilitating patients and combining them with cross-linking at the same time, and that takes cross-linking to a whole new level,” he said.

FDA status

Two FDA trials, sponsored by Peschke Meditrade and Topcon, ended due to financial constraints; the lengthy trials needed were not likely to recoup enough money for the companies to continue the projects, Stulting said.

The intellectual property associated with cross-linking is relatively small, Stulting said. It can be done with a properly calibrated ultraviolet light and riboflavin that is formulated at a local pharmacy.

The original Dresden protocol for cross-linking, described in a 2003 article in the *American Journal of Ophthalmology*, outlined a procedure in which the central corneal epithelium is abraded, photosensitizing riboflavin drops are applied for a half hour or more, and the eyes are exposed to ultraviolet light at a wavelength of 370 nm with an irradiance of 3 mW/cm² at a distance of 1 cm for 30 minutes.

The interaction of riboflavin and ultraviolet light induces a reactive oxygen species that forms additional covalent bonds between collagen molecules in the cornea with no damage to the epithelium. This, in turn, stiffens the cornea.

Despite the long European experience, well-controlled clinical trials must be performed in the U.S. Cross-linking itself requires long periods of study to establish its efficacy because the current indicators of efficacy require a significant amount of time to show change. Furthermore, the changes are small, so a large number of patients must be treated. In addition, there are no direct measures of corneal stiffening in vivo, so surrogate measures are used instead.

“The FDA will not grant an approval based on peer-reviewed information that appears elsewhere, only from a monitored, approved, FDA-sponsored clinical trial,” Stulting said. “That process is expensive, it’s time-consuming, and as is the case, two companies stopped the trials because of the cost.”


R. Doyle Stulting

“The bottom line is, like all things in advanced ophthalmic technology, we’re about 10 to 15 years behind the rest of the world,” Waring said. “It’s a serious issue because we can’t readily provide treatment that would benefit patients and we know are safe and efficacious and would prevent patients from going on to get much more invasive surgical procedures.”

On the horizon

Donnenfeld said that even more experimental uses are being considered for cross-linking, including treating recalcitrant infections that do not respond well to antifungal therapy. This involves debriding the epithelium and applying a higher energy for a longer amount of time. Although cross-linking has been examined for fungi, bacteria and *Acanthamoeba*, early research shows efficacy appears to be in fungal keratitis, “where conventional drugs don’t really work that well,” he said.

Stulting said that cross-linking is already used in other countries for treatment of corneal melt and infectious keratitis and prevention of ectasia.

Other experiments are seeking faster delivery of riboflavin through the epithelium or using higher powers of ultraviolet light to shorten treatment times. The original Dresden protocol applied 3 mW/cm2 of irradiance over 30 minutes. Since then, Donnenfeld said, there has been a lot of interest in reducing the amount of time, all the way down to as little as 3 minutes of exposure using 30 mW/cm2. While some studies show that there is a drop in efficacy above 15 mW/cm2, no data in humans yet support that finding.

Currently, multicenter clinical trials of accelerated cross-linking are being conducted in the U.S. by Avedro, Hersh said.

A. John Kanellopoulos, MD, an OSN Europe Edition Board Member, reported at the ASCRS meeting that he uses a variety of ultraviolet light fluences depending upon the procedure.


A. John Kanellopoulos

“With 10 years of CXL experience and over 3,000 cases, we have introduced and reported on multiple new applications and techniques of CXL, such as higher fluence, combining CXL and LASIK, and combining CXL and topography-guided PTK,” he later told *Ocular Surgery News*.

“We have, in our experience, enough evidence to advocate LASIK Xtra in hyperopia, as it seems to stabilize the cornea steepening desired and initially achieved,” he said.

For infections, he combines a lower fluence of 3 mW/cm2 with longer treatment times to achieve a bactericidal effect.

Donnenfeld said that more researchers are looking to combine cross-linking and LASIK, in a procedure referred to as LASIK Xtra (Avedro), to prevent regression in hyperopic LASIK.

In conventional procedures, “the incidence of ectasia is so low, there’s very little need for that,” Donnenfeld said. “But for higher-risk patients, combining with cross-linking may be very reasonable. And if it is shown to stabilize the cornea and stop hyperopes from regressing, then you really will have a nice adjunct to what we’re doing now.”

Kanellopoulos explained his protocol for LASIK Xtra.

“We had an oxymoron, because we’re traditionally thinking that cross-linking flattens the cornea. And in hyperopia, we want to keep the cornea steeper. Interestingly, this is the area where [cross-linking] works the best,” he said.

He applies riboflavin at the end of the procedure, carefully masking the LASIK flap with a dry wipe. He then uses high-fluence cross-linking of 30 mW/cm2 for 80 seconds.

Standard hyperopic LASIK patients can lose 1 D of refraction per year after the first to third year postoperatively, and it appears that cross-linking the cornea with LASIK Xtra can prevent that, Kanellopoulos said.

“In a contralateral eye study of 27 hyperopic patients published … in the *Journal of Refractive Surgery*, we found conclusive evidence that the eye randomized to have hyperopic LASIK Xtra did much better at 2 years than the fellow eye that had standard hyperopic LASIK, although both started with good correction,” he said. “Evaluation of the hyperopic LASIK effect in lieu of topographic keratometry is convincing, in my opinion, of this intrinsic to hyperopia effect.”

Kanellopoulos said it is theorized that in standard hyperopic LASIK, an intrinsic biomechanical effect takes place, resulting in “bulging” and central flattening, diminishing the desired correction, long term. It is this undesired effect that LASIK Xtra appears to counteract, he said.

“From a research standpoint, there’s a lot of interesting questions that still need to be answered or solved with cross-linking, such as what’s the ideal amount of energy, the ideal time of exposure, the ideal saturation level of the cornea, pulsing of the treatments vs. non-pulsing, combined treatments with PRK and collagen shrinkage procedures,” Hardten said. “These are all questions that need to be answered. From a patient care standpoint, just the sheer access to the ability to do cross-linking, without the burden of the necessity of [being part of] a clinical trial, would be helpful.”– *by Ryan DuBosar*

References:

Combined collagen crosslinking/ultraviolet-A and PRK or LASIK in forme fruste keratoconus or eyes with potentially elevated risk of ectasia. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01726283. Updated Nov. 9, 2012.
Corneal collagen cross-linking for ectasia (CXL). ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT00674661. Updated April 8, 2013.
Hersh PS, et al. *J Cataract Refract Surg.* 2011;doi:10.1016/j.jcrs.2010.07.030.
Kanellopoulos A, et al. *Cornea*. 2007;doi:10.1097/ICO.0b013e318074e424.
Kanellopoulos AJ, et al. *J Refract Surg*. 2012;doi:10.3928/1081597X-20121005-05.
Mazzotta C, et al. *Cornea*. 2011;doi:10.1097/ICO.0b013e3181e16de5.
Safety and effectiveness study of the VEGA UV-A system for cross-linking in eyes with keratoconus and ectasia. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01398852. Updated Jan. 25, 2013.
Safety study of the VEGA UV-A system to treat ectasia. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01398839. Updated Jan. 25, 2013.
Safety study of the VEGA UV-A system to treat keratoconus. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01190306. Updated Jan. 28, 2013.
Tuft SJ, et al. *Ophthalmology*. 1994;doi:10.1016/S0161-6420(94)31313-3.
Update on corneal collagen cross-linking symposium. Presented at: American Society of Cataract and Refractive Surgery meeting; April 19-23, 2013; San Francisco.
Wollensak G, et al. *Am J Ophthalmol*. 2003;doi:10.1016/S0002-9394(02)02220-1.

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Disclosures: Hersh is the paid medical monitor for Avedro, which makes products used in corneal collagen cross-linking. Kanellopoulos is a consultant to Avedro. Rubinfeld is an owner and shareholder of CXLUSA LLC. Donnenfeld, Hardten, Stulting and Waring have no relevant financial disclosures.

Is epithelium-on a potential modality for cross-linking compared with epithelium-off?

Epithelium-on offers advantages when done properly

Cross-linking is a critical step to treating patients with ectactic corneal diseases. It stops the progression of ectasia, and we also commonly see improvement in corneal shape and vision. We are working on ways to make the cross-linking procedure shorter and the postoperative course even safer and, of course, to increase the efficacy of the treatment.


William B. Trattler

There are two camps, epithelium-on vs. epithelium-off. Many doctors still perform epithelium-off because it has a long track record, and there are some peer-reviewed articles suggesting that epithelium-on cross-linking is not effective. However, these poor results stem from the fact that the methods for riboflavin loading into the cornea were flawed, resulting in insufficient riboflavin concentrations in the cornea. Therefore, it should not be surprising that the results from these studies were underwhelming. In contrast, epithelium-on cross-linking performed with proper loading techniques results in improvement in vision and corneal shape similar to that seen with epithelium-off cross-linking but with a more rapid return to functional vision, as well as a much lower risk profile.

Currently, CXLUSA has 15 study sites throughout the U.S., and the investigators are providing data that supports both the safety and efficacy of epithelium-on cross-linking. We have treated many interesting patients, including patients who have experienced progressive corneal weakening from Hibiclens exposure, as well as a family member who surprisingly developed keratoconus at the age of 12 years. Because epithelium-on procedures are less invasive with faster visual recovery, less

pain, faster return to contact lens wear and less risk of haze, my prediction is that within the next few years, epithelium-on cross-linking will be the preferred technique for performing cross-linking.

William B. Trattler, MD, *is a Healio.com/Ophthalmology Board Member. Disclosure: Trattler is a consultant for CXLUSA.*