

CORNEA

Collagen Crosslinking: Research Offers Promise and Poses Questions

BY MIRIAM KARMEL, CONTRIBUTING WRITER

In 2003, a group of German researchers reported a novel way to stop the progression of keratectasia in patients with keratoconus. They described a minimally invasive treatment—collagen crosslinking, or CXL—which involved the interaction of ultraviolet A light (UVA) with the photosensitizer riboflavin (vitamin B₂). It was simple and inexpensive to perform, and following treatment, the cornea was less likely to bow forward as it does in keratoconus and LASIK-induced ectasia. In their pilot study, the researchers demonstrated a 328.9 percent increase in the rigidity of the human cornea using CXL.¹

In 2008, some of those same researchers confirmed the effectiveness of CXL in a much larger study involving 488 eyes in 272 patients.² The researchers had such confidence in CXL that the second study lacked a control group, on the grounds a control group would be ethically unacceptable.

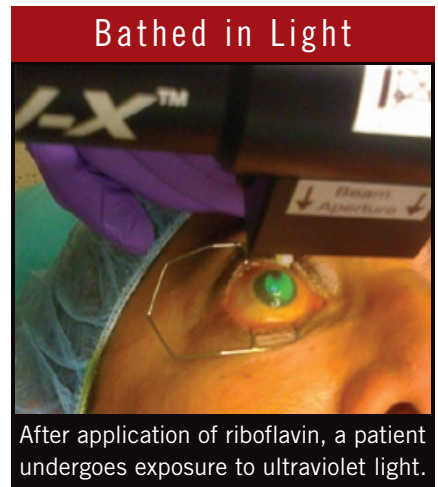
R. Doyle Stulting, MD, PhD, professor of ophthalmology and director of cornea, external disease and refractive surgery at Emory University, noted that data from the German studies show that “the effect not only does not wear off, but perhaps increases as time goes on.” In the 2008 study, steepening decreased significantly by 2.68 D in the first year; 2.21 D in the second year; and 4.84 D in the third year. The BCVA improved significantly (≥ 1 line) in 53 percent of 142 eyes in the first year.²

Today, CXL is being used around the world, with the exception of the United States, where it is currently the focus of a multicenter clinical trial to study its benefits in patients with progressive keratoconus and corneal ectasia after refractive surgery. “We’re probably the last country to have it available to our patients with keratoconus,” said Dr. Stulting, who is the Medical Monitor for the trial. Final results are expected later this year, but Dr. Stulting said that preliminary results are consistent with what has been reported internationally. Those reports have shown that CXL decreases corneal curvature and thickness, regularizes corneal surface and in some cases improves UCVA and BCVA.

Popular Procedure

Assuming FDA approval, William B. Trattler, MD, an investigator in the multicenter trial, predicted that CXL will become the primary tool for treating patients with keratoconus, which is one of the foremost conditions that lead to corneal transplants. “Once this technology becomes FDA-approved, I believe that the majority of anterior segment surgeons will rapidly incorporate this procedure into their practice because it is a relatively simple yet effective treatment,” said Dr. Trattler, a Miami ophthalmologist in private practice.

Patient interest. In the meantime, patients are already asking about CXL, said David G. Hwang, MD, professor of ophthalmology and director of the



After application of riboflavin, a patient undergoes exposure to ultraviolet light.

the University of California, San Francisco. “There’s a lot of buzz about this.”

The buzz, perhaps premature, is understandable. Other therapeutic options—spectacles, contact lenses and Intacs—merely correct refractive errors. However, progression of keratoconus can still occur, with an estimated 20 percent of patients eventually requiring corneal transplantation.

Several uses. CXL, on the other hand, reportedly stops the progression of keratoconus. “It’s a novel way of stiffening the cornea,” Dr. Stulting said, adding that the procedure has many potential applications, including the treatment of infectious corneal ulcers, noninfectious corneal melts and corneal edema. CXL also portends a future in which treatment of keratoconus occurs at earlier stages to preserve better visual acuity, over the lifetime of the patient.

CXL also could expand the pool of

refractive surgery patients, the ones who are currently excluded out of concern that removing tissue from the cornea could further weaken it and induce ectasia, Dr. Stulting said. “This procedure gives us the potential opportunity to identify those patients, crosslink them and treat them safely with LASIK or PRK.”

Show Us More Data

“The potential is huge,” said Yaron S. Rabinowitz, MD, regarding that prospective refractive surgery market. “That’s why it’s generating so much excitement.” For now, Dr. Rabinowitz, who has been studying the genetics of keratoconus for more than a decade, is awaiting further results. “The cross-linking actually stiffens the cornea. But no rigorous controlled study absolutely proves that it works,” he said. “All the indicators are that it does possibly work, but the scientific studies need to be more rigorous, and if they are it will become more commonly accepted.”

Age and K questions. Dr. Rabinowitz, who practices at the Cornea Genetic Eye Institute at Cedars-Sinai Medical Center and is clinical professor of ophthalmology at the University of California, Los Angeles, expressed concern about the advanced age of many of the patients in the German studies. He noted that keratoconus typically progresses between puberty and age 30, after which patients are less likely to progress. Given the age of many patients in the German studies, he said, “It’s hard to know whether the treatment stopped them from progressing or whether they would have stopped anyway.”

Dr. Rabinowitz also questioned the use of a single K reading as an endpoint in the studies, noting that since there is likely to be variability from measurement to measurement, a single reading might skew the results. He suggested that more accurate data could be derived from the sum of multiple data points averaged over the apex, and by tracking progression over time.

On the plus side, Dr. Rabinowitz said the studies show CXL is safe. In

Skin Two Corneas, Add Riboflavin, Cook for 30 Minutes

CXL, a treatment borrowed from materials science, and developed by Theo Seiler, MD, PhD, at the University of Dresden, stiffens the cornea by exposing it to ultraviolet light after it is saturated with riboflavin. The goal is to halt the progression of keratoconus and post-LASIK ectasia. Here are the essential steps for CXL:

1. Remove the corneal epithelium.
2. Apply riboflavin 0.1 percent solution to the exposed surface as a photosensitizer.
3. After 30 minutes, examine the eye with blue light for the presence of a yellow flare in the anterior chamber, which indicates riboflavin saturation of the corneal tissue. If flare is not detected, continue instilling riboflavin.
4. Perform pachymetry to confirm the corneal stroma (after epithelial removal) is at least 400 μm thick. This is to minimize UVA light exposure to the endothelium. If less than 400 μm , instill two drops of hypotonic riboflavin 0.1 percent every 10 to 15 seconds until the corneal thickness increases to at least 400 μm .
5. Begin UVA irradiation, adding 1 drop of riboflavin every two minutes for 30 minutes.
6. Postoperative treatment is similar to that for PRK, including bandage contact lens, topical steroids, antibiotics, artificial tears and oral NSAIDs.

Clinical trials. Enrollment is ongoing for a number of crosslinking studies. For more information, interested physicians can go to www.clinicaltrials.gov and enter “corneal crosslinking” in the search field.

fact, he’s planning a study of both CXL and Intacs, in which he’ll test whether CXL with Intacs will produce a greater reduction in cylinder and steep K than Intacs alone.

Killing keratocytes? The long-term effects of CXL on the cornea’s ability to respond to stress, infection, disease and wound healing are still not known, said Dr. Hwang. “The ultraviolet light treatment not only crosslinks the collagen, but in the short term also wipes out the keratocytes that are in the anterior and mid stroma within the irradiated zone,” said Dr. Hwang. He raised similar concerns about the potential effect of UVA light on dendritic cells within the corneal stroma, which drive normal immune responses in the cornea.

“The real issue is that you’re making a fundamental biologic and cellular change in the cornea,” said Dr. Hwang. “What will happen to these corneas in the case of injury or infection? Will there be an aberrant response to infection or wounding or surgery due to the fact that you’ve depleted the normal supply of cells in the cornea? Will the keratocytes and other cells that are depleted by UV irradiation be replaced, and, if so, to what extent and in what

time frame?” He said while these concerns aren’t showstoppers, they need to be addressed. He added that due to sampling and time limitations, the clinical trial isn’t likely to answer them.

Down the road. Natalie A. Afshari, MD, agreed that it could take years before the effects of CXL are completely understood. Dr. Afshari, associate professor of ophthalmology and director of cornea and refractive surgery fellowship at Duke University, noted that to avoid irradiating endothelial cells, the treatment protocol requires the cornea to be at least 400 μm . But she questioned the long-term effect of irradiation on the stromal cells and the endothelial cells. “We need to follow patients over time to make sure we’re not losing too many cells.”

In the meantime, Dr. Afshari has referred patients who can’t tolerate contact lenses to the CXL trial. She has fewer qualms about CXL when the alternative is a corneal transplant. Then CXL is another option, she said. “If the patient loses some corneal cells, we can always do the transplant later.”

As Dr. Trattler said, “It’s not a miracle cure. You’re essentially stopping the progression of a progressive disease.”

CXL's Future

Looking forward, Dr. Hwang predicted that CXL may have a reasonable therapeutic ratio between benefits and complications and side effects. But he warned that the medical community will need to establish clear guidelines for its use. "As often happens following the adoption of any innovative technology, some people may try to push the envelope well beyond the recommended parameters and indications, and then we could see issues."

For now, Dr. Hwang said he looks forward to the clinical trial results. "I'm not an advocate. Nor am I a skeptic. But I share a lot of healthy concerns about it, as well as hopefulness that the technology will have some benefits. It's not going to be a panacea, but it has the potential for fulfilling a specific and needed role in corneal therapeutics."

As Dr. Stulting put it: "It's a rare opportunity that a physician is able to find the treatment for a disease that has had no treatment during his career. And that's what we have here."

1 Wollensak, G. et al. *J Cataract Refract Surg* 2003;29(9):1780-1785.

2 Raiskup-Wolf, F. et al. *J Cataract Refract Surg* 2008;34:796-801.

Drs. Afshari, Hwang, Rabinowitz and Trattler report no related financial interests. Dr. Stulting is a consultant for Peschke Meditrade, a distributor of UVA devices.

Cornea on the O.N.E.

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