

COLLAGEN CROSS-LINKING

New Applications
Emerging
but U.S. Studies
Falter

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Corneal collagen cross-linking (CXL) was first reported in 2003 by a group of German researchers as a novel approach to arresting the progression of keratoconus and LASIK-induced ectasia. This minimally invasive treatment buttresses the natural architecture within the cornea to preserve the gracefully domed shape and prevent it from growing steep and irregular.

The details are simple: A solution of vitamin B₂ (riboflavin) is administered topically to the cornea and then activated by ultraviolet-A light for about 30 minutes. The effect of UVA light on the riboflavin creates new bonds between collagen fibrils in the stroma, conferring new mechanical strength on the cornea. In one early study, researchers demonstrated a 328.9 percent increase in the rigidity of the human cornea.¹

The only element that might create a complication is that some specialists remove the epithelium before the procedure to enhance penetration of the riboflavin. In any case, the results thus far have excited both the physician and patient advocate communities. "Corneal cross-linking has the potential to arrest the

IT SOUNDS SAFE AND SIMPLE:

Apply a few drops of vitamin B₂, shine a little light, and suddenly a dangerously thin cornea is made sturdy.

But some U.S. trials have been stalled, prompting American patients to go abroad for this treatment.

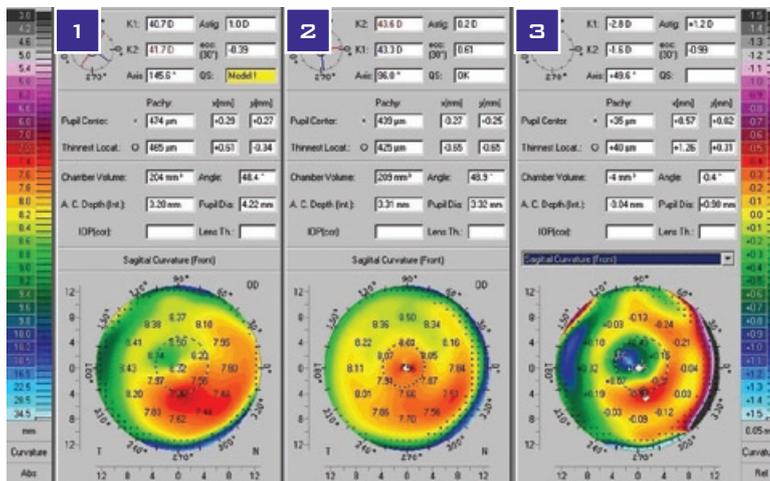
development of keratoconus and post-refractive ectasia at an early stage,” said Francis W. Price Jr., MD, in private practice in Indianapolis. “Perhaps we will reach the point where corneal transplants will no longer be needed for these conditions.” Catherine Warren, RN, executive director of the National Keratoconus Foundation (www.nkcf.org), agreed. “CXL is a ray of hope for those who have keratoconus.”

Progress derailed. Recently, however, that ray of hope flickered when two large, multicenter clinical trials testing CXL in keratoconus and ectasia were halted in the United States (see “Why Is a Promising Therapy Stalled?”). What appeared to be a solid treatment backed by promising results from international studies and anecdotal reports has become a lesson in frustration, both for doctors wanting to offer that ray of hope, and for patients desperate to stop the progression of keratoconus, which is the cause of about 15 percent of corneal transplants performed in the United States.² Some American patients are now traveling outside the United States for CXL, though others may be lucky enough to enroll in the few small, surviving American studies.

Meanwhile, the search for new CXL applications continues in the United States and abroad, as researchers are trying it for everything from corneal melting disorders and bullous keratopathy to infectious keratitis, corneal edema and Terrien keratopathy. It is also being used for keratoconus in combination with other procedures, such as PRK and corneal inlays. Some key examples of CXL applications are explored below, followed by questions regarding the progress of the U.S. studies.

CROSS-LINKING IN FOUR EXAMPLES

Combination PRK with CXL. A. John Kanellopoulos, MD, introduced the concept of combining CXL with a partial PRK.^{3,4} The rationale for this one-two procedure is first to normalize an irregular cone with topography-guided PRK and then to stabilize the ectatic process with CXL. Dr. Kanellopoulos is an associate professor of ophthalmology at New York University but also practices in Athens, where keratoconus appears to be endemic and where he has treated over 800 cases of keratoconus and more than 50 post-LASIK ectasia eyes.



VISUAL CORRECTION ⇒ ANATOMICAL INSULT ⇒ ANATOMICAL CORRECTION. (1) Two-year postop LASIK with normalization of irregular astigmatism; UCVA is 20/20 and BCVA is 20/15 with +0.25–0.25 @95. (2) Topography by Wavelight Oculyzer shows three-year post-LASIK inferior steepening and progressive ectasia. Visual acuity at this stage is 20/30 with +1.25 –2.75 @135. (3) Improvement achieved with topography-guided PRK and same-day CXL.

For the PRK, Dr. Kanellopoulos utilizes the topography-guided platform by WaveLight in highly irregular corneas that are usually beyond the limits of wavefront measuring devices. He said that in one of his studies, the combined PRK/CXL, same-day cases had better UCVA and BCVA and less corneal scarring than the control group, which got sequential treatments. By combining the procedures, Dr. Kanellopoulos has seen a reduction in grafts by 80 percent over the last six years.

But the limitations of the procedure are still unknown, Dr. Kanellopoulos said. For example, he asked, how much ectasia and what types of ectasia can safely and predictably be corrected? Is there a minimum pre-CXL corneal thickness that will not respond to treatment?

Corneal edema and stromal melting. CXL, which causes stiffening and compaction of the corneal lamellae, thus reducing swelling, also has the potential to minimize stromal melting and corneal edema from endothelial dysfunction, Dr. Price hypothesized. “This might be an alternative to corneal transplants for bullous keratopathy.”

Infectious keratitis. Dr. Price also has been evaluating CXL to treat infectious keratitis. He has launched a single-center, physician-sponsored study that will enroll 200 subjects randomized to 15- or 30-minute UVA treatments. It is designed to evaluate how effective CXL is in treating infections that are full thickness in the cornea. “We know that the treatment kills the keratocytes and it can kill organisms in the cornea as well,” he said, explaining that the

interaction of UVA light and riboflavin forms free oxygen radicals, which are believed to have a cytotoxic effect in addition to the CXL effect.

“Ultimately, CXL may be used to kill any pathogen in the cornea,” Dr. Price said, adding that currently UVA alone is used to kill bacteria, fungi, viruses and protozoa in water bottles for campers. It is also used to purify serum and for larger-scale water treatment. The challenge in CXL is to avoid killing the endothelium. “So we typically limit the cytotoxic dose to about 300 μm in depth,” Dr. Price said.

If CXL succeeds in eliminating antibiotic-resistant organisms, it may prove more effective than topical or systemic medications, said Dr. Price. Given the dearth of research to develop new antibiotics, “You might say this is planning for the future as pathogens develop increasing antibiotic resistance.”

Terrien disease. Researchers from Barcelona reported on two patients with Terrien disease at the Academy’s Joint Meeting in San Francisco last October. Both patients had a UCVA of 20/400, which improved with treatment to a BCVA of 20/25 in one patient and a UCVA of 20/80 in the other. They said CXL appears safe and effective, with at least a short-term improvement of the topographic and refractive parameters.⁵

PERFECTING THE PROCEDURE

Let there be light (and riboflavin).

For straightforward management of a thinning cornea, most researchers are adhering to the original protocol, one which was also used in the stalled multicenter trials mentioned above. This entails removal of the epithelium followed by instillation of riboflavin to saturate the entire cornea. Then a carefully determined dose of UVA light is delivered to the cornea for 30 minutes.

Epi-on/epi-off. Doctors are already exploring ways to improve the procedure. In one modification, called “epi-on,” the epithelium is not removed. “That’s one of the changes in the procedure that people would like to see happen,” said Peter S. Hersh, MD, professor of clinical ophthalmology and chief of cornea and refractive surgery at the University of Medicine & Dentistry of New Jersey in Newark. “It would be simpler for the patient.” Dr. Hersh is also an investigator with the halted multicenter trials. He added that there’s interest in focal treatments that localize CXL, rather than cross-

linking the entire cornea. And doctors are questioning the relative merits of varying the intensity or timing of the procedure. “I think CXL really holds great promise and right now is the only intervention to diminish the progression of keratoconus in patients who have progressive keratoconus. We would like to see it developed, refined and hopefully approved in the U.S.,” Dr. Hersh said.

Brian S. Boxer Wachler, MD, leaves the epithelium intact when he performs CXL, which he renamed C3-R³ in 2004. Removing the epithelium can increase the risks and side effects, including corneal infections, ulcers, haze, scarring and infiltrates. “When you remove the epithelium it’s absolutely not benign,” said Dr. Boxer Wachler, who first performed cross-linking in his Beverly Hills office six years ago. The key to success, Dr. Boxer Wachler said, is to get the riboflavin to penetrate the epithelium into the cornea, which he achieves by loosening the tight junctions with a preservative.⁶ “When doctors prescribe a glaucoma eyedrop, do they ask patients to scrape off their epithelium in order for the drug to penetrate? Of course not. Riboflavin penetration works via the same mechanism.” He cited several studies that support leaving the epithelium on.^{7,8,9}

But does epi-on work? The epi-on/epi-off debate continues, said R. Doyle Stulting Jr., MD, PhD, professor of ophthalmology at Emory University in

ONE YOUNG MAN AND HIS DETERMINED MOTHER

“I would have gone to the moon, if it meant that my son would have some improvement in his vision,” said Maryalice Caddigan, in describing her search for a doctor to treat her son Michael’s aggressively progressive keratoconus. Ms. Caddington had watched, helplessly, as Michael’s vision got progressively worse, starting at age 11, when he received his first pair of spectacles. Within a year, Michael had gone through six or seven prescriptions, until glasses no longer helped and contact lenses slid off his eye.

Michael had visited three ophthalmologists before finding Douglas F. Buxton, MD, at New York Eye & Ear Infirmary, who told him about CXL. But because of his age, Michael did not qualify for the trials. “When we were turned down, I went online. I didn’t know where to turn. I was devastated,” said Ms. Caddigan. “At that point his condition was so aggressive. He’s 12 and can’t read a blackboard or write in a book. His whole life was on hold. As a mom, I had to do everything I could.”

Through the Internet, she found The National Keratoconus Foundation, where Catherine Warren, RN, put her in touch with the Boston Foundation for Sight. There, Michael was fitted for scleral lenses, which corrected his vision. At that point, Michael was ready for CXL. Last October, he made the second of two 10-day trips (one eye per trip) to Germany for CXL to slow the disease progression.

The keratoconus is slowing, Ms. Caddigan said. Michael, who is now 13, is scheduled to return to Germany in April for a follow-up exam. Interim visits will be with Dr. Buxton in New York. In the meantime, Ms. Caddigan wants doctors to know about CXL. Ms. Warren agreed. “Patients want information about this treatment, but many doctors are unaware that it exists.”

Atlanta and medical monitor of the multicenter trials. While acknowledging that doctors would like to provide CXL without epithelial removal, he is hesitant to adopt the epi-on procedure without solid laboratory and theoretical evidence. “Riboflavin does not penetrate an intact, normal epithelium,” he said. “That’s very clear from laboratory studies and clinical observations. So those who do not remove the epithelium have to damage the epithelium in some way in order to get the riboflavin into the cornea.” He added that there are no good data showing that the epi-on procedure actually does disrupt the epithelium sufficiently for absorption of the riboflavin. The burden of proof is on those who don’t remove the epithelium, he said. “Those who remove the epithelium have excellent data to back it up.”

WHY IS A PROMISING THERAPY STALLED?

The two largest U.S. multicenter trials—one to study CXL for ectasia, the other for keratoconus—were halted last June due to issues that have not been publicly disclosed. Peschke Meditrade, the distributor of the UVA light device designed for CXL and the funder of the studies, did not respond to multiple requests from *EyeNet* for an explanation of the trials’ suspension. But several concerned parties *EyeNet*

spoke to suggested two plausible reasons for the stall:

- Drugs or devices like CXL that are composed of inexpensive, readily available, low-tech materials offer a very thin return on the investment typically required to bring a new therapy to market in the United States.
- Regulatory rigor in the United States—both revered and reviled for what has been called its majestic pace—is generally hailed for producing safe products but can also keep promising treatments out of reach for desperate patients as large, long trials plod toward a conclusion.

“In my opinion, one of the problems here is not enough potential for profit because of the lack of solid intellectual property protection for cross-linking that would make a sponsor willing to fund the high cost of clinical trials,” said Dr. Stulting. “This is a technology that is available internationally, and we’re having a hard time making it available here because one sponsor has been unable to support the regulatory costs of multicenter trials. I think it’s unfortunate and it leaves us in a very difficult position. It remains to be seen what will happen in the future.”

Dr. Hersh shared similar thoughts. “I believe that the multicenter U.S. trials were halted because of funding difficulties,” said Dr. Hersh. “Cornea surgeons and doctors are frustrated at not having this modality at our hands, particularly because we’re dealing with a patient population that really has no other alternative to decrease the progression of the disease that they have.”

Data are good so far. Adding to the frustration of derailed studies is the sense that CXL works. “The international data have been rather compelling regarding the efficacy of this procedure,” said Dr. Hersh, who treated some 80 patients prior to the trial’s suspension. “Both from what we’re seeing in our own patients and from data in fairly long-lived clinical trials outside the U.S., CXL has been shown to stabilize the cornea in keratoconus and ectasia in patients over the course of the studies.”

Dr. Stulting agreed. “The international data are consistent and very strong for supporting the use of CXL for treatment of keratoconus, corneal ectasia and perhaps other indications as well.”

What’s possible now. Dr. Hersh said that the large U.S. trials were going well before their pause and could still yield solid data. “The quality of our study is going to give us information that was really unavailable thus far. It was one of those

PEARLS FOR CXL FOLLOW-UP

When patients return from CXL surgery abroad, they will require follow-up care. Here’s some advice on how to provide it.

Dr. Buxton: “This is equivalent to taking care of postoperative PRK. The healing process is on the surface of the eye, so you want to watch for corneal ulcers and sterile infiltrates. By the time the post-CXL patient comes to you, they are on antibiotics, steroids and some lubrication and they may be wearing a soft contact lens.” Other tips:

- Do not do gonioscopy or anything that touches the ocular surface.
- Check the IOP at the first visit to make sure the patient hasn’t overresponded to the steroids. But do not take the pressure every time because you want to avoid interfering with the ocular surface.
- Stop the antibiotic abruptly once the surface is intact and stable, as you would with any epithelial defect or post-PRK.
- Taper the steroids; do not stop cold turkey.
- Schedule follow-up visits every month to six weeks for an intact cornea and at least weekly if there is a defect.

Dr. Hersh: “There is a tried-and-true protocol from the trials. So I do counsel that if patients are seeking treatment elsewhere to be sure they are undergoing the same protocol as in the FDA trial.”

Dr. Stulting: “All the patients I sent over came back within a couple of days, and I monitored them here. You manage them just like you would manage any other epithelial defect. You treat them with antibiotics and steroids and monitor for delayed epithelial healing and infections.”

gold-standard, prospective, controlled studies where we'll learn a lot as time goes on. We currently are analyzing our patient group, over 50 of whom are now more than a year past treatment."

Fortunately, smaller trials are still in motion or are planned, according to both Drs. Stulting and Hersh. "We are currently in the process of seeking approval for a single-center study at our practice," said Dr. Hersh. And Dr. Stulting already heads a small, physician-sponsored study at Emory University.

In the meantime, the best Dr. Hersh can offer his keratoconus and ectasia patients are regular checkups for progression, with a battery of tests and current treatments, including contact lenses, Intacs and corneal transplantation. And he warns patients to avoid eye rubbing, since that pressure adds stress to the cornea, exacerbating the disease.

Pediatrics has no time to wait for studies. Erin Stahl, MD, a pediatric ophthalmology fellow at Children's Mercy Hospital in Kansas City, Mo., obtained FDA approval last September to treat 10 children on a compassionate-use basis. "These patients need to be treated and they need to be treated now," Dr. Stahl said. Keratoconus progresses more rapidly in the youngest population than in adults, she said. It is also common to see keratoconus in children with Down syndrome, where it tends to be rapidly progressive and often leads to the need for corneal transplantation.

Dr. Stahl's goal is to pursue FDA approval for CXL in children. "This may come about in conjunction with future adult trials or as a separate study protocol," she said.

As information increases, so does frustration. For some patients, approval can't come quickly enough. "Patients know that CXL is available in Europe and Canada and other countries," Ms. Warren said. "They want to be able to see better and want this to stop progressing before they need a corneal transplant." (See "One Young Man and His Determined Mother.") "It's a patient group intensely interested in their own care and very knowledgeable," said Dr. Hersh, noting that he gets several requests a day about CXL.

When the trial was under way, he told his patients to consider enrolling. Now, he said, "I tell them it's being done overseas and that's a viable option." A

MEET THE EXPERTS

Douglas F. Buxton, MD Attending surgeon at the New York Eye & Ear Infirmary and clinical professor of ophthalmology at New York Medical College. *Financial disclosure: None.*

Peter S. Hersh, MD Professor of clinical ophthalmology and chief of cornea and refractive surgery at the University of Medicine & Dentistry of New Jersey in Newark. *Financial disclosure: None.*

A. John Kanellopoulos, MD Associate professor of ophthalmology at New York University and in private practice in Athens, Greece. *Financial disclosure: Has received lecture fees from WaveLight.*

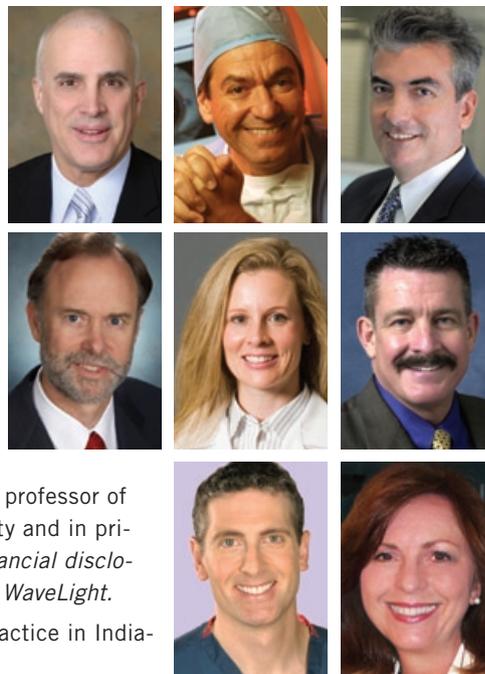
Francis W. Price Jr., MD In private practice in Indianapolis. *Financial disclosure: None.*

Erin Stahl, MD Pediatric and refractive surgery fellow at Children's Mercy Hospital, Kansas City, Mo. *Financial disclosure: None.*

R. Doyle Stulting, Jr., MD, PhD Professor of ophthalmology, Emory University. *Financial disclosure: Consultant for Peschke Meditrade and Priavision.*

Brian S. Boxer Wachler, MD Director of the Boxer Wachler Institute in Beverly Hills. *Financial disclosure: Owns the trademark to C3-R³.*

Catherine Warren, RN Executive director of the National Keratoconus Foundation.



couple of his patients have done just that. "This is a very motivated and interested group."

What next? Someday, doctors in the United States should be able to give patients more than information. "I think it will eventually get approved—sometime in the distant future," Dr. Stulting said. But for now, the aborted trials "leave CXL in the U.S. with a big question mark over it."

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