In this month’s column, we focus on corneal crosslinking. Crosslinking was approved by the U.S. Food and Drug Administration in April 2016 for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. The approved device (KXL System, Avedro) was released in fall 2016 amid much excitement and anticipation. Since then, adoption has been gradual, in part due to high out-of-pocket costs for patients because of the lack of insurance coverage. As insurers begin to come on board, we are likely to see wider utilization of this procedure for a broader range of indications. At this time, limited treatment parameters are available to surgeons in the U.S. The Dresden protocol, which involves corneal epithelial debridement, application of riboflavin eye drops to the eye for 30 minutes, and subsequent exposure of the eye for 30 minutes to 365 nm UVA light at an irradiance of 3.0 mW/cm², is currently the only option available in the U.S. Our international colleagues have an array of accelerated and transepithelial treatment protocols to choose from.

Our experts share pearls for patient selection and treatment, strategies for counseling patients appropriately, and views on where this technology is headed in the coming years. We asked Michael Raizman, MD, Michael Greenwood, MD, Peter Hersh, MD, A. John Kanellopoulos, MD, and Russel Swan, MD, for their thoughts.

Thanks to Charles Weber, MD, and Bryan Lee, MD, the inaugural co-editors of the “YES connect” column. Zachary Zavodni, MD, and I look forward to continuing their work.

Naveen Rao, MD
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Crosslinking procedure performed on a patient Source: Michael Greenwood, MD

“If [crosslinking] is widely recognized and widely available, we can diminish the need for transplants for keratoconus and significantly reduce the number of patients who require contact lens fitting.”
—Michael Raizman, MD
From patient selection to tracking progression, postop care, and future directions

The playing field for those interested in getting into corneal collagen crosslinking—from experienced surgeons to those still young in their career—is relatively level. The procedure received approval from the U.S. Food and Drug Administration (FDA) a little more than a year ago.

“I think the procedure itself is a simple surgical procedure that doesn’t require great prior surgical skill and has a very fast learning curve. It’s an ideal procedure for a young surgeon to take on,” said Michael Raizman, MD, Ophthalmic Consultants of Boston, who has performed hundreds of crosslinking procedures within the last 5 years. He was an investigator for Avedro’s (Waltham, Massachusetts) clinical trial.

Michael Greenwood, MD, Vance Thompson Vision, Fargo, North Dakota, said although he didn’t learn crosslinking while in residency, it was one of the first procedures he performed on his own after training.

“There’s not a whole lot to learn from a technical standpoint as a new surgeon, but it’s who to do it on and what to watch out for that are part of the learning curve,” he said.

The FDA approved Avedro’s Photrexa Viscous, Photrexa, and KXL System—riboflavin solutions and a UVA light system—in April 2016 for treatment of progressive keratoconus and corneal ectasia post-refractive surgery, following the standard Dresden protocol. Crosslinking, however, has been available in other parts of the world and CE marked for more than a decade.

Patient selection

“The key, as with many procedures, is understanding who’s the right candidate and who is not,” Dr. Raizman said.

Patients who are candidates for crosslinking in the U.S. under the FDA’s approval are those with progressive keratoconus who are at least 14 years old or those who have corneal ectasia post-refractive surgery. According to the Dresden protocol, which is the procedural technique approved by the FDA for use with the Avedro system, corneal thickness needs to be at least 400 µm after the epithelium is removed.

“In my mind, [a crosslinking candidate] is anyone who has progressive corneal ectasia, whether it’s from keratoconus, pellucid marginal degeneration, or post-refractive surgery ectasia. You want to treat the people who have progression, you want to treat them early because you don’t want patients to lose any vision,” Dr. Greenwood said. “The hardest part of being a young surgeon is doing a procedure on an eye that corrects to 20/20 for fear of doing harm to that patient, having him or her lose vision. They are the hardest patients to counsel simply for the fact that you’re going to be taking their eye that’s 20/20 and doing a painful procedure that has a long recovery, and their vision is probably going to fluctuate and get a little bit worse before it gets better. The discussion you have to have with them is that this is something that is preventative and that’s going to be beneficial, so they never lose the best corrected vision that they have now.”

In terms of determining progression, Peter Hersh, MD, founder, Cornea and Laser Eye Institute, Hersh Vision Group, Teaneck, New Jersey, said the best way is to follow the keratoconic patient
with serial topography, especially looking at maximum keratography on the corneal topography as well as simulated K readings.

Dr. Hersh, medical monitor for the FDA crosslinking trials, acknowledged that this information might not be available for all patients due to a lack of past corneal topographies or use of different devices, making it difficult to compare measurements. As such, it’s important to take the patient’s subjective visual history (e.g., “Has your vision been getting worse over time?”) and the actual change in refraction. If a medical record of refraction over time is not available, Dr. Hersh said looking at the patient’s old glasses can be helpful.

“Increase in myopia or particularly an increase in astigmatism is another indication of progression,” he said.

Age is also a factor in determining when to offer crosslinking. In younger patients—those 15 to 25 years old—A. John Kanellopoulos, MD, clinical professor of ophthalmology, New York University Medical School, New York, and medical director, Laservision.gr Institute, Athens, Greece, said keratoconus is more unpredictable and thus requires close follow-up, every 3 months, to document progression. Dr. Kanellopoulos said while topography is helpful for tracking progression, he noted research that suggests the most sensitive metric is the index of height decentration, which is available on most Pentacam (Oculus, Arlington, Washington) and Placido disc topographies. From 25 to 35 years old, Dr. Kanellopoulos said keratoconus patients become less prone to abrupt, unexpected changes and could be followed up with every 6 months to a year. Similarly, keratoconus progression becomes even less likely at 35 and older.

“Nevertheless, we’ve seen changes in patients in their 50s, 60s, and 70s. Although an exception, one cannot exclude any progression of keratoconus while the patient’s age advances,” Dr. Kanellopoulos said.

Russell Swan, MD, in fellowship, Vance Thompson Vision, Sioux Falls, South Dakota, echoed a similar sentiment, saying that if a younger keratoconus suspect was referred with documented increasing astigmatism or degradation in best corrected visual acuity, even with one topography or Pentacam image that showed changes consistent with keratoconus, a surgeon could feel justified in recommending early crosslinking without long-term evaluation to reduce risk of progression and thus reduce risk of losing the ability to maximize best corrected vision.

As for cases of post-refractive surgery corneal ectasia, age is not so much a factor for monitoring progression as these cases are more unpredictable, Dr. Kanellopoulos said. He added that in his practice the most sensitive criteria for evaluating a patient with corneal ectasia is looking at corneal epithelium maps obtained with anterior segment OCT.

Dr. Kanellopoulos warned that detection of keratoconus can be masked by epithelium remodeling, which is why he advises epithelium mapping. If it is unavailable, he advised looking at topographic maps, not just keratometries, and looking at the steepest part of the cornea. “An increase in the index of height decentration seems to be the most sensitive proof for the diagnosis of keratoconus with the exception of the central ‘nipple’ cones,” he said.

The current, on-label procedure for crosslinking in the U.S. requires epithelial debridement and a corneal thickness of 400 µm after this procedure. The cornea (as thick as 350 µm) can be swelled up to 50 µm using a hypotonic riboflavin solution, to allow for safe crosslinking.
“Patients who have very thin corneas are not candidates, and I have seen cases of damage to the endothelium from crosslinking performed on a thin cornea,” Dr. Raizman said. There are different epithelial debridement techniques, and Dr. Raizman said each is effective and depends on the physician’s preference. Dr. Raizman uses a round blade and removes the epithelium in a manner similar to what is done for PRK. Dr. Hersh uses 20% alcohol in either a 9-mm birdbath or a 9-mm cellulose sponge. Drs. Greenwood and Swan also said they use dilute alcohol to perform a superficial keratectomy, finding the alcohol makes epithelium removal easier.

Dr. Kanellopoulos said it’s his preference to perform phototherapeutic keratectomy if the epithelium and cornea are regular, but if the epithelium does not show regularity, he uses the Epi-Bowman’s Keratectomy procedure (Orca Surgical, New York) with the Epi Clear device (Orca Surgical). One also has to take into account corneal scars when considering candidacy for crosslinking.

“Does the patient need transplantation?’ … Crosslinking is only going to diminish corneal transplant in those patients who are correctable by glasses or contact lenses. If the corneal scar requires a transplant, there is no need to do the crosslinking,” Dr. Hersh said, adding that if crosslinking is performed in the face of a scar, perhaps one that is not visually significant, there may be risk for greater incidence of corneal haze.

According to Dr. Kanellopoulos, in some cases the scar can be removed intraoperatively before crosslinking, which is important as the scar could overshadow the UV light and limit the crosslinking effect in the thinnest, most biomechanically unstable part of the cornea.

Following the FDA-approved, on-label Dresden protocol makes patient selection, overall, fairly simple, Dr. Raizman said, but he added that he expects it to become a bit more complex in the future as crosslinking is being considered in combination with other procedures, such as PRK or intracorneal ring segments, and in light of newer treatment protocols.

**Postop care and results**

The physicians interviewed varied only slightly in their postop care of crosslinking.

Dr. Raizman said he’ll apply a bandage contact lens and direct the patient to use a fluoroquinolone antibiotic drop four times a day for a week until the epithelium is healed; he’ll remove the contact lens at 1 week as well. He also uses prednisolone acetate 1% four times a day for 1 week and then once a day for a month. He manages pain with oral nonsteroidal and oral narcotics as needed.

Similarly, Dr. Hersh uses an antibiotic/corticosteroid four times a day for a week and a bandage contact lens for 4 to 5 days. He stops the antibiotic at the end of 1 week and tapers the steroid. Dr. Kanellopoulos uses an antibiotic/steroid combination but for 10 days, followed by a steroid drop for at least a month. He advises protection from UV light—sunglasses and hat wearing—as well as high doses of vitamin C for 2 months. Dr. Greenwood said he uses an antibiotic/steroid combination four times a day for a week, followed by a taper to two times a day for a week. He fits all of his crosslinking patients with dissolvable punctal plugs, finding that they speed healing and prevent haze formation.
Although all the physicians interviewed said they’ve seen a strong success rate of crosslinking halting progression in their keratoconus patients, Drs. Swan and Greenwood warned that within the first 6 months after surgery, topographies and vision in these patients can get worse before they get better. A randomized controlled study with 3 years of follow-up saw an average of 2 D of flattening from baseline at 1 year and found this decrease in Kmax was consistent at 3 years with some further improvement observed between year 2 and 3. In terms of further flattening, Dr. Hersh said research has shown that improved vision is more likely in patients who had worse vision to begin with, 20/40 or more.

Greenstein et al. performed a multifactorial study that looked at indicators of outcomes and found the only predictor of improvement of corneal topography of 2 D or more was a higher maximum K of 55 D or more.4

**Future of crosslinking**

Dr. Raizman said epithelium-on (epi-on) treatments should be the goal for this procedure. It’s moving in that direction, but at the moment, there’s no evidence that epi-on crosslinking is as effective as epi-off, he said. Research continues on various methods to improve penetration of riboflavin through the epithelium into the stroma—iontophoresis and new riboflavin solutions.

Dr. Hersh said epi-on procedures, currently considered off-label in the U.S., could be particularly suited for patients whose corneas are too thin for the standard protocol, even with swelling, and those who currently have 20/20 corrected vision. “The reason I say that is there is some risk of loss of corrected visual acuity in crosslinking patients. Whether this is because of corneal haze or epithelial remodeling or just general potential adverse events from a crosslinking procedure, we have shown there may be a slightly greater likelihood of a patient who has good vision losing a line of best corrected vision,” he said, adding that the patient thus could be a candidate for epi-on crosslinking.

Another application for the epi-on technique is treating low doses of myopia, hyperopia, and astigmatism. Photorefractive intrastromal crosslinking (PiXL, Avedro) is currently being researched and received the CE mark with the company’s Mosaic device.

As for other protocols that deviate from the standard Dresden protocol, Dr. Raizman said he thinks accelerated treatments can be as effective, and pulsed-light therapy and use of supplemental oxygen probably enhance the effectiveness of crosslinking, perhaps of epi-on treatments as well. It’s unknown whether these other protocols will move toward FDA approval, Dr. Raizman said, due to the difficulty and cost of conducting a large-scale clinical trial. “Some things we may be able to do off-label in the United States, but again, it’s hard to know,” he said.

Crosslinking is also undergoing evaluation to eradicate infectious microbes without antibiotics, and Dr. Kanellopoulos said it has been shown to reduce cases of corneal melt where it is very probable. “It appears to make the cornea more resistant to enzymatic digestion,” he said.
As a final word of advice, Dr. Raizman reiterated how important it is for all ophthalmologists to screen teenagers and young adults for keratoconus when they come in with a change in refractive error.

“If [crosslinking] is widely recognized and widely available, we can diminish the need for transplants for keratoconus and significantly reduce the number of patients who require contact lens fitting. We can keep our patients seeing well with spectacles if we’re diligent with screening patients and treating them early on. This will require that this procedure be widely available and provided by a large number of comprehensive ophthalmologists and not just limited to small centers and corneal specialists,” Dr. Raizman said.

Dr. Hersh said in terms of learning the technique, his best advice is to visit a surgeon experienced with crosslinking, but courses offered at the ASCRS•ASOA Symposium & Congress and other meetings can be educational as well.

References


Editors’ note: Drs. Hersh and Raizman have financial interests with Avedro. Dr. Kanellopoulos has financial interests with Alcon (Fort Worth, Texas), Avedro, i-Optics (The Hague, the Netherlands), Johnson & Johnson Vision (Santa Ana, California), and TrueVision (Santa Barbara, California). Drs. Greenwood and Swan have no financial interests related to their comments.

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