Epithelial-on crosslinking shows promise

by Michelle Dalton, EyeWorld Contributing Editor

Early results are similar to epi-off techniques and may be beneficial for older patients as well

FOR MORE THAN A DECADE, corneal crosslinking has been discussed, described, and used worldwide as a means of treating keratoconus. In Europe, patients as young as 9 years are undergoing the procedure, but it remains under investigation in the United States. The procedure has been shown in various studies to stop the progression of keratoconus, improve or reduce corneal steepness, and improve best corrected visual acuity. Once thought to be limited to younger patients in whom keratoconus is still developing and progressing, some studies have shown older adults can benefit as well. Corneal crosslinking with riboflavin and ultraviolet (UV) light is being performed at roughly 400 centers worldwide, including several in the United States under the CXL-USA Study Group. Preliminary results from one of the study centers were presented earlier this year, with more results expected sometime in the third or fourth quarter, said Roy S. Rubinfeld, M.D., Washington Eye Physicians & Surgeons, Chevy Chase, Md. In the CXL-USA Study, which began in October 2009, subjects initially underwent the original, epithelial-off technique. Jodi Luchs, M.D., F.A.C.S., co-director, Department of Refractive Surgery, North Shore/Long Island Jewish Health System, N.Y., and one of the study investigators, explained that the epi-off technique involves anesthetic drops, epithelial removal, riboflavin drops for 30 minutes (after which the physician checks the cornea for riboflavin saturation), exposure to UV light for 30 minutes, placement of a bandage contact lens, and post-op treatment "similar to PRK," he said. In the most common crosslinking procedures, the UV irradiance is about 3 milliwatts per square centimeter, and the uncorrected visual acuity is between 360 and 370 nanometers, depending on which device is being used. The CXL-USA Study Group is using a medical UV light source used off-label under an Investigational Review Board approval, said Dr. Rubinfeld, who helped design the study. In epi-off, the epithelium is debrided "so the riboflavin can penetrate fully through the cornea," he said. "The epithelium was originally thought to be the primary barrier to penetration of the riboflavin into the corneal stroma."

Patients undergoing the epi-off procedures are "uncomfortable for the first few days as the epithelial defect is healing," Dr. Luchs said. "I think the pain with epi-off is even a little more intense than the pain from a simple PRK procedure." Other variables may dissuade some potential candidates from the procedure as well, he said. In most published studies, corneal curvature can increase after the epi-off procedures, and vision can worsen for months post-op before improving, he added.

"The CXL-USA group postulated that an epi-on procedure might allow faster visual recovery, a much more comfortable procedure, reduce the risk of infection, and reduce the risk of late onset corneal haze," he said. Late haze after crosslinking may occur because "as the cornea starts to

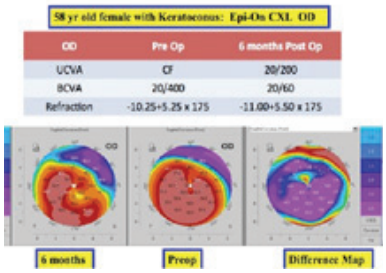
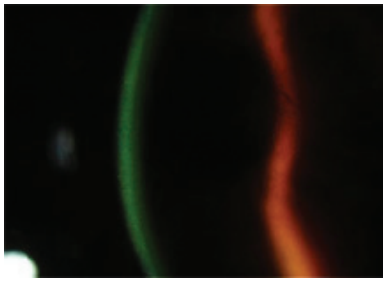


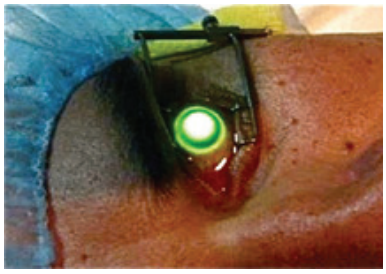
Figure 1. Difference map showing the improvement in corneal shape 6 months after epi-on crosslinking

SOURCE: WILLIAM TRATTLER, M.D.



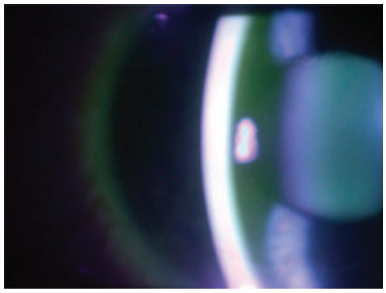
A slit lamp example of a cornea loaded with riboflavin undergoing the epi-on procedure

SOURCE: ROY RUBINFELD, M.D.



An example of a patient undergoing an epi-off procedure

SOURCE: ROY RUBINFELD, M.D.



Riboflavin penetrating throughout the entire corneal stroma (as demonstrated by the flare in the anterior chamber) during an epi-on procedure

SOURCE: JODI LUCHS, M.D.

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heal, the keratocytes start to repopulate and can become activated, resulting in the deposition of non-native collagen," Dr. Luchs said, who added he has never seen late onset haze in any of his crosslinking patients, although haze following epi-off crosslinking has been described in many peer-reviewed articles.

Epi-on crosslinking (or transepithelial crosslinking) was originally described by Brian Boxler Wachler, M.D., Beverly Hills, Calif., in 2004, and then by Roberto Pinelli, M.D., in Italy, Drs. Luchs and Rubinfeld said. The main concern with an epi-on procedure is whether or not the surgeon can get enough riboflavin to penetrate the cornea, Dr. Luchs said. "If you can't get enough riboflavin, then number one, is it still a safe procedure, since one role of the riboflavin is to absorb some of the UV light? The other issue is if you don't have enough riboflavin, can you have an effective crosslinking procedure?" The UV energy entering the eye might potentially damage other intraocular structures, he said. One downside to the epi-on procedure is the longer procedure time—anywhere from 30 to 50 minutes longer primarily to achieve good corneal riboflavin loading, Dr. Luchs said. Epi-on also cannot be combined with other simultaneous procedures involving epithelial debridement, such as topo-guided PRK, he said.

CXL-USA preliminary study results

The CXL-USA Study is a prospective, non-randomized, multicenter study evaluating both epi-on and epi-off crosslinking on up to 1,000 eyes with follow-up through 6 months. Patients could be enrolled in the study if they had keratoconus, forme fruste keratoconus, pellucid, post-LASIK ectasia, or RK with diurnal visual fluctuations. Additionally, patients could be as young as 12, but the corneal thickness had to be at least 300 microns. Any thinner than 300 microns and patients "could run into potential damage because the corneas may not be thick enough to absorb the UV light," Dr. Luchs said. "The initial protocol was for 1,000 eyes. We're doing bilateral crosslinking, but we could do unilateral if necessary," Dr. Rubinfeld said. The protocol criteria began with epi-off as the technique, "but as we started to hear more about transepithelial procedures, we started to try to replicate the results the European studies had. Our study is an outcome study, not randomized, so the flexibility to alter the procedure of choice was available."

Providing the patient meets all the study criteria, he/she will now generally undergo epi-on, Dr. Rubinfeld said. For those with corneas closer to the lower end of the corneal thickness inclusion parameters of the study, they can sometimes be swelled to "at least 400 microns. In some, that still won't happen even with hypotonic eye drops. For those patients, we can offer the epi-off procedure [and] debride the epithelium, which will allow the cornea to swell more to safer thickness levels," Dr. Luchs said. Dr. Luchs presented preliminary results from one of the centers involved in the study; this particular center evaluated 36 patients who underwent the epi-on procedure and 20 who underwent the epi-off, he said. "Looking at the difference maps of the corneal topography is the key here," he said. "Difference maps show the improvement in corneal shape, and that's what correlates best with the improvements in visual functioning and the BCVA [best corrected visual acuity] these patients will experience." The improvement in the overall shape of the cornea correlates best with the improvement in visual function. At 3 months, 52.6% of the epi-off eyes had improved BCVA, and 63.9% of those in the epi-on group had improved BCVA. By 6 months, 45% of those in the epi-off group had improved BCVA, and 62.5% of those in the epi-on group had improved BCVA. Dr. Luchs said people who had epi-off tend to see significantly worse at first, "which may be due to the scraping of the epithelium," he said. After the epithelium has been debrided and begins to grow back on, "it does so in a uniform thickness across the cone. So it will mimic the underlying corneal curvature without the masking effect of epithelial thinning over the cone."

He believes in the long term both sets of patients will be able to see better, but those in the epi-on group will do so quicker and less painfully. Initially it was thought keratoconus naturally stops progressing some time in the late fourth decade of life and therefore, crosslinking would be ineffective or unnecessary. What the CXL-USA Study Group found, however, was that older patients are experiencing "an improvement in the quality of their vision, despite their age," Dr. Luchs said. Additionally, the crosslinking procedure is "reasonably noninvasive, and they don't lose the potential to pursue other options if required, such as Intacs [Addition Technology, Sunnyvale, Calif.] and corneal transplants."

Dr. Rubinfeld noted a "substantial number of patients have now exited the study," since follow-up was designated to be 6 months. "There has not been a case of progression or regression," he said. "What we're finding is the earlier a patient is treated, the more likely we are to stop progression of these diseases. There doesn't seem to be any benefit in waiting until the disease is severe to treat the patient. In Europe, patients are being treated as young as 9. If you compare the safety and efficacy of corneal transplant to early crosslinking, crosslinking wins. Preventing these diseases (as in most of medicine) is better than treating them."

Editors' note:
Drs. Luchs and Rubinfeld are investigators in the CXL-USA Study. Dr. Rubinfeld also holds patents on the device used in the study.

Contact information:

Luchs: 516-785-3900, jluchs@aol.com
Rubinfeld: 301-654-5114, rubinkr1@aol.com