Epi-On or Epi-Off? Only Time Will Tell

By Linda Roach

The search for ways to improve corneal collagen cross-linking (CXL) has ignited interest among corneal subspecialists in a fundamental dilemma: epithelium on or off? The notion that cross-linking might not require surgeons to remove the epithelium has been a common theme heard from the podium and during hallway discussions and dinnertime conversations at recent research meetings.

"Everybody is talking about this," said Roy S. Rubinfeld, MD, who is in private practice with Washington Eye Physicians & Surgeons in Chevy Chase, Md., and is a clinical associate professor at Georgetown University Medical Center and on staff at Washington Hospital Center in Washington, D.C.

"This is a very hot topic, and the time has come that we talk about it," Dr. Rubinfeld said. "There is a lot of confusion in the field."

Less Pain, Fast Healing

At the International Congress on Surface Ablation, Femto-Lasers & Cross-Linking, held on July 31 and Aug. 1 in Utah,[1] Dr. Rubinfeld was one of several speakers who told attendees that early studies of trans-epithelial cross-linking suggest that it might hurt less, heal faster and reduce risk compared with the standard protocol now used around the world.

So far, however, there is a scarcity of published data from well-controlled, prospective trials to support the wave of enthusiasm about epi-on treatment. A recent search of medical literature indexed by Medline/PubMed shows only a handful of prospective, controlled studies on trans-epithelial cross-linking.[2,3]

Nevertheless, case reports, retrospective analyses and clinical experience suggest that the epi-on procedure is at least as safe and effective as the standard procedure, said William B. Trattler, MD, director of cornea at the Center for Excellence in Eye Care in Miami and a volunteer assistant professor at the University of Miami's Bascom Palmer Eye Institute. And it might even be better, because it appears to be less risky, he said.

Similar Visual Outcomes

Drs. Trattler and Rubinfeld are investigators in CXL USA, a physician-sponsored, prospective research effort at 12 U.S. sites that will compare the results of epi-on and epi-off cross-linking treatments.

They reported at the Utah meeting on early visual results in 254 of their own patients. At both three and six months after surgery, about half of 184 epi-on patients had better BSCVA than before CXL. That compared to BSCVA gains in 70 epi-off patients of 31 percent and 24 percent, respectively.

"There's no question that there's a long history for the epithelium-off procedure, and we know that it works," Dr. Trattler said. "But in our study, we're getting the same visual outcomes with trans-epithelial treatments, but without the risk of haze, corneal ulcer and delayed epithelial healing."

Europe Is Paying Attention
Even in Europe, where the standard cross-linking protocol originated, the pressure to switch to epithelium-sparing CXL is mounting, said Aleksandar Stojanovic, MD, chief of refractive surgery at University Hospital of North Norway and medical director at SynsLaser Clinic in Tromsø and Oslo.

"It seems that trans-epithelial cross-linking is gaining momentum at this point," Dr. Stojanovic said.

"Like most European surgeons, my own experience started with epi-off procedures," Dr. Stojanovic said. "But now I think that epi-on is safer and visual rehabilitation is faster than when the epithelium is removed."

Today, he performs his cross-linking with an epi-on protocol he developed that makes the corneal epithelium permeable to riboflavin. Outcomes in patients followed for one to three years have been comparable to those from standard cross-linking, he said.

Preventing Corneal Ulcer
Dr. Stojanovic switched to trans-epithelial cross-linking after he and a colleague each had a patient with post-CXL corneal ulcer. Complications after epi-off procedures are uncommon, but Dr. Stojanovic was concerned.

"The main complication I worry about with removing the epithelium is corneal ulcer, and I've never heard of anyone getting it with epi-on CXL," he said.

Currently, he is enrolling patients in a controlled, contralateral epi-on vs. epi-off clinical trial to treat keratoconus.[4]

Words of Caution
Corneal collagen cross-linking has been widely adopted worldwide by ophthalmologists outside the United States. It was approved in Europe in 2006, but U.S. availability depends on the results of several ongoing company-sponsored FDA trials of UVA devices; these trials all use the standard epi-off protocol.

A German/Swiss group led by Theo Seiler, MD, developed "the Dresden protocol," which is the standard method of corneal cross-linking. The protocol's first step is removal of the normally impermeable corneal epithelium. This is followed by the instillation of 0.1% riboflavin in an isotonic Dextran solution (Pharmacosmos, Holbaek, Denmark).

The riboflavin diffuses into the stroma, where it fuels the collagen-stiffening process (by reacting to UVA with the release of free radicals) and shields the lens, retina and corneal endothelium from UVA toxicity.

After a slit-lamp exam to confirm that sufficient riboflavin is in the stroma, the surgeon begins the cross-linking by shining a UVA light into the eye for 30 minutes.

Trans-epithelial CXL looks like a potential successor to the epi-off procedure but these early results should be regarded with caution, advised R. Doyle Stulting, MD, PhD, director of corneal disease and research at Woolfson Eye Institute in Atlanta. Dr. Stulting is medical monitor for a CXL trial being conducted in 160 keratoconus and 160 ectasia patients that is sponsored by Topcon Medical Systems, Inc., of Oakland, N.J.

"The jury isn't in yet," said Dr. Stulting. "And there may be some patients who would be better for one type of procedure than another."

Extreme Skepticism Initially
When Brian Boxer Wachler, MD, of Beverly Hills, Calif., and Roberto Pinelli, MD, of Brescia, Italy, began performing trans-epithelial procedures a few years ago,[5] many other CXL researchers were profoundly skeptical of the improved outcomes that the two doctors were claiming, recalled Stephen D. Klyce, PhD, an adjunct professor of ophthalmology at Mount Sinai School of Medicine in New York who is an expert on corneal physiology.

"When surgeons started to make the claim that they were doing cross-linking with the epithelium on, people thought this couldn't be true. They thought it was ridiculous," Dr. Klyce said.

But a look through the basic science literature might have changed their minds.

"I published papers back in the 1970s showing that you could make the corneal epithelium permeable pharmacologically," he said.

"Just as Good"

Despite such uncertainty about some of the details, believers in the potential of epi-on corneal cross-linking hope to convince others that this modification to the standard procedure is worth trying.

"Surgeons want to be convinced that epi-on is as good as epi-off," Dr. Trattler said. "If we can get results that are just as good as the original protocol – or if they're even close to that – that says to me that epi-on cross-linking should be our first choice."

Dr. Stulting assesses epi-on's future more cautiously. He hopes that U.S. ophthalmologists keep their eyes on the bigger picture, remembering that whether the epithelium is removed or not, corneal cross-linking will be life-changing for their patients with sight-stealing conditions like progressive keratoconus.

"I'd tell them that as soon as corneal cross-linking gets approved in the U.S. they need to either start doing it themselves or find someone they can refer to that will," Dr. Stulting said.

"Because I think cross-linking is going to be the treatment of choice for keratoconus," he said. "We basically have a disease for which there has been no treatment – and now we have one."

References

1. The International Congress on Surface Ablation, Femto-Lasers & Cross-Linking, July 31-Aug. 1, 2011, in Deer Valley, Utah. http://www.CXLCongress.com
2. Leccisotti A, Islam T. Trans-epithelial corneal collagen cross-linking in keratoconus. *J Refract Surg.* 2010;26(12):942-948.
3. Ertan A, Karacal H, Kamburo*ğ*ulu G. Refractive and topographic results of transepithelial cross-linking treatment in eyes with intacs. *Cornea.* 2009;28(7):719-723.
4. Protocol posted at ClinicalTrials.gov website, accessed Aug. 15, 2011.
5. Boxer Wachler BS, Pinelli R, Ertan A, Chan CC. Safety and efficacy of transepithelial crosslinking (C3-R/CXL) [letter]. *J Cataract Refract Surg.* 2010;36(1):186-818; author reply 188-189.
6. Baiocchi S, Mazzotta C, Cerretani D, Caporossi T, Caporossi A. Corneal crosslinking: riboflavin concentration in corneal stroma exposed with and without epithelium. *J Cataract Refract Surg.* 2009;35(5):893-899.
7. Raiskup F, Spoerl E. Corneal cross-linking with hypo-osmolar riboflavin solution in thin keratoconic corneas. *Am J Ophthalmol.* 2011;152(1):28-32.e1.

Financial Disclosures

Dr. Rubinfeld is an investigator for the CXL USA studies.
Dr. Trattler is an investigator for the CXL USA studies.
Dr. Klyce is a consultant with Clinical Research Consultants, which is conducting the Topcon cross-linking clinical trial.
Dr. Stulting is medical monitor for the Topcon trial.
Dr. Stojanovic has no financial interests to declare.