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LINDSTROM'S PERSPECTIVE

Learning process ongoing for corneal collagen cross-linking

by Richard L. Lindstrom, MD

No commercial method of corneal collagen cross-linking, or CXL, is currently approved in the U.S. However, CXL is commercially available in most other countries, and even in America, several company- and investigator-sponsored studies have allowed a significant number of patients to be treated.

First, let me state that while we have learned much, we have much to learn, and surgeons around the world are using CXL in very different ways, generating vigorous debate, as noted in this issue's cover story.

Our group at Minnesota Eye Consultants has participated in two company-sponsored protocols over the last decade, one sponsored by Peschke and the other by Topcon, with the goal of obtaining U.S. Food and Drug Administration approval. In these clinical trials, patients with evidence of progressive keratoconus were enrolled, and we used what many have come to call the classic "Dresden" protocol, pioneered by Theo Seiler, MD, PhD, and Michael Mrochen, PhD. In this approach, the corneal epithelium is scraped off out to a 10 mm to 11 mm diameter, and the cornea is saturated with riboflavin drops and then irradiated with ultraviolet light. I call this treatment therapeutic corneal cross-linking (therapeutic CXL or TCXL). Nearly always, because of the associated morbidity and potential for complications, only one eye is treated at a time.

What are some of the things we learned with all our patients now more than 1 year postoperative and many patients more than 5 years after treatment?

First, we learned that any study with a goal of FDA approval of a pharmaceutical in the U.S. is very time consuming and very expensive. Neither of the companies noted above chose to continue the process toward FDA approval because of poor early outcomes and the extraordinary costs involved to continue the effort.

Another company, Avedro, using a similar classic Dresden epithelium-off approach, has now succeeded in completing a FDA reviewable data set and hopefully will present to the FDA panel in 2014. I hope we will therefore see a first approval for a epithelium-off classic Dresden protocol CXL in the U.S. for progressive keratoconus in some range of severity by 2015. That would be a very positive development for the field, in my opinion.

Back to a few other key personal learnings. We learned that the chosen metric of the maximum keratometry value (Kmax) on the Oculus Pentacam is far from an ideal metric. If one measures this value five times in the same patient a few minutes apart, disparate numbers are generated, as very small changes in patient fixation and surface wetting change the measurement significantly in a steep cornea, with a Kmax well off the visual axis. A single Kmax reading is not to be relied upon; using as many as five and then averaging the middle three may provide a more useful number. Nonetheless, despite much effort, no better parameter to measure in clinical trials has evolved, although many are being evaluated.

We also learned that with the classic Dresden epithelium-off cross-linking, Kmax and patients' visions and refractions are often worse after surgery for several months. This is because of the significant healing period and the impact of compensatory epithelial hyperplasia, hypoplasia and corneal remodeling. The epithelium in a patient with keratoconus is thin over the cone and thicker in the surround as the body tries to smooth the cornea, just as in an epithelial facet or as noted in PRK for high myopia. This is important for both study design and patient counseling.

I advise my patients that the 1-year outcome is the first important endpoint, that CXL and epithelial and corneal remodeling can continue for as long as 5 years based on keratoplasty experience, and that they may be worse after treatment for as long as 6 months. It is, of course, quite discouraging for patients to pay a significant fee, suffer through a miserable postoperative experience, and then see worse than they did before the procedure. Much hand-holding and encouragement are required, and some patients do not choose to have their second eyes treated.

In addition, because of this prolonged corneal remodeling, clinical trials need to extend to at least 1 year and preferably longer when comparing treatment to control or one technique to another.

Finally, we have been reminded that removing the corneal epithelium for a 10 mm to 11 mm diameter and then irradiating the cornea with ultraviolet light generates significant pain, prolonged re-epithelialization and all the complications noted throughout the years of PRK, only worse. These include death of nearly all the corneal keratocytes in the treatment zone, delayed epithelial healing, corneal haze, which in some cases can be visually significant, and the occasional corneal thinning/melt or severe scar. In a patient with progressive keratoconus who is on his way to needing a keratoplasty, the risk-benefit ratio for this treatment remains positive, but for milder cases, I believe we need something less invasive with less morbidity.

In my next commentary, I will discuss our more recent experience in an investigator-sponsored clinical trial with CXLUSA using a less-invasive epithelium-on treatment approach. In addition, I will discuss preliminary experience using this technique in combination with conductive keratoplasty, Intacs (Addition Technology), phototherapeutic keratectomy and PRK.

Patients with moderate to severe progressive keratoconus accept the pain and hassle of classical epithelium-off Dresden protocol CXL with the simple goal of stabilizing the cornea and reducing the probability of a future keratoplasty, and for me, the risk-benefit ratio supports this treatment. For this reason I expect that the FDA panel will agree and vote to support approval of classic epithelium-off CXL for the patient with significant progressive keratoconus. Still, my patients and I would strongly prefer a treatment or combination of treatments that can both stabilize their cornea and enhance their visual function and quality of life by improving their uncorrected and best corrected vision.

Many patients are not impressed with the fact that their Kmax is 1.2 D flatter at a year if their vision is unchanged or even worse. Fortunately, after CXL, most patients can be fit with a gas permeable or scleral contact lens, but they are often far from ecstatic about their outcome. The progress my patients and I are hoping for is similar to the transition that we experienced in cataract surgery as we evolved during my career from intracapsular cataract extraction and a pair of aphakic spectacles to the miracle of modern-day refractive cataract surgery. I want to be able to safely treat patients with very early nonprogressive keratoconus with a minimally invasive procedure with high safety. In the patient with more severe disease, in addition to stabilizing the cornea, I want to reduce the associated astigmatism and spherical refractive error and enhance both uncorrected and best corrected vision and quality of life. Perhaps, just dreaming a little, I want to safely treat the 10% to 15% of patients I turn down for LASIK or PRK with a combined procedure including CXL, reducing or even eliminating the chance for ectasia after corneal refractive surgery. In a nutshell, I want to transition to an approach that I would label as refractive corneal collagen cross-linking (refractive CXL or RCXL). OSN