OCULAR SURGERY NEWS

Applications, advances in cross-linking offer treatment opportunities for variety of patients

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Richard L. Lindstrom, MD

Collagen cross-linking is a very exciting new treatment modality for the ophthalmologist engaged in treating corneal disease.

The number of patients who might benefit include the approximately 200,000 with some form of congenital or acquired corneal ectasia; those with significant progressive hyperopic shift and fluctuating vision after radial keratotomy (RK), at least another 300,000; perhaps the 15% of patients presenting for laser corneal refractive surgery who are turned down because of thin or atypical corneas, another 100,000-plus; and maybe even the routine LASIK or PRK patient. When I add it all together, with a few orphans to boot, such as unresponsive corneal ulceration, Terrien's disease and the like, it is possible to project numbers, depending on how safe the surgery and how aggressive the surgeons might be, that settle in between 500,000 to 1 million procedures per year in the United States alone once U.S. Food and Drug Administration approval is achieved and the market matures.

If so, corneal cross-linking (CXL) would represent an important new office-based surgical procedure for ophthalmologists and the industry that supports us. To date, no CXL treatment method has achieved FDA approval, but several FDA clinical trials and another group of physician-sponsored studies operating with institutional review board (IRB) approval have allowed about 200 U.S.-based surgeons to gain significant experience with CXL.

Our group of four corneal surgeons at Minnesota Eye Consultants now has more than 5 years of experience treating a variety of patients with CXL. My personal thoughts on the experience gained in our participation in three clinical trials is the subject of this commentary.

We started as participants in the Peschke Meditrade-sponsored clinical trial. We were all convinced, from listening to and observing the outcomes of our European colleagues, that FDA approval of CXL would be easily obtained. The study was designed to measure the so-called "K max," or the steepest point on the cornea, as the outcome variable, looking for enhanced stability vs. control in progressive keratoconus. The study designers, convinced that the procedure was effective, designed an ethical study using epithelium-off CXL in which patients were randomized into treatment and control groups, but the control eyes were allowed to be crossed over to treatment at 3 months postoperative.

The treatment, while relatively straightforward, was definitely painful for the patient, perhaps twice as much as a PRK. The larger epithelial defects healed in most patients with a bandage contact lens, and the same adjuncts that had been proven to be helpful in PRK, including a bandage contact lens,

topical NSAIDs and oral pain medication, helped the patients through the somewhat-longer-than-PRK healing time. Visual recovery and corneal epithelial remodeling were slow, and to our surprise, many corneas were actually steeper at 3 months than before treatment. Further research has helped us understand this paradoxical response as being dependent on epithelial wound healing.

In the untreated eye with long-term keratoconus, the epithelium thins over the steepest part of the cornea, making it flatter. After epithelium-off CXL, a more normal-thickness epithelium initially forms, resulting in an epithelium-induced artifactual steepening. Needless to say, a treatment that at 3 months resulted in many, if not most, corneas being steeper rather than flatter than controls did not result in an approvable FDA data set. Realizing the enormous costs associated with FDA approval in the U.S., Peschke Meditrade lost heart and withdrew to the easier and less-expensive outside-the-U.S. marketplace.

Fortunately, as we followed our patients longer term, the artifactual steepening noted at 3 months resolved, and long-term results confirmed the global experience of stability, or even mild relative corneal flattening, at 1 year and longer post-treatment. While some patients required treatment for persistent epithelial defects, and corneal haze was observable in most and a problem in a few, the complication rate was, in our opinion, acceptable and appropriate for a patient with documented progressive corneal ectasia.

We signed up for our second clinical trial with Topcon, again an epithelium-off trial with a goal of FDA approval. Déjà vu: The costs to the company were also too much for our sponsor to accept, and this trial was abandoned before approval, as well.

So, while some of our colleagues decided to simply treat patients off label without FDA approval when they deemed it to be in their best interests, we chose to enter a third trial, a physician-sponsored, IRB-approved clinical trial under the auspices of CXLUSA. This has proven to be a great decision, as we can now treat epithelium-off or epithelium-on and use advanced riboflavin formulations and fractionated UV light delivery. We can also combine our treatments with conductive keratoplasty (CK), PRK, Intacs (Addition Technology) or various combinations of the three. The learning has been exponential, as experience has been shared with the more than 36 investigators at 18 clinical sites in this very constructive clinical trial.

While data are accumulating, my current impression is that good outcomes can be obtained with advanced technology using an epithelium-on approach. This reduces patient morbidity significantly, and nonhealing epithelial defects and significant corneal haze are now only a bad memory. In addition, the combination of apical CK with epithelium-on CXL is showing great promise in reducing astigmatism and improving both uncorrected and best corrected visual acuities. The same is true for epithelium-on Intacs with CXL, epithelium-on CK and Intacs with CXL, and epithelium-off simultaneous PRK with CXL. Knowledge is expanding rapidly, and results are preliminary, but I now expect to not only stabilize my patients with corneal ectasia, but also simultaneously improve their topography, refraction, BCVA and even uncorrected visual acuity. Some of the outcomes are absolutely amazing, and as confidence grows, we are finding ourselves treating patients with milder disease.

Although I have not yet treated any patients without a diagnosis of corneal ectasia (including RK with progressive hyperopia and fluctuating vision in that class), many surgeons around the world are pioneering CXL in combination with LASIK and CXL in combination with PRK, as well as taking a new look at various forms of CXL combined with thermal keratoplasty.

I am ever more convinced that CXL is a significant advance in our therapeutic capability, that we are still learning the breadth of its potential applications and that most patients in the future will be treated with a combination of CXL and another corneal reshaping procedure. In addition, the CXL opportunity, in my opinion, is significantly larger than originally projected, and I expect even more rapid progress once the multinational strategics engage and put to work the magic of competition and greater financial and intellectual resources.