The Promise of Corneal Collagen Cross-linking

The benefits of this form of treatment are well documented, but research continues.

BY WILLIAM B. TRATTLER, MD; ROY S. RUBINFELD, MD;
PARAG A. MAJMUDAR, MD; AND SANDY T. FELDMAN, MD

Corneal collagen cross-linking (CXL) is being used worldwide as a first-line treatment for keratoconus, pellucid marginal degeneration, and post-LASIK ectasia. CXL has been shown to be both safe and effective in well over 100 peer-reviewed articles and, by September 2006, all 25 nations in the European Union had approved the procedure. In those countries, patients as young as 10 routinely undergo this form of treatment when they are first diagnosed with keratoconus. Due to the regulatory process, CXL remains investigational in the United States.

This article discusses when to provide CXL to patients and the various methods of cross-linking. It also reviews some of the procedures that may be combined with CXL, such as topography-guided PRK, intracorneal ring segments, and phakic IOLs.

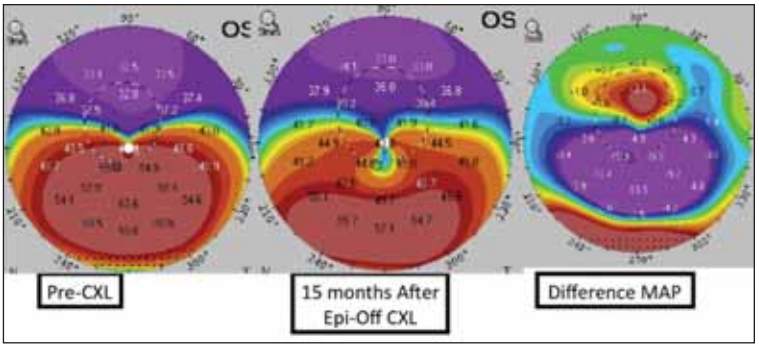

Figure 1. A 43-year-old man underwent epithelium-off CXL. The Pentacam Comprehensive Eye Scanner's (Oculus, Inc., Lynnwood, WA) difference map shows flattening of the inferior steep areas of the cornea and steepening of the superior flat areas of the cornea. This demonstrates how CXL can help shift the cornea to a less irregular shape.

TIMING

Patients can benefit from CXL as soon as they are diagnosed with keratoconus, pellucid marginal degeneration, or post-LASIK ectasia. The procedure will almost always halt progression of the ectatic condition. In a large percentage of patients, CXL can lead to an improvement in the corneal shape, UCVA, and BCVA and decrease astigmatism.[1-4] Treatment can also increase patients' contact lens tolerance, because regularization of the cornea may allow for better contact lens fitting.

As expected, CXL in the early stages of disease is more successful than in the advanced stages.[3] Treatment may help prevent the corneal thinning and apical scarring typical of advanced keratoconus. After CXL, many patients can resume wearing their contact lenses in a few days or a few weeks. Their vision gradually improves weeks to months after treatment, as the cornea undergoes remodeling. In some cases, improvement continues for many years.[1]

METHODS

A point of contention regarding CXL concerns the epithelium. Traditionally, surgeons remove this tissue before applying riboflavin eye drops for 30 minutes,[5,6] after which the cornea is exposed to ultraviolet (UV) light for 30 minutes (Figure 1). The surgeon places a bandage contact lens on the eye, and the healing process progresses similarly to PRK. This approach presents a small risk of corneal infection, because the epithelial defect can take 4 to 6 days to heal. In addition, corneal haze is not uncommon, especially in patients who have delayed epithelial healing.

Brian Boxer Wachler, MD, and Roberto Pinelli, MD, have described an alternate technique: epithelium-on CXL.[7,8] The surgeon instills riboflavin drops over an intact corneal epithelial surface. Once enough riboflavin has been absorbed, the cornea is exposed to UV light for 30 minutes. The major advantages of this approach are rapid visual recovery, a lower risk of infection and haze, and less ocular discomfort. Controlled studies have shown that epithelium-on CXL halts the progression of keratoconus.[9]

The major question is whether or not removing the epithelium provides a greater degree of cross-linking.

Comparative studies or methods by which to quantify the amount of cross-linking are needed to provide this answer. In the meantime, both techniques appear to be effective.

ONGOING RESEARCH AND COMBINED PROCEDURES

No UV light devices are currently approved by the FDA for CXL, and such approval may not occur for a few years. Nevertheless, multiple sites in the United States are providing this form of treatment, typically as part of an investigational study. For example, Dr. Rubinfeld has organized the CXLUSA study, involving 10 US sites (locations listed at CXLUSA.com). The goal of this prospective, multicenter study is to compare the results of epithelium-on versus epithelium-off CXL in patients with different levels of keratoconus, pellucid marginal degeneration, forme fruste keratoconus, and post-LASIK ectasia. The CXLUSA study is also evaluating the efficacy of the procedure in patients with RK who experience diurnal visual fluctuations.

Additional research is underway, including a randomized epithelium-off CXL study organized by James Reidy, MD, as well as a CXL study with Peter Hersh, MD, comparing two different formulations of riboflavin. Topcon Medical Systems, Inc. (Oakland, NJ), is sponsoring a prospective, randomized study comparing epithelium-off CXL with sham treatment for patients with keratoconus. Yaron Rabinowitz, MD, is heading up a prospective, randomized study comparing CXL alone and CXL with Intacs (Addition Technology, Inc., Des Plaines, IL) for the treatment of keratoconus.

Internationally, eye surgeons have the option of performing CXL alone or combining it with another procedure. For example, John Kanellopoulos, MD, and Simon Holland, MB, FRCSC, advocate performing topography-guided reshaping of the cornea for keratoconus or post-LASIK ectasia to remove corneal asymmetry, followed by immediate CXL. Dr. Kanellopoulos also treats all patients with adjuvant mitomycin C to help reduce corneal haze. The results to date of topography-guided PRK combined with CXL appear very positive.[10] As mentioned earlier, CXL may be combined with the placement of Intacs.[11] Alternatively, patients can undergo the procedures separately, with Intacs implanted 6 to 12 months after CXL. Additional options for procedures to combine with CXL include topography- or wavefront-guided PRK and the implantation of a phakic IOL. The results of sequential treatments appear positive.[12]

CONCLUSION

The evidence to date of the benefits of CXL for patients with early and/or progressive ectatic corneal conditions suggests that these individuals will benefit from treatment as soon as they are diagnosed, whether abroad or as part of a clinical trial in the United States. Further research and advances should greatly benefit these patients. ■

Sandy T. Feldman, MD, is medical director of ClearView Eye & Laser Medical Center in San Diego. She acknowledged no financial interest in the products or companies mentioned herein. Dr. Feldman may be reached at (858) 452-3937; sfeldman@clearvieweyes.com.

Parag A. Majmudar, MD, is an associate professor, Cornea Service, Rush University Medical Center, Chicago Cornea Consultants, Ltd. He acknowledged no financial interest in the products or companies mentioned herein. Dr. Majmudar may be reached at (847) 882-5900; pamajmudar@chicagocornea.com.

Roy S. Rubinfeld, MD, is in private practice with Washington Eye Physicians & Surgeons in Chevy Chase, Maryland. Dr. Rubinfeld is also a clinical associate professor of ophthalmology at Georgetown University Medical Center/Washington Hospital Center in Washington, DC. He holds a financial interest in CXLUSA. Dr. Rubinfeld may be reached at (301) 654-5290; rubinkr1@aol.com.

William B. Trattler, MD, is the director of cornea at the Center for Excellence in Eye Care in Miami. He is a consultant to CXLUSA. Dr. Trattler may be reached at (305) 598-2020; wtrattler@earthlink.net.

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