Update on the US Status of CXL

A US study will evaluate accelerated cross-linking.

BY JOHN A. VUKICH, MD

For the past 13 years, surgeons outside the United States have commonly performed corneal collagen cross-linking (CXL) as the first line of treatment to restore corneal stability in keratoconic and ectatic eyes. The traditional approach involves applying riboflavin solution to the eye for 30 minutes, followed by 30 minutes of exposure to ultraviolet A light at a fluence of 3 mW/cm^2. Avedro, Inc., has submitted a new drug application to the FDA for a cross-linking study at these parameters, and recently, the company began a trial that will evaluate accelerated CXL (see *Avedro's CXL Study*). The American-European Congress of Ophthalmic Surgery (ACOS) is sponsoring the next accelerated CXL study, ACOS-KXL-001.

ABOUT THE ACOS STUDY

The Multi-Center, Randomized, Controlled Evaluation of the Safety and Efficacy of Corneal Collagen Cross-Linking in

AVEDRO'S CXL STUDY

By Peter S. Hersh, MD

As the medical monitor for Avedro, Inc., I have seen interest in corneal collagen cross-linking (CXL) grow dramatically during the past few years. The procedure's promise as the first modality to slow the progression of ectatic corneal diseases excites ophthalmologists and patients alike.

In March 2012, Avedro submitted a new drug application to the FDA based on the first multicenter, controlled clinical trials of CXL for the treatment of keratoconus and corneal ectasia. The in-depth analysis of this study fully outlined the successful outcomes of the CXL trials. In the trial, patients were randomized to either a treatment or a control group. To assess the efficacy of CXL, the primary outcome indicator that my fellow investigators and I looked at was the difference in the change in maximum keratometry (K_{max}), as measured by corneal topography over time, between the treatment and control groups. With more than 350 eyes treated for keratoconus and ectasia, our findings were as follows.

Looking at the outcome of K_{max} change (topography-derived maximum keratometry), we found a 2.60 D difference in the average change from baseline in the CXL-treated group versus the control group in patients with keratoconus; the treatment group improved, whereas the control group progressed. Similarly, we found a 1.40 D mean difference in K_{max} in the treated versus control group in the patients with ectasia. Both groups of patients met the study endpoint of a difference of 1.00 D or more in the mean change in K_{max} from baseline between treatment and control.

In both the keratoconus and ectasia groups, mean UCVA and BSCVA improved in the treated patients. In fact, approximately 28% to 33% of patients experienced an improvement of more than 2 lines.

I now have the pleasure of serving as the medical monitor for Avedro's accelerated CXL study, A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (riboflavin ophthalmic solution) for Corneal Collagen Cross-Linking. My fellow investigators and I will evaluate the safety and efficacy of accelerated (4-minute) CXL performed with Avedro's KXL System for reducing maximum corneal curvature. In this study, patients will be randomized to a treatment arm or a sham control group. Treatment will involve 30 mW/cm^2 of ultraviolet A illumination for 4 minutes after the administration of riboflavin. This dosage contrasts with the 30-minute administration of ultraviolet A light at a power of 3 mW/cm^2 that was used in previous studies. We hope that the new treatment modality will advance the clinical science of CXL. We are also pleased that the addition of the American-European Congress of Ophthalmic Surgery's study sites will provide more information regarding optimal treatment parameters.

Peter S. Hersh, MD, is a professor of clinical ophthalmology and chief of cornea and refractive surgery and UMDNJ-New Jersey Medical School in Newark, New Jersey. He is a visiting research collaborator at Princeton University in Princeton, New Jersey, and is in private practice with the Cornea and Laser Eye Institute-Hersh Vision Group in Teaneck, New Jersey. Dr. Hersh may be reached at (201) 883-0505; phersh@vision-institute.com.

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Eyes with Keratoconus or Corneal Ectasia after Refractive Surgery will be conducted at up to 100 investigational sites across the United States. The trial will enroll patients with keratoconus or post-LASIK ectasia. Investigators will evaluate and compare the safety and efficacy of three treatment regimens for CXL performed with VibeX (riboflavin ophthalmic solution) and the KXL System (agent and system from Avedro, Inc.) for reducing corneal curvature. Eyes will be randomized to one of the three treatment groups by treatment condition (keratoconus or corneal ectasia) and will all receive active treatment.

The ACOS study has several purposes. The large number of sites will enable patients all over the country to enroll in the trial and obtain potentially sight-saving treatment. Through this study, investigators such as myself will have rapid access to data from a large cohort of patients so that we may evaluate the dose response curve. A total of 8,000 eyes could undergo CXL in this study. We will test three doses of irradiation: 15, 30, and 45 mW/cm^2. Which is most appropriate? Moreover, is CXL only ultraviolet A dose dependent, or does it also depend on duration? The information we gather will demonstrate how to balance the protocol for patients' safety, comfort, convenience, and outcomes.

CONCLUSION

Currently, there is no FDA-approved medical therapy to control the progression of keratoconus. CXL, however, has shown promising success internationally and in US clinical trials for stabilizing corneal curvature and slowing or stopping keratoconic progression. In the future, the procedure has great potential for a variety of corneal therapies. Already, international surgeons are incorporating accelerated CXL into their standard LASIK procedures and introducing it in antimicrobial applications. As the medical monitor of the ACOS trial, I look forward to bringing this promising procedure to a broad group of geographically diverse patients throughout 2012. ■

John A. Vukich, MD, is a partner at the Davis Duehr Dean Center for Refractive Surgery in Madison, Wisconsin. Dr. Vukich may be reached at (608) 282-2000; javukich@facstaff.wisc.edu.