CXL in Clinical Trials

An overview of results from two US studies.

BY LAURA STRAUB, EDITOR-IN-CHIEF

The use of corneal collagen crosslinking (CXL) for the treatment of keratoconus and postoperative ectasia continues to gain credibility. The procedure first described 10 years ago by researchers led by Theo Seiler, MD, PhD, in Dresden, Germany,[1] is now being practiced around the world. In the United States, however, US Food and Drug Administration (FDA) regulations are slowing down the momentum this therapy has had elsewhere. Two US clinical trials, one of which is sponsored by the American-European Congress of Ophthalmic Surgery (ACOS; See *ACOS: An Overview* for more information), may help get CXL fast-tracked for approval in the United States.

CXL has become common practice in Europe. While there are several variations in treatment paradigms, all current CXL protocols include exposing the cornea to ultraviolet-A (UV-A) light for up to 30 minutes after it is soaked with riboflavin. Acting as a photosensitizer, the riboflavin absorbs the UV-A light and generates highly reactive singlet oxygen that causes crosslinking of collagen fibers to increase the stiffness of the cornea. By increasing the covalent bonds among the collagen molecules, CXL can significantly increase the diameter of collagen fibers.

In the United States, surgeons are exploring the safety and efficacy of various CXL protocols in multicenter clinical trials. A description of two ongoing US clinical studies of CXL are below.

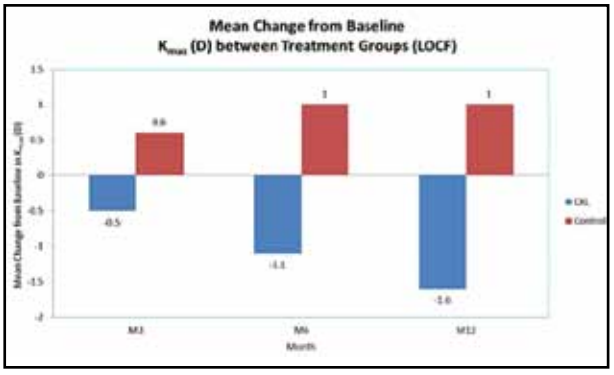


Figure 1. The change in K max in patients with keratoconus.
LCOF = last observation carried forward

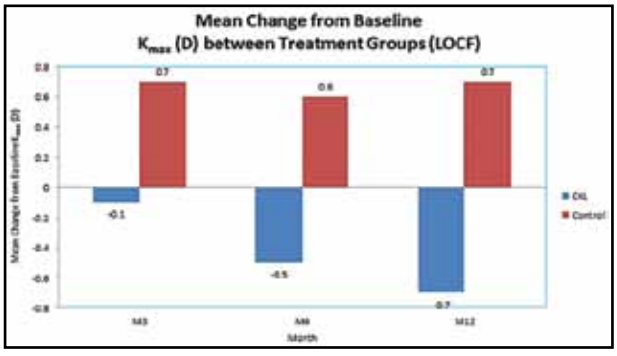


Figure 2. The change in K max in patients with corneal ectasia.
LCOF = last observation carried forward

Figures 1 and 2 courtesy of Michael Gordon, MD

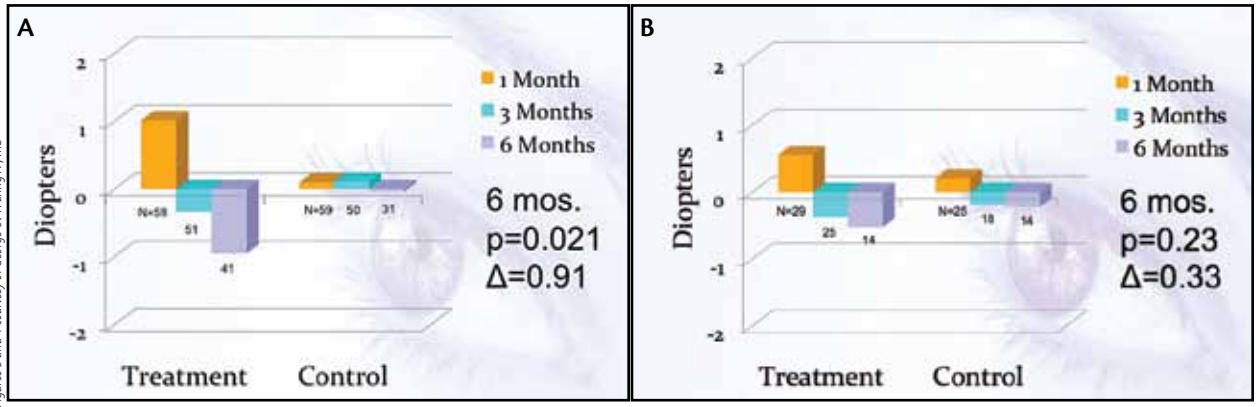
AVEDRO

John Vukich, MD, medical monitor of the ACOS-sponsored Avedro clinical trial for CXL, recently announced that up to 4,000 eyes will be enrolled at 100 sites across the United States in a nonrandomized clinical trial using the Keraflex KXL crosslinking system (Avedro). Mild, moderate, or severe keratoconus or corneal irregularity consistent with ectasia as a result of radial keratectomy, PRK, or LASIK must be present to be included in the study. All included eyes must have a BCVA worse than 20/20, which corresponds with less than 55 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and a steepest keratometry (K max) of 47.00 D or more, which signifies progressive keratoconus. Dr. Vukich further discusses the study protocol in an interview on Eyetube.net (eyetube.net/?v=tinun).

This study will evaluate two UV-A treatment regimens, 15 mW/cm^2 of fluence and 45 mW/cm^2 of fluence, and will last 1 year. The clinical endpoint will be K max, and the trial will begin "in the very near future," Dr. Vukich said.

"The advantage is that these are very rapid treatments, either 2 minutes and 40 seconds or 8 minutes," he said in the Eyetube interview. "These [treatment times] are significantly less time for the patient to be exposed to the light."

In a presentation made at the recent ACOS-Dulaney Winter Meeting in Aspen, Colorado, Michael Gordon, MD, reviewed data from his own participation in Avedro's FDA crosslinking trials.[2] A total of 160 patients with keratoconus or corneal ectasia were enrolled: 80 in an active CXL group that underwent CXL with epithelial removal, administration of 0.1% riboflavin for 30 minutes, and UV-A exposure



Figures 3 and 4 courtesy of George O. Waring IV, MD

Figure 3. Changes in K max at 1, 3, and 6 months in the (A) keratoconus and (B) corneal ectasia groups.

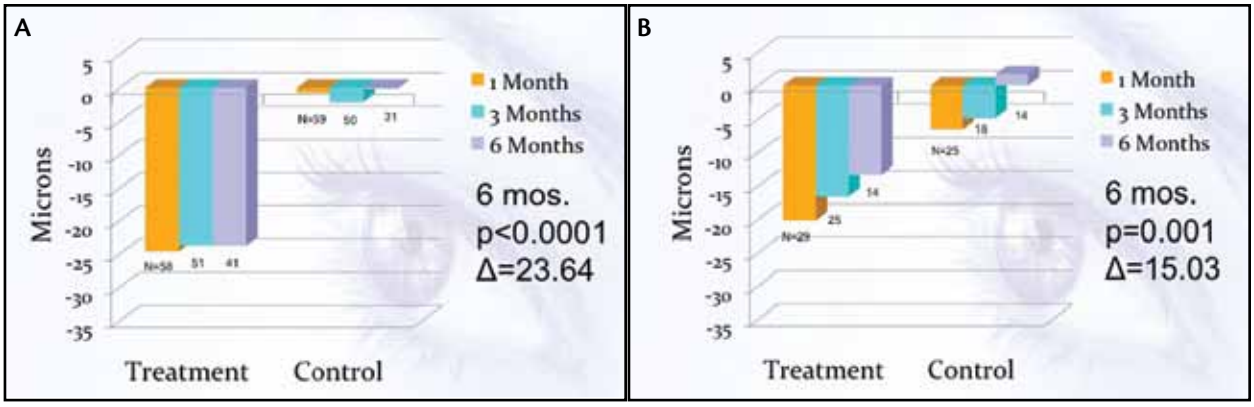


Figure 4. Changes in corneal thickness in the (A) keratoconus and (B) corneal ectasia groups.

for 30 minutes at 3 mW/cm^2; and 80 in a control group that received 0.1% riboflavin but did not undergo epithelial removal or UV-A exposure.

Dr. Gordon stated that K max improved more favorably in patients with keratoconus who underwent CXL and that, at 3, 6, and 12 months, this improvement met the definition of success (ie, difference between treatment groups of 1.00 D or more in the mean change in K max from baseline). The change in K max in patients with keratoconus is depicted in Figure 1.

Likewise, CXL treatment improved K max more favorably than the control treatment in patients with corneal ectasia. This improvement met the definition of success only at months 6 and 12. The change in K max in patients with corneal ectasia is depicted in Figure 2.

A small number of serious adverse events were reported; none were related to riboflavin or UV-A irradiation. Dr. Gordon also said that reduction in K max in both the keratoconus and corneal ectasia groups was accompanied by improvement or stabilization of visual acuity. In the keratoconus group, patients gained up to 4.3 and 5.9 letters of UCVA and BCVA, respectively. In the corneal ectasia group, up to 5.2 and 5.8 letters of UCVA and BCVA were gained, respectively. Dr. Gordon concluded that the CXL protocol provided statistically significant and clinically meaningful effects for all patients and that the treatment was safe and well tolerated.

TOPCON/SOOFT

US clinical trials are also underway for a CXL treatment strategy devised by Topcon/Sooft Italia. Speaking at the ACOS-Dulaney Winter Meeting, George O. Waring IV, MD, shared results from an interim analysis of a prospective, block-randomized treatment clinical trial of CXL for keratoconus or corneal ectasia after LASIK or PRK using the Vega UVA System.[3] In this study, CXL was performed in one eye

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ACOS: AN OVERVIEW

The American-European Congress of Ophthalmic Surgery (ACOS) is a new society designed for leading anterior segment surgeons, ophthalmic industry executives, select venture capitalists, and inventors of technology. ACOS provides a platform for education and advocacy representing the mutual interests of these groups and brings leading ophthalmologists and innovators of technologies together to advance vision care and improve patients' quality of life.

ACOS was established in early 2011. In addition to three annual US-based meetings, a European meeting in Cannes, France is plannned for this summer.

of 186 patients, 119 with keratoconus and 67 with ectasia. Treatment was randomized by severity based on K max. The clinical endpoints were K max at 6 months and BCVA, UCVA, and manifest refraction; follow-up extended to 1 year.

The changes in K max at 1, 3, and 6 months in the keratoconus and corneal ectasia groups are depicted in Figure 3, and the changes in corneal thickness in these two groups are depicted in Figure 4. Dr. Waring said that the greatest effect of the CXL treatment was seen in eyes with moderate to severe keratoconus or corneal ectasia. The complications were mild, not vision-threatening, and did not relate to the CXL treatment but rather to the epithelial removal, he said.

Based on this interim analysis, Dr. Waring said that CXL appears to be a safe and effective treatment for ectatic corneal diseases that halts progression and produces slight regression of disease.

CONCLUSION

As the markets in which CXL is approved and available expand, the indications for this treatment will also grow. This is an exciting time for surgeons who treat patients with keratoconus and corneal ectasia, and *CRST Europe* will continue to update readers on the progress made in delivery, safety, and long-term results of CXL. ■

1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135(5):620-627.
2. Waring GO IV. FDA Trial Results CXL. Paper presented at: the ACOS-Dulaney Winter Meeting; February 26-29, 2012; Aspen, Colorado.
3. Gordon M. FDA Trial Results CXL. Paper presented at: the ACOS-Dulaney Winter Meeting; February 26-29, 2012; Aspen, Colorado.

TAKE-HOME MESSAGE

- In the Avedro clinical trial, the CXL protocol provided statistically significant and clinically meaningful effects for all patients.
- In the Topcon/Sooft clinical trial, CXL halted progression and produced slight regression of the disease.