Seeing clearer with CXL

by **Vanessa Caceres** EyeWorld Contributing Writer

AT A GLANCE

- CXL has generated much interest since its U.S. approval for progressive keratoconus and ectasia.
- Further studies of CXL are focusing on accelerated CXL and transepithelial CXL.
- Research is underway abroad on the use of CXL with refractive surgery, and similar research is beginning in the U.S.
- Results are mixed regarding CXL to treat infectious keratitis.

Where the U.S. market stands now, what approaches could be used in the future

The U.S. Food and Drug Administration (FDA) approval of corneal crosslinking (CXL) last year for progressive keratoconus and ectasia brought an additional welcome treatment to the U.S. market, physicians said.

"It's a very important approval," said **Peter Hersh, MD**, director of the Cornea and Laser Eye Institute, Teaneck, New Jersey; professor, Rutgers Medical School, Newark, New Jersey; and visiting research collaborator, Princeton University, Princeton, New Jersey. "Because of its unique ability to decrease progression of KC and ectasia, we've seen widespread incorporation into ophthalmic practice, especially among cornea surgeons. It's been adopted very quickly." Dr. Hersh was the medical monitor for the U.S. clinical trials for approval that were done by Avedro (Waltham, Massachusetts), the only company in the U.S. that currently offers FDA-approved CXL via its Photrexa Viscous, Photrexa, and KXL System.

About 10,000 CXL treatments have been performed with the Avedro system since the FDA approval, said **Rajesh Rajpal, MD**, chief medical officer of Avedro, and founder of See Clearly Vision Group, Washington, DC area.

Evolving treatment parameters

Currently, there's an accelerated CXL study underway that has completed enrollment and should be submitted to the FDA in the near future, said **J. Bradley Randleman, MD**, professor of clinical ophthalmology, director of cornea, external disease, and refractive surgery, and medical director, USC Roski Eye Institute, Beverly Hills, California. The study uses the Avedro KXL protocol with 30 mW treatment.

"The most basic process in the works is standard accelerated protocols, where total irradiance remains constant, but fluence increases and treatment time decreases," Dr. Randleman said. He contrasts this with higher irradiance accelerated protocols, where both fluence and total irradiation increase. "The concept is that accelerated protocols may not provide the same total treatment effect and depth as the standard protocol, so increasing fluence for a reduced time may allow for equal treatment efficacy but also maintain safety," he said.

There is also research on the use of pulsed CXL. "The hypothesis is that the CXL reaction has multiple pathways, and one of these is oxygen-dependent," Dr. Hersh said. "It's thought that by using pulsed UV light during the dark phases, there will be replenishment of oxygen, and it will have a more robust crosslinking reaction."

Another area under investigation is transepithelial CXL (or epithelium-on) and its relative effectiveness; the current FDA approval is for epi-off. At Dr. Hersh's practice, there is a physician-sponsored investigational new drug study regarding the transepithelial technique, as well as the use of CXL and Intacs (Addition Technology, Lombard, Illinois). The latter study looks at the safety, efficacy, and timing of CXL and Intacs, either done the same day or performed sequentially over 3 months. These results will be available shortly.

There's interest in the use of devices with a higher power along with epi-on treatments for shorter treatment duration of CXL; clinical trials in the U.S. for this are being planned, Dr. Rajpal said.

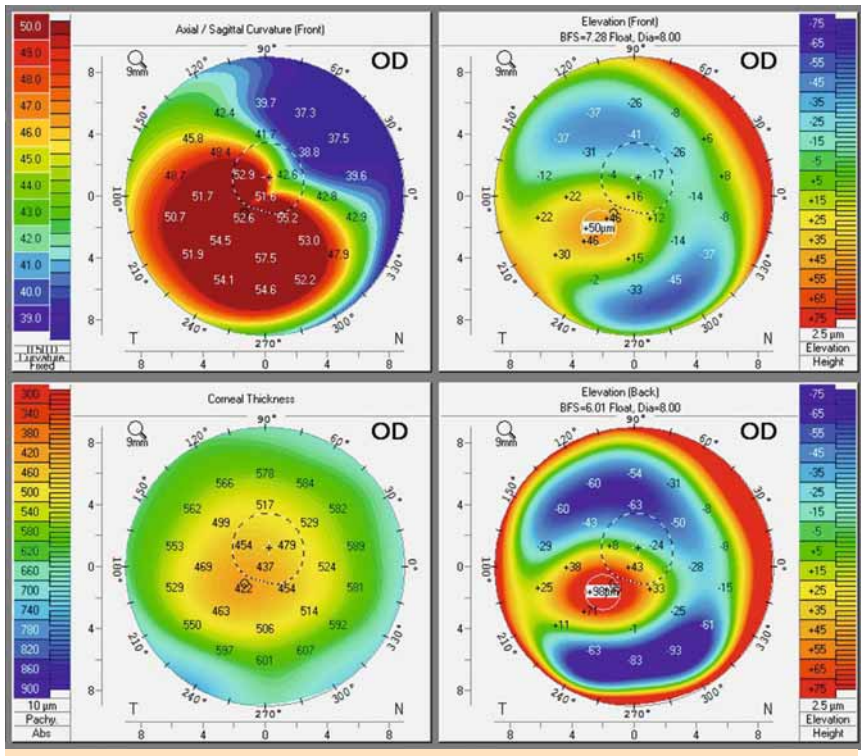
Other areas under investigation include the use of oxygen to varying degrees with the CXL procedure and the use of other carriers beyond dextran, including HPMC, for riboflavin.

CXL and refractive surgery

One area with much interest for CXL is with refractive surgery. Avedro is planning its first U.S.-based trial for photorefractive intrastromal corneal collagen CXL (PiXL) for low myopia, followed by one for presbyopia.

With PiXL, myopic errors are treated with topical riboflavin and then cornea exposure to ultraviolet light delivered by Avedro's Mosaic device, which has a CE mark in Europe and approval from Health Canada but is not yet approved in the U.S.

"Presbyopia is something most ophthalmologists would like to treat, and we have preliminary data to show it may be possible with PiXL," Dr. Rajpal said.



Imaging of corneal ectasia after LASIK

continued on page 33

Seeing clearer – from page 31

Views from Asia-Pacific

Colin CHAN, MD
Vision Eye Institute
L3 270 Victoria Avenue, Chatswood, NSW, Australia
Tel. no. +61-2-94249999
colchan@gmail.com

It is great to see crosslinking approved by the FDA in the U.S. In Australia, crosslinking has been performed routinely since 2006 and the reported experience has been overall positive.

There is no age restriction in Australia and like Dr. Raizman I find the age restriction by the FDA on crosslinking to patients 14 and older somewhat perplexing. As he stated there is reasonable safety data on pediatric crosslinking[1-3] and I have regularly crosslinked patients under the age of 14. I am so impressed at how brave some of these children are as very few need a general anesthetic. Typically, I find the haze response is more pronounced in the younger age group and so I will usually do a more prolonged taper of topical steroids. I have also had to crosslink a few patients again after 10 years if they were very young to begin with.

The key point Dr. Raizman states is that it is the patients below the age of 14 who need crosslinking more as it is these patients who progress more rapidly. I completely agree. This leads to the need for corneal transplantation at a younger age. I will explain this to parents who are understandably anxious about having their beloved child have a procedure at such a young age. When the prospect of a transplant in the near future is raised, I find parents very quickly choose to do the crosslinking.

I have a slightly different approach to Dr. Berdahl's with young patients. He stated that he would be inclined to crosslink young patients straight away without documenting topographic progression of the keratoconus. I have had at least 20 young patients over the past 10 years who did not progress especially if they were active eye rubbers with significant allergic disease. In these patients, I encourage avoiding eye rubbing and prescribe mast cell stabilizers such as Zaditen (ketotifen fumarate eye drops, Novartis, Basel, Switzerland) or Patanol (olopatadine HCl eye drops, Alcon, Fort Worth, Texas) to be taken routinely for 1–2 months to help break the habit. If their allergy is more severe I will refer these children to an allergist for consideration of desensitization/immunotherapy. I then watch these patients very carefully, doing topography every 3 months as I do agree that these patients can very rapidly progress, even as much as 1–2 D of cylinder every 3 months.

Currently in Australia, few corneal specialists perform crosslinking and topographic ablation. My concern is that even with a crosslinked cornea, there would be a risk of keratoconic progression in years to come if the cornea was ablated. I look forward to seeing 5-year data on topographic ablations and crosslinking but for the moment, I am not comfortable with the concept.

I note Prof. Randleman's comments regarding accelerated crosslinking and I look forward to more data. I have been performing epi-off accelerated crosslinking with the Avedro system now for more than 2 years and have been pleased with the results. I have not had to repeat any treatments as yet. I have definitely observed a lesser degree of haze formation with the accelerated protocol compared to the standard 30-minute irradiance with the original UVX. This may mean that there is a lesser degree of crosslinking achieved but this may still be adequate given we do not know the exact amount of crosslinking necessary to stop progression of keratoconus for any given patient. Indeed, my hope is that in the future we will be able to titrate the amount of crosslinking required according to the biomechanics and age of the patient, thereby avoiding extra unnecessary crosslinking.

References

1. Panos GD, Kozeis N, Balidis M, Moschos MM, Hafezi F. Collagen Cross-Linking for Paediatric Keratoconus. *Open Ophthalmol J.* 2017 Jul 31;11:211–216. doi: 10.2174/1874364101711010211. eCollection 2017.

2. Viswanathan D, Kumar NL, Males JJ. Outcome of corneal collagen crosslinking for progressive keratoconus in paediatric patients. *Biomed Res Int.* 2014;2014:140461. doi: 10.1155/2014/140461. Epub 2014 Jun 11.

3. Vinciguerra P, Albé E, Frueh BE, Trazza S, Epstein D. Two-year corneal crosslinking results in patients younger than 18 years with documented progressive keratoconus. *Am J Ophthalmol.* 2012 Sep;154(3):520–6. doi: 10.1016/j.ajo.2012.03.020. Epub 2012 May 24.

Editors' note: Dr. Chan declared no relevant financial interests.

The treatment of myopia with CXL is for about 1 to 1.5 D, or below what is typically treated with PRK or LASIK. The use of CXL for low myopia would treat in the center of the cornea, while for presbyopia it would treat the periphery.

Research presented by European ophthalmologists at European Society of Cataract & Refractive Surgeons (ESCRS) meetings last year reported positive results in small studies of PiXL for low myopia, according to reports from Avedro.

Outside the U.S., there have been studies of LASIK Xtra (Avedro), where CXL is used in conjunction with LASIK or PRK. "There's some evidence that it allows the treatment to be more predictable and perhaps reduce the risk of ectasia," Dr. Rajpal said.

Within Avedro's trials, results may come soonest from the PiXL trial for low myopia followed by PiXL for presbyopia, Dr. Rajpal said.

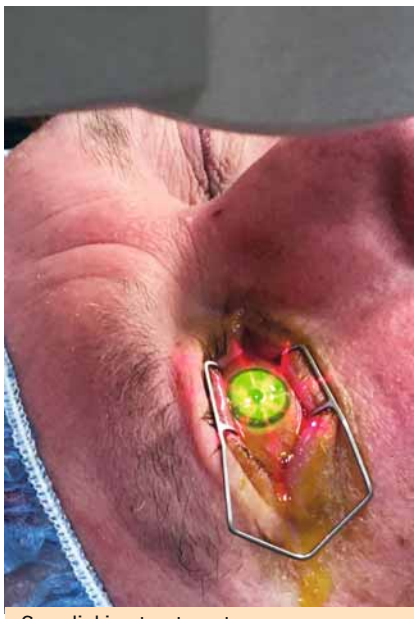
CXL and infectious keratitis

There's some buzz, mostly abroad, about the use of CXL for the treatment of bacterial, fungal, and *Acanthamoeba* infections. The results appear mixed so far. "Shallower, earlier bacterial infections appear to respond best, while fungal infections also appear efficacious. There's an uncertain impact on *Acanthamoeba* infections," Dr. Randleman said.

"I think the results are somewhat equivocal," Dr. Hersh said. "There are some reports that show it's efficacious, and other reports show no difference compared to traditional therapy." Still, he sees a lot of interest and promise in this potential use.

Obtaining coverage

One challenging area since the introduction of CXL in the U.S. has been insurance reimbursement. As Dr. Hersh pointed out, there are high costs involved with getting a procedure like CXL approved, and there's a relatively small subset of patients who require treatment. "Unlike a drug approval that treats millions, the number of keratoconus and ectasia patients is substantially smaller in the U.S.," he said. He also mentioned the long 8-year period that was needed to reach FDA approval.



Crosslinking treatment

Source (all): J. Bradley Randleman, MD

"It's frustrating to us as ophthalmologists because this is very valuable to patients, and we want them to have good access," he said.

This quandary has led to the development of the Avedro Reimbursement Customer Hub (ARCH) program. The program helps with submission to insurance and appeals, and it helps patients who may not be able to afford treatment with cost issues, Dr. Rajpal said. **EWAP**

Editors' note: The physicians have financial interests with Avedro.

Contact information

Hersh: phersh@vision-institute.com
Rajpal: rrajpal@seeclearly.com
Randleman: JamesBradley.Randleman@med.usc.edu