Cover Story

CXL in 2015: At a Crossroads

Techniques, concepts, and indications in the field are constantly changing.

By Farhad Hafezi, MD, PhD

Corneal collagen crosslinking (CXL), initially described by Spoerl and colleagues,1 has extended far beyond its original indication of progressive keratoconus. Some clinicians might wonder how this technique can be so versatile and used in so many different ways. The versatility comes from the fact that crosslinking is one of the most basic elements of corneal architecture. Just as an architect can conceptualize different elements of a building using similar means and techniques, it is only now that we are recognizing the possibilities that the technique of crosslinking has for acting on corneal tissue.

Research in the field of CXL is highly dynamic; techniques, concepts, and indications are constantly evolving. This article attempts to provide a comprehensive outlook on the current state of the art of CXL technology in 2015. Given the speed of development, an outlook article written 12 months from now for 2016 would (hopefully) read quite differently.

CXL for Ectasia

Ectasia of various origins (keratoconus, pellucid marginal degeneration, and post-LASIK ectasia) remains the main indication for CXL. Epithelium (epi)-off techniques using no more than 9 mW/cm² seem to be efficient for these indications.2-4 The year 2014 has again seen vigorous debate on refinements of the technique, intended to either accelerate CXL or reduce postoperative pain and inflammation.

Accelerated CXL. Intensities of up to 30 mW/cm² are already in clinical use to accelerate the procedure; however, there is still doubt regarding the biomechanical effectiveness of CXL at these high intensities. Our research group showed4 that the biomechanical effect of CXL decreases distinctly at irradiations higher than 9 mW/cm². The Bunsen-Roscoe law of reciprocity states that, “a photochemical reaction will stay constant if the total energy is constant: a shortened irradiation time at higher irradiance should lead to the same increase in biomechanical stiffness as a longer irradiation time at lower irradiance.”5 Apparently, this law of photochemistry cannot be applied to the biomechanical effect of CXL in a living organism (Figure 1).

Most published clinical evidence pertains to 3 mW/cm² for 30 minutes (the original Dresden protocol) or 9 mW/cm² for 10 minutes. For intensities higher than 9 mW/cm², publications are sparse and lack documented stabilization of progression.6

Epi-on techniques to reduce postoperative pain and inflammation. The success of epi-on techniques depends on both riboflavin and oxygen availability (see Why Do High Intensities and Epi-On Techniques Fail in Stabilizing Corneal Biomechanics?). Various riboflavin solutions have been tested for the ability to strengthen corneal biomechanics in the laboratory; yet some
commercially available solutions fail to work under either experimental or clinical conditions. Likewise, some modifications of epi-on solutions that seem to induce a satisfying effect in the laboratory have led to unsatisfying clinical results (epi-on multicenter study; personal data). When riboflavin is transported through the epithelium using an active process (eg, iontophoresis), laboratory results seem promising; however, clinical evidence has not been reported yet.

CXL PLUS
CXL in combination with refractive laser surgery procedures, also referred to as CXL Plus, may be applied to improve visual quality in keratoconus by depth-limited tissue regularization (the Athens protocol), to prevent ectasia after LASIK (LASIK Xtra); or to treat low myopia as a standalone procedure. A few warnings:

- Although the Athens protocol can improve visual quality and increase distance BCVA, clinicians should proceed with caution, as long-term data (more than 5 years) on biomechanical stability is sparse.
- LASIK Xtra has been proposed to reduce the risk of iatrogenic ectasia; however, given that ectasia after LASIK has become an extremely rare event, proving that the combination of rapid CXL and LASIK is effective would require a large study with more than 10,000 eyes. In other words, with LASIK Xtra, the surgeon is opting to conduct an additional procedure after LASIK that has not been proven to be effective but that can increase the risk of unpredictable changes in corneal curvature.
- The flattening effect of CXL in normal corneas has not yet been well defined. If a normal cornea behaves even remotely similarly to a keratoconic cornea, then we have not yet learned to control the process of flattening precisely enough to allow refractive corrections of myopia.

PACK-CXL FOR INFECTIOUS KERATITIS
Infectious keratitis and related corneal ulcers are a major cause of global blindness, with several million people affected every year in developing countries. In view of the alarming 2014 report of the World Health Organization (WHO) regarding increasing resistance to antibiotics in medicine, alternative therapies to antibiotic therapy would be highly appreciated. The use of photoactivated chromophore for infectious keratitis CXL (PACK-CXL) might represent such an approach.

It may be possible to use PACK-CXL in the treatment of bacterial, fungal, and mixed corneal ulcers; a proof-of-principle study was conducted by our group in 2008. This technique seems to work efficiently in early and more superficial ulcers and as an adjuvant or last-resort treatment in large and deep ulcers. In the distant future, PACK-CXL may also be an option for treating Acanthamoeba keratitis. However, it has not been shown to be effective yet, and more laboratory and clinical research is needed.

At the time of this writing, a large prospective, randomized multicenter trial was scheduled to commence in December 2014 to focus on PACK-CXL as a first-line treatment modality in previously untreated corneal infiltrates and small ulcers. PACK-CXL alone will be compared with antimicrobial treatment, the current standard of care.

ELUCIDATING CXL MOLECULAR MECHANISMS
In the past, CXL technology was mostly driven by an interesting trial-and-error approach, by which new clinical techniques were sometimes introduced with little to no experimental, laboratory, or clinical data supporting the claim. An ideal way to better understand which genes and proteins play a role in crosslinking would be to work in transgenic organisms, in which a single gene out of many thousands can be selectively overexpressed (enhanced) or knocked out.

The mouse would be an ideal animal for that purpose because thousands of transgenic strains exist already. There is an obstacle with using a mouse model, however: Whereas...
epi-off CXL is possible without too many obstacles (Figure 2), analyzing the biomechanical response of the mouse cornea has failed so far due to technical limitations—the mouse cornea is only 1 mm in diameter. After several years of building customized setups and experimenting, we succeeded in measuring stress-strain measurements in the mouse eye (Kling et al, in preparation for publication). Our mouse model might open new alleys for the identification of yet unknown factors and players in this fascinating field.

By Kristina Mikek, MD

My CXL predictions for 2015 will be relegated to five areas.

No. 1: CXL in children. CXL in the adult population has received a good deal of attention in recent years, yet treatment advances are slower to reach children. Several studies, however, have shown that CXL works just as well in pediatric populations.1-4 In 2015, we must commit to changing our outlook on treating keratoconus in children. Instead of following the same protocols as we do for adults, which is to first document progression of the disease prior to CXL treatment, we should consider performing CXL immediately after keratoconus is diagnosed. Surgeons who treat a lot of keratoconus patients know that, in children, the disease most definitely will progress. It should be our first priority to stop keratoconus at the earliest possible stage. In my clinic, I have two teenagers with keratoconus who developed corneal hydrops because CXL was not performed when the disease was detected. In both patients, the consequence was corneal transplantation in 2 years’ time. My personal protocol is therefore to include CXL in the treatment of pediatric keratoconus in all cases.

No. 2: Epithelium (epi)-off versus epi-on. In 2015, epi-off will continue to be the best approach in my hands. With that said, some solutions may be available in the near future to help promote the diffusion of riboflavin and make the epi-on technique more efficient.

No. 3: Technology. Ongoing studies will prove which amount and duration of ultraviolet-A illumination is best. Most people who perform CXL in 2015 will likely use moderate dosing and duration, such as 9 mW/cm² for 10 minutes.

No. 4: Combined CXL treatments. I agree with Theo Seiler, MD, PhD, that we must be cautious with CXL, as treatment prolongs long-term effects. If we perform a combined procedure (CXL plus laser refractive surgery) there could be an unpleasant refractive surprise. I suggest waiting for the outcomes of CXL treatment before performing surgery that aims to improve visual results, be it laser or phakic IOL implantation.

No. 5: New trends. What we are waiting for—and I believe will work—is a strategy to treat corneal infections with CXL. This new procedure and other new solutions and techniques will likely surface in 2015.

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By A. John Kanellopoulos, MD

In 2015, the six most important developments in CXL will be the following:

**No. 1:** FDA approval of a riboflavin ophthalmic solution/KXL System (Avedro);

**No. 2:** Wider acceptance and popularization of epithelium (epi)-on CXL using a higher concentration of riboflavin and a higher energy level;

**No. 3:** Wider application of refractive CXL, a topographically customized transepithelial approach to CXL that aims to correct low degrees of myopia, hyperopia, and astigmatism;

**No. 4:** Increased use of CXL as an effective adjunct to LASIK—especially hyperopic LASIK but to a lesser extent myopic LASIK—mainly because basic science has shown that the technique acts as a biomechanical modulator in stabilizing routine LASIK (Once it is FDA-approved, I predict that LASIK CXL will become the standard of care in the United States overnight);

**No. 5:** A large number of US clinicians opting for the Athens Protocol (combined topography-guided partial PRK normalization of ectatic corneas with higher-fluence CXL), which will be a direct result of the heightened use of topography-guided excimer ablations (currently being rolled out by Alcon); and,

**No. 6:** New ectasia criteria, as spurred by the formal approval of CXL in the United States.

The application of newer, more sensitive metrics for ectasia and keratoconus, along with the availability of effective CXL techniques in the United States, may be the equivalent of introduction of the smallpox vaccine: no more clinical keratoconus.

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