PACK-CXL: Defining CXL for Infectious Keratitis


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In medicine, groundbreaking and paradigm-changing treatments often arise from the most simple concepts and constructs, and they often do not require expensive equipment to administer.

THE CONCEPT OF CXL

In 1998, the proof-of-principle for corneal collagen cross-linking (CXL) was born from such a "simple" concept. Combining ultraviolet-A light and a chromophore (vitamin B2, riboflavin), the cornea could be stiffened within a mere half hour and progressive thinning diseases such as keratoconus could be halted.[1,2] Although still considered a relatively new concept, CXL is now in clinical use worldwide.

Cross-links in the cornea are not a technique, but rather a physiological principle of all connective tissue. This might explain the enormous versatility of the method of CXL: soon after the proof-of-concept in progressive keratoconus, additional indications were established. These include CXL for postoperative ectasia, CXL for bullous keratopathy, CXL in combination with refractive laser procedures (CXL-Plus), and, most interestingly, CXL for infectious keratitis.[3-12]

THE NEW TERM: PACK-CXL FOR INFECTIOUS KERATITIS

All attendees present for the 9th Annual International CXL Congress held in Dublin, Ireland, were included in the discussion of terminology and polled to decide the best term to define this new cross-linking application of the cross-linking concept. Although no "perfect" term surfaced, the best option advanced, and the one promoted for adoption was PACK-CXL: Photo Activated Chromophore for Keratitis. Although the "CXL" suffix is in some ways redundant, the thought (proposed by Cynthia Roberts, PhD) was to link the now ubiquitous CXL abbreviation to the new "PACK" terminology to help unite the literate and facilitate communication on past and future research on the topic.

Photoactivation of a chromophore can act like a disinfectant, reducing the microbial load of a liquid or a tissue. This concept has been in clinical use in transfusion medicine for more than a decade, and may rely on three mechanisms that occur during the light-activation of the chosen chromophore:

1. Intercalation of the chromophore (eg, riboflavin) with the nucleic acids of the pathogen and inhibition of replication.[13]
2. Damage to the pathogen's cell walls caused by massive amounts of reactive oxygen species.[14,15]
3. Changes in the tertiary structure of the surrounding stromal collagen fibers, making it difficult for the collagenases to dock to their cleavage sites and exert their function.[16]

Clinically, the proof-of-principle of the efficacy of PACK-CXL in treating therapy-resistant microbial keratitis was given in a case series of 5 patients in 2008.[17] Three years later, Makdoumi et al.[18] performed a prospective trial with two arms, where one arm comprised patients treated with photoactivated riboflavin only, in the absence of additional antimicrobial treatment. All 16 eyes reported improvement following CXL. The first randomized prospective trial (Geneva–Cairo trial) showed similar promising results,[19] and other smaller and larger case series have been published.[20]

THE FUTURE OF PACK-CXL: ACCESS TO ALL

Piggybacked on the initial concept of CXL, PACK-CXL has the potential to become a game changer in the treatment of corneal infections. Whereas extended contact lens wear is the major cause of corneal infections

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in developed countries, minor corneal trauma, combined with significant barriers to access to the healthcare system, is causative for corneal ulcers in developing countries, turning corneal infections into a major cause of global blindness.[21-23]

To allow PACK-CXL to make a significant effect globally, the treatment parameters need to address unmet medical needs. These needs include shortening the treatment time, using more efficient chromophores than riboflavin, and providing the technology to every ophthalmologist.

Several research groups are currently working on this exciting new topic. Researchers from Geneva, Switzerland, are currently developing CXL technology that would allow performing a PACK-CXL procedure at the slit lamp, without using expensive operating room infrastructure or additional equipment.

In developed countries, treating a complex corneal infection often may cost thousands of U.S. dollars.[24] PACK-CXL provides promises of a less expensive, faster, and more efficient way to kill harmful pathogens that cause corneal infections and later scarring, in a non-pathogen–specific manner and with little cost when compared to conventional pharmaceutical care.

The future might see small portable devices that will allow the comprehensive ophthalmologist to perform a PACK-CXL treatment as soon as the diagnosis of an early infiltrate or a beginning ulcer is made. We look forward to the widespread availability and application of PACK-CXL to shift the paradigm for infectious keratitis management.

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