

PACK-CXL: Corneal Cross-linking for Treatment of Infectious Keratitis

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Abstract

This article discusses corneal cross-linking (CXL) and how it transitioned from a modality for treating corneal ectatic disorders to an inventive means of treating infectious keratitis. Initially, CXL was successfully developed to halt the progression of ectatic diseases such as keratoconus, using the standard Dresden protocol. Later, indications were extended to treat iatrogenic ectasia developing after laser-assisted *in situ* keratomileusis (LASIK) and photo-refractive keratectomy (PRK). At the time, it had been postulated that the combination of ultraviolet light with riboflavin could not only biomechanically strengthen the cornea but also was capable of destroying living cells and organisms including keratocytes and pathogens. Thus a new and innovative concept of treatment for infectious keratitis emerged through the use of CXL technology. Initially only advanced infectious melting ulcers resisting standard microbicidal therapy were treated with CXL in addition to standard therapy. In subsequent studies CXL was also used to treat bacterial keratitis as first line therapy without the use of concomitant antibiotic therapy. With the increasing interest in CXL technology to treat infectious keratitis and to clearly separate its use from the treatment of ectatic disorders, a new term was adopted at the 9th CXL congress in Dublin for this specific indication: PACK-CXL (photoactivated chromophore for infectious keratitis). PACK-CXL has the potential to eventually become an interesting alternative to standard antibiotic therapy in treating infectious corneal disorders, and may help reduce the global burden of microbial resistance to antibiotics and other therapeutic agents.

Keywords: Corneal Cross-linking; Corneal Ulcer; Infection; Keratitis; Riboflavin; Ultraviolet A

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INTRODUCTION

Corneal cross-linking (CXL) is a technique that was initially developed in Germany and Switzerland to halt the progression of keratoconus.^[1] The technique employs riboflavin drops and 365 nm ultraviolet-A light to generate additional cross-links in the cornea. Specifically, the riboflavin acts as a chromophore and releases free radicals, thus creating new bonds between collagen fibers and proteoglycans. These additional cross-links increase the overall biomechanical strength of the cornea. A number of studies have shown that CXL has become an effective treatment for patients with keratoconus, providing long-term stabilization of the anterior corneal curvature.^[2-7]

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The successful use of CXL to treat keratoconus led to its application in treating postoperative ectasia after LASIK and PRK. This treatment resulted in both short-term and long-term stabilization of K values, other topographical indices and improvement of corrected distance visual acuity (CDVA).^[8-12]

NEW PERSPECTIVES

Photo-activation of riboflavin has been used for years in photochemical pathogen inactivation technologies (PCT)

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for fresh-frozen plasma (FFP). This form of photo-activation enabled donor blood to be treated for various pathogens, such as bacteria and viruses, by inactivating them. As a result, the risk of infection for blood recipients was significantly reduced.^[13-17]

Recently, the antimicrobial effect of riboflavin photo-activation has been explored for potential application in ophthalmic infectious diseases; specifically, its use in corneal collagen cross-linking has been suggested as a treatment modality for infectious keratitis. In 2000, Schnitzler, Spoerl and Seiler reported their use of CXL for stabilization of non-infectious corneal melting of various causes in four patients.^[18] The melting process stopped in three out of four patients, which delayed surgical treatment. This early trial demonstrated the efficacy of CXL in biomechanically stabilizing structurally altered corneas without inducing ectasia.

In 2008, Iseli et al conducted the first study to treat melting corneas exclusively of infectious origin with CXL.^[19] Five patients were enrolled including three patients with mycobacterial keratitis and two others with fungal keratitis. All cases had been unresponsive to regular topical and systemic treatment and had developed corneal melting. All eyes received treatment using the technical parameters of the Dresden protocol (3 mW/cm² for 30 minutes).^[1] In four of five patients, the melting process was halted; the fifth patient had persistent corneal melting caused by an immune reaction without any remaining active pathogen. CXL proved to be effective not only in stabilizing a melted cornea, but more importantly, in killing pathogens of different origins in advanced and therapy-resistant keratitis. Additional case studies on the effect of CXL treatment on melting corneas showed similar results.^[20-43]

In light of these promising results from multiple studies, Makdoui (2011) reported a non-randomized clinical study to investigate the efficacy of CXL as first line therapy for treating bacterial keratitis. A total of 16 patients (13 patients with diagnosed corneal ulcers and 3 patients with corneal infiltrates) without any prior topical or systematic treatment were treated with standard 3 mW/cm² CXL as outlined in the Dresden protocol.^[1] Complete epithelial healing occurred in 15 of 16 patients, and all of them demonstrated symptomatic improvement and reduced inflammation, although two patients needed supplemental antibiotic therapy. This study suggests that CXL might be effective not only in treating advanced ulcerative infectious keratitis as an adjuvant, but also for treating early-stage bacterial infiltrates as first-line treatment.

CXL's antimicrobial effect is due to the effect of UV light interacting with riboflavin as the chromophore. UV light has already been used as an antimicrobial treatment for disinfecting water, surfaces and air. It damages both the DNA and RNA of pathogens, including bacteria and viruses, and renders them inactive.^[44-47] Additionally,

the riboflavin absorbs photons and generates reactive oxygen species (ROS). Those free radicals create covalent connections between specific amino acids in surrounding collagen fibers and proteoglycan molecules, resulting in new covalent bonds.^[7] In 2008, a study presented data showing the antimicrobial effect of riboflavin photoactivated by UV-A light on agar plates. Researchers also compared the antimicrobial effect of CXL with that of UVA light alone. The latter was found to be less effective in killing specific microbial strains. Furthermore, riboflavin alone did not show any significant bactericidal effect in the experiment.^[44]

THE FUTURE OF CXL TREATMENT

The Dresden protocol was developed to treat corneal ectatic disorders and has proven to be safe based on long-term results. Physicians and researchers exploring new applications for CXL treatment have so far used this safe and proven Dresden protocol almost exclusively, without modifications. Now that a growing body of evidence shows that standard treatment is effective in infectious keratitis, it might be possible to improve the treatment by modifying parameters in the protocol such as time, duration of irradiance applied and even the type of chromophore, to determine whether modifications lead to better outcomes for patients. Most interestingly, Richoz et al have recently shown that an accelerated protocol using 18 mW/cm² for 5 minutes and even 36 mW/cm² for 2.5 minutes allows to maintain the same high bacterial killing rate observed in earlier studies using the Dresden protocol.^[48]

To encourage exploration of different applications of CXL and modifications of the Dresden protocol, the ninth CXL congress in 2013 established separate designations to distinguish between the use of CXL in treating ectasias and the use of CXL in infectious keratitis. The latter is now known as photo-activated chromophore for infectious keratitis (PACK)-CXL.^[25] The use of CXL and PACK-CXL may have the added benefit of allowing treatment of infectious corneal diseases without using antibiotics. As microbial resistance to antibiotics increases, new lines of treatment will be needed to replace them and thus CXL may be a promising new alternative treatment modality in the future.

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