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SPECIAL FEATURE

Collagen Crosslinking for Corneal Infection

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Collagen crosslinking (CXL) using riboflavin and UVA light can strengthen the corneas of patients with ectatic disorders. The application of riboflavin and UVA light is also known to inactivate microbial pathogens, suggesting that it may be an effective tool for treating infectious keratitis.

Riboflavin- and UVA light-mediated collagen crosslinking is demonstrating safety and efficacy in treating corneal ectasias (Figure 1). The idea of adapting this protocol to treat corneal infections (referred to in this context as iCXL) comes from the antimicrobial applications of UVA and riboflavin in other areas. The first literature evidence of successful in vivo application of UVA and riboflavin to inactivate microorganisms was published in 1960, after the procedure was used to treat tobacco plants infected with tobacco mosaic virus.[1] Furthermore, UVA light alone has been used for decades to inactivate microorganisms in drinking water and on surfaces; and the combination of UVA light and riboflavin is widely used to sterilize blood products.

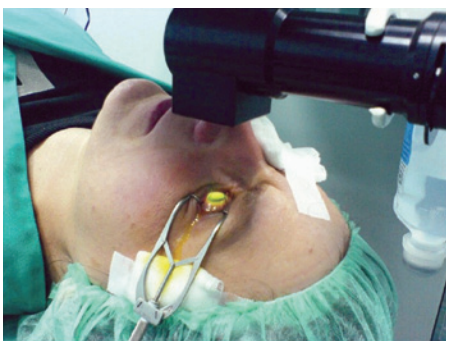

FIGURE 1 Corneal collagen crosslinking in progress: the cornea is soaked with riboflavin and irradiated with UVA. *(Source: Jankov MR, Jovanovic V, Nikolic L, Lake JC, Kymionis G, Coskunseven E. Corneal collagen cross-linking.* Middle East Afr J Ophthalmol. *2010 Jan-Mar;17[1]:21-7.)*

Mechanism

The mechanism by which iCXL acts on infectious keratitis is not completely understood. Riboflavin (vitamin B2) passes easily through lipid membranes and can insert itself into nucleic acid chains. When riboflavin is exposed to UVA it produces reactive oxygen species that oxidize nucleic acid residues, causing damage to DNA and RNA. The UVA itself is also directly damaging nucleic acids. It has been shown in vitro that UVA and riboflavin can inactivate a wide range of microorganisms, including many of the bacteria and fungi responsible for ocular infections.[2]

In addition to direct toxicity to infectious pathogens there are likely secondary benefits to treating corneal infections with UVA and riboflavin. The iCXL procedure may slow the progression of corneal infection and lessen scarring by reducing collagen degradation and inactivating leucocytes.

Opportunities

Treating corneal infections with UVA and riboflavin application has several attractive aspects. While antibiotics, especially the fluoroquinolones, have been exceptionally safe and effective, resistance is eroding their efficacy. In a recent large national surveillance study of ocular isolates, 46.5% of *Staphylococcus aureus*, 58.3% of coagulase-negative staphylococci, and 9.0% of *Pseudomonas aeruginosa*, were not susceptible to at least two antibacterial drug classes. Ironically, the more we use antibiotics, the more resistant the bacteria become.

Unlike UVA and riboflavin application, antibiotics are used heavily in human and veterinary medicine and agriculture, giving bacteria numerous

COLLAGEN CROSSLINKING FOR KERATITIS	
☑	Rationale
	— Kills wide range of pathogens
	— Strengthens cornea
	— Effective against resistant bugs
	— Little chance of inducing resistance
☑	Procedure
	— Remove epithelium (if necessary)
	— Flood cornea with riboflavin solution
	— Apply UVA
☑	Studies/Case Reports
	— Only a handful published
	— Studies small and uncontrolled
☑	Study findings
	— Prevents melting
	— Resolves infiltrates
	— Full epithelial regrowth
	— May be effective without antibiotics

opportunities to develop resistance. Having an effective non-antibiotic means of treating infections could reduce or perhaps even eliminate the likelihood of this worrisome complication.

Other potential advantages of UVA and riboflavin application over antibiotics include eliminating the ocular surface toxicity and avoiding compliance issues associated with the need for frequent antibiotic administration. Finally, there may be a benefit of cost reduction considering the increasing price of antibiotics.

Challenges

Evaluating the clinical efficacy of UVA and riboflavin treatment for infectious keratitis has some inherent difficulties. The large spectrum of pathogens, severity of the disease, depth of the infection, size of the involved area, time period before UVA and riboflavin is introduced, and ocular and systemic comorbidities all represent challenges to conduct well-designed, large, prospective, randomized trials comparing the safety and efficacy of UVA and riboflavin application to routine antibiotics.

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Protocol

Currently, a number of smaller studies evaluating the efficacy and safety of iCXL for corneal infections are underway. The treatment protocol is virtually identical to the procedure used to treat keratoconus and other corneal ectatic disorders. The typical steps include:

- Removal of the epithelium, if necessary
- Saturation of corneal stroma with riboflavin
- Application of UVA light for 30 minutes
- Bandage contact lens and routine antibiotics per discretion of the treating physician

The procedure can be employed as a first-line therapy, after initiation of routine antibiotics, or when routine antibiotics fail to control the infection. The common study endpoints include closure of the epithelial defect and resolution of the infiltrate. Investigators in the US and abroad are working to optimize the parameters of treatment, including duration and intensity of UVA exposure, repeatability, and fine-tuning of indications and contraindications.

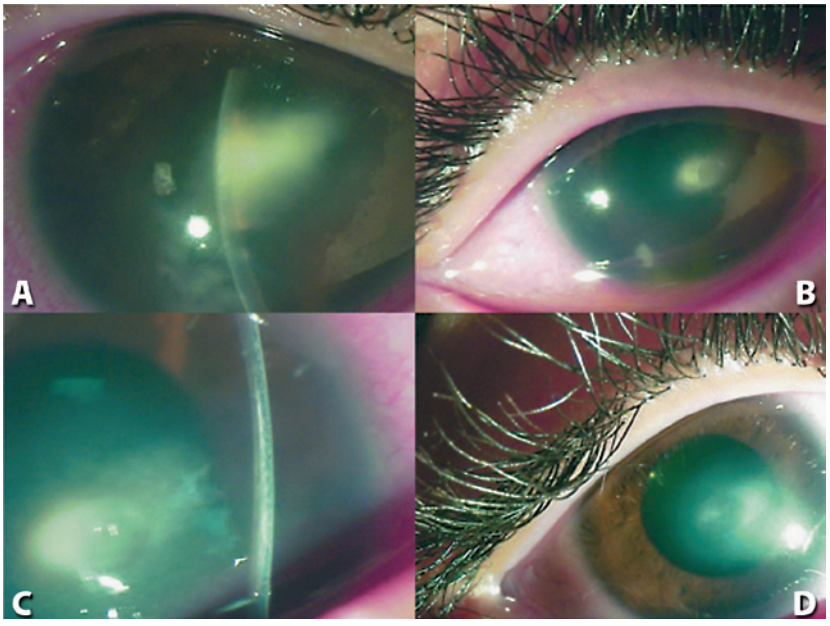


FIGURE 2 (A) Initial presentation of keratitis caused by *Staphylococcus aureus* and unresponsive to treatment with fortified antibiotics. (B and C) 2 weeks after crosslinking treatment. (D) 2 months post-procedure; infection resolved, but visually significant scarring remains. *(Source: Anwar HM, El-Danasoury AM, Hashem AN. Corneal collagen crosslinking in the treatment of infectious keratitis.* Clin Ophthalmol. *2011;5:1277-80.)*

Results

A small number of case series and case reports on UVA and riboflavin application to treat corneal infections have been published in peer-reviewed literature, and the topic is presented and discussed at ophthalmic meetings around the world.

Authors of several reports treated patients whose corneal ulcers progressed despite intensive conventional antimicrobial therapy. They noted that after iCXL the stromal melt was halted and the corneal epithelial defect closed (Figure 2).[3,4,5]

> *More studies need to be done to better understand the optimal indications, dosage, timing, and potential side effects of this novel approach*

Perhaps the most striking evidence of the safety and efficacy of iCXL published thus far comes from Makdoumi's group. The authors described a prospective study involving 16 eyes in which patients had not been given antibiotics prior to the UVA and riboflavin application.[5] After the procedure, antibiotic therapy was initiated only if progression of the infec-

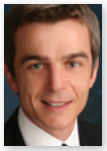
tion was suspected. All eyes showed reduction in symptoms and inflammatory signs. Interestingly, the use of antibiotics was necessary only in two out of 16 eyes.

Where We Stand

The clinical observations after iCXL for infectious keratitis are very encouraging. However, more studies need to be done to better understand the optimal indications, dosage, timing, and potential side effects of this novel approach. It is possible that over time iCXL will be used more broadly in patients with infectious keratitis. It is also possible that iCXL will become a standalone procedure, replacing antibiotics as the standard of care for at least some cases of infectious keratitis.

THE BOTTOM LINE

The UVA and riboflavin application used in collagen crosslinking for corneal ectasia has been successfully applied in cases of infectious keratitis. The potential benefits of iCXL in patients with infectious keratitis include inhibition of microorganisms, strengthening of the corneal stroma, and reduction of inflammation and scarring. The procedure may reduce or in some cases perhaps eliminate the need for antibiotics, consequently leading to reduction in ocular toxicity and resistance associated with the use of antibiotics. Further studies are warranted before iCXL becomes more broadly employed in clinical practice.



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