Cross-linking with photoactivated riboflavin promising treatment for infectious keratitis

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Photoactivated chromophore induces oxidative stress and binds to DNA, disrupting pathogens and preventing them from replicating.


Corneal cross-linking for infections keratitis with corneal melting did not accelerate corneal healing but resulted in fewer complications than antimicrobial therapy alone, a study found.

No serious complications occurred in eyes that underwent corneal cross-linking with photoactivated chromophore for keratitis (PACK-CXL) combined with antimicrobial therapy. The term PACK-CXL was created to distinguish the procedure from corneal cross-linking for the treatment of keratoconus.

“It was a very efficient adjuvant therapy. The real indication would be early onset. We are interested in treating the infiltrates … because there we can fully eradicate the bacteria and even probably the fungi without the use of antibiotics.” Farhad Hafezi, MD, PhD, the corresponding author, said in an interview with Ocular Surgery News.

Hafezi noted that by reducing the need for expensive antibiotics, PACK-CXL may help clinicians satisfy an unmet need in developing countries such as India, where more than 2 million new cases of infectious keratitis are reported annually.

“If you put it into a more global view, we’ve been using cross-linking for keratoconus for 15 years now, and that’s a rare disease. It’s a bad disease, but it’s rare,” he said.

“What we are trying to do is meet the unmet needs. The combination of PACK-CXL might be a really powerful weapon in the future.”

The study was published online ahead of print in Ophthalmology.

Potential mechanisms of action

Hafezi said three biologic processes are involved in PACK-CXL. First, photoactivation creates free radicals that induce oxidative stress and disrupt bacterial cell membranes.
“They might induce cross-links, but moreover, it’s oxidative stress. We have a huge amount of oxidative stress on any living organism on the surface. It simply kills the pathogens, whether it’s a bacterium or fungi,” Hafezi said.

Second, riboflavin binds to the DNA of the pathogen and suppresses replication.

Third, photoactivation changes the tertiary structure of the collagen fibers and makes it harder for collagenases to dock to their cleavage sites.

**Patients and parameters**

The prospective study conducted in Egypt included 21 eyes of 21 patients with advanced infectious keratitis and corneal melting who underwent PACK-CXL combined with antimicrobial therapy.

A control group included 19 eyes of 19 patients who underwent antimicrobial therapy alone.

Eyes undergoing PACK-CXL had the corneal epithelium removed in an area up to 9 mm in diameter. Target corneal thickness of the area without epithelium was between 350 µm and 500 µm. In corneas thicker than 500 µm, swelling was reversed with 70% glycerol drops applied at 2- to 3-second intervals for 5 minutes.

Baseline logMAR corrected distance visual acuity was 2.16 in the study group and 2.01 in the control group. The difference was insignificant.

*Staphylococcus* was the most commonly identified bacterial micro-organism in culture samples, and *Aspergillus* was the most common fungal species isolated.

**Outcomes and observations**

Mean time to healing was 39.76 days in the study group and 46.05 days in the control group. The difference was statistically insignificant.

Corrected distance visual acuity after treatment and healing was 1.64 in the study group and 1.67 in the control group, also an insignificant difference.

Mean ulcer size was significantly greater in the study group than in the control group (width: $P = .004$; length: $P = .007$).

Corneal perforation occurred in three patients in the control group; one patient had recurrent infection. No serious complications were identified in the study group.

Limbitis was identified in all patients in the study group, but it resolved in 5 to 7 days in all but one case. Limbitis persisted for 3 weeks after treatment in one patient.
Hafezi and colleagues plan to conduct a multicenter trial at eight to 10 sites in different countries.

“We will again do small ulcers without any use of antibiotics and a control group that has conventional treatment,” he said. – by Matt Hasson

References:

For more information:
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Disclosure: Hafezi is a co-inventor of PCT/CH 2012/000090 application (UV light source).

PERSPECTIVE

This is a very interesting paper by the Cairo and Geneva groups on the use of cross-linking in the treatment of advanced infectious keratitis with cornea melting. It is well-known that cross-linking creates corneal stiffening and resistance of stroma collagen to enzymatic digestion. It has also been demonstrated in several studies that the activation of riboflavin as a chromophore by UV light makes it induce antimicrobial activity, possibly by either the oxygen radicals released or the activated flavin trimer having primary antibiotic activity.

I think the significance of the study is greater than just a small clinical investigation, if one considers that corneal blindness worldwide is an extreme threat to not only vision but also the well-being of a large part of the global population. This treatment is extremely low budget and utilizes simple technology, and its potential clinical use globally can have a significant impact in the cornea epidemiology.

I think further studies may help validate these data, but nevertheless, it is a very interesting subject.

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*OSN Europe Edition Board Member*

Disclosures: Kanellopoulos is a consultant for Alcon, Allergan, Avedro and Optovue.