

EVIDENCE-BASED CXL

Epi-on, higher UV power, shorter treatment tantalise, but only epi-off is proven. *Howard Larkin reports*

Despite many experiments with corneal crosslinking (CXL) technologies designed to preserve the epithelium and shorten the procedure, the traditional method involving epithelium removal and 30 minutes of 3mW/cm² ultraviolet radiation remains the only proven CXL treatment for keratoconus, Frederik Raiskup MD, PhD, FEBO told the XXXII Congress of the ESCRS in London.

Dr Raiskup noted some promising tests of various epi-on, high-power radiation and iontophoresis CXL approaches. But some early studies are inconsistent, and long-term clinical studies demonstrating safety and efficacy are lacking.

“We still are not finished (investigating these technologies) and these results are not evidence-based,” he said.

PROMISING BUT UNPROVEN

Removing the corneal epithelium is painful and exposes the cornea to possible infection and melting, risking persistent epithelial defects and permanent stromal scars, Dr Raiskup noted.

Preserving the epithelium might reduce these risks, but an intact epithelium prevents diffusion of riboflavin in the cornea, which is essential for crosslinking to occur.

Dr Raiskup and colleagues experimented with epi-on using various pharmacological agents in a rabbit model, and found that adding BAC and hypoosmolar sodium chloride provided adequate riboflavin concentration in the cornea compared with epi-off (*Curr Eyes Res. 2012 Mar;37(3):234-8*). However, clinical trials uncovered safety problems including postoperative epithelial defects.

“What was working in an experimental study was not working in vivo in human corneas.”

Other studies of pharmacologically assisted transepithelial CXL results are mixed, Dr Raiskup said. One cohort study found the process “appeared to halt keratoconus progression with a statistically significant improvement in visual acuity and topographic parameters” (*Filippello et al. J Cataract Refract Surg Feb 2012; 38(2):283-291*).

More typically conclusions are more modest, along the lines of “a limited but favourable effect” (*Leccisotti A et al. J Refract Surg Dec 2010; 26(12):942-948*).

Microscopic examinations also find uneven evidence of corneal structural changes. Still, many epi-on adjuncts remain to be studied, as do the effects of some known substances, he added.

A study using femtosecond-cut pockets was also successful (*Kanellopoulos AJ et al. J Refract Surg 2009; 25:1034-1037*). However, whether this is safer than epi-off is unclear, Dr Raiskup noted. Accelerating CXL by increasing radiation fluence is also promising but unproven in the long-term, Dr Raiskup noted. One randomised prospective trial found 30mW/cm² for four minutes 20 seconds gave results similar to conventional epi-off CXL (*Sherif AM. Clin Ophthalmol 2014; 8:1435-1440*).

Other studies suggest a limit of about 40mW/cm² and at least two minutes UV before crosslinking ceases to be effective (*Wernli J et al. IOVS 2013; 54:1176-1180*), while others suggest a lack of oxygen causes the stiffening effect to drop off sharply as fluence rises and times drop (*Hammer A et al. IOVS 2014; 55:2881-2884*). Total UV exposures up to 40 per cent higher than standard in some accelerated protocols have not been evaluated for safety, he added.

Iontophoresis is also promising, with several studies showing intact epithelium with evidence of corneal stiffening and reduced K values in patients despite lower concentration of riboflavin in stromal tissue compared with epi-off CXL, Dr Raiskup said. Long-term clinical results have yet to be assessed.

EVIDENCE FOR EPI-OFF

Epi-off CXL has a long track record including randomised trials showing halting of keratoconus progression at 36 months (*Wittig-Silva C et al. Ophthalmology 2014; 121:812-821*), and improved K values and corrected distance visual acuity at nine to 12 years follow-up from early patients treated at Dresden, Dr Raiskup said (*Journal of Cataract and Refract Surg 2014: In Print*).

“We can say without any pangs of conscience that epi-off is still now the way to treat our patients with progressive keratoconus,” he said.

Still, a review of more than 2,000 published epi-off papers found just 49 methodologically sufficient for analysis, including eight reporting on four randomised clinical trials, 29 prospective studies and 12 retrospective studies. The majority of the evidence was graded low, and “uncertainty remains about duration of benefit” (*Craig JA et al. The Ocular Surface 2014; 12(3): 202-214*).

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