CORNEAL CROSSLINKING

Techniques now in testing could reduce treatment time, improve effectiveness

by Howard Larkin in Milan

New techniques for improving corneal crosslinking now in development could significantly shorten treatment times, improve corneal strength and increase the flattening effect in treating keratoconus, presenters told the XXX Congress of the ESCRS.

“The standard protocol takes 70 minutes. This is too long and needs to be shortened,” said Silvia Schumacher PhD, IROC Science to Innovation AG, Zurich, Switzerland. Research suggests it may be possible to achieve similar clinical results while shortening by half or more both the riboflavin pre-soak time and the ultraviolet-A irradiation time, currently 30 minutes each.

To achieve adequate penetration of riboflavin deep enough in the cornea for effective crosslinking to occur at 300 microns or more, the standard crosslinking protocol calls for maintaining a riboflavin solution layer 100 microns thick on the corneal surface by replenishing it every five minutes for 30 minutes, Dr Schumacher noted. Theoretically, this soak time could be shortened by increasing the riboflavin available on the surface either by shortening the re-administration interval or increasing the thickness of the solution layer.

By shortening re-administration intervals to three and one minute while maintaining the 100 micron solution layer and 30 minute soak time, Dr Schumacher and her colleagues did observe higher than standard concentrations of riboflavin at all corneal depths. Indeed, one-minute intervals produced a concentration curve very close to the theoretical ideal of their diffusion model. However, shorter intervals would also require more nursing time to administer, she noted.

But by increasing the depth of the riboflavin solution on the cornea to 400 microns using rings to hold it in place and sticking with a five minute re-administration interval, Dr Schumacher was able to nearly double the riboflavin concentrations in the stroma up to about 325 microns, which is the layer where crosslinking occurs.

Halving pre-soak time would reduce costs and improve patient experience. But Dr Schumacher emphasised that the approach is still theoretical and has not been clinically tested.

“Changing the application protocol of riboflavin affects your clinical results. Wait for clinical validation before trying this at home,” she cautioned.

Iontophoresis Another potential approach to speeding riboflavin corneal diffusion is iontophoresis, said Rita Mencucci MD, University of Florence, Italy. Known since the late 1800s, it works by applying an electrical current to an ionisable substance to increase its mobility across a surface.

Riboflavin is a good candidate because it has a small molecular weight, is negatively charged at physiological pH and is highly soluble in water, Dr Mencucci said. By applying a charge of 1.0 mA/cm², riboflavin solution is pulled into the cornea, potentially reducing soak times to five minutes. However, critical questions remain unanswered, including whether the process actually works, whether it is safe and what are optimal exposure parameters.

In an ex vivo study assessing potential impact on the stroma, keratocyte population and potential endothelial damage, Dr Mencucci compared a control group of untreated human corneas with groups exposed to five minutes iontophoresis and riboflavin only, to iontophoresis plus 30 minutes of UVA at 3mW/cm², and iontophoresis plus nine minutes of UVA at 10 mW/cm² (Figure 1).

Histological and immunohistochemical analysis 48 hours after treatment showed no difference in endothelial cell condition among the four groups, suggesting the crosslinking protocols maintained an adequate endothelial safety margin (Figure 2). However, in the two UVA-irradiated groups, keratocyte apoptosis was detected and fewer keratocytes were visible in the anterior stromal layers than in the untreated and iontophoresis-only groups (Figures 3 and 4). Loss of keratocytes is considered a necessary first step to initiate crosslinking. Both irradiated groups also showed thicker collagen fibres in the outer layers, with the 10 mW group showing thicker fibres and a better defined border between crosslinked and uncrosslinked areas than the 3 mW group.

The results suggest the 10 mW/cm² nine minute irradiation time could be safe and effective, Dr Mencucci said. It also suggests potential for combining iontophoresis with crosslinking.

“It represents an exciting new frontier in ophthalmic therapeutics.”

Increasing peripheral strength

The strength of crosslinked corneas might also be improved by increasing the volume of crosslinked tissue, said Michael Mrochen PhD, also of IROC Science to Innovation AG. This could be done while maintaining an endothelial safety zone by altering the UVA beam profile to deliver more power peripherally.

UVA exposure currently is calibrated to crosslink tissue down to a safety margin at the central cornea, which is about 536 microns thick in a normal eye. However, with a homogenous beam profile, tissue is crosslinked to the same depth peripherally even though the safety margin is progressively deeper due to a steeper angle of incidence and greater corneal thickness.

At 5.0mm peripherally, the average corneal thickness increases to 711 microns, which means crosslinking depth should be increased 63 per cent to reach the safety margin, Dr Mrochen said. For eyes with keratoconus, the cornea is thinnest over the cone, but is near normal peripherally, he noted.

Increased crosslinking depth can be achieved by using a 25 per cent higher light intensity at the periphery, Dr Mrochen said. This achieves two things, a larger volume of crosslinked tissue and stronger crosslinking effect within the first 100 microns of stroma. Both contribute to increased biomechanical strength while reducing central light intensity, which may reduce corneal haze.

Six-month data from trials in Ireland and Germany indicate that enhanced beam profile induces a greater flattening effect than standard crosslinking, Dr Mrochen said. Clinical research is ongoing.