Is accelerated corneal collagen cross-linking for keratoconus the way forward? Yes

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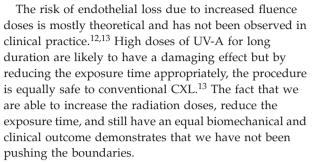
The recent introduction of accelerated crosslinking (CXL) has sparked a great amount of interest in the ophthalmic community. CXL causes corneal stromal collagen fibre stiffening through photopolymerisation of riboflavin.^{1,2} The settings of conventional CXL, as per Dresden protocol, are $3 \,\mathrm{mW/cm^2}$ irradiance from a 370-nm light source to illuminate the riboflavin-treated eye for 30 min leading to a cumulative dose of 5.4 J/cm^{2,3} The concept of accelerated CXL is based on the Bunden-Roscoe reciprocity law,⁴ where an overall cumulative dose of 5.4 J/cm² is achieved with treatment parameters set at higher intensity and simultaneous reduction in exposure time. In accordance with this, animal studies found that an equivalent corneal stiffness increase to conventional CXL can be achieved with illumination intensity of up to $40-45 \,\mathrm{mW/cm^2}$, corresponding to illumination times of $\sim 2 \text{ min.}^5$ Although the Bunden-Roscoe reciprocity law may be valid for a certain dose range and therefore a true linear relationship between dose and time is unlikely to exist, the radicals that generate the cross-links are formed in a shorter period of time when the radiation intensity is increased from 3 to 10 mW/cm².⁶ Initial studies, performed on porcine eyes, showed that accelerated CXL performed at 10 mW/cm² for 9 min was equivalent to conventional CXL in biomechanical stiffness.^{6,7}

When the cornea is treated with conventional CXL a demarcation line is seen at $\sim 300 \,\mu m.^{8,9}$ This demarcation line, seen in anterior segment optical coherence tomography (AS-OCT), demonstrates the depth of treatment with the corneal stroma lying anterior to this demarcation line that has been cross-linked and

hence strengthened. Although keratoconus, at least during its early stages, is a predominantly posterior corneal disease, it is thought to be the anterior weaker stroma that needs to be strengthened to halt disease progression and subsequent ectasia. It is precisely this part of the cornea that is treated and stiffened with accelerated CXL, as a demarcation line is seen with AS-OCT at an average depth of 100–150 μ m.¹⁰ In addition, the fact that the photodynamic reaction is limited to the anterior 100–150 μ m of the cornea enables treatment, at least in theory, of thin corneas ($<400 \mu m$) whose treatment is not routinely advisable with standard conventional CXL. Accelerated CXL would allow treatment of a considerably larger amount of patients compared with the conventional CXL.

Favourable results have been observed with accelerated CXL and have been reported to be equal to conventional CXL.¹¹ In a randomised prospective study of 21 patients with mean follow-up of 46 months, Kanellopoulos found that accelerated CXL was comparable with conventional CXL in terms of its visual improvement and longevity.¹¹ Mean sphere was reduced by ~2.5 dioptres in both groups. Both the accelerated and the conventional CXL groups had an average reduction in K_{max} of 2–3 dioptres.¹¹

Clinically, several studies have found no increase or significant endothelial loss in corneas that underwent accelerated CXL.^{10,11} Microscopically, more keratocyte apoptosis was observed in the accelerated CXL group immediately after treatment but a similar repopulation was observed after 6 months.¹⁰ There is transient nerve plexus damage due to epithelial debridement and irradiation. However, these microscopic differences observed immediately after accelerated CXL seem to be of little consequence in the long run.¹⁰



The duration of the accelerated CXL procedure is considerably less than that of the conventional CXL, making the procedure itself more patient friendly and reducing the need for anaesthesia in certain patient groups. A reduced treatment time would allow a greater turnover of patients, making a department more efficient, reduce waiting times for treatment, and ultimately the ability to treat a greater number of patients. Accelerated CXL shows evolution of an established technique in which preliminary research has found it to be at least equally effective and safe.

Conflict of interest

The authors declare no conflict of interest.

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M Tsatsos^{1,2}, C MacGregor¹, N Kopsachilis² and D Anderson¹

¹Southampton Eye Unit, Southampton University Hospitals NHS Trust, Southampton, UK and ²Moorfields Eye Hospital NHS Foundation Trust, London, UK

Correspondence: M Tsatsos, Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK. Tel: +44 (0)23 8079 4579; Fax: +44 (0)23 8079 4120. E-mail: michaeltsatsos@hotmail.com