Late-Onset Deep Stromal Scarring After Riboflavin-UV-A Corneal Collagen Cross-Linking for Mild Keratoconus

Riboflavin–UV-A corneal collagen cross-linking (CXL) is a new technique that aims to arrest keratoconus progression. Riboflavin adsorbed to corneal stromal collagen fibers is activated by UV-A light, with the formation of cross-links between collagen fibrils that confer greater corneal rigidity.

Initial clinical experience suggested that the technique was safe, but stromal haze formation is a complication that is increasingly being recognized.

Herrmann et al described a case of transient subepithelial haze that resolved with topical steroids. Of greater concern, Raiskup et al and Mazzotta et al have described permanent stromal haze after CXL, with an incidence rate up to 8.6%. In both of these articles, the haze was relatively mild and occurred in eyes with advanced keratoconus.

The aim of this article is to describe the clinical and in vivo confocal microscopic findings of deep stromal scar formation after CXL in 2 patients with mild keratoconus.

Methods. An ongoing trial on the safety and efficacy of CXL that commenced in November 2008 at our center has enrolled 30 subjects to date. Briefly, subjects aged 18 years or older with progressive keratoconus, best-corrected visual acuity better than 20/40, and minimum corneal thickness of 400 mm or greater are included. Keratoconus is defined by 1 or more of the following signs: stromal thinning, conical protrusion, Fleischer ring, Vogt striae, and anterior stromal scarring.

All CXL procedures are performed according to a standard protocol. Subjects are asked to discontinue contact lens wear 3 days before surgery and to discontinue vitamin C supplements 1 week before surgery. Pachymetry is performed to ensure a thickness greater than 400 µm before the epithelium is removed in several areas within a central 8- to 9-mm zone. Riboflavin/Dextran solution is instilled as a viscous eye drop every 2 minutes for 30 minutes, and corneal penetration is checked by noting homogenous yellow fluorescence in the anterior chamber on a slitlamp before proceeding. The UV-A light is then focused on the cornea using the UV-X illumination system (IROC, Zurich, Switzerland) for 30 minutes with continued instillation of riboflavin solution every 2 minutes. Illumination intensity (3 mW/cm²) is checked with the included light meter prior to each treatment. After surgery, all subjects receive a topical antibiotic-steroid combination and a bandage contact lens.

Confocal microscopy is performed using the Heidelberg Retina Tomograph III Rostock Cornea Module (Heidelberg Engineering GmbH, Dossenheim, Germany) before and 3 months after surgery, with scans performed in the central 4 mm of the cornea.

All study procedures are performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent is obtained from the subjects, and the study has been approved by the institutional review board of the Singapore Eye Research Institute.

Report of Cases. Case 1. A 23-year-old Chinese man with bilateral keratoconus had preoperative refraction OS of −0.50 diopters (D)/−3.50×170 D. Spectacle acuity was logMAR +0.04, the maximum keratometric (Kmax) measurement was 46.9 D, and the corneal thickness was 563 µm, consistent with Krumeich stage 1 keratoconus. The cornea was clinically clear, and in the immediate period after CXL, epithelial healing was uneventful and the cornea stayed clear. However, at the 3-month visit, a dense, deep paracentral stromal scar was noted adjacent to the apex of the cone (Figure 1A) at approximately 300 µm depth on anterior segment optical coherence tomography. The refraction was altered to −0.50D/−7.00D × 100, best-spectacle acuity was logMAR +0.16, and Kmax increased to 51.6 D. At 6 months, the opacity remained unchanged but visual acuity was correctable with a rigid gas permeable lens to logMAR 0.00. Confocal microscopy revealed a regular epithelial mosaic and normal subepithelial nerve plexus morphology. The subepithelial zone revealed changes typical of a post-CXL reaction including increased keratocyte density and reflectivity, stromal hyperreflectivity, and multiple highly reflective spindle-shaped fibroblast processes. The deeper stroma revealed atypical and previously unreported changes. In the anterior part of the scar (Figure 1B), keratocyte density was reduced and there were dense hyperreflective bands in a reticular pattern. Keratocyte nuclei assumed attenuated, elongated forms suggestive of fibroblastic transformation. Deeper scans showed dense, homogenous, hyperreflective tissue with no cellular structures seen (Figure 1C). The deep stroma and endothelium posterior to the scar were normal.

Corneal topography performed before (Figure 1D) and 6 months after (Figure 1E) surgery corresponded to the increase in astigmatism. No further surgery was performed, and the patient was prescribed a rigid gas permeable lens for correction of astigmatism.

Case 2. This 23-year-old Indian man had a preoperative refraction of −3.00D/−3.50×25 (logMAR acuity +0.40). His Kmax was 50.1 D, corneal thickness was 483 µm, and the cornea was clinically clear prior to surgery. After 6 months of follow-up, the patient was reviewed for the second session of CXL for the contralateral eye.

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CXL. Cross-linking was performed, and the postoperative period was uneventful. Three months after surgery, a deep stromal haze developed just inferior to the visual axis, similar to that observed in our first case but smaller in size and density (Figure 2A). Postoperative refraction was $-2.50 \ D /-2.50 \times 30$ D with best acuity of logMAR + 0.04. Confocal microscopy findings were similar to those in case 1. The midstromal scar (Figure 2B) contained reduced keratocyte numbers, prominent hyperreflective bands with partial obscuration of cellular details, and elongated keratocyte nuclei.

Comment. Cross-linking is a promising technique for arresting keratoconus progression. Recent articles have, however, highlighted an important complication of permanent stromal haze formation. While it was fortunate that stromal scar formation in our cases occurred near the apex of the cone, away from the central visual axis, the induction of a large, permanent astigmatic shift in the first case resulted in a poorer spectacle acuity but acuity with rigid lenses was maintained at logMAR 0.00. Of note, this complication occurred at a relatively high rate of 2 of 30 cases (7%).

The clinical and confocal microscopic findings in our series differ from those in the literature. Both cases had Krumeich stage I or mild
keratoconus. The published cases that developed haze either had stage III keratoconus or more advanced changes including thinner corneas, higher keratometry values, and prominent Vogt striae. 

Mazzotta et al reported that hyporeflective bands in a reticular pattern representing stromal microstraia prior to CXL could be a confocal sign of advanced keratoconus, predicting haze formation. This pattern was not seen in our cases, consistent with the milder clinical picture. Despite the lower risk profile of our patients, both developed dense, deep stromal scars that were morphologically different and more severe than the faint haze described by Mazzotta et al and Raiskup et al. 

The deep stromal scar also occurred at the junction between the treated and untreated cornea along the demarcation line, which has not been previously described. Mazzotta et al also described increased keratocyte density in the region of the scar, in contrast to the reduced keratocyte population in our cases. Riboflavin–UV-A exposure typically causes keratocyte apoptosis in the early postoperative period, and we speculate that a sublethal effect in the deep stroma where the UV-A irradiation dose is lower may lead instead to fibroblastic transformation and an aberrant scarring response. This would explain the delayed reaction seen and, if proven in subsequent study, may suggest that longer or higher-intensity UV-A irradiation is indicated. Performing a modification of the technique in which the epithelium is not removed may also help prevent this complication.

In conclusion, deep corneal stromal scarring may complicate CXL for mild keratoconus and, if severe, may lead to a significant increase in astigmatism.

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Multifaceted Chemotherapy for Trilateral Retinoblastoma

Trilateral retinoblastoma (TRB) occurs in 3% of patients with unilateral or bilateral germline retinoblastoma. This midline malignant neuroectodermal tumor arises commonly in the pineal gland (77%-83% of patients) and less frequently in the paraspinal region (17%-23% of patients).

Trilateral retinoblastoma is difficult to treat and usually fatal. Complete resection is seldom possible for tumors in the pineal or paraspinal locations. Craniospinal irradiation is too damaging to the growth, intellectual, cognitive, and endocrine functions, particularly for chil-