

# Cross-linking for the Management of Pellucid Marginal Degeneration in a Case of an Unsuccessful Implantation of Intracorneal Ring Segments

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## ABSTRACT

We present a case of progressive pellucid marginal degeneration (PMD) treated with cross-linking (CXL) after a previous unsuccessful implantation of intracorneal ring segments. One year after surgery, an increase in the corneal biomechanical properties accompanied by an improvement in corrected visual acuity and a decrease in the magnitude of corneal coma-like aberrations was observed. However, the magnitude of the refractive cylinder and keratometry increased whereas the internal astigmatism was reduced by 3.93 D. CXL in a cornea with a progressive PMD seems to induce not only changes in the anterior corneal surface, but also in the posterior corneal surface.

**Keywords:** Corneal collagen cross-linking, Pellucid marginal degeneration, Confocal microscopy.

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## INTRODUCTION

Corneal collagen cross-linking (CXL) is a therapeutic technique aimed at stabilizing the corneal mechanical properties and at preventing the progression of ectatic corneal condition. With this technique, the photosensitizer riboflavin (vitamin B2) and ultraviolet A (UVA) light with a wavelength of 370 nm is used to induce specific chemical reactions in the corneal stroma, resulting in the formation of covalent bonds between the collagen molecules, fibers and microfibrils.<sup>1,2</sup> This option has been suggested as useful for the management of pellucid marginal degeneration (PMD),<sup>3</sup> even as a combined simultaneous treatment with other options.<sup>4,5</sup> We report the use of CXL to manage a case of progressive PMD with a previous unsuccessful implantation of intrastromal corneal ring segments (ICRS).

## CASE REPORT

A 30-year-old male patient with diagnosed PMD presented to the Keratoconus Unit at Visum Alicante Ophthalmologic Institute in 2009, with a complaint of unsatisfactory vision in his left eye. The patient was contact lens intolerant and had been implanted 3 years before with ICRS for the

management of corneal irregularity. At the time of examination, the uncorrected distance visual acuity (UDVA) was 0.05 in the left eye (Snellen scale). The corrected distance visual acuity (CDVA) was 0.4 (Snellen scale) with a manifest refraction of Plano  $-6.75 \times 100^\circ$ . Corneal topographic and aberrometric analyses were performed in this left eye by means of the CSO system (CSO, Costruzione Oftalmici Strumenti, Firenze, Italy). The central keratometric values were 37.99 (K1) and 50.48 (K2) D. For corneal thickness analysis, pachymetry mapping by optical coherence tomography (Visante OCT, Carl Zeiss Meditec AG, Jena, Germany) was used, with an average central corneal thickness of 488  $\mu\text{m}$  for the left eye. Corneal biomechanical were also evaluated in this eye by means of the ORA system (Ocular Response Analyzer, Reichert, Buffalo, NY, USA), obtaining a values of 7.1 and 7.3 mm Hg for the corneal hysteresis (CH) and corneal resistance factor (CRF) respectively. The Goldmann intraocular pressure was 13 mm Hg. Biomicroscopic and fundus examination showed no abnormality in the ocular structure and clinical condition of the left eye except for the presence of a corneal PMD treated with two intrastromal ring segments. Specifically, KeraRing segments (Mediphacos, Belo Horizonte, Brazil) were implanted, one of 0.15 mm of thickness superiorly and another of 0.25 mm of thickness inferiorly. The entrance incision was made at  $160^\circ$ .

After revising the corneal topographic and aberrometric data of the last visit prior to attending with the visual complaints, we decided to plan a CXL procedure because clear signs of ectasia progression were present: Increase in refractive against-the-rule refractive astigmatism, visual instability, significant inferior steepening and increase in coma-like aberrations. The protocol followed for surgery was the same used for keratoconic corneas. The corneal epithelium of the 9 mm central area was removed mechanically by using a crescent knife. Riboflavin 0.1% solution in dextrose was applied subsequently every 5 minutes for 15 to 20 minutes. Afterwards, the UVA light emitter (370 nm of wavelength) was directed to the cornea and focused on the apex at a distance of 5.0 cm in order to obtain a radiant energy of  $3.0 \text{ mW/cm}^2$  for 30 minutes. The CSO CBM Vega X-Linker system (CSO, Firenze, Italy) was used for this procedure in all cases. During the time of

irradiation, one drop of riboflavin 0.1% was applied every 3 minutes as well as the protection of limbus and conjunctiva by viscoelastic was maintained. Informed consent following the tenets of Helsinki declaration was signed by the patient prior to the surgery. Approval of local ethics committee was obtained for this investigation.

At 1 month postoperatively, despite the improvement of the UDVA to 0.1, no improvement in CDVA was observed. Manifest refraction was  $+2.5 -9.0 \times 100^\circ$ . A slight haze was observed in the biomicroscopic examination that resolved spontaneously with time (Figs 1A and B).

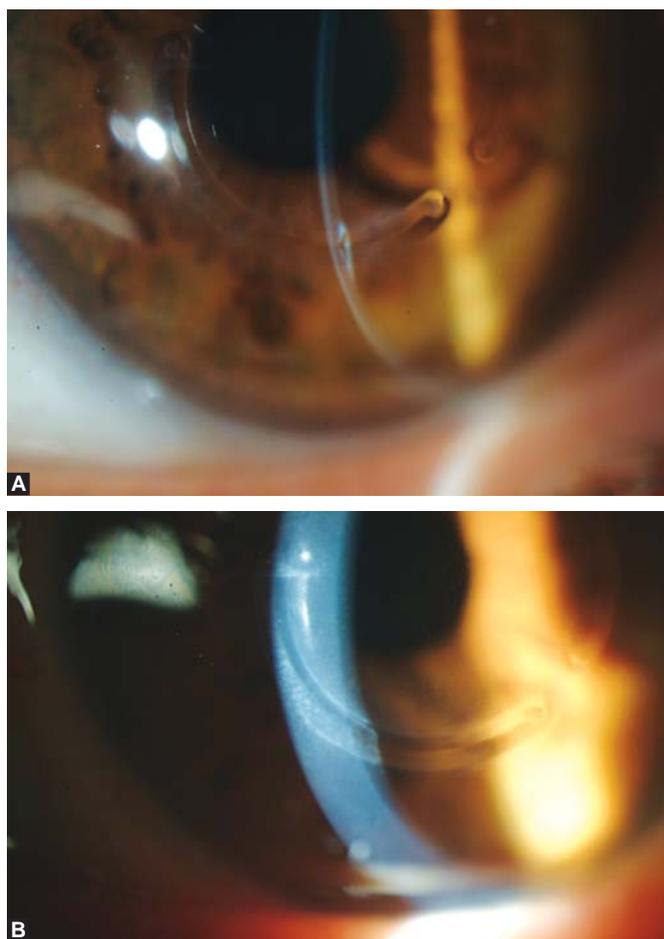
At 12 months, the UDVA had improved significantly from 0.4 to 0.7, with a manifest refraction of  $+3.75 -10.0 \times 100^\circ$ . The following data were obtained in this visit: keratometric readings of 39.76 and 51.90 D, central corneal thickness of 488  $\mu\text{m}$ , CH of 10.1 mm Hg and CRF of 8.5 mm Hg. Some corneal topographic changes in the anterior corneal surface occurred during the follow-up (Fig. 2).

As expected, this has an effect on anterior corneal aberrations. Specifically, the Zernike coefficient corresponding to the primary spherical aberration increased

from 0.78  $\mu\text{m}$  preoperatively to 1.01  $\mu\text{m}$  at 12 months postoperatively. However, a slight decrease in primary coma root mean square (RMS) was observed, which changed from 2.50  $\mu\text{m}$  preoperatively to 2.23  $\mu\text{m}$  postoperatively.

The internal astigmatism (IA) was also calculated as the vectorial difference between refractive (calculated to the corneal plane) and corneal astigmatism, following a previously described standard protocol.<sup>6</sup> This IA is equivalent to the combination of the toric components of the crystalline lens and the posterior corneal surface. The preoperative IA was  $6.18 \times 94^\circ$ , whereas the IA was  $5.19 \times 102^\circ$  and  $2.25 \times 100^\circ$  at 1 and 12 months postoperatively.

Confocal microscopic evaluation was also performed by means of the ConfoScan 4.0 system with the z-ring adapter (NIDEK Co. Ltd, Gamagori, Japan). The confocal microscopy revealed an absence of the superficial and sub-basal nerve plexus in the early postoperative period with subsequent regeneration over time. The confocal analysis also revealed the presence of highly reflective activated keratocytes with signs of corneal edema at the level of the anterior stroma in the early period after surgery (Fig. 3).



**Figs 1A and B:** Frontal image obtained with a slit-lamp biomicroscope of the case of PMD with an unsuccessful outcome with ICRS analyzed in the current case report: (A) before CXL, and (B) after CXL

## DISCUSSION

Corneal collagen CXL with riboflavin and UVA has been considered to be a safe and effective treatment for keratoconus. There are several studies reporting a large and significant increase in the biomechanical strength of the cornea after applying this specific procedure.<sup>7,8</sup> Besides the biomechanical changes, significant refractive and corneal topographic changes have been also reported in some case series. PMD is another ectatic condition in which the peripheral corneal stroma is affected. This ectatic corneal disease can lead to a significant visual deterioration, especially if it progresses with time and affects the central cornea. In such cases, the use of the CXL could be helpful as a therapeutic option, especially when other options as the implantation of ICRS have failed to avoid the progression of the ectasia and the regularization of the corneal profile. The aim of the current case report is to show the potential applicability of CXL in a cornea with PMD previously implanted with ICRS achieving a poor outcome as well as to describe in detail the morphological and microscopic changes occurring with this therapeutic technique in such a case.

In the presented case, corneal topography revealed the presence of a significant against-the-rule astigmatism and large amounts of coma-like aberrations that had increased significantly during the last year of follow-up. CXL was thought to be a good solution for such case in order to avoid the progression of the ectasia. As previously commented,

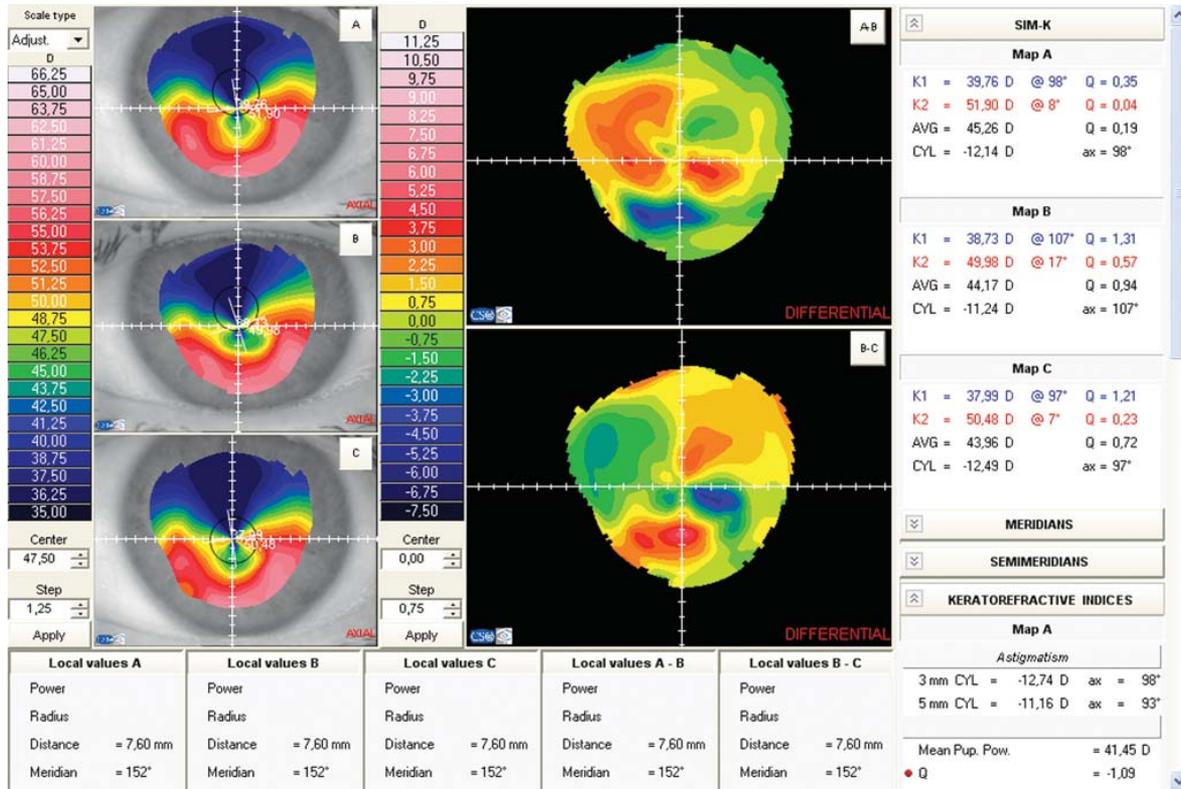


Fig. 2: Differential corneal topographic map (right) showing the difference between the corneal topographic pattern before CXL (upper left) in the PMD case evaluated and its pattern (lower left) after CXL

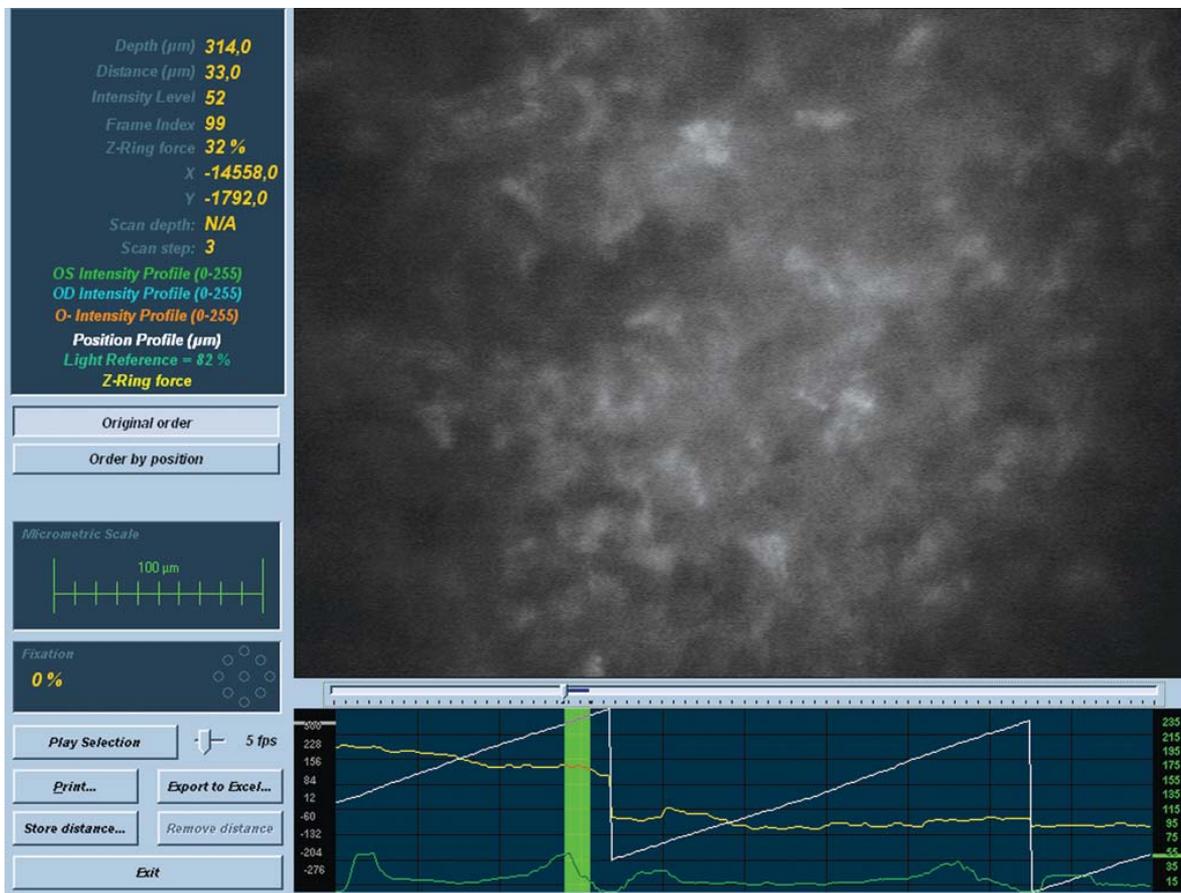


Fig. 3: Confocal microscopy picture of the anterior stroma (100 µm of depth) of the PMD cornea evaluated 12 months after CXL. As shown, there is still evidence of the presence of highly reflective activated keratocytes at the level of the anterior stroma

this option has been demonstrated to be useful for PMD management, even in a simultaneous combination with other treatments.<sup>3-5</sup>

At 1 year follow-up, an increase of 2.8 mm Hg in CH and 1.4 mm Hg in CRF was observed in the ORA biomechanical parameters. This increase was revealing a change in the biomechanical properties of the cornea with CXL, but we do not know which component, elasticity or viscosity, had been modified. It should be noted that the exact physical meaning of these parameters is still not well understood. These biomechanical modifications were accompanied by other positive clinical changes, as an improvement in CDVA of 3 Snellen lines, a decrease of 0.27  $\mu\text{m}$  in the RMS for corneal coma-like aberrations and a reduction of 3.93 D in the magnitude of the IA. However, the magnitude of the refractive cylinder increased by 3.25 D and the sphere became significantly more positive (a change from plano to +3.75). In addition, keratometric readings also increased (1.77 D K1 and 1.42 D K2) and the spherical aberration became more positive (change of 0.23  $\mu\text{m}$ ). Therefore, some of the clinical outcomes obtained in this case seemed contradictory. However, it should be considered that the posterior corneal surface had not been evaluated directly and it could have had a role in our case.

The IA is the result of the combination of the toric components of the crystalline lens and the posterior corneal surface, and therefore its variability should be largely influenced by changes in the astigmatism of the posterior corneal surface provided that we assume an approximately constant and limited contribution of the lenticular astigmatism in noncataractous eyes to the internal and refractive astigmatism. Therefore, in our case the very significant change in IA seems to be in relation with the change in the toricity and possibly in the regularity of the posterior corneal surface. Other factor that could have accounted for the change in IA could have been an increase in the regularization of both corneal surfaces leading to a more reliable subjective refraction. Indeed, the study of changes in refractive cylinder in keratoconus has been demonstrated to be problematic due to the poor reliability of cylinder determined by subjective refraction in this kind of eyes.<sup>9</sup> Manifest astigmatism (considering all ocular optics) is measured by proving several spherocylindrical lenses and detecting which of them provides the best focus according to the subject criteria. However, in keratoconic eyes or eyes affected of other modalities of corneal ectasia the higher order aberrations become very important as a consequence of corneal shape deformation, and then the perceived blur is not only due to the spherocylindrical error. We observed in our case small changes in the aberrations of the anterior corneal surface after the surgery. This

supports the idea of posterior corneal changes occurring in this case after CXL.

The relationship among corneal biomechanics and corneal topographic profile of the anterior corneal surface is complex and it does not follow a simple linear relationship. Therefore, not always a biomechanical change is in relation with a specific topographic change. It should be remembered that the main objective of the CXL treatment is to modify the biomechanical properties of the cornea; it is not a refractive procedure. Furthermore, all case series about CXL outcomes are focused on the analysis of the anterior corneal surface, but the cornea is a 3D structure with two optical surfaces. Therefore, changes occurring in the corneal structure after CXL should be monitored in future studies with a Scheimpflug photography-based system which provides information about the anterior and posterior corneal surfaces, the corneal thickness distribution and even about corneal volume. In the current case, a Scheimpflug-based topographic system was not available when the patient was reviewed and then the clinical information was insufficient for understanding the real and complete effect of CXL.

Regarding confocal microscopic findings, similar reaction as that observed in keratoconic corneas after CXL was observed in this case of PMD: Absence of sub-basal nerve plexus with regeneration over time and a reduction of the keratocyte density of the anterior and posterior stroma with also a regeneration during the follow-up.<sup>10</sup> These changes may be in relation with the change in the biomechanical behavior of this cornea undergoing CXL.

## CONCLUSION

This case report is showing the potential applicability of CXL in a cornea with a progressive PMD, allowing a visual improvement and a change in the biomechanical properties of the cornea. This applicability of CXL should be evaluated in future prospective studies including significant samples of cases. Furthermore, we have found some evidence of a potential change in the posterior corneal surface with CXL in this specific type of ectatic corneas. Future research is mandatory ascertaining, if the posterior corneal surface as well as corneal volume is modified with CXL, as a consequence of the variations induced in the corneal biomechanical properties. We need also a longer follow-up in this case in order to corroborate the stability of the ectatic process. It should be noted that CXL is not neglecting the other options of PMD management, because there is still a variability regarding the surgical decision in cases of PMD depending on the clinical condition and according to the surgeon experience and opinion.

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