LETTERS

Marked remodelling of the anterior corneal surface following collagen cross-linking with riboflavin and UVA

Corneal collagen cross-linking with riboflavin/ultraviolet A (CXL) is a method for the treatment of progressive keratectasia.[1 2] In 60% of patients, CXL leads to arrest of progression, and in 40%, even a regression of K_{max} values is observed.[2] Here, we report three cases that did not display regression but rather displayed a massive remodelling with K_{max} reduction of up to 9.5 dioptres (D), accompanied by formation of a deep

Table 1 Corneal parameters before and after cross-linking with riboflavin/ultraviolet A (CXL)

Case no	Preoperative swelling	Before CXL			After CXL			Maximal regression (D)
		Refraction	BSCVA	K_{max} (D)	Refraction	BSCVA	K_{max} (D)	
1	Yes	2.00−4.00×112	20/50	50.2	0.5−1.00×100	20/25	47.6	7.4
2	No	5.00−5.75×14	20/63	55.9	0.25−2.50 ×62	20/20	48.6	7.5
3	No	1.00−7.0×103	20/50	53.1	0.0−2.0×95	20/20	44.6	9.5

BSCVA, best spectacle-corrected visual acuity.

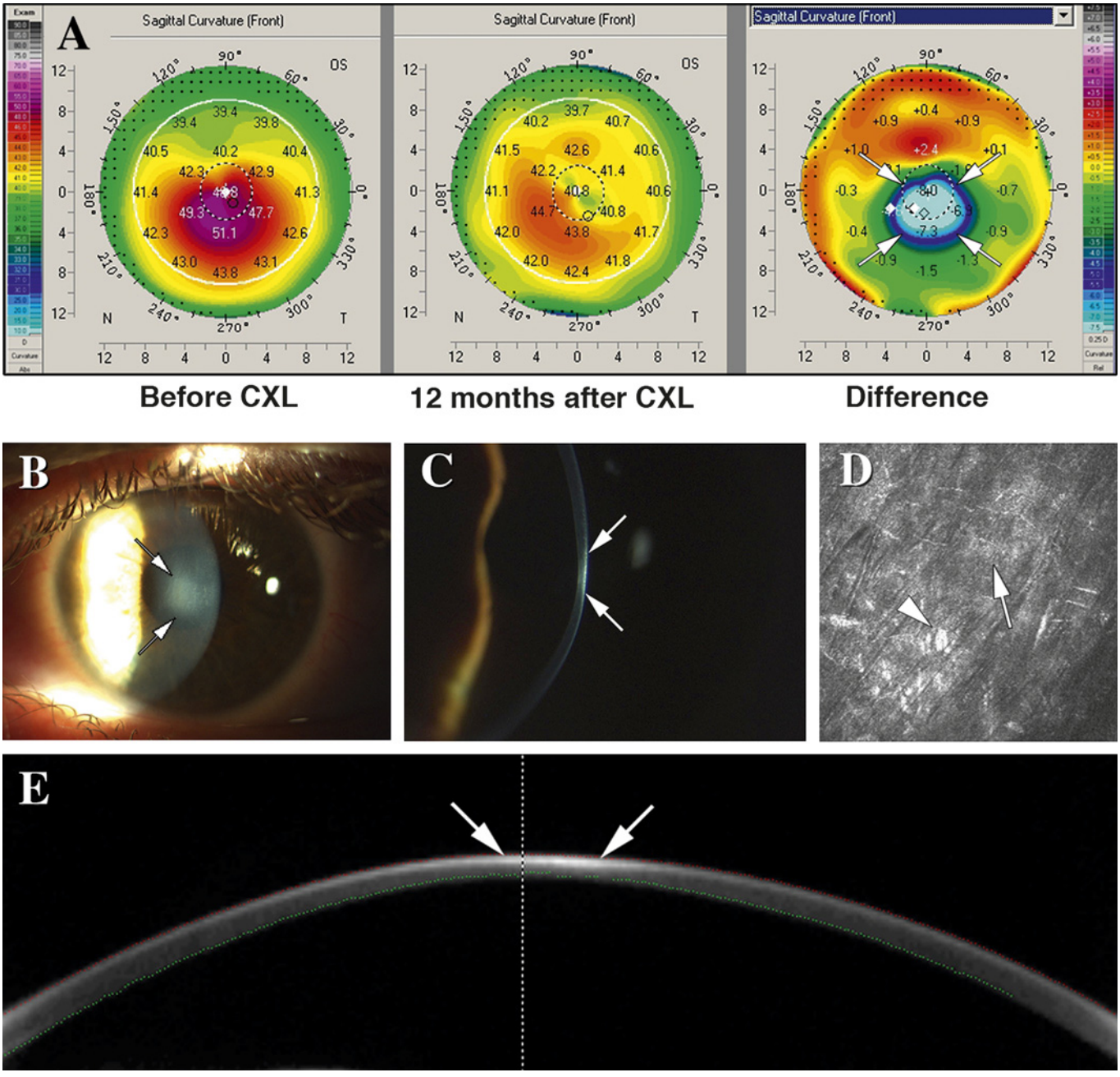

Figure 1 Remodelling process following cross-linking with riboflavin/ultraviolet A (CXL): topographical changes and assessment of stromal haze. (A) Scheimpflug analysis of the anterior corneal surface (true net power) before (left) and 12 months after CXL (middle). The difference image (right) shows a strong reduction in K_{max} values readings of up to 9.5 D. (B, C) Slit-lamp images of the central deep stromal haze (arrows) in the left eye. (D) Corneal confocal microscopic sections of the anterior corneal stroma at 170 μm depth. The stroma shows activated keratocytes (arrow) and hyper-reflective deposits corresponding to subepithelial fibrosis (arrowhead). (E) High-resolution Scheimpflug imaging of the corneal haze (arrows).

stromal opacity and a distinct increase in best spectacle-corrected visual acuity (BSCVA).

METHODS

Three eyes of three patients with progressive keratoconus were included in this interventional case series. Progression was defined as an increase in K_{max}>1.0 D within 12 months.[3] Pre- and postoperative examinations included corneal topography (Keratograph C, Oculus, Wetzlar, Germany), Scheimpflug imaging (Pentacam, Oculus, Wetzlar, Germany) and slit-lamp examination. CXL was performed as published previously.[4]

REPRESENTATIVE CASE

For an overview of corneal characteristics, please refer to table 1.

A 27-year-old man (case 1) was referred to us for bilateral keratoconus in April 2007. Previous topographies demonstrated progression in the right cornea, whereas the left cornea was stable.

We performed CXL in the right eye using hypo-osmolar riboflavin[4]: after abrasion, the minimal stromal thickness was 376 µm. Isoosmolar riboflavin solution was applied for 30 min, and ultrasound pachymetry showed a minimal stromal thickness of 382 µm. Hypo-osmolar riboflavin was applied every 20 s for a further 5 min, and corneal thickness increased to 417 µm. In cases 2 and 3, minimal corneal thickness was more than 400 µm after abrasio, and the standard protocol with isoosmolar riboflavin solution was used.

A trace haze was noted at 4 weeks postoperatively.[5] At 6 months, the haze had disappeared, and Scheimpflug analysis showed the (commonly observed) regression of K_{max} values of up to 2.8 D (data not shown).

At this point, the patient reported a decrease in VA in his left eye. Scheimpflug analysis showed keratoconus progression, and we performed CXL in November 2008. The early postoperative period was uneventful with a 1.0 haze at 4 weeks. At 6 months postoperatively, a 2.0 haze was noted, and regression was 6.8 D. At 12 months after surgery, the haze had consolidated to a deep stromal opacity (figure 1B, C, E), and the maximal regression was 9.5 D (figure 1A). BSCVA had increased to 20/20 from 20/50 preoperatively, and confocal microscopy (HRT Cornea module, Heidelberg Engineering, Germany) showed fibrosis of the stroma at a depth of 160–250 µm (figure 1D).

DISCUSSION

Regression of K_{max} is commonly observed following CXL.[2 6] Recently, a K_{max} regression by a mean of 2.68 D in 62% of patients at 1 year after CXL was reported.[2] Regression occurs between 6 and 36 months postoperatively and is often accompanied by an increase in BSCVA.

In contrast, our cases showed massive corneal remodelling with K_{max} regression of up to 9.5 D. This remodelling might be due to a reorganisation of the corneal stroma: subsequent to CXL, cellular processes such as keratocyte apoptosis and necrosis, and transformation of surrounding keratocytes to myofibroblasts take place in the anterior stroma.[7 8] Other morphological changes include a significant increase in the keratocyte proliferation in cross-linked corneas and an increase in collagen fibre diameter.[9]

Remodelling was accompanied by formation of a central stromal haze-like opacity, and BSCVA improved distinctly. The underlying mechanisms of this flattening effect are unknown and may include unintentional increases in riboflavin concentration, prolonged UV irradiation but also an individual predisposition.

Little is known about the similarities in the nature of haze after PRK and CXL. Subepithelial haze following PRK extends to a depth of approximately 60 µm below the epithelium and is transient in nature. In the case of the transient post-CXL haze commonly observed, the changes in reflectivity extend to the depth of the demarcation line (270–330 µm),[5] possibly due to the migration of inflammatory cells. The stromal opacities observed here also extend to a depth of approximately 300 µm (figure 1D). We propose the term 'deep stromal haze' for this phenomenon. The current follow-up in these patients is up to 12 months, and only a minor diminution was observed in the extent of 'deep stromal haze,' suggesting that the changes observed here might not be transient but rather permanent. The occurrence of this flattening effect is rare. We have performed more than 1000 CXL procedures in previous years and have observed this effect in three eyes only.

We report a massive corneal remodelling following CXL, concomitant with a distinct increase in BSCVA. Understanding the underlying mechanism would allow this effect to be induced reproducibly in every CXL procedure for the benefit of the patient.

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Donor tissue preparation for Descemet membrane endothelial keratoplasty

We are pleased to note that Dr Zarei-Ghanavati and his team have replicated our technique (originally presented at the American Academy of Ophthalmology meeting in Atlanta 2008 and subsequently published)[1] and agree that it is a viable, quicker and easier alternative to conventional donor preparation for Descemet membrane endothelial keratoplasty (DMEK) surgery.[2] The process of pneumatic dissection described is essentially similar to ours; however, they have overlooked some key adaptations which further maximise the potential of this novel technique.

We performed a superficial keratectomy using a 300 µm microkeratome head prior to performing the pneumatic dissection. In the event of failure to separate Descemet and endothelium (5% in our series), this additional step ensures that the tissue can still be used for Descemet stripping automated endothelial keratoplasty surgery and thus eliminates wastage. Furthermore, the anterior lamella obtained may be utilised for other cases.