Complications of Corneal Collagen Cross-Linking

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David O'Brart

20.1 Introduction

Riboflavin/Ultraviolet A (UVA) corneal collagen cross-linking (CXL) is the first treatment modality that may halt the progression of keratoconus and other corneal ectatic disorders. Within the scientific literature there are multiple published prospective case series [1–12] and randomised controlled trials [13–15] with up to 36-month follow-up supporting its efficacy in keratoconus, including paediatric [16, 17] and advanced cases [18], pellucid marginal degeneration [19, 20] and iatrogenic ectasia [21–23]. In addition to cessation of progression, most investigators have also reported consistent improvements in visual, keratometric and topographic parameters with time [1–23].

Its precise mechanism of action at a molecular level is as yet not fully determined. At present follow-up is limited to 7–10 years but suggests continued stability and improvement in corneal shape with time [24, 25]. Most published data is with epithelium-off techniques [1–25]. Epithelium-on studies suggest some efficacy but less than with the epithelium-off procedures and long-term data are not currently available [26–28]. The use of Riboflavin/UVA CXL for in management of infectious and non-infectious keratitis appears very promising [29–32]. Its use in the management of bullous keratopathy is equivocal [33–35].

20.2 Adverse Effects of CXL

Whilst clinical studies indicate that it is a safe procedure with few sight-threatening complications, adverse events can occur. Complications attributable to CXL include corneal haze and scarring, infectious and non-infectious keratitis, endothelial failure, treatment failure with progression of ectasia, excessive corneal flattening with associated hyperopic shift and possible limbal stem cell changes.

20.3 Anterior Corneal Haze (the "Demarcation" Line)

An anterior, mid-stromal haze occurs in the majority of eyes after CXL, typically appearing at 2–6 weeks and clearing by 9–12 months (Fig. 20.1). It appears to be the result of an increased "density of extracellular" matrix and arises at a depth of 300–350 μm [36, 37]. It forms the so-called

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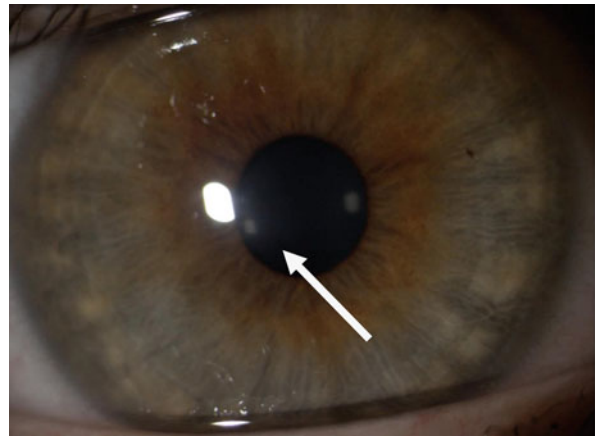

Fig. 20.1 Self- limiting stromal haze (*white arrow*) 3 months after CXL

"demarcation line" which can be easily seen on slit lamp examination [38]. As this change is self-limiting, topical cortical steroids are not indicated. The "demarcation line" has been shown to be shallower with accelerated, high fluence CXL [39] and with epithelium-on treatments [40]. It has been postulated that it represents the demarcation between cross-linked and non-cross-linked tissue and has been used by some investigators as a means of quantifying the efficacy of CXL [39]. However, it has be shown to be shallower in older patients and eyes with more advanced keratoconus receiving the same technique, with the depth of the line not being correlated to visual or keratometric changes at 6 months [41]. It is generally thicker centrally and more shallow in the para-central treated cornea [42, 43], with a deeper depth of the line centrally being found in one study to be related to a larger decrease in corneal thickness within the first 12 months after surgery [44]. Therefore while CXL is undoubtedly associated with the development of an anterior/mid-stromal haze during the first year after surgery, there is a yet no absolute evidence that it is the true delineation between cross-linked and uncross-linked tissue and may only represent a natural wound healing response. Until more evidence is forthcoming it would be unwise to consider in depth as an accurate way to assess the efficacy of any particular CXL technique [45].

20.4 Corneal Scarring

Persistent loss of corneal transparency (scarring) over the axial cornea/cone apex rather than transient changes may occur after CXL (Fig. 20.2). Raiskup et al. reported stromal scarring in 14 (8.6%) of a series of 163 eyes at 12 months [46]. Compared to eyes without such changes, affected eyes had a higher pre-operative apex power (average power 72.0 dioptres (D)), higher 3.00 mm keratometry (average 54.75D) and thinner central pachymetry (average 420 micrometers (μm)) compared to unaffected eyes. On the basis of these findings, Raiskup et al. advised caution and careful patient counselling before CXL is undertaken in patients with advanced keratoconus [46]. However, scarring with associated impairment of post-operative visual performance has been reported in mild cases of keratoconus after CXL [47]. Therefore, all patients need to be carefully counselled pre-operatively as to this possible occurrence. Stromal scarring may also be more prevalent in eyes receiving simultaneous photorefractive keratectomy (PRK) followed by CXL. Kymoinis et al. documented the occurrence of posterior linear haze formation persistent at 12 months in a series of 13 (46%) of 26 such treated eyes [48], while Guell reported late onset deep stromal scarring in a similarly treated patient that reoccurred after 2 years [49].

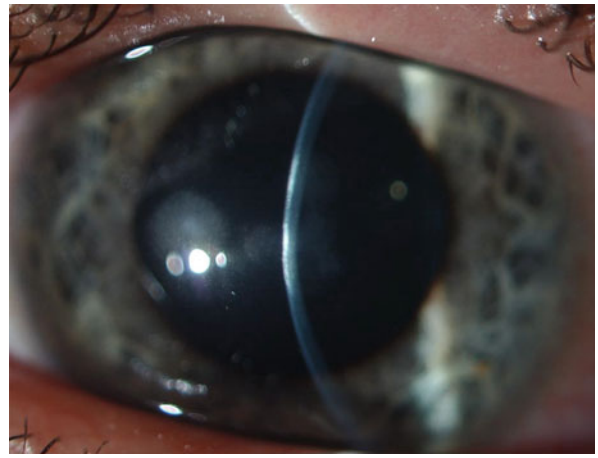

Fig. 20.2 Corneal scarring following keratitis after CXL (courtesy of Dr. Carina Koppen)

20.5 Failure of Treatment: Progression

With the standard epithelium-off technique, utilising Riboflavin 0.1 % and UVA at 3 mw/cm^2 for 30 min, the vast majority of patient achieving a follow-up of over 5 years demonstrate no progression of ectasia [24, 25, 50, 51]. Raskup-Wolf et al. in a series of 241 eyes with a follow-up of over 6 months documented progression in only 2 cases (0.8 %), which subsequently underwent re-treatment [52]. Koller et al. in their series of 117 eyes, all of which reached 12-month follow-up, reported progression of ectasia in 9 eyes (7.6 %) [53], while Ivarsen in 28 eyes with advanced keratoconus, all with a maximum keratometry greater than 55.0D and a mean follow-up of 22 months, documented progression in only one eye (3.5 %) [18]. Similarly, Sloot in a series of 53 eyes with 12-month follow-up, documented progression in only 5 (8 %), with little difference between advanced and mild keratoconic cases [54]. Such results are very encouraging and offer great hope for the control of this often visually debilitating disease [55]. Indeed although published follow-up is still limited at present in the 102 eyes reported in the long-term follow-up studies of Theuring, O'Brart and Poli, progression was evident in only 8 % of cases at 5–10 years [25, 50, 51].

20.6 Sterile Infiltrates

Sterile infiltrates occurring during the early postoperative period are not infrequent (Fig. 20.3). They typically present within the first days/weeks after CXL and resolve after within a month with topical corticosteroid medication. Koller et al. reported sterile infiltrates in 8 eyes (7.6 %) in a series of 117 cases, which resolved within 4 weeks with topical dexamethasone 0.1 % treatment [53]. Lam et al. reported a cluster of 4 cases of sterile keratitis and compared them retrospectively to 144 eyes their group treated with no such problem. They found eyes with sterile infiltrates generally had advanced keratoconus with maximum keratometry values greater than 60.0D and central corneal thicknesses less than 425 μm [56].

20.7 Non-infectious Keratitis

Whilst transient, non-sight threatening, sterile infiltrates are not uncommon, serious cases of non-infectious keratitis following CXL with significant visual loss have been occasionally reported. Koppen et al. published four cases occurring within 4 days of CXL. Two of their patients were atopic, two had permanent visual loss and one eye underwent penetrating keratoplasty [57]. Eberwein reported a single case of corneal melting associated with activation of

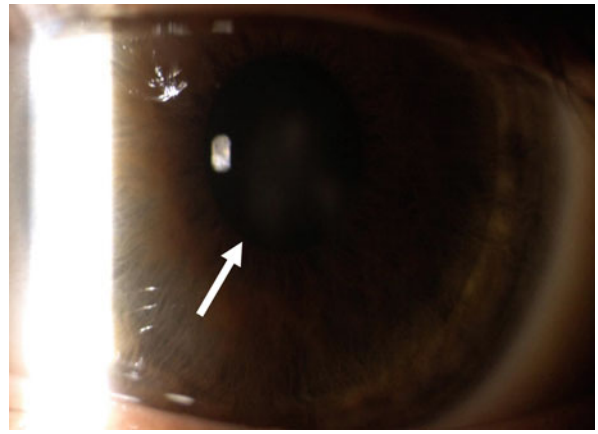

Fig. 20.3 Sterile infiltrates occurring within 1 week of CXL (*white arrow*), which gradually cleared by 6 weeks

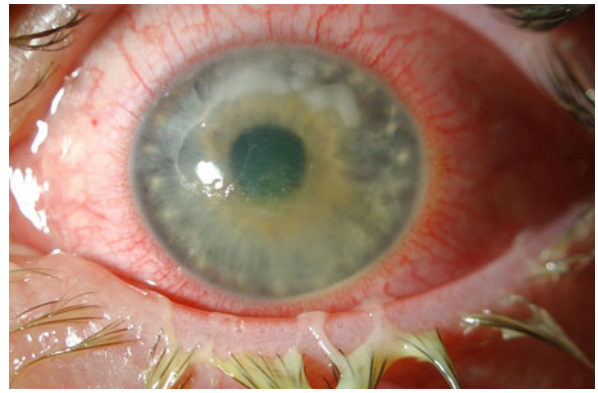

Fig. 20.4 Infectious keratitis after CXL (courtesy of Dr. Carina Koppen)

herpes simplex keratitis, which necessitated penetrating keratoplasty [58]. Whilst such episodes are rare, it is necessary to counsel patients pre-operatively of such serious sight-threatening adverse events. It is also prudent to control atopic eye disease prior to CXL, with topical and if indicated systemic medication, and to give prophylactic systemic Acyclovir to patients with a history of previous Herpetic Eye disease.

20.8 Infectious Keratitis

Infectious keratitis following CXL has been reported (Fig. 20.4). This is to be expected as debriding the corneal epithelium can expose the corneal stroma to microbial infection, during the operative and early healing phases. Most case reports of microbial infection have been bacterial in nature. Infections with *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and Coagulase-negative Staphylococcus have been published with resultant documented permanent visual loss [59–62]. A number of these cases have been associated with post-operative bandage contact lens use and misuse and it is necessary to inform patients not to replace, remove or try to clean these lenses themselves.

The precise incidence of microbial keratitis is as yet undetermined. It would be expected to have a much rarer occurrence than other operative procedures involving corneal epithelial debridement given the potential role of CXL in the management of corneal microbial infections [30, 63]. Shetty et al. reported four cases of infectious keratitis following CXL in a series of 2350 patients (1715 epithelium-off CXL, 310 epithelium-on CXL), giving an overall incidence of 0.0017 %

[64]. Similar to previously published reports all their cases were treated with an epithelium-off technique. All were due to Methicillin-resistant Staphylococcus Aureus (MRSA) and all had atopic dermatitis and conjunctivitis [64]. Similar to Shetty, Facciani and Rana reported post-CXL microbial keratitis due to MRSA, with an association with atopic dermatitis in one case [65] and perforation in two eyes [66]. Such reports, while anecdotal re-enforce the need to control atopic dermatitis and conjunctivitis prior to CXL and to counsel patients pre-operatively of such rare sight-threatening complications.

In addition to bacterial keratitis, other microbial pathogens have been implicated. Rama reported a case of acanthamoeba keratitis in a patient that had rinsed his bandage contact lens in tap water post-operatively and then replaced it [67]. Al-Qarni reported two cases of dendritic ulceration occurring with 2 weeks after CXL in patients with no previous history of herpetic keratitis, that responded well to topical antiviral therapy [68].

These case reports, whilst few in number compared to the hundreds of thousands of eyes that have undergone CXL worldwide, highlight the possible rare occurrence of this sight-threatening complication and the need to inform patients to immediately report and seek urgent medical advice if there is any increasing pain and redness after the initial 12–24 h period post-operatively or the occurrence of purulent discharge, so that if infectious keratitis if present it can be promptly and appropriately managed.

20.9 Endothelial Failure

Endothelial failure has been reported very occasionally after CXL resulting in corneal oedema post-operatively. Sharma et al. in a retrospective series of 350 patients treated with a standard epithelium-off protocol in eyes with corneal thicknesses greater than 400 μm after epithelial removal reported persistent problems in five patients (1.4 %), 2 of whom (0.6 %) required penetrating keratoplasty [69]. Bagga et al. reported a single case with keratouveitis and endothelial failure that required keratoplasty [70]. Whilst such complications are rare, they highlight the need to warn patients pre-operatively of severe sight-threatening complications and the very occasional need for keratoplasty after CXL. The aetiology of such problems has not been fully elucidated but endothelial damage after CXL may occur even in corneas with adequate thickness perhaps due to severe stromal thinning intra-operatively due to the use of hyper- and iso-osmolar Riboflavin solutions and/or lack of homogenicity with hot spots in the UV beams associated with the use of diodes and limited focusing/alignment systems.

20.10 Excessive Axial Flattening and Hyperopic Shift

O'Brart et al. in a long-term study of 36 eyes who underwent a standard epithelium-off technique and followed up for 7 years demonstrated continued statistically significant flattening of corneal topographic parameters between 1 and 5 years [24]. At 7 years this continued corneal flattening had resulted in a mean hyperopic shift of almost +0.8D. Eight (22 %) of the 36 eyes of the 36 patients (with a mean age less than 28 years) examined in this study experienced a hyperopic shift of over +2.0D compared to pre-operative refractive status and 4 eyes (11 %) had more than +3.0D of hyperopic refractive change [24] (Fig. 20.5). Such refractive changes with time need to be taken into consideration in the already hyperopic patient. In addition, the use of CXL has been postulated in the non-ectatic routine refractive surgery patient to improve post-operative refractive and corneal biomechanical stability in the so-called LASIK Extra procedure [71, 72]. CXL in these eyes might result in late and progressive corneal flattening and unwelcome long-term hyperopic refractive outcomes. Caution needs to be adopted with such treatments and potential patients counselled pre-operatively concerning these possible changes with time.

Indeed, occasionally corneal flattening can be very excessive. Santhiago reported two cases, one a 28-year-old woman with flattening of greater

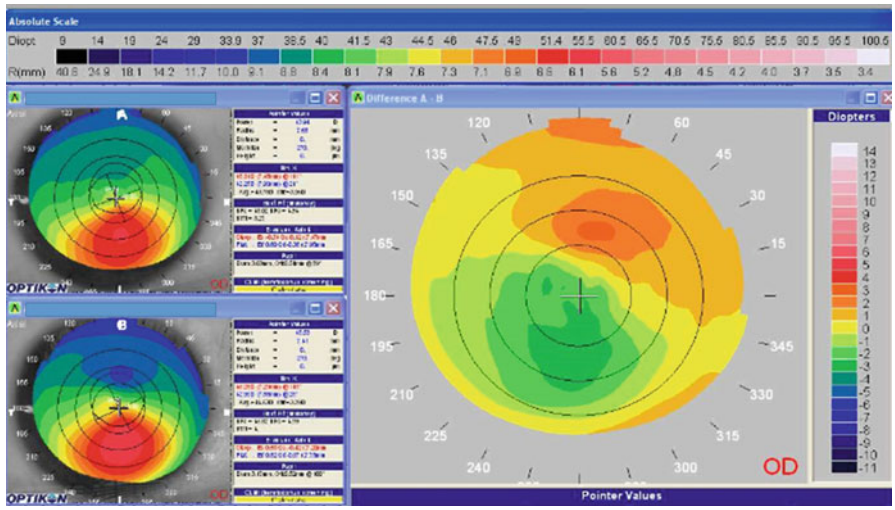

Fig. 20.5 Comparison map pre-operative and 8 years showing almost 4.0 dioptres of corneal flattening with a 28-year-old patient with a +3.0 dioptre hyperopic shift

than 14.0D and the other a 14-year-old boy with flattening of 7.0D at 12 months [73], while Kymionis reported a 23-year-old woman with over 11.0D of corneal flattening, with associated corneal thinning of over 220 μm during a 5-year follow-up period [74]. The pathophysiology of such changes is at yet unclear. Santhiago postulated that such cases may be more apparent with a central cone location and more advanced disease resulting in a greater CXL and wound healing effect. However, in their cases there was no excessive corneal thinning while in that reported by Kymionis this occurred, suggesting perhaps differing mechanisms for this occurrence.

20.11 Potential Limbal Stem Cell Damage

CXL is typically undertaken on young individuals. UVA radiation is known to have potential mutagenic and toxic cellular effects. Corneal limbal stem cells could theoretically be adversely affected by UVA radiation, with potential damage not being clinically evident for years/decades following CXL. Moore et al. exposed cultured corneal epithelial cells and ex vivo corneal tissue to the standard clinical cross-linking protocol and found evidence of oxidative nuclear DNA damage in corneal limbal epithelial cells [75]. Vimalin et al. subjected cadaveric eyes to CXL and demonstrated damage to limbal epithelial cells with a drop in viable cells [76]. Both investigators demonstrated that such changes could be easily avoided by avoiding UVA limbal irradiation/shielding the limbus at the time of CXL.

As yet long-term clinical studies have shown no evidence of limbal stem cell dysfunction with up to 7–10 year follow-up [24, 25]. However, such changes may take decades to occur. In a single case report, Krumeich described a patient who presented with conjunctival intraepithelial neoplasia 2 years after CXL and deep anterior lamellar keratoplasty [77]. While causation between CXL and the development of CIN cannot be established with a single case report, it seems entirely prudent to protect the limbus and avoid its irradiation during CXL.

20.12 Summary

CXL offer great promise for the corneal ectatic disorders. Whilst it is a relatively simple outpatient procedure with good efficacy and an excellent safety profile, sight-threatening complications can occur albeit rarely. Patients need to be counselled pre-operatively of these potential

adverse events. Conjunctival atopy, if present, needs to be adequately controlled pre-operatively and it is advised to give systemic prophylaxis if there is a previous history of ocular Herpes simplex. Patients need to be fully informed not to abuse post-operative contact lens wear and return if any symptoms of infectious keratitis occur. It is advisable to avoid UVA irradiation of the limbus during the procedure.

Compliance with Ethical Requirements David P.S. O'Brart declares that he has no conflict of interest. He holds a non-commercial grant from Alcon, Inc. for research into Femtosecond laser assisted cataract surgery. No human or animal studies were carried out by the author for this review.

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