REVIEW/UPDATE

Corneal crosslinking: Current protocols and clinical approach

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Members of the ASCRS Cornea Clinical Committee performed a review of the current literature on the corneal crosslinking (CXL) procedure for treating corneal ectasia. The members explored the data on the techniques currently in use and under investigation, including their advantages, safety profiles, risks, and cost analyses, compared with data on corneal transplantation. They concluded that CXL limits the progression of keratoconus, thus reducing the need for transplantation. They also found that compared with permitting the disease to progress naturally, CXL techniques carry significant and long-term cost and safety benefits, primarily by reducing the need for corneal transplantation. Studies of various CXL techniques (eg, epithelium-on treatment, changes in ultraviolet light parameters, riboflavin composition) continue with the ultimate goal of improving the procedure's safety and efficacy.

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Keratoconus has been described as a noninflammatory progressive ectatic disorder of the cornea that begins in early adolescence and can advance from mild visual changes to severe loss of corrected distance visual acuity (CDVA).[1,2] Some research has suggested an inflammatory component to keratoconus.[3] Keratoconus appears to have a complex multifactorial genetic inheritance pattern in which environmental factors, such as eye rubbing, have a significant role in its progression.[4,5] There are some strong associations with other systemic disorders, such as atopic disease, Down syndrome, and other collagen vascular disorders.[6] The worldwide incidence of keratoconus has been reported to be 1 in 2000 people,[1] although more recent articles estimate 86:100 000 worldwide,[2] 44:100 000 in Denmark,[7] and 1:191 in adolescent school children in New Zealand (1:45 in Maori participants in cohort).[8]

Keratoconus initially presents as a gradual worsening of uncorrected vision with increasing levels of astigmatism. This pattern of irregular thinning and ectasia of the corneal tissue can result in significant higher-order aberrations (HOAs) to the visual system, including monocular multiplopia and coma.[9] This can continue to advance from regular astigmatism that is correctable with spectacles to irregular astigmatism that might require the use of rigid contact lenses to eventual severe disease requiring corneal transplantation. Until recently, the approval of corneal crosslinking (CXL), there was no effective treatment to limit disease progression. Before the advent of CXL, it was estimated that 11% to 27% of patients with keratoconus would go on to require corneal transplantation because severe thinning and ectasia and/or scarring would not be further amenable to optical correction.[10,11] Corneal crosslinking, first studied in the late 1990s, has been found to have a strengthening and stabilizing effect on the corneal tissue.[12,13] Corneal crosslinking was approved by the U.S. Food and Drug Administration (FDA) in 2016. The technique is projected to significantly reduce disease progression and the need for transplantation.

The mechanical stability of the cornea is primarily determined by the structure of the collagen molecules and their spatial arrangement. The long collagen fibrils extend from

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limbus to limbus. Crosslinkages stabilize this mechanical state and prevent the collagen fibrils in the curved cornea from sliding apart. Pathologic changes to the tissue occur because of an increase in the degree of crosslinkage (eg, in diabetes mellitus or scars) or a decrease (eg, in Ehlers-Danlos syndrome). The maintenance of the physiologic function of the degree of crosslinkage must be very well regulated. With age alone, the number of crosslinkages, along with the rigidity of the structures, increase.[14,15] This can be observed in the cornea, skin, ocular lens, blood vessels, and cartilage of the joints. Sunlight and smoking cause analogous changes.[16,17]

Under physiologic conditions, collagen molecules are enzymatically crosslinked in the extracellular space by the enzyme lysyl oxidase after they have left the cell.[18] The collagen thereby attains its natural firmness, stability, and tissue-specific elastic properties. In Ehlers-Danlos syndrome, for example, there is a lysyl oxidase deficiency; in keratoconus, it is assumed that a lysyl oxidase gene defect is present[19,20] or that an increased pH level in the tear liquid, seen with keratoconus, interferes with the activity of the lysyl oxidase[21] (although other mechanisms have been proposed). With keloids and scars, the activity of this enzyme is heightened.[22] In 1998, Spoerl et al.[23] proposed the CXL method, which has proved efficacious in halting the progression of ectatic corneal diseases with low rates of complications. This photochemical treatment creates additional chemical bonds between the stromal collagen fibers by photopolymerization, which theoretically increases the stiffness. After exposure to ultraviolet-A (UVA) radiation, riboflavin (vitamin B2) acts as a photomediator as its molecules absorb energy, reach an excited state, and subsequently produce free radicals to induce new chemical bonds.[23]

The photooxidative CXL method with riboflavin and UVA light for stiffening the cornea has unique advantages over other photomediators, such as having a localized effect and a short period of therapy and leaving the transparency of the cornea unaltered. Riboflavin is nontoxic and is bioavailable as a medication. In this photochemical reaction, free radicals are created by UV light. To increase the effectiveness of this process in the presence of UV radiation, riboflavin, a special photosensitizer (transfer molecule), is used. When riboflavin absorbs energy from UV light, it gets excited.[24]

Two 2 types of reactions, type I and type II, occur in CXL. For type II reactions, oxygen is necessary. However, if the necessary oxygen is depleted by UV light, type I reactions dominate.[12] In this photochemical process, active locations along the collagen molecule chain react with each other, intermolecularly or intramolecularly, and create covalent connections between the amino acids (especially histidine, hydroxyproline, hydroxylysine, tyrosine, and threonine); thus, the so-called crosslinkages are created. The prerequisite for the initiation of a chemical reaction by light is the absorption of this light by the reactive system. The CXL effect occurs only where riboflavin is activated by UV light. Riboflavin is effective not only as a generator of free radicals but also as a radical scavenger at high concentrations; thus, there is a balance between the formation and the destruction of free radicals.[15] Hence, the increase in the concentration of riboflavin does not necessarily increase the rate of creation of free radicals; rather, a state of saturation is reached.

According to the photochemical law of reciprocity (Bunsen-Roscoe law),[25] the same photochemical effect can be achieved with reduced illumination time and correspondingly increased irradiation intensity, meaning that a 3-minute irradiation at 30 mW/cm^2, 5-minute irradiation at 18.0 mW/cm^2, and 10-minute irradiation at 9.0 mW/cm^2 should provide the same effect obtained with a 30-minute irradiation at 3.0 mW/cm^2, all delivering 5.4 J/cm^2 of energy. Because 1 J = 1 W × second, 3 minutes of irradiation (180 seconds) at 30 mW/cm^2 (0.03 W/cm^2) corresponds to 5.4 J/cm^2 ($180 \times 0.03 = 5.4$ J).[25] However, the expected consistency in the photochemical effect according to this law does not ensure that the clinical outcome will be the same when adjusting the illumination/irradiation values.

SUMMARY OF PIVOTAL CROSSLINKING TRIAL

The concept of using CXL to help patients with keratoconus was first described in 2003 by Wollensak et al.[26] In this small study of 23 eyes, progression stopped in all eyes and 16 eyes showed signs of regression. For the first time it appeared as though there might be a treatment to stop the progression of keratoconus. With such exciting news and encouraging results, CXL rapidly gained interest, and multiple publications showed the stability of keratoconus after treatment. The majority of the early studies had no control group or poorly defined study entry criteria, making it difficult to interpret results. It was not until the publication from the United States Crosslinking Study Group in 2017[27] that the FDA felt comfortable giving its stamp of approval for CXL for the indication of keratoconus and corneal ectasia after refractive surgery in the U.S.

Although other studies provide additional data, this section focuses on the 2017 keratoconus trial. The keratoconus trial was multicenter, prospective, randomized, and sham-controlled. Enrollment criteria included age 14 years or older with an axial topography consistent with keratoconus with a maximum keratometry (K) value of 47.0 diopters (D) or more, an inferior-to-superior ratio of than 1.5 or more, a CDVA worse than 20/20, and corneal thickness of 300 µm or more. To be enrolled in the study, the patients' keratoconus also had to be progressive. Progression was defined as 1 or more of the following changes over 24 months: an increase of 1.0 D or more in the steepest K measurement, an increase of 1.0 D or more in the manifest cylinder, or an increase of 0.5 D or more in the manifest refraction spherical equivalent.

Patients were randomized to sham treatment or actual treatment, which consisted of epithelium-off (epi-off) treatment in which the cornea was soaked with riboflavin 0.1% for 30 minutes. Before UVA treatment, the cornea was required to measure 400 µm or greater; if thinner, the

cornea was hydrated with hypotonic riboflavin until the pachymetry measured a minimum of 400 μm. The cornea was then exposed to UVA light at an irradiance of 3.0 mW/cm^2 for 30 minutes. Sham treatment patients received the same topical riboflavin but did not have epithelial defect creation; in addition, the UVA light source was not turned on.

Over 12 months, the keratoconus treatment group had a decrease in the maximum K value of 1.6 D. In contrast, the control group had an overall increase in the maximum K value of 1.0 D. Thus, the overall difference between treatment and control was 2.6 D over 12 months. Only 6% of the treated eyes continued to show progression with steepening of 2.0 D or more. Eyes that had a K value of 55.0 D or greater tended to show more flattening after treatment, and no independent factors of failure could be determined.

Overall vision improved in the treatment group by more than 1 line of corrected vision. An improvement in CDVA of 2 lines occurred in 23% of eyes, while 6% continued to lose vision. Continued progression and scar formation were the most common reasons for loss of corrected vision. The only predictor identified in the improvement in corrected vision was a preoperative CDVA of 20/40 or worse. These patients were 5.9 times more likely to have improved vision 1 year after the procedure. Uncorrected visual acuity also improved in the study, but not as significantly.

Full healing after CXL can take up to 1 year. Many patients will initially experience worsening in vision and K values at the 1-month timepoint, followed by gradual recovery. The prolonged healing period after CXL is a function of the resolution of corneal haze and the time needed for compensatory epithelial remodeling on the corneal surface. Patients should be aware of the changes in vision and that it takes several months for full recovery.

Adverse events were carefully followed during the study. The most common adverse event was corneal haze. The haze was the worst at 1 month and then resolved over the ensuing months, often resolving by 1 year. No endothelial cell loss was noted during the study. An infectious keratitis rate of 0.3% was reported in the study, showing the importance of rapid healing of the epithelial defect.[27]

EPITHELIUM-OFF VERSUS EPITHELIUM-ON CORNEAL CROSSLINKING

Corneal crosslinking was first introduced as an epi-off procedure for treating keratoconus. In the U.S., only 1 CXL device–drug combination has been approved by the FDA for the treatment of keratoconus and ectasia; it is indicated for epi-off use. However, retaining the epithelium is attractive to many clinicians.[28]

The standard epi-off CXL procedure (Dresden protocol) involves the removal of 8.0 to 9.0 mm of central corneal epithelium. This is followed by instillation of riboflavin 0.1% with 20% dextran (10 mg riboflavin-5-phosphate in 10 mL of 20% dextran) on the cornea for approximately 30 minutes. Then, the cornea is exposed to UVA radiation at a wavelength of 365 to 370 nm and an irradiance of 3 mW/cm^2 for 30 minutes to deliver a total energy of 5.4 J/cm^2.[29,30]

Because of the removal of epithelium, epi-off CXL has been associated with several complications, including the risk for infections during epithelial healing, delayed reepithelialization, temporary visual blur, corneal haze, corneal melting, and severe postoperative pain resulting from exposure of corneal nerves and the release of inflammatory mediators.[31,32] To prevent these problems and to reduce the healing time and discomfort for patients, researchers began to explore ways to perform CXL without removing the epithelium (ie, epithelium-on [epi-on] CXL). Initial studies of the epi-on technique used the same riboflavin concentration that was used for epi-off procedures (ie, riboflavin 0.1% concentration with 20% dextran). However, it is difficult for the hydrophilic molecule of riboflavin to penetrate through the lipophilic epithelium. Investigators subsequently tried to address this problem by adding enhancers or adjunctive agents to the riboflavin solution, such as benzalkonium chloride, tetracaine, trometamol, ethylenediaminetetraacetic acid,[29,33] and hydroxypropyl methylcellulose.[34] These substances weaken the epithelial intercellular junctions, thereby increasing epithelial permeability and enabling better penetration of the riboflavin solution into the corneal stroma.[33,35]

A review of the published literature showed that several studies have directly assessed whether epi-on CXL is equivalent to epi-off CXL in terms of the efficacy of preventing further progression of keratoconus. Some researchers used standard riboflavin concentrations (ie, riboflavin 0.1% with 20% dextran) in both procedures, while others changed the riboflavin and/or dextran concentration to achieve better results. In these studies, the exposure to UV radiations was the same; that is, irradiance of 3 mW/cm^2 for 30 minutes, delivering total energy of 5.4 J/cm^2.

Two studies using riboflavin 0.1% concentration with 20% dextran have produced contrasting results. Nawaz et al.[36] (40 eyes; 20 epi-off and 20 epi-on) found that both epi-off CXL and epi-on CXL could halt keratoconus progression. There were no significant differences in visual acuity or K values between the 2 groups. The 2 procedures were equal in terms of biometric results (central pachymetry values at 3-month and 6-month follow-up) and postoperative complications, except for persistent stromal haze in 10% of eyes in the epi-off CXL group, which decreased between 3 months and 12 months. In contrast, Godefrooij et al.[37] (61 eyes; 26 epi-off and 35 epi-on) found that epi-off CXL was more effective in halting progression and produced better flattening of the maximum K values.

Because of its high viscosity, dextran inhibits the penetration of riboflavin through the epithelium[38]; therefore, some studies evaluated riboflavin 0.1% with a lower concentration of dextran (15%). Magli et al.[39] (39 pediatric [<18 years] eyes; 23 epi-off and 16 epi-on) and Rossi et al.[40] (20 eyes; 10 epi-off and 10 epi-on) found that both epi-off CXL and epi-on CXL halted the progression of keratoconus in all treated eyes over the 12-month follow-up. In contrast, 2 studies using 15% dextran found the epi-on eyes had greater progression of keratoconus than epi-off eyes. Çerman et al.[41] (60 eyes; 30 epi-off

and 30 epi-on) found disease stabilization in 97% of epi-off eyes and 80% of epi-on eyes, and Kocak et al.[31] (36 eyes; 19 epi-off and 17 epi-on) reported disease stabilization in 89% of epi-off eyes and 35% of epi-on eyes. Çerman et al.,[41] however, associated the higher progression of keratoconus in epi-on eyes to the more advanced and progressive keratoconus in the epi-on group in their study. Notwithstanding the differences in keratoconus progression, all 4 studies reported faster visual recovery and a reduction in pain and epithelial healing infections in eyes treated with epi-on CXL and more complications (eg, postoperative pain, corneal haze, transient corneal edema, and glare disability) in eyes treated with epi-off CXL.

Some investigators removed dextran from the riboflavin formulation and increased the concentration of riboflavin. Akbar et al.[34] (64 eyes; 32 epi-off and 32 epi-on) increased the concentration to 0.25% in the epi-on group only. However, Stojanovic et al.[32] (20 patients in a contralateral-eye study; 1 eye treated with epi-off and fellow eye with epi-on) increased the concentration to 0.5% in both groups. Although Akbar et al. found disease stabilization in 94% of epi-off eyes and 74% of epi-on eyes, Stojanovic et al. reported no keratoconus progression after treatment in either group. Both studies reported advantages of epi-on CXL, such as less postoperative pain, faster visual recovery, and a decrease in epithelial healing problems. Stojanovic et al. compared their study's results with those in other studies using a 0.1% riboflavin concentration and observed that there was greater improvement in simulated K values, maximum K values, and HOAs with the standard riboflavin 0.1%. Stojanovic et al. hypothesized that this might be the result of more rapid oxygen consumption by the higher riboflavin concentration (0.5%) in the stroma, thereby reducing the efficiency of the riboflavin in CXL.

One consideration when performing epi-off CXL is that significant corneal dehydration might occur during the riboflavin-loading period. To prevent dehydration and the risk for thinning, some surgeons might choose to remove the speculum during the loading period and allow the lid to remain closed before UV light therapy is initiated.

The epi-on CXL procedure has been performed outside the U.S. as well as on an investigational or off-label basis in the U.S. For example, 3 transepithelial CXL procedures are undergoing clinical trials. One is Ribostat CXLO (CXL Ophthalmics LLC), which yielded significant visual gains that remained stable 2 years after treatment in a trial of 592 eyes published in 2018.[42]

The second procedure being studied is Ribocross TE (IROS Srl), which uses a vitamin E solution (VE-TPGS) to enhance the corneal permeability of riboflavin.[43] In a prospective nonrandomized clinical trial of 25 eyes with progressive mild-to-moderate keratoconus,[44] the use of Ribocross TE with low-dose UVA resulted in statistically significant gains in visual acuity, refraction, and corneal topography after 2 years.

Last, clinical trials are currently underway for an epi-on procedure devised by Avedro, Inc. The technique uses a new preparation of riboflavin (Paracel) along with supplemental oxygen.[A]

Another technique, iontophoresis-assisted epi-on CXL, is also being adapted. The aim of this approach is to enhance the delivery of charged riboflavin molecules through the epithelium using an electric current.[45] Although the technique is evolving, initial results suggest that riboflavin penetration with iontophoresis-assisted CXL is still not as deep as with epi-off CXL. In a recent small study, Lombardo et al.[46] compared the 2-year outcomes between standard CXL and CXL with transepithelial iontophoresis. Although clinically significant topographic, visual, and refractive improvements were found 2 years after transepithelial iontophoresis CXL, eyes treated with standard CXL had more significant corneal apex flattening.

In addition to the concerns regarding a suboptimum riboflavin concentration, there are also concerns that during epi-on CXL, the epithelium or the riboflavin within the epithelial layer might absorb incident UVA light and attenuate the UVA power reaching the corneal stroma.[36] Thus, the actual crosslinking effect might be shallower and less complete at all levels compared with what occurs with equivalent dosing with epi-off CXL. Even as Wernli et al.[47] have documented the applicability of the Bunsen-Roscoe law of photochemical reciprocity for riboflavin–UVA epi-off crosslinking up to 45 mW/cm^2, there are suggestions that increasing the irradiance to 45 mW/cm^2 (while keeping the total energy delivered the same [5.4 J/cm^2] or increasing it further) might improve the crosslinking effect with epi-on procedures. These suggestions were studied by Zhang et al.[48] (28 eyes) and Shen et al.[49] (17 eyes), who performed epi-on CXL with riboflavin 0.25% and an irradiance of 45 mW/cm^2. The procedure was pulse-illuminated (1 second on and 1 second off) for 5 minutes 20 seconds, delivering 7.2 J/cm^2 total energy. This is because continuous UVA illumination is known to cause a rapid depletion of oxygen in a riboflavin-soaked cornea and turning the UV light off leads to its replenishment (to its original level) within 3 to 4 minutes. Therefore, pulsing the UV light during CXL treatment is believed to maintain better oxygen concentration and produce a better and deeper crosslinking effect.[50] Both papers reported the procedure was safe and effective in halting keratoconus progression.

A review of the literature documenting the comparative efficacy of epi-on versus epi-off CXL in halting keratoconus progression found inconsistent results. The inconsistencies might be the results of variations in study design or patient populations, such as age, keratoconus disease severity, riboflavin concentration, or UVA irradiance and illumination intensity. At present, there is insufficient evidence that epi-on CXL is as effective as epi-off CXL. Clinical trials are being conducted to evaluate the outcomes of epi-on CXL using higher concentrations of riboflavin (0.146%[B]; 0.185%, and 0.250%[A]), higher UV irradiance (continuous/pulsed), and higher delivery of total energy (as much as

10 J/cm^2). If riboflavin solutions and protocols can eventually be developed so that both procedures are equally effective at halting the progression of keratoconus, epi-on CXL would have clear advantages in terms of comfort, visual recovery, and avoidance of complications.

REFRACTIVE EFFECTS OF CORNEAL CROSSLINKING

The impact of CXL on keratometry has been studied. In the pooled dataset from the U.S. Phase III Clinical trials of patients with progressive keratoconus,[27] an initial steepening of mean maximum K was observed at 1 month (change 1.5 D) followed by flattening between 1 month and 3 months (change 1.8 D). Flattening continued between 3 months and 6 months and between 6 months and 12 months, resulting in a mean flattening of 1.6 D $\pm$ 4.2 (SD) between baseline and 12 months after surgery ($P < .001$). In a prospective randomized controlled clinical trial performed in Australia,[51] patients with progressive keratoconus were followed at baseline and 3, 6, 12, 24, and 36 months after conventional epi-off CXL (treatment group). A mean improvement in treated eyes was observed, showing flattening of the maximum K value by 1.03 $\pm$ 0.19 D at 36 months. Most of the change in the maximum K value occurred during the first 24 months, with changes being less marked during the third year. A prospective longitudinal cohort study in Italy followed 62 eyes of 47 pediatric keratoconus patients having conventional epi-off CXL over 10 years.[52] The baseline and follow-up measurements documented that the maximum K value improved significantly 6 months after treatment (1.07 D; $P = .0454$), and this improvement remained statistically significant up to the eighth year of follow-up.

In the pooled dataset from the U.S. Phase III Clinical trials of patients with progressive keratoconus,[27] there was a significant improvement (5.7 letters) in the CDVA between before surgery and 12 months after surgery in the CXL-treated group. In the control group, there was a gain of approximately 2.2 letters. The difference in the change in CDVA at 1 year between the CXL treatment group and control group was 3.5 letters, a statistically significant finding ($P < .01$). Patients completed a questionnaire that scored various subjective vision function parameters, which included subjectively noted photophobia, difficulty driving at night, difficulty reading, diplopia, fluctuation in vision, glare, halo, starburst, dryness, pain, and foreign-body sensation. All 11 parameters analyzed in the study showed improvement after 12 months in the CXL treatment group, with 6 reaching statistical significance (night driving, difficulty reading, diplopia, glare, fluctuation in vision, and foreign-body sensation).

In a prospective longitudinal cohort study following 62 eyes of 47 pediatric keratoconus patients having conventional epi-off CXL over 10 years, the CDVA improved significantly by 1 month after CXL, and this improvement persisted at all follow-up visits (6 months, and 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 years), with the exception of the third month after treatment ($P = .3299$).[52] Coma values improved, statistically significant by the first postoperative month ($P = .0001$), maintaining statistical significance through 10 years follow-up.

Some researchers have studied the efficacy of combining CXL procedures with various refractive technologies, such as topography-guided techniques, but a review of these studies is beyond the scope of this article.

COMPLICATIONS

Corneal crosslinking–related complications can occur soon after the procedure or in the long term. They can be infectious or noninfectious, mostly related to inflammation and abnormal healing.

Infectious Complications

The incidence of infectious keratitis after CXL is extremely low, reaching 0.0017% of the cases in countries that traditionally report a high volume of corneal infections.[53] A systematic review published in 2016 and performed between the years 2000 and 2013 found only 10 published cases of infectious keratitis after CXL.[54]

This low number of cases might be related to the fact that the procedure damages keratocytes and kills bacteria and fungi, which is why it is also used to treat corneal infections. Nevertheless, infection can occur; most frequently, infectious keratitis occurs soon after the procedure. Epithelial debridement and the use of a therapeutic soft contact lens and topical corticosteroids in the immediate postoperative period can be considered contributing factors that facilitate the entrance and proliferation of microorganisms in the denuded stroma.[54]

In the same systematic review, Abbouda et al.[54] selected 10 articles with level 3 evidence in which it was possible to analyze the etiology, management, treatment, and visual outcome. The main group of pathogens reported included bacteria followed by herpes virus, fungal, and *Acanthamoeba* infection. Among bacterial pathogens, the most virulent was *Pseudomonas aeruginosa*, which was treated with fortified antibiotics; however, corneal transplantation was required to improve vision.[55] Less virulent organisms, such as *Escherichia coli* and *Staphylococcus epidermidis*, were identified in 2 publications; both responded well to topical antibiotic therapy.[56] Polymicrobial keratitis was found to be associated with *Streptococcus salivarius* and *Streptococcus oralis*, with an acceptable visual outcome after topical treatment with fortified antibiotics.[57]

As for viral infections, there were 2 reports of cases of herpes keratitis after CXL.[58,59] It has been suggested that UVA light could be a potent stimulus to trigger and/or induce reactivation of latent herpes simplex virus infections.[58,59] The incidence of herpetic keratitis was low, and postoperative management led to the recovery of the preoperative visual acuity level in both cases. At present, there is no evidence that the use of systemic antiviral prophylaxis is beneficial; however, it would be useful to analyze this in a randomized study.

Fungal infection caused by *Fusarium solani* and *Microsporidia* were reported after CXL.[60,61] The time to onset

was long compared with the onset of other pathogens. In both cases, topical treatment controlled the infection; however, the visual outcome was poor and corneal transplantation was indicated.

The only case caused by *Acanthamoeba* developed corneal melting 5 days after CXL.[62] Once the microorganism was identified, topical hexamidine and polyhexamethylene biguanide were added. Even with clinical treatment, the cornea perforated and therapeutic penetrating keratoplasty (PKP) was performed.

Noninfectious Complications

Corneal Haze and Deep Stromal Opacity Corneal crosslinking–induced stromal haze results from the healing response secondary to the effect of UVA–riboflavin CXL in the cornea.[63–67] It has a dust-like appearance and affects the anterior stromal layers; this differs from the reticular subepithelial haze induced by photorefractive keratectomy.[68] In most cases, CXL haze improves up to 1 year. However, in almost 9% of cases, the opacity is denser, remains for a longer time, and significantly affects visual acuity.[64]

The pathophysiology of haze seems to be related to the production of altered collagen by activated keratocytes that migrate in the anterior stroma. This process starts weeks after the acute loss of keratocytes that occurs after the procedure and is completed at approximately 6 months.[68–71] Other mechanisms might be involved, such as proteoglycan–collagen interactions and glycosaminoglycan hydration.[68]

Risk factors include reduced corneal thickness preoperatively and an increased mean K value.[64] Other possible risk factors include older age and a preoperative reticular pattern of stroma detected by in vivo confocal microscopy.[65,67] Intraoperative factors that increase keratocytes apoptosis are a low concentration of riboflavin in the cornea, an excessive time of UVA exposure, and a short corneal soaking time, all of which might increase the chances for the development of significant haze and must be carefully controlled during the UVA–riboflavin CXL procedure.[72]

Kato et al.[73] described 3 cases with deep stromal opacity after corneal CXL that presented different clinical features than the temporary or permanent stromal haze induced by CXL. This condition developed in the deeper stromal corneal layers after 2 months postoperatively, became more evident at 3 to 6 months, and was accompanied by corneal curvature flattening. The authors suggest that the deep stromal opacity might be an exaggerated form of the demarcation line after the CXL procedure. Interestingly, all these cases presented mild diffuse corneal infiltration, sometimes with anterior chamber reaction and ciliary injection, indicating that the condition is associated with an intense inflammatory process in the anterior segment of the eye.

Excessive Flattening Most CXL corneas usually evolve to a stable or slightly flatter keratometry over a 2-year period.[74,75] Excessive postoperative flattening of the maximum corneal curvature (>5.00 D) might occur in a few cases, affecting the predictability of the procedure.[74,75] This effect can be explained by the combination of an increase in the regional tissue elastic modulus, the depth of CXL, and the central ectasia location.[75,76] Santhiago et al.[75] described 2 cases of excessive flattening (7.0 D and 14.0 D) that occurred in the first year after CXL. One of the patients was young (14 years old), which corroborates the observation of other authors that pediatric corneas that had CXL tend to flatten more intensely than those in other age groups.[75–77] These cases illustrate the importance of keeping a close follow-up of patients who have CXL, especially younger ones. The K values become less reliable as the severity increases, which might affect the certainty of excessive flattening in these eyes.

Peripheral Sterile Infiltrates Peripheral sterile infiltrates can occur in the early period of after CXL.[78] Ghanem et al.[78] reported 7 (0.97%) of these lesions in 720 eyes with keratoconus that had the procedure. The infiltrates had a ring shape and affected the anterior stroma in the peripheral cornea between the treated area and untreated area. In most cases, the lesions occurred a few days after the treatment. In 1 case, the infiltrates developed in the second week after CXL and an epithelial defect was observed.[78] All cases responded to topical corticosteroids. The authors hypothesized that the peripheral infiltrates that occur after riboflavin–UVA CXL could represent immune responses to generated non-self antigens.[78] Phototoxicity and exposure to topical medications, such as nonsteroidal antiinflammatory or antibiotic agents, might trigger this reaction.[78,79] Important differential diagnoses include infectious keratitis and marginal catarrhal infiltrates induced by a *Staphylococcus* immune reaction.[78,80]

Corneal Endotheliitis Direct damage by UVA has been implicated as the most important factor involved in noninfectious corneal endotheliitis.[81,82] Intraoperative corneal thinning during UV exposition might facilitate the endothelial damage.[82,83] However, stromal thinning occurs in each case, which makes one believe there are additional causative factors in cases of corneal edema and endotheliitis; 1 factor is an inflammatory reaction to the riboflavin solution used during CXL treatment.[83] Other possible causative factors include the delivery of excessive energy resulting from incorrect UVA light focus or calibration, a lack of or error in pachymetry reading during surgery, acute hydrops, and preexisting Fuchs endothelial dystrophy.[82,84] Corneal crosslinking can also reactivate viral infections, such as herpes simplex, zoster, and cytomegalovirus and/or activate the host immune response, starting an endothelial inflammatory process.[83]

ECONOMIC ANALYSIS OF CORNEAL CROSSLINKING

Patients with progressive keratoconus might have a reduced quality of life and require corneal transplantation to restore vision. This surgery consumes significant resources in terms of surgical time, follow-up, and donor tissue. After surgery, patients require ongoing care to monitor for

complications, such as graft rejection, graft failure, and intraocular pressure elevation. Corneal crosslinking, which halts the progression of keratoconus, would allow those affected to avoid progressive visual decline and corneal surgery.

The first report to evaluate the cost effectiveness of CXL was published in 2015[85] and used treatment and monitoring costs in a Markov mathematic model from the National Health Services National Tariff report (2012–2013). The authors concluded that if CXL could arrest keratoconus before substantial progression, the patient's quality of life would approach that of unaffected individuals (85% probability of being cost-effective at a threshold of £30 000 per quality-adjusted life years [QALYs]). The QALY is a composite value comprising mortality and morbidity and expressing the number of healthy years gained from treatment. Healthcare resources routed to transplantation surgery and follow-up would also be made available for other disease states, and demands on donor tissue availability would decrease.

Two studies to date have examined the effect of CXL on the requirement of corneal transplantation for keratoconus. Sandvik et al.[86] found a 25% decrease in the rate of PKP in the 6 years after the introduction of CXL in Norway compared with 1 year before implementation of routine CXL for mild to moderate keratoconus. In a study performed in the Netherlands, Godefrooij et al.[87] reported similar findings 3 years after the introduction of CXL. Given this evidence, Godefrooij et al.[88] next published their analysis of the procedure's cost-effectiveness. The authors used a Markov-type model incorporating the following published data: treatment effects and disease progression based on individual patient data from 2 randomized controlled trials[51,89]; transplantation rates based on the Collaborative Longitudinal Evaluation of Keratoconus Study,[90] which contained more than 8000 patient years of data on visual acuities, quality of life, and corneal transplantation rates; and graft failure rates from the Australian graft registry.[91] Their analysis showed that the incremental cost-effectiveness ratio (difference in lifetime costs/difference in lifetime health outcomes) associated with CXL for progressive keratoconus was €54 384 (US$59 822) per QALY gained when the CXL effectiveness duration was set at 10 years. By increasing the stabilizing effect of CXL to the patient's lifespan, the incremental cost-effectiveness ratio decreased to €10 149/QALY (US$11 163/QALY), meaning a higher level of cost-effectiveness. If the stabilizing effect were 15 years or longer, the incremental cost-effectiveness ratio would be less than 1× the gross domestic product per capita threshold in the Netherlands and thus be very cost-effective.

A final study in the literature on this subject by Leung et al.[92] used patient-level microsimulation models to evaluate the comparative cost-effectiveness of early CXL versus PKP for keratoconus in Canada. Lifetime costs and QALYs for CXL were estimated to be Can$5530 (Can$4512, discounted) and 50.12 QALYs (16.42 QALYs, discounted). Lifetime costs and QALYs for PKP were Can$2675 (Can$1508, discounted) and 48.93 QALYs (16.09 QALYs, discounted). The discounted incremental cost-effectiveness ratio comparing CXL with PKP was Can$9090 per QALY gained, which falls well below the thresholds generally used to evaluate the cost-effectiveness of health interventions in Canada (range Can$20 000 to Can$100 000 per QALY) and the U.S. (US$50 000 per QALY).

In conclusion, there is strong evidence for the cost-effectiveness of CXL in progressive keratoconus. Furthermore, the current literature likely underestimates the cost savings from CXL because the procedure might also be used in patients with post-laser in situ keratomileusis ectasia and pellucid marginal degeneration. The cost-savings analyses presented are important for policy decision makers and insurance company regulators to consider.

CONCLUSION

In conclusion, CXL has been available internationally for several years and was approved in the U.S. in 2016. This is the first procedure proven to limit the progression of keratoconus; therefore, it might decrease the need for corneal transplantation. Cost analysis has shown that the long-term cost of CXL is significantly less than the cost of keratoconus progression, in particular because of the potential decreased need for transplantation. In addition, the risks of CXL are substantially fewer than the risks of transplantation. Studies of different techniques, including epi-on treatment, changes in UV light parameters, and riboflavin composition, continue to proceed with the hope of improving the safety and efficacy of the procedure.

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