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Ophthalmic Technology Assessment

Safety and Efficacy of Epithelium-Off Corneal Collagen Cross-Linking for the Treatment of Corneal Ectasia

A Report by the American Academy of Ophthalmology

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Purpose: To review the evidence on the safety and effectiveness of epithelium-off corneal collagen cross-linking (CXL) for the treatment of progressive corneal ectasia.

Methods: A literature search of the PubMed database was most recently conducted in March 2024 with no date restrictions and limited to studies published in English. The search identified 359 citations that were reviewed in abstract form, and 43 of these were reviewed in full text. High-quality randomized clinical trials comparing epithelium-off CXL with conservative treatment in patients who have keratoconus (KCN) and post–refractive surgery ectasia were included. The panel deemed 6 articles to be of sufficient relevance for inclusion, and these were assessed for quality by the panel methodologist; 5 were rated level I, and 1 was rated level II. There were no level III studies.

Results: This analysis includes 6 prospective, randomized controlled trials that evaluated the use of epithelium-off CXL to treat progressive KCN (5 studies) and post–laser refractive surgery ectasia (1 study), with a mean postoperative follow-up of 2.4 years (range, 1–5 years). All studies showed a decreased progression rate in treated patients compared with controls. Improvement in the maximum keratometry (Kmax) value, corrected distance visual acuity (CDVA), and uncorrected distance visual acuity (UDVA) was observed in the treatment groups compared with control groups. A decrease in corneal thickness was observed in both groups but was greater in the CXL group. Complications were rare.

Conclusions: Epithelium-off CXL is effective in reducing the progression of KCN and post–laser refractive surgery ectasia in most treated patients with an acceptable safety profile.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Assessment is to review systematically the available literature and research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment prepared by the Ophthalmic Technology Assessment Committee Cornea and Anterior Segment Disorders panel is to review the evidence on the safety and efficacy of corneal collagen cross-linking (CXL) for the treatment of corneal ectasia, including keratoconus (KCN) and post–laser refractive surgery ectasia.

Background

Keratoconus is a noninflammatory, usually bilateral and asymmetric, progressive corneal ectasia that can significantly affect vision due to worsening myopia and irregular astigmatism.[1] Before the introduction of CXL, available treatments addressed only the refractive consequences of KCN with glasses, specialty contact lenses, and intrastromal ring segments but did not modify disease progression or its prognosis. Progression to advanced disease may lead to loss of best-corrected vision due to corneal opacification or contact lens intolerance requiring corneal replacement. In fact, KCN remains a common indication for penetrating keratoplasty globally.[2,3] Likewise, KCN-like corneal ectasia also can occur as a complication of laser refractive surgery.[4] Corneal collagen cross-linking is a minimally invasive procedure

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designed to reduce the progression of corneal ectasia by creating stronger chemical bonds between collagen fibrils.[5,6] A photosensitizer, riboflavin (vitamin B2), is used in combination with ultraviolet A (UV-A, 365 nm) light to induce a photochemical reaction that results in the formation of covalent bonds between collagen molecules and between collagen molecules and proteoglycans through oxidative stress.[7] Potential advantages of the use of CXL to slow or arrest progression of corneal ectasia include a reduction of associated visual disability by preserving uncorrected and best-corrected vision, and a decrease in the need for corneal transplantation and its well-known sight-threatening complications.

The most commonly reported risks of CXL include pain, infection, delayed epithelial healing, stromal haze, photophobia, and treatment failure. Other rare complications reported in the literature include corneal perforation, excessive corneal flattening, noninfectious endotheliitis, and endothelial failure.[8] Wollensak et al[5] published the first clinical study using CXL for the treatment of progressive KCN in adult patients. Since then, many more studies have been published, and CXL has been widely adopted for the treatment of both KCN and post−laser refractive surgery ectasia.[9-11] Briefly, the most commonly used and traditional technique described by Wollensak et al, known as the "Dresden protocol," consists of removing epithelium in the central 9-mm zone followed by applying 0.1% riboflavin in 20% dextran every 2 minutes for 30 minutes. The cornea is then irradiated with UV-A light (370 nm) for 30 minutes at 3 mW/cm^2 for a total energy of 5.4 J/cm^2. Minimum corneal thickness of 400 μm is generally required before irradiation to prevent endothelial cell damage.[5] A number of modifications to the Dresden protocol have been proposed, mainly to reduce the treatment time (accelerated CXL) and postoperative healing time (epithelium-on CXL) and to expand indications to corneas thinner than 400 μm (sub-400 protocol).[12] Evidence suggests that some accelerated techniques are comparable in efficacy to the Dresden technique and that epithelium-on CXL may be safer but perhaps slightly less effective than epithelium-off techniques, with varied results in comparative studies that are largely dependent on the type of riboflavin used and its ability to penetrate the corneal epithelium.[13-16] Newer techniques and riboflavin formulations currently being studied may result in increased efficacy of epithelium-on CXL. Although some consider the Dresden protocol to be the gold standard because of its status as the first widely accepted technique, epithelium-off techniques and some accelerated protocols are equally effective.[17]

Although the use of CXL also has been proposed in combination with refractive correction procedures and intrastromal ring implants, for the treatment of refractory infectious keratitis and for the prevention of corneal melt in keratoprosthesis,[18,19] this assessment focuses on epithelium-off CXL and its use in progressive KCN and post−laser refractive surgery ectasia.

Food and Drug Administration Status

The Food and Drug Administration (FDA) approved CXL system (KXL; Avedro Inc.) to treat patients with progressive KCN and post−laser in situ keratomileusis ectasia in April 2016. Currently, there are 2 FDA-approved solutions for use in CXL, including riboflavin 59-phosphate in 20% dextran ophthalmic solution 0.146% (Photrexa Viscous) and riboflavin 59-phosphate ophthalmic solution 0.146% (Photrexa). Both formulations are intended to be used with the KXL system.[8] The FDA-approved procedure follows the Dresden epithelium-off protocol.[8] The Photrexa Viscous formulation is used in all CXL procedures, whereas the hypotonic formulation of riboflavin without dextran (Photrexa) is used only in cases where corneal pachymetry is less than 400 μm after the initial induction period with Photrexa Viscous.[8] Other CXL systems and riboflavin formulations that allow accelerated and trans-epithelial (epithelium-on) procedures are used in other countries but are not currently FDA approved in the United States.

Questions for Assessment

The purpose of this assessment is to address the following questions: (1) Is epithelium-off CXL safe and effective for the treatment of progressive corneal ectasia due to KCN and post−laser refractive surgery? (2) Does epithelium-off CXL provide a clinically significant benefit to patients with progressive ectasia secondary to KCN and post−laser refractive surgery?

Description of Evidence

A literature search was last conducted in March 2024 in the PubMed database with no date restrictions and limited to studies published in English. The search strategy can be found in the Appendix (available at www.aaojournal.org). The search identified 359 citations that were reviewed in abstract form, and 43 were reviewed in full text. High-quality randomized clinical trials comparing epithelium-off CXL with conservative treatment in patients who have KCN and post−refractive surgery ectasia were included. The panel decided to include only the most rigorously designed randomized controlled clinical trials with at least 12 months of follow-up. Therefore, case-control, cohort studies, clinical trials comparing CXL techniques, and studies for alternative indications were excluded. When more than one article was found for the same or similar cohort, the study with the longest follow-up and more complete dataset was selected.

The panel deemed 6 articles, all randomized clinical trials, to be of sufficient relevance to be included. These were evaluated by the panel methodologist (R.M.S.), who assigned level of evidence ratings to each of the selected articles based on the rating scale developed by the Oxford Centre for Evidence-Based Medicine.[20] A level I rating was assigned to well-designed and well-conducted randomized

clinical trials; a level II rating was assigned to well-designed case-controlled and cohort studies and lower-quality randomized trials; and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-controlled studies. Five articles were rated level I, and 1 article was rated level II. No articles were rated level III.

Published Results

Table 1 summarizes the 6 studies included in this assessment. All studies were performed in patients with documented progressive corneal ectasia. Five of the 6 studies were specifically for patients with KCN, and 1 study was dedicated to post−refractive surgery ectasia. The intervention for all studies was epithelium-off CXL. Five of the 6 studies[21-25] followed the standard Dresden protocol and 1 study (Larkin et al[26]) used an accelerated protocol (0.1% riboflavin, saline, hydroxypropyl methylcellulose administered every 2 minutes for 10 minutes and continuous UV-A light of 10 mW/cm^2 for 5.4 J/cm^2 total energy over 9 minutes). Follow-up ranged from 1 to 5 years, with a mean of 29 months (2.4 years). Eyes were randomized to CXL or conservative treatment. For the purpose of these studies, conservative treatment was defined as observation with spectacles and contact lenses as necessary for vision.

Stabilization of Progressive Corneal Ectasia

All studies included in this assessment demonstrated efficacy of CXL treatment to stabilize corneal ectasia.[21-26] There remains controversy in the literature as to the best parameter to detect corneal ectasia progression. The article "Global Consensus on Keratoconus and Ectatic Diseases" published in 2015 suggested that progression be defined as a consistent and meaningful change in at least 2 of the following parameters: (1) steepening of the anterior corneal surface, (2) steepening of the posterior corneal surface, and (3) thinning or an increase in the rate of the corneal thickness change from the periphery to the thinnest point.[27] The majority of studies on CXL in the published literature do not follow this recommendation strictly, but anterior corneal curvature is the most commonly used parameter to determine progression and CXL effect. Anterior maximum keratometry (Kmax) was the main outcome measure considered across all studies in this assessment except for Larkin et al,[26] who considered mean corneal power in the steepest meridian (K2) as the main outcome measure. However, the study by Larkin et al also reported Kmax results for both groups, allowing for comparison with the other studies. Five of the 6 studies had provisions in their protocol allowing participants in the standard of care arm to either crossover to the treatment arm if progression was detected or to undergo compassionate CXL.[21,22,24-26] The method of last observation carried forward was used in some of the studies to compare groups when significant data were missing due to crossover at the end of the study. Considering that all patients included in the studies had progressive disease when enrolled, this may have resulted in an underestimation of the difference between groups.

Topographic outcomes for the included studies are summarized in Table 2. The definition of progression varied slightly among studies and is described in Table 2. Progression in the untreated control groups ranged from 14% to 46% compared with 4% to 12% in the treatment groups.[21-26] The difference in the rate of progression between treatment and control groups reached statistical significance in all studies. It is important to note that not all patients in the control group showed progression, supporting the indication for treatment only in progressive disease. On the other hand, a small number of patients treated with CXL showed topographic evidence of progression, which underscores the need for long-term follow-up after treatment.

Three of the studies included patients 14 years old and older,[21,22,24] but the study by Larkin et al[26] was the only one dedicated to children with progressive KCN (ages 10−16 years) included in this assessment. Evaluating the efficacy of CXL in this age group is critical because an inverse correlation between age at diagnosis and severity has been reported, with a 7-fold higher risk of requiring corneal transplantation in children.[28,29] This study found an adjusted mean difference in K2 of −3.0 diopters (D) favoring CXL at 18 months. The results are comparable to the rest of the studies, and the reported progression in the untreated group is the highest of the 6 studies. The calculated unadjusted odds ratio suggests 90% lowered odds of progression in the CXL arm compared with patients receiving only standard of care (odds ratio, 0.1; 95% CI, 0.02−0.48; $P = 0.004$).[26] The study allowed for patients randomized to standard of care with documented progression to crossover to the treatment arm no earlier than 9 months after randomization.

Hersh et al[21] evaluated the efficacy of CXL in post−laser refractive surgery ectasia. The study found a decrease in mean Kmax of 0.7 D from baseline at 1 year after CXL, whereas the untreated eyes continued to progress (1.3 D difference in Kmax change between treatment and control, $P < 0.0001$ at 12 months). Progression in the treated eyes was 4% (3/91 eyes), confirming that efficacy of CXL in post−refractive surgery ectasia is similar to that observed in progressive KCN.[21]

The results from randomized controlled trials included in this analysis support efficacy of CXL in stabilizing progressive corneal ectasia for the intermediate term of 2.4 years (range, 1−5 years). Recently, a follow-up of 2 of the cohorts included in this assessment (Hersh et al[21,22]) was published reporting overall long-term stability in 65.8% of eyes.[30] A higher percentage of eyes with KCN (81.8%) compared with eyes with post−refractive laser ectasia (50%) remained stable at the 10-year follow-up.[30] These results are definitely encouraging but should be interpreted with caution because only 19 of the 181 initially treated eyes are included, and therefore the study lacks statistical power to confirm 10-year efficacy of epithelium-off CXL. Although level I studies have not yet confirmed long-term efficacy, several nonrandomized studies have reported corneal stabilization in 76% to 100% of treated eyes at 7 to 10 years, with higher rates of progression after treatment seen in those treated before 15 years of age and those with higher keratometry values at the time of treatment.[9-11,31]

Table 1. Summary of Included Studies

Authors (Year)	Title	Level of Evidence	No. of Eyes	Age (yrs; Mean ± SD)	Gender (n = Eyes; Male/Female)	Type of Ectasia	Collagen Cross-Linking Intervention	Follow-up (mos)
Wittig-Silva et al (2014)[25]	A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results	I	94 (46 CXL; 48 control)	25.6 ± 6.2 (CXL) 25.8 ± 6.4 (control)	143/62	KCN	Standard epi-off	36
Lang et al (2015)[23]	Prospective, randomized, double-blind trial to investigate the efficacy and safety of corneal cross-linking to halt the progression of keratoconus	II	29 (15 CXL; 14 control)	28	23/6	KCN	Standard epi-off	36
Hersh et al (2017)[22]	United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment	I	166 (90 CXL; 76 control)	33 ± 10.9	143 /62	KCN	Standard epi-off	12
Meyer et al (2021)[24]	Five-year results of a prospective, randomised, contralateral eye trial of corneal crosslinking for keratoconus	I	152 (76 CXL; 76 control)	21.1 ± 6.7	NR	KCN	Standard epi-off	60
Larkin et al (2021)[26]	Effect of Corneal Cross-linking versus Standard Care on Keratoconus Progression in Young Patients. The KERALINK Randomized Controlled Trial	I	55 (30 CXL; 28 control)	15.2 ± 1.4	44/16	KCN	Accelerated epi-off	18
Hersh et al (2017)[21]	U.S. Multicenter Clinical Trial of Corneal Collagen Crosslinking for Treatment of Corneal Ectasia after Refractive Surgery	I	179 (91 CXL; 89 control)	43.5 (CXL) 41.8 (control)	122/57	Post–refractive surgery ectasia	Standard epi-off	12

CXL = corneal collagen cross-linking; epi = epithelium; KCN = keratoconus; NR = not reported; SD = standard deviation.

Table 2. Postoperative Topographic Parameters after Corneal Collagen Cross-Linking

Authors (year)	Group	Mean Change in Group Kmax from Baseline (D) ± SD				Progression Based on Change in Keratometry	
		Baseline	*12 Mos*	*18 Mos*	*36 Mos*	*60 Mos*	% (*n* = *eyes*)	*Study Definition of Progression*
Wittig-Silva et al (2014)[25]	Control	51.18 ± 4.03	+1.20 ± 0.28	NR	1.75 ± 0.38	NR	39.6%* (19/48)	>2 D increase in Kmax
	CXL	52.87 ± 4.31	−0.72 ± 0.15	NR	1.03 ± 0.19	NR	4.2%* (1/46)	
Lang et al (2015)[23]	Control	50.9 ± 5.7	+0.11	NR	+0.11 ± 0.61†	NR	14%* (2/15)	1 D increase per year in younger than 20-year-olds and 0.2 D increase per year in the complete cohort
	CXL	47.3 ± 2.2	−0.35	NR	−0.35 ± 0.58†	NR	6.6%* (1/14)	
Hersh et al (2017)[22]	Control	60.4 ± 8.9	+1.0 ± 5.1	NR	NR	NR	NR	≥2 D increase in Kmax in treatment group
	CXL	60.9 ± 9.2	−1.6 ± 4.2	NR	NR	NR	12%* (11/90)	
Meyer et al (2021)[24]	Control	55.9 ± 7.5	1.26 ± 2.20	NR	NR	1.71 ± 2.46	46% (16/35)	>1.0 D increase in Kmax at 5 yrs
	CXL	59.7 ± 7.0	−1.27 ± 2.38	NR	NR	−1.45 ± 2.25	5.7% (2/35)	
Larkin et al (2021)[26]	Control	57.2 ± 5.7	NR	+3.1*	NR	NR	43% (12/28)	>1.5 D increase in K2
	CXL	56.0 ± 4.8	NR	+1*	NR	NR	7% (2/30)	
Hersh et al (2017)[21]	Control	54.8 ± 6.40	+0.6 ± 2.1D	NR	NR	NR	NR	≥2 D increase in Kmax in treatment group
	CXL	55.4 ± 6.86	−0.7 ± 2.1	NR	NR	NR	4% (3/91)	

CXL = corneal collagen cross-linking; D = diopters; Kmax = maximum keratometry; K2 = mean corneal power in the steepest meridian; NR = not reported; SD = standard deviation.
*Calculated from reported values.
†Per year.

The long-term efficacy of CXL can be indirectly assessed by examining the number of keratoplasties performed for corneal ectasia. The studies included in this assessment did not directly evaluate this outcome measure; however, the number of primary penetrating keratoplasties for KCN and other ectatic disorders has been decreasing for the past 8 years in the United States according to the Eye Bank Association of America's statistical report.[32] Likewise, other studies outside the United States have reported a significant decrease in the number of keratoplasties performed in patients with KCN after the introduction of CXL.[33-35] It is likely that CXL is not the only factor leading to this finding and that improvement in contact lens technology also played a significant role.[36-39]

Visual Acuity Results

The 6 studies included in this assessment reported visual improvement in treated eyes compared with control eyes (Table 3).[21-26] The difference in uncorrected distance visual acuity (UDVA) between groups was statistically significant in all studies except Meyer et al.[24] In addition, corrected distance visual acuity (CDVA) was better in the CXL group compared with the control group in 2 of 5 studies on KCN eyes and in the study on post−refractive surgery ectasia eyes at the end of the follow-up period.[21,22,26] Larkin et al[26] and Hersh et al[22] both showed a significant difference in UDVA and CDVA between treated and untreated eyes, favoring CXL. Specifically, Hersh et al[22] found that CXL was associated with an improvement of more than 1 line of mean CDVA 1 year after surgery. Conversely, Wittig-Silva et al[25] and Meyer et al[24] showed a significant improvement in UDVA compared with baseline in the treatment group at all time points, up to 36 and 60 months, respectively. However, final CDVA was not different between the groups. Lang et al[23] also did not show a significant difference in CDVA.

In agreement with the results observed in patients with KCN, Hersh et al[21] reported that in patients with post−refractive surgery ectasia, one third of treated eyes had a clinically significant improvement in CDVA (32% gained 2 or more lines, 44% remained unchanged, and 4% lost 2 or more lines). Of the eyes that experienced loss of CDVA, there was no identified adverse event. Multifactorial analysis identified eyes with a preoperative CVDA of less than 20/40 as the only predictor of visual acuity improvement after treatment. Both UDVA and CDVA were significantly better in the CXL group compared with the control group at 1 year.[21]

Corneal Thickness

Corneal collagen cross-linking appears to cause a decrease in the mean central corneal thickness (CCT), decreasing the usefulness of CCT as a parameter to detect progression in eyes that have undergone treatment. Four of the 6 included studies reported results on mean CCT or thinnest point.[23-26] Three of the studies found a more significant decrease in CCT in the CXL treatment group compared with the control group, whereas Larkin et al found no difference in apical thickness between the groups at 18 months.[23-26]

Table 3. Postoperative Visual Acuity after Corneal Collagen Cross-Linking

Authors (Year)		Follow-up	Uncorrected Visual Acuity (logMAR) Mean (SD) Baseline	Uncorrected Visual Acuity (logMAR) Mean (SD) Final	P Value*	Corrected Visual Acuity (logMAR) Mean (SD) Baseline	Corrected Visual Acuity (logMAR) Mean (SD) Final	P Value*
Wittig-Silva et al (2014)[25]	Control	36 mos	0.81 (0.40)	0.10 (0.034)†	0.001	0.28 (0.26)	−0.05 (0.03)†	0.347
	CXL		0.93 (0.39)	−0.15 (0.06)†,§		0.33 (0.26)	−0.09 (0.03)†,§	
Lang et al (2015)[23]	Control	36 mos	NR	NR		0.39 (0.37)	0.23 (0.27)	0.38
	CXL					0.25 (0.15)	0.22 (0.14)	
Hersh et al (2017)[22]	Control	12 mos	0.93 (0.22)‡	0.88 (0.22)‡	>0.05	0.44 (0.27)‡	0.40 (0.27)‡	<0.01
	CXL		0.86 (0.25)‡	0.77 (0.28)‡,§		0.43 (0.27)‡	0.33 (0.24)‡,§	
Meyer et al (2021)[24]	Control	60 mos	0.64 (0.41)	0.02 (0.29)†	0.06	0.28 (0.23)	−0.02 (0.20)†	0.76
	CXL		0.81 (0.34)	−0.13 (0.31)†,§		0.33 (0.26)	−0.04 (0.23)†	
Larkin et al (2021)[26]	Control	18 mos	0.7 (0.4)	0.8 (0.6)	0.002	0.5 (0.4)	0.6 (0.6)	0.002
	CXL		0.6 (0.4)	0.5 (0.3)		0.5 (0.4)	0.4 (0.4)	
Hersh et al (2017)[21]	Control	12 mos	0.80 (0.27)‡	0.80 (0.31)‡	<0.001	0.33 (0.23)‡	0.34 (0.24)‡	<0.0001
	CXL		0.81 (0.26)‡	0.72 (0.32)‡,§		0.36 (0.26)‡,§	0.36 (0.25)‡	

CXL = corneal collagen cross-linking; logMAR = logarithm of the minimum angle of resolution NR = not reported; SD = standard deviation.
*Statistically significant difference between CXL and control groups.
†Change from baseline.
‡Calculated from reported results. Original results were reported in Early Treatment Diabetic Retinopathy Study (ETDRS) letters read on a Lighthouse ETDRS chart, 2nd edition. This specific chart has a value of logMAR 1.0 upon successful completion of the top/largest line. Thus, the conversion from letters to logMAR for this specific chart is logMAR = 1.1 − 0.02* (number of Lighthouse 2nd edition letters read).
§Statistically significant difference from baseline. Not reported in Lang et al[23] and Larkin et al.[26]

Safety

Ocular adverse events after CXL were rare across all studies. The most commonly reported adverse event was persistent corneal haze after 12 months (4.6%).[21-24] Not all patients with persistent corneal haze experienced loss of CDVA; however, some did. Infectious keratitis was reported in 0.6% (2/347) of treated eyes across the 6 studies included in this assessment, resulting in loss of more than 2 lines of CDVA in 1 eye.[22,24] Sterile corneal infiltrates were reported in 4 eyes.[24,25] Other reported adverse events included epithelial downgrowth under the LASIK flap in 1 eye likely related to flap edge trauma, highlighting the importance of careful epithelial removal during the CXL procedure in patients post-LASIK.[21]

On average, loss of CDVA (2 Snellen lines or more; 10 Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution letters or more) was observed in approximately 4.6% (16/347) of treated eyes. Specifically, 2 eyes lost vision due to disease progression, 3 eyes due to persistent stromal haze, and 1 eye due to infectious keratitis. Nine eyes with reported CDVA loss had no other associated adverse events or disease progression, and in these cases loss of vision was due to collagen remodeling induced by treatment.[21-25] Unfortunately, loss of CDVA or corneal scarring was not specifically reported for the control group in most of the included studies, except for Lang et al,[23] who found an equal number of eyes in both the control and treated groups with loss of CDVA without a specific associated reason. Prior studies have evaluated vision loss as part of the natural history of KCN. Most notably, the Collaborative Longitudinal Evaluation of Keratoconus study found a 19% and 31% decrease of 10 or more Early Treatment Diabetic Retinopathy Study letters in high-contrast and low-contrast best-corrected visual acuity, respectively, in at least 1 eye over 8 years of follow-up.[40] This same study found an 8-year incidence of corneal scarring of 20%.[40]

Damage to endothelial cells due to exposure to free radicals generated during the CXL process is a concern.[41] Cytotoxicity studies suggest a minimum threshold of 400 μm in corneal thickness to mitigate a UV-A effect on endothelial cells.[42] All studies included the use of hypotonic riboflavin as part of the protocol to achieve minimum corneal thickness before UV-A exposure. Only 3 studies reported endothelial cell counts and showed no difference between groups.[21,22,25] No endothelial decompensation was reported in any of the treated patients; however, persistent corneal edema after CXL has been reported in the literature.[21-26,43]

Other severe adverse events such as corneal melt and perforation have been described in the literature[44] but were not reported in any of the included studies. The absence of some complications previously described in the literature may represent a trend toward lower complication rates related to increased surgeon experience and stricter inclusion/exclusion criteria. Risk factors associated with complications after CXL reported in the literature include CDVA better than 20/25 and age more than 35 years, suggesting that refining CXL indications may further reduce the risk of complications.[31]

Economic and Quality of Life Considerations

None of the included studies directly addressed the issues of cost or accessibility of CXL. However, there are several published studies providing strong economic evidence for the

cost-effectiveness of CXL in KCN.[45-49] Specifically, Leung et al[47] found an incremental cost-effectiveness ratio of Can$9090/quality-adjusted life years (QALYs) when comparing CXL with conventional management, including keratoplasty. This calculated incremental cost-effectiveness ratio falls well below the range of Can$20 000 to Can$100 000/QALY and below US$50 000/QALY, thresholds generally used to evaluate the cost-effectiveness of health interventions in Canada and the United States, respectively.[47] Likewise, Lindstrom et al[48] used a discrete-event microsimulation lifetime model from the U.S. payor's perspective and found that CXL was associated with a lifetime cost savings of $43 759 per patient and that it was considered cost-effective within 2 years and cost-saving within 4.5 years. In this model, patients undergoing CXL were 25% less likely to undergo penetrating keratoplasty and spent 27.9 fewer years in advanced-disease stages.[48] Despite the reported favorable cost-effectiveness, variable insurance coverage remains a barrier to CXL access in the United States.

Larkin et al[26] evaluated quality of life using the 25-item Cardiff Visual Ability Questionnaire for Children and the Child Health Utility 9D questionnaires. The study found no evidence of difference in quality of life between CXL and standard of care at 18 months after surgery. However, it is possible that differences may be detected with longer follow-up.[26] Hersh et al[22] used a patient questionnaire to assess subjective visual function at baseline and 1 year after surgery. The study did not compare groups but rather reported changes from baseline in the treatment group and found that several parameters had a statistically significant improvement after CXL, including night driving, difficulty reading, diplopia, glare, fluctuation in vision, and foreign-body sensation.[22] A similar trend was observed specifically in the post−refractive surgery population, with most subjective visual parameters showing improvement, but only night driving reached a statistically significant difference at 1 year.[21]

Study funding and author financial disclosures can be found in Table S4 (available at www.aaojournal.org).

Conclusions

Epithelium-off CXL appears to decelerate or arrest progression of KCN and post−laser refractive surgery ectasia in most adults as well as children ages 10 to 16 years for at least 2.4 years after treatment. Longitudinal studies are needed to establish whether the effect on disease progression induced by CXL is permanent. In this patient population, CXL treatment also results in a clinically significant benefit in corneal curvature and UDVA. According to the results of these studies, epithelium-off CXL should be considered a first-line treatment for patients with progressive KCN and post−laser refractive surgery ectasia. A small percentage of treated eyes may continue to progress, and long-term follow-up is recommended. Adverse events associated with the procedure are rare, and the benefit of treatment likely outweighs the risk of morbidity from advanced disease and contact lens− and keratoplasty-related complications.

Future Research

Longer follow-up studies will help elucidate whether a higher percentage of untreated patients progress over more time. This question is particularly important for the younger age group who, as expected, demonstrated the highest rates of progression without treatment. Another consideration in the pediatric population is that children with developmental disabilities have a higher risk of KCN. Further research is necessary to determine if this specific population has a higher rate of complications or lower rates of success, given that eye-rubbing behavior may persist even after treatment. Further studies are also needed to understand fully the safety and efficacy of retreatments in the small number of patients who show progression after CXL and whether technique modifications are required in these cases. Likewise, expanding CXL indications to more advanced disease and thinner corneas is of interest. Research into imaging and diagnostic techniques that would allow better definition of progression parameters and the ideal timing for CXL treatment is also important. Finally, research continues with the goal of refining the CXL technique, including personalized treatments, improved riboflavin formulations, and oxygen supplementation with the potential to improve efficacy and safety, shorten the procedure, and result in less postoperative pain and fewer complications related to epithelium removal.

Footnotes and Disclosures

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Conception and design: Cortina, Greiner, Kuo, Li, Miller, Shtein, Veldman, Yin, Kim, Shen

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Abbreviations and Acronyms:
CCT = central corneal thickness; **CDVA** = corrected distance visual acuity; **CXL** = corneal collagen cross-linking; **D** = diopters; **FDA** = Food and Drug Administration; **KCN** = keratoconus; **Kmax** = maximum keratometry; **QALY** = quality-adjusted life year; **UDVA** = uncorrected distance visual acuity; **UV-A** = ultraviolet A.

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References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297−319.
2. Keane M, Coffey N, Jones V, et al. *The Australian Corneal Graft Registry Report: 2021/22 Report*. Adelaide, Australia: Department of Ophthalmology, Flinders University and South Australian Health and Medical Research Institute; 2012. v. 85.
3. Qureshi S, Dohlman TH. Penetrating keratoplasty: indications and graft survival by geographic region. *Semin Ophthalmol*. 2023;38:31−43.
4. Seiler T, Koufala K, Richter G. Iatrogenic keratectasia after laser in situ keratomileusis. *J Refract Surg*. 1998;14:312−317.
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620−627.
6. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol*. 2006;17:356−360.
7. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97−103.
8. Belin MW, Lim L, Rajpal RK, et al. Corneal cross-linking: current USA status: Report from the Cornea Society. *Cornea*. 2018;37:1218−1225.
9. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34:796−801.
10. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal collagen cross-linking with riboflavin and ultraviolet A light for pediatric keratoconus: ten-year results. *Cornea*. 2018;37:560−566.
11. Godefrooij DA, Soeters N, Imhof SM, Wisse RP. Corneal cross-linking for pediatric keratoconus: long-term results. *Cornea*. 2016;35:954−958.
12. Epstein RJ, Belin MW, Gravemann D, et al. Epismart cross-linking for keratoconus: a phase 2 study. *Cornea*. 2023;42:858−866.
13. Ng SM, Ren M, Lindsley KB, et al. Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus. *Cochrane Database Syst Rev*. 2021;3:CD013512.
14. Lombardo M, Giannini D, Lombardo G, Serrao S. Randomized controlled trial comparing transepithelial corneal cross-linking using iontophoresis with the Dresden protocol in progressive keratoconus. *Ophthalmology*. 2017;124:804−812.
15. Henriquez MA, Rodriguez AM, Izquierdo Jr L. Accelerated epi-on versus standard epi-off corneal collagen cross-linking for progressive keratoconus in pediatric patients. *Cornea*. 2017;36:1503−1508.
16. Shetty R, Pahuja NK, Nuijts RM, et al. Current protocols of corneal collagen cross-linking: visual, refractive, and tomographic outcomes. *Am J Ophthalmol*. 2015;160:243−249.
17. Iqbal M, Gad A, Kotb A, Abdelhalim M. Analysis of the outcomes of three different cross-linking protocols for treatment of paediatric keratoconus: a multicentre randomized controlled trial. *Acta Ophthalmol*. 2024;102:e105−e116.
18. Van Tigchelt L, Van Eijgen J, Delbeke H. Alternative indications for corneal crosslinking. *J Cataract Refract Surg*. 2021;47:1360−1366.
19. Kanellopoulos AJ, Asimellis G. Long-term safety and efficacy of high-fluence collagen crosslinking of the vehicle cornea in Boston keratoprosthesis type 1. *Cornea*. 2014;33:914−918.

20. Oxford Centre for Evidence-Based Medicine Levels of Evidence Working Group. The Oxford 2011 levels of evidence, 2014, Oxford Centre for Evidence-based Medicine. https://www.Cebm.Net/wp-content/uploads/2014/06/cebm-levels-of-evidence-2.1.Pdf. Accessed April 19, 2024.
21. Hersh PS, Stulting RD, Muller D, et al. U.S. Multicenter clinical trial of corneal collagen crosslinking for treatment of corneal ectasia after refractive surgery. *Ophthalmology*. 2017;124:1475–1484.
22. Hersh PS, Stulting RD, Muller D, et al. United States multicenter clinical trial of corneal collagen crosslinking for keratoconus treatment. *Ophthalmology*. 2017;124:1259–1270.
23. Lang SJ, Messmer EM, Geerling G, et al. Prospective, randomized, double-blind trial to investigate the efficacy and safety of corneal cross-linking to halt the progression of keratoconus. *BMC Ophthalmol*. 2015;15:78.
24. Meyer JJ, Jordan CA, Patel DV, et al. Five-year results of a prospective, randomised, contralateral eye trial of corneal crosslinking for keratoconus. *Clin Exp Ophthalmol*. 2021;49:542–549.
25. Wittig-Silva C, Chan E, Islam FM, et al. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. 2014;121:812–821.
26. Larkin DFP, Chowdhury K, Burr JM, et al. Effect of corneal cross-linking versus standard care on keratoconus progression in young patients: the Keralink randomized controlled trial. *Ophthalmology*. 2021;128:1516–1526.
27. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea*. 2015;34:359–369.
28. Buzzonetti L, Bohringer D, Liskova P, et al. Keratoconus in children: a literature review. *Cornea*. 2020;39:1592–1598.
29. Leoni-Mesplie S, Mortemousque B, Touboul D, et al. Scalability and severity of keratoconus in children. *Am J Ophthalmol*. 2012;154:56–62 e51.
30. Greenstein SA, Yu AS, Gelles JD, et al. Long-term outcomes after corneal cross-linking for progressive keratoconus and corneal ectasia: a 10-year follow-up of the pivotal study. *Eye Contact Lens*. 2023;49:411–416.
31. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg*. 2009;35:1358–1362.
32. Eye Bank of America. *2021 Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America; 2021.
33. Chilibeck CM, Brookes NH, Gokul A, et al. Changing trends in corneal transplantation in Aotearoa/New Zealand, 1991 to 2020: effects of population growth, cataract surgery, endothelial keratoplasty, and corneal cross-linking for keratoconus. *Cornea*. 2022;41:680–687.
34. Godefrooij DA, Gans R, Imhof SM, Wisse RP. Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking. *Acta Ophthalmol*. 2016;94:675–678.
35. Hagem AM, Thorsrud A, Saethre M, et al. Dramatic reduction in corneal transplants for keratoconus 15 years after the introduction of corneal collagen crosslinking. *Cornea*. 2024;43:437–442.
36. Koppen C, Kreps EO, Anthonissen L, et al. Scleral lenses reduce the need for corneal transplants in severe keratoconus. *Am J Ophthalmol*. 2018;185:43–47.
37. Ling JJ, Mian SI, Stein JD, et al. Impact of scleral contact lens use on the rate of corneal transplantation for keratoconus. *Cornea*. 2021;40:39–42.
38. Sarezky D, Orlin SE, Pan W, VanderBeek BL. Trends in corneal transplantation in keratoconus. *Cornea*. 2017;36:131–137.
39. Thanitcul C, Varadaraj V, Canner JK, et al. Predictors of receiving keratoplasty for keratoconus. *Am J Ophthalmol*. 2021;231:11–18.
40. Wagner H, Barr JT, Zadnik K. Collaborative longitudinal evaluation of keratoconus (CLEK) study: methods and findings to date. *Cont Lens Anterior Eye*. 2007;30:223–232.
41. Gokhale NS. Corneal endothelial damage after collagen cross-linking treatment. *Cornea*. 2011;30:1495–1498.
42. Santhiago MR, Randleman JB. The biology of corneal cross-linking derived from ultraviolet light and riboflavin. *Exp Eye Res*. 2021;202:108355.
43. Sharma A, Nottage JM, Mirchia K, et al. Persistent corneal edema after collagen cross-linking for keratoconus. *Am J Ophthalmol*. 2012;154:922–926 e921.
44. Agarwal R, Jain P, Arora R. Complications of corneal collagen cross-linking. *Indian J Ophthalmol*. 2022;70:1466–1474.
45. Godefrooij DA, Mangen MJ, Chan E, et al. Cost-effectiveness analysis of corneal collagen crosslinking for progressive keratoconus. *Ophthalmology*. 2017;124:1485–1495.
46. Salmon HA, Chalk D, Stein K, Frost NA. Cost effectiveness of collagen crosslinking for progressive keratoconus in the UK NHS. *Eye (Lond)*. 2015;29:1504–1511.
47. Leung VC, Pechlivanoglou P, Chew HF, Hatch W. Corneal collagen cross-linking in the management of keratoconus in Canada: a cost-effectiveness analysis. *Ophthalmology*. 2017;124:1108–1119.
48. Lindstrom RL, Berdahl JP, Donnenfeld ED, et al. Corneal cross-linking versus conventional management for keratoconus: a lifetime economic model. *J Med Econ*. 2021;24:410–420.
49. Sandvik GF, Thorsrud A, Raen M, et al. Does corneal collagen cross-linking reduce the need for keratoplasties in patients with keratoconus? *Cornea*. 2015;34:991–995.