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Corneal Crosslinking for Progressive Keratoconus and Corneal Ectasia: Summary of US Multicenter and Subgroup Clinical Trials

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Purpose: The multicenter studies reviewed were designed to evaluate the safety and efficacy of corneal collagen crosslinking (CXL) for the treatment of progressive keratoconus and corneal ectasia after laser refractive surgery. The results of these studies led to approval by the United States Food and Drug Agency for both conditions in 2016. This paper reviews these studies, as well as single-center substudies investigating other aspects of crosslinking outcomes.

Methods: As part of prospective, randomized, controlled clinical trials, the treatment group received standard CXL, and the sham control group received only riboflavin ophthalmic solution. The primary efficacy criterion was maximum keratometry (K_{max}) 1 year after CXL. Secondary outcomes were corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA). Safety and adverse events were analyzed. In single-center substudies, corneal topography, ocular aberrations, corneal haze measurements, corneal thickness, corneal biomechanics, subjective visual function, and outcomes predictors were also investigated. This paper presents a general review of the design and outcomes of crosslinking in these studies.

Results: In the crosslinking treatment group, K_{max} flattened by 1.6 diopters (D) and 0.7 D in eyes with keratoconus and ectasia, respectively. In both studies, there was continued progression in the control group. The CDVA improved by an average of 5.7 logMAR letters (LL) in the keratoconus treatment group and by 5.0 LL in the ectasia group. In both studies, corneal haze was the most frequently reported crosslinking-related adverse finding. This was most prominent at 1 month and generally returned to baseline between 3 and 12 months. In general, corneal topography, ocular aberrations, and subjective visual function improved after crosslinking.

Conclusions: In the US multicenter trials, CXL was shown to be safe and effective in stabilizing K_{max}, CDVA, and UDVA in eyes with progressive keratoconus or corneal ectasia.

Translational Relevance: Corneal crosslinking was originally developed in the laboratory at the University of Dresden in the late 1990s. The combination of ultraviolet-A light and riboflavin was found to be the most effective of a number of different modalities tested to increase the biomechanical strength of the cornea. The clinical study design for the US multicenter clinical trials of crosslinking demonstrated the safety and effectiveness of this technique for treatment of progressive keratoconus and corneal ectasia, bringing this important advancement to patients in the United States.

Introduction

Keratoconus and corneal ectasia after refractive surgery are diseases characterized by thinning and biomechanical weakness of the cornea, resulting in irregular corneal astigmatism and decreased visual acuity.[1,2] The structural integrity of the cornea depends on the lamellar organization of the collagen fibers that comprise the corneal stroma, regulated by an interconnecting network of proteoglycans. The pathogenesis of the biomechanical weakness in keratoconus appears, in part, secondary to the loss and/or slippage of collagen fibrils and changes to the extracellular matrix.[3] In addition, there is less interweaving of the collagen lamellae in the anterior stroma, generally the repository of corneal strength, and a significant loss of lamellae inserting into Bowman's layer.[4]

The pathogenesis of ectasia after refractive surgery similarly remains to be fully elucidated. In many cases, it is likely that the ectatic cornea had a predisposition to keratoconus or biomechanical weakness preoperatively.[5–7] In addition, the possibility remains that removal of tissue during laser refractive surgery thins the cornea enough to destabilize its architectural structure, precipitating frank ectasia. Specific risk factors for ectasia include preoperative high myopia, thin residual stromal bed, total percentage of tissue altered by both the flap thickness and tissue removed, forme fruste keratoconus, and irregular preoperative topography.[8–10]

Corneal collagen crosslinking (CXL) is a treatment designed to decrease the progression of keratoconus and corneal ectasia after refractive surgery.[11–15] Additional studies have reported that crosslinking can also have beneficial visual, optical, and topographic effects, including improvement in corneal steepness, visual acuity, topography irregularity indices, higher order aberrations (HOAs), and subjective visual function in some patients.[16–23] In this paper, we review the study design and results from the pivotal US multicenter clinical trials that led to the United States Food and Drug Administration (FDA) approval of CXL in eyes with progressive keratoconus and corneal ectasia after laser refractive surgery.[24,25] In addition, results of substudies looking at other outcomes are reviewed.

Study Methodology

Patients were enrolled as part of two separate multicenter prospective, randomized, sham-controlled clinical trials—one to treat progressive keratoconus and the other to treat corneal ectasia after refractive surgery—conducted in support of an FDA New Drug Application (NDA no. 203324) for a corneal crosslinking (iLink; Glaukos, San Clemente, CA) with Photrexa Viscous (0.146% riboflavin ophthalmic solution with 20% dextran), Photrexa (0.146% riboflavin ophthalmic solution), and the KXL System (Glaukos). Randomization was computer generated, and both the patient and the investigator were aware of the randomly assigned group.

For both studies, inclusion criteria included patients 14 years of age or older, axial topography pattern consistent with keratoconus, maximum keratometry (K_{max}) on corneal topography (Pentacam; Oculus, Wetzlar, Germany) $\geq$ 47.0 diopters (D), an inferior–superior difference greater than 1.5 D on topography mapping, corrected distance visual acuity (CDVA) worse than 20/20, and corneal thickness as measured on the Pentacam of $\geq$300 µm. In the keratoconus study, progressive keratoconus was defined as one or more of the following changes over a period of 24 months: an increase of 1.0 D or greater in the steepest keratometry measurement, an increase of 1.0 D or greater in manifest cylinder, or an increase of 0.5 D or greater in manifest refraction spherical equivalent. In the ectasia study, inclusion criteria required an axial topography pattern consistent with corneal ectasia (including relative inferior steepening with inferior–superior difference). Exclusion criteria included patients with a history of corneal surgery (except for the previous LASIK or photorefractive keratectomy [PRK] procedure), corneal pachymetry $<$ 300 µm, and history of corneal disease that would interfere with healing after the procedure, such as chemical injury or delayed epithelial healing in the past. Patients pregnant or lactating during the study were excluded.

Treatment of Randomized Groups

Patients were initially randomized into a treatment or control group. The treatment group received standard ultraviolet-A (UVA)–riboflavin CXL treatment, performed according to the methodology described by Wollensak et al.[11] Initially, a topical anesthetic agent was administered, and the central 9.0-mm epithelium was removed by mechanical debridement. Riboflavin ophthalmic solution in 20% dextran was then administered topically every 2 minutes for 30 minutes. Riboflavin absorption throughout the corneal stroma and anterior chamber flare was confirmed by slit-lamp examination.

Ultrasound pachymetry was performed, and if the cornea was thinner than 400 µm then hypotonic riboflavin ophthalmic solution without dextran was administered, one drop every 10 seconds for 2-minute sessions, after which ultrasound pachymetry

was performed to ascertain that the stroma had swollen to 400 μm or greater. This was repeated in 2-minute sessions until adequate corneal thickness was obtained. The cornea was aligned and exposed to UVA 365-nm light for 30 minutes at an irradiance of 3.0 mW/cm^2.

During UVA exposure, administration of the riboflavin/dextran solution was continued every 2 minutes. Postoperatively, antibiotic and corticosteroid drops were administered, a soft contact lens bandage was placed, and the eye was reexamined at the slit-lamp. The contact lens was removed after the epithelial defect had closed. Antibiotics and corticosteroid drops were continued four times daily for 1 week and 2 weeks, respectively. Patients had complete examinations at 1, 3, 6, and 12 months postoperatively.

The control group received the riboflavin ophthalmic solution in 20% dextran alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for 30 minutes. Next, the cornea was exposed to a sham treatment in which the UVA light was not turned on, during which time riboflavin was administered topically every 2 minutes for an additional 30 minutes. Per the study protocols, the patients were allowed to cross over and receive full CXL treatment after the 3-month follow-up examination.

Statistical Analysis

Randomization was generated by the sponsor and allocated to each study site in a numbered sequence of envelopes containing subject assignment. The primary efficacy endpoint was the difference between the CXL group and the control group. Because the control group was eligible to receive treatment after the 3-month visit, those eyes that subsequently received treatment were considered lost to follow-up.

As a result of this crossover of control eyes to the treatment group, only two control eyes in each of the studies were available for examination at 12 months. Therefore, a last observation carried forward (LOCF) method was used to impute missing data for the 12 month analysis of the control group. In the LOCF analysis, efficacy data prior to crossover were carried forward to month 12, the study endpoint. The significance of the individual outcome changes from preoperative to 1-year postoperative were presented as *P* values ($P < 0.05$).

Results

The progressive keratoconus study included 205 eyes of 205 patients (102 in the treatment group, 103 in the control group). The ectasia study included 179 eyes of 179 patients (91 in the treatment group, 88 in the control group).

In the ectasia treatment and control groups, 166 eyes had previous LASIK, eight eyes had previous LASIK with a PRK enhancement, and five eyes had undergone previous PRK alone. The mean ages of patients enrolled in the keratoconus study and the ectasia study were 31.1 and 43.5 years, respectively.

Maximum Keratometry on Topography

The preoperative mean K_{max} in the keratoconus study was 60.9 ± 9.5 D in the treatment group, and K_{max} was 60.4 ± 8.9 D in the control group. In the treatment group, K_{max} significantly flattened by 1.6 ± 4.2 D ($P < 0.001$); in the control group, there was a significant steepening of K_{max} by 1.0 ± 5.1 D ($P < 0.001$) 1 year after treatment. The 2.6-D difference between the treatment and control groups was statistically significant ($P < 0.0001$).

In the ectasia study, mean K_{max} was 55.4 ± 6.9 D in the treatment group and 54.8 ± 6.4 D in the control group. Mean K_{max} significantly flattened by 0.7 ± 2.1 D in the treatment group ($P < 0.05$) 1 year after CXL. In the control group, there was a significant steepening by 0.6 ± 2.1 D ($P < 0.05$). Similar to the keratoconus study, the 1.3-D difference between the ectasia treatment and control groups was statistically significant ($P < 0.0001$). Data stratified to individual eyes are shown in in Figure 1.

Visual Acuity

In the keratoconus treatment group, preoperative uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) were 11.9 ± 12.2 logMar letters (LL) and 33.2 ± 13.4 LL, respectively. In the keratoconus control group, preoperative UDVA and CDVA were 8.2 ± 11.0 LL and 32.8 ± 13.6 LL, respectively. In the treatment group, UDVA improved by 4.4 LL and CDVA improved by 5.7 LL 1 year after treatment. These changes were all statistically significant ($P < 0.05$). In the control group, there was a gain of 2.6 LL of UDVA and 2.2 LL of CDVA; however, these changes failed to reach statistical significance. Regarding these changes in CDVA 1 year after CXL, there was a statistically significant difference between the treatment and control group ($P < 0.01$). However, regarding changes in UDVA, there was no statistically significant difference between the treatment and control groups.

In the ectasia treatment group, preoperative UDVA and CDVA were 14.4 ± 13.5 LL and 37.0 ± 13.0 LL, respectively. In the ectasia treatment group, UDVA

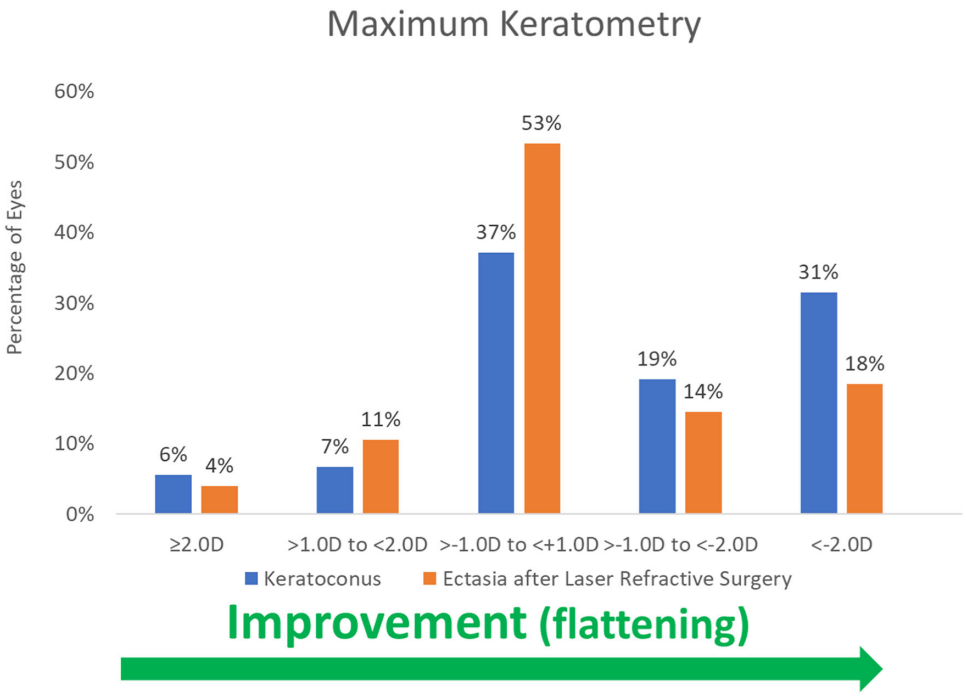

Figure 1. Percentage of individual eyes with a change in maximum keratometry (D) (multicenter data).

improved by 4.5 LL ($P < 0.001$); in the control group, there was a decrease of 0.1 LL of UDVA ($P > 0.05$). CDVA improved by 5.0 LL in the treatment group ($P < 0.001$) and improved by 0.3 LL in the control group ($P > 0.05$). These differences between the treatment and control groups were statistically significant ($P < 0.001$). Data stratified to individual eyes are shown in Figure 2.

Corneal Topography Indices

In a single-center substudy to assess changes in corneal topography indices after CXL, 71 eyes (49 keratoconus, 22 ectasia after laser refractive surgery) were assessed.[19] Quantitative descriptors of corneal topography measured with the Pentacam topographer

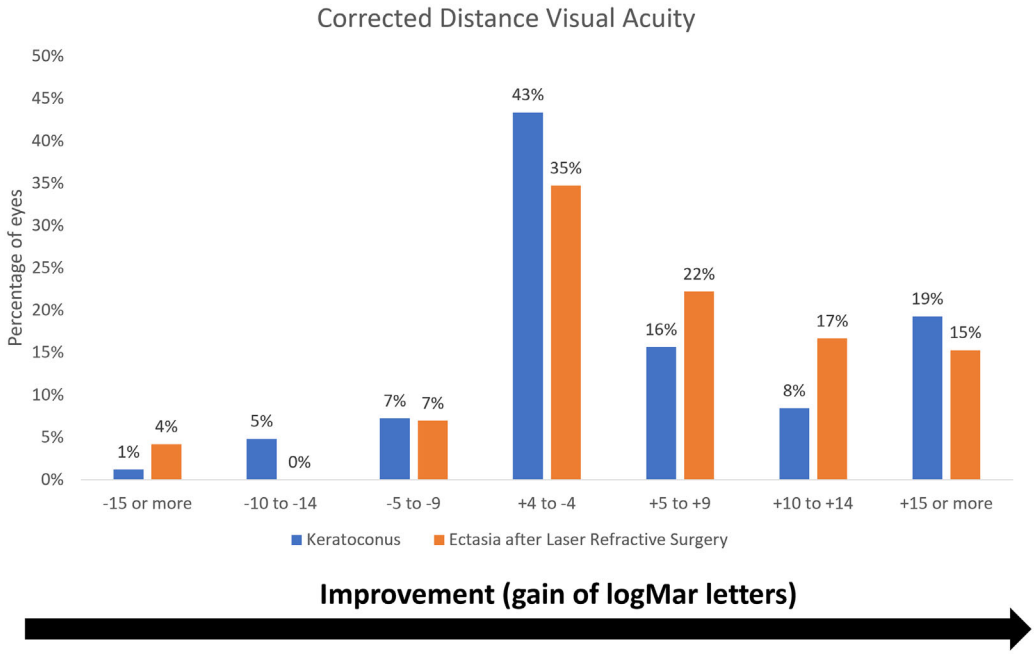

Figure 2. Percentage of individual eyes with a change in corrected distance visual acuity (letters) (multicenter data).

Table 1. Higher Order Aberrations in Keratoconus and Ectasia Subgroups

Aberration	Total HOAs	Spherical Aberrations	Total Coma	Primary Coma	Vertical Coma	Horizontal Coma	Trefoil Coma
Keratoconus							
ACHOA ($n = 64$)							
Preoperatively	4.57 ± 2.09	1.34 ± 0.85	4.32 ± 2.01	4.28 ± 2.00	3.95 ± 1.96	1.26 ± 1.02	0.36 ± 0.35
1 y	4.11 ± 1.92[a]	1.18 ± 0.61[a]	3.88 ± 1.93[a]	3.84 ± 1.91[a]	3.53 ± 1.85[a]	1.10 ± 0.94[a]	0.45 ± 0.46
PCHOA ($n = 64$)							
Preoperatively	8.83 ± 4.87	3.17 ± 2.25	8.13 ± 4.54	7.94 ± 4.45	7.17 ± 4.02	2.66 ± 2.59	0.98 ± 0.81
1 y	8.85 ± 4.45	3.00 ± 1.82	8.22 ± 4.27	8.07 ± 4.20	7.34 ± 3.90	2.65 ± 2.17	1.10 ± 0.86
OHOA ($n = 31$)							
Preoperatively	2.83 ± 1.08	0.80 ± 0.40	2.69 ± 1.07	2.65 ± 1.07	2.34 ± 1.13	0.47 ± 0.37	0.93 ± 0.46
1 y	2.55 ± 1.17[a]	0.73 ± 0.33	2.43 ± 1.16[a]	2.39 ± 1.15[a]	2.13 ± 1.14[a]	0.40 ± 0.34	0.83 ± 0.52
Ectasia							
ACHOA ($n = 32$)							
Preoperatively	4.89 ± 2.78	1.51 ± 0.57	4.57 ± 2.86	4.53 ± 2.85	4.22 ± 2.82	1.27 ± 0.95	0.40 ± 0.38
1 y	4.61 ± 2.79[a]	1.50 ± 0.52	4.27 ± 2.89[a]	4.21 ± 2.90[a]	3.93 ± 2.84	1.21 ± 0.99	0.36 ± 0.26
PCHOA ($n = 32$)							
Preoperatively	8.95 ± 5.17	3.22 ± 2.27	8.19 ± 5.24	8.05 ± 5.16	7.39 ± 5.06	2.48 ± 1.96	1.01 ± 0.63
1 y	8.38 ± 5.17[a]	2.98 ± 1.70	7.74 ± 5.03	7.62 ± 4.98	7.02 ± 4.79	2.32 ± 2.04	0.86 ± 0.73
OHOA ($n = 17$)							
Preoperatively	2.74 ± 0.87	1.09 ± 0.41	2.45 ± 0.97	2.42 ± 0.97	1.86 ± 1.04	0.77 ± 0.57	1.07 ± 0.46
1 y	2.67 ± 0.85	1.00 ± 0.42	2.41 ± 0.94	2.39 ± 0.94	1.91 ± 0.90	0.84 ± 0.61	0.97 ± 0.42

[a]Indicates a significant change compared to preoperative measurements ($P < 0.05$).

included seven indices: index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index, minimum radius of curvature (R_{min}), index of height asymmetry, and index of height decentration. In the entire patient cohort, there were significant postoperative improvements at 1 year compared with baseline in ISV ($P < 0.001$), IVA ($P < 0.001$), KI ($P < 0.001$), and R_{min} ($P < 0.001$). There were no significant differences between the keratoconus and ectasia subgroups. Additionally, improvements in postoperative indices were not correlated with changes in either CDVA or UDVA.

Higher Order Aberrations

In a single-center study designed to determine the changes in HOAs after CXL, we reported on 96 eyes (64 keratoconus, 32 ectasia) of 73 patients.[18] An untreated fellow eye control group included 42 eyes (26 keratoconus, 16 ectasia). Corneal and total ocular HOAs were measured at baseline and 12 months after CXL using the Pentacam and LADARWave aberrometer (Alcon, Ft. Worth TX), respectively. Anterior corneal HOAs (ACHOAs), posterior corneal HOAs (PCHOAs), and total ocular HOAs (OHOAs) were calculated as a root mean square wavefront error. Total OHOAs and ACHOAs significantly improved in the keratoconus treatment group, and total ACHOAs and PCHOAs improved in the ectasia treatment group (Table 1). There were no significant differences between the keratoconus and ectasia subgroups, and CXL-mediated changes in ACHOAs, PCHOAs, and OHOAs were not associated with improvement in visual acuity or most subjective visual symptoms on the patient questionnaire.

Subjective Patient Questionnaire

In a single-center substudy to assess subjective visual function after crosslinking, 107 eyes of 76 patients underwent CXL for keratoconus ($n = 71$) or ectasia after laser refractive surgery ($n = 36$).[16] Patients completed a questionnaire concerning their visual symptoms, administered preoperatively and at 1 year. They ranked self-reported symptoms of photophobia, difficulty night driving, difficulty reading, diplopia, fluctuations in vision, glare, halo, starburst, dryness, pain, and foreign body sensation on a scale from 1 to 5 (1 = none, 2 = mild, 3 = moderate, 4 = marked, 5 = severe). In the keratoconus treatment group, six of the 11 subjective visual parameters significantly improved 1 year after CXL. In the ectasia treatment group, one of the subjective visual parameters significantly improved. In both treatment groups, there was no worsening of subjective visual function in any of the remaining parameters (Fig. 3).

Predictors of CXL Outcomes

In another single-center substudy, regression analysis was performed to determine predictors of CXL

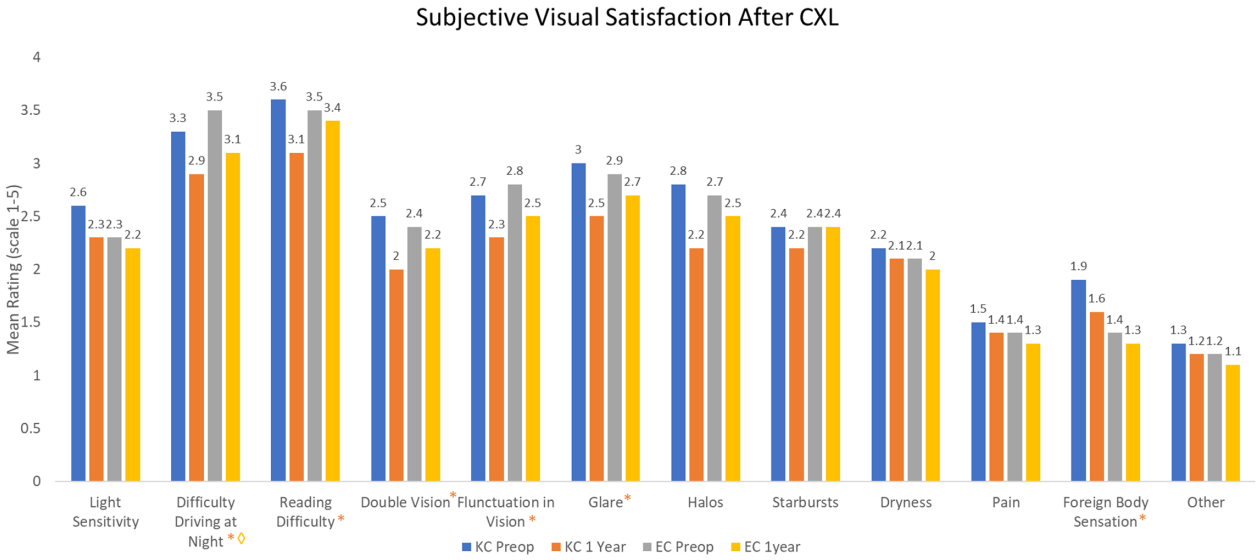

Figure 3. Each bar represents the mean rating on the subjective questionnaire (scale 1–5) at baseline and 1 year after CXL (multicenter data). *Statistically significant change for patients with keratoconus (keratoconus). ◊Statistically significant change for patients with ectasia after refractive surgery.

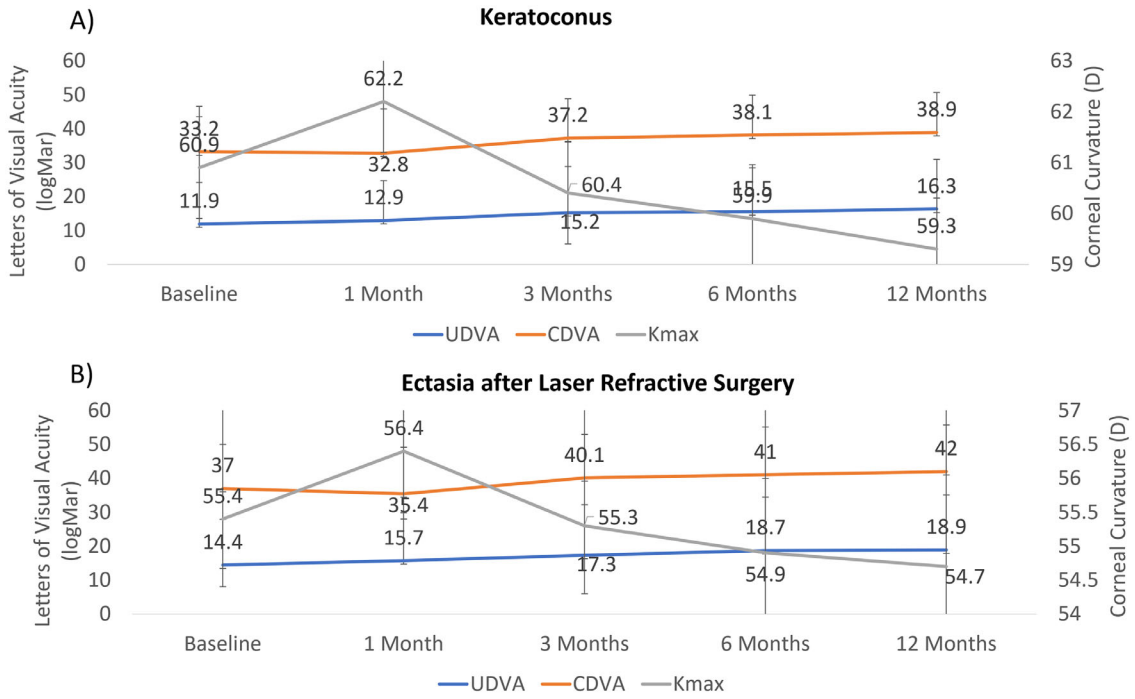

Figure 4. Change in visual acuity (uncorrected distance visual acuity – UDVA, corrected distance visual acuity – CDVA) over time after CXL (multicenter data). Change in maximum keratometry (K_{max}) over time after CXL. (A) Keratoconus. (B) Ectasia after laser refractive surgery.

outcomes (specifically, CDVA and K_{max}).[21] Variables included preoperative disease (keratoconus or corneal ectasia), cone location, age, gender, UDVA, CDVA, manifest refraction spherical equivalent, K_{max}, thinnest pachymetry, and corneal haze. The two significant predictors of CXL outcomes were preoperative CDVA and preoperative K_{max}. More postoperative improvement was observed in eyes with a preoperative CDVA worse than 20/40 and preoperative K_{max} of 55.0 D or steeper. Specifically, eyes with a preoperative CDVA of 20/40 or worse were 5.9 times more likely to improve $\geq$ 2 Snellen lines, and eyes with a $K_{max} \geq 55$ D were 5.4 times more likely to have topographic flattening $\geq$ 2 D. Furthermore, there was a trend, which did not

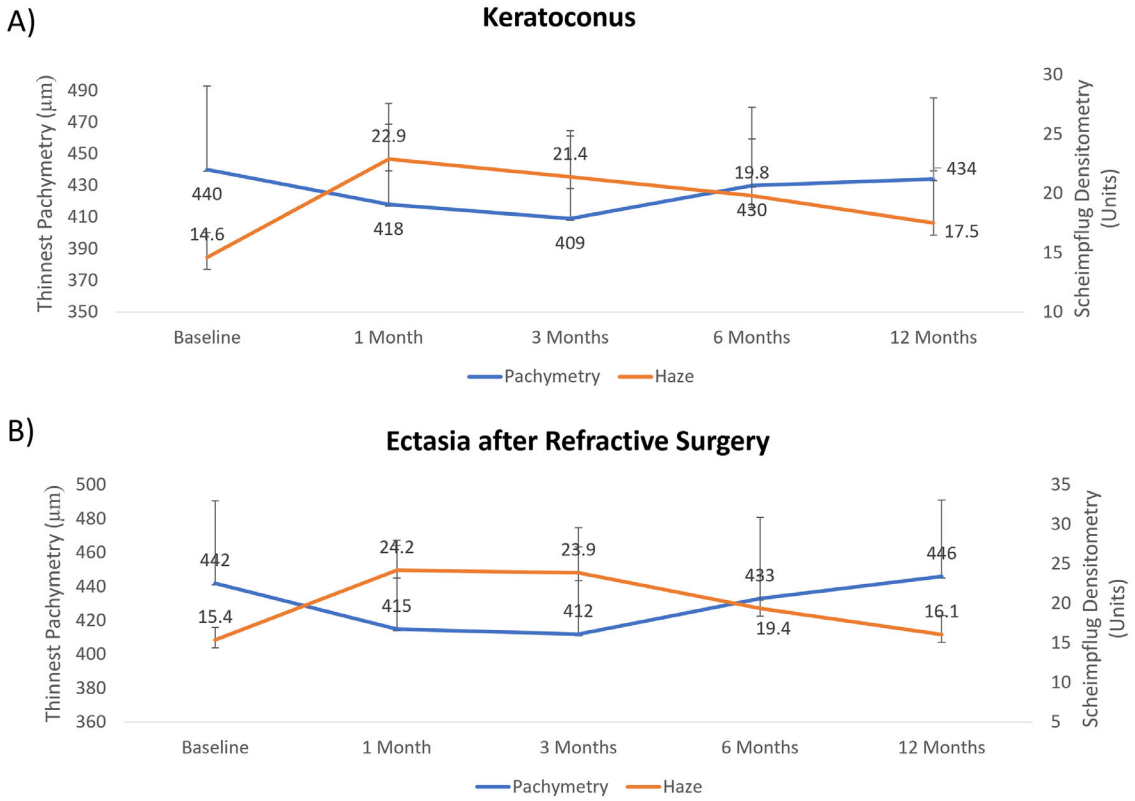

Figure 5. Change in thinnest pachymetry and Scheimpflug densitometry over time after CXL (single-center data). (A) Keratoconus. (B) Ectasia after laser refractive surgery.

meet statistical significance, suggesting that eyes with a CDVA of better than 20/40 preoperatively had a greater propensity to lose one line of CDVA (15.1%) than eyes with a worse preoperative CDVA (7.8%).

Corneal Thickness Changes

In a single-center substudy to determine the changes in corneal thickness over time after crosslinking, 82 eyes (54 keratoconus, 28 ectasia after laser refractive surgery) of 65 patients were evaluated.[22] Apical pachymetry ($Pach_{apex}$), thinnest pachymetry ($Pach_{thin}$), and pupil-center ($Pach_{pupil}$) pachymetry were measured using the Pentacam at baseline and at 1, 3, 6, and 12 months. The treatment group was compared with both a fellow eye and sham procedure control group.

Preoperative $Pach_{thin}$ was 440.7 ± 52.9 µm. After CXL, the cornea initially thinned at 1 month (change, –23.8 ± 28.7 µm; $P_{0–1} < 0.001$) and 3 months (–7.2 ± 20.1 µm; $P_{1–3} = 0.002$), followed by a recovery of the corneal thickness at 6 months (+20.5 ± 20.4 µm; $P_{3–6} < 0.001$). At 1 year, apex and pupil-center thickness returned to baseline ($P_{pachpupil} = 0.11$; $P_{pachapex} = 0.06$); however, the thinnest pachymetry remained slightly decreased from baseline (change from baseline, –6.6 ± 22.4 µm; $P_{0–12} = 0.01$). The recovery of corneal thickness was more rapid in patients with ectasia than keratoconus.

Treatment Time Course

In both studies, there was a similar postoperative time course. Initially, there was worsening of visual acuity and steepening of the cornea 1 month after CXL. This was followed by stabilization between 1 and 3 months and improvement between 3 and 12 months after treatment (Fig. 4).[23] This time course was consistent with the postoperative haze (measured by Scheimpflug densitometry) and changes in corneal pachymetry after CXL treatment (Fig. 5).[17]

Adverse Events

In the multicenter keratoconus trial, 293 eyes were followed in the safety database; in the multicenter ectasia trial, 219 eyes were included. The most common reported adverse event was stromal haze after CXL; 57% and 68% of patients had postoperative stromal haze in the keratoconus and ectasia treatment groups, respectively. At 12 months, two eyes had remaining

Table 2. Percentage of Adverse Events Reported in Eye Treated With CXL for Keratoconus and Ectasia After Refractive Surgery (Multicenter Data)

Adverse Event	Keratoconus Treatment Group (%)	Ectasia Treatment Group (%)
Corneal opacity (haze)	57	68
Punctate keratitis	25	20
Corneal striae	24	9
Epithelial defect after 1 wk	23	26
Eye pain	17	26
Blurred vision	16	17
Photophobia	11	19
Conjunctival hyperemia	10	Not reported
Ocular irritation	10	9
Decreased visual acuity	10	11
Dry eye	6	14
Increased lacrimation	5	10

stromal haze, and one eye had a stromal scar in the keratoconus treatment group. In the ectasia treatment group, five eyes had remaining stromal haze and one eye had a stromal scar 1 year after CXL.

To better define the degree and time course of corneal haze after CXL, a single-center substudy was done that looked at 50 eyes.[17] To objectively measure haze, corneal densitometry using Scheimpflug imagery was performed, and the changes were analyzed over time. A similar analysis was performed using clinician determined slit-lamp haze.

Preoperative corneal densitometry was 14.9 ± 1.93 (Pentacam densitometry units). Densitometry peaked at 1 month (23.4 ± 4.40; $P < 0.001$); little change was seen at 3 months (22.4 ± 4.79; $P = 0.06$). Densitometry decreased between 3 and 6 months (19.4 ± 4.48; $P < 0.001$) and between 6 and 12 months. At 12 months, in the entire cohort and keratoconus subgroup, densitometry did not completely return to baseline (cohort mean, 17.0 ± 3.82; $P < 0.001$); however, in the ectasia group, densitometry did return to baseline (16.1 ± 2.41; $P = 0.15$) (Fig. 5). The postoperative course of slit-lamp haze was similar to the objective densitometry measurements over time. Increased haze, measured by densitometry, did not correlate with postoperative clinical outcomes.

In the keratoconus treatment group, there was one severe ocular event. This patient was reported to have an ulcerative keratitis on postoperative day 3. The keratitis resolved after antibiotic therapy. In the ectasia treatment group, there was also one severe ocular adverse event reported. This patient was reported to have epithelial ingrowth beneath the LASIK flap on the postoperative month 1 visit, and the ingrowth resolved after a flap lift with removal of the epithelial cells. Most of the other adverse events reported were related to the epithelial healing in the early postoperative period (Table 2).

Discussion

Traditionally, patients with keratoconus and ectasia after laser refractive surgery have been treated with rigid gas-permeable contact lenses and, in more severe cases, penetrating keratoplasty.[26–29] Corneal crosslinking, which, uniquely, arrests the progression of these diseases, has been one of the most important advances in their treatment.[23–25,30] Early international studies showed efficacy in reducing the progression of keratoconus and also showed that crosslinking can have beneficial visual and topographic outcomes.[31–34]

Corneal crosslinking was approved in 2016 by the FDA as a drug and device combination (Glaukos) for the treatment of progressive keratoconus and corneal ectasia after laser refractive surgery. The two prospective randomized clinical controlled trials that formed the clinical basis for FDA approval were two of the largest studies performed on this treatment and compared a treatment group with a sham control group.[24,25]

With regard to study analysis, because the control group was eligible to receive treatment after the 3-month visit, many control eyes did not have data available subsequent to that visit. To account for this, a LOCF analysis was used to impute missing data for the 12-month analysis of treatment versus control. The justification for this methodology relies on the fact that keratoconus and ectasia are progressive conditions without spontaneous remission or improvement. Thus, untreated eyes would be expected to progress or, at best, remain stable per the natural history of the disease. Therefore, an LOCF model would seem to be a conservative methodology to compare the efficacy of CXL to control; the control data are imputed going forward as no further change, whereas disease progression, in fact, would be expected in the setting of progressive keratoconus and ectasia. Such progression would increase the difference between treatment and control as compared with the LOCF model. A further limitation of the control group is that the epithelium was not removed in these eyes; therefore, any contribution of de-epithelialization to outcomes could not be assessed.

In both US pivotal multicenter trials, CXL was found to stabilize keratoconus and corneal ectasia 1 year after treatment. Notwithstanding the differences

of 2.6 D and 1.3 D between treatment and control at 12 months in the keratoconus and ectasia groups, respectively, as found using the LOCF model, looking at the treatment group alone, for which complete 1-year data are available, there was a 1.6-D average improvement in K_{max} with keratoconus and a 0.7-D improvement in eyes with ectasia.

There was a mild, statistically significant, improvement of CDVA and UDVA in both treatment groups. There was also an improvement of many subjective visual outcomes; however, the influencing factors for these visual acuity improvements remain unclear. HOAs are a significant cause of visual impairment in keratoconus and ectasia; therefore, improvement of these aberrations might be expected to predict improvement in vision after CXL. In a single-center analysis[18] of HOAs, despite a significant improvement in total ocular and anterior corneal aberrations, there were no correlations between these aberrations and the improvements in UDVA or CDVA after CXL. Furthermore, despite improvement in four of seven Pentacam indices (ISV, IVA, KI, and R_{min}),[19] there were also no meaningful correlations with UDVA and CDVA.

In general, there appeared to be a less robust response to CXL in eyes treated for corneal ectasia after refractive surgery when compared with eyes with KC. At baseline, ectatic corneas were not as steep as those in the keratoconus trial. Additionally, the location of maximum keratometry tends to be more peripheral in eyes with ectasia. Studies have reported a more robust CXL response in eyes with a steeper and more central maximum keratometry, suggesting that the topographic attributes of the ectatic cornea may mitigate the CXL response.[21,35] Furthermore, biomechanical differences caused by the LASIK flap; possible differences in the riboflavin diffusion rate in a post-LASIK cornea, especially at the flap interface; and intrinsic pathophysiologic differences between keratoconus and ectasia may all contribute to the different CXL outcomes.

In addition to preoperative disease as a possible predictor of CXL outcomes, patients with worse CDVA (>20/40) and higher keratometry readings ($K_{max} \geq 55.0$ D) in general were found to more likely to have improvement after CXL.[21] Notwithstanding the generally good outcomes, ophthalmologists should counsel patients about the risk of a possible loss of visual acuity postoperatively, particularly in eyes with a preoperative CDVA better than 20/40.

The clinical time course after crosslinking is similar for both keratoconus and cornea ectasia. There was a significant worsening of vision and steepening of the cone at 1 month postoperatively, little change at 3 months, and improvement thereafter. These postoperative outcomes appear to be related to both stromal and epithelial remodeling over time after crosslinking. Furthermore, this time course appears to be consistent with the postoperative thinning and crosslinking associated with corneal haze changes over time.

With regard to the safety of crosslinking, early in the postoperative course patients are subject to the typical complications of the epithelial wound healing process. In the US multicenter trial for CXL in keratoconus patients, 22.5% of patients had a remaining epithelial defect, and, in the trial for ectasia, 26% of patients had a remaining epithelial defect 1 week after their procedure. After the initial epithelial wound healing, crosslinking-associated cornea haze was reported in over 50% of treated eyes.

Crosslinking-associated corneal haze differs in clinical character from haze after other procedures, such as excimer laser photorefractive keratectomy. The former is a dust-like change in the corneal stroma or a mid-stromal demarcation line,[36] whereas the latter has a more reticulated appearance. Corneal haze has been confirmed using confocal microscopy and can be objectively quantified using Scheimpflug densitometry.[37,38] Similar to the time course of clinical outcomes after crosslinking, there appears to be an increase in haze that peaks at 1 month and plateaus between 1 and 3 months. Between 3 and 6 months, the cornea begins to clear and continues to return toward baseline at 1 year.

Corneal thinning also occurs early in the CXL postoperative course.[3–6,14–17] Postoperatively, similar to the time course of crosslinking-associated corneal haze and crosslinking clinical outcomes, the cornea appears to thin at 1 month and at 3 months and to re-thicken between 3 and 12 months. The physiology of this initial thinning and subsequent rethickening is not entirely clear; however, epithelial remodeling is likely an early factor in corneal thickness changes. Furthermore, anatomic and structural changes of corneal collagen fibrils, such as compression of collagen fibrils,[10,23] changes in corneal hydration[24] and edema,[25,26] keratocyte apoptosis,[13,27,28] changes in glycosaminoglycans,[29] and other processes, might be implicated in the distinct clinical time course after CXL.

Corneal crosslinking is an essential treatment to stabilize and even improve the visual acuity and topography of patients with keratoconus and post-refractive surgery ectasia. This was confirmed in the prospective randomized controlled US pivotal multicenter trials for patients with keratoconus and corneal ectasia after refractive surgery, which led to FDA approval. International long-term studies have reported continued stability in a majority of patients 7 to 10 years after CXL.[39–43] Further follow-up is required to determine

the long-term stability of patients treated in the US multicenter trials. Such studies are ongoing.

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References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297–319.
2. Scarcelli G, Besner S, Pineda R, Kalout P, Yun SH. In vivo biomechanical mapping of normal and keratoconus corneas. *JAMA Ophthalmol*. 2015;133:480–482.
3. Meek KM, Tuft SJ, Huang Y, et al. Changes in collagen orientation and distribution in keratoconus corneas. *Invest Ophthalmol Vis Sci*. 2005;46:1948–1956.
4. Morishige N, Wahlert AJ, Kenney MC, et al. Second-harmonic imaging microscopy of normal human and keratoconus cornea. *Invest Ophthalmol Vis Sci*. 2007;48:1087–1094.
5. Dawson DG, Randleman JB, Grossniklaus HE, et al. Corneal ectasia after excimer laser keratorefractive surgery: histopathology, ultrastructure, and pathophysiology. *Ophthalmology*. 2008;115:2181–2191.e1.
6. Ambrosio R, Jr. Post-LASIK ectasia: twenty years of a conundrum. *Semin Ophthalmol*. 2019;34:66–68.
7. Ferreira-Mendes J, Lopes BT, Faria-Correia F, Salomao MQ, Rodrigues-Barros S, Ambrosio R, Jr. Enhanced ectasia detection using corneal tomography and biomechanics. *Am J Ophthalmol*. 2019;197:7–16.
8. Randleman JB, Russell B, Ward MA, Thompson KP, Stulting RD. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology*. 2003;110:267–275.
9. Tabbara KF, Kotb AA. Risk factors for corneal ectasia after LASIK. *Ophthalmology*. 2006;113:1618–1622.
10. SX Jin, Dackowski E, Chuck RS. Risk factors for postlaser refractive surgery corneal ectasia. *Curr Opin Ophthalmol*. 2020;31:288–292.
11. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
12. Vinciguerra P, Camesasca FI, Albe E, Trazza S. Corneal collagen cross-linking for ectasia after excimer laser refractive surgery: 1-year results. *J Refract Surg*. 2009;26:486–497.
13. Seiler T, Koufala K, Richter G. Iatrogenic keratectasia after laser in situ keratomileusis. *J Refract Surg*. 1998;14:312–317.
14. Salgado JP, Khoramnia R, Lohmann CP, Winkler von Mohrenfels C. Corneal collagen crosslinking in post-LASIK keratectasia. *Br J Ophthalmol*. 2011;95:493–497.
15. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2007;33:2035–2040.
16. Brooks NO, Greenstein S, Fry K, Hersh PS. Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. *J Cataract Refract Surg*. 2012;38:615–619.
17. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *J Cataract Refract Surg*. 2010;36:2105–2114.
18. Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. *J Cataract Refract Surg*. 2012;38:292–302.
19. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:1282–1290.
20. Greenstein SA, Fry KL, Hersh PS. In vivo biomechanical changes after corneal collagen crosslinking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial. *Cornea*. 2012;31:21–25.
21. Greenstein SA, Hersh PS. Characteristics influencing outcomes of corneal collagen crosslinking for keratoconus and ectasia: implications for patient selection. *J Cataract Refract Surg*. 2013;39:1133–1140.
22. Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:691–700.

23. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:149–160.
24. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK, U.S. Crosslinking Study Group. Multicenter clinical trial of corneal collagen crosslinking for treatment of corneal ectasia after refractive surgery. *Ophthalmology*. 2017;124:1475–1484.
25. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK, U.S. Crosslinking Study Group. United States multicenter clinical trial of corneal collagen crosslinking for keratoconus treatment. *Ophthalmology*. 2017;124:1259–1270.
26. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. *Cornea*. 2011;30:1510–1516.
27. Gordon MO, Steger-May K, Szczotka-Flynn L, et al. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. *Am J Ophthalmol*. 2006;142:923–930.
28. Zadnik K, Barr JT, Steger-May K, et al. Comparison of flat and steep rigid contact lens fitting methods in keratoconus. *Optom Vis Sci*. 2005;82:1014–1021.
29. Zadnik K, Barr JT, Edrington TB, et al. Corneal scarring and vision in keratoconus: a baseline report from the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Cornea*. 2000;19:804–812.
30. Hersh PS, Lai MJ, Gelles JD, Lesniak SP. Transepithelial corneal crosslinking for keratoconus. *J Cataract Refract Surg*. 2018;44:313–322.
31. Baiocchi S, Mazzotta C, Cerretani D, Caporossi T, Caporossi A. Corneal crosslinking: riboflavin concentration in corneal stroma exposed with and without epithelium. *J Cataract Refract Surg*. 2009;35:893–899.
32. Mazzotta C, Balestrazzi A, Traversi C, et al. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. *Cornea*. 2007;26:390–397.
33. Mazzotta C, Traversi C, Paradiso AL, Latronico ME, Rechichi M. Pulsed light accelerated crosslinking versus continuous light accelerated crosslinking: one-year results. *J Ophthalmol*. 2014;2014:604731.
34. Vinciguerra P, Albe E, Trazza S, Seiler T, Epstein D. Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus. *Arch Ophthalmol*. 2009;127:1258–1265.
35. Greenstein SA, Fry KL, Hersh PS. Effect of topographic cone location on outcomes of corneal collagen cross-linking for keratoconus and corneal ectasia. *J Refract Surg*. 2012;28:397–405.
36. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea*. 2006;25:1057–1059.
37. Mazzotta C, Balestrazzi A, Baiocchi S, Traversi C, Caporossi A. Stromal haze after combined riboflavin-UVA corneal collagen cross-linking in keratoconus: in vivo confocal microscopic evaluation. *Clin Exp Ophthalmol*. 2007;35:580–582.
38. Lai MJ, Greenstein SA, Gelles JD, Hersh PS. Corneal haze after transepithelial collagen crosslinking for keratoconus: a Scheimpflug densitometry analysis. *Cornea*. 2020;39:1117–1121.
39. Seifert F, Seufert F, Hommes D, et al. Ten year results after corneal collagen crosslinking with riboflavin and UV-A irradiation (CXL) for keratoconus – when to repeat CXL? *Invest Ophthalmol Vis Sci*. 2019;60:339.
40. 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.
41. Nicula C, Nicula D, Pop RN. Results at 7 years after cross-linking procedure in keratoconic patients. *J Fr Ophtalmol*. 2017;40:535–541.
42. Raiskup F, Theuring A, Pillunat LE, Spoerl E. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. 2015;41:41–46.
43. Shafik Shaheen M, Lolah MM, Pinero DP. The 7-year outcomes of epithelium-off corneal crosslinking in progressive keratoconus. *J Refract Surg*. 2018;34:181–186.