Corneal Collagen Cross-Linking: A Review of 1-Year Outcomes

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Purpose: To review outcomes of corneal collagen cross-linking (CXL) for keratoconus (KC) or ectasia in a cornea subspecialty practice.

Methods: Results from controlled clinical trials at a single site cornea subspecialty practice, including 104 eyes (66 KC and 38 ectasia). Outcomes and the natural course of changes in postoperative parameters including maximum keratometry (K_{Max}), uncorrected visual acuity (UCVA), and best-corrected visual acuity (BCVA) over 12 months are reviewed. In addition, corneal topography indices, wavefront higher-order aberrations, and the natural history of wound healing after CXL are discussed. Characteristics associated with CXL outcomes are reviewed as well. In predicting treatment outcomes for K_{Max} and BCVA, the preoperative patient characteristics examined were gender, age, disease group, cone location, thinnest pachymetry, UCVA, BCVA, and K_{Max}.

Results: At 1 year, an average of 1.7 diopter (D) flattening in K_{Max} was found. Mean BCVA improved slightly more than 1 line (from 0.35 ± 0.24 to 0.23 ± 0.21 logMAR). All postoperative parameters similarly follow a trend of worsening between baseline and 1 month, and improvement thereafter. More specifically, quantitative improvements are typically seen at 3 months and may continue between 3 and 12 months. A review of baseline patient characteristics indicated that (1) eyes with preoperative K_{Max} of 55 D or steeper were 5.4 times more likely to gain 2 D or more of K_{Max} flattening at 1 year after CXL, and (2) eyes with preoperative BCVA of 20/40 or worse were 5.9 times more likely to gain 2 or more Snellen lines at 1 year after CXL. Conversely, no baseline characteristic was found to correlate with treatment complications of continual topographic steepening or loss of vision.

Conclusions: Corneal collagen cross-linking seems to be effective in decreasing progression of KC, with improvements in optical measures in many patients. Postoperative parameters discussed within this review followed a seemingly reproducible trend in their natural course over 12 months. Generally, the trend observed was immediate worsening between baseline and 1 month, resolution at approximately 3 months, and improvement thereafter. In predicting outcomes after CXL, no patient characteristics showed correlations with negative treatment outcomes such as loss of vision or continual topographic steepening. However, steeper K_{Max} ($\geq$55 D) and poorer BCVA ($\leq$20/40) at the time of treatment correlated with better postoperative K_{Max} and BCVA outcomes at 1 year, respectively. These outcome predictors should be considered when offering CXL to patients with KC or postoperative corneal ectasia.

Key Words: Corneal collagen cross-linking—Treatment outcomes/decisions—Keratoconus—Corneal ectasia.

Biomechanical weakening in keratoconus (KC) and postoperative corneal ectasia results in focal protrusion of the corneal apex and consequent corneal surface optical irregularity. Progressive visual impairment and potential blindness can occur typically because of the induced irregular astigmatism, higher-order aberrations (HOA), and stromal scarring.[1–3] Conventional spectacle lenses often fail to achieve visual improvement, and gas-permeable contact lenses are usually needed to rehabilitate visual functions required to perform daily living tasks. As the disease severity advances, generally from the second through fifth decade of life, contact lens intolerance may develop, necessitating penetrating keratoplasty (PK) in 10% to 20% of cases.[1,4–6] Physicians may help patients to maintain or improve their quality-of-life if treatment options can be offered to slow down or halt disease progression, which may also enable patients to defer the need for corneal grafts.

Recently, corneal collagen cross-linking (CXL) has emerged as a promising management option for KC and corneal ectasia. It has been repeatedly demonstrated in successfully stabilizing progressive corneal ectatic disorders with good safety profile.[7–13] In CXL, the interaction of ultraviolet-A (UVA, 365 nm) and riboflavin leads to cross-linking within the collagen and intracellular matrix of the stroma, most predominantly in the anterior 300 μm, resulting in strengthening of the cornea.[12,14,15]

In addition to the principal goal of disease stabilization, investigators have also reported improvements in topographic, aberrometric, refractive, and visual outcomes after CXL.[16–20] Given its relatively low treatment failure and complication rates, CXL has become widely accepted, internationally, as one of the frontline treatment options for KC and postoperative ectasia. Notwithstanding, continual disease progression and further loss of vision have been observed in some patients after CXL, but specific factors have yet to be clearly elucidated in forecasting treatment outcomes. Thus, the main purpose of this review is to summarize CXL results released by a single U.S. surgical center regarding the natural courses of postoperative parameters and their implications to both patient selection criteria and treatment outcomes.

PATIENTS AND METHODS

We review outcomes of CXL clinical trial results of a U.S. corneal subspecialty center (CLEI Center for Keratoconus, The

Cornea and Laser Eye Institute-Hersh Vision Group, Teaneck, NJ). A total of 104 eyes (66 KC and 38 ectasia) were included, which make up the largest patient database reported by a single U.S. center to date. The course of postoperative parameters across 1 year and preoperative predictors for treatment outcomes are reviewed.

Patients with progressive KC or ectasia after laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) were enrolled as part of a multicenter prospective randomized controlled clinical trial. This study was approved and monitored by an investigational review board, was U.S. Health Insurance Portability and Accountability Act compliant, and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

The inclusion criteria included patients aged 14 years or older and axial topography consistent with KC or corneal ectasia. Progressive KC or ectasia was defined as 1 or more of the following changes over a period of 24 months: an increase of 1.0 diopter (D) or more in the steepest keratometry, 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. Exclusion criteria included a history of corneal surgery (except previous LASIK or PRK), chemical injury, delayed epithelial healing, and a corneal thickness less than 300 μm.

Postoperative parameters monitored over a 12-month period included maximum keratometry (K_{Max}) derived from computerized corneal topography analysis, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), topographic indices, HOA, corneal haze, and pachymetry. In predicting postoperative outcomes of K_{Max} and BCVA, the preoperative patient characteristics evaluated were gender, age, disease group, cone location, pachymetry, K_{Max}, UCVA, and BCVA. Subject number in each of the above subgroups varied depending on the number of eyes that had reached the end point of 1 year at the time when data analysis was performed.

CXL TREATMENT PROTOCOL

The author (P.S.H.) treated all 104 eyes using the surgical protocol first described by Wollensak et al.[7] After application of topical anesthesia, mechanical debridement of corneal epithelium was performed over a central 9 mm treatment zone. Initial loading of riboflavin (0.1% in 20.0% Dextran T500 Solution; Medio-Cross; Peschke Meditrade, GmbH, Hunenberg, Switzerland) took place by applying topical riboflavin in 2-min intervals during the initial 30 min. At the conclusion of the loading phase, stromal riboflavin saturation is confirmed through slitlamp examination by P.S.H., as seen in Fig. 1A,B.

Ultrasonic pachymetry was performed to ensure a minimum corneal thickness of 400 μm before UVA light exposure.[21] If less than 400 μm, hypotonic riboflavin (0.1% in sterile water, Medio Cross hypotonic) was instilled with 10-s intervals over a 2-min session; this was repeated until 400 μm was obtained in pachymetry measurement. Once adequate tissue thickness is confirmed, corneal treatment zone was then exposed to a UVA source emitting selective wavelength of 365 nm (UVX system; IROC Innocross AG, Zurich, Switzerland) at an irradiance of 3.0 mW/cm². Riboflavin drops continued to be administered every 2 min during this 30-min UVA exposure phase.

At the end of each treatment, antibiotic and corticosteroid drops were instilled before the placement of a therapeutic bandage lens (ACUVUE OASYS, Vistakon, Johnson & Johnson Vision Care, Inc.). Therapeutic lens was removed within 3 to 5 days, pending epithelial healing. In addition, topical antibiotic and corticosteroid usage were continued for 1 week and 2 weeks, respectively (gatifloxacin 0.5% ophthalmic solution and prednisolone acetate 1% ophthalmic suspension; Allergan, Inc., Irvine, CA).

OUTCOME MEASUREMENTS

Keratometry

Keratometry measurements were derived from a rotating Scheimpflug topography instrument (Pentacam; Oculus, Inc.). K_{Max} changes over the 1-year period (baseline, 1, 3, 6, and 12 months) were assessed. In addition to establishing postoperative trends in keratometry, these data were also used to explore potential relationships between the keratometric changes across all visits and the final visual and keratometric outcomes at 1 year.

Visual Acuity

The uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were measured over the period of 1 year (baseline, 1, 3, 6, and 12 months). Both UCVA and BCVA testing were performed under controlled lighting conditions through high-contrast Sloan letters on a Lighthouse Early Treatment of Diabetic Retinopathy Study visual acuity chart (second edition). All patients were tested monocularly at a standard testing distance of 4 m. However, if no letter could be read at 4 m, visual acuity (VA) test was then conducted at a shorter reference distance of 2 m to increase visual angles subtended by the Sloan letters. Visual acuity measurements were subsequently converted to logMAR values.[22] Additionally, postoperative changes in both BCVA and UCVA were analyzed to determine if they have predictive values to final post-CXL outcomes at 1 year.

Topography Indices

A rotating Scheimpflug camera system (Pentacam; Oculus, Inc.) was used to generate 7 topography indices, reflecting the level of corneal irregularity. Indices data were collected across all visits within a 1-year period (baseline, 1, 3, 6, and 12 months). The indices generated by the Scheimpflug unit were as follows: Index of Surface Variance (a general measure of anterior surface regularity), Keratoconus Index (index of severity for KC), Central Keratoconus Index (index of severity for KC found in central area designated by device software), Index of Vertical Asymmetry (difference between corneal curvature at two designated superior and inferior locations), Minimum Radius of Curvature (smallest value of radius localized in tested field), Index of Height Asymmetry (difference between elevation points at two designated superior and inferior locations), and Index of Height Decentration (vertical decentration at point of maximum corneal elevation). In addition, changes in KC indices during postoperative period were used to explore for possible correlations with post-CXL topographic and VA outcomes.

Higher-Order Aberrations

Total ocular HOA were measured over a 6.5-mm pupillary zone across the 1-year period (baseline, 1, 3, 6, and 12 months) through a Shack-Hartmann aberrometer (LadarWave, Alcon Laboratories, Inc.). Higher-order aberrations data collected were total HOA
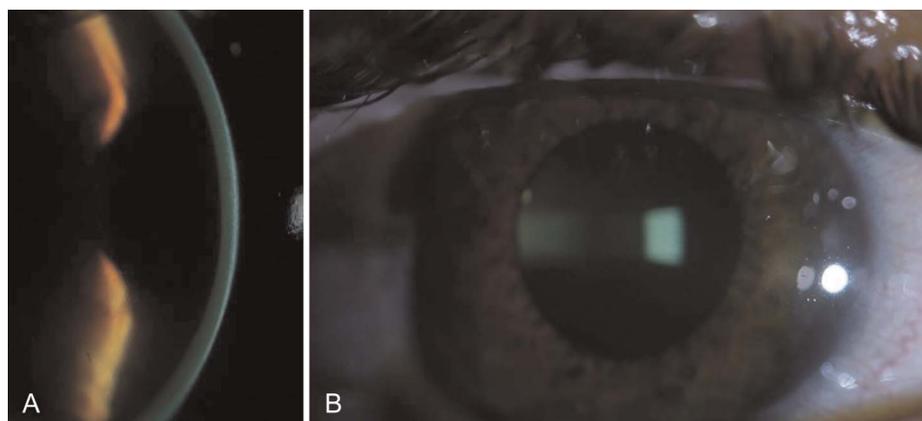
FIG. 1. (A) Corneal saturation with riboflavin observed through a slitlamp. (B) Presence of riboflavin in anterior chamber after riboflavin loading phase as seen through a slitlamp. `full color online`

(third to sixth order), spherical aberrations, third-order coma, vertical coma, horizontal coma, total coma (combined third and fifth order), and trefoil. Moreover, changes in HOA and changes in VA between the baseline and 12-month visits were analyzed to explore the predictive values of changes in the natural course of HOA.

Corneal Thickness

A rotating Scheimpflug camera device (Pentacam; Oculus, Inc.) was used to measure the thinnest pachymetric point within the central 9-mm diameter area across a 1-year period (baseline, 1, 3, 6, and 12 months). Ultrasound pachymetry (Sonagage, Inc., Cleveland, OH) was used only at preoperative examination to confirm the corneal thickness data from Scheimpflug device during the same visit; efforts were taken by the examiner to localize the area of apex using both slitlamp observation and the maps generated by the Scheimpflug scanning software. In addition to monitoring the natural course of changes in corneal thickness after CXL, these data are also used in a subgroup analysis to explore its correlations to postoperative changes in UCVA, BCVA, and K_{Max}.

Corneal Haze

To quantitate CXL-associated corneal haze, corneal densitometry using a rotating Scheimpflug camera was undertaken (Pentacam; Oculus, Inc.). Scheimpflug images were taken over the treatment zone throughout the monitoring period of 1 year (baseline, 1, 3, 6 and 12 months); densitometry scores from the central 4 mm area along the same meridian were then used for objective comparison between visits.

Corneal haze was also subjectively graded at slitlamp by the principle examiner (P.S.H.) at each examination visit. This secondary measurement was compared with densitometry scores to further enhance clinical confidence in the objective data collected. The slitlamp grading scheme proposed by the examiner (P.S.H.) used a scale from 0 to 4: 0+—clear cornea with no evidence of stromal haze, 1+—cornea with focal areas of minimal stromal haze, 2+—cornea with diffused areas of minimal stromal haze, 3+—cornea with focal or diffuse areas of dense stromal haze that somewhat obscures iris structure detail, 4+—cornea with focal or diffuse areas of dense stromal haze that obscures iris structure detail[23] (Fig. 2A,B).

The absolute corneal haze value at each time point and its natural course across the entire 1-year period were also analyzed for possible associations with outcome parameters such as BCVA, K_{Max}, mean Keratometry, and thinnest pachymetry.

Preoperative Patient Characteristics Associated With CXL Outcomes

In addition to tracking the natural course of the above postoperative outcome variables, preoperative patient attributes were also evaluated to determine whether any baseline characteristic correlated with final CXL treatment outcome at 1 year. Preoperative patient attributes reviewed were age, gender, ocular diagnosis, UCVA, BCVA, cone location, corneal thickness, and K_{Max}. Clinical success or failure was defined by improvement or worsening in keratometry or VA. A BCVA gain of 2 or more lines at 12 months was qualified as visual improvement, whereas a loss of 1 line or more was considered as loss of vision; similarly, a 2 D or more flattening in K_{Max} was defined as clinical improvement, whereas steepening of 1 D or more in K_{Max} was considered as CXL treatment failure.

RESULTS OF CXL

### Topography Outcomes

Keratometry

Seventy-one eyes (49 KC and 22 ectasia) were included in this subgroup analysis. Keratometric data were collected using a Scheimpflug device across all time points (baseline, 1, 3, 6, and 12 months). Average flattening in K_{Max} at 1 year was found to be 1.7 D. K_{Max} remained stable or decreased in 90.2% of eyes after CXL; by contrast, K_{Max} steepened in the remaining 9.8% of eyes, with 4.2% eyes showing 2 D or greater steepening.

A significant steepening in K_{Max} was observed at 1 month ($P<0.001$), which was succeeded by a significant keratometric flattening between study intervals of 1 to 3 months and 3 to 6 months (Fig. 3). Difference in K_{Max} data between 6 and 12 months was not found to be statistically significant; however, the mean K_{Max} reduction of 1.7 D at 12 months obtained statistical significance when compared with baseline ($P<0.001$).[11]

Topographic Indices

Seventy-one eyes (49 KC and 22 ectasia) were included in this subgroup analysis. At 1 year, 4 of the 7 Scheimpflug topographic indices showed significant improvement when compared with their baseline values: ISV, IVA, R_{min}, and KI (all $P<0.001$). Explanations of the topographic indices were aforementioned under the section of Outcome Measurements.

FIG. 2. (A) Grade I+ CXL-associated haze. (B) Grade II+ CXL-associated haze. CXL, corneal collagen cross-linking. [full color online]
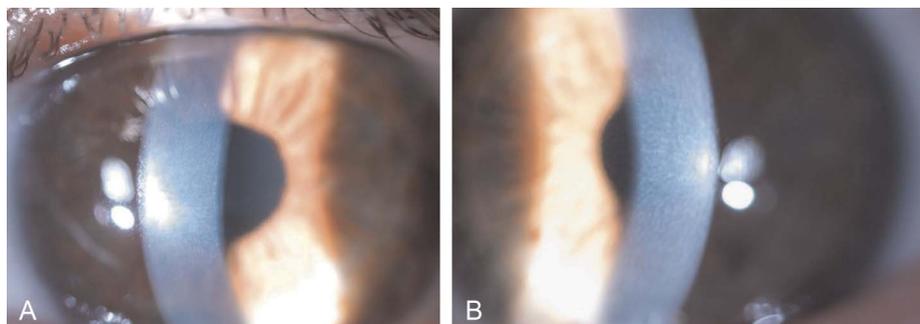
The general trends in the natural courses of these indices were significant worsening at 1 month, followed by significant improvement between both the intervals of 1 to 3 months and 3 to 6 months. Thereafter, no meaningful differences were found between 6 and 12 months. There were no correlations found between improvements in BCVA and KC indices at 1 year.[19]

Aberrometric Outcomes

Higher-Order Aberrations

Ninety-six eyes (64 KC and 32 ectasia) were included in this subgroup analysis. At the end of 1 year, significant improvement in total HOA, spherical aberrations, third-order coma, total coma, and trefoil were observed. No correlations were found between any of the above HOA measurements and postoperative changes in both UCVA and BCVA.[20]

Visual Acuity Outcomes

Visual Acuity

Seventy-one eyes (49 KC and 22 ectasia) were included in this subgroup analysis. Mean BCVA improved by slightly more than 1 Snellen line, improving from 0.35 logMAR at baseline to 0.23 logMAR at 12 months, which reached statistical significance ($P<0.001$).

BCVA remained the same or improved from baseline presentation in 91.5% of eyes, whereas only 1.4% of eyes had a loss of 2 or more lines. A review of BCVA time course (Fig. 4) showed a slight worsening at 1 month ($P=0.33$), with significant improvements found

between both study intervals of 1 to 3 months and 3 to 6 months (both $P<0.01$); there was no statistical significance between 6 and 12 months ($P=0.27$).

There was an average of 1 line improvement in UCVA, from 0.84 logMAR at baseline to 0.77 logMAR at 12 months ($P=0.04$). UCVA remained unchanged or improved in 81.7% of eyes, whereas 8.5% of eyes reported a loss of 2 or more UCVA lines. The time course of UCVA mirrored the trend of BCVA, where mild worsening at 1 month and improvement thereafter was seen. Nonetheless, the only study time point where one observes a significant UCVA change was when comparing 12-month visit with baseline. Although we have previously reported subjective improvements in patients' visual acuities occurring after CXL[24], this subgroup analysis did not yield correlations between objective acuity measurements over time and post-operative outcome at 1 year.[11]

Morphologic and Wound-Healing Outcomes

Corneal Thickness

Eighty-two eyes (54 KC and 28 ectasia) were included in this subgroup analysis. Significant corneal thinning ($P<0.01$) was found between baseline and 1 month, which was followed by further thinning between 1 and 3 months ($P<0.002$). Meaningful corneal thickening was observed between 3 and 6 months ($P<0.001$), with no significant differences found between 6 and 12 months ($P=0.13$). The trend of this natural course can be seen in
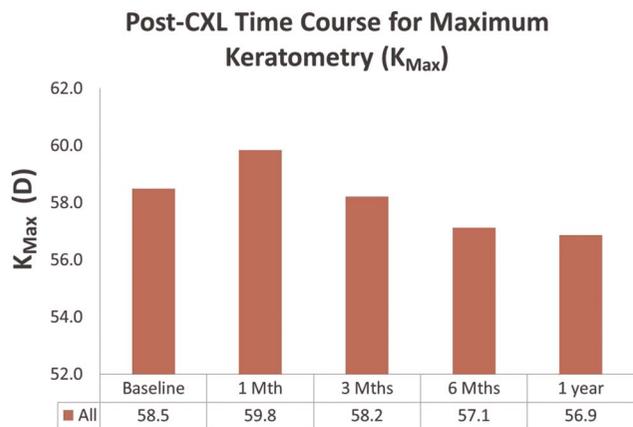
Post-CXL Time Course for Maximum Keratometry (K$_{Max}$)

	Baseline	1 Mth	3 Mths	6 Mths	1 year
All	58.5	59.8	58.2	57.1	56.9

FIG. 3. Natural course in K$_{Max}$ after CXL across the period of 1 year. CXL, corneal collagen cross-linking; K$_{Max}$, maximum keratometry on topography. [full color online]

Post-CXL Time Course In UCVA and BCVA

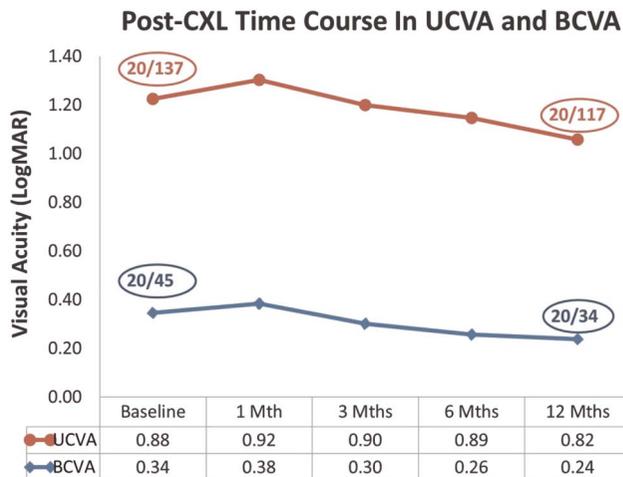|	Baseline	1 Mth	3 Mths	6 Mths	12 Mths
UCVA	0.88	0.92	0.90	0.89	0.82
BCVA	0.34	0.38	0.30	0.26	0.24

FIG. 4. Natural course in UCVA and BCVA after CXL across the period of 1 year. CXL, corneal collagen cross-linking; BCVA, best-corrected visual acuity; UCVA, uncorrected visual acuity. [full color online]
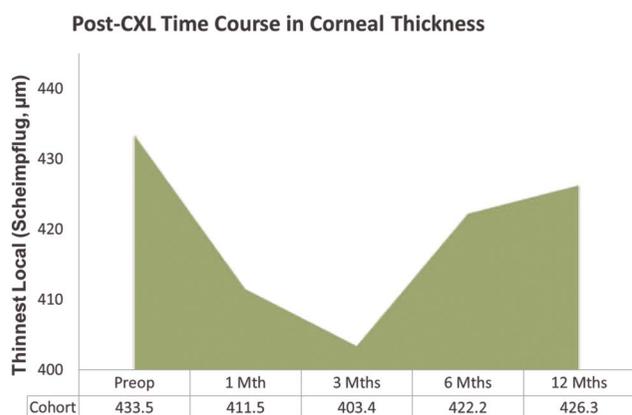
Post-CXL Time Course in Corneal Thickness

	Preop	1 Mth	3 Mths	6 Mths	12 Mths
Cohort	433.5	411.5	403.4	422.2	426.3

FIG. 5. Natural course in corneal thickness after CXL across the period of 1 year. CXL, corneal collagen cross-linking. full color online

Figure 5. It is of note that pachymetric data at 1 year remained slightly decreased compare to baseline (P=0.01). Analysis of the natural course in corneal thickness over time did not yield any correlation to postoperative changes in UCVA, BCVA, or K_{Max}.[25]

CXL-Associated Corneal Haze

Fifty patients (31 KC; 19 ectasia) were included in this subgroup analysis. CXL haze had been noted in more than 90% of eyes; here, a Scheimpflug camera device was used to document the natural course of this post-operative finding. The Scheimpflug device graded corneal density on a scale from 0 to 100, which allowed for an objective measurement for corneal haze. There was a significant increase in mean densitometry score or corneal haze between baseline and 1 month (P<0.001). Although such trend appeared to plateau between 1 and 3 months (P=0.15), a significant decrease in haze was seen between study visits of 3 and 6 months (P<0.001) and 6 and 12 months (P<0.001). Analysis did not render clear correlations between changes in corneal haze and changes in post-operative outcome parameters such as BCVA, K_{Max}, mean keratometry, and thinnest pachymetry.[23]

Preoperative Characteristics Associated With CXL Outcomes

One hundred four eyes (66 KC and 38 ectasia) were included in this subgroup analysis. This subgroup analysis was performed to explore the predictive values of preoperative patient characteristics to postoperative keratometric and visual outcomes at 1 year. Preoperative patient data included were age, gender, disease group, UCVA, BCVA, cone location, corneal thickness, and K_{Max}.[26,27]

In predicting for a positive keratometric outcome at the end of 12 months, the preoperative K_{Max} was revealed as the lone significant predictor for such improvement. Eyes with preoperative K_{Max} of 55 D or steeper appeared to be 5.4 times more likely to have 2 D or more flattening in postoperative K_{Max} at 1 year (OR=5.4; 95% confidence interval [CI], 2.1–14.0). Conversely, no strong predictor was found in predicting CXL treatment failure, as all eyes were equally likely to experience K_{Max} steepening at 1 year after CXL treatment.

Preoperative BCVA was shown to be the sole baseline factor with significant correlation to positive visual outcomes at 1 year. Eyes with preoperative BCVA of 20/40 or worse appeared to be 5.9 times more likely to improve 2 or more Snellen lines at 1 year after CXL. Comparatively, there was a suggestive trend that eyes with baseline BCVA better than 20/40 were potentially associated with the negative visual outcome of losing 1 or more BCVA lines at 12 months (OR=0.9; CI, 0.24–3.40); however, this observation failed to achieve statistical significance.[27]

DISCUSSION

Though not approved by FDA in the United States, corneal collagen cross-linking, internationally, has emerged as a frontline treatment option for KC and ectasia, particularly in those patients with documented disease progression. Corneal collagen cross-linking has been purported to enhance corneal biomechanics[14,28] and stabilize these progressive corneal ectatic disorders with good clinical safety profile.[7–13] Improvements in topographic, visual, refractive, and aberrometric parameters have also been reported; notwithstanding, continual disease progression and further loss of vision have been observed in some patients after CXL treatment.[11,13,16–20]

It would also be beneficial to patient management if physicians could more accurately describe the natural course at different postoperative time points, which may help to establish proper patient expectations regarding treatment responses and prognosis with post-operative visual rehabilitation options such as contact lenses. Precisely, the intention of this review is to shed light on the above outcome variables by reporting on the salient trends observed in our patient cohort during the initial 12 months immediately after receiving CXL.

Topography-Derived Keratometry

An average of 1.7 D flattening in K_{Max} was found at 1 year. Our finding of K_{Max} improvement supports findings from other studies that also have reported K_{Max} flattening ranging from 1.42 to 2.01 D.[7,16,23] While monitoring the course of postoperative keratometric responses in this patient cohort, we further observed a trend of significant K_{Max} steepening at 1 month that was succeeded by significant K_{Max} flattening between the intervals of 1 to 3 months and 3 to 6 months. The trend of K_{Max} flattening between 6 and 12 months appeared to plateau and did not reach statistical significance. This is in contrast with those findings reported by Raiskup-Wolf et al.,[16] and Caporossi et al.[18] who described continual flattening in K_{Max} even beyond 1 year.

Keratoconus Indices

Given the correspondence in the postoperative keratometric changes detailed in our patient cohort and in the literature, it is of particular interest to explore if similar relationships also exist among topographic KC indices measured during the same postoperative period. At 12 months after CXL, 4 of the 7 Scheimpflug indices significantly improved: ISV, IVA, R_{min}, and KI. This somewhat corroborates with previous findings reported by Koller et al., where 4 Pentacam indices were also found to be improved at 1 year after CXL: R_{min}, KI, CKI, and IHA.[29] It is not clear why different indices improved in different patient population, and it will require further future studies to delineate the differences in the responses of these indices.

The general trend observed in the natural course of other postoperative parameters described thus far in our patient cohort can also be seen with these KC indices: significant worsening in

these KC indices at 1 month, followed by improvements thereafter until 6 months, which then plateaus between 6 and 12 months. Once again, there were no correlations found between improvements in KC indices and BCVA outcome at 1 year, although many patient cases in the literature have reported concomitant improvements in corneal topography and VA after CXL.[16–18]

Higher-Order Aberrations

The improved topographic characteristics after CXL, both in K_{Max} and in KC indices, may indicate reduced corneal irregularity and subsequently decreased HOA. A detailed review of aberrometric outcome parameters showed significant improvements. The improved HOA domains recorded are total HOA, spherical aberrations, third-order coma, total coma, and trefoil. Similar findings of reduced total HOA, spherical aberrations, and coma have also been reported Vinciguerra et al.[17] Regardless, no correlations were found in this patient cohort between improvements in HOA and postoperative outcomes in UCVA and BCVA at 1 year.

Visual Acuity

Clinical studies have shown that CXL may also ameliorate VA in addition to topographic and aberrometric outcomes.[16–18] Changes in visual outcome were carefully documented over time because a comprehensive understanding of postoperative time course in visual responses will greatly help physicians in setting realistic patient expectations after CXL.

The time courses of UCVA and BCVA mirrored each other; again, both followed a similar trend as other postoperative parameters discussed earlier. Worsening in VA can be observed at 1 month; thereafter, a trend of significant improvements was observed between 1 to 3 months and 3 to 6 months. This trend of improvement is maintained up to 6 months, with no significant differences found in VA outcomes between 6 and 12 months.

Mean UCVA improved approximately by 1 Snellen line, from 0.84 logMAR at baseline to 0.77 logMAR at 12 months. It remained unchanged or improved in 81.7% of eyes, whereas 8.5% of eyes reported a loss of 2 or more UCVA lines. Perhaps more importantly, mean BCVA gained slightly more than 1 Snellen line, improving from 0.35 logMAR at baseline to 0.23 logMAR at 12 months. Ultimately, BCVA remained the same or improved from baseline presentation in 91.5% of eyes, whereas 1.4% of eyes reported a loss of 2 or more lines.

Corneal Haze

Stromal haze was observed in more than 90% of the eyes in this cohort[23]; indeed, this clinical appearance has been widely noted after CXL.[13,30,31] Raiskup et al.[32] suggested that the density of post-CXL haze may be higher in those with more advanced KC. To date, despite utilization of confocal microscopy, the etiologies of CXL-associated haze and its implications to treatment outcomes have been elusive.

At 1 year, possible correlations were initially found between absolute degrees of haze on densitometry and thinner pachymetry, poorer UCVA and BCVA, and steeper mean keratometry and K_{Max} values. Nonetheless, such correlations were not confirmed by further analyses between changes in haze and changes in other clinical measurement outcomes over time. Moreover, it is noteworthy that confocal microscopy studies were also inconclusive in determining

the relationship between the presence of stromal haze and visual outcomes in subjects treated with CXL.[33] The clinical significance of corneal haze, therefore, may need to be further explored via future studies.

Corneal Thickness

Progressive corneal thinning has generally been regarded as a sign of worsening in keratectatic diseases, and yet, such events have been described in many cases after CXL treatment.[9,17,18,29] Therefore, understanding the natural history of corneal pachymetry after CXL can serve as a foundation for proper evaluations of this procedure's efficacy and safety.

The natural course of the pachymetric changes across the 12 months corresponded well with the time courses of corneal haze: significant worsening or thinning between baseline and 3 months with subsequent improvement between 3 and 12 months; however, pachymetric data still remained mildly decreased at 1 year in comparison to baseline. The underlying mechanisms of corneal thickness changes in its postoperative course are yet unclear. Further analysis did not render clear correlations between changes in corneal thickness and changes in postoperative UCVA, BCVA, or K_{Max}.[25]

Preoperative Patient Characteristics and Implications to Selection Criteria

In general, VA appeared to improve after CXL, although the militating factors of this positive outcome are not currently well understood. Therefore, preoperative characteristics were subsequently investigated in search of potential clinical correlates for post-CXL K_{Max} and VA outcomes. Delineating such predictive factors can aid the refinement of inclusion criteria, which may further increase safety profile of this promising management option.

Preoperative patient data included in this review were age, gender, disease group, UCVA, BCVA, cone location, corneal thickness, and K_{Max}. Although no baseline patient attributes seemed to strongly predict for the undesirable outcome of topographic steepening after CXL; however, treated eyes with preoperative K_{Max} of 55 D or steeper were actually found to be 5.4 times more likely to experience K_{Max} flattening of 2 D or more. A previous study had also similarly reported a preoperative K_{Max} greater than 54 D being associated with greater tendency of postoperative topographic improvement.[34]

In terms of postoperative BCVA outcome, preoperative BCVA was the sole baseline factor that consistently emerged as a robust postoperative BCVA predictor. Namely, eyes with entry BCVA of 20/40 or worse appeared to be 5.9 times more likely to improve 2 or more Snellen lines at 1 year after CXL treatment. Conversely, eyes with entry BCVA better than 20/40 were found to be weakly associated with the negative outcome of losing 1 or more BCVA lines at 12 months; however, this patient variable of BCVA better than 20/40 failed to achieve statistical significance.[27]

Thus, it would appear that keratoconus and ectasia eyes with higher level of disease severity in our cohort, whether presenting with 55 D or greater in K_{Max} or 20/40 or worse in VA, have greater potential for topographic and visual improvement after CXL. Such findings may make the decision process more straightforward in offering CXL as a treatment option to those with more advanced disease staging, and particularly in those patients who present with documented disease progression as patients included in this cohort (Fig. 6). Of note, a separate report[6] from the Collaborative Longitudinal Evaluation of Keratoconus Study (CLEK Study) found that
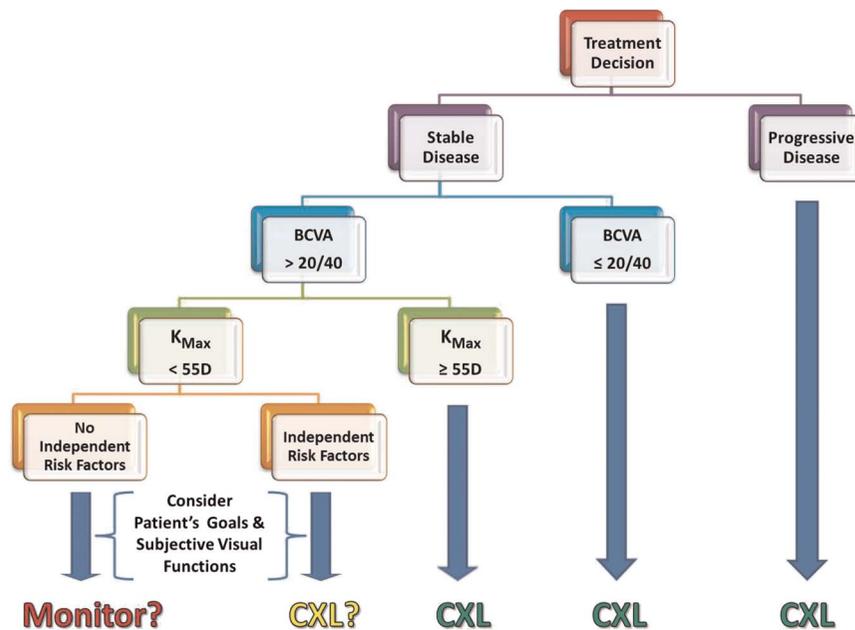
FIG. 6. A tentative guide to CXL treatment considerations. BCVA, best-corrected distance visual acuity; CXL, corneal collagen cross-linking; K_{Max}, maximum keratometry on topography. `full color online`

eyes with BCVA worse than 20/40 and steep keratometric value of greater than 52 D were associated with increased risk for PK. Therefore, using the inclusion criteria of BCVA of 20/40 or worse and/or K_{Max} steeper than 55 D to guide CXL treatment decision may also render the additional clinical benefit in potentially deferring the need for PK in this patient subpopulation.

Corneal collagen cross-linking considerations may be more complex in KC or postoperative ectasia patients with stable disease, BCVA better than 20/40, and/or K_{Max} flatter than 55 D. On one hand, CXL has shown to be highly successful in stabilizing KC and ectasia with very low complication rate; however, these patients with higher visual functioning may also be more sensitive to the sequelae of negative treatment outcomes. No preoperative patient factors were found to predict the undesirable consequences of further visual loss and/or continual topographic steepening. Further studies will be required to clarify the presence of other independent risk factors to guide the management decision of whether to closely monitor this group of patient or to offer CXL treatment even before disease progression is detected. Of note, Davis et al.[35] from CLEK Study group reported on patient characteristics associated with further loss of vision: (1) better BCVA, (2) steeper corneal curvatures, (3) presence of Vogt striae, and (4) non-Hispanic white race. These independent risk factors, in addition to other risk factors that may arise through future research efforts, should be kept in mind when considering CXL treatment benefits for the group of patients presenting with stable disease, relatively flat corneal curvatures, and good BCVA.

It should be noted that halting disease progression may not be the primary goal of CXL treatment in these patients with stable disease entity. Instead, CXL may offer the additional benefits of possibly preventing or deferring the future need for corneal transplantation in some of these patients where the onset of disease progression can be greatly delayed or potentially prevented. Moreover, if positive treatment outcomes of further visual and/or topographic improvements can be obtained, this may potentially provide better spectacle or contact lens experiences during postoperative period. As an example of examining post-operative patient experiences with contact lenses after CXL, our center conducted a small prospective randomized clinical trial where 10 subjects (8 KC and 2 ectasia) were fit in a hybrid contact lens design (Clearkone, SynergEyes, Inc., Carlsbad, CA) at 3 months after having undergone CXL (unpublished data; Chang CY, Shin A, Hersh PS, 2012). Prior to CXL procedure, only 62.5% eyes (5/8) claimed partial or good contact lens tolerance whereas 90% eyes (9/10) reported satisfactory contact lens tolerance at the conclusion of this contact lens study. Although this may serve as early evidence of possibly improved contact lens tolerance in post-CXL patients, it is also important to remember the limitations of using only one lens design with a small subject pool. As the cumulative number of patients undergoing CXL increases in United states, future studies with larger sample size, more diversified lens designs, and longer study duration can be orchestrated to investigate the possible influences of CXL treatment to postoperative contact lens rehabilitation in the KC and ectasia population.

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