Corneal Crosslinking in Refractive Corrections

Viral V. Juthani[1] and Roy S. Chuck[1]

[1] Department of Ophthalmology and Visual Sciences, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA

Corneal crosslinking has been well-described for the treatment of progressive corneal ectasias. Although the goal of treatment in these conditions is the decrease in the risk of progressive steepening of the cornea, studies have shown that flattening of the cornea is achieved in many cases. This finding has led to the postulation that corneal crosslinking may have a potential role in the primary treatment of myopia, and that targeted approaches with more specialized patterns of treatment may be used as primary treatments for astigmatism and hyperopia. In this review, we provide a summary of the clinical and laboratory-based studies evaluating corneal crosslinking as a primary, solitary, refractive treatment for myopia, hyperopia, and astigmatism. Clinical studies thus far are small case series. The primary benefit of refractive corneal crosslinking seems to be the correction of small myopic or hyperopic refractive errors without the need for corneal incisions or tissue removal.

Translational Relevance: The clinical application of corneal crosslinking relies on a good understanding of the biomechanical effect of various treatment parameters on corneal tissue. We discuss the results of the clinical and laboratory studies evaluating corneal crosslinking as a primary refractive treatment.

Introduction

Modern corneal refractive surgery involves the reshaping of the cornea using excimer laser ablation technology with or without a corneal flap, or the extraction of a corneal lenticule from within the stroma, using the femtosecond laser. These modalities result in permanent alterations and loss of tissue, and the potential for biomechanical weakening of the cornea. They also carry their own sets of unique advantages and disadvantages. In the case of surface ablation procedures, there is often significant associated discomfort to the patient, and increased risks of corneal haze and infection. In flap-based procedures, flap-related complications may occur, including flap dislocation, striae, and epithelial ingrowth. Small incision lenticule extraction, or SMILE, also carries risks of retained debris at the interface, inflammation, and infection. Owing to these potential risks, patients may be poor candidates for refractive surgery or may be unwilling to accept the risks and continue with spectacle correction or contact lenses. The risk of corneal ectasia has also been a significant barrier to patient accep-

tance of refractive surgery. Nonablative modalities such as orthokeratology, conductive keratoplasty), and laser thermokeratoplasty were, therefore, introduced; however, these approaches are limited in their stability over time. The use of corneal crosslinking in conjunction with orthokeratology was explored in a few clinical studies. The duration of effect was still limited likely because the effect is secondary to epithelial redistribution; however, the rate of regression may be diminished.[1–3] The holy grail of corneal refractive surgery is therefore a procedure in which a permanent, stable, and painless change to the corneal shape is achieved in a nonablative and nonincisional manner.

Corneal collagen crosslinking (CXL) was first described in 1997 by Spoerl et al.[4] It has been subsequently used for many years as a means of stabilizing ectatic corneas in keratoconus and iatrogenic corneal ectasia. In this procedure, covalent bonds are created between amino groups within the collagen molecules or between proteoglycan core proteins and collagen to make the anterior corneal stroma more rigid.[5] Riboflavin, which acts as a photosensitizer in the crosslinking reaction, is applied topically to the cornea and allowed to penetrate into the corneal stroma.

Ultraviolet-A (UVA) light is then used to excite the riboflavin, causing it to interact with molecular bonds in the collagen fibers, and inducing them to crosslink, which enhances the diameter and rigidity of the fibers.[6,7] A more recent study has also demonstrated that riboflavin–UVA crosslinks most likely also occur within proteoglycan core proteins and between proteoglycan core proteins attached to an individual fibril or adjacent fibrils.[8] Over the years, numerous studies have observed anterior corneal flattening in cases of corneal ectasia treated with CXL.[9–11] An improved understanding of CXL has subsequently led to the theorization that CXL could also be used in healthy corneas to produce a predictable and reproducible alteration in corneal shape and be used to treat myopia, hyperopia, and astigmatism. The original idea of using CXL for primary refractive correction originated based on the findings of Hersh et al.[12] in 2011 that both uncorrected distance visual acuity and corrected distance visual acuity had significantly improved at 1 year in eyes that had undergone CXL in keratoconus or corneal ectasia patients. In 2011, Sinha Roy and Dupps[13] also provided a proof of concept of patient-specific differential refractive responses to CXL. Using three-dimensional finite element models, they showed that smaller, focal, cone-centered CXL simulations provided the greatest topographic effects.[13] In 2016, Seiler et al.[14] performed a clinical study comparing the efficacy of customized CXL with standard CXL. The authors found that the ΔK_{max} was greater in the customized CXL group. Shetty et al.[15] also compared the effect of four different customized CXL methods in keratoconic eyes. In this study, the authors found that a ring tangential map protocol provided the greatest decrease in curvature ($P < 0.05$) and greatest improvement in uncorrected visual acuity and corrected distance visual acuity per unit energy dose to the cornea ($P > 0.05$), compared with a uniform treatment, a sector axial map protocol, and a ring axial map protocol. Brooks et al.[16] also suggested that patients experience subjective improvement in visual function after undergoing CXL for keratoconus and corneal ectasia. In 2013, Park and Chuck[17] reexamined the effect of CXL in mild post-LASIK ectasia, based on a study by Celik et al.[18] The authors found a difference in the mean spherical equivalent between the control group and the LASIK-CXL of –0.53 ± 0.22 as motivation for further consideration of CXL for myopia correction.

Unlike conventional CXL, which uses broad-beam UVA light, photorefractive intrastromal corneal crosslinking is performed through the delivery of specific patterns and intensities of UVA irradiation based on patient characteristics, such as corneal topography and refractive error. This focal irradiation results in localized changes to the corneal biomechanics and flattening to induce more customized refractive changes.[19] A transepithelial approach also has inherent advantages over on epithelial-off approach, including decreased patient discomfort, faster visual recovery, and a decreased risk of infection. However, the epithelium restricts the stromal bioavailability of all photochemical constituents, including the photosensitizer, oxygen, and UV light. Stromal UV-A can be improved by increasing the incident irradiance, riboflavin absorption can be improved by adding a cytotoxic additive such as benzalkonium chloride to the drug formulation, and supplemental oxygen has recently been investigated to improve oxygen concentrations in the stroma.[20] Oxygen plays an important role in CXL; the photochemical reaction can follow a type I (aerobic) or type II (anaerobic) pathway. The aerobic pathway leads to a more efficient generation of oxygen radicals compared with the anaerobic pathway, although crosslink formation is possible in both situations.[21] It has been demonstrated that a stable hyperoxic environment with the use of an environmental chamber can improve oxygen diffusion and subsequently improve the biomechanical impact.[17] Pulsed delivery of UV-A irradiation with a predetermined on and off pattern has also been theorized to improve the diffusion of oxygen into the stroma and allow a greater effect by allowing reoxygenation of the corneal stroma and outward diffusion of riboflavin byproducts.[22] Several studies compared the results of continuous versus pulsed irradiance in the accelerated protocols and demonstrated a deeper demarcation line and greater apoptotic effect with the pulsed approach.[23–25] Although pulsed CXL shows promising results, further studies are required to determine the ideal pulsing approach. The use of higher irradiance in accelerated and transepithelial approaches has been shown to be safe, but has potential side effects, including endothelial cell toxicity, especially in corneas less than 400 microns.

Most of the studies that have used CXL for primary refractive corrections thus far are small case series using the KXL II CXL device (Glaukos Corp/Avedro Inc., Waltham, MA), which was CE Marked for photorefractive intrastromal crosslinking (PiXL) in 2014 or the Mosaic CXL device (Avedro Inc./Glaukos Corp), which was CE Marked for PiXL in 2015. There is also variability in several of the treatment parameters, including the mode of crosslink formation, riboflavin delivery, energy, treatment pattern, and treatment duration. In this article, the studies investigating CXL for primary refractive corrections are reviewed. There is also significant interest and literature on the role of CXL as an adjunctive procedure combined with other refractive surgical procedures, or so-called CXL-plus; however, this topic is not discussed in this article.

CXL in Myopia

The first reported clinical use of CXL as a primary refractive treatment was by Kanellopoulos in 2014.[26] Before treatment, riboflavin solution was applied to the intact epithelium. Eyes were then treated with the KXL II CXL device that delivered 30 mW/cm^2 of surface fluence on the pupillary aperture for a total exposure time of 4 minutes (12.4 J/cm^2) in a myopic pattern. An average of 2.3 diopters (D) of flattening of was reported in the first week in all four cases, which regressed to 1.44 D at 1 month, and remained stable at 6 months of follow-up. No adverse reactions were noted, and there was no significant change in the endothelial cell counts or corneal clarity.

In 2017, Lim et al.[19] reported a series of 14 eyes that underwent PiXL with customized control of a topographic distribution of UV fluence in a myopic pattern. The cornea was prepared with a proprietary solution composed of dextran-free riboflavin 0.25% with benzalkonium chloride, ethylenediaminetetraacetic acid, and trometamol in hydroxypropyl methylcellulose (Paracel Part 1, Avedro Inc./Glaukos Corp), 1 drop every 90 seconds for 4 minutes, then a second solution containing dextran-free riboflavin 0.22% in saline without benzalkonium chloride (Paracel Part 2, Avedro Inc.), 1 drop every 90 seconds for 6 minutes, then rinsed with balanced salt solution. The UVA delivery device (Mosaic System, Avedro Inc.) was used to deliver PiXL treatments through the application of a central spot pattern with a variable fluence depending on the preoperative refraction, based on a nomogram provided by Avedro Inc. The range of preoperative refractions were between −0.75 and −2.65 D. At 12 months of follow-up, a mean manifest refraction spherical equivalent decrease of 0.72 ± 0.43 D was observed and a mean K-mean flattening of 0.47 ± 0.46 D was noted. There were no major adverse reactions. Some eyes were noted to have transient corneal haze, which subsided and was not visually significant.

Elling et al.[28] reported a series of 26 eyes that underwent PiXL in 2017 with the Mosaic system.[27] The methodology was similar to the study by Lim et al., with the main exception being that mechanical debridement of the corneal epithelium was performed. Total fluence was either 10 or 15 J/cm^2, depending on the preoperative refractive error. A mean change of 0.99 ± 0.47 D in the manifest spherical equivalent was noted compared with baseline at 6 months of follow-up. No serious adverse events occurred in any patient. A subsequent update to the 6-month data showed stability of the flattening effect at 12 months of follow-up.[28]

In 2018, a case report by Sachdev and Ramamurthy[29] also described PiXL in a patient with −1.25 D refraction. High fluence UVA irradiation of 15 J/cm^2 was delivered over the central 4 mm, using the Mosaic device. Oxygen was supplemented externally in this case to increase the efficacy of the transepithelial approach. At 3 months postoperatively, a mean central flattening of 1.8 D was noted. No adverse reactions occurred.

Another prospective series was reported by Hout et al.[30] in 2018, in which 19 patients underwent photorefractive keratectomy in the dominant eye and transepithelial PiXL in the nondominant eye. ParaCel Parts 1 and 2 were used to prepare the cornea, followed by pulsed UVA irradiation for a fluence of 15 J/cm^2, but with a 6-mm treatment zone. Supplemental oxygen was also given. This study showed an improvement in uncorrected distance visual acuity from baseline in both groups, but less improvement in the photorefractive keratectomy eyes than in CXL eyes. Of the 19 patients, 13 (68.4%) were more satisfied with the outcome in the photorefractive keratectomy–treated eye. A mean central flattening of 0.74 ± 0.54 D was noted at 6 months of follow-up in the CXL group.

A sixth series reported in 2020 by Sachdev et al.[31] also used supplemental oxygen to increase the efficacy of the transepithelial approach. In this prospective study, 50 eyes were included. The cornea was prepared for CXL with ParaCel part 1 and part 2 solutions. UVA irradiation was delivered using the Mosaic system in the central 4.0-mm zone with a total fluence of 15 J/cm^2 using an accelerated protocol (30 mW/cm^2) and a pulsed approach. The decrease in the mean refractive spherical equivalent was 1.23 ± 0.6 at 6 months of follow-up. A mean central flattening of 1.66 D was noted at 6 months of follow-up.

Fredriksson et al.[32] also evaluated the effect of PiXL on low-grade myopia, and compared three treatment protocols. Group 1 underwent epi-on PiXL with a 4-mm zone in a high oxygen environment, group 2 underwent epi-on PiXL with a 4-mm zone under room air conditions, and group 3 underwent epi-on PiXL with a 6-mm zone and a high oxygen environment. The initial analysis showed an insufficient or absent treatment effect in group 2 and an unacceptable degree of initial side effects in group 3, including light sensitivity and ocular irritation. Therefore, enrollment in these groups was halted and 29 eyes were treated with the group 1 protocol. Twelve initial eyes were treated in group 2 and 12 eyes were treated in group 3. Group 1 showed a greater decrease in the manifest refraction spherical equivalent than group 2 at all follow-up

Table 1. Summary of Crosslinking Studies for Primary Myopic Corrections – Energy Parameters

Authors	Arm	Crosslinking Device	Wavelength	Total Fluence	Irradiance	Pulsed Illumination	Treatment Time	Treatment Zone (mm)
Kanellopoulos[26]	—	KXL II Device	365 nm	12.4 J/cm^2	30 mW/cm^2	N	4 min	4
Lim et al.[19]	—	Mosaic System	365 nm	10 or 15 J/cm^2	45 mW/cm^2	Y	Nomogram based	4.5
Elling et al.[28]	—	Mosaic System	365 nm	10 or 15 J/cm^2	30 mW/cm^2	Y	Nomogram based	4
Sachdev et al.[31]	—	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	4
Hout et al.[26]	—	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	6
Sachdev et al.[29]	—	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	4
Fredriksson et al.[32]	Arm 1	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	4
	Arm 2	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	6
	Arm 3	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	4
Naslund et al.[33]	Arm 1	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	4 mm homogenous zone
	Arm 2	Mosaic System	365 nm	15 J/cm^2	30 mW/cm^2	Y	16 min, 40 sec	4 mm annular zone

Table 2. Summary of Crosslinking Studies for Primary Myopic Corrections: Treatment Parameters

Authors	Arm	Riboflavin (%)	Cytotoxic Additive	Epithelium	Supplemental Oxygen
Kanellopoulos[26]	—	0.25	BAC	Epi-on	No
Lim et al.[19]	—	0.25	BAC	Epi-on	No
Elling et al.[28]	—	0.10	None	Epi-off	No
Sachdev et al.[31]	—	0.25	BAC	Epi-on	Yes
Hout et al.[30]	—	0.25	BAC	Epi-on	Yes
Sachdev et al.[29]	—	0.25	BAC	Epi-on	Yes
Fredriksson et al.[32]	1	0.25	BAC	Epi-on	Yes
	2	0.25	BAC	Epi-on	Yes
	3	0.25	BAC	Epi-on	No
Naslund et al.[33]	1	0.25	BAC	Epi-on	Yes
	2	0.25	BAC	Epi-on	Yes

BAC, benzalkonium chloride.

periods and similar difference to group 3 (1.08 ± 0.53 vs 1.10 ± 0.58 at 12 months follow-up).

Recently, Naslund et al. evaluated the treatment effect of two different CXL protocols for the treatment of low myopia.[33] In this prospective trial, one eye of each study subject was randomized to a homogenous 4.0 mm treatment zone of UVA irradiation, while the fellow eye underwent a 4.0 mm annular treatment zone. A central zone of 2.0 mm in this group was untreated. The other treatment parameters were the same as in the protocol used by Sachdev et al.,[27] including the use of supplemental oxygen. Similar improvements in uncorrected visual acuity and manifest refraction spherical equivalent were seen for the homogeneous and annular protocols at 1 month: logarithm of the minimum angle of resolution (LogMAR) -0.52 (-0.59, -0.39) and -0.49 (-0.59, -0.39), respectively. The treatment effect remained stable at 24 month follow-up. Tables 1, 2, and 3 summarize the data from these myopia treatment studies.

CXL for Hyperopia

Currently, options for surgical refractive correction for hyperopia involve steepening the central corneal

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Table 3. Summary of Crosslinking Studies for Primary Myopic Corrections: Study Designs and Results

Authors	Study Design	Study Arm	No. of Eyes	Follow-up	Mean Preoperative MRSE (D)	Δ MRSE (D)	Baseline LogMAR UCVA	LogMAR UCVA at Last Follow-up
Kanellopoulos[26]	Prospective case series	—	4	6 months	Not reported	—	<1.30	Not reported
Lim et al.[19]	Prospective case series	—	14	12 months	−1.62 ± 0.60	0.75 ± 0.42	0.48 ± 0.25	0.23 ± 0.19
Elling et al.[28]	Prospective case series	—	45	12 months	−1.72 ± 0.60	0.90 ± 0.40	0.48 ± 0.28	0.14 ± 0.16
Sachdev et al.[31]	Prospective case series	—	50	6 months	−1.61 ± 0.70	1.23 ± 0.60	0.63 ± 0.25	0.13 ± 0.18
Hout et al.[30]	Prospective case series	—	19	6 months	−1.43 ± 0.31	0.72 ± 0.42	0.68 ± 0.20	0.33 (SD not reported)
Sachdev et al.[29]	Case report	—	1	3 months	−1.25	—	0.48	0
Fredriksson et al.[32]	Randomized Trial	Arm 1 (4-mm zone, supp O_2)	15	12 months	−1.37 ± 0.52	1.04 (SD not reported)	0.60 ± 0.24	0.06 ± 0.17
		Arm 2 (6-mm zone, supp O_2)	6	12 months	−1.58 ± 0.34	1.08 (SD not reported)	0.51 ± 0.25	0.24 ± 0.38
		Arm 3 (4-mm zone, no O_2)	12	12 months	−1.29 ± 0.43	0.19 (SD not reported)	0.60 ± 0.21	0.46 ± 0.31
Naslund et al.[33]	Randomized Trial	Arm 1 (4-mm homogenous zone)	14	24 months	−1.25 (−1.81, −1.19)	−0.25 (−0.75, 0.00)	0.56 (0.46, 0.74)	0.03 (−0.07, 0.30)
		Arm 2 (4-mm annular zone)	14	24 months	−1.25 (−1.81, −1.25)	−0.50 (−0.84, 0.00)	0.53 (0.44, 0.76)	0.14 (0.01, 0.28)

MRSE, manifest refraction spherical equivalent; UCVA, uncorrected visual acuity.

curvature and increasing corneal power through ablation of the midperiphery.[34] Corneal crosslinking offers the advantage of altering the corneal shape in a nonablative, nonincisional manner, thereby decreasing the risk of biomechanical weakening. Thus far, only one clinical study has been performed evaluating the effect of PiXL for the correction of hyperopia. Stodulka et al.[34] enrolled 22 low hyperopic eyes, 16 of which were low hyperopic surprises after cataract surgery. The PiXL method was performed using ParaCel parts 1 and 2 for riboflavin absorption, and subsequent application of UVA irradiation with supplemental oxygen. The Mosaic system delivered 30 mW/cm^2 UVA irradiance in pulsed intervals of 1 second on and 1 second off to a 5.0- to 9.0 mm diameter annulus. The authors reported a reduction in spherical equivalent from +0.75 D (+0.63 to 1.06 D) preoperatively to +0.25D (0.0 to +0.50 D) at 12 months of follow-up with a median refractive change of −0.69 D. No significant adverse reactions were noted. In terms of safety, no eye lost any lines of UDVA. Change in the preoperative corrected distance visual acuity of 0.0 logMAR to 0.025 logMAR to 0.0 (0.0 to 0.0 logMAR) at 12 months postoperatively was not significant ($P < 0.5$).

CXL for Astigmatism Correction

There are currently no clinical studies using CXL for the refractive correction of corneal astigmatism. There are, however, computational modeling studies evaluating the effect of patterned CXL for astigmatism. Seven et al.[35,36] studied the effect of CXL on anterior corneal astigmatism using finite element analysis. The corneal geometries from 10 patients with irregular or regular astigmatism were exported from a clinical tomography system. Finite element models of each eye were generated, and four treatment patterns were simulated. All treatment patterns resulted in mean reductions of astigmatism; however, the bow-tie pattern produced the greatest decrease . This simulation suggests that patterned collagen crosslinking could lead to clinically significant reductions in corneal astigmatism.

Novel Crosslinking Modalities

More recently, novel surgical approaches to induce crosslink formation, and achieve refractive corrections using the femtosecond laser, have been described. These technologies have offered a new method of providing focal alterations in the corneal tissue to produce targeted refractive changes using selective treatment patterns. Wozniak et al.[37] used blue (480 nm) femtosecond pulses to induce a refractive index change in corneal tissue. Wang et al.[38] described another approach using infrared pulses to induce the formation of a low-density plasma to generate an ionization field within the corneal stroma. This process results in the production of reactive oxygen species which interact with the surrounding proteins to form crosslinks without the use of riboflavin. In this ex vivo study, 15 eyes underwent corneal flattening and were paired with 10 controls, whereas 13 eyes underwent irradiation for steepening and were paired with 10 controls. In the group with the flattening treatment, an effective refractive power of about 12% (mean 5.11 D) was initially observed with some regression to 3.45 D (mean). This value was determined by placing the eye in a custom-built eye chamber. The topography before and after treatment was paired with a corresponding "virtual vision" where an effective refractive power of 43.5 D corresponded with 20/20 vision. In the steepening group, a ring-shaped treatment region was used and the authors reported a significant effect. In vivo studies were also performed in a rabbit model. The mean change in the effective refractive power 48 hours after treatment was 1.74 D and 1.64 D in the steepening group and flattening groups, respectively. These changes remained stable at three months follow-up.

Bradford et al.[39,40] describe a distinct approach referred to as nonlinear optical collagen crosslinking. In this approach, two photons of near infrared femtosecond laser light excite riboflavin, thus generating oxygen free radicals and subsequent collagen crosslinking, similar to UVA CXL. Ex vivo rabbit corneas were studied, along with 14 live rabbits using 50 to 150 kHz amplified femtosecond pulses. Amplified pulses generated increased collagen autofluorescence and mechanical stiffening, and resulted in a decrease in corneal topography measurements by 1.0 ± 0.8 D by 1 month.

Conclusions

The primary benefit of refractive corneal crosslinking thus far seems to be the correction of small myopic refractive errors without the need for corneal incisions or tissue removal. Other potential advantages over conventional refractive surgery options may include the simplicity of the procedure for the surgeon, a possibly improved safety profile, and likely decreased equipment costs. Some drawbacks of the procedure may include longer treatment times, longer healing

or stabilization times, and a lower range of correction, as well as possibly decreased refractive precision. The ability to titrate treatments to the desired effect is achieved is another potential area of improvement in refractive corneal crosslinking. Minimally invasive biomechanical measurements are emerging that could potentially provide intraoperative and postoperative feedback to assist in the monitoring and titration of treatments. Two of these methods are Brillouin microscopy and ultrasound elastography. Brillouin microscopy is a technique that uses a low-power near-infrared laser beam to determine longitudinal modulus or mechanical compressibility of tissue by analyzing the return signal spectrum.[41,42] It can potentially provide point-by-point three-dimensional mapping of corneal biomechanics.[43] Ultrasound elastography is another corneal biomechanics measurement method that uses high-frequency ultrasound examination to determine local material properties by measuring tissue displacement as a function of an applied stress. Ultrasound elastography systems evaluate one of two different types of corneal responses to stress—compressional strain along the axis of the applied force or shear strain created by laterally propagating waves.[44] Optical coherence elastography is a conceptual extension of ultrasound elastography. It uses light scatter to measure local tissue displacement as a function of applied stress.[45] OCT may assist in the determination of the demarcation line created during CXL, or the boundary between crosslinked and uncrosslinked tissue. It may also give real-time, intraoperative feedback on CXL procedures to tailor patient-specific treatments.[46,47] Although there remain challenges involved in the clinical translation of these technologies, there is a promise for future applications in CXL.

The ideal candidates for intrastromal crosslinking are likely to be patients with low myopia who wish to be free of contact lenses or glasses but are unwilling to proceed with conventional refractive surgeries for fear of the surgery, ectasia, or other complications; patients with mild residual refractive error after cataract surgery or laser refractive surgery; or patients with low myopia who are determined to be poor candidates for conventional refractive surgery. Having a minimum corneal thickness of 400 microns may limit the applicability of the technology in the post-laser refractive surgery group, but this cut-off may be reconsidered in the future. In addition, the long-term stability of these treatments needs to be verified. The dose–effect relationship of the treatment needs to be investigated further and a nomogram is needed to produce accurate and reproducible results. There is also a need for active tracking on CXL systems. Although the KXL II device has a passive eye tracking system, uncompensated motion imparts significant blur to the UV beam, which may result in degraded spatial localization, a decrease in the refractive impact, and nonuniformity in treatments.[48] Active eye tracking, in which eye movement is compensated by changes in the UV beam in real-time, is available in the Mosaic device. This feature is important to avoid potential limbal stem cell damage and unwanted or diminished refractive effects.

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