Optimizing Corneal Cross-Linking in the Treatment of Keratoconus: A Comparison of Outcomes After Standard- and High-Intensity Protocols

Arthur B. Cummings, FCS (SA), MMed (Ophth), FRCSEd, Rebecca McQuaid, MSc,* Stephanie Naughton, BSc (Hons),* Elizabeth Brennan, BSc (Hons),* and Michael Mrochen, PhD†*

Purpose: To evaluate and compare the safety and efficacy of accelerated (AXL) and standard corneal cross-linking (CXL) protocols in patients with progressive keratoconus.

Methods: Progressive keratoconus patients (14–40 years) received either standard-intensity CXL or high-intensity CXL (AXL). Corneas were exposed to ultraviolet-A 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm^2 in the standard CXL group and to ultraviolet-A 365 nm light for 10 minutes at 9.0 mW/cm^2 in the AXL group. Changes in uncorrected visual acuity, best spectacle-corrected visual acuity, refractive astigmatism, K_{max}, and K_{mean} were used to determine treatment efficacy. Safety was determined by the incidence of adverse events and occurrence of loss of 2 or more lines of best spectacle-corrected visual acuity. Outcomes for CXL versus AXL were compared to determine differences in safety and efficacy between treatment groups.

Results: Thirty-six eyes of 34 patients (mean age, 27.9 ± 7.6 years) underwent AXL; 66 eyes of 53 patients (mean age, 30.0 ± 8.0 years) underwent standard-intensity CXL. There was no significant difference in any outcome measures between the groups. For AXL, there seemed to be more corneal flattening, with a statistically significant reduction in K_{mean} at 6 and 12 months postoperatively, when compared preoperatively ($P < 0.01$). There were no adverse events or complications in any patients.

Conclusions: There was more corneal flattening in AXL patients 6 to 12 months postoperatively, suggesting that AXL may be a promising alternative to CXL in stabilizing corneal ectasia.

Key Words: corneal cross-linking, keratoconus, ectasia

(*Cornea* 2016;35:814–822)

Treatment for keratoconus, a typically bilateral, noninflammatory, progressive disorder characterized by thinning and steepening of the inferior or central cornea, irregular astigmatism, and loss of best-corrected visual acuity, was once limited to spectacles and rigid contact lenses or invasive treatments such as penetrating keratoplasty.[1] Although these treatments are still widely used to manage keratoconus, patients now have numerous other options available to them including photorefractive keratectomy, intrastromal corneal ring segments, phakic intraocular lenses, and corneal collagen cross-linking (CXL).[1]

CXL was first evaluated in porcine eyes by Spoerl et al[2] in 1998, who found that compared with untreated corneas, treatment with riboflavin and UV-irradiation and weak glutaraldehyde increased biomechanical stiffening of the cornea. However, it was findings from a prospective, nonrandomized clinical pilot study in 23 eyes with moderate or advanced progressive keratoconus that put CXL in the spotlight, with data showing that treatment with riboflavin drops and ultraviolet-A (UVA) irradiation (370 nm, 3 mW/cm^2 for 30 minutes) halted the progression of keratoconus in all eyes and caused disease regression in 16 eyes (70%).[3] Since then, a number of clinical studies have confirmed the ability of CXL to stabilize and regularize the cornea, in turn helping to improve visual acuity in patients with keratoconus[4–10] and postoperative LASIK ectasia.[11,12] Consequently, many ophthalmologists have welcomed CXL into their treatment armamentarium.

In CXL, photo-oxidative cross-links are induced by a photosensitizer (riboflavin) and UV light. The generation of collagen crosslinks is, therefore, largely determined by the concentration of riboflavin and wavelength, time, and energy dose of the light source. The standard CXL treatment protocol for a patient with progressive keratoconus is exposure to UVA light (3 mW/cm^2) for 30 minutes and is termed the Dresden protocol. Interestingly, however, data from an experimental study in which 180 porcine eyes were randomly assigned to 10 different treatment groups with different CXL illumination intensities, ranging from 3 to 90 mW/cm^2 and corresponding illumination times from 30 minutes to 1 minute with a constant energy dose of 5.4 J/cm^2, showed that there was a statistically significant difference (compared with control) in corneal stiffness in the groups that received 3 to 45 mW/cm^2 UVA, but not in those that received more than 45 mW/cm^2.[13] Moreover, data from a study by Krueger and Spoerl showed that whereas CXL induced a 1.3- to 1.5-fold increase in corneal stiffness compared with control ($P < 0.05$), there was no significant difference between UVA doses

Received for publication November 9, 2015; revision received February 5, 2016; accepted February 6, 2016. Published online ahead of print April 7, 2016.

From the *Wellington Eye Clinic, Dublin, Ireland; and †IROC Science to Innovation AG, Zürich, Switzerland.

M. Mrochen is the founder and CEO of IROC Science AG. The other authors have no funding or conflicts of interest to disclose.

Reprints: Arthur B. Cummings, FCS (SA), MMed (Ophth), FRCSEd, The Wellington Eye Clinic, Level 2 Suite 36 Beacon Hall, Beacon Court, Sandyford, Dublin, Ireland D18 T8P3 (e-mail: abc@wellingtoneyeclinic.com).

(ie, 2 mW/cm^2, 45 minutes; 3 mW/cm^2, 30 minutes; 10 W/cm^2, 9 minutes; and 15 mW/cm^2, 6 minutes) (Krueger R, Spoerl E. Paper presented at the IV International Congress of CXL, 2008). Importantly, Kannellopoulos,[14] who investigated the safety of 7 mW/cm^2 with an illumination time of 15 minutes, found that no adverse events or negative biomechanical effects, that is, ectasia or epithelial in-growth, occurred as a result of higher intensity UVA irradiation.

Collectively, these findings suggest that by increasing the irradiation intensity but keeping the illumination dose at 5.4 J/cm^2, it may be possible to more than halve CXL treatment time. Reduced treatment time could help to improve practice efficiency and throughput volumes, increase patient comfort, and reduce the risk of corneal dehydration. Theoretically, the risk of infection is also reduced as the denuded cornea is exposed for a shorter period.

Although initial data suggest that accelerated, high-intensity CXL (AXL) may have a place in the treatment of keratoconus, most studies employing this treatment protocol have been performed in porcine or donor human corneal eyes. Kissner et al recently undertook a clinical study employing a new-generation, beam-optimized AXL system known as the UV-X 2000 lamp (IROC Innocross AG, Switzerland). However, although their findings showed that K_{apex} was significantly lower than preoperative values without endothelial cell loss or other side effects, they did not directly compare these outcomes with those from a standard CXL treatment protocol (Kissner A, Raiskup F, Spoerl E, Pillunat LE. High intensity corneal collagen cross-linking with optimized beam profile, presented at ARVO 2012). Consequently, we sought to evaluate and compare the performance and safety of standard-intensity CXL (30 minutes at 3 mW/cm^2) using the UV-X 1000 lamp with high-intensity AXL (10 minutes at 9 W/cm^2) using the UV-X 2000 lamp in patients with a confirmed diagnosis of keratoconus.

MATERIALS AND METHODS

Study Design and Patients

This Ethics Committee–approved single-center, single-surgeon study compared safety and efficacy outcomes after standard CXL and high-intensity AXL treatment protocols for the treatment of progressive keratoconus. Data for the standard-intensity regimen were gathered retrospectively from patients who underwent CXL at the Wellington Eye Clinic, Dublin, Ireland, between 2007 and 2011, whereas data for the AXL protocol were obtained prospectively between July 2011 and September 2012. Patients were made aware of the risks involved, and written informed consent was obtained from all patients according to the principles specified in the Helsinki protocol and its amendments.

Inclusion criteria included being 14 to 40 years of age and a finding of advanced keratoconus defined as one or more of the following changes over a period of 24 months or less: an increase of ≥1.00 D in the steepest keratometry value (K_{max}), an increase of ≥1.00 D in astigmatism evaluated by subjective manifest refraction, and myopic shift [decrease in the spherical equivalent (SE)] of ≥0.50 D on subjective manifest refraction. Patients were also required to have evidence of central or inferior steepening on the Pentacam map, axial topography consistent with keratoconus, the presence of one or more slit-lamp findings associated with keratoconus such as Fleischer ring, Vogt striae, corneal thinning or corneal scarring, minimum corneal thickness greater than 400 μm at the thinnest point of the cornea measured by the Pentacam, I-S ratio >1.5 on the Pentacam map or topography map, and best spectacle-corrected visual acuity (BSCVA) 20/25 or better. Other than rigid contact lens and spectacles, none of the patients included in the study had undergone any previous treatment for keratoconus.

Patients were not eligible for inclusion in the study if they had a history of ocular herpes simplex or of previous corneal or cataract surgery, nystagmus, or any other condition that, in the investigator's opinion, would interfere with or prolong healing. Patients with a known sensitivity to study medications were also excluded.

Endpoints/Outcome Measures

Changes in the following endpoints were used to determine efficacy after standard CXL and high-intensity AXL protocols: uncorrected visual acuity (UCVA), BSCVA, refractive astigmatism, K_{max}, and K_{mean}. Safety was determined by the incidence of adverse events and occurrence of loss of 2 or more lines of BSCVA. All participants were evaluated preoperatively, and at day 0 (treatment day), day 1, day 5, 1 month, 3 months, 6 months, and 1 year postoperatively.

Preoperative and Postoperative Examinations

All patients underwent a detailed clinical assessment before and after receiving CXL or AXL treatment. At each visit, measurements were taken using the Allegro Oculyzer (WaveLight Laser Technologie AG, Erlangen, Germany) and Allegro Topolyzer (Placido disk-based) platform (WaveLight Laser Technologie AG). Ocular coherence tomography was also used 1 month postoperatively to measure the depth of the cross-linked cornea. Manual keratometry, manifest refraction, BCVA, and intraocular pressure were obtained at baseline and after the procedure. To monitor the safety of the CXL postoperatively, frequent slit-lamp examinations, ophthalmic examination, and observation of complaints were conducted at each visit.

Surgical Procedure and Treatment Protocol

All surgeries were performed on an outpatient basis under topical anesthesia (Proxymethacaine 0.5%); antibiotic drops and oral sedatives were given before treatment, at the investigator's discretion. The corneal epithelium was removed using 20% alcohol for 30 seconds. A topical riboflavin solution (0.1%) containing between 0% and 20% dextran, depending on cornea thickness, was then applied to the treated eye every minute for 20 to 30 minutes, after which the anterior chamber was checked for riboflavin absorption under a slit-lamp. Once the investigator was satisfied with

riboflavin absorption, the patient's head was positioned under the UV-X lamp and UV treatment was commenced.

The low-intensity procedure was undertaken using the UV-X 1000 lamp during which the cornea was exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm^2 to achieve an illumination dose of 5.4 J/cm^2. The high-intensity protocol was undertaken using the UV-X 2000 lamp, which features an optimized beam profile designed to take into account the thickness distribution of the cornea, thereby maximizing cross-linking volume and improving cross-linking at the periphery of the cornea.[15] During the high-intensity protocol, the cornea was exposed to UVA 365 nm light for 10 minutes at an irradiance of 9.0 mW/cm^2 in the center and 12 mW in the periphery, to achieve an illumination dose of 5.4 J/cm^2. Ultrasound pachymetry was measured at 3 and 7 minutes during exposure of UVA light during the AXL procedures and at 5-minute intervals during the CXL procedures (Fig. 1).

After CXL and AXL, antibiotic eye drops were applied (Maxitrol, 4 times daily for 7 days), a therapeutic contact lens was inserted, and the eye was bandaged or covered with an eye patch.

Statistical Analysis

Previously published data[16] suggest a mean paired difference of 1.5 D in K_{max} between preoperative and postoperative values with a standard deviation (SD) of 3. Considering a type I error and a power of 0.8, a sample size of a minimum 34 eyes was determined. For each device, changes in outcome measures (UCVA, BSCVA, refractive astigmatism, K_{max} and K_{mean}) at 1, 3, 6, and 12 months postoperative versus preoperative values were compared and analyzed for statistical significance using a paired t test and Wilcoxon Signed Rank test. Outcome measures were also compared between the 2 devices using the Mann–Whitney test and an independent t test. The level of significance was set at $P < 0.05$ across all outcome measures and between devices.

RESULTS

Patient Disposition and Baseline Demographics

In total, 36 eyes of 34 patients (mean age, 27.9 ± 7.6 years) underwent high-intensity AXL, whereas 66 eyes of 53 patients (mean age, 30.0 ± 8.00) underwent standard-intensity CXL. The majority of patients who underwent standard-intensity CXL and AXL were male (CXL, 27.3% female and 72.7% male; AXL, 18.4% female and 81.6% male).

In the CXL group, 6 eyes had keratoconus grade 1, 18 eyes had grade 2, 18 eyes had grade 3 and 24 had grade 4 on the Amsler–Krumeich classification of keratoconus scale. In the AXL group, 5 eyes had grade 1 keratoconus, 14 eyes had grade 2 keratoconus, 7 eyes had grade 3 keratoconus, and 10 eyes had 4 keratoconus.

Visual Acuity

Uncorrected Visual Acuity

Figure 2 shows changes in UCVA through 12 months postoperatively. In the CXL group, there was a statistically significant improvement in UCVA from 0.26 (SD ±0.24) preoperatively to 0.35 (SD ±0.29) at 3 months postoperatively ($P = 0.015$). Although improvements in UCVA from preoperative measures were also observed 6 and 12 months postoperatively, these improvements were not statistically significant. In the group of patients treated with AXL, mean UCVA improved from 0.32 (SD ±0.23) preoperatively to 0.37 (SD ±0.32), 0.35 (SD ±0.32), and 0.42 (SD ±0.33) at 3, 6, and 12 months postoperatively. However, the improvement in UCVA was only statistically significant at 12 months

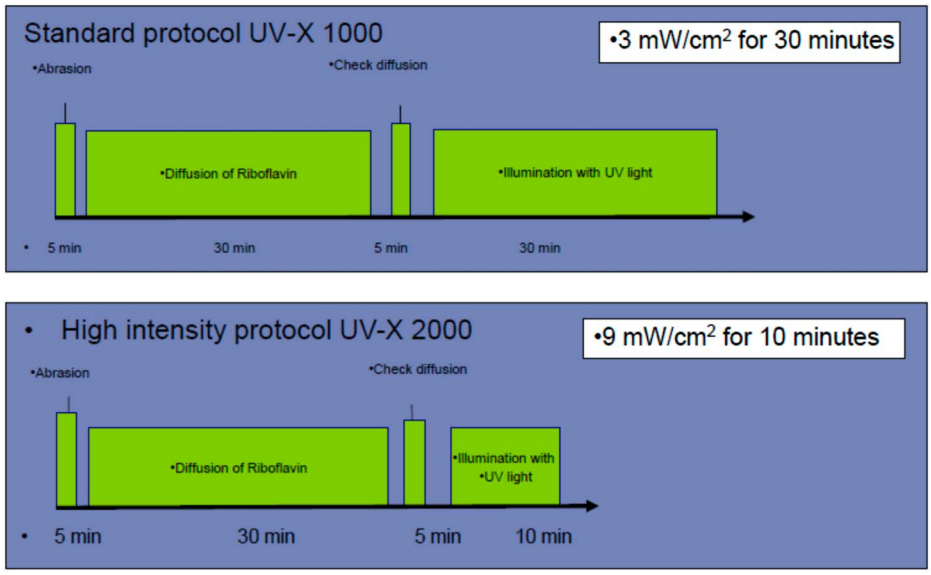
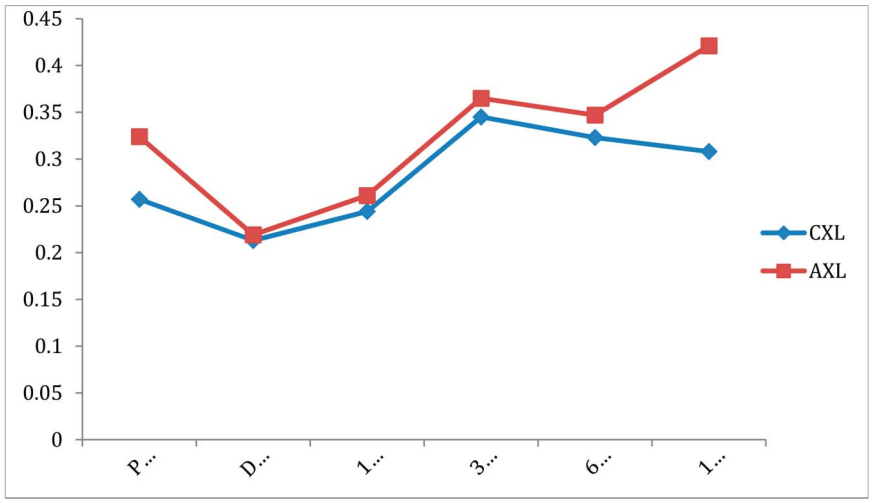


FIGURE 1. CXL (standard) versus AXL (high intensity) protocol.



	Preoperative	Day 5	1 month	3 months	6 months	12 months
			CXL			
Mean	0.26	0.21	0.24	0.35*	0.32	0.31
SD	0.24	0.17	0.22	0.29	0.28	0.25
N	63	39	46	38	35	29
			AXL			
Mean	0.32	0.22	0.26	0.37	0.34	0.42*
SD	0.23	0.13	0.17	0.32	0.32	0.33
N	37	26	28	26	30	28

*CXL, 3 month minus pre-op SIG (^) p < 0.05; AXL, 12 months minus pre-op SIG (^) p < 0.05

FIGURE 2. Change in UCVA through 12 months postoperatively.

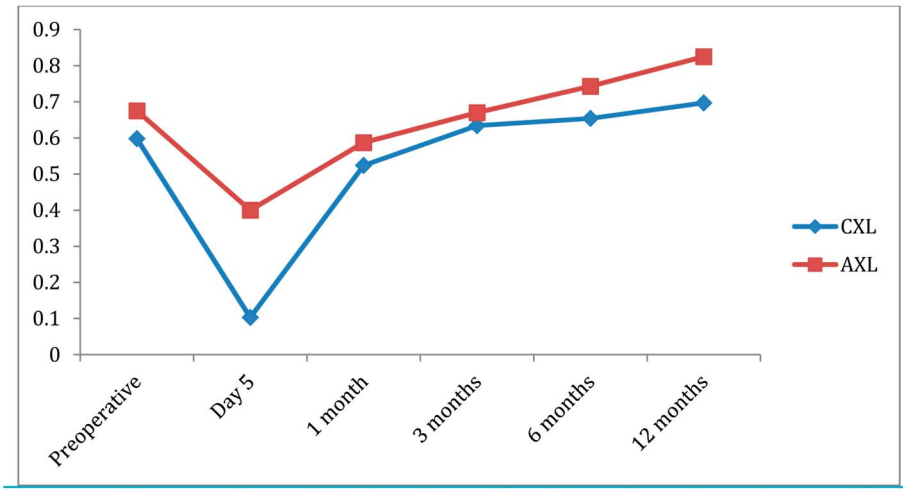
postoperatively ($P < 0.05$). There was no significant difference in UCVA between devices at any time point.

BSCVA

In the group of patients treated with standard-intensity CXL, compared with preoperative measures, there was a statistically significant improvement in mean BSCVA at 12 months postoperatively ($P = 0.043$). There was also a highly significant improvement in mean BSCVA in the high-intensity AXL group at 12 months postoperatively ($P < 0.001$) (Fig. 3). There was no significant difference in BSCVA between devices at any time point.

Refraction

Refractive outcomes for CXL and AXL are shown in Table 1. In both standard CXL and AXL treatment groups, mean SE remained stable through 12 months postoperatively. There were significant reductions in the magnitude of mean cylinder from baseline, from 1 month onwards in the CXL



	Preoperative	Day 5	1 month	3 months	6 months	12 months
			CXL			
Mean	0.60	0.10	0.52	0.63	0.65	0.70*
SD	0.30	0.24	0.31	0.36	0.35	0.31
N	63	39	46	38	35	39
			AXL			
Mean	0.68	0.40	0.59	0.67	0.74	0.84*
SD	0.27	0.31	0.30	0.28	0.29	0.22
N	36	10	31	27	30	28

*CXL, 12 month minus pre-op SIG (^) p<0.05; AXL, 12 months minus pre-op very highly significant (^) p <0.001

FIGURE 3. Change in BSCVA through 12 months postoperatively.

group. In contrast, there was no significant change in the mean cylinder in high-intensity AXL-treated patients at any of the follow-up visits. In both standard- and high-intensity treatment groups, there was no significant change in mean axis from preoperative values through 12 months of follow-up. Although there was no significant difference in SE or sphere between devices, CXL effected a significantly ($P < 0.05$) greater reduction in cylinder compared with AXL at 1 month postoperatively.

Keratometry

Changes in keratometry (K_{max} and K_{mean}) through 12 months postoperatively are shown in Figures 4 and 5, respectively. In the high-intensity AXL group, there was a reduction in mean preoperative K_{max} through 12 months postoperatively. However, this reduction was not statistically significant at any of the follow-up times analyzed. In contrast, there was a statistically significant reduction in mean K_{max} at 12 months postoperatively in the standard-intensity CXL group ($P < 0.05$). In patients treated with standard-intensity CXL, there was no statistically significant improvement in K_{mean} at any of the follow-up visits, compared with preoperative values. However, in the AXL group, there were significant reductions ($P < 0.01$) in K_{mean} at 6 months and 1 year postoperatively, compared with preoperative values. There was no significant difference between devices in either K_{max} or K_{mean}.

Safety

There were no adverse events or complications in any patients in either group. In the AXL group, no patients lost any lines of BSCVA by 1 year postoperatively. In the standard CXL group, 1 patient lost 1 line of BSCVA at 1 year postoperatively.

TABLE 1. Refractive outcomes

Parameter	Preoperative	Day 5	1 Month	3 Months	6 Months	12 Months
CXL						
SE						
Mean	−3.06	−1.85	−3.38	−2.36	−2.97	−2.86
SD	4.10	2.22	4.32	2.86	3.54	4.14
Cylinder*						
Mean	−3.14	−2.90	−2.76	−2.25	−2.69	−2.50
SD	2.10	1.33	2.02	1.60	1.96	2.19
Axis						
Mean	81.13	82.40	92.74	97.09	97.69	93.63
SD	45.90	49.08	43.04	46.31	41.32	42.12
AXL						
SE						
Mean	−2.00	−3.15	−2.56	−2.78	−2.03	−2.43
SD	2.17	1.88	1.88	2.91	1.88	2.54
N	36	6	29	25	23	24
Cylinder						
Mean	−3.16	−3.03	−3.48	−3.32	−3.22	−2.94
SD	2.49	2.38	2.14	2.27	2.00	2.17
N	37	9	31	26	29	27
Axis						
Mean	86.14	95.56	94.42	82.65	76.69	94.93
SD	39.31	32.83	43.95	43.37	40.18	44.26
N	37	9	31	26	29	28

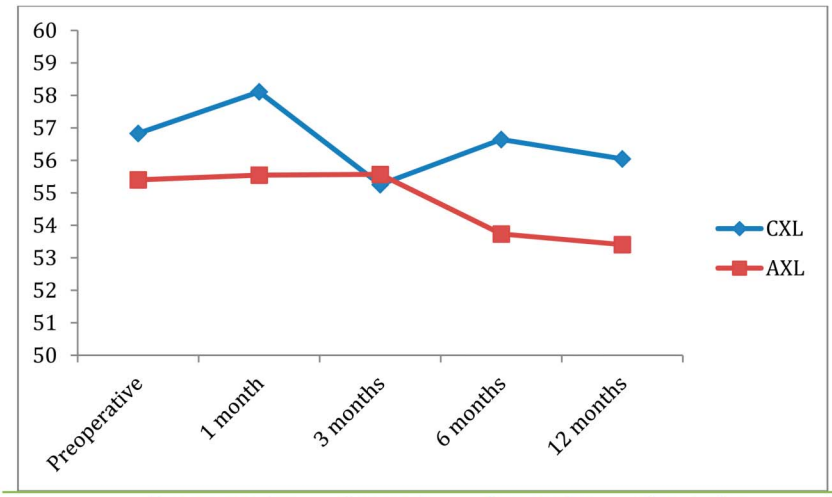
*Significant reductions in magnitude from baseline from 1 month onwards.

DISCUSSION

Previously published studies suggest that increasing the irradiation intensity of CXL (but keeping the illumination dose at 5.4 J/cm^2) may allow CXL treatment time to be halved, which in turn may confer numerous benefits including increased patient comfort and reduced side effects, that is, corneal dehydration and infection and shortened keratocyte exposure time (Kissner A, Raiskup F, Spoerl E, Pillunat LE. High intensity corneal collagen cross-linking with optimized beam profile, presented at ARVO 2012).[13,14,17] Thus far, however, the majority of studies evaluating high-intensity AXL have been performed ex vivo. The aim of the present study, therefore, was 2-fold: to evaluate the safety and efficacy of AXL and standard CXL protocols in patients with progressive keratoconus and to compare outcomes resulting from the 2 protocols.

Although CXL is not a refractive procedure, data from the current study indicate that both protocols (standard CXL and AXL) were associated with improvements in UCVA through 12 months postoperatively. In the CXL group, this improvement was statistically significant 3 months postoperatively ($P = 0.015$), but not at subsequent follow-up visits. In the group of patients treated with AXL, the improvement in UCVA was statistically significant at the 12-month postoperative visit ($P < 0.05$), but not at earlier time points. Because the Bunson–Roscoe law of reciprocity states that the CXL procedure with 30 minutes of 3-mW treatment will provide the same energy to the cornea as the AXL procedure with 10 minutes of 9-mW exposure (both providing 5.4 mJ/cm^2 in total), the main difference in the CXL and AXL procedures is the beam profile. The delayed improvement in visual acuity after AXL then is most likely because of the optimized beam profile, rather than the energy dose. A similar observation was noted in a 23-eye clinical study by Cinar et al. Specifically, mean uncorrected distance visual acuity improved from 0.97 ± 0.41 logarithm of the minimum angle of resolution (logMAR) to 0.76 ± 0.45 logMAR 6 months after high-intensity AXL ($P = 0.332$), whereas mean corrected distance visual acuity improved from 0.49 ± 0.30 to 0.34 ± 0.22 logMAR ($P = 0.026$).[18] Cinar et al also observed statistically significant improvements in sphere, cylinder, and SE after AXL, as did Kanellopoulos[19] in a 21-eye study of patients with bilateral keratoconus who were treated with AXL in one eye and standard CXL in the fellow eye. In contrast, findings in the present study showed that mean SE, mean cylinder, and mean axis remained stable through 12 months postoperatively after AXL. Interestingly, CXL effected a significantly greater reduction in cylinder than AXL at 1 month postoperatively. However, it is important to note that subjective refractions in keratoconus patients are notoriously difficult and nonrepeatable because of the multifocal optics of the distorted cornea. Refraction, therefore, is a negligible value.

A reduction in mean K_{max} from preoperative through 12 months postoperative was observed in the AXL group; however, this reduction was not statistically significant. In contrast, there was a statistically significant reduction in mean K_{max} at 12 months postoperatively in the standard-intensity CXL group. However, in patients treated with



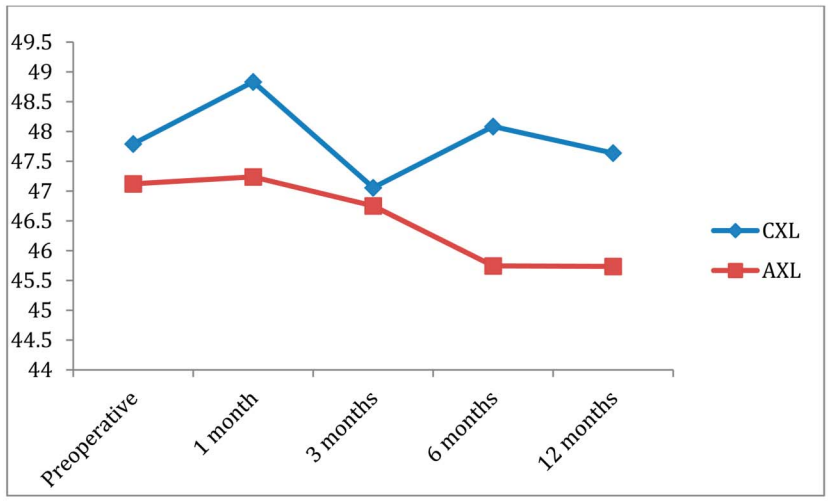
	Preoperative	1 month	3 months	6 months	12 months
CXL					
Mean	56.83	58.11	55.25	56.66	56.05*
SD	7.71	8.28	7.77	7.70	7.48
N	66	40	35	43	53
AXL					
Mean	55.40	55.55	55.57	53.74	53.41
SD	8.14	7.21	7.64	7.13	6.38
N	36	34	29	29	28

*CXL, 12 month minus pre-op SIG (^) p<0.05; AXL, no significant differences overall, although 1 year minus pre-op borderline significant reduction.

FIGURE 4. Change in K_{max} through 12 months postoperatively.

standard-intensity CXL, there was no statistically significant improvement in K_{mean} at any of the follow-up visits, compared with preoperative values, but in the AXL group, there were significant reductions in K_{mean} at 6 months and 1 year postoperatively. Additionally, the area of AXL effect was more noticeable in the peripheral cornea than in the central cornea as would be expected with an optimized beam profile. Further, the slit-lamp appearance of haze was evenly spread with CXL, whereas with AXL it presented in a donut form with more haze in the periphery and less in the center—a clear indication that the 2 devices deliver energy in 2 different patterns. The depth of CXL effect was also less in the central cornea and deeper in the periphery with AXL. Although there was no significant difference between devices in either K_{max} or K_{mean}, statistical significance does not necessarily reflect clinical significance. The fact that the cornea is flattening or no longer steepening is important in patients with keratoconus. As the condition leads to progressive corneal steepening, any stabilization (ie, no further steepening) or any flattening is a significant clinical event—even if not a significant statistical event.

Overall, outcomes were comparable for AXL- and CXL-treated patients. Importantly, therefore, both methods seem to be effective in stabilizing keratoconus. Consequently, AXL may afford keratoconus patients with the same benefits of standard CXL treatment, but without the discomfort and potential side effects associated with longer treatment duration. Findings also support the safety of AXL. In both groups, there was a statistically significant improvement in mean BSCVA at 12 months postoperatively. Moreover, no patients in the AXL experienced a loss in BSCVA at 12 months postoperatively (compared with preoperative mean BSCVA), and only 1 eye lost BSCVA (1 line) in the standard CXL group. There were no additional complications in either



	Preoperative	1 month	3 months	6 months	12 months
CXL					
Mean	47.80	48.83	47.06	48.08	47.64
SD	4.52	5.05	4.77	4.69	4.22
N	66	40	35	43	53
AXL					
Mean	47.12	47.24	46.75	45.75*	45.74*
SD	4.76	4.36	4.19	3.87	3.61
N	36	34	29	29	28

*CXL, no significant differences overall; AXL, significant reductions ($p<0.01$) at 6 months and 1 year compared with pre-op

FIGURE 5. Change in K_{mean} through 12 months postoperatively.

treatment group. Potentially, however, AXL may be safer than CXL as it has slightly less effect in the central corneal (because of the optimized beam profile), theoretically lowering the risk of endothelial cell damage in the optically active central cornea.

The study had several limitations, namely the relatively small number of eyes included in each treatment group. Additionally, the parameters used are perhaps not ideal for evaluating the progression and regression of keratoconus after treatment. In the present study, we did not look at index of height decentration and index of surface variance as others have.[20] However, these parameters were included in another study undertaken at our center and we found that index of height decentration and index of surface variance did not add any value over and above K_{max} and K_{mean}, but simply correlated well with K_{max} and K_{mean} (Cummings AB,

McQuaid R. Determining efficacy of high intensity CXL outcomes for the treatment of keratoconus: K-Max or surface height indices? presented at ESCRS 2014).

Although further studies with larger patient numbers and longer follow-up times are needed to validate these findings, data suggest that AXL may be a safe and effective alternative to CXL in stabilizing corneal ectatic disease and may also have a greater corneal flattening effect than standard CXL if the optimized beam profile is being used.

REFERENCES

1. Vazirani J, Basu S. Keratoconus: current perspectives. *Clin Ophthalmol.* 2013;7:2019–2030.
2. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res.* 1998;66:97–103.
3. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620–627.
4. Toprak I, Yildirim C. Effects of corneal collagen crosslinking on corneal topographic indices in patients with keratoconus. *Eye Contact Lens.* 2013;39:385–387.
5. Steinberg J, Ahmadiyar M, Rost A, et al. Anterior and posterior corneal changes after crosslinking for keratoconus. *Optom Vis Sci.* 2014;91: 178–186.
6. Ghanem RC, Santhiago MR, Berti T, et al. Topographic, corneal wavefront, and refractive outcomes 2 years after collagen crosslinking for progressive keratoconus. *Cornea*. 2014;33:43–48.
7. Sloot F, Soeters N, van der Valk R, et al. Effective corneal collagen crosslinking in advanced cases of progressive keratoconus. *J Cataract Refract Surg.* 2013;39:1141–1145.
8. Guber I, Guber J, Kaufmann C, et al. Visual recovery after corneal crosslinking for keratoconus: a 1-year follow-up study. *Graefes Arch Clin Exp Ophthalmol.* 2013;251:803–807.
9. Caporossi A, Mazzotta C, Baiocchi S, et al. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol.* 2010;149:585–593.
10. Wittig-Silva C, Whiting M, Lamoureux E, et al. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *J Refract Surg.* 2008;24:S720–S725.
11. Hafezi F, Kanellopoulos J, Wiltfang R, et al. Corneal collagen cross-linking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg.* 2007;33:2035–2040.
12. Kanellopoulos AJ. Post-LASIK ectasia. *Ophthalmology*. 2007;114:1230.
13. Schumacher S, Oeftiger L, Mrochen M. Equivalence of biomechanical changes induced by rapid and standard corneal cross-linking, using riboflavin and ultraviolet radiation. *Invest Ophthalmol Vis Sci.* 2011;52: 9048–9052.
14. Kannellopoulos AJ. Collagen cross-linking in early keratoconus with riboflavin in a femtosecond laser-created pocket: initial clinical results. *J Refract Surg.* 2009;25:1034–1037.
15. IROC Innocross. *UV-X 2000: The IROC Innocross Illumination System*. Available at: http://www.innocross.ch/product/uv-x-2000/. Accessed, July 30, 2014.
16. Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg.* 2008;34:796–801.
17. O'Brart DPS. Corneal collagen cross-linking: a review. *J Optom.* 2014;7: 113–124.
18. Çınar Y, Kürşat Cingü A, Turkcu FM, et al. Accelerated corneal collagen cross-linking for progressive keratoconus. *Cutan Ocul Toxicol.* 2014;33: 168–171.
19. Kanellopoulos AJ. Long-term results of a prospective randomized bilateral eye comparison trial of higher fluence, shorter duration ultraviolet A radiation, and riboflavin collagen cross linking for progressive keratoconus. *Clin Ophthalmol.* 2012;6:97–101.
20. Kanellopoulos AJ, Dupps WJ, Seven I, et al. Toric topographically customized transepithelial, pulsed, very high-fluence, higher energy and higher riboflavin concentration collagen crosslinking in keratoconus. *Case Rep Ophthalmol.* 2014;5:172–180.