Accelerated Pulsed High-Fluence Corneal Cross-Linking for Progressive Keratoconus

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• PURPOSE: To report on 2-year results of accelerated corneal collagen cross-linking (CXL) in progressive ectasia using the Avedro KXL system.

• DESIGN: Prospective interventional case series.

• METHODS: A total of 870 patients (1,192 eyes) attending Moorfields Eye Hospital after CXL were included. All patients undergoing CXL had progressive keratoconus. Corneas with a minimum stromal thickness < 375 μm were excluded. Riboflavin 0.1% soak duration was 10 minutes. High-fluence pulsed UVA was delivered at 30 mW/cm^2 for 4 minutes, with a 1.5-second on/off cycle (total energy 7.2 J/cm^2). Subjective refractive, corneal tomography, and specular microscopy were performed at baseline, 6, 12, and 24 months postoperatively. The primary outcome measure was a change in maximum keratometry (Kmax) at 24 months.

• RESULTS: Twelve- and 24-month follow-up data were available on 543 and 213 patients, respectively (mean age 25.4 ± 6.6 years). In mild cones (Kmax < 55 diopter [D]), mean keratometry remained unchanged at 24 months. In more advanced disease, we observed modest corneal flattening compared to baseline (Kmax 63.2 ± 6.5 D vs 61.9 ± 8.1 D, $P = .02$), but no significant changes in central keratometry (K1 or K2). Keratometric stabilization was confirmed in 98.3% of eyes. Mean CDVA, manifest refraction and endothelial cell density did not change. Overall, 2.7% of eyes lost more than 2 lines of CDVA.

• CONCLUSION: Accelerated pulsed CXL is a safe, effective, and refractively neutral intervention (at 2 years) to halt disease progression in keratoconus. (Am J Ophthalmol 2021;221:9–16. © 2020 Elsevier Inc. All rights reserved.)

CORNEAL COLLAGEN CROSS-LINKING (CXL) AIMS TO halt disease progression in keratoconus. It is effective in more than 90% of treated eyes, with small improvements in corneal shape and vision additionally observed in some patients.[1–7] The original Dresden protocol,[8] the only FDA-approved iteration of CXL, described removal of the corneal epithelium with application of riboflavin drops prior to UVA exposure of irradiance (power) 3 mW/cm^2 for 30 minutes (total energy 5.4 J/cm^2). Randomized controlled trials support the use of this protocol in progressive keratoconus.[2,3]

Accelerated protocols have largely superseded the Dresden protocol in which the same total UVA energy dose is delivered as a shorter, higher-power burst.[9–13] The premise of shorter UVA delivery, according to Bunsen's law of reciprocity, is that the same total energy can be delivered in a fraction of the time by increasing the power (energy = power × time). Reduced treatment times may allow for more efficient and less costly access for patients, but evidence for efficacy and safety is incomplete, with evaluation of results complicated by variations in total energy, irradiance and/or treatment time, as well as more contemporary pulsed UV delivery devices.[9,12,14–20] It is also unclear whether accelerated CXL can avoid uncontrolled hyperopic refraction changes secondary to progressive flattening of corneal curvature—a well-recognized consequence of Dresden protocol CXL.[21] In patients with early keratoconus, and particularly in patients undergoing combined photorefractive keratectomy and CXL, a neutral mean keratometric outcome may be preferable.

To examine treatment safety, efficacy, and keratometric neutrality after accelerated CXL, using a widely marketed contemporary high-fluence (30 mW/cm^2) pulsed light protocol, we report 2-year results from a large prospective case series.

MATERIALS AND METHODS

• STUDY DESIGN: This was a prospective, uncontrolled case series of patients with progressive keratoconus. This study was reviewed by the Research Governance Committee and approved as an audit project by the Clinical Audit Working Group at Moorfields Eye Hospital NHS Foundation Trust (reference CA17/CED/03) in line with Interventional Procedure Guidance (IPG466) of the National Institute for Health and Care Excellence (NICE).

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TABLE 1. Defining Disease Progression in Early Keratoconus (Group 1) and Moderate/Advanced Keratoconus (Group 2) Prior to Accelerated High-Fluence Pulsed Corneal Cross-Linking

Group 1 (Kmax < 55 D) (1 or More)	Group 2 (Kmax ≥ 55 D) (1 or More)
• ≥ 1 D increase Kmax	• ≥ 2.5 D increase Kmax
• ≥ 1 D increase front K1 or K2	• ≥ 2.5 D increase front K1 or K2
• ≥ 0.5 D increase back K2	• ≥ 22 μm decrease minimum corneal thickness
• ≥ 16 μm decrease minimum corneal thickness	

Kmax = maximum keratometry, K1 = flat keratometry in the central 3 mm zone, K2 = steep keratometry in central 3 mm zone.
Criteria for determining progression in early and moderate/advanced keratoconus, based on differences in measurement repeatability limits in early and advanced keratoconus.[21]

• **PARTICIPANTS:** Patients were identified from a dedicated electronic medical record database of all patients aged 16 years and older attending the Early Keratoconus Clinic (EKC) in our institution. The database includes keratometric and refractive data entered prospectively in clinic and at the time of surgery. We extracted a consecutive series of all eyes intended follow-up. All patients undergoing CXL had progressive keratoconus, defined by a clear referral history of disease progression prior to first review in the EKC, or documented corneal tomographic changes from baseline measurement above contemporary 95% measurement repeatability limits for the Pentacam HD Scheimpflug corneal tomographer (Oculus Optikgeräte GmbH, Wetzlar, Germany) in keratoconus (Table 1).[22] Patients were excluded if the examination was consistent with pellucid marginal degeneration (inferior band corneal thinning separated from the corneoscleral limbus by a relatively uninvolved area 1-2 mm in width). Exclusion criteria included pregnancy or breastfeeding, uncontrolled ocular surface disease, or a minimum corneal thickness less than 375 μm.

• **ASSESSMENTS:** All assessments were performed in the EKC by optometrists or technicians trained in manifest refraction, corneal tomography, and data entry. All contact lens wearers were instructed to discontinue contact lens wear at least 1 week for soft contact lenses or 2 weeks for hybrid and rigid gas permeable lenses prior to all examinations. At 6, 12, and 24 months after treatment, subjective refractive, corneal tomography, specular microscopy, and slit-lamp examination were performed. Up to 3 corneal tomography scans were taken aiming to achieve an "OK" quality specification. Automated endothelial cell analysis was performed using a non-contact specular microscope (Konan Medical, Inc). This device was not available when we first began treatments, so it is reported in the latter 391 eyes only.

The primary outcome measure was a change in maximum keratometry (Kmax) at 24 months using the same limits of repeatability as for preoperative progression (Table 1). Secondary outcome measures were anterior keratometry of the steep (K2 front) and flat (K1 front) axes in the central 3-mm zone, posterior keratometry of the steep axis (K2 back), corrected and uncorrected distance visual acuity (CDVA, UDVA), corneal thickness at the thinnest point, and endothelial cell density (ECD). Baseline visual acuity was initially measured in Snellen before a switch to logMAR (logarithm of the minimum angle of resolution) acuity during the course of the study, because of change in visual acuity testing charts at our institution. Changes greater than measurement repeatability limits (Table 1) in 2 or more corneal shape indices, as proposed by the Global Delphi Panel of Keratoconus and Ectatic Diseases,[23] were used to determine post-CXL progression (ie, treatment failure or success).

• **SURGICAL PROCEDURE:** Following topical instillation of proxymetacaine 0.5%, tetracaine 1%, and povidone-iodine 5%, the eyelashes were taped and a eyelid speculum inserted. The corneal epithelium was manually debrided to approximately 9 mm, following which dextran-free riboflavin 0.1% solution in hydroxypropyl methylcellulose (VibeX Rapid; Avedro, Inc, Waltham, Middlesex County, MA) was applied every 2 minutes, with the final riboflavin application at 8 minutes after soak initiation. The excess riboflavin was gently washed away from the corneal surface with a balanced salt solution. Ultraviolet-A (UVA) light exposure was performed at a wavelength of 370 nm using the KXL System (Avedro, Inc). The treatment parameters were as follows: UVA irradiance = 30 mW/cm^2, exposure time = 8 minutes, pulse = 1.5 seconds on and 1.5 seconds off, total energy = 7.2 J/cm^2. Supplemental riboflavin was not applied during UVA exposure.

At the end of the procedure, the eye was generously irrigated with balanced salt solution before application of preservative-free dexamethasone 0.1% and chloramphenicol 0.5% and a bandage contact lens (Purevision; Bausch & Lomb, Inc, Rochester, NY). Postoperatively, patients were prescribed a tapered course of preservative-free topical dexamethasone 0.1%, moxifloxacin and hyaluronic acid 0.1% for 1 week, along with topical diclofenac 0.1%, cyclopentolate 1% BD and 50 mg oral diclofenac thrice a day for 3 days. Patients were additionally provided with 3 minims of proxymetacaine 0.5% for PRN use in the early

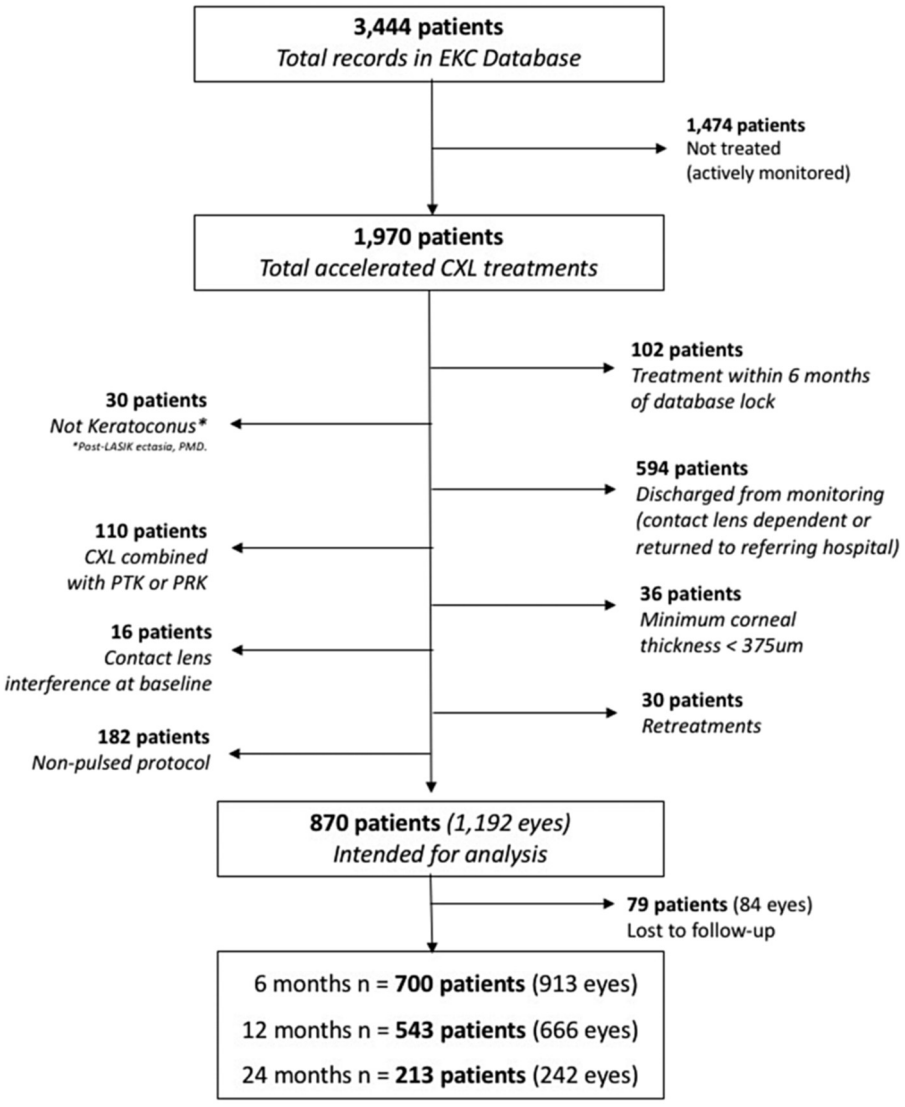

FIGURE 1. Accountability flow chart showing patient selection and follow-up. EKC = Early Keratoconus Clinic, PMD = pellucid marginal degeneration, CXL = corneal cross-linking, PTK = phototherapeutic keratectomy, PRK = photorefractive keratectomy.

postoperative period. The bandage contact lens was removed at 1 week, after which all therapy was discontinued except topical hyaluronic acid 0.1% 4 times a day and fluorometholone 0.1% 4 times a day for 1 month.

• **DATA COLLECTION AND STATISTICAL ANALYSIS:** Anonymized data were retrieved from the Early Keratoconus Clinic Microsoft.NET SQL database (Microsoft Corp, Redmond, California, USA) and exported to Excel software for analysis (version 15.24 2016; Microsoft Corp). The threshold for clinically significant loss/gain of CDVA was set at 2 lines or more (0.20 logMAR) change compared to preoperative values. For purposes of statistical analysis, Snellen visual acuities were converted to logMAR equivalents (−log decimal acuity). Data are presented as means ± standard deviation. Paired Student *t* tests were used to compare baseline and 24-month postoperative data. A *P* value less than .05 was considered significant.

RESULTS

OF 1,970 CONSECUTIVELY PATIENTS TREATED AT THE POINT of database lock, 870 were intended for in-house follow-up. Patients who remained dependent on contact lenses to work, as well as those unwilling to travel from their referring hospital, were discharged from further monitoring. Figure 1 shows an accountability flowchart of subject selection.

Of the 870 patients (1,192 eyes) meeting inclusion criteria for the study, mean (SD) age was 25.4 (6.6) years.

TABLE 2. Keratometric Data for Early Keratoconus (Group 1) Patients Treated With Accelerated High-Fluence Pulsed Corneal Cross-Linking for Progressive Disease

Parameter	Baseline (n = 409)	6 mo (n = 313)	12 mo (n = 212)	24 mo (n = 82)	*P* Value[a]
Kmax (D)	51.4 ± 3.8	51.5 ± 4.2	51.3 ± 4.6	51.0 ± 6.4	.15
K2 front (D)	46.4 ± 3.4	46.4 ± 3.7	46.4 ± 4.0	45.9 ± 5.7	.08
K1 front (D)	43.6 ± 3.2	43.5 ± 3.5	43.6 ± 3.7	43.2 ± 5.4	.14
K2 back (D)	−6.8 ± 0.6	−6.9 ± 0.7	−6.8 ± 0.7	−6.8 ± 0.9	.31
K1 back (D)	−6.2 ± 0.7	−6.2 ± 0.6	−6.2 ± 0.6	−6.2 ± 0.80	.48
Pachymetry[b] (μm)	464 ± 46	462 ± 47	459 ± 58	462 ± 65	.66

D = diopter.

Accelerated high-fluence pulsed corneal cross-linking for progressive keratoconus.

[a]Paired *t* test of baseline compared with 24-months.

[b]Pachymetry at the thinnest location.

The majority of eyes treated had Stage I or II disease (modified Krumeich classification): Stage I (n = 397 eyes), Stage II (n = 434), Stage III (n = 115), Stage IV (n = 245). For the purposes of keratometric progression analysis, eyes were divided into those with mild keratoconus (Group 1, Kmax < 55 D, n = 409) and moderate/severe keratoconus (Group 2, Kmax ≥ 55 D, n= 784).

Overall, 79 (9.1%) of 870 patients failed to return for scheduled assessments, and 12- and 24-month follow-up data were available on 666 and 242 eyes, respectively, at the point of database lock. In group 1, overall mean keratometry remained unchanged at 24 months. In group 2, we observed modest flattening in Kmax at 24 months compared to baseline (63.2 ± 6.5 D vs 61.9 ± 8.1 D, $P = .02$), but no significant changes in central keratometry (K1 or K2). Full baseline and postoperative keratometric data are presented in Tables 2 and 3. At 24 months, we observed treatment failure (ie, progression in 2 or more corneal shape indices), in 2 (2.4%) of 82 group 1 eyes and 3 (1.9%) of 160 group 2 eyes. Failure rate for all treated eyes was 4 (1.7%) of 242 eyes. We observed continued progressive flattening in Kmax in 3 eyes in group 1 (1-, 1.1-, and 1.3-D reduction in Kmax) and a further 3 eyes in group 2 (3.1-, 5.2-, and 5.2-D reduction in Kmax). When measured centrally (anterior K2), no eyes progressively flattened in either group. Overall, 6 (2.5%) of 242 eyes exhibited continued flattening (as measured by Kmax). One eye in group 2 exhibited pronounced central flattening (with stromal thinning) of more than 9 D by the first postoperative assessment, but thereafter remained stable.

Eyes with Stage II disease showed a statistically significant improvement in UDVA at 24-months, improving from logMAR 0.68 ± 0.35 at baseline to logMAR 0.40 ± 0.26 at 24-months ($P = .001$). There was otherwise no significant change in mean CDVA or UDVA for all other stages. We observed no clinically, or statistically significant changes in the refractive status of treated eyes. Full visual function data is shown in Table 4.

There were no significant changes in mean minimum pachymetry: Group 1: 464 ± 46 μm baseline, 462 ± 65 μm 24 months ($P = .66$); Group 2: 430 ± 37 μm baseline, 430 ± 51 μm 24 months ($P = .84$). Similarly, we observed no significant differences in mean ECD in either group at 12 or 24 months (Group 1: 2,821 ± 398 mm^{-2} baseline, 2,891 ± 521 mm^{-2} 24 months, $P = .180$; Group 2: 2,776 ± 362 mm^{-2} baseline, 2,791 ± 462 mm^{-2} 24 months, $P = .31$). No eyes clinically decompensated.

There was 1 case of presumed infective keratitis (culture negative) presenting within the first week postoperatively. A central corneal scar developed resulting in a loss of 5 logMAR lines of corrected acuity. Thirty-four (3.9%) of 870 eyes developed sterile infiltrates that quickly responded to further topical steroids. In Stage 1 and 2 disease, in which subjective refraction end-points were more repeatable, 4 (2.7 %) of 149 eyes at 24 months lost 2 lines or more of CDVA, none of which lost more than 3 lines (20, 24, 24, and 27 EDTRS letters, respectively). No corneal scarring was evident in these eyes.

DISCUSSION

OUR RESULTS DEMONSTRATE THAT ACCELERATED PULSED CXL can successfully halt disease progression, with keratometric stabilization confirmed in 98.3% of eyes. The treatments produced no central corneal flattening and no refractive shift. This stabilization over 2 years can be viewed in light of the expected rate of progression *without* CXL, with a recent meta-analysis demonstrating a significant increase in Kmax of 0.7 D (95% confidence interval, 0.31-1.14, $P = .003$) at 12 months in untreated eyes.[24]

Accelerated protocol development, in part driven by the practical advantages of improved patient comfort and

TABLE 3. Keratometric Data for Moderate/Advanced Keratoconus (Group 2) Patients Treated With Accelerated High-Fluence Pulsed Corneal Cross-Linking for Progressive Disease

Parameter	Baseline (n = 784)	6 mo (n = 601)	12 mo (n = 454)	24 mo (n = 160)	*P* Value[a]
Kmax (D)	63.2 ± 6.5	63.1 ± 6.8	62.4 ± 6.9	61.8 ± 8.1	.02[c]
K2 front (D)	53.4 ± 5.2	53.8 ± 5.5	53.1 ± 5.5	52.8 ± 6.3	.14
K1 front (D)	49.1 ± 4.7	49.3 ± 5.1	49.1 ± 5.0	48.7 ± 5.6	.33
K2 back (D)	−8.1 ± 0.9	−8.2 ± 1.0	−8.1 ± 1.0	−8.2 ± 1.1	.23
K1 back (D)	−7.2 ± 0.9	−7.3 ± 0.9	−7.3 ± 0.9	−7.3 ± 1.0	.63
Pachymetry[b] (μm)	430 ± 37	427 ± 41	431 ± 40	430 ± 51	.84

D = diopter
[a]Paired *t* test of baseline compared with 24 months.
[b]Pachymetry at the thinnest location.
[c]Statistically significant.

greater patient turnover, may offer additional advantages over standard "Dresden" CXL. There is, however, conflicting evidence regarding its effectiveness as compared to standard treatment.[25] Some groups have reported significantly less corneal flattening in accelerated CXL vs standard treatment.[26,27] The reasons for this apparent reduced tissue effect are uncertain but may be related to excessive oxygen consumption with higher UV fluences and subsequent reduced oxygen availability, which is a crucial ingredient in the photochemical CXL process.[9,13] A further related variable is the extent to which UVA light is attenuated before it hits the cornea by the pre-corneal film of riboflavin that some practitioners replenish with further drops applied during the exposure. This would be in keeping with the results from Shetty and associates who reported that irradiance of 9 mW/cm^2 for 10 minutes and 18 mW/cm^2 for 5 minutes had comparable results to standard CXL, but 30 mW/cm^2 for 3 minutes was not as effective.[18] Conversely, Shajari and associates reported in their meta-analysis that accelerated CXL with high irradiation intensity for short treatment time (30 mW/cm^2 for 3 minutes) resulted in comparable corneal flattening compared to standard CXL, but accelerated CXL with irradiance of 18 mW/cm^2 for 5 minutes appeared less efficacious.[19] Hashemi and associates reported comparable outcomes using 18 mW/cm^2 for 5 minutes, but found that greater corneal flattening was achieved with the standard protocol.[17] A meta-analysis by Wen and associates also suggests improved flattening of Kmax with standard CXL vs accelerated protocols.[19]

Besides shape changes induced by CXL, apparent tissue changes in patients following standard and accelerated CXL protocols have been investigated. A demarcation line, typically visible at approximately 300 μm following the Dresden protocol, is thought to represent the border between treated tissue (anterior to the line) and untreated tissue (posterior to the line). Touboul and associates observed, by confocal microscopy, that the demarcation line following accelerated CXL (30 mW/cm^2 for 3 minutes, total energy 5.4 J/cm^2) lies more superficial, at a mean depth of 100-150 mm.[28] However, Kymionis and associates saw no such difference by optical coherence tomography comparing Dresden and an alternative protocol (9 mW/cm^2 for 14 minutes, total energy 7.56 J/cm^2), with mean demarcation line depths of 337 and 322 μm, respectively.[29] These conflicting findings may reflect the differences in irradiance, time, and total energy exposure employed in these 2 studies. For the time being, the published literature lacks longer-term studies of corneal shape and vision using these protocols to prove whether a more superficial treatment, as suggested with accelerated protocols, is any less effective. We acknowledge a limitation of the data presented in this series without optical coherence tomography findings.

Regardless of the incomplete evidence base, "less" cross-linking may not be such a bad thing. Progressive corneal flattening for 10 years or longer has been estimated to occur in more than 6% of eyes treated with standard CXL.[21] Our data recorded no incidences of central flattening (measured by K2) and just 2.5% of eyes progressively flattening at the cone apex (Kmax) at 2 years. Analogous to progressive steepening with untreated disease, the visual consequences of long-term progressive flattening, principally unstable prescriptions and a hyperopic shift, should not be underestimated. These early treatments used the UV-X CXL device (IROC, Zurich, Switzerland), comprising an array of 7 overlapping diodes with a resultant nonhomogenous beam profile of varying intensity across the treatment zone. The beam profile of this device, working at a nominal irradiance of 5.4 J/cm^2 results in zones of central hot-spots of higher surface irradiance (up to 8.4 J/cm^2) and peripherally low irradiance zones (3.7 J/cm^2).[30] The disparity in treatment efficacy reported in the literature may, in part, be a function of the beam profile of the treatment device used, with "overtreatment" hot-spots over a central cone causing more flattening than areas exposed to less UV irradiance. The homogenous (top-hat) beam profile used in

TABLE 4. Visual Function and Refractive Outcomes for Patients Treated With Accelerated High-Fluence Pulsed Corneal Cross-Linking for Progressive Disease

Parameter Stage	Baseline	6 mo	12 mo	24 mo	*P* Value[a]
CDVA (logMAR)					
I	0.03 ± 0.14	0.05 ± 0.14	0.05 ± 0.13	0.05 ± 0.12	.113
II	0.16 ± 0.19	0.19 ± 0.19	0.18 ± 0.18	0.14 ± 0.14	.273
III	0.26 ± 0.20	0.26 ± 0.16	0.29 ± 0.19	0.25 ± 0.14	.739
IV	0.38 ± 0.25	0.47 ± 0.27	0.41 ± 0.25	0.40 ± 0.23	.547
UDVA (logMAR)					
I	0.39 ± 0.32	0.37 ± 0.32	0.17 ± 0.22	0.31 ± 0.28	.144
II	0.68 ± 0.35	0.63 ± 0.30	0.59 ± 0.35	0.40 ± 0.26	.001[b]
III	0.76 ± 0.37	0.77 ± 0.36	0.76 ± 0.39	0.48 ± 0.35	.177
IV	0.94 ± 0.37	1.00 ± 0.36	0.99 ± 0.40	0.93 ± 0.33	.878
Sphere (D)					
I	0.65 ± 2.18	0.71 ± 2.37	0.97 ± 2.35	1.01 ± 1.82	.143
II	0.98 ± 2.79	1.08 ± 2.86	1.07 ± 2.99	1.54 ± 2.55	.089
III	0.26 ± 3.89	0.78 ± 4.05	0.75 ± 3.56	0.03 ± 3.82	.816
IV	0.50 ± 5.22	1.06 ± 5.52	0.31 ± 5.79	1.28 ± 4.90	.348
Cylinder (D)					
I	−2.87 ± 1.79	−2.91 ± 1.86	−3.22 ± 2.02	−2.82 ± 1.47	.793
II	−4.77 ± 2.27	−4.88 ± 2.31	−4.89 ± 2.24	−5.00 ± 2.52	.456
III	−5.63 ± 3.02	−6.22 ± 3.15	−6.54 ± 3.54	−5.54 ± 3.17	.904
IV	−7.24 ± 3.89	−8.02 ± 4.13	−7.91 ± 4.15	−8.09 ± 3.81	.165
SEq (D)					
I	−0.79 ± 1.97	0.72 ± 2.11	−0.62 ± 2.11	−0.41 ± 1.69	.088
II	−1.41 ± 2.66	−1.36 ± 2.76	−1.37 ± 2.97	−0.96 ± 2.40	.150
III	−2.56 ± 3.66	−2.27 ± 3.91	−2.52 ± 3.50	−2.74 ± 3.93	.851
IV	−3.12 ± 5.08	−2.92 ± 5.02	−3.64 ± 5.34	−2.77 ± 4.29	.633

CDVA = corrected distance visual acuity, D = diopter; SEq spherical equivalent, logMAR = logarithm of the minimum angle of resolution, UDVA = uncorrected distance visual acuity

[a]Paired *t* test of baseline compared with 24-mo.

[b]Statistically significant.

more contemporary CXL devices, including the KXL System (Avedro Inc) as in our case series, may help to yield a more stable and refractively neutral treatment effect on the cornea with little overall flattening and, importantly, reduced incidence of continued long-term flattening. This is especially useful when CXL is combined with excimer laser treatments so as to avoid unintended hyperopic refractive changes over time.[31]

The safety profile of high irradiance UV exposure is still uncertain. Cingu and associates reported transient signs of endothelial stress after high irradiance CXL of 18 mW/cm^2 for 5 minutes, but this resolved completely at 6 months.[32] Hatch and associates reported a statistically significant but not clinically significant reduction in ECD with irradiance of 9 mW/cm^2 for 10 minutes.[33] Shetty and associates compared UVA irradiance protocols: 3 mW/cm^2 for 30 minutes, 9 mW/cm^2 for 10 minutes, 18 mW/cm^2 for 5 minutes, and 30 mW/cm^2 for 3 minutes.[18] They reported a reduction in ECD at 6 and 12 months in all groups, but there was no statistically significant difference between the groups. In a meta-analysis comparing standard and accelerated CXL, Shajari and associates reported that endothelial cell loss was greater with accelerated protocols at 1 month, but greater with the standard protocol at 6 and 12 months.[19] Meta-analysis by Wen and associates reported that accelerated CXL induced less endothelial cell loss compared to standard CXL.[34] Using our accelerated pulsed CXL protocol, we found stable ECD at all time points in group 1. There was a reduction in ECD from 2,776 ± 362 mm^2 at baseline to 2,337 ± 1,013 at 6 months in group 2, but this recovered by 12 months. We acknowledge the large standard deviations to this analysis that, in part, reflect the challenges in automated specular microscopy in steep corneas and are a limitation in meaningfully documenting these changes over time.

We recorded no significant changes in CDVA, with only Stage II eyes reporting a 2-line gain in UDVA. We are unable to explain this in the absence of any clinically significant reduction in refractive error. We acknowledge the methodological weakness of changing vision charts, with

baseline testing in Snellen acuity before a switch to logMAR acuity during the course of the study, because of change in visual acuity testing protocol at our institution. Ozgurhan and associates similarly documented unchanged sphero-cylindrical errors in a series of 44 eyes with similar CXL parameters (30 mW/cm^2 for 4 minutes, total energy 7.2 J/cm^2), with modest improvements in uncorrected and corrected visual acuity.[16] Chart letter sequence familiarity (ie, learning effect) has previously been suggested to account for improved visual outcomes even in control groups in randomized studies.[3]

Notwithstanding the limitations highlighted above, our study reports the largest series of 2-year outcomes following accelerated pulsed CXL for progressive keratoconus (30 mW/cm^2 for 8 minutes [pulsed 1.5 seconds on/1.5 seconds off], total energy 7.2 J/cm^2). Our results show this protocol is effective at halting progression of keratoconus. We acknowledge that the evidence base is still lacking with conflicting results, and that longer-term outcomes are required to confirm keratometric and refractive neutrality past 2 years.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

DANIEL M. GORE: CONCEPTUALIZATION, METHODOLOGY, Formal analysis, Writing - original draft, Writing - review & editing, Project administration. **Marcello T. Leucci:** Software, Validation, Formal analysis. **Su-yin Koay:** Writing - original draft. **Nikolaos Kopsachilis:** Methodology, Investigation, Project administration. **Michael N. Nicolae:** Methodology, Investigation, Project administration. **Michail I. Malandrakis:** Methodology, Investigation, Project administration. **Vijay Anand:** Methodology, Resources, Project administration. **Bruce D. Allan:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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