Accelerated CXL for stage 2 to 3 progressive keratoconus: 24-month outcomes

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Background: *Ultraviolet (UV-X) corneal collagen cross-linking (CXL) involves photopolymerization of corneal collagen and in recent decades has been commonly employed for the treatment of stage 2 to 3 keratoconus. The high-intensity illumination of the UV-X™ 2000 Crosslinking System (Avedro, Inc., Waltham, Massachusetts) provides accelerated CXL (A-CXL), reducing treatment time threefold (to 10 minutes) compared with conventional CXL protocol.*

Purpose: *To assess 24-month outcomes of A-CXL for stage 2 to 3 progressive keratoconus.*

Material and Methods: *One hundred and nineteen patients (167 eyes) who underwent ACXL for keratoconus were included in this study. At 24 months, ocular changes were assessed in 40 eyes. A-CXL was carried out using the UV-X™ 2000 Crosslinking System at an irradiation intensity of 9 mW/cm².*

Results: *Mean astigmatism decreased by 1.15 D to 3.02 ± 1.73 (SD) D (for n=40 eyes) and mean corneal refractive power as assessed by Kmax decreased by 3.4 D to 54.4 ± 6.62 (SD) D (median value, 54.3 D; n=40 eyes) at 24 months compared to baseline values. Mean thinnest local corneal thickness increased by 3.0 µm (mean value, 462.7± 34.3 (SD) µm; median value, 455.5 µm; n=40 eyes; p = 0.009), mean uncorrected visual acuity increased by 0.2, and mean best-corrected visual acuity increased by 0.25 at 24 months compared to baseline values. Of the 40 eyes examined at 24 months, BCVA improved in 34 eyes (85%).*

Conclusion: *A-CXL for stage 2 to 3 progressive keratoconus resulted in a steady state of the pathological process, decrease in astigmatism by 1.15 D, decrease in corneal refractive power as assessed by Kmax by 3.4 D, and an increase in thinnest local corneal thickness by 3.0 µm for the total study cohort, and improvement in BCVA in 85% of eyes at 24 months.*

Keywords:
keratoconus, cornea, cross-linking

Introduction

Progressive degeneration of the collagen structure of the cornea underlies keratoconus and impairs corneal mechanical strength properties, resulting in corneal bulging, opacification and frequently scarring and substantially decreased vision [1-6].

The disease most commonly affects both eyes and is most commonly found in adolescents [7, 8]. In addition, in Ukraine, it is the second most common indication for keratoplasty. A study from the UK found that the incidence of keratoconus was 4.4 times higher in Asians than in white patients [9, 10].

The etiology is considered multifactorial with genetic, endocrine, allergic and immune influences, but genetic influence is most widely recognized [11]. Of the patients enrolled at 16 clinical centers in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study, 13.5% reported a family history [12].

Ultraviolet (UV-X) corneal collagen cross-linking (CXL) involves photopolymerization of corneal collagen and in recent decades has been commonly employed for the treatment of stage 2 to 3 keratoconus. Photochemical ionization takes place and riboflavin is destroyed (with release of free oxygen) by exposure to UV-A radiation generated by the UV-X system. Free oxygen-derived radicals cause cross-linking between -CH and –CN groups in collagen molecules, which induces their binding to form a 3D meshwork. Numerous additional bounds between corneal collagen fibers result in a significant improvement of corneal mechanical strength and rigidity. Biomechanical studies have shown that corneal rigidity increases by 350%-380% after cross-linking [13-26].

Several corneal CXL protocols are available, including an epithelial-off standard protocol of 3 mW/cm^2 intensity at 370 nm over an exposure time of 30 minutes (now termed the ''Dresden protocol''); accelerated CXL protocols carried out in a shorter period such as 3, 5, or 10 minutes by using 30, 18, or 9 mW/cm^2 irradiance; and transepithelial

CXL protocol (without corneal de-epithelization) [13, 17, 27].

The high-intensity illumination of the UV-X™ 2000 Crosslinking System (Avedro, Inc., Waltham, Massachusetts) provides accelerated CXL, reducing treatment time threefold (to 10 minutes) compared with conventional CXL protocol [13]. Recent studies by Sadoughi [28] and Shajari [29] found that accelerated CXL with 9 mW/cm^2 irradiation for 10 min had similar refractive, visual, keratometric, and aberrometric results and less adverse effects on the corneal thickness and endothelial cells as compared with the conventional method after 12 months follow-up. Those studies, however, concluded that clinical trials with longer follow-ups were needed.

We have previously reported on 6-month and 12-month treatment outcomes for keratoconus patients treated with CXL [4].

The purpose of the current study was to assess 24-month outcomes of accelerated CXL for stage 2 to 3 progressive keratoconus.

Material and Methods

One hundred and nineteen patients (167 eyes; 90 men and 29 women) aged 12-57 years (25.3 ± 8.55 SD years; median value, 25 years) who underwent A-CXL for keratoconus were included in this study. Of these eyes, 77 (46.1%) had stage 2 keratoconus, and 90 (53.9 %) had stage 3 keratoconus (Amsler-Krumeich classification). Stage II keratoconus and stage 3 keratoconus were uniformly distributed among men and women (46% and 54%, respectively). In addition, of the 167 eyes, 28 (16.8%) were involved in a unilateral process, and 139 (83.2%) were involved in a bilateral process. Bilateral cross-linking was conducted in 48 (35%) of the 139 eyes. Fifteen fellow eyes required keratoplasty for stage 3 keratoconus. Disease duration until the CXL treatment ranged from one year to 20 years, with a mean value of (3 ± 2.65 SD) years. The disease was diagnosed within 2 years from the onset in 55.1% of cases. Male patients were significantly more frequently diagnosed within five years from the onset of the disease, whereas female patients were significantly more frequently diagnosed within two years from the onset of the disease ($\chi^2 = 28.3$, $p = 0.0004$).

Family history of refractive errors (myopia and/or astigmatism) and association of occurrence of keratoconus progression with stress were reported by 46.2% and 44.6%, respectively, of male patients, and 53.8% and 19.2%, respectively, of female patients. In addition, 26.9% of female patients reported association of occurrence of keratoconus progression with delivery.

Patients underwent biomicroscopy, refractometry, and corneal confocal biomicroscopy (Confoscan 4, NIDEK Co., Ltd., Aichi, Japan) in addition to a routine eye examination. Pentacam® apparatus (Oculus Inc., Wetzlar, Germany) was used to perform keratography and corneal pachymetry and to estimate corneal refractive power.

Kmax was used as a measure of corneal refractive power, and thinnest local corneal thickness was measured. Uncorrected (UCVA) and best-corrected (BCVA) visual acuities were assessed using the Shevalev chart and the Sivtsev chart and categorized as 1 (VA ≤ 0.1), 2 (VA ≤ 0.3), and 3 (VA > 0.3).

Studies were performed preoperatively and at 6, 12, 18 and 24 months postoperatively. Studies at months 6, 12, 18 and 24 involved 167 eyes, 149 eyes, 65 eyes, and 40 eyes, respectively.

Accelerated CXL was carried out using the UV-X™ 2000 Crosslinking System at an irradiation intensity of 9 mW/cm². Corneal epithelium was debrided using a diameter of 7.0, 7.5, or 8.0 mm according to corneal topography data. Intraoperative corneal pachymetry was performed thereafter and after the cornea was soaked with riboflavin solution for 15 minutes. The duration of CXL UVA laser exposure was 10 minutes. At the end of procedure, a bandage soft contact lens was placed on the eye. Antiseptics, agents promoting corneal regeneration, preservative-free tear substitutes and (if indicated) antibiotics and antiviral agents were prescribed postoperatively. The bandage soft contact lens was removed after re-epithelization was complete.

Mean, error of mean, median, quartile, standard deviation (SD), quartile, and variation range values were calculated. The Shapiro–Wilk and Kolmogorov–Smirnov tests were performed to determine normality of data distribution. Comparison between groups was made using the Student's t test with Levene's test for homogeneity of variance or the Mann-Whitney U test. A one-way ANOVA (F-distribution) or Friedman chi-square test were used to compare characteristics measured under three or more different sets of conditions for the same sample of patients. Kendall concordance test was used to assess the strength of association between variables. Statistical analyses were conducted using Statistica 9.0 (StatSoft, Tulsa, OK, USA) software.

Results

Complete corneal re-epithelization was noted 3 to 5 days (mean value, 3.8 ± 0.73 SD days) after CXL. At day 3, day 4 and day 5, complete corneal re-epithelization was noted in 44 eyes (26.3 %), 80 eyes (48 %) and 43 eyes (26 %), respectively. The bandage soft contact lens was removed after re-epithelization was complete. No intra-operative complication was noted in any patient.

Mean astigmatism decreased from 4.16 ± 2.11(SD) D (for n=167 eyes) at baseline to 3.91 ± 2.34 (SD) D (for n=167 eyes) at 6 months, and 3.79 ± 2.56 (SD) D (for n=149 eyes) at 12 months. In addition, compared to baseline values, it decreased by 1.15 D to 3.02 ± 1.73 (SD) D (for n=40 eyes) at 24 months ($\chi^2 = 74.3$, $p = 0.000$) (Table 1 and Fig. 1).

Mean corneal refractive power as assessed by Kmax decreased from 57.8 ± 6.83 (SD) D (range, 45.2 to 68.7 D; median value, 57.9 D; n=167 eyes) at baseline by 1.0 D to

57.0 ± 6.91 (SD) D (median value, 57.0 D; n=167 eyes) at 6 months, and by 1.9 D to 55.9 ± 6.93 (SD) D (median value, 55.0 D; n=149 eyes) at 12 months (p = 0.000). In addition, it did not change significantly (mean value, 55.9± 7.19 (SD) D; median value, 55.8 D; n=65 eyes) at 18 months compared to 12-month values, and decreased by 3.4 D to 54.4 ± 6.62 (SD) D (median value, 54.3 D; n=40 eyes) at 24 months compared to baseline values (p = 0.000) (Table 2 and Fig. 2).

Mean thinnest local corneal thickness was 459.7 ± 36.6 (SD) μm (median value, 454 μm; n=167 eyes) at baseline, and did not change significantly (mean value, 465.5± 37.1 (SD) μm; median value, 450.0 μm; n=167 eyes) at 6 months. In addition, compared to baseline values, there was no significant change in thinnest local corneal thickness at 12 months (mean value, 453.7± 55.5 (SD) μm; median value, 455.0 μm; n=149 eyes; p = 0.48) and 18 months (mean value, 455.1± 35.0 (SD) μm; median value, 455.0 μm; n=65 eyes; p = 0.6). There was, however, a significant increase in thinnest local corneal thickness by 3.0 μm (mean value, 462.7± 34.3 (SD) μm; median value, 455.5 μm; n=40 eyes; p = 0.009) at 24 months compared to baseline values (Table 3 and Fig. 3).

Mean UCVA increased by 0.12 at 6 months, 0.14 at 12 months, 0.17 at 18 months, and 0.2 at 24 months (Table 4) compared to baseline values. In addition, of the 40 eyes examined at 24 months, UCVA improved in 25 eyes (62.5% (CI, 49.2%-75.3%)). Table 5 presents changes in UCVA at 24 months compared to baseline values for eyes relevant to various visual acuity categories.

Mean BCVA increased by 0.17 at 6 months, 0.21 at 12 months and 18 months, and 0.25 at 24 months after accelerated CXL compared to baseline values (Table 6). In addition, of the 40 eyes examined at 24 months, BCVA improved in 34 eyes (85% (CI, 71.5%-91.7%)). Moreover, the portion of eyes with vision correctable by spectacles increased by 6%, from 79% to 85%. The number of eyes with vision correctable by spectacles was 132/167 (95% CI, 72.1 – 84.5%) at baseline and 34/40 (95% CI, 71.5 – 91.7%) at 24 months.

Table 7 presents changes in BCVA at 24 months compared to baseline values for eyes relevant to various visual acuity categories.

In 3 eyes, sterile corneal infiltrates were observed postoperatively; they were noted to resolve completely at day 7 to 10.

Discussion

Therefore, by 24 months after A-CXL for stage 2 to 3 progressive keratoconus, a steady state of the pathological process was achieved in all cases.

Keratoconus stabilization was accompanied by a decrease of astigmatism by 1.15 D and of the corneal refractive power by 3.4 D; and recovery of corneal thickness (453.7 ± 55.5(SD) μm) at 18 months and increase in corneal thickness by 3.0 μm to 462.7 ± 34.3 (SD) μm at 24 months compared to baseline values. In addition, UCVA and BCVA improved in 62.3% and 85% of cases, respectively, and confocal microscopy found that recovery of normal corneal architectonics was complete at 12 months and maintained at the last follow-up 24 months after CXL.

Our findings are in agreement with those from a recent study by German and Austrian ophthalmologists [28] who conducted a meta-analysis to compare the results of standard and accelerated corneal cross-linking with the follow-up not exceeding 18 months. They concluded that consideration of less corneal thinning favours A-CXL, whereas the deeper demarcation line and greater changes in minimum keratometric values in C-CXL may indicate a higher treatment efficacy. Altogether, C-CXL, as well as A-CXL, provides successful results in the strengthening of corneal tissue.

In the current study, 90% of patients reported improved quality of vision and improved spectacle tolerance.

Conclusion

Accelerated CXL for stage 2 to 3 progressive keratoconus resulted in a steady state of the pathological process, decrease in astigmatism by 1.15 D, decrease in corneal refractive power as assessed by Kmax by 3.4 D, and an increase in thinnest local corneal thickness by 3.0 μm for the total study cohort, and improvement in BCVA in 85% of eyes at 24 months.

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Table 1. Changes in astigmatism at 24 months after accelerated corneal cross-linking (n=40)

Time points	Diopters	Confidence interval -95.00%	Confidence interval +95.00%	p
baseline	4.17	3.44	4.89	
6 months	3.45	2.82	4.08	0.000022
12 months	3.29	2.69	3.89	0.000007
18 months	3.11	2.52	3.7	0.000007
24 months	3.02	2.42	3.61	0.000007

Note: p, significance of difference compared to baseline as assessed by Dunnett's test

Table 2. Changes in corneal refractive power as assessed by Kmax 24 months after accelerated corneal cross-linking (n=40)

Time points	Diopters	Confidence interval -95.00%	Confidence interval +95.00%	p
baseline	57.1	55.0	59.1	
6 months	56.2	54.2	58.2	0.001276
12 months	55.1	53.0	57.2	0.000008
18 months	54.7	52.6	56.8	0.000008
24 months	54.4	52.3	56.5	0.000008

Note: p, significance of difference compared to baseline as assessed by Dunnett's test

Table 3. Changes in thinnest local corneal thickness 24 months after accelerated corneal cross-linking (n=40)

Corneal thickness	Diopters	Confidence interval -95.00%	Confidence interval +95.00%	p
baseline	458.6	448.1	469.0	
6 months	460.3	449.2	471.4	0.2749
12 months	460.7	449.6	471.8	0.1230
18months	461.3	450.0	472.7	0.0294
24 months	462.7	451.4	474.0	0.0004

Note: p, significance of difference compared to baseline as assessed by Dunnett's test

Table 4. Changes in uncorrected visual acuity 6, 12, 18 and 24 months after accelerated corneal cross-linking (n=40)

Time points	n	Uncorrected visual acuity						
		M	SD	median	min	max	Q1	Q2
baseline	167	**0.28**	0.24	0.17	0.02	1.0	0.1	0.4
6 months	167	**0.4**	0.27	0.3	0.02	1.0	0.17	0.6
12 months	149	**0.42**	0.28	0.35	0.04	1.0	0.2	0.6
18 months	65	**0.45**	0.28	0.4	0.06	1.0	0.2	0.6
24 months	40	**0.48**	0.28	0.4	0.05	1.0	0.25	0.7

Note: n, number of patients; M, mean value; SD, standard deviation; Q1, lower quartile; Q2, upper quartile

Table 5. Changes in uncorrected visual acuity (UCVA) for various categories of baseline UCVA 24 months after accelerated corneal cross-linking

Category of baseline UCVA	Before treatment eyes (%)	24 monthseyes (%)
1. ≤ 0.1	17 (42.5%)	1 (2.5%)
2. ≤ 0.3	12 (30.0%)	15 (37.5%)
3.>0.3	11 (27.5%)	24 (60.0%)
Total	40 (100%)	40 (100%)

Table 6. Changes in best-corrected visual acuity (BCVA) 6, 12, 18 and 24 months after accelerated corneal cross-linking

Time points	n	Best-corrected visual acuity						
		M	SD	median	min	max	Q1	Q2
baseline	167	**0.48**	0.27	0.5	0.02	1.0	0.25	0.7
6 months	167	**0.65**	0.26	0.6	0.02	1.0	0.4	0.8
12 months	149	**0.69**	0.26	0.7	0.1	1.0	0.4	0.85
18 months	65	**0.69**	0.25	0.7	0.14	1.0	0.5	1.0
24 months	40	**0.73**	0.23	0.7	0.17	1.0	0.5	1.0

Note: n, number of patients; M, mean value; SD, standard deviation; Q1, lower quartile; Q2, upper quartile

Table 7. Changes in best-corrected visual acuity (BCVA) for various categories of baseline BCVA 24 months after accelerated corneal cross-linking

Category of baseline visual acuity	Before treatment eyes (%)	24 months eyes (%)
1. ≤ 0,1	2 (5.0 %)	0 (0 %)
2. ≤ 0.3	14 (35.0 %)	2 (5.0 %)
3.> 0.3	24 (60.0%)	38 (95.0%)
Total	40 (100%)	40 (100%)

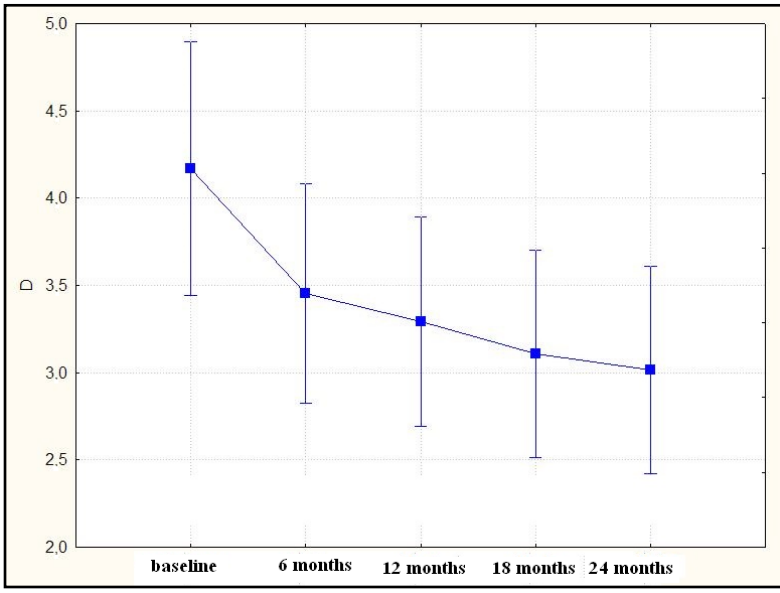

Fig. 1. Changes in astigmatism 6, 12, 18 and 24 months after accelerated corneal cross-linking. The X axis displays time points in months after treatment and the Y axis displays the astigmatism in diopters

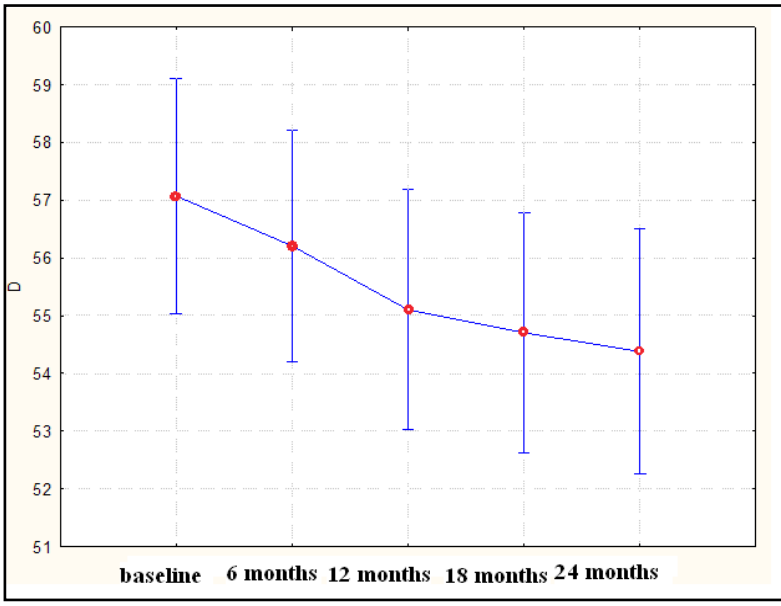

Fig. 2. Changes in corneal refractive power as assessed by Kmax 6, 12, 18 and 24 months after accelerated corneal cross-linking (n=40) Note: The X axis displays time points in months after treatment and the Y axis displays the corneal refractive power in diopters

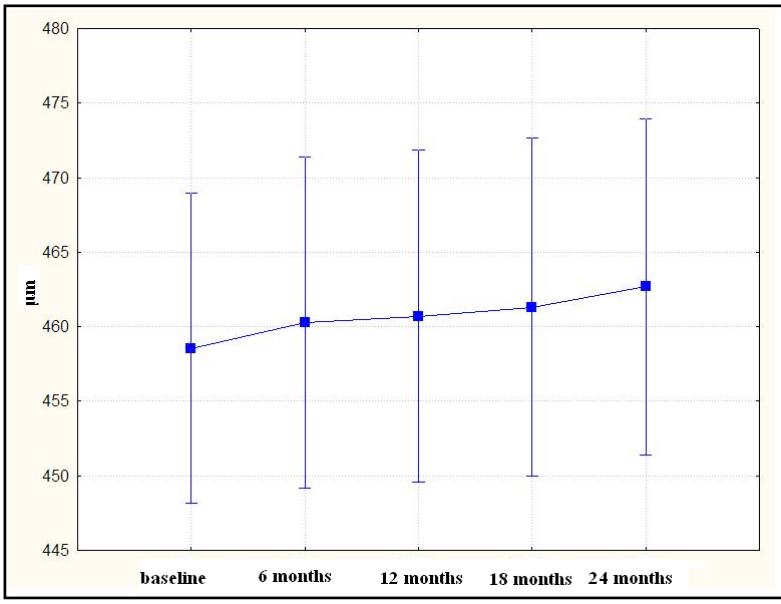

Fig. 3. Changes in thinnest local corneal thickness 6 , 12, 18, and 24 months after accelerated corneal cross-linking (n=40) Note: The X axis displays time points in months after treatment and the Y axis displays the thinnest local corneal thickness in µm