


Transepithelial Accelerated Crosslinking for Progressive Keratoconus: A Critical Analysis of Medium-Term Treatment Outcomes

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Purpose: To report the 4-year outcomes of transepithelial accelerated corneal collagen crosslinking (TE-ACXL) in the treatment of eyes with progressive keratoconus (KC).

Methods: Eyes of patients who underwent TE-ACXL (6mW/cm² for 15 minutes) for progressive KC and presented 48 months of follow-up were included. Corrected distance visual acuity (CDVA), keratometry measurements (Kmax, maximum keratometry, Kmean, mean keratometry and Astg, corneal astigmatism), thinnest corneal thickness (PachyMin), and topographic, and tomographic indices (specifically the posterior radius of curvature from the 3.0 mm centered on the thinnest point of the cornea (PRC), and the D-index) were analysed preoperatively and every 12 months after TE-ACXL, up to 48 months. Progression after TE-ACXL was considered when eyes presented ≥ 1 criteria: (1) increase of ≥ 1 D in Kmax or increase of ≥ 0.75 D in Kmean or increase of ≥ 1 D in Astg; (2) reduction of ≥ 0.085 mm in PRC; (3) decrease $\geq 5\%$ in PachyMin.

Results: 41 eyes from 30 patients were included, with a mean age at crosslinking of 20.90 \pm 4.69 years. There was a significant increase in Kmean (+0.64 \pm 1.04 D, $p < 0.001$; +0.98 \pm 1.49 D, $p < 0.001$; +1.27 \pm 2.01 D, $p < 0.001$; +1.13 \pm 2.00 D, $p = 0.006$) and a significant decrease in PRC throughout follow-up (-0.12 \pm 0.22, $p = 0.002$; -0.15 \pm 0.24, $p < 0.001$; -0.17 \pm 0.43, $p = 0.021$; -0.16 \pm 0.43, $p = 0.027$). PachyMin decreased significantly at 36 and 48 months (-8.50 \pm 15.93 μ m, $p = 0.004$; -7.82 \pm 18.37, $p = 0.033$). According to our progression criteria, there was a major progression rate throughout follow-up (57.1%, 61.1%, 58.8%, and 67.9%, respectively). Surgery and follow-up were uneventful in all subjects. Eleven eyes (26.8%) required further procedures, ≥ 36 months after the initial TE-ACXL, due to persistent progressive disease.

Conclusion: TE-ACXL proved to be a safe therapeutic option for progressive KC. However, its efficacy is deemed unsatisfactory, as a notable proportion of affected eyes may continue to advance within a 4-year timeframe, necessitating additional procedures to halt the disease's course.

Keywords: progressive keratoconus, trans-epithelial corneal crosslinking, epi-on crosslinking, keratoconus progression

Introduction

Keratoconus (KC) is a progressive, bilateral, and typically asymmetric corneal disease associated with both genetic factors (family history) and environmental factors (eye rubbing and nocturnal ocular compression).¹⁻⁵ Nowadays, it is no longer considered non-inflammatory, as many pro-inflammatory factors have been linked to its etiopathogenesis.⁶⁻⁹ Typically, it presents with paracentral corneal thinning and steepening, leading to progressive irregular astigmatism.^{4,5} Epidemiological indices of KC conspicuously vary around the world, with prevalence rates ranging from as low as 0.2 to as high as 4790 per 100000 persons. Incidence figures, though available in a limited number of studies, also exhibit wide dispersion, ranging from as low as 1.5 to as high as 25 per 100000 persons per year. Prevalence rates have typically been higher in India, Iran, and the Middle East, while incidence rates are elevated among individuals of

Asian ancestry.^{4,10,11} Currently, corneal tomography and biomechanics are the most useful tools for early diagnosis,¹² while topographic, tomographic, and pachymetric parameters are usually combined to monitor disease progression.^{13,14} The “Global Consensus on Keratoconus and Ectatic Diseases” defined ectasia progression as a consistent change in ≥ 2 of the following parameters: (1) steepening of the anterior corneal surface; (2) steepening of the posterior corneal surface; (3) thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point. Furthermore, the consensus panel agreed that a change in both uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) is not required to document progression, and that while specific quantitative data are lacking to further define progression, these data would likely be machine/technology specific.¹⁵ Although not validated, some parameters are frequently used as KC progression criteria in the literature, in studies that use the Pentacam[®] tomography system (OCULUS Optikgeräte GmbH, Wetzlar, Germany).^{13,16–21} However, KC progression after corneal collagen crosslinking (CXL) is usually determined through longitudinal evaluation of specific topographic or tomographic parameters, such as maximum keratometry (Kmax), mean keratometry (Kmean), corneal astigmatism (Asthg), posterior radius of curvature from the 3.0 mm centered on the thinnest point (PRC), or minimum pachymetry (PachyMin).^{22,23} Some studies also use longitudinal CDVA evaluation to determine KC progression after CXL.^{24,25}

Keratoconus treatment has improved significantly in recent years, with the development of new treatment modalities, for earlier stages of the disease, decreasing the disease progression and the need of keratoplasty, improving patients' vision-related quality of life.²⁶ CXL is one of these effective treatment modalities. It is a safe and minimally invasive intervention. Its primary objective is to improve the corneal biomechanical properties and decrease disease progression.^{27,28} The Dresden Protocol, first described by Wollensak et al²⁹ is considered the standard (or conventional, C-CXL) procedure, as it was the first established CXL protocol. It involves epithelium removal to facilitate stromal riboflavin impregnation, followed by application of a 0.10% riboflavin 5-phosphate solution for 30 minutes, and exposure to UVA radiation (365 nm, 3 mW/cm²) for 30 minutes, resulting in a total energy dose of 5.4 J/cm².²⁹ Nevertheless, numerous studies on this technique reported low rates of significant complications, including infectious keratitis, sub-epithelial haze, sterile corneal infiltrates, corneal scarring, postoperative pain, and delayed visual rehabilitation. The primary risk factor appeared to be the 8 to 9 mm of corneal de-epithelialization required for the Dresden protocol (epi-off).^{28,30–32} In response to these reported complications, alternative options such as partial de-epithelialization,^{33–35} mechanical disruption without debridement,^{36,37} and direct application of trans-epithelial techniques (TE-CXL or epi-on) were developed.^{38,39} Subsequently, accelerated protocols (A-CXL) emerged, grounded in the Bunsen-Roscoe law of photochemical reciprocity, thereby maintaining the total dose of radiation energy. Finally, a combination of the trans-epithelial approach and the accelerated protocol gave rise to transepithelial accelerated crosslinking (TE-ACXL).^{28,32,40,41} Nonetheless, the efficacy of TE-ACXL may be constrained by several factors. The primary challenge involves the penetration of riboflavin, a large water-soluble molecule, through the corneal epithelium. As the corneal epithelium is inherently lipophilic, it forms a barrier that impedes the easy passage of such molecules. To enhance riboflavin diffusion, alternative approaches include adding substances that can loosen tight junctions of corneal epithelial cells, such as ethylenediaminetetraacetic acid (EDTA). A buffering agent, trometamol (Tris), is commonly incorporated to maintain a stable pH in the riboflavin solution, thereby improving the efficacy of EDTA. Additionally, benzalkonium chloride (BAC) may be utilized due to its surfactant properties, which affect the integrity of tight junctions between corneal epithelial cells, leading to increased permeability. Furthermore, TE-ACXL faces the challenge of potential partial absorption of UVA by the corneal epithelium, limiting oxygen diffusion to the corneal stroma. Another consideration is the assumption underlying TE-ACXL, suggesting that increasing irradiation intensity over a reduced period has an equivalent biological effect in the cornea compared to longer exposure periods with lower energy. However, this premise may not necessarily hold true.^{38,42} Hence, comprehensive, long-term studies on the efficacy and safety of TE-ACXL are necessary to fully evaluate the effectiveness of this technique in managing progressive KC and to identify the specific patient populations that will derive the greatest benefits from its application. The purpose of the present study is to evaluate the visual, topographic, tomographic and pachymetric 4-year outcomes, as well as associated complications, in patients with progressive keratoconus who underwent a single treatment of TE-ACXL.

Methods

Study Design

Retrospective, single-center, observational, cohort study of eyes with progressive keratoconus who underwent TE-ACXL (6 mW/cm² for 15 minutes), from January 2016 to July 2019, and were followed for at least 48 months afterwards in the Department of Ophthalmology of Centro Hospitalar Universitário de São João (Porto, Portugal). The study was approved by the Institutional Ethics Review Board of the institution. The protocol conformed with the canons of the Declaration of Helsinki for research involving human participants, as well as the European Union's General Data Protection Regulation. Informed consent was waived in view of the retrospective nature of the study.

The study's inclusion criteria were: age between 18 and 32, pachymetry at its thinnest point (PachyMin) ≥ 380 μm , and documented progression of keratoconus in at least two Pentacam HR[®] (OCULUS Optikgeräte GmbH, Wetzlar, Germany) exams, with a minimum interval of 12 months between the two exams before the procedure. Progression after TE-ACXL was considered when eyes presented ≥ 1 criteria: (1) increase of $\geq 1\text{D}$ in Kmax or increase of $\geq 0.75\text{D}$ in Kmean or increase of $\geq 1\text{D}$ in Astg; (2) decrease of ≥ 0.085 mm in PRC; (3) decrease $\geq 5\%$ in PachyMin. These criteria were similar to previous published criteria for assessing KC progression after CXL.^{22–25} Exclusion criteria were previous history of cornea surgery, presence of corneal leucoma, severe dry eye, compromised corneal epithelial healing, active infectious keratitis, connective tissue disease, pregnancy or lactation.

Clinical, visual, corneal topographic, tomographic, and pachymetric parameters were evaluated preoperatively and every 12 months postoperatively up to 48 months. CDVA was recorded via a Snellen chart and converted to logarithm of minimal angle of resolution (logMAR) units. Kmax, Kmean, Astg, PRC, PachyMin, index of height decentration (IHD), index of vertical asymmetry (IVA), index of surface variance (ISV), keratoconus index (KI), Pentacam[®] topographical keratoconus classification (KC; Pentacam[®]-derived Amsler-Krumeich stages), and the Belin/Ambrósio D-index were determined using the Pentacam HR[®] (OCULUS Optikgeräte GmbH, Wetzlar, Germany). Disease progression was assessed every 12 months after TE-ACXL. Evidence of postoperative KC progression, according to the previous criteria, or need of other corneal procedures were interpreted as treatment failures.

Surgical Technique and Postoperative Care

All surgeries were performed in the operative room. Topical local anesthesia was used, with oxybuprocaine hydrochloride 4mg/L eyedrops. A special TE riboflavin magistral preparation, prepared by the hospital pharmacy, containing 0.25% riboflavin, EDTA, Tris, BAC, and 0.45% phosphate-buffered saline, was instilled in the cornea every 3 minutes for 30 minutes before UV-A irradiation. Corneal stromal saturation was confirmed through slit-lamp assessment of the anterior chamber flare. Afterwards, patients were exposed for 15 minutes to an UV-A light beam, with an intensity of 6mW/cm², to achieve a total energy dose of 5,4J/cm². During this period, to avoid corneal dehydration, both riboflavin magistral preparation and sterile balance sodium solution (BSS[®] Sterile Irrigating Solution, Alcon[®]) eyedrops were administered alternatively every 3 minutes. In the postoperative period, topical antibiotic eye drops (ofloxacin 0.30%, Floxedol[®], EDOL[®]) were prescribed for a week, steroids eye drops (fluorometholone 0.10%, FML[®], Liquifilm[®]) were prescribed for 2 weeks and nonpreserved sodium hyaluronate 0.15% eyedrops (HYABAK[®], Théa[®]) were prescribed as needed. Patients were reviewed the following day, at 3 months, and every 6 months thereafter.

Statistical Analysis

Categorical variables were summarized as counts and proportions. Continuous variables were described as mean and standard deviation (or median and interquartile range, when they did not present a normal distribution). The postoperative variation in CDVA, topographic, tomographic, and pachymetric parameters was obtained by subtracting their preoperative values from the subsequent measurements at each follow-up visit (positive delta values represented an increase in that parameter, whilst negative delta values depicted a decrease). Preoperative and postoperative outcomes were compared with paired *t*-tests or the Wilcoxon test, while multiple related samples were compared via within-subjects ANOVA test. Comparisons between the group of eyes that had progression throughout our study and those that did not present progression were conducted with independent samples *t*-tests, Mann–Whitney U, Chi-square, and Fisher's

exact tests, as suitable. The same methodology was used to compare eyes that required further corneal procedures and eyes that did not require further corneal procedures. A p-value lower than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics software (version 29.0 for Mac OS; SPSS Inc., Chicago, IL, USA).

Results

The present study included 41 eyes from 30 patients, 22 male and 8 female patients. Bilateral TE-ACXL was performed in 11 patients (9 male and 2 female patients). Mean baseline age was 20.90 ± 4.69 years (ranging from 18 to 32). [Table 1](#) summarizes baseline parameters. KC preoperative distribution is depicted in [Figure 1](#). 18 out of 41 eyes presented grade 3 KC, while 6 eyes presented grade 2, 6 eyes presented grade 2.5, and 6 eyes presented grade 3.5 KC. All 41 eyes completed the 48-month follow-up, with no intraoperative or postoperative complications. However, 11 eyes from the original 41 eyes were excluded from the comparison between 48 months and baseline values because they were submitted to either an epithelial-off crosslinking ($n=6$), an intracorneal ring segment ($n=4$), or a corneal penetrating transplant ($n=1$), after 36 months of follow-up. These eyes presented either significant KC progression despite TE-

Table 1 Baseline Demographic, Clinical, Visual, Corneal Topographic, Tomographic and Pachymetric Characteristics of Patients Undergoing Trans-Epithelial Accelerated Crosslinking

Parameter	n = 30 patients
Patients [male:female]	30 [22:8]
Age at crosslinking	20.90 ± 4.69
Eye rubber	9 (30)
Allergic conjunctivitis	10 (33.3)
Atopy	11 (36.7)
Asthma	2 (6.7)
Parameter	n = 41 eyes
CDVA (logMAR)	0.47 ± 0.36
K1 (D)	46.98 ± 3.72
K2 (D)	50.51 ± 4.45
Astg (D)	3.53 ± 1.91
Kmax (D)	57.83 ± 5.71
Kmean (D)	48.66 ± 3.97
PRC (mm)	4.79 ± 0.47
PachyMin (μm)	453.20 ± 35.97
ISV	101.35 ± 30.83
IVA	1.09 ± 0.39
IHD	0.16 ± 0.06
KI	1.27 ± 0.12
D-Index	9.99 ± 3.21
KC	2.66 ± 0.66

Notes: Categorical data are presented as n (%). Continuous data are presented as mean \pm standard deviation (SD), or median \pm interquartile range for skewed data.

Abbreviations: μm , micrometer; Astg, astigmatism (K2-K1); CDVA, corrected distance visual acuity; D, diopter; IHD, index of height decentration; ISV, index of surface variance; IVA, index of vertical asymmetry; K1, flat keratometry; K2, steep keratometry; KI, keratoconus index; KC, Pentacam[®] topographic keratoconus classification; Kmax, maximum keratometry; Kmean, mean keratometry; logMAR, logarithm of minimal angle of resolution; PachyMin minimum pachymetry; PRC, posterior radius of curvature from the 3.0 mm centered on the thinnest point of the cornea.

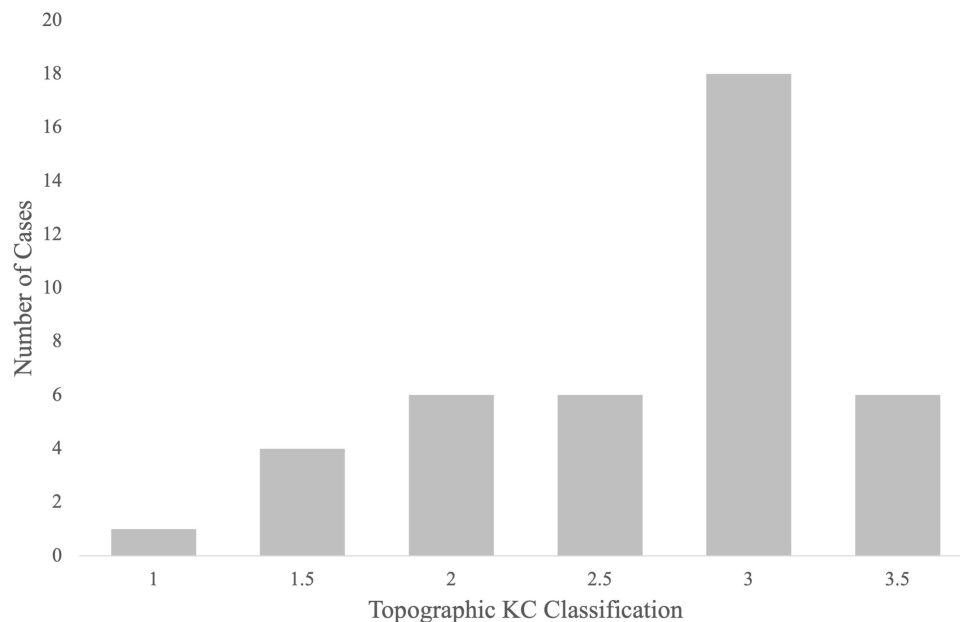


Figure 1 Distribution of baseline Pentacam® topographic keratoconus classification (KC; Pentacam®-derived Amsler-Krumeich stages).

ACXL, with anterior corneal steepening and corresponding visual deterioration, or significant deterioration in CDVA, which could not be corrected through contact lenses or glasses. There were no cases of corneal scar development or endothelial toxicity due to the TE-ACXL procedure. Table 2 summarizes the variation in CDVA, topographic, tomographic and pachymetric parameters, throughout follow-up.

Table 2 Mean Changes in Visual, Corneal Tomographic, Topographic and Pachymetric Parameters Between 12, 24, 36, and 48 Months and Baseline Values

Variables	Post-TE-ACXL							
	Δ 12-Months		Δ 24-Months		Δ 36-Months		Δ 48-Months	
	N = 35		N = 36		N = 34		N = 28	
	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value
CDVA (logMAR)	-0.10 ± 0.29	0.045	-0.10 ± 0.33	0.099	-0.07 ± 0.34	0.226	-0.17 ± 0.33	0.013
Astg (D)	0.02 ± 1.05	0.924	0.03 ± 1.09	0.855	0.08 ± 1.33	0.721	0.02 ± 1.46	0.949
Kmax (D)	0.45 ± 2.07	0.211	0.58 ± 2.16	0.119	1.08 ± 2.40	0.013	0.61 ± 3.03	0.299
Kmean (D)	0.64 ± 1.04	<0.001	0.98 ± 1.49	<0.001	1.27 ± 2.01	<0.001	1.13 ± 2.00	0.006
PRC (mm)	-0.12 ± 0.22	0.002	-0.15 ± 0.24	<0.001	-0.17 ± 0.43	0.021	-0.16 ± 0.43	0.027
PachyMin (μm)	-1.69 ± 12.96	0.447	-4.25 ± 15.31	0.105	-8.50 ± 15.93	0.004	-7.82 ± 18.37	0.033
ISV	0.15 ± 11.58	0.941	0.37 ± 11.73	0.852	2.70 ± 15.45	0.323	-0.21 ± 18.42	0.951
IVA	-0.02 ± 0.16	0.385	-0.05 ± 0.17	0.079	-0.03 ± 0.20	0.396	-0.06 ± 0.25	0.207
IHD	-0.003 ± 0.03	0.526	-0.002 ± 0.02	0.531	-0.005 ± 0.03	0.391	-0.012 ± 0.05	0.200
KI	0.004 ± 0.05	0.687	-0.001 ± 0.04	0.830	0.01 ± 0.07	0.342	-0.01 ± 0.06	0.677
D-index	0.51 ± 1.03	0.007	0.69 ± 1.25	0.002	1.02 ± 1.72	0.002	1.15 ± 1.64	<0.001

Notes: 11 eyes were excluded from the comparison between 48 months and baseline values because they were submitted to either an epithelial-off crosslinking (n=6), an intracorneal ring segment (n=4) or a corneal penetrating transplant (n=1), after 36 months of follow-up. Significant p values are highlighted in bold.

Abbreviations: μm, micrometer; Astg, astigmatism (K2-K1); CDVA, corrected distance visual acuity; D, diopter; IHD, index of height decentration; ISV, index of surface variance; IVA, index of vertical asymmetry; KI, keratoconus index; Kmax, maximum keratometry; Kmean, mean keratometry; logMAR, logarithm of minimal angle of resolution; PachyMin, minimum pachymetry; PRC, posterior radius of curvature from the 3.0 mm centered on the thinnest point of the cornea; TE-ACXL, transepithelial accelerated corneal collagen crosslinking; SD, standard deviation.

Visual Acuity

Figure 2 illustrates CDVA evolution over time. The mean baseline CDVA was 0.47 ± 0.36 logMAR units (which corresponds approximately to a Snellen visual acuity of 20/63). Mean variation was -0.10 ± 0.20 logMAR units at 12 months ($p=0.045$), -0.10 ± 0.33 logMAR units at 24 months ($p=0.099$), -0.07 ± 0.34 logMAR units at 36 months ($p=0.226$), and -0.17 ± 0.33 logMAR units at 48 months postoperatively ($p=0.013$). BCVA improved significantly at 12 and at 48 months. Final BCVA was 0.29 ± 0.30 logMAR units (which corresponds approximately to a Snellen visual acuity of 20/40).

Topography and Topographic Indices

The mean preoperative Kmax was 57.83 ± 5.71 D. There were no significant variations in this parameter, except at 36 months ($+1.08 \pm 2.40$ D; $p=0.013$). At 48 months, Kmax increased by less than 1D ($+0.61 \pm 3.03$; $p=0.299$). Average baseline Kmean was 48.66 ± 3.97 D. There was a significant increase in Kmean throughout follow-up [$+0.64 \pm 1.04$ D at 12 months ($p<0.001$); $+0.98 \pm 1.49$ D at 24 months ($p<0.001$); $+1.27 \pm 2.01$ D at 36 months ($p<0.001$), and $+1.13 \pm 2.00$ D at 48 months ($p=0.006$)]. There were no significant variations in corneal astigmatism throughout follow-up (Table 2). Figures 3 and 4 depict the

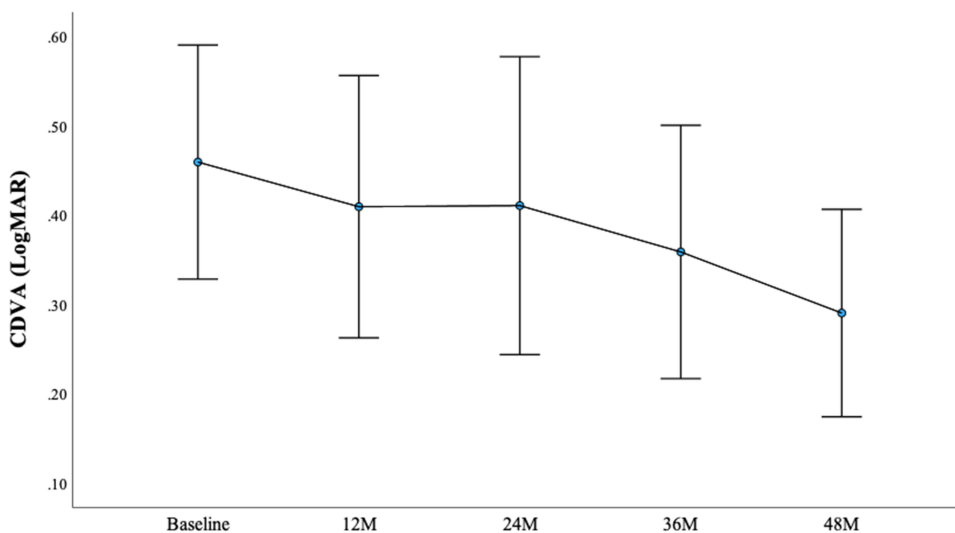


Figure 2 Corrected distance visual acuity (CDVA) in logMAR notation at baseline, 12, 24, 36, and 48 months after Trans-Epithelial Accelerated Crosslinking (TE-ACX).

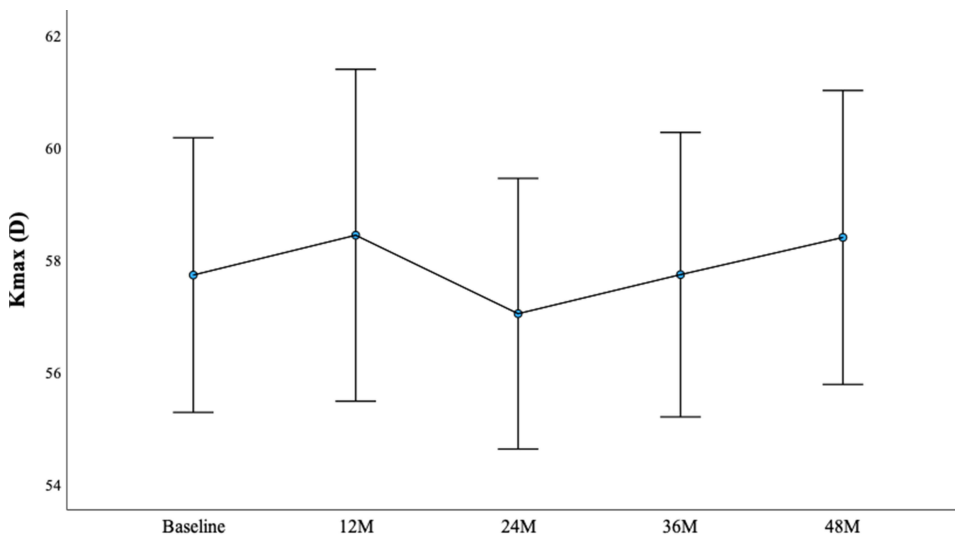


Figure 3 Maximum keratometry (Kmax) in diopters (D) at baseline, 12, 24, 36, and 48 months after Trans-Epithelial Accelerated Crosslinking (TE-ACX).

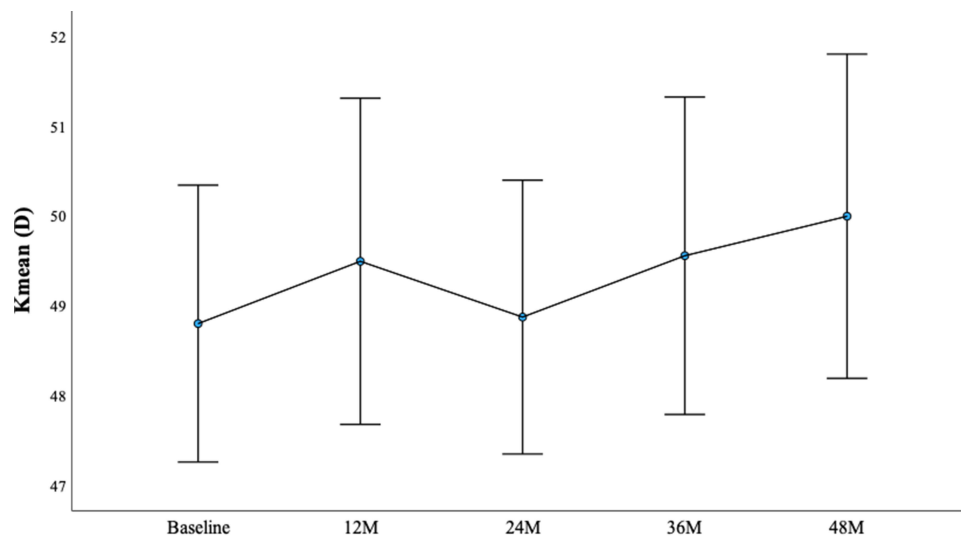


Figure 4 Mean keratometry (Kmean) in diopters (D) at baseline, 12, 24, 36, and 48 months after Trans-Epithelial Accelerated Crosslinking (TE-ACX).

evolution of Kmax and Kmean, respectively, throughout follow-up. There were no significant variations in ISV, IVA, IHD, or KI throughout follow-up.

Tomography, Tomographic Indices, and Pachymetry

The mean baseline PachyMin and D-index values were $453.20 \pm 35.97 \mu\text{m}$ and 9.99 ± 3.21 units, respectively. There was a significant decrease of PachyMin at 36 months ($-8.50 \pm 15.93 \mu\text{m}$; $p=0.004$), and at 48 months (-7.82 ± 18.37 ; $p=0.033$). Figure 5 depicts the evolution of PachyMin throughout follow-up. Additionally, there was a significant increase in the D-index throughout follow-up [$+0.51 \pm 1.03$ units at 12 months ($p=0.007$); $+0.69 \pm 1.25$ units at 24 months ($p=0.002$); $+1.02 \pm 1.72$ units at 36 months ($p=0.002$); $+1.15 \pm 1.64$ units at 48 months ($p<0.001$)]. Regarding PRC, there was a significant decrease in this parameter throughout follow-up (-0.12 ± 0.22 at 12 months; $p=0.002$; -0.15 ± 0.24 at 24 months; $p<0.001$; -0.17 ± 0.43 at 36 months; $p=0.021$; -0.16 ± 0.43 at 48 months; $p=0.027$).

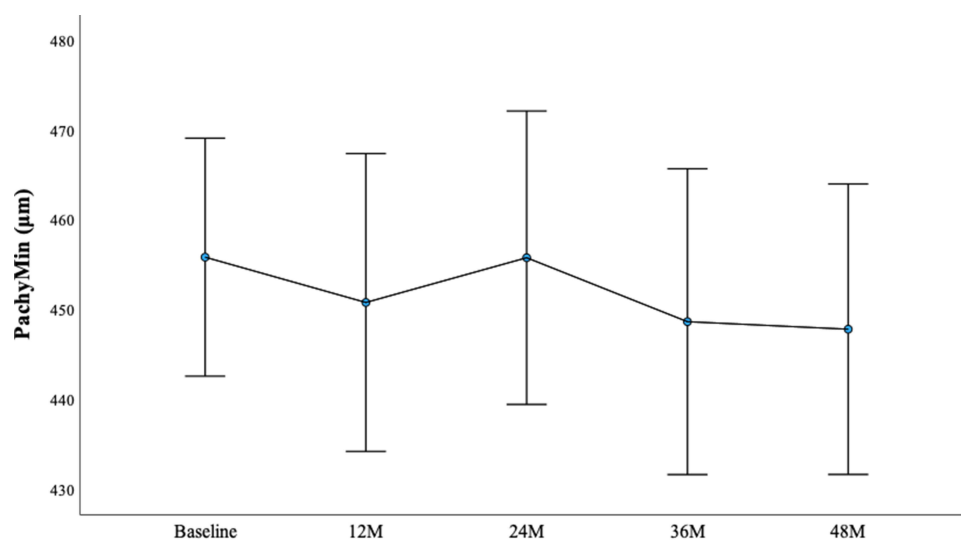


Figure 5 Minimum pachymetry (PachyMin) in micrometres (μm) at baseline, 12, 24, 36, and 48 months after Trans-Epithelial Accelerated Crosslinking (TE-ACX).

Progression and Need of Further Procedures

Table 3 discriminates the number of patients that presented at least one progression criteria at 12, 24, 36, and 48-month follow-up. There was an increase ≥ 1.0 D in Kmax in 25.7% (9/35) of the studied eyes at 12 months, 33.3% (12/36) at 24 months, 35.3% (12/34) at 36 months and 35.7% (10/28) at 48 months. Regarding Kmean, 42.9% (15/35) of the study eyes registered an increase ≥ 0.75 D at 12 months, 47.2% (17/36) at 24 months, 55.9% (19/34) at 36 months, and 42.9% (12/28) at 48 months. There was a reduction of at least 0.085 mm in PRC in 54.2% (19/35) of the study eyes at 12 months, 52.8% (19/36) at 24 months, 52.9% (18/34) at 36 months, and 53.6% (15/28) at 48 months. There was a decrease of $\geq 5\%$ in PachyMin in 2.9% (1/35) of the study eyes at 12 months, 11.1% (4/36) at 24 months, 17.6% (6/34) at 36 months, and 13.8% (4/29) at 48 months.

Twenty out of 35 eyes (57.1%) presented progression at 12 months, 22 out of 36 eyes (61.1%) presented progression at 24 months, 20 out of 34 eyes (58.8%) presented progression at 36 months, and 19 out of 28 eyes (67.9%) presented progression at 48 months. All 11 eyes that required further procedures after 36 months of follow-up presented progression at 12 months, at 24 months, and at 36 months.

The baseline parameters of the group that presented progression and the group that did not progress throughout follow-up were compared in **Table 4**. There were no significant differences in baseline age, CDVA, corneal Astg, Kmax, Kmean, PRC, PachyMin, and D-index. Additionally, the baseline characteristics of the group that required further corneal procedures and the group that did not require further procedures throughout follow-up were compared in **Table 5**. There were also no significant differences in baseline age, CDVA, corneal Astg, Kmax, Kmean, PRC, PachyMin, and D-index.

Discussion

In our retrospective study, 41 eyes from 30 patients underwent TE-ACXL (with chemical enhancers for trans-epithelial riboflavin diffusion, and an UV-A light beam intensity of 6mW/h for 15 minutes to achieve a total dose intensity of 5,4J/cm²) due to progressive KC. These patients were followed for 48 months. Eleven eyes required additional procedures, 36 months or later after the initial TE-ACXL. There were no significant differences in baseline age, CDVA, corneal Astg, Kmax, Kmean, PRC, PachyMin, and D-index between eyes that required further corneal procedures and eyes that did not require further interventions. Our primary outcome was the detection of progression of the KC, despite TE-ACXL. After undergoing TE-ACXL, there was a significant improvement in CDVA at 12 and at 48 months. However, there was also a significant increase in Kmean and D-index throughout follow-up, and a significant decrease in PRC and PachyMin (only at 36 and 48 months for the latter). Furthermore, 20/35 eyes (57.1%), 22/36 eyes (61.1%), 20/34 eyes (58.8%), and 19/28 eyes (67.9%) presented progression at 12, 24, 36, and 48 months. All 11 eyes that required further procedures after 36 months of follow-up presented progression at 12 months, at 24 months, and at 36 months. There were no

Table 3 Number and Proportion of Eyes Classified as Progressors According to the Criteria Defined in the Methods Section

Variables	Cut-off Value	Post-TE-ACXL			
		Δ 12-Months	Δ 24-Months	Δ 36-Months	Δ 48-Months
		N = 35	N = 36	N = 34	N = 28
		N (%)	N (%)	N (%)	N (%)
Kmax (D)	≥ 1 D increase	9 (25.7)	12 (33.3)	12 (35.3)	10 (35.7)
Kmean (D)	≥ 0.75 D increase	15 (42.9)	17 (47.2)	19 (55.9)	12 (42.9)
Astg (D)	≥ 1 D increase	2 (5.7)	2 (4.9)	5 (14.7)	4 (14.3)
PRC (mm)	≥ 0.085 mm decrease	19 (54.2)	19 (52.8)	18 (52.9)	15 (53.6)
PachyMin (μ m)	$\geq 5\%$ decrease	1 (2.9)	4 (11.1)	6 (17.6)	4 (13.8)

Notes: 11 eyes were excluded from the comparison between 48 months and baseline values because they were submitted to either an epithelial-off crosslinking (n=6), an intracorneal ring segment (n=4) or a corneal penetrating transplant (n=1), after 36 months of follow-up.

Abbreviations: μ m, micrometer; Astg, astigmatism; D, diopter; Kmax, maximum keratometry; Kmean, mean keratometry; PachyMin, minimum pachymetry; PRC, posterior radius of curvature from the 3.0 mm centered on the thinnest point of the cornea; TE-ACXL, transepithelial accelerated corneal collagen crosslinking.

Table 4 Baseline Parameters: Progressive Vs Non-Progressive Post TE-ACXL Keratoconus Cases

Variable at Baseline	12 Months		p value	24 Months		p value	36 Months		p value	48 Months		p value
	Progression	No Progression		Progression	No Progression		Progression	No Progression		Progression	No Progression	
	N = 20	N = 35		N = 22	N = 36		N = 20	N = 34		N = 19	N = 28	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age (years)	20.20 ± 4.54	20.80 ± 4.78	0.708	20.09 ± 3.57	20.71 ± 4.76	0.657	20.16 ± 4.15	21.86 ± 5.48	0.318	20.00 ± 1.87	20.75 ± 3.95	0.716
CDVA (logMAR)	0.56 ± 0.37	0.36 ± 0.35	0.129	0.53 ± 0.35	0.42 ± 0.41	0.371	0.56 ± 0.36	0.39 ± 0.32	0.158	0.43 ± 0.43	0.63 ± 0.46	0.546
Astg (D)	3.89 ± 2.26	2.97 ± 1.47	0.183	3.80 ± 1.99	3.36 ± 1.89	0.522	4.07 ± 2.30	3.29 ± 1.38	0.264	2.56 ± 1.41	3.80 ± 1.78	0.280
Kmax (D)	59.31 ± 4.63	56.39 ± 6.96	0.146	58.25 ± 3.85	56.08 ± 6.38	0.266	58.61 ± 5.05	55.95 ± 4.03	0.115	59.82 ± 1.71	55.83 ± 3.84	0.126
Kmean (D)	49.63 ± 3.55	47.61 ± 4.60	0.152	49.17 ± 3.05	47.11 ± 3.84	0.083	49.65 ± 3.33	47.34 ± 3.44	0.061	49.32 ± 2.39	46.75 ± 4.06	0.272
PRC (mm)	4.69 ± 0.46	4.85 ± 0.47	0.297	4.73 ± 0.37	4.94 ± 0.54	0.186	4.73 ± 0.46	4.95 ± 0.30	0.113	4.41 ± 0.42	4.96 ± 0.27	0.057
PachyMin (µm)	445.25 ± 32.87	457.20 ± 43.32	0.380	447.36 ± 35.50	465.57 ± 34.53	0.139	452.58 ± 36.82	457.86 ± 39.78	0.701	464.60 ± 24.23	427.50 ± 35.67	0.105
D-index	10.93 ± 2.88	9.67 ± 3.42	0.252	10.24 ± 2.51	8.90 ± 3.60	0.201	10.27 ± 3.28	9.21 ± 2.56	0.313	10.87 ± 2.20	10.04 ± 1.59	0.562

Abbreviations: µm, micrometer; Astg, astigmatism (K2-K1); CDVA, corrected distance visual acuity; D, diopter; Kmax, maximum keratometry; Kmean, mean keratometry; logMAR, logarithm of minimal angle of resolution; PachyMin, minimum pachymetry; PRC, posterior radius of curvature from the 3.0 mm centered on the thinnest point of the cornea; SD, standard deviation; TE-ACXL, Trans-Epithelial Accelerated Crosslinking.

Table 5 Baseline Parameters: Eyes Requiring versus Eyes Not Requiring Additional Procedures

Variable at Baseline	Required Further Procedures	Did Not Require Further Procedures	p value
	N = 11	N = 30	
	Mean ± SD	Mean ± SD	
Age (years)	18.50 ± 3.66	17.90 ± 4.39	0.508
CDVA (logMAR)	0.50 ± 0.42	0.46 ± 0.34	0.875
Astg (D)	3.22 ± 1.72	3.67 ± 1.99	0.667
Kmax (D)	58.08 ± 3.68	57.73 ± 6.42	0.678
Kmean (D)	48.30 ± 3.93	48.80 ± 4.04	0.699
PRC (mm)	4.66 ± 0.41	4.84 ± 0.49	0.302
PachyMin (µm)	446.75 ± 39.54	455.86 ± 34.76	0.528
D-index	10.53 ± 2.08	9.79 ± 3.55	0.325

Abbreviations: µm, micrometer; Astg, astigmatism (K2-K1); CDVA, corrected distance visual acuity; D, diopter; Kmax, maximum keratometry; Kmean, mean keratometry; logMAR, logarithm of minimal angle of resolution; PachyMin, minimum pachymetry; PRC, posterior radius of curvature from the 3.0 mm centered on the thinnest point of the cornea; SD, standard deviation.

intraoperative or postoperative complications regarding the procedure. Therefore, even though there was a significant improvement in CDVA, most eyes still progressed after undergoing TE-ACXL, which raises questions about its effectiveness in halting progression in KC, especially considering that there are newer techniques to improve CXL's efficacy and effectiveness.

Corneal CXL has been widely used for several years, with multiple prospective and relevant studies demonstrating its safety and effectiveness in progressive keratoconus.^{29,43} This treatment modality specifically targets the pathophysiology of the disease, decreasing or even ceasing its progression.^{2,28,44,45} In order to reduce associated complications, several modifications to the conventional Dresden protocol have been proposed, with overall favourable results.⁴⁶ One of this modified protocols, the TE-ACXL protocol, has been thoroughly investigated since its initial development, reflecting the significant interest in this method, which naturally has a lower rate of associated complications. Most studies acknowledge its safety and short-term efficacy, albeit most of them agree that additional long-term studies are required.^{47–57}

A significant number of non-randomized comparative trials (NRCTs), randomized clinical trials (RCTs), systematic reviews and meta-analyses have been published on the comparison between transepithelial and epithelium-off crosslinking.^{58–60} Wen et al performed a systematic review and meta-analysis in 2018 which included 8 comparative studies (5 randomized controlled trials and 3 non-randomized comparative trials), with a follow-up of 12 months.⁵⁹ In their review, there were no significant differences in the 12-month variation of UDVA and CDVA after epi-off or TE-CXL. More recently, in 2021, D'Oria et al also published a systematic review and meta-analysis on this comparison, which included a total of 15 studies (9 RCTs and 6 were NRCTs), with a follow-up of 12 to 36 months after CXL.⁵⁸ In their study, the CDVA improved significantly more in eyes that underwent epi-off CXL, but there were no significant differences in postoperative UDVA variation. Buzzonetti et al also reported a significant improvement in CDVA from baseline to 3 years in pediatric patients with progressive KC who underwent epi-off CXL, while patients who underwent TE-CXL presented no significant differences in CDVA throughout follow-up.⁶¹ Regarding topographic postoperative differences between epi-on and epi-off CXL, Wen et al reported that the reduction in Kmean was significantly higher with epi-off CXL when compared to the TE-CXL. When the TE-CXL groups were separated into subgroups of those using chemical additives and those using iontophoresis, the differences were even more apparent. TE-CXL using chemical additives to enhance riboflavin absorption and epi-off CXL presented a similar decrease in Kmean, while TE-CXL using iontophoresis presented a significantly lower reduction in Kmean when compared to epi-off CXL.⁵⁹ Henriquez et al also reported a significantly lower flattening in the Kmean in patients who undergo TE-ACXL (−0.09 D; $p=0.33$ vs −3.18 D; $p<0.001$ in the epi-off CXL). Their study presented a 5-year follow-up.²² D'oria et al reported

a significantly higher flattening of Kmax with epi-off CXL.⁵⁸ As for pachymetry changes, D’Oria et al reported no significant differences in central corneal thickness (CCT) changes.⁵⁸ As for adverse events, the postoperative discomfort and pain is significantly lower in patients who undergo TE-CXL, as expected.²³ Furthermore, in the review by Shalchi et al, which included 51 NRCTs of epi-off (45) and TE-CXL (6), haze, scarring and microbial keratitis were only reported in epi-off CXL studies, with none were reported in TE-CXL studies.⁶² D’Oria et al reported that TE-CXL protocols were significantly less prompt to have risks of delay in epithelial healing and persistent stromal haze, while there were no significant differences for endothelial cell density (ECD) variation, development of sterile infiltrates, or development of microbial keratitis.⁵⁸ Finally, Wen et al did not compare re-treatment rates or progression rates in both protocols, while D’Oria et al did not find significant differences in the progression rates in both CXL protocols.^{58,59}

There is an extremely relevant issue with TE-CXL, which is the wide variety of TE-CXL protocols and approaches currently used. There are many methodologies to increase corneal epithelial permeability to riboflavin (different chemical enhancers, iontophoresis), and multiple UVA irradiation protocols (18 mW/cm² irradiation for 5 minutes, 10 mW/cm² irradiation for 9 minutes, 6 mW/cm² for 15 minutes, 3 mW/cm² irradiation for 30 minutes, or even used pulsed protocols of irradiation of 45 mW/cm² for 5:20 min), though the total irradiation dose is generally similar (5.4 J/cm²).⁵⁸ Naturally, with this lack of currently agreed upon TE-CXL protocol, drawing conclusions about the non-inferiority of TE-CXL when compared to epi-off CXL is difficult. Furthermore, there are still no RCTs that compare the long-term outcomes (at least 5 years) of TE-CXL and epi-off CXL.

We compared our results to other large prospective studies with a long follow-up (≥ 36 months) that used TE-ACXL: Al Fayed et al, who evaluated 36 patients with a baseline age of 24.8 ± 4.2 years, Kmean of 48.2 ± 3.6 D, and CDVA of 0.2 ± 0.2 logMAR units;²³ and, Henriquez et al, who evaluated 32 patients with a baseline age of 13.2 ± 2.6 years, Kmean 47.32 ± 2.78 D, and CDA of 0.19 ± 0.17 logMAR units).²² In our study, we found a significant improvement in CDVA of 0.10 ± 0.29 logMAR units and 0.17 ± 0.33 logMAR units in BCVA at 12 and 48 months, respectively. Henriquez et al (who used a transepithelial riboflavin solution of 0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose, and 0.007% BAC, and irradiated the eyes for 5 minutes with an intensity of 18 mW/cm²) reported a significant improvement in CDVA of 0.09 ± 0.17 logMAR units and 0.06 ± 0.19 logMAR units at 12 and 60 months postoperatively.²² Al Fayed et al (who used a solution of tetracaine 1% with benzalkonium chloride 0.02% every 2 minutes, for 30 minutes, before starting no-dextran riboflavin drops, and irradiated the eyes for 30 minutes with an intensity of 3 mW/cm²) reported a decrease in CDVA of 0.02 and 0.06 logMAR units at 12 and 36 months, respectively.²³ In our study, there were no significant differences in Kmax throughout follow-up, while Kmean increased significantly throughout follow-up ($+0.64 \pm 1.04$ and $+1.13 \pm 2.00$ at 12 and 48 months, respectively). Al Fayed et al reported a significant increase in Kmax of around $+0.75$ and $+1.00$ D at 24 and 36 months, respectively, while Henriquez et al did not find significant differences in Kmax or Kmean at 12 or 60 months.^{22,23} In our study, PachyMin decreased significantly at 36 and 48 months (-8.50 ± 15.93 and -7.83 ± 18.37 μ m), while Henriquez et al reported no significant changes at 12 months and a significant increase of 7.33 ± 11.78 μ m at 60 months.²² In our study, there was a significant decrease in the PRC and a significant increase in the D-index throughout follow-up (from 12 to 48 months). None of the two aforementioned studies evaluated these parameters. Finally, regarding progression, we report a progression rate of 57.1%, 61.1%, 58.8%, and 67.9%, at 12, 24, 36 and 48 months respectively, while Henriquez et al reported a progression rate of 9.37% (3/32 eyes) at 60 months (progression was defined as an increase >1 D in steep keratometry assessed between 2 tests with at least 2 months apart), and Al Fayed et al reported a progression rate of 55% at 36 months (progression was defined as an increase in Kmax >1.00 D compared with the preoperative baseline examination).^{22,23} Our progression rate if we only considered progression as an increase >1 D in Kmax would be 25.7% (9/35), 33.3% (12/36), 35.3% (12/34), and 35.7% (10/28), at 12, 24, 36, and 48 months, respectively. Comparing our progression rate to the other 2 prospective RCTs, we had a lower progression rate than Al Fayed et al and a higher progression rate than Hernandez et al. Our study sample (baseline age of 20.90 ± 4.69 years, Kmean of 48.66 ± 3.97 D, and CDVA of 0.47 ± 0.36 logMAR units) was more similar to the one from Al Fayed et al than to the one from Henriquez et al.^{22,23}

Age at diagnosis is an important risk factor for progression. In fact, the eyes of younger patients tend to progress more rapidly than their adult counterparts.^{20,63,64} In fact, progression in pediatric patients with KC occurs in approximately 80% of the cases.⁶⁵ Nonetheless, in our study, isolated TE-ACXL halted KC progression in around

40% of the eyes at 36 months and 30% of the eyes at 48 months. Therefore, this procedure is still relevant in progressive KC management, especially considering its excellent safety profile and low risk of adverse events.^{58,59} It seems that epi-off CXL might be more aggressive in improving CDVA and flattening keratometry readings when compared with TE-ACXL.^{58,59} This fact should be taken into account when deciding between epi-off CXL and TE-ACXL for an individual patient. For instance, cases with higher keratometry readings and worse CDVA will probably benefit more from an epi-off CXL, while cases with mild KC, lower keratometry values, and reasonable CDVA can probably be safely managed with TE-ACXL.

Our study limitations include its retrospective and non-randomized nature, the lack of a comparison epi-off CXL group, and the lack of corneal endothelial cell density longitudinal evaluation. However, we believe that we have a relevant sample size of eyes that underwent TE-ACXL (when compared to other relevant studies that were published on this technique) and that our follow-up of 48 months allows for a reasonable evaluation of long-term outcomes of TE-ACXL. Nevertheless, there is still a significant need for RCTs that define the best TE-CXL protocol and that compare long-term outcomes of epi-off and TE-CXL. Only then will we be able to clearly define which cases should be treated with epi-off, and which cases should be treated with TE-CXL.

In conclusion, our results demonstrate that TE-ACXL was a safe treatment for eyes with progressive KC, increasing CDVA 4 years after the initial procedure. However, a significant proportion of eyes with progressive KC will still likely progress after being treated with TE-ACXL, requiring further procedures to halt disease progression.

Abbreviations

A-CXL, accelerated corneal collagen crosslinking; CDVA, Corrected distance visual acuity; CXL, Crosslinking; C-CXL, Conventional crosslinking; LogMAR, logarithm of minimal angle of resolution; IHD, Index of height decentration; ISV, Index of surface variance; IVA, Index of vertical asymmetry; K1, Flat Keratometry; K2, Steep Keratometry; KC, Keratoconus classification; Kmax, Maximum keratometry; Km, Mean keratometry; SD, Standard-deviation; TE-ACXL, Transepithelial accelerated corneal collagen crosslinking; TE-CXL, transepithelial corneal collagen crosslinking; UVA, Ultraviolet A.

Data Sharing Statement

Access to any supplemental information such as the study protocol or anonymized data can be available from the Corresponding Author upon reasonable request.

Ethics/Ethical Approval

The study was approved by the Institutional Ethics Review Board of Centro Hospitalar Universitário de São João, Porto, Portugal (certificate approval number CES284/2021). The protocol conformed with the canons of the Declaration of Helsinki for research involving human participants, as well as the European Union's General Data Protection Regulation. Informed consent was waived in view of the retrospective nature of the study. This article was redacted according to the recommendations of The Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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