ORIGINAL ARTICLE

Topography-Guided Corneal Crosslinking for Keratoconus: Is It Enough to Treat the Cone?

Crosslinking Guiado pela Topografia para Tratamento do Queratocone: Será Suficiente Tratar o Cone?

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ABSTRACT

INTRODUCTION: Our objective is to report topographic and refractive outcomes in the first year following topography guided corneal crosslinking (TG-CXL) for keratoconus, with special focus given to the morphological changes in the superior, non-treated, corneal stroma.

METHODS: Retrospective study. We included patients with progressive keratoconus who underwent TG-CXL: The epithelium was removed using phototherapeutic keratectomy with a 50 µm ablation within a 7.0 mm optic zone, followed by riboflavin application each 2 minutes for 10 minutes, and topography guided irradiation with ultraviolet-A, with treatment energies ranging from 10 to 5.4 J/cm^2 and fluence of 10 mw/cm^2. Patient data was collected at baseline, 3, 6 and 12 months postoperatively and included maximum keratometry (Kmax), mean anterior keratometry values within 5 points of a 3 mm diameter circle centered at the pupil, in the superior (S index) and inferior (I index) halves of the cornea, central corneal thickness, thinnest point pachymetry, subjective refraction and best corrected visual acuity (BCVA).

RESULTS: Twenty-seven eyes from 24 patients were included. Kmax was significantly flattened at 6 months (-0.92 ± 1.58 D; p=0.011) and 1 year (-0.83 ± 1.64 D; p=0.016) postoperatively. I index decreased significantly at 6 months (-0.81 ± 1.10 D; p=0.002) and 1 year (-0.83 ± 1.11 D; p=0.001), while the S index increased significantly at 6 months (0.93 ± 1.70 D; p=0.016) and 1 year (0.81 ± 1.42 D; p=0.008). There were no significant differences in Kmax (0.16 ± 0.99 D; p=0.457), I index (-0.004 ± 0.60 D; p=0.978) and S index (-0.04 ± 0.99 D; p=0.864) between 6 and 12 months postoperatively. The BCVA improved significantly at 1 year (difference of -0.13 ± 0.14 logMAR to baseline; p<0.001), while there was a significant myopic increase in spherical refractive error (difference of -1.05 ± 2.08 D to baseline; p=0.017).

CONCLUSION: TG-CXL leads to flattening of Kmax and superior corneal steepening at 1 year postoperatively. These keratometric changes seem to stabilize at 6 months. Spherical myopic refractive error increased and BCVA improved during follow-up. These results support TG-CXL as a valuable procedure in progressive keratoconus.

KEYWORDS: Corneal Cross-Linking; Corneal Topography; Cross-Linking Reagents; Keratoconus; Patient Outcome Assessment.

RESUMO

INTRODUÇÃO: O objetivo deste estudo é avaliar os resultados refrativos e topográficos durante o primeiro ano após a realização de crosslinking guiado pela topografia corneana (CXL-TG) no queratocone.

MÉTODOS: Estudo retrospetivo. Foram incluídos pacientes com queratocone em progressão, submetidos a CXL-TG: O epitélio foi removido por queratectomia fototerapêutica, com ablação de 50 μm e zona ótica de 7,0 mm, seguido de aplicação de riboflavina a cada 2 minutos por um período de 10 minutos e irradiação topo-guiada com luz ultravioleta A (energias entre 10 e 5,4 J/cm^2, fluência de 10 mw/cm^2). Foram colhidos dados relativos ao baseline, 3, 6 e 12 meses pós-operatório. Os parâmetros avaliados foram a queratometria máxima (Kmax), o valor médio da queratometria anterior em 5 pontos de um círculo centrado na pupila com 3 mm de diâmetro, medidos na metade superior (S index) e inferior (I index) da córnea, espessura central da córnea, refração subjetiva e melhor acuidade visual corrigida (MAVC).

RESULTADOS: Foram incluídos 27 olhos de 24 doentes. Verificou-se uma redução significativa do Kmax aos 6 meses (-0,92 ± 1,58 D; p=0,011) e 1 ano (-0,83 ± 1,64 D; p=0,016) pós-operatório. O *I index* foi também reduzido aos 6 (-0,81 ± 1,10 D; p=0,002) e 12 meses (-0,83 ± 1,11 D; p=0,001), enquanto o *S index* aumentou aos 6 (0,93 ± 1,70 D; p=0,016) e 12 meses (0,81 ± 1,42 D; p=0,008). Entre os 6 e 12 meses não se verificaram diferenças significativas no Kmax (0,16 ± 0,99 D; p=0,457), *I index* (-0,004 ± 0,60 D; p=0,978) e *S index* (-0,04 ± 0,99 D; p=0,864). A MAVC melhorou após 1 ano (diferença de -0,13 ± 0,14 logMAR para o *baseline*; p<0,001), havendo também um aumento da miopia em 1 ano (diferença de -1,05 ± 2,08 D para o *baseline*; p=0,017).

CONCLUSÃO: O CXL-TG leva a redução do Kmax e aumento da curvatura anterior da metade superior da córnea, após 1 ano. As alterações queratométricas atingem a estabilidade aos 6 meses. Verificou-se melhoria da MAVC e aumento da miopia no primeiro ano pós-operatório. Os nossos resultados sugerem que o CXL-TG é um procedimento promissor no tratamento de queratocone em progressão.

PALAVRAS-CHAVE: Avaliação do Resultado no Doente; Crosslinking Corneano; Queratocone; Reagentes de Ligações Cruzadas; Topografia Corneana.

INTRODUCTION

Keratoconus is a bilateral, although asymmetric corneal ectasia characterized by progressive corneal thinning and protrusion leading to irregular astigmatism and deterioration of visual acuity.[1,2] Corneal collagen crosslinking (CXL) is an established therapeutic approach with proven effectiveness in halting the progression of keratoconus.[3–5]

The popularity of CXL has fueled multiple lines of research trying to improve on the original procedure. Nowadays, several different protocols have been published and are used worldwide, expanding on the indications and applications of CXL.[6,7] In conventional CXL, the epithelium is removed from a central 9mm zone which is subsequently uniformly irradiated with ultraviolet-A (UVA) light (following riboflavin impregnation).[6] Topography-guided CXL (TG-CXL) is a recent innovation based on the principle that more energy should be applied to the most ectatic area for optimal results. The reasoning behind this approach is that the structural weakness in keratoconus is focused on the cone area, and not an homogenous reduction in corneal stability.[8] Therefore, treatment effect should be aimed at the weak cornea – usually inferiorly – and the superior, stable cornea would need little or no crosslinking.

Following up with those assumptions, TG-CXL provides surgeons with a new treatment platform that allows for irradiation to be tailored to each patient's cornea instead of uniformly applied to the whole cornea. In previous studies, this approach was found to have comparable safety to conventional CXL and results in greater flattening of Kmax, with better refractive and visual outcomes.[9–11]

Although in TG-CXL most energy will be delivered to the keratoconic cone, usually the central-inferior cornea, it is not straightforward that the superior cornea is left unchanged by this procedure. The subsequent redistribution of biomechanical stress in the cornea may lead to changes in the superior half of the cornea as well. Thus far, reports have been conflicting, with previous studies reporting either significant steepening of the superior cornea[11] or no significant changes.[9] As such, this study aimed to determine refractive and topographic outcomes, focusing on the changes in curvature for the superior and inferior halves of the cornea, during the first year following TG-CXL.

METHODS

STUDY DESIGN

Retrospective study. The inclusion criteria were patients with progressive keratoconus (progression defined as an increase in maximum keratometry (Kmax) ≥ 1.0D in the previous year, pachymetry thinning ≥5 µm, D-index increase ≥0.42)[12] as measured by corneal tomography [Wavelight Oculyzer II, Alcon Laboratories Inc., Fort Worth, Texas, USA]), that were subject to TG-CXL. Eyes with previous ocular surgery, concomitant ocular diseases and pregnant or breast-feeding patients were excluded.

SURGICAL PROCEDURE

The epithelium was removed using phototherapeutic keratectomy (PTK) (Wavelight Allegretto, Alcon Laboratories Inc., Fort Worth, Texas, USA): a 50 µm ablation within a 7.0 mm optic zone was performed in every patient. Riboflavin 0.1% with hydroxypropyl methylcellulose (HPMC) (VibeX Rapid, Avedro Inc., Waltham, Massachusetts, USA) was then instilled on the cornea every 2 minutes, for a total period of 10 minutes, prior to irradiation. A UVA irradiation pattern was designed for each individual patient (Mosaic System, Avedro Inc., Waltham, Massachusetts, USA) based on 3 concentric circular areas centered on the point of thinnest corneal pachymetry. Transitions between zones occurred at the regions of greatest change in anterior axial corneal curvature. The radiance exposure was 10 J/cm2 in the innermost circle, 7.2 J/cm^2 in the intermediate and 5.4 J/cm^2 on the outermost circle (Fig. 1). The fluence was set to 10 mw/cm^2.

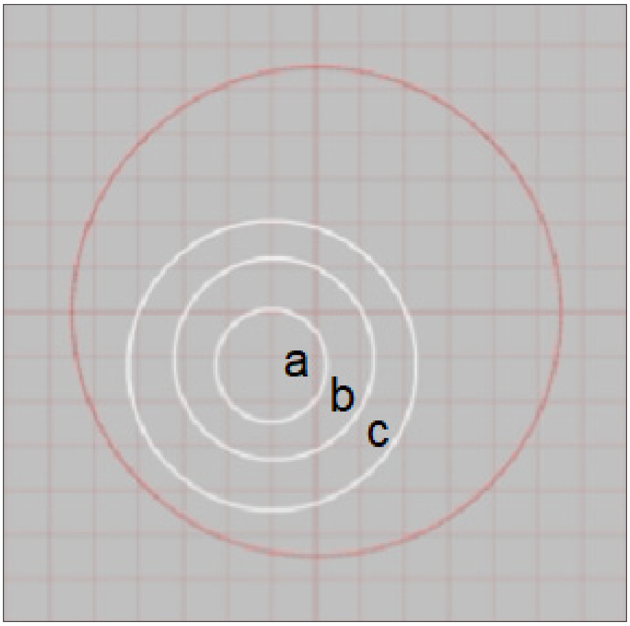

Figure 1. Topography guided crosslinking treatment planification. The radiance exposure is 10 J/cm^2 in the innermost circle (a), 7.2 J/cm^2 in the intermediate (b) and 5.4 J/cm^2 on the outermost circle (c). The diameter of these circles are 2.5, 4.5 and 6.5 mm respectively.

The postoperative medication regimen included topical fluoroquinolone drops (moxifloxacin 0.5%, 5 times per day) for one-week, artificial tear drops for one month and an oral non-steroid anti-inflammatory drug (clonixin 300 mg, up to 3 times a day) for 3 days. The operated eye was patched to facilitate re-epithelialization, after which a topical corticosteroid drop regimen (fluorometholone acetate 0.1%, 4 times per day for a week, followed by a 3-week taper) was started.

DATA COLLECTION

Data was collected from patient's clinical records from baseline, 3, 6 and 12 months postoperatively. Collected variables included best corrected visual acuity (BCVA), subjective refraction sphere and cylinder, Kmax, central corneal thickness (CCT) and pachymetry of the thinnest point. Additionally, and accordingly to the methodology previously described by Cassagne *et al* (2017),[9] data was collected on the anterior keratometry values from 5 points in the superior half of the cornea corresponding to the intersection of a 3mm diameter circle centered at the pupil and the 30º, 60º, 90º, 120º and 150º axes. The mean value from these 5 points is referred to as the superior (S) index. The mean value is also calculated for the 5 points corresponding to the intersection of the inferior part of the circle with the 210º, 240º, 270º, 300º, and 330º axes which is referred to as the inferior (I) index (Fig. 2).

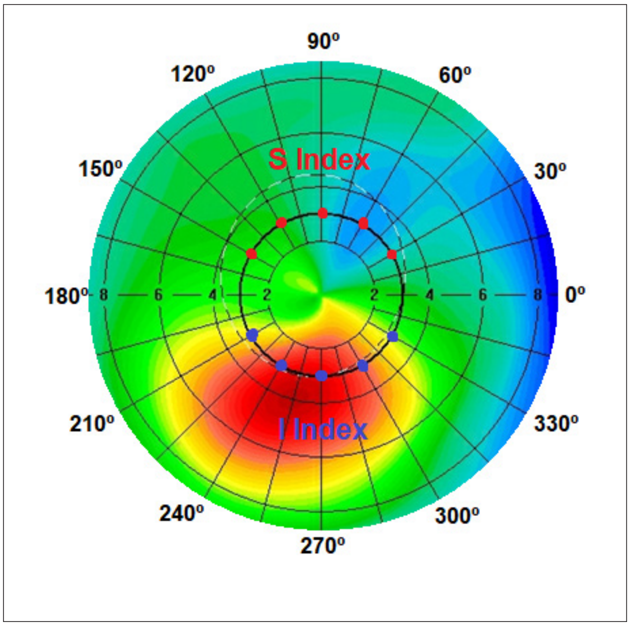

Figure 2. Schematic representation of superior (S) and inferior (I) indexes on a corneal topography image. Points constituting the S index are pictured in red and points constituting the I index are pictured in blue.

STATISTICAL ANALYSIS

Statistical analysis was performed using the software IBM SPSS Statistics version 26 (Armonk, New York, USA).

Descriptive statistics were computed for all variables. Normality was assessed using the Shapiro-Wilk test. Paired samples T-test was used to compare variables at different time points. Correlations were tested using Pearson correlation test. A p value <0.05 was considered statistically significant.

RESULTS

Twenty-seven eyes from 24 patients were included. Most patients were male (62.5%), with a mean age of 23.6 ± 8.5 years (median of 22.8 years).

Since 9 patients (33% of the sample) did not repeat corneal imaging at 3 months postoperatively, this data was excluded, and only baseline, 6 and 12 month data was analyzed. The baseline Kmax was 56.66 ± 4.19 D, with a significant flattening being observed at both 6 months (-0.92 ± 1.58 D; *p*=0.011) and 1 year (-0.83 ± 1.64 D; *p*=0.016) postoperatively. I index decreased significantly at both 6 months (-0.81 ± 1.10 D; *p*=0.002) and 1 year (-0.83 ± 1.11 D; *p*=0.001) of follow-up. On the other hand, S index increased significantly at 6 months (0.93 ± 1.70 D; *p*=0.016) and 1 year (0.81 ± 1.42 D; *p*=0.008). Comparing topography data between 6 and 12 months postoperatively, there was no significant difference found for Kmax (0.16 ± 0.99 D; *p*=0.457), I index (-0.004 ± 0.60 D; *p*=0.978) and S index (-0.04 ± 0.99 D; *p*=0.864). All corneal tomography related outcomes can be found in Table 1. A typical example for topographic changes following TG-CXL is presented in Fig. 3.

Significant improvements in BCVA were seen starting at 3 months postoperatively (difference of -0.065 ± 0.13 logMAR to baseline; *p*=0.016), and up to 1 year (difference of -0.127 ± 0.14 logMAR to baseline; *p*<0.001). Subjective refraction revealed a significant myopic increase in refraction at the 1-year visit for both sphere (difference of -1.05 ± 2.08 D to baseline; *p*=0.017) and spherical equivalent (difference of -1.05 ± 1.99 D to baseline; *p*=0.012), while the cylinder did not significantly change in the same time frame (difference of -0.01 ± 1.01 D to baseline; *p*=0.962). Visual acuity and subjective refraction related outcomes are presented in Table 2. No significant correlation was

Table 1. **Corneal tomography changes following topography guided corneal crosslinking (TG-CXL).**

		Baseline	6 months (difference)	1 year (difference)	6 – 12 months (difference)
Kmax (D)	Mean ± SD	56.66 ± 4.19	-0.92 ± 1.58	-0.83 ± 1.64	0.16 ± 0.99
	95% CI	55.00 to 58.31	-1.60 to -0.24	-1.49 to -0.17	-0.27 to 0.59
	p value		**0.011**	**0.016**	0.457
S Index (D)	Mean ± SD	43.79 ± 2.93	0.93 ± 1.70	0.81 ± 1.42	-0.04 ± 0.99
	95% CI	42.63 to 44.95	0.19 to 1.67	0.24 to 1.38	-0.46 to 0.39
	p value		**0.016**	**0.008**	0.864
I Index (D)	Mean±SD	52.87 ± 3.29	-0.81 ± 1.10	-0.83 ± 1.11	-0.004 ± 0.60
	95% CI	51.57 to 54.17	-1.28 to -0.34	-1.27 to -0.38	-0.26 to 0.26
	p value		**0.002**	**0.001**	0.978
CCT (μm)	Mean ± SD	473.2 ± 36.9	-7.4 ± 8.7	-2.2 ± 11.9	4.3 ± 8.8
	95% CI	458.6 to 487.8	-11.2 to -3.7	-7.0 to 2.6	0.5 to 8.1
	p value		**<0.001**	0.355	**0.029**
Thinnest Pachymetry (μm)	Mean ± SD	446.6 ± 38.5	-13.0 ± 14.6	-8.0 ± 12.8	4.0 ± 12.0
	95% CI	431.4 to 461.9	-19.3 to -6.8	-13.2 to -2.9	-1.2 to 9.2
	p value		**<0.001**	**0.004**	0.128

Bold text highlights statistically significant *p* values (<0.05); SD – standard deviation; CI – confidence interval; CCT – central corneal thickness

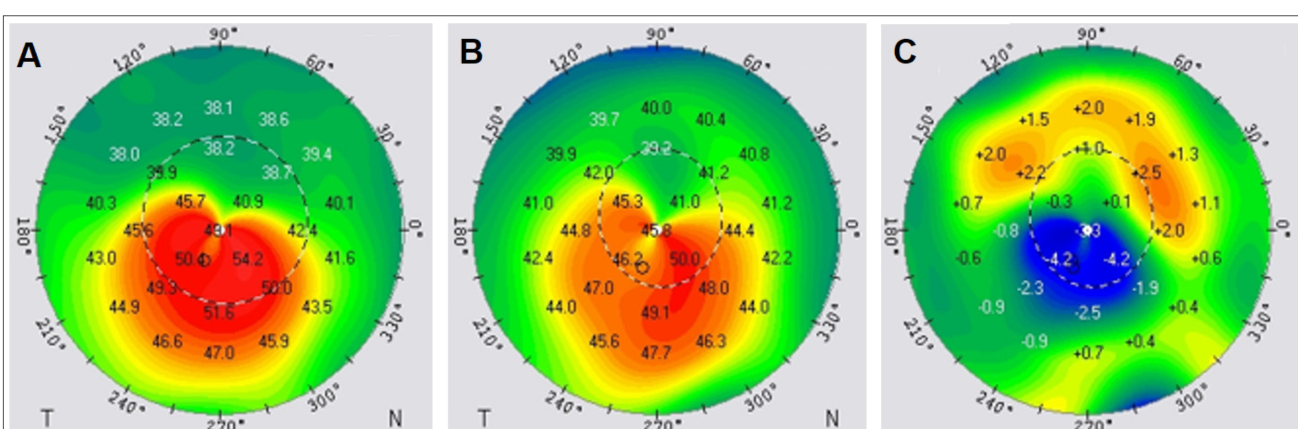

Figure 3. Axial curvature maps of a patient's right eye treated with topography guided crosslinking. Imaging from baseline (A), 12 months after the procedure (B) and 12 month-baseline difference map (C) is presented.

Table 2. **Visual acuity and refractive changes following topography guided corneal crosslinking (TG-CXL).**

		Baseline	3 months (difference)	6 months (difference)	1 year (difference)	6 – 12 months (difference)
BCVA (LogMAR)	Mean ± SD	0.32 ± 0.21	-0.07 ± 0.13	-0.11 ± 0.15	-0.13 ± 0.14	-0.02 ± 0.06
	95% CI	0.24 to 0.40	-0.12 to -0.01	-0.17 to -0.05	-0.19 to -0.07	-0.04 to 0.01
	p value		**0.016**	**0.001**	**<0.001**	0.119
Sphere (D)	Mean ± SD	-1.46 ± 2.22	-1.29 ± 1.85	-1.25 ± 2.32	-1.05 ± 2.08	0.16 ± 1.25
	95% CI	-2.34 to -0.58	-2.04 to -0.54	-2.21 to -0.29	-1.89 to -0.21	-0.36 to 0.68
	p value		**0.002**	**0.013**	**0.017**	0.529
Cylinder (D)	Mean ± SD	-2.62 ± 1.27	0.45 ± 1.01	0.09 ± 1.39	-0.01 ± 1.01	-0.10 ± 1.01
	95% CI	-3.12 to -2.12	0.05 to 0.86	-0.48 to 0.66	-0.42 to 0.40	-0.52 to 0.32
	p value		**0.031**	0.749	0.962	0.624
Spherical Equivalent (D)	Mean ± SD	-2.77 ± 2.33	-1.06 ± 1.74	-1.21 ± 2.14	-1.05 ± 1.99	0.11 ± 0.85
	95% CI	-3.70 to -1.85	-1.76 to -0.36	-2.09 to -0.32	-1.86 to -0.25	-0.24 to 0.46
	p value		**.005**	**.009**	**0.012**	0.525

Bold text highlights statistically significant p values (<0.05); BCVA – best corrected visual acuity; SD – standard deviation; CI – confidence interval

found between the change in refractive sphere and: Kmax (r=-0.116, *p*=0.565), S index (r=-0.267, *p*=0.188) or I index (r=-0.121, *p*=0.573), from baseline to 1 year postoperatively.

The most frequent post-operative adverse event was the development of transient corneal haze, reported in 14.8% of eyes. One eye developed sterile infiltrates. There were no cases of infection.

DISCUSSION

Previous studies have demonstrated significant improvements in keratometry and visual acuity following TG-CXL for keratoconus.[9–11] The current study shows similar results with a significant flattening of Kmax being found at both 6 months and 1 year, as well significant improvements in BCVA over this time period.

One of the rationales provided by authors to explain the improvement in BCVA after TG-CXL is the regularization of anterior keratometry. Conventional CXL aims for a global strengthening of the stroma by applying the same effect uniformly across the central cornea. This effect is seen in the results of most conventional CXL series: there is uniform central flattening but whatever asymmetry exists before treatment is maintained afterwards.[10,11] With TG-CXL, an asymmetric treatment plan is utilized to obtain an asymmetric flattening effect, one that globally favors a more normal anterior surface.

In our series, anterior keratometry changes in the superior and inferior halves of the cornea were assessed utilizing the S and I indexes.[9,13] A significant reduction in the I index and a significant increase in the S index was found (1 year change in I and S indexes respectively: -0.83 D and +0.81D). This combination of inferior flattening and superior steepening was observed by other authors,[10,11] albeit not by all describing this technique.[9] In fact, Seiler *et al* (2016)[10] purposefully introduced an index, named “Regularization Index”, to measure this surface normalization effect.

We attribute this superior steepening to a more advantageous redistribution of biomechanical forces in the stroma. Nevertheless, a reasonable objection could be made that this steepening is due to continued progression in the non-crosslinked superior cornea. Our analysis, however, also demonstrated that this superior steepening ceases by 6 months postoperatively since there was no significant difference between 6 and 12 months for the S index (difference of -0.04 ± 0.99 D; *p*=0.864). Additionally, no significant changes were found for I index or Kmax during the same period (Table 1). As such, our data suggests more of an immediate rebalance of the corneal structure, followed by keratometric stability 6 months after the procedure.

Central corneal thickness did not significantly vary at the 1 year time point (*p*=0.355), although an initial significant decrease in thickness was noted 6 months postoperatively. A similar tendency, also using Scheimpflug tomography measurements, has been previously reported in a conventional CXL study (although statistical significance was not assessed).[5] Thinnest pachymetry was significantly reduced at 1 year (mean change of -8.0μm; *p*=0.004), as previously reported by Seiler, *et al* (2016).[10] Again, thinning was not observed between 6 and 12 months, suggesting stability beyond 6 months of follow-up. Noticeably, Scheimpflug pachymetric measurements after CXL are prone to error due to haze-induced backscatter,[14] making these changes difficult to interpret.

There was no significant correlation between the changes in spherical refractive error and S index (no correlation found with for Kmax or I index either). This suggests that the myopic increase in subjective refraction cannot be solely attributable to the steepening of the superior half of the cornea, and other factors must contribute towards this refractive change. Nevertheless, such a refractive change is not inherent to TG-CXL, as Nordstrom *et al* (2016) reported a significant myopic decrease at 1 year of follow-up.[11]

Limitations to this study include its retrospective nature and a follow-up limited to one year.

In conclusion, this study showed that a customized topography-guided crosslinking procedure regularizes the anterior corneal keratometry in keratoconus, as superior corneal steepening and inferior flattening were observed, making both corneal halves more similar to each other. It also reduces Kmax and leads to significant improvements in BCVA. Hence, TG-CXL should be seen as a valuable therapeutic approach in the context of progressive keratoconus.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

TC and JG: Responsible for data gathering.

TC, JG, AR: Responsible for creating the manuscript.

JG, AR, MQJ, JM: Supervised this project and contributed with their expertise to its conclusion.

All authors read and approved the final manuscript.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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REFERENCES

1. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. Cont Lens Anterior Eye. 2010;33:157-66; quiz 205. doi:10.1016/j.clae.2010.04.006
2. Santodomingo-Rubido J, Carracedo G, Suzaki A, Villa-Collar C, Vincent SJ, Wolffsohn JS. Keratoconus: An updated review. Cont Lens Anterior Eye. 2022;45:101559. doi:10.1016/j.clae.2021.101559
3. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol. 2010;149:585-93. doi:10.1016/j.ajo.2009.10.021
4. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg. 2009;35:1358-62. doi:10.1016/j.jcrs.2009.03.035
5. Asri D, Touboul D, Fournié P, Malet F, Garra C, Gallois A, et al. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French National Reference Center for Keratoconus. J Cataract Refract Surg. 2011;37:2137-43. doi:10.1016/j.jcrs.2011.08.026
6. Beckman KA, Gupta PK, Farid M, Berdahl JP, Yeu E, Ayres B, et al. Corneal crosslinking: Current protocols and clinical approach. J Cataract Refract Surg. 2019;45:1670-9. doi:10.1016/j.jcrs.2019.06.027
7. Wu D, Lim DK, Lim BX, Wong N, Hafezi F, Manotosh R, et al. Corneal cross-linking: the evolution of treatment for corneal diseases. Front Pharmacol. 2021;12:686630. doi:10.3389/fphar.2021.686630
8. Roberts CJ, Dupps WJ. Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg. 2014;40:991-8. doi:10.1016/j.jcrs.2014.04.013
9. Cassagne M, Pierné K, Galiacy SD, Asfaux-Marfaing MP, Fournié P, Malecaze F. Customized topography-guided corneal collagen cross-linking for keratoconus. J Refract Surg. 2017;33:290-7. doi:10.3928/1081597X-20170201-02
10. Seiler TG, Fischinger I, Koller T, Zapp D, Frueh BE, Seiler T. Customized corneal cross-linking: one-year results. Am J Ophthalmol. 2016;166:14-21. doi:10.1016/j.ajo.2016.02.029
11. Nordström M, Schiller M, Fredriksson A, Behndig A. Refractive improvements and safety with topography-guided corneal crosslinking for keratoconus: 1-year results. Br J Ophthalmol. 2017;101:920-5. doi:10.1136/bjophthalmol-2016-309210
12. Shajari M, Steinwender G, Herrmann K, Kubiak KB, Pavlovic I, Plawetzki E, et al. Evaluation of keratoconus progression. Br J Ophthalmol. 2019;103:551-7. doi:10.1136/bjophthalmol-2017-311651
13. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. J Refract Surg. 1995;11:371-9. doi:10.3928/1081-597X-19950901-14
14. Mencucci R, Paladini I, Virgili G, Giacomelli G, Menchini U. Corneal thickness measurements using time-domain anterior segment OCT, ultrasound, and Scheimpflug tomographer pachymetry before and after corneal cross-linking for keratoconus. J Refract Surg. 2012;28:562-6. doi:10.3928/1081597X-20120703-02

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