Original research article

EJO European Journal of Ophthalmology

European Journal of Ophthalmology
1–5

DOI: 10.1177/1120672119872375
journals.sagepub.com/home/ejo
SAGE

Efficacy of pulsed-light accelerated crosslinking in the treatment of progressive keratoconus: Two-year results

Selman Belviranli and Refik Oltulu

Abstract

Purpose: The aim of this study was to evaluate the 2-year results of epithelium-off pulsed-light accelerated corneal collagen crosslinking treatment in progressive keratoconus using 30 mW/cm^2 ultraviolet A light for 6 min with a total dose of 5.4 J/cm^2.

Methods: A total of 30 eyes of 22 patients with documented progressive keratoconus and treated with epithelium-off pulsed-light accelerated corneal collagen crosslinking using the KXL® crosslinking device (Avedro Inc, Waltham, MA, USA) were included in this retrospective study. Corneal tomographic measurements and best spectacle-corrected visual acuity were compared using analysis of variance with repeated measurements between the baseline visit (before the corneal collagen crosslinking treatment), and the sixth month, first, and second year visits.

Results: Flat keratometry (K1), steep keratometry (K2), and mean keratometry (Km) decreased significantly at sixth month, first, and second years ($p < 0.001$, $p = 0.001$, and $p < 0.001$, respectively). Maximum keratometry (Kmax) decreased from 55.40 ± 4.90 D at baseline to 54.82 ± 4.68 D, 54.80 ± 5.12 D, and 54.65 ± 5.36 D at sixth month, first year, and second year, respectively ($p = 0.007$). The best spectacle-corrected visual acuity improved from 0.34 ± 0.24 logMAR at baseline to 0.25 ± 0.16 logMAR, 0.22 ± 0.15 logMAR, and 0.17 ± 0.13 logMAR at sixth month, first year, and second year, respectively ($p < 0.001$). At the second year visit, best spectacle-corrected visual acuity remained stable (no lines lost) with respect to the baseline in 8 eyes and increased 1 or more lines in 22 eyes.

Conclusion: Pulsed-light accelerated corneal collagen crosslinking using 30 mW/cm^2 ultraviolet A light for 6 min with a total dose of 5.4 J/cm^2 is an effective treatment modality in cases with progressive keratoconus—it stops progression at 2 years also regresses some of the cases.

Keywords

Keratoconus, accelerated crosslinking, pulsed ultraviolet A light

Date received: 13 November 2018; accepted: 7 August 2019

Introduction

Keratoconus is a progressive ectatic disorder of the cornea characterized by abnormal protrusion and thinning.[1] Until recently, treatment options for keratoconus—including spectacles, contact lenses and intracorneal ring implantation—were not able to stop the progression of the disease and up to 20% of the patients with keratoconus eventually required keratoplasty.[2,3] Clinical application of corneal collagen crosslinking (CXL) has revolutionized the management of ectatic corneal disorders by inhibiting the progression of the disease. CXL treatment is aimed at increasing the mechanical resistance and biochemical stability of the cornea by inducing the formation of crosslinks between collagen fibrils using riboflavin as a photosensitizer and ultraviolet A (UVA) light. Wollensak

Department of Ophthalmology, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey

Corresponding author:
Selman Belviranli, Department of Ophthalmology, Meram School of Medicine, Necmettin Erbakan University, 42080 Konya, Turkey.
Email: drselman@gmail.com

et al.[4] reported the first clinical application of the treatment in 2003. Their treatment procedure included removal of the central corneal epithelium, application of 0.1% riboflavin in 20% dextran solution, and irradiation of the cornea with 370 nm UVA light at 3 mW/cm^2 for 30 min with a total dose of 5.4 J/cm^2.[4,5] This classical procedure is commonly called the "Dresden protocol." Several studies have confirmed the safety and efficacy of this protocol for stopping the progression of ectatic corneal disorders.[6–12]

In recent years, studies have focused on accelerated CXL protocols which aim to shorten the duration of treatment without impairing its efficacy. Accelerated protocols are based on the law of photochemical reciprocity (the Bunsen–Roscoe law), which implies that increasing the exposure dose and reducing the exposure time at a constant total energy level will produce the same effect.[13] New generation CXL devices allow application of UVA doses up to 45 mW/cm^2. On the contrary, the presence of oxygen is required for CXL, but high-exposure doses of UVA light cause a rapid decrease in the oxygen concentration.[14,15] In order to increase the efficacy of CXL treatment by replenishing the consumed oxygen, research has focused on pulsing the UVA light with "on" and "off" periods. Studies show increased efficacy of pulsed-light accelerated corneal collagen crosslinking (PLA-CXL) treatment in comparison with continuous-light accelerated corneal collagen crosslinking (CLA-CXL) treatment.[16–19] In previous clinical studies of PLA-CXL treatment, an increased total UVA dose of 7.2 J/cm^2 was used. In this study, we aim to evaluate the 2-year results of epithelium-off PLA-CXL treatment in keratoconus using 30 mW/cm^2 UVA light for 6 min (1 s on and 1 s off) with a total dose of 5.4 J/cm^2, same as the Dresden protocol without increasing the total dose.

Materials and methods

Patients with documented progressive keratoconus and treated with epithelium-off PLA-CXL between April 2014 and April 2015 were retrospectively reviewed and 30 eyes of 22 patients (9 males, 13 females; mean age: 22.7 ± 7.2 years, range: 14–38 years) were included in the study. The right eye in six patients, the left eye in eight patients, and both eyes in eight patients were included. Based on the Amsler–Krumeich classification, 12 of the 30 eyes (40.0%) were at stage 1, 10 eyes (33.3%) were at stage 2, 6 eyes (20.0%) were at stage 3, and 2 eyes (6.7%) were at stage 4. This study was approved by the local clinical research ethics committee and followed the tenets of the Declaration of Helsinki.

Progression criteria for CXL treatment included an increase in maximum keratometry (Kmax) by 1 D or more or a reduction in the visual acuity by one or more Snellen lines over the last year. CXL treatment was applied on corneas thicker than 400 µ and without corneal scars and signs of infection. Patients with pregnancy, lactation, systemic diseases, dry eye disease, a history of herpetic eye diseases, glaucoma, uveitis, intraocular tumors, and previous ocular surgery were excluded.

The KXL® crosslinking device (Avedro Inc, Waltham, MA, USA) was used for the CXL treatment. In the CXL procedure, under local anesthesia, after administration of 50% alcohol, the corneal epithelium was removed by a spatula in the central 9 mm diameter area. A 0.1% solution of riboflavin with hydroxypropyl methylcellulose (Vibex Rapid®; Avedro Inc, Waltham, MA, USA) was applied for 10 min at intervals of 2 min each. After corneal soaking with riboflavin, UVA light at 30 mW/cm^2 was applied for 6 min with 1 s on and 1 s off intervals and a total energy dose of 5.4 J/cm^2 was achieved. After the CXL procedure, a therapeutic soft contact lens bandage was applied until complete re-epithelization. Topical antibiotics (moxifloxacin hydrochloride, Vigamox®) q.i.d. for 1 week, topical steroids (dexamethasone sodium phosphate, Dexa-Sine SE®) q.i.d. for 1 month, and artificial teardrops were administered postoperatively.

Corneal tomographic measurements and best spectacle-corrected visual acuity (BSCVA) were compared between the baseline visit (before the CXL treatment) and the sixth month, first year, and second year visits. Patients were examined with the Pentacam® Scheimpflug rotating camera system (Oculus Optikgeräte GmbH, Wetzlar, Germany) in standard dim light conditions. Parameters evaluated in the study included flat keratometry (K1), steep keratometry (K2), mean keratometry (Km), maximum keratometry (Kmax), topographic astigmatism of the anterior surface (Ast), thickness of the thinnest point (Thin), front elevation at the thinnest point (Ef), back elevation at the thinnest point (Eb), index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), center keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD), and minimum sagittal curvature (Rmin). BSCVA was evaluated using Snellen Charts and converted to logMAR units for the statistical analysis.

Data were expressed as mean ± standard deviation (SD). Normality was checked for each continuous variable. Analysis of variance (ANOVA) with repeated measurements was used to compare the parameters between baseline, sixth month, first year, and second year visits. Statistical analyses of the data were performed using the SPSS 20.0 software and a p value of less than 0.05 was considered statistically significant.

Results

Flat keratometry (K1) decreased from 47.20 ± 2.59 D at baseline to 46.85 ± 2.57 D at sixth month, 46.73 ± 2.61 D at first year, and 46.53 ± 2.55 D at second year ($p < 0.001$). Steep keratometry (K2) decreased from 50.78 ± 4.02 D at baseline to 50.41 ± 3.83 D at sixth month, 50.41 ± 4.01 D at

Table 1. Tomographic parameters, tomography-derived indices, and visual acuity at each visit and change in each parameter from baseline to second year visit.

	Baseline	Sixth month	First year	Second year	*p*	Δ 2 years
K1 (D)	47.20 ± 2.59	46.85 ± 2.57	46.73 ± 2.61	46.53 ± 2.55	<**0.001**	–0.67 ± 0.71
K2 (D)	50.78 ± 4.02	50.41 ± 3.83	50.41 ± 4.01	50.27 ± 3.95	**0.001**	–0.51 ± 0.78
Km (D)	48.90 ± 3.14	48.54 ± 3.07	48.48 ± 3.15	48.31 ± 3.08	<**0.001**	–0.58 ± 0.72
Kmax (D)	55.40 ± 4.90	54.82 ± 4.68	54.80 ± 5.12	54.65 ± 5.36	**0.007**	–0.75 ± 1.04
Ast (D)	3.58 ± 2.15	3.55 ± 1.91	3.70 ± 2.06	3.73 ± 2.11	0.406	+0.14 ± 0.52
CCT (μ)	463.6 ± 35.4	455.2 ± 43.9	459.0 ± 41.5	457.8 ± 44.2	**0.027**	–5.8 ± 17.4
Thin (μ)	445.1 ± 37.6	435.8 ± 44.4	440.1 ± 41.3	438.0 ± 46.0	**0.015**	–7.1 ± 17.2
Ef (μ)	28.83 ± 8.44	21.63 ± 8.80	21.00 ± 10.41	20.50 ± 10.93	**0.010**	–3.33 ± 5.96
Eb (μ)	50.17 ± 17.05	49.57 ± 17.59	49.73 ± 17.42	50.23 ± 17.60	0.909	+0.07 ± 5.48
ISV	85.20 ± 25.79	83.13 ± 26.69	81.47 ± 26.91	80.57 ± 28.40	**0.003**	–4.63 ± 7.87
IVA	0.87 ± 0.29	0.86 ± 0.29	0.84 ± 0.31	0.84 ± 0.33	0.182	–0.04 ± 0.13
KI	1.23 ± 0.10	1.22 ± 0.10	1.22 ± 0.10	1.22 ± 0.11	0.141	–0.01 ± 0.03
CKI	1.07 ± 0.03	1.06 ± 0.04	1.06 ± 0.04	1.05 ± 0.04	<**0.001**	–0.01 ± 0.01
IHA	33.67 ± 27.15	37.26 ± 25.75	36.63 ± 26.68	35.63 ± 24.49	0.664	+1.95 ± 17.64
IHD	0.12 ± 0.05	0.11 ± 0.05	0.11 ± 0.05	0.11 ± 0.05	**0.043**	–0.01 ± 0.02
Rmin	6.13 ± 0.51	6.20 ± 0.50	6.21 ± 0.55	6.23 ± 0.57	**0.001**	+0.10 ± 0.14
BSCVA (logMAR)	0.34 ± 0.24	0.25 ± 0.16	0.22 ± 0.15	0.17 ± 0.13	<**0.001**	–0.17 ± 0.17

p: statistical significance in the analysis of variances; Δ 2 years: change in each of the parameters from baseline to second year visit; K1: flat keratometry; K2: steep keratometry; Km: mean keratometry; Kmax: maximum keratometry; Ast: topographic astigmatism; CCT: central corneal thickness; Thin: thickness of the thinnest point; Ef: front elevation at the thinnest point; Eb: back elevation at the thinnest point; ISV: index of surface variance; IVA: index of vertical asymmetry; KI: keratoconus index; CKI: center keratoconus index; IHA: index of height asymmetry; IHD: index of height decentration; Rmin: minimum sagittal curvature; BSCVA: best spectacle-corrected visual acuity in logMAR.
Statistically significant results are given in bold.

first year, and 50.27 ± 3.95 D at second year ($p = 0.001$). Mean keratometry (Km) decreased from 48.90 ± 3.14 D at baseline to 48.54 ± 3.07 D at sixth month, 48.48 ± 3.15 D at first year and 48.31 ± 3.08 D at second year ($p < 0.001$). Maximum keratometry (Kmax) decreased from 55.40 ± 4.90 D at baseline to 54.82 ± 4.68 D at sixth month, 54.80 ± 5.12 D at first year, and 54.65 ± 5.36 D at second year ($p = 0.007$). Mean change in Kmax was −0.59 ± 1.41 D in the first 6 months, −0.60 ± 1.11 D in the first year, and −0.75 ± 1.04 D in the first 2 years. At the second year visit, Kmax decreased more than 1.0 D in 12 eyes and more than 2.0 D in 4 eyes from the baseline. Kmax remained in the +1 and −1 D range in 18 eyes. Topographic astigmatism did not change significantly ($p = 0.406$).

Corneal thickness at the thinnest point decreased from 445.1 ± 37.6 μ at baseline to 435.8 ± 44.4 μ at sixth month, 440.1 ± 41.3 μ at first year, and 438.0 ± 46.0 μ at second year ($p = 0.015$). Central corneal thickness decreased from 463.6 ± 35.4 μ at baseline to 455.2 ± 43.9 μ at sixth month, 459.0 ± 41.5 μ at first year, and 457.8 ± 44.2 μ at second year ($p = 0.027$).

When we look at the tomography-derived indices, ISV, CKI, and IHD showed a statistically significant decrease ($p = 0.003$, $p < 0.001$, and $p = 0.043$, respectively) and Rmin showed a statistically significant increase ($p = 0.001$). IVA, KI, and IHA did not change significantly ($p = 0.182$, $p = 0.141$, and $p = 0.664$, respectively).

The BSCVA improved from baseline 0.34 ± 0.24 logMAR to 0.25 ± 0.16 logMAR at sixth month, 0.22 ± 0.15 logMAR at first year, and 0.17 ± 0.13 logMAR at second year ($p < 0.001$). There was a mean gain of −0.17 ± 0.17 logMAR in BSCVA in 2 years. At the second year visit, BSCVA remained stable (no lines lost) with respect to the baseline in 8 eyes and increased by 1 or more lines in 22 eyes.

Comparisons of each parameter between the four visits, statistical significance in the ANOVAs and the change in each parameter in 2 years (from baseline to second year visit, Δ 2 years) are shown in Table 1.

There were no reported intraoperative or postoperative complications. Re-epithelization was completed in 4 days in all cases. Excessive haze formation or excessive progressive flattening was not reported in any of the cases.

Discussion

The classical procedure of CXL treatment, the Dresden protocol, has been confirmed to be safe and effective in inhibiting the progression of keratoconus.[6–12] However, due to the long duration of this treatment protocol, studies have focused on accelerated CXL treatment modalities in order to shorten the duration of treatment. Based on the law of photochemical reciprocity (the Bunsen–Roscoe law), short-duration treatments are possible by increasing

the illumination intensity. Initial studies on accelerated CXL treatment included 9 mW/cm^2 UVA intensity for 10 min. Cınar et al.[20] included 23 eyes and reported the stabilization effect of CXL with 9 mW/cm^2 UVA light for 10 min. Similarly, Elbaz et al.[21] reported the stabilizing effect of accelerated CXL with 9 mW/cm^2 UVA intensity at 1-year follow-up. Later, studies using higher UVA intensities were performed. In a study including 28 eyes with a follow-up time of 21 months, Alnawaiseh et al.[22] showed that accelerated CXL with 18 mW/cm^2 for 5 min was effective in stopping the progression of the disease. Mita et al.[23] reported improvement in visual acuity and keratometry readings in 39 eyes 6 months after CXL treatment using 3 min UVA irradiance at a level of 30 mW/cm^2. Tomita et al.[24] reported that both conventional CXL and accelerated CXL with 30 mW/cm^2 were safe and effective. On the contrary, Shetty et al.[25] compared different CXL protocols and reported better outcomes in the conventional CXL group (3 mW/cm^2 for 30 min) and accelerated CXL groups with illumination intensities 9 mW/cm^2 for 10 min and 18 mW/cm^2 for 5 min compared to 30 mW/cm^2 irradiance for 3 min. With the increase in the UVA intensity, the question is whether every level of UVA intensity will be equally effective. The Bunsen–Roscoe law for CXL treatment may only be valid within a specific dose range. In an ex vivo study using porcine corneas, Wernli et al.[26] showed that the CXL effect decreases with illumination intensities higher than 40–50 mW/cm^2 and treatment times under 2 min. Hammer et al. reported a significant decrease in the biomechanical effect of CXL when using high illumination intensities in an ex vivo study with porcine corneas. It is postulated that with high illumination intensities, increased oxygen consumption may lead to decreased efficacy.[27,28]

CXL treatment starts with an oxygen-dependent photochemical reaction. In the first 10–15 s, oxygen concentration rapidly decreases, and the CXL process continues in the oxygen-independent phase. In order to replenish the consumed oxygen, studies focused on pulsed UVA light applications with on and off periods. Mazzotta et al.[16] compared the functional results of PLA-CXL (30 mW/cm^2 UVA light for 8 min) and CLA-CXL (30 mW/cm^2 UVA light for 4 min), and they reported keratoconus stability 1 year after the treatments in both modalities but better functional outcomes and deeper stromal penetration in the PLA-CXL group. In another study, Mazzotta et al.[18] reported a higher apoptotic effect in the pulsed treatment. In both studies with both pulsed-light and continuous-light treatments, they used an increased total UVA dose according to the standard protocol, 7.2 J/cm^2. Aldahlawi et al.[19] compared the effect of different CXL protocols on corneal enzymatic resistance and reported an increased resistance after pulsed-light high intensity CXL (30 mW/cm^2 for 8 min, total dose 7.2 J/cm^2), compared to the continuous-light high intensity CXL at 30 mW/cm^2 for 4 min (total dose 7.2 J/cm^2) and at 30 mW/cm^2 for 3 min (total dose 5.4 J/cm^2). But in this study, they did not evaluate the application of pulsed UVA light at 30 mW/cm^2 for 6 min with a total dose of 5.4 J/cm^2. Moramarco et al. compared the depth of the corneal stromal demarcation line between two CXL modalities: continuous UVA light at 30 mW/cm^2 for 4 min and pulsed UVA light at 30 mW/cm^2 for 8 min. In both groups, the total UVA energy applied was the same, 7.2 J/cm^2, and they reported a deeper stromal demarcation line using pulsed UVA light.[17] Similarly, Mazzotta et al.[18] reported an increased depth of the demarcation line in the PLA-CXL treatment in comparison with the CLA-CXL treatment. These findings can be interpreted as the increased effect of pulsed UVA light compared to continuous UVA light, because previous studies have indicated that the stromal demarcation line depth possibly represents the effectiveness of the CXL treatment.[29,30] Considering all these studies, PLA-CXL seems to be effective with high UVA intensities. But clinical studies of PLA-CXL with UVA light at 30 mW/cm2 intensity used an increased total dose of 7.2 J/cm^2. Mazzotta et al.[31] reported the stabilizing effect and safety of PLA-CXL with a total dose of 5.4 J/cm^2 at the 2-year follow-up, using UVA light at 15 mW/cm^2 intensity. In an animal study, Turkcu et al.[32] compared the advanced oxidation protein product (AOPP) levels between the Dresden protocol (3 mW/cm^2 UVA light for 30 min), CLA-CXL (30 mW/cm^2 UVA light for 3 min), and PLA-CXL (30 mW/cm^2 UVA light for 6 min). They found increased AOPP levels in the PLA-CXL group, and they concluded that PLA-CXL with 30 mW/cm^2 UVA light for 6 min with a total dose of 5.4 J/cm^2 seems to be more effective at forming cross-links between collagen fibrils in the animal model.

In this study, we evaluated the clinical results of PLA-CXL using 30 mW/cm^2 UVA light for 6 min without increasing the total dose according to the standard protocol, 5.4 J/cm^2. With this treatment modality, the steep, flat, mean, and maximum keratometries decreased at sixth month, first, and second years. BSCVA improved at sixth month and further improved at first and second years. None of the eyes showed progression at the end of 2 years, and no postoperative complications were reported. The lack of data regarding the depth of the stromal demarcation line after CXL treatment was a limitation of this study. Based on previous studies, the demarcation line depth could provide additional information in evaluating the treatment efficacy.[29,30]

We conclude that PLA-CXL using 30 mW/cm^2 UVA light for 6 min with a total dose of 5.4 J/cm^2 is an effective treatment modality in cases with progressive keratoconus—it stops progression at 2 years also regresses some of the cases. Further studies, with more cases and a longer follow-up, are needed to validate these findings.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This study was approved by the Clinical Research Ethics Committee of the Necmettin Erbakan University Meram School of Medicine.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol* 1998; 42: 297–319.
2. Raiskup F and Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. I. principles. *Ocul Surf* 2013; 11: 65–74.
3. Lytle G. Advances in the technology of corneal cross-linking for keratoconus. *Eye Contact Lens* 2014; 40(6): 358–364.
4. Wollensak G, Spoerl E and Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol* 2003; 135(5): 620–627.
5. Spoerl E, Huhle M and Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res* 1998; 66(1): 97–103.
6. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea* 2007; 26(4): 385–389.
7. Chang CY and Hersh PS. Corneal collagen cross-linking: a review of 1-year outcomes. *Eye Contact Lens* 2014; 40(6): 345–352.
8. Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet—a light in keratoconus: long-term results. *J Cataract Refract Surg* 2008; 34(5): 796–801.
9. Meiri Z, Keren S, Rosenblatt A, et al. Efficacy of corneal collagen cross-linking for the treatment of keratoconus: a systematic review and meta-analysis. *Cornea* 2016; 35(3): 417–428.
10. Gumus K, Mirza E, Erkilic K, et al. Preliminary results of cross-linking with riboflavin/UV-A in patients with progressive keratoconus. *Turk J Ophthalmol* 2010; 40: 18–24.
11. Caporossi A, Mazzotta C, Baiocchi S, et al. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol* 2010; 149: 585–593.
12. Oltulu R, Satirtav G, Donbaloglu M, et al. Six-month outcomes of corneal crosslinking with dextran-free isotonic riboflavin solution. *Arq Bras Oftalmol* 2016; 79(3): 147–150.
13. Mastropasqua L. Collagen cross-linking: when and how? A review of the state of the art of the technique and new perspectives. *Eye Vis (Lond)* 2015; 2: 19.
14. Davies E and Colby K. Controversies in corneal collagen cross-linking. *Int Ophthalmol Clin* 2015; 55(4): 1–11.
15. Krueger RR, Herekar S and Spoerl E. First proposed efficacy study of high versus standard irradiance and fractionated riboflavin/ultraviolet a cross-linking with equivalent energy exposure. *Eye Contact Lens* 2014; 40(6): 353–357.
16. Mazzotta C, Traversi C, Paradiso AL, et al. Pulsed light accelerated crosslinking versus continuous light accelerated crosslinking: one-year results. *J Ophthalmol* 2014; 2014: 604731.
17. Moramarco A, Iovieno A, Sartori A, et al. Corneal stromal demarcation line after accelerated crosslinking using continuous and pulsed light. *J Cataract Refract Surg* 2015; 41(11): 2546–2551.
18. Mazzotta C, Traversi C, Caragiuli S, et al. Pulsed vs continuous light accelerated corneal collagen crosslinking: in vivo qualitative investigation by confocal microscopy and corneal OCT. *Eye (Lond)* 2014; 28(10): 1179–1183.
19. Aldahlawi NH, Hayes S, O'Brart DP, et al. Enzymatic resistance of corneas crosslinked using riboflavin in conjunction with low energy, high energy, and pulsed UVA irradiation modes. *Invest Ophthalmol Vis Sci* 2016; 57(4): 1547–1552.
20. Cınar Y, Cingü AK, Turkcu FM, et al. Accelerated corneal collagen cross-linking for progressive keratoconus. *Cutan Ocul Toxicol* 2014; 33: 168–171.
21. Elbaz U, Shen C, Lichtinger A, et al. Accelerated (9-mW/cm2) corneal collagen crosslinking for keratoconus—a 1-year follow-up. *Cornea* 2014; 33(8): 769–773.
22. Alnawaiseh M, Rosentreter A, Böhm MR, et al. Accelerated (18 mW/cm²) corneal collagen cross-linking for progressive keratoconus. *Cornea* 2015; 34: 1427–1431.
23. Mita M, Waring GO 4th and Tomita M. High-irradiance accelerated collagen crosslinking for the treatment of keratoconus: six-month results. *J Cataract Refract Surg* 2014; 40(6): 1032–1040.
24. Tomita M, Mita M and Huseynova T. Accelerated versus conventional corneal collagen crosslinking. *J Cataract Refract Surg* 2014; 40: 1013–1020.
25. Shetty R, Pahuja NK, Nuijts RM, et al. Current protocols of corneal collagen cross-linking: visual, refractive, and tomographic outcomes. *Am J Ophthalmol* 2015; 160(2): 243–249.
26. Wernli J, Schumacher S, Spoerl E, et al. The efficacy of corneal cross-linking shows a sudden decrease with very high intensity UV light and short treatment time. *Invest Ophthalmol Vis Sci* 2013; 54: 1176–1180.
27. Kymionis GD, Tsoulnaras KI, Grentzelos MA, et al. Evaluation of corneal stromal demarcation line depth following standard and a modified-accelerated collagen cross-linking protocol. *Am J Ophthalmol* 2014; 158: 671.e1–675.e1.
28. Hammer A, Richoz O, ArbaMosquera S, et al. Corneal biomechanical properties at different corneal cross-linking (CXL) irradiances. *Invest Ophthalmol Vis Sci* 2014; 55(5): 2881–2884.
29. Seiler T and Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea* 2006; 25(9): 1057–1059.
30. Doors M, Tahzib NG, Eggink FA, et al. Use of anterior segment optical coherence tomography to study corneal changes after collagen cross-linking. *Am J Ophthalmol* 2009; 148(6): 844.e2–851e2.
31. Mazzotta C, Baiocchi S, Bagaglia SA, et al. Accelerated 15 mW pulsed-light crosslinking to treat progressive keratoconus: two-year clinical results. *J Cataract Refract Surg* 2017; 43(8): 1081–1088.
32. Turkcu UO, Yuksel N, Novruzlu S, et al. Protein oxidation levels after different corneal collagen cross-linking methods. *Cornea* 2016; 35(3): 388–391.