Corneal Cross-Linking in Keratoconus Using the Standard and Rapid Treatment Protocol: Differences in Demarcation Line and 12-Month Outcomes

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Purpose. To compare the occurrence rate and depth of the demarcation line and topographical outcome after corneal cross-linking (CXL) for keratoconus using two different treatment protocols.

Methods. A retrospective analysis of 131 eyes with progressive keratoconus treated with CXL using riboflavin and UV-A was performed. Eyes were treated either with the standard Dresden protocol (30 minutes irradiation, 3 mW/cm^2, UV-XTM 1000) or a rapid protocol (10 minutes irradiation, 9 mW/cm^2, UV-XTM 2000). The presence and depth of the corneal demarcation line was assessed with an anterior segment optical coherence tomography device 1 month after CXL by a masked observer. Corneal topography and tomography was performed at baseline and at 12-month follow-up with Pentacam and the TMS (Topographic Modeling System) device.

Results. In the standard protocol group, 76.5% (62/81) of treated corneas revealed a demarcation line 1 month after CXL, whereas such a demarcation line was observed in only 22% (11/50) of eyes treated with the rapid protocol ($P < 0.0001$). The demarcation line was significantly more superficial in the rapid protocol group ($P = 0.004$). Corneal topography values between baseline and 12 months after CXL showed a mean change of −0.76 diopters (D) in K_{max} (SD ± 2.7) in the standard protocol group versus a mean change of +0.72 D in K_{max} (SD ± 1.5) in the rapid protocol ($P = 0.007$).

Conclusions. The rapid CXL protocol negatively influences the occurrence and depth of the demarcation line 1 month after CXL. Our results show a negative effect on the topographical outcome 1 year after CXL.

Keywords: cross-linking, cornea, demarcation line, keratoconus, riboflavin UV-A treatment, standard Dresden protocol, rapid protocol, corneal topography

Keratoconus is a corneal ectasia with progressing corneal thinning and scarring ultimately leading to visual deterioration. Collagen cross-links have been identified early as an important factor to limit disease progression.[1] Over the last 10 years, cross-linking (CXL) with riboflavin and UV-A has evolved to be a valid treatment option for progressive keratoconus. Wollensak and Spoerl[2] first introduced CXL with the standard Dresden protocol with 30 minutes UV irradiation and 3 mW/cm^2 UV intensity as an effective treatment for increasing corneal rigidity and thus halting progression of keratoconus. Since then, several studies have been published on the safety of the standard Dresden protocol[3] and its long-term effectiveness.[4,5] Furthermore, the application has been extended from the adult setting to the pediatric population (<18 years).[6,7] With evolving technical advances, commercially available UV light sources have been developed, making CXL more efficient with shorter UV exposure times, higher UV intensities, and pulsed light compared with continuous light settings.[8] Various accelerated CXL protocols have been described and its effect on biomechanical properties on porcine corneas stated as equal to the standard protocol.[9] Yet, ex vivo studies also suggest a distinction between various accelerated CXL protocols by providing evidence for a drop in efficiency with increased UV illumination intensity while maintaining equal surface energy.[9] Clinical studies have been recently published comparing the standard protocol with a continuous light accelerated CXL protocol with 3 minutes UV irradiation time and 30 mW/cm^2 UV intensity in a total of 48 eyes, showing no difference in the occurrence rate of the demarcation line and corneal topography at 1-year follow-up.[10] Elbaz et al.[11] recently published a comparable study of 16 eyes showing effective stabilization of topographic parameters 12 months after accelerated CXL. On the other hand, further studies observe a decreased depth of the demarcation line (DLD) after using the rapid CXL protocol with 10 minutes of irradiation time and 9 mW/cm^2, suggesting a reduced effectiveness.[12]

The aim of our study was to compare the rapid CXL protocol (10 minutes of continuous irradiation time and 9 mW/cm^2 UV intensity) with the well known standard Dresden protocol (30 minutes of continuous irradiation time and 3 mW/cm^2 UV intensity) in a large patient population. For this purpose, we compared corneal stromal demarcation line at 1 month and corneal topography at the 12-month follow-up.

Methods

Study Design

Data were collected and analyzed retrospectively from 131 eyes with progressive keratoconus that underwent CXL treatment at

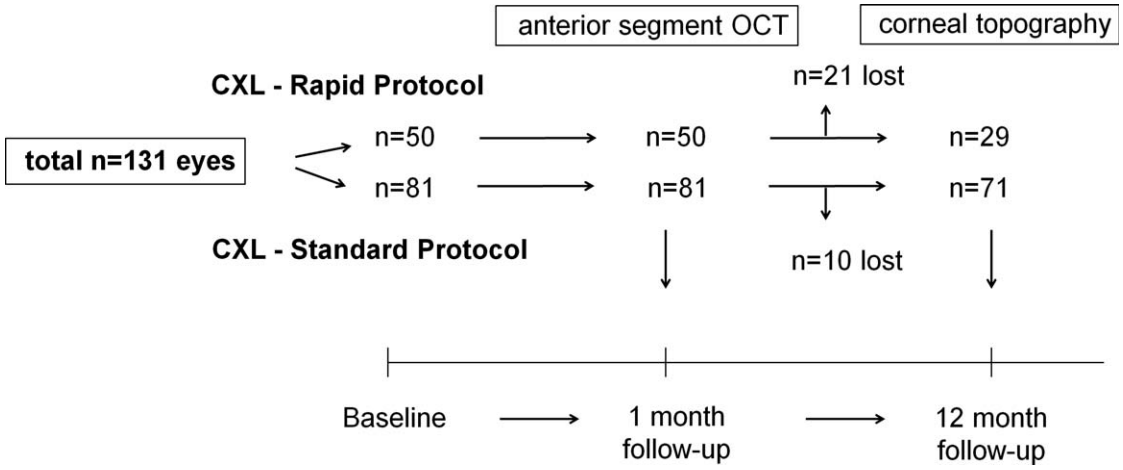

Figure 1. Study outline demonstrating the time course of CXL treatment using the rapid or standard protocol and follow-up examinations. Follow-up included anterior segment OCT at 1 month after CXL and corneal topography at 12 months after CXL using Pentacam and TMS-4 topographer, respectively.

the Department of Ophthalmology of the University Hospital in Bern, Switzerland, between 2008 and 2014. Patients were properly informed and written consent obtained according to the tenets of the Declaration of Helsinki. Data collection included analysis of the presence and depth of the demarcation line 1 month after CXL and evaluation of corneal topography at the 12-month follow-up. Thirty-one eyes were excluded from analysis at 12 months due to missing follow-up. The study design is outlined in Figure 1.

A progression of keratoconus was defined as an increase of $\geq$1 diopter (D) in the steepest radius of curvature of the anterior corneal surface (K_{max}) in the preceding 1 year. Patients were subjected to CXL treatment using the standard Dresden protocol from 2008 to 2012 and the rapid CXL protocol starting 2013. Patients with prior corneal surgery or corneal infection were excluded from the retrospective analysis.

CXL Protocol

Patients were subjected to CXL treatment using the standard Dresden protocol[2] and the rapid CXL treatment.[13] All patients were treated preoperatively with tetracaine hydrochloride 1% (Novartis Pharma Schweiz AG, Risch, Switzerland) and the periorbital area prepared with disinfecting betadine (Mundipharma Medical Company, Hamilton, Bermuda). After insertion of a lid speculum, eyes were washed with diluted betadine. After antiseptic measures a corneal abrasion of 8 to 9 mm in diameter was performed using a hockey knife. The application of iso-osmolar riboflavin 0.1% eye drops (riboflavin-5-phosphate 0.1%; Streuli & Co, Uznach, Switzerland)—prepared with Dextran T500 20%, (university hospital pharmacy, Inselspital Bern, Switzerland) or Medio cross eye drops (riboflavin 0.1% with Dextran 20%, Peschke Meditrade, Waldshut-Tiengen, Germany)—was administered repeatedly during 5 minutes alternating with tetracaine or balanced salt solution (BSS) for a total of 20 minutes. Pachymetric measurements were performed and the procedure continued once a corneal thickness of more than 400 μm was confirmed. A cornea thinner than 400 μm was swelled according to a published protocol with hypotonic eye drops (Innocross-R, Riboflavin 0.1% with NaCl 0.9%; Peschke Meditrade).[14] After a positive Tyndall phenomenon of the anterior chamber was detected using a handheld slit lamp, the UV-A irradiation was started. Corneas treated with the standard Dresden protocol received UV-A irradiation for 30 minutes using an illumination device (UV-XTM 1000; IROC Innocross, Zug, Switzerland) with an intensity of 3 mW/cm^2. Corneas treated with the rapid protocol were UV-A irradiated for 10 minutes using an illumination device (UV-XTM 2000; IROC Innocross) with an intensity of 9 mW/cm^2. Riboflavin treatment (1 drop every 2 minutes alternating with BSS) was continued in both treatment protocols. After the procedure, all patients received ofloxacine eye drops 0.3% (Bausch & Lomb, Zug, Switzerland) four times a day (qid) until the corneal erosion healed. Fluorometholone liquifilm eye drops 0.1% (Allergan, Pfäffikon, Switzerland) were administered qid thereafter for a maximum of 1 month.

Anterior Segment OCT

Anterior segment optical coherence tomography (HRT Spectralis-Cornea Version 1.3.0.0; Heidelberg Engineering, Heidelberg, Germany) was performed 1 month after CXL. The presence and the depth of the corneal demarcation line were analyzed retrospectively by a masked observer using a viewing module (HRA Spectralis, version 5.6.4.0). We measured the DLD centrally to determine the absolute depth and related to the total central corneal thickness (CCT) to determine the depth/CCT ratio. To compare corneal topography with the depth of corneal demarcation line, a DLD $\geq$60% of total corneal stroma was considered deep and $<$60% superficial according to past published studies.[15]

Corneal Topography

Corneal topography was measured prior and 12 months after CXL treatment using a tomography device (Pentacam HR; Oculus, Wetzler, Germany) and the topographic modeling system (TMS-4) (Tomey Corp., Tokyo, Japan). The steepest radius of curvature of the anterior corneal surface (K_{max}) as measured by Pentacam, and the keratometry value of the steep (K_s) and flat meridian (K_f), as measured by TMS-4 topographer, were used to evaluate corneal topography changes; ΔK_{max}, ΔK_s, and ΔK_f were calculated.

Statistical Analysis

Statistical analysis was performed using statistical software (SPSS Statistics, version 21; IBM Corp., Armonk, NY, USA). All data were examined for normal distribution using the Shapiro-Wilk test. The *t*-test for independent values was used to compare the means of patient characteristics (age, best

TABLE. Patient Characteristics

	Pre-CXL Rapid Protocol	Pre-CXL Standard Protocol	*P* Value
Progressive keratoconus, *n*	50	81	
Age, mean ± SD	26.14 ± 10.25	28.62 ± 10.53	0.7
BSCVA at baseline, logMAR	0.28 ± 0.29	0.3 ± 0.26	0.94
Corneal thickness at thinnest point, μm	470.14 ± 45.92	463.89 ± 41.94	0.96
K_s, D	51.1 ± 4.52	51.66 ± 5.54	0.19
K_f, D	46.17 ± 3.46	46.32 ± 4.18	0.04
K_{max}, D	54.49 ± 4.49	56.3 ± 6.98	0.17

Characteristics show equal patient distribution in the rapid and standard protocol group for age, BSCVA, corneal thickness at thinnest point, keratometric value for the steep meridian (K_s) and the steepest radius of curvature of the anterior corneal surface (K_{max}). There was a difference observed in the keratometric value for the flat meridian (K_f) between the standard and rapid protocol group ($P = 0.04$).

spectacle corrected visual acuity [BSCVA], corneal thickness, K_s, K_f, K_{max}) between the standard and rapid protocol group (Table), and to compare the means of demarcation line (DL) depth (Fig. 2B) and ΔK_f, ΔK_s, and ΔK_{max} (Figs. 3, 4) between the rapid and the standard protocol group. The Fisher's exact test was applied to test for a significant difference in the occurrence of the demarcation line between the two study groups (Fig. 2A). Comparisons were considered significant, if a P value <0.05 was observed.

RESULTS

Patient Characteristics

A total of 131 eyes were analyzed, 81 in the standard protocol group and 50 in the rapid protocol group. Patients in the rapid protocol group had a mean age of 26.14 years (SD ± 10.25) versus 28.62 years (SD ± 10.53) in the standard protocol group ($P = 0.7$). Best spectacle corrected visual acuity, corneal thickness at the thinnest point, as well as corneal topography values measured by Pentacam (K_{max}) and TMS topographer (K_s) prior to CXL were not significantly different in the two treatment groups ($P > 0.05$, each). There was a significant greater value of the flat meridian in the standard protocol group observed ($P = 0.04$). A summary of patient characteristics is shown in the Table.

Demarcation Line at 1-Month Follow-Up

Of the eyes studied, 62 of 81 (76.5%) showed a clear demarcation line on OCT evaluation 1 month after CXL using the standard Dresden protocol. We observed a significantly lower occurrence rate of the demarcation line; it was found only in 11 of 50 eyes (22%), using the rapid treatment protocol (Fig. 2A, $P < 0.0001$). Retrospective analysis of the DLD as measured by anterior chamber OCT at central corneal location showed a deeper localization of the demarcation line after CXL in the standard treatment group compared with the rapid treatment group (standard: mean: 323.14 μm ± SD 76.04; rapid: mean: 245.45 μm ± SD 59.05; Fig. 2B, $P = 0.004$). A similar ratio was obtained for the DLD in relation to the total corneal thickness of the standard versus rapid protocol group (Fig. 2C, $P = 0.004$).

Corneal Topography at 12-Month Follow-Up

Corneal topography at baseline and at the 12-month follow-up were compared between the standard and rapid CXL protocol

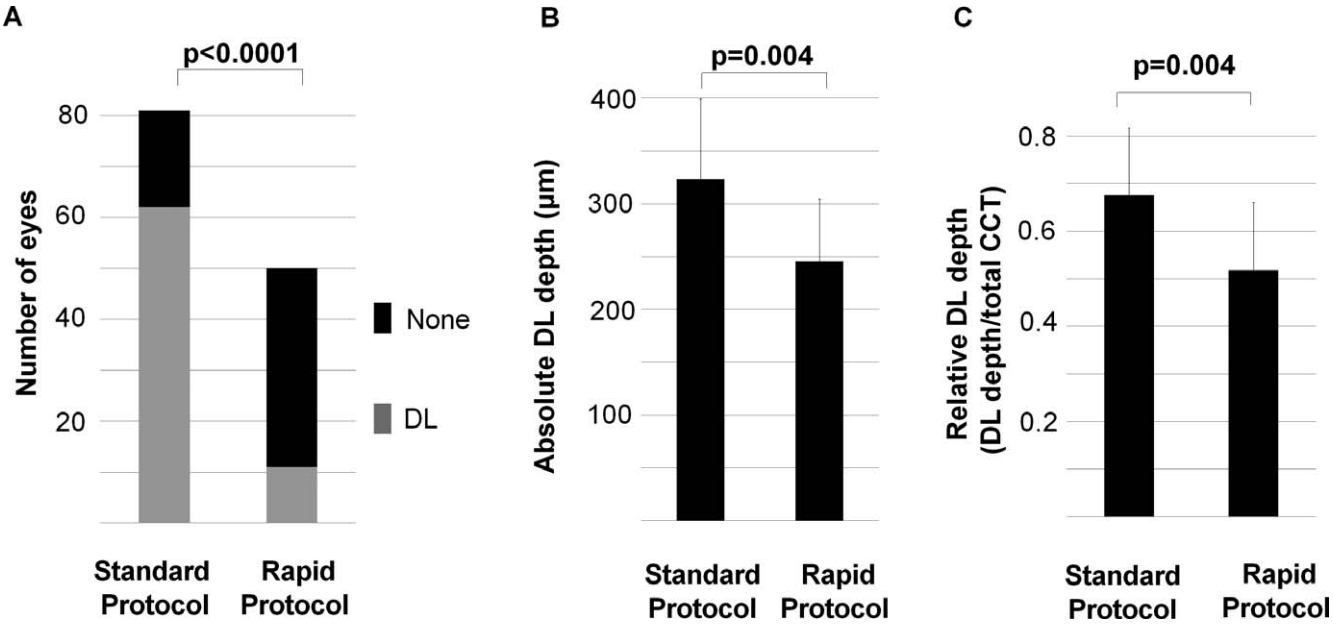

FIGURE 2. (**A**) *Bar graphs* showing increased occurrence of the DL 1 month after CXL using the standard protocol compared with the rapid protocol ($P < 0.0001$). (**B**) *Bar graphs* showing a significant difference in the absolute DLD 1 month after CXL between the rapid and the standard protocol ($P = 0.004$). (**C**) *Bar graphs* showing a significant difference in the relative depth of the DL in relation to CCT 1 month after CXL between the rapid and the standard protocol ($P = 0.004$).

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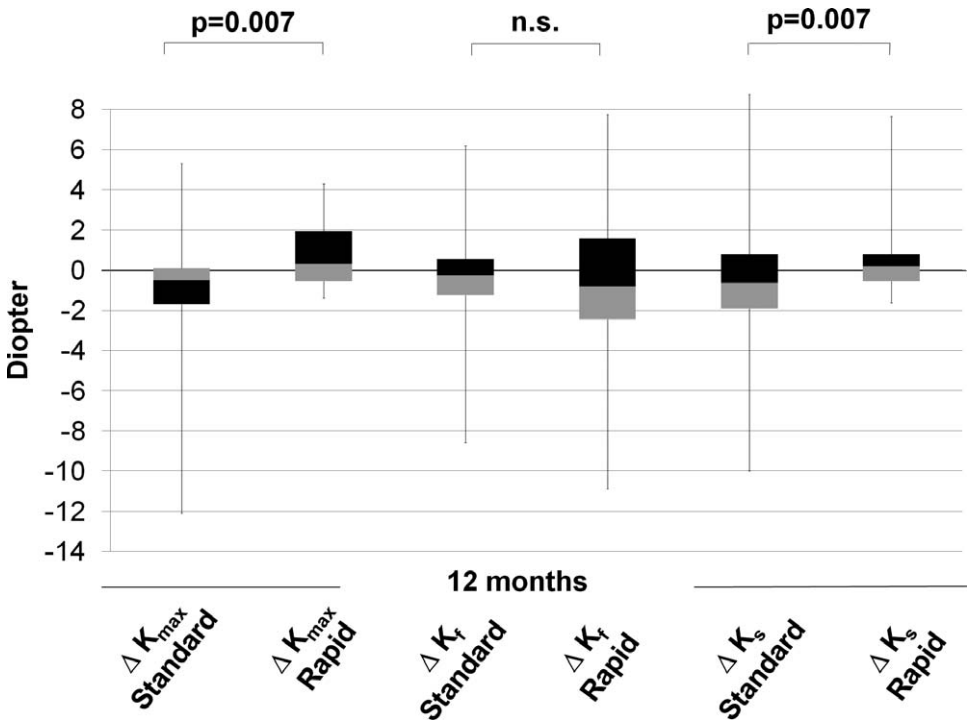

Figure 3. *Box plots* showing significant difference in the change of corneal topography between the rapid and standard CXL protocol. Depicted are the median, 25% percentile, 75% percentile of ΔK_{max} and ΔK_s. The maximum and minimum values are represented by the *error bars*. No significant difference was observed for ΔK_f ($P = 0.74$; n.s., not significant), whereas ΔK_{max} and ΔK_s differed significantly between the two groups (both $P = 0.007$).

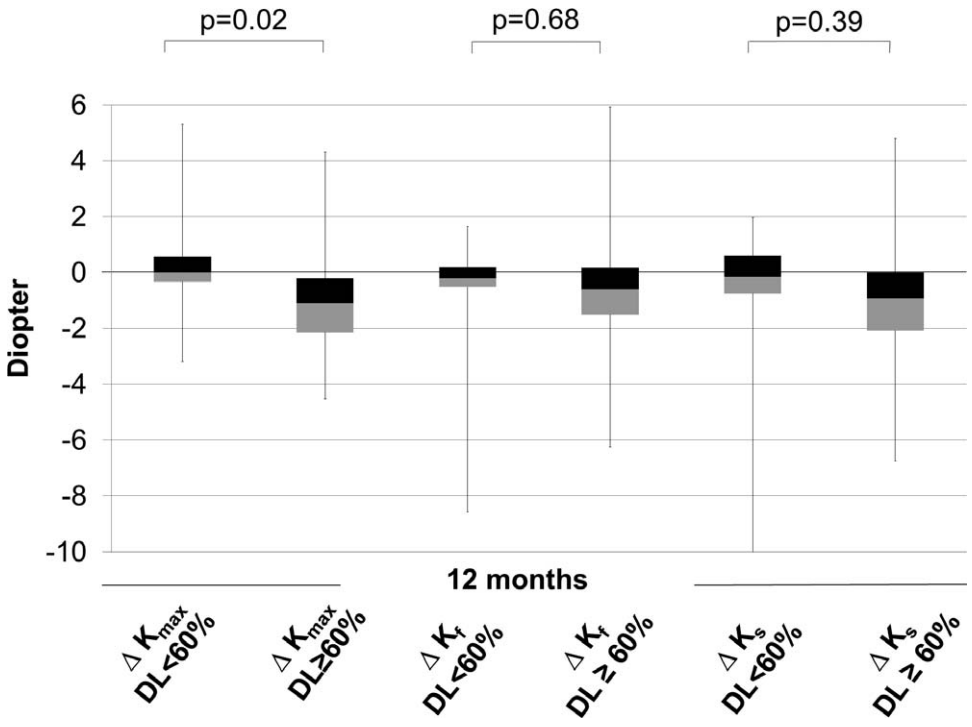

Figure 4. *Box plots* showing difference in the change of corneal topography between corneas with superficial DL (depth <60% of CCT) and deep DL (depth ≥60% of CCT) for both treatment protocols. Median, 25% percentile, 75% percentile of ΔK_{max}, ΔK_f, and ΔK_s are depicted. The maximum and minimum values are represented by the *error bars*. A significant difference was observed for ΔK_{max} ($P = 0.02$); no significant differences were observed for ΔK_f and ΔK_s ($P = 0.68$, $P = 0.39$).

group. Results showed a significant difference between the treatment groups for ΔK_{max} (standard: ΔK_{max}: −0.76 D [± SD 2.71], rapid: ΔK_{max}: +0.72 D [± SD 1.5]; $P = 0.007$) and ΔK_s (standard: ΔK_s: −0.8 D [± SD 2.35], rapid: ΔK_s: +0.52 D [± SD 1.64]; $P = 0.007$). No significant difference was detected for ΔK_f (standard: ΔK_f: +0.42 D [± SD 2.25], rapid: ΔK_f: +0.61 D [± SD 3.45]; $P = 0.74$).

Demarcation Line Versus Corneal Topography

Changes of corneal topography (ΔK_{max}, ΔK_s, and ΔK_f) were compared with DLD for both treatment groups. Comparing eyes with a superficial DLD with those with a deep DLD revealed a significant difference in ΔK_{max} (DLD <60%: ΔK_{max}: +0.4 D [± SD 1.95] versus DLD ≥60%: ΔK_{max}: −0.97 D [± SD 1.88]; $P = 0.02$). Difference between ΔK_s and ΔK_f were not statistically significant (DLD <60%: ΔK_s: −0.62 D [± SD 2.68] versus DLD ≥60%: ΔK_s: −1.16 D [± SD 1.97]; $P = 0.399$), (DLD <60%: ΔK_f: −0.73 D ± SD 2.18, DLD ≥60%: ΔK_f: −0.43 D ± SD 2.28; $P = 0.68$; Fig. 4).

Discussion

Cross-linking is a promising treatment approach for progressive keratoconus. Many studies have been conducted using the first published standard Dresden protocol to halt the progression of keratoconus.[16,17] Many accelerated cross-linking protocols are now commercially available that increase UV intensity while decreasing irradiation time, applying an equal total surface dose of 5.4 J/cm^2. Past studies have shown the equivalence of the standard and rapid protocol with regard to biomechanical properties mostly in animal studies.[18] Clinical studies were performed up to date in small patient cohorts showing no significant difference in effectiveness between the two CXL treatment protocols.[10,11] These clinical studies likely lacked sufficient power to detect a significant difference due to small patient cohorts. The aim of our study was to evaluate effectiveness of the rapid CXL protocol with 10 minutes UV irradiation time and 9 mW/cm^2 UV intensity in a larger patient population. For this purpose, we compared the occurrence rate and DLD in 131 eyes and evaluated corneal topography at the 12-month follow-up in a total of 100 eyes. The results of our retrospective analysis suggest a superior effectiveness of the standard protocol in comparison to the rapid protocol with regard to the occurrence of the corneal demarcation line and corneal topography at 12-month follow-up. These results are of importance for current CXL treatment strategies.

First, we demonstrate an equal patient distribution within the standard and rapid CXL protocol groups, especially with respect to age ($P = 0.7$), BSCVA ($P = 0.94$), K_{max}, K_s, and corneal thickness at thinnest point ($P = 0.96$). The corneal thickness prior to CXL was more than 400 μm in both treatment groups. A greater value of K_f was observed in the rapid protocol group ($P = 0.04$), indicating an unequal distribution of K_f at baseline. Visual acuity was measured at subsequent time points but not included in the analysis at follow-up due to its high variability in keratoconus.

Second, we demonstrate that increasing UV intensity and decreasing irradiation time has a negative effect on the occurrence of the demarcation line one month after CXL. The result of our study showed a lower occurrence rate of 22% (11/50) in eyes treated with the rapid protocol versus an occurrence rate of 76.5% (62/81) in eyes treated with the standard Dresden protocol. Furthermore, the demarcation line was significantly deeper in the standard protocol group compared with the rapid protocol (standard: mean of 323.14 μm ± SD 76.04; rapid: mean of 245.45 μm ± SD 59.05, $P = 0.004$). These data are in accordance with a recently published study analyzing the stromal demarcation line after CXL using the rapid and standard protocol in a smaller study group of 21 eyes.[12] An explanation for this observation may theoretically be a limited diffusion rate for riboflavin-dextran eye drops solutions in corneas treated for a decreased time during the rapid protocol. Past studies have shown that diffusion of riboflavin-dextran eye drops is decreased by reducing the time of contact.[19]

In addition, the results of our study showed a significant difference of mean change in corneal topography for ΔK_{max} and ΔK_s between baseline and 12-month follow-up in the standard and rapid group as measured by two independent techniques (Fig. 3). Our data show for the first time an unequal effect on corneal topographic values 12 months after CXL between the standard and rapid protocol. These results are in line with the unequal occurrence and depth of the demarcation line. Using the rapid protocol the mean DLD was measured as less than 300 μm (corresponding to 50% of central total corneal depth) 1 month after CXL. Past studies report an effective CXL treatment with a DLD of at least 300 μm (i.e., 60% of central total corneal depth).[15] When analyzing corneal topography, we observed a significant difference in the change of ΔK_{max} between corneas with superficial DLD (DLD <60%) and deep DLD (DLD ≥60%; Fig. 4). As a significant change for ΔK_s and ΔK_f was not observed, the predictability of a profound DLD as a marker for successful CXL may be limited.

Furthermore, the results of our study are in accordance with a recent publication on porcine corneas showing a significant decrease of stiffness when using high irradiance/short irradiation time settings.[20]

In contrast, data recently published by Tomita et al.[10] showed no statistically significant difference in mean corneal topography values at 12-month follow-up between the standard and the accelerated CXL protocol with 3 minutes irradiation time and 30 mW/cm^2 UV-intensity. The authors furthermore reported no difference in the occurrence of the demarcation line. It remains unclear, whether a difference in the treatment protocol (3 vs. 10 minutes irradiation time) or the application of dextran-free riboflavin eye drops (VibeX Rapid; Avedro, Waltham, MA, USA) result in the difference of efficiency. Furthermore, the exact number of eyes examined at 12-month follow-up is not clearly stated.

When analyzing a mean change of the keratometric value of the flat meridian (ΔK_f), no significant difference was observed between the standard and rapid protocol ($P = 0.74$). These results may be a result of an unequal distribution of K_f at baseline, masking a true difference between the treatment groups.

The present study has several strengths. First, based on a well-defined patient cohort, we performed the largest comparative analysis of corneal CXL to date with 131 progressive keratoconus eyes. Moreover, we measured corneal topography values with two independent techniques and performed a two-treatment analysis. On the other hand, the interpretation of the results may be hampered by the asymmetrical distribution of patient numbers between the two treatment groups, and the absence of randomization. Furthermore, due to loss of follow-up number of eyes evaluated at baseline and 12-month follow-up were not the same, limiting the validity of this study.

In conclusion, increasing UV intensity to 9 mW/cm^2 and decreasing UV irradiation time to 10 minutes has a negative effect on the occurrence and depth of the demarcation line 1 month after CXL. In addition, the study shows that in eyes treated with the rapid protocol these findings are associated with increased steepening of the anterior cornea when compared with eyes treated with the standard CXL protocol. In contrast, corneas treated with the standard protocol

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stabilized or flattened. For the first time, indications for a decreased efficiency of CXL using the rapid treatment protocol have been found.

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References

1. Cannon DJ, Foster CS. Collagen crosslinking in keratoconus. *Invest Ophthalmol Vis Sci*. 1978;17:63–65.
2. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
3. Spoerl E, Hoyer A, Pillunat LE, Raiskup F. Corneal cross-linking and safety issues. *Open Ophthalmol J*. 2011;5:14–16.
4. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34:796–801.
5. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. 2014;121:812–821.
6. Vinciguerra P, Albe E, Frueh BE, Trazza S, Epstein D. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. *Am J Ophthalmol*. 2012;154:520–526.
7. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R, Balestrazzi A. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. *Cornea*. 2012;31:227–231.
8. Mazzotta C, Traversi C, Caragiuli S, Rechichi M. Pulsed vs continuous light accelerated corneal collagen crosslinking: in vivo qualitative investigation by confocal microscopy and corneal OCT. *Eye (Lond)*. 2014;28:1179–1183.
9. Wernli J, Schumacher S, Spoerl E, Mrochen M. 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.
10. Tomita M, Mita M, Huseynova T. Accelerated versus conventional corneal collagen crosslinking. *J Cataract Refract Surg*. 2014;40:1013–1020.
11. Elbaz U, Shen C, Lichtinger A, et al. Accelerated (9-mW/cm2) corneal collagen crosslinking for keratoconus-A 1-year follow-up. *Cornea*. 2014;33:769–773.
12. Kymionis GD, Tsoulnaras KI, Grentzelos MA, et al. Corneal stroma demarcation line after standard and high-intensity collagen crosslinking determined with anterior segment optical coherence tomography. *J Cataract Refract Surg*. 2014;40:736–740.
13. Chan E, Snibson GR. Current status of corneal collagen cross-linking for keratoconus: a review. *Clin Exp Optom*. 2013;96:155–164.
14. Hafezi F, Mrochen M, Iseli HP, Seiler T. Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas. *J Cataract Refract Surg*. 2009;35:621–624.
15. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea*. 2006;25:1057–1059.
16. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97–103.
17. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Current Opin Ophthalmol*. 2006;17:356–360.
18. Schumacher S, Oeftiger L, Mrochen M. Equivalence of biomechanical changes induced by rapid and standard corneal cross-linking, using riboflavin and ultraviolet radiation. *Invest Ophthalmol Vis Sci*. 2011;52:9048–9052.
19. Arboleda A, Kowalczuk L, Savoldelli M, et al. Evaluating in vivo delivery of riboflavin with coulomb-controlled iontophoresis for corneal collagen cross-linking: a pilot study. *Invest Ophthalmol Vis Sci*. 2014;55:2731–2738.
20. Hammer A, Richoz O, Arba Mosquera S, Tabibian D, Hoogewoud F, Hafezi F. Corneal biomechanical properties at different corneal cross-linking (CXL) irradiances. *Invest Ophthalmol Vis Sci*. 2014;55:2881–2884.