AUTHOR QUERIES

DATE 3/17/2009
JOB NAME ICO

ARTICLE ICO201238
QUERIES FOR AUTHORS Koller et al

THIS QUERY FORM MUST BE RETURNED WITH ALL PROOFS FOR CORRECTIONS

AU1) Please provide department (if any) for the second affiliation.

AU2) Please note that keywords have been taken from the provided pdf. Please check.

AU3) Please check if "PRK" could be spelled out as "photorefractive keratectomy" in the sentence "The haze in the anterior…."

AU4) As per style, the Tables must be cited in text in consecutive numerical sequence. Please check.

AU5) Please check the edits made to the sentence "After insertion of an…."

AU6) Please check if the supplier's name "Peschkemed Meditrade" could be changed to "Peschke Meditrade" in the sentence "After this, the eye was irradiated…."

AU7) Please note that "Kanelopoulos and coworkers" has been changed to "Kanellopoulos and Binder" in the sentence "In an earlier study…" as per the reference list. Please check.

AU8) Please note that as per style, "gender" should be changed to "sex" unless confused with sex act. Hence, please check if "gender" could be changed to "sex" in the sentence "On the other hand, the control…."

AU9) Please clarify "maximal curvature $R_{\min}$" in the sentence "Several parameters would have been useful…."

AU10) Please update Ref. 11.

AU11) Please provide in-text citation for Refs. 20–23.

AU12) Please provide editor name(s) and publisher location for Ref. 23.

AU13) Please note that "ABR," "CKI," "IHA," "IHD," "ISV," "IVA," and "KI" have been spelled out as "aberration coefficient," "center keratoconus index," "index of height asymmetry," "index of height decentration," "index of surface variance," "index of vertical asymmetry," and "keratoconus index" in the footnote of Table 2. Please check.

AU14) Please note that "CKI," "IHA," "IHD," "ISV," and "KI" have been spelled out as "center keratoconus index," "index of height asymmetry," "index of height decentration," "index of surface variance," and "keratoconus index" in the footnote of Table 3. Please check.

MS NO: ICO201238

Scheimpflug Imaging of Corneas After Collagen Cross-Linking

Tobias Koller, MD, Hans Peter Iseli, MD,* Farhad Hafezi, MD, PhD,* Paolo Vinciguerra, MD,† and Theo Seiler, MD, PhD**

Purpose: To compare geometrical shape factors of keratoconus corneas after cross-linking (CXL) by means of Scheimpflug imaging with those of untreated fellow eyes.

Setting: Institut für Refraktive und Ophthalmo-Chirurgie, Zürich, Switzerland.

Methods: Scheimpflug imaging of the anterior segments was performed with the Pentacam (Oculus, Wetzlar, Germany) in 21 patients with progressive keratectasia before and after CXL. Only 1 eye per patient was treated with corneal cross-linking using the riboflavin/UV-A approach, the fellow eye serving as control. The following corneal parameters and their postoperative evolution during 1 year after treatment have been evaluated: minimal curvature radius and its location, thickness at the thinnest point, location of the thinnest point, anterior and posterior elevation, conoid asphericity constants of the anterior and posterior surface, and 7 keratoconus indices. Statistical comparison was performed by means of the Wilcoxon test.

Results: None of the treated eyes showed topographic progression in contrast to the untreated group where 8 eyes experienced significant progression. Minimal curvature radius increased significantly after 1 year compared with preoperative (6.14–6.21 mm), whereas in the untreated fellow eye, it significantly decreased (6.94–6.86 mm). Minimal corneal thickness was significantly reduced after treatment ($P < 0.002$ at 12 months). The cornea showed an evolution toward a more regular shape as indicated by a significant reduction in 4 of 7 keratoconus indices. No complications of CXL occurred in this small study group.

Conclusions: After cross-linking, the corneal shape undergoes a process of regularization. This process is active during the first year after treatment and may continue. Longer follow-up is warranted to estimate the full amount of regression of the keratectasia after CXL.

Received for publication May 28, 2008; revision received September 29, 2008; accepted October 12, 2008.

AU1 From the *Institut für Refraktive und Ophthalmo-Chirurgie, Zürich, Switzerland; and †Istituto Clinico Humanitas, Milano, Italy.

The authors have no financial interest in the devices and medications used in this study.

Reprints: Theo Seiler, MD, PhD, Institut für Refraktive und Ophthalmo-Chirurgie, Stockerstrasse 37, CH-8002 Zürich, Switzerland (e-mail: info@iroc.ch).

Key Words: keratoconus, cross-linking, riboflavin, Scheimpflug imaging AU2

(*Cornea* 2009;00:000–000)

One of the characteristics of keratectasia is a reduced biomechanical strength of the cornea caused by a still unknown etiologic factor.[1–3] More than 10 years ago, corneal cross-linking (CXL) by means of riboflavin and ultraviolet light was proposed as a therapeutic approach to improve the biomechanical and biochemical properties of the cornea.[4,5] The first reports on clinical experience with this treatment for corneal melting appeared in 2000.[6] In 2003, a halt in progression of keratectasia after CXL was shown in eyes with documented progression before the treatment.[7] The authors reported a decrease in maximal K reading during the first postoperative years. This finding was confirmed by Caporossi et al[8] in 2006 who presented a 3-month follow-up after CXL. Other applications of CXL include iatrogenic keratectasia after laser in situ keratomileusis (LASIK)[9,10] and infectious keratitis.[11] Recently, a much longer follow-up time of 3–6 years of patients with CXL was reported.[12] The majority of the eyes treated showed at least stabilization of the corneal curvature, and 2 patients needed retreatment.

In this prospective controlled study, the changes in geometric shape factors of front and back surface of corneas after cross-linking were compared with those of the untreated fellow eyes by means of Scheimpflug imaging.

PATIENTS AND METHODS

Study Group and Protocol

Forty-two eyes of 21 patients with progressive keratectasia were enrolled in this study. Progression of the keratectasia was verified by repeated Scheimpflug images over at least 1 year, and the one eye showing a more advanced state or a stronger progression based on maximal anterior curvature was treated. The untreated fellow eye served as a control. Only eyes with mild to moderate keratoconus (maximal K reading <58 diopters, minimal corneal thickness > 400 μm) were included in the treatment group. Because of the broad overlap of the diagnoses of pellucid marginal degeneration and keratoconus, we did not distinguish between these clinical subentities (keratoconus: 8, pellucid marginal degeneration: 4, and mixed: 9 patients). Eyes with preoperative corneal opacities were not accepted because

Scheimpflug photography may give false results of the posterior surface and corneal thickness in such cases. Additional exclusion criteria were ocular pathology other than keratectasia, in detail corneal guttata or other endothelial irregularities, history of recurrent erosions, age under 18 years, actual or intended pregnancy, nonavailability for follow-up examinations during 3 years, and connective tissue diseases. The study protocol was approved by the Ethikkommittee des Kantons Zürich. The patients were not charged for the CXL treatment. The age of the study group was 32.3 ± 9.8 years, range 18–51 years.

The patients were examined preoperatively, early postoperatively (1–3 days until epithelial healing), at 1 month, 6 months, and 12 months after CXL. At every follow-up, except the early postoperative, a standard examination was performed consisting of autorefractometry and autokeratometry (Humphrey Model 599; Zeiss, Jena, Germany), corneal topography (Keratograph C; Oculus, Wetzlar, Germany), Scheimpflug imaging (Pentacam 70700; Oculus), manifest refraction using the fogging technique, unaided and best spectacle–corrected visual acuity (BSCVA), applanation tonometry, and slit-lamp inspection of the anterior and posterior segments of the eyes. The haze in the anterior stroma was graded according to the
AU3 scale used after PRK.[13]

Patients using rigid contact lenses were asked not to use their lenses for at least 3 weeks before the preoperative examination and 1 month after treatment. The lenses had to be removed at least 3 weeks before each follow-up examination.

Scheimpflug Imaging and Evaluation

The Pentacam system consists of a Scheimpflug camera and a monochromatic light source (475 nm), which rotate together around the optical axis of the system. This optical axis is aligned collinear to the visual axis of the eye to be measured both manually (by the operator) and automatically (by the system software). Only Pentacam's automatic release mode was used, optimizing correct focus and improving reproducibility of the measurement. In 2 seconds, the camera captures 25 slit images of the anterior segment of the eye and small eye movements are corrected simultaneously. Each slit image of a surface (anterior and posterior cornea) consists of 500 elevation points with reference to the apex of the cornea. According to the Scheimpflug principle, the anterior corneal surface is distortion free but all successive layers are not.[14] By means of ray tracing algorithms, the posterior corneal surface is reconstructed and geometrical optical distortions arising from the anterior surface are taken into account. Only measurements displaying the sign "OK" were accepted.

In some cases with transient corneal haze and a visible demarcation line,[15] the posterior surface of the cornea was
F1 not detected correctly. The cornea displayed in Figure 1 had a corneal haze graded "1+" and a demarcation line that was easily visible at the slit lamp. The difference in contrast in the Scheimpflug image between the cross-linked layer and the non–cross-linked cornea at a wavelength of 475 nm was obviously high enough to be automatically detected as "back surface of the cornea" by the software of the Pentacam. Therefore, we inspected all original Scheimpflug images at the 1-year postoperative follow-up for this artifact. In case of an artifact, the information from the back surface of the cornea was ignored (n = 2).

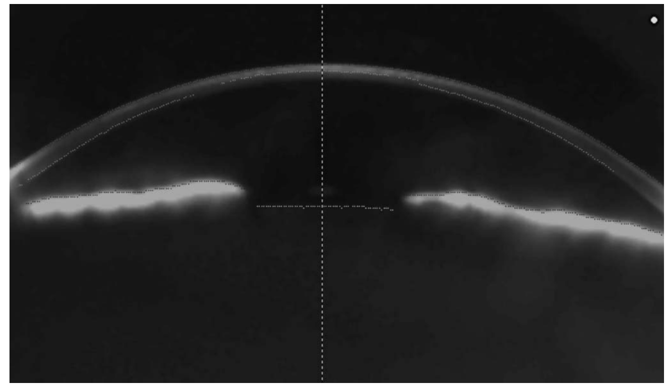

FIGURE 1. Scheimpflug image of a cornea 1 month after CXL. The anterior stroma shows enhanced light scattering that strongly interferes with the automatic detection of the back surface of the cornea. At the slit lamp, the haze was graded 1+.

The following Pentacam parameters were used for further analysis: (1) corneal thickness at the thinnest point; (2) location of the thinnest point (*x*, *y* with reference to the apex); (3) minimal curvature radius R_{min}; (4) location of the minimal curvature (*x*, *y* with reference to the apex); (5) asphericity constants Q_{ant} and Q_{post} of the anterior and posterior corneal surface; (6) keratoconus indices index of surface variance, index of vertical asymmetry, keratoconus index, center keratoconus index, index of height asymmetry, index of height decentration, and aberration coefficient (Table 2); and T2 AU4
(7) height and location of the maximum of anterior and posterior elevation map (float) with reference to the preoperative best-fit sphere.

The location of special points on the cornea is given in Cartesian coordinates (*x*, *y*) with reference to the apex, which were converted into polar coordinates (*r*, φ) because in this study, only the radial distance to the apex was of interest, which we called eccentricity. The conic approximation leading to the asphericity constants Q_{ant} and Q_{post} and the posterior and anterior elevation (float) was calculated within a circular area with a diameter of 8 mm. As a reference area for the maximal elevation and its eccentricity, the preoperative best-fit sphere was chosen. A minimal height of 5 μm was required to accept the maximal elevation to be different from zero. The keratoconus indices refer to the anterior surface of the cornea and are explained in Table 1. T1

To obtain a measure for progression/regression, the reproducibility of the R_{min} measurement was evaluated in 10 eyes. Seven consecutive Scheimpflug images of 10 eyes were taken in 1 session. The standard deviation of these measurements ranged from 0.017 to 0.039 mm with a mean of 0.024 mm. A significant increase in R_{min} (regression) or decrease in R_{min} (progression) was accepted if R_{min} changed more than 3 maximally measured standard deviations (more than ±0.12 mm that is equivalent to approximately ±1.0 diopters).

Treatment

Topical anesthesia of the cornea was obtained using oxybuprocaine 0.4% and tetracaine 0.6% alternating every

TABLE 1. Keratoconus Indices

	Name	Description
ISV	Index of surface variance	Curvature variation from the mean curvature
IVA	Index of vertical asymmetry	Curvature difference between superior and inferior
KI	Keratoconus index	Compares keratoconus sector with normal sector
CKI	Center keratoconus index	Compares central with peripheral cornea curvature
IHA	Index of height asymmetry	Height difference between superior and inferior
IHD	Index of height decentration	Vertical decentration of height data
ABR	Aberration coefficient	Zernike coefficients of the anterior corneal surface

3 minutes for 15 minutes not only to achieve anesthesia but also to alleviate corneal abrasion. After insertion of an eyelid speculum, a corneal abrasion with a diameter of 9 mm was performed followed by the instillation of 0.1% riboflavin AU5 drops every 3 minutes for 30 minutes. A rim of epithelium of at least 0.5 mm from the blue-white border was preserved. The riboflavin drops were prepared immediately before the treatment by mixing 0.5% aqueous riboflavin solution (Streuli & Co, Uznach, Switzerland) with 20% dextran T-500 solution (Roth, Karlsruhe, Germany). Thereafter, central corneal pachymetry using ultrasound was performed. In cases with a central thickness (without epithelium) of less than 400 μm, additional 0.1% riboflavin drops without dextran were applied until the thickness exceeded 400 μm. The eyes were then inspected at the slit lamp to ensure that the riboflavin has arrived in the aqueous (blue light). After this, the eye was irradiated for 30 minutes with UV-A with an irradiance of AU6 3 mW/cm^2 (UV-X; Peschkemed Meditrade, Huenenberg, Switzerland). During irradiation, the cornea was moistened every 3 minutes with 0.1% riboflavin drops and oxybuprocaine drops at the patient's discretion. At the end of the procedure, antibiotic ointment (ofloxacine 0.3%) was applied and the eye was patched. The patient was asked to use the antibiotic ointment 5 times a day for 3 days. After epithelial healing, the patients used topical fluorometholone twice a day for 1 week.

Statistical Evaluation

Two variables of the same cornea (eg, *Q* factors of the anterior and posterior surface), the same variable at different times during the follow-up, and the same variable of the cross-linked and untreated fellow eye were compared using the Wilcoxon test (2 sided). The correlation of variables and its 1-sided significance was calculated using the Spearman rank correlation test. All calculations were performed with WinSTAT for Excel (R. Finch Software, 2002). Statistical significance was accepted if $P < 0.05$.

RESULTS

The demographic data demonstrate a strong skew toward male patients (male to female = 6:15) and left eyes

TABLE 2. Preoperative and Postoperative Shape Factors

	Cross-Linked Corneas			Control Corneas		
	Preoperative	12 Mo	*P*	Preoperative	12 Mo	*P*
Minimal thickness/μm	452	440	0.002	478	471	0.22
Eccentricity/mm	0.91	0.89	0.55	1.01	0.96	0.43
R_{min}/mm	6.14	6.21	0.01	6.94	6.86	0.002
R_{min}/D	55.0	54.3	0.01	48.6	49.2	0.002
Eccentricity/mm	1.55	1.57	0.69	2.0	1.81	0.09
Q_{ant}	−0.7	−0.69	0.09	−0.35	−0.4	0.02
Q_{post}	−0.58	−0.62	0.13	−0.38	0.35	0.33
ISV	98	95	0.09	54	57	0.06
IVA	1.10	1.09	0.63	0.65	0.67	0.20
KI	1.27	1.25	0.02	1.14	1.14	0.15
CKI	1.08	1.06	0.03	1.01	1.02	0.02
IHA	31.4	24.7	0.04	19.3	21.5	0.64
IHD	0.09	0.09	0.92	0.05	0.06	0.04
ABR	2.29	2.3	0.76	1.55	1.70	0.12
Anterior float/μm	36.9	35.9	0.28	18.7	19.1	0.52
Eccentricity/mm	1.37	1.42	0.09	1.59	1.44	0.18
Posterior float/μm	74.5	76.4	0.35	41.6	45.1	0.03
Eccentricity/mm	1.33	1.24	0.06	1.61	1.52	0.06

AU13 ABR, aberration coefficient; CKI, center keratoconus index; IHA, index of height asymmetry; IHD, index of height decentration; ISV, index of surface variance; IVA, index of vertical asymmetry; KI, keratoconus index.

(OD:OS = 7:14). Three eyes of the control group showed neither topographical nor clinical signs of keratectasia. All patients completed the 1-year follow-up.

Epithelial healing was completed between 1 and 3 days after treatment in all cases. The yellow staining of the cornea had disappeared at 1 day after surgery. At the 1-month examination, the anterior stroma showed haze ranging from trace (+0.5) to +1 and in the deeper stroma, the demarcation line was visible in 18 of the 21 eyes at a depth of 50%–80% gradually moving forward and fainting at subsequent visits. In 3 eyes at 1 month after treatment, the demarcation line led to the wrong detection of the posterior surface of the cornea and the information of the posterior surface including corneal thickness was neglected. At the 6-month examination, all corneas were clear except 2 cases where discrete scarring structures were visible in the deep stroma. At no time after treatment, we detected any irregularity at the endothelial level such as localized edema or scarring at the slit lamp.

The temporal evolution of the change in thickness at the thinnest point of the cornea is depicted in Figure 2. The reduction in thickness was statistically significant up to 12 months after CXL.

The average values of the other parameters measured preoperatively and at 1 year after treatment are listed in Table 2 for the treatment and the control groups. The *P* values refer to the statistically paired comparison between preoperative and 1-year postoperative values, and statistically significant differences are highlighted. Standard deviations or confidence intervals were not used because they have no clinical meaning in this representation but may describe only the inhomogeneity of the groups. It is worth to point out that even in this very gross analysis, a statistically significant flattening (R_{min}) in the cross-linked corneas is revealed, whereas the untreated corneas significantly progressed. Similarly, a decrease in the treated and an increase in the untreated eye were detected with the keratoconus indices keratoconus index, center keratoconus index, and index of height asymmetry, which indicates a shift toward a more regular cornea in the treatment group.

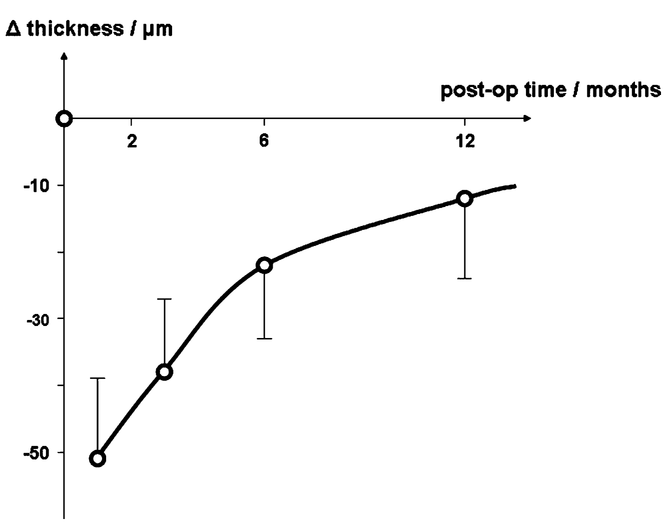

FIGURE 2. Reduction in corneal thickness (mean ± SE of mean) at the thinnest point as a function of time after treatment. The difference to preoperative thickness was statistically significant during the first year after surgery.

A more detailed view of the corneal processes after CXL requires an analysis of the changes of the parameters during the first postoperative year in comparison with the untreated fellow eye. In Table 3, all changes of parameters are listed that showed *P* values of 0.05 and less in the basic analysis (demonstrated in Table 2). The strongest significance between treatment and control groups ($P = 0.0009$) is detected with the change in maximal curvature. The reduction after CXL in 4 of the 7 keratoconus indices is in substantial contrast to the increase in the untreated cornea, indicating again a continued progression in corneas without CXL.

The rate of progression/regression is demonstrated in Table 4. In the treated group, no eye progressed during the first year after CXL but 8 eyes showed significant regression. None of the untreated control eyes showed regression, but 7 experienced significant progression.

To demonstrate the temporal evolution of the corneal processes triggered by CXL, Figure 3 compares the course of the increase in minimal curvature radius (flattening) during the first year after CXL with the decrease in the control eyes (steepening). It is obvious that the flattening process has not ended at 1 year after CXL.

DISCUSSION

The major findings of this prospective and controlled clinical study are (1) maximal curvature regressed significantly within the first year after CXL in contrast to the untreated fellow eye that continued to progress, (2) optically measured corneal thickness is significantly reduced after CXL, and (3) 4 of 7 keratoconus indices show a significant reduction at 1 year compared with the untreated control, indicating an evolution toward a more regular corneal front surface.

Both Wollensak et al[7] and Caporossi et al[8] report a reduction in maximal K readings after CXL, which is confirmed in this study. According to the Dresden reports,[7,12] this flattening process may continue for years. In this study, for the first time, a control is included that compares this flattening

TABLE 3. Changes in Corneal Shape Factors

	Cross-Linked Corneas		Control Corneas		
	Average	SD	Average	SD	*P*
ΔMinimal thickness/μm	−12.6	12.7	−1.75	12.2	0.018
ΔR_{min}/mm	0.066	0.10	−0.08	0.10	0.0009
ΔR_{min}/D	−0.62	0.9	+0.57	0.8	0.0009
ΔQ_{ant}	0.008	0.157	−0.05	0.11	0.019
ΔISV	−2.67	6.02	2.76	6.85	0.011
ΔKI	−0.015	0.03	0.006	0.019	0.021
ΔCKI	−0.006	0.01	0.006	0.009	0.001
ΔIHA	−6.7	12	2.2	11	0.025
ΔIHD	0.0009	0.015	0.007	0.018	0.32
ΔPosterior float/μm	1.9	12.3	4.05	7.1	0.37

CKI, center keratoconus index; IHA, index of height asymmetry; IHD, index of height decentration; ISV, index of surface variance; KI, keratoconus index.

TABLE 4. Progression Versus Regression in the Verum and Control Group

Group	Progression ($\Delta R_{min} \leq -0.12$ mm)	Unchanged (-0.12 mm $< \Delta R_{min} < +0.12$ mm)	Regression ($\Delta R_{min} \geq +0.12$ mm)
Untreated	7	14	0
CXL	0	13	8

with the progression that happened in the fellow eye without CXL (Tables 3, 4; Fig. 3). Three eyes of the control group did not show signs of keratectasia and did, therefore, not contribute to the progression. Nevertheless was the steepening in the control group highly significant.

Already at the 1-month postoperative examination, a significant reduction of the pachymetry at the thinnest point by approximately 50 μm on average was observed, which is not in agreement with the results of Caporossi et al.[8] Using ultrasound pachymetry, the Siena Group reports a statistically nonsignificant increase in central corneal thickness by 30 μm at 1 month after treatment, slightly reducing to 20 μm at 3 months. The authors interpret this increase as corneal edema that clears with time. However, measuring corneal thickness in keratoconus corneas by means of ultrasound pachymetry seems to be questionable because of various reasons.[16,17] In corneas with moderate and severe keratoconus, Ucakhan et al[17] found a significant smaller central corneal thickness measured with the Pentacam compared with ultrasound pachymetry and a relatively poor correlation between the 2 techniques. During the early postoperative phase, one could discuss the reduced corneal thickness as a measurement artifact because of the haze seen in almost all patients. At 12 months, however, an optical artifact is unlikely because the corneas appeared clear at the slit lamp and even with the blue light of the Scheimpflug system, only minimal opacity was detected below the anterior corneal surface. As shown in Figure 2, however, the thinning has been reduced to approximately 10 μm with the trend to reduce further. In the

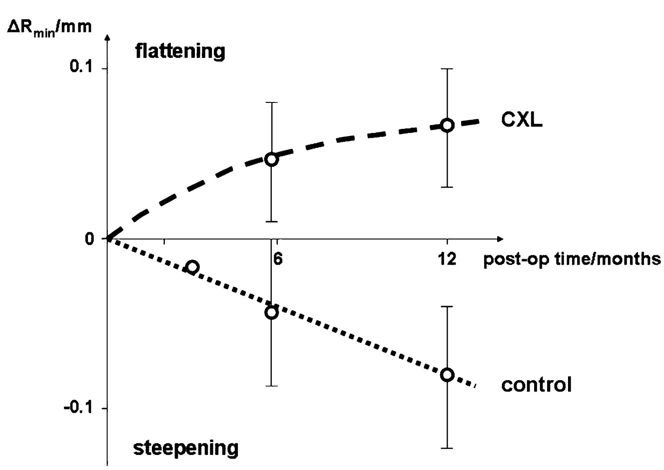

FIGURE 3. Minimal curvature radius change compared with preoperative ΔR_{min} (median ± SE of mean) for CXL and untreated fellow eye. The flattening of the treated eyes appears not to have reached the final amount at 1 year after CXL. The differences between preoperative and postoperative started to be statistically significant at 6 months after treatment.

untreated fellow corneas, a distinct but statistically significant thinning occurred, which is consistent with a continued progression of keratectasia in these eyes.

Currently, we have no good explanation for this "compression" effect after CXL except being an optical or electronic artifact. Corneal thickness in the normal cornea is regulated by the corneal endothelium that maintains a negative osmotic pressure inside the stroma. Any "enhanced activity" of the endothelium after CXL was purely speculative, and therefore, we have to assume intrastromal shrinking processes because of chemical bonds induced by the radicals formed during CXL. Alternatively, a change in refractive index of the cross-linked stroma might be an explanation leading to a false thinner result of optical ray tracing. More experimental studies including the swelling behavior of the cornea after CXL will be needed to elucidate this complex.

CXL in central iatrogenic keratectasia after LASIK can result in a significant reduction of the ectasia.[10] A similar process seems to occur in the cornea with primary keratoconus but to a much smaller extent. The maximal anterior elevation (anterior float) showed a certain reduction of the cone peak (Table 3), which was not statistically significant at any time after treatment. However, in none of the eyes treated, we saw a dramatic reduction of the ectasia that may occur after CXL of corneas with iatrogenic keratectasia.[10] The localized keratectasia after LASIK with a typical diameter of only 1 mm and less may be the reason for the stronger leveling out effect.

In the first clinical pilot study on CXL for keratoconus, Wollensak et al[7] reported a small increase in BSCVA after the treatment. This was confirmed by Caporossi et al[8] who attributed it to a more symmetrical postoperative shape of the cornea. The significant reduction of the keratoconus indices presented in this study goes indeed along with a tendency toward a more regular shape of the cornea, which may explain the improvement in BSCVA. The nature of this process is unknown. Correlation analysis of BSCVA and the keratoconus indices and a longer follow-up may prove whether it is the more regular cornea that provides better vision.

From the temporal evolution of the flattening ΔR_{min} (Fig. 3) and the reduction in corneal thickness (Fig. 2), one can easily see that the process of regularization has not come to a final stage at 1 year after surgery but may continue. In an earlier study, we reported favorable visual results after customized surface ablation in cases of forme fruste of keratoconus,[18] which stimulated Kanellopoulos and Binder[19] to use topography-guided customized ablation after CXL. Such an optical homogenization of the anterior surface by means of customized surface ablation might be very helpful in contact lens–intolerant patients but should be performed at earliest when the corneal shape has achieved stability that seems to take more than 1 year. AU7

Using the fellow eye as a control, there is an implicit assumption that the 2 eyes would have behaved similarly had neither eye been treated. According to our clinical experience, this assumption is not correct. On the other hand, the control group selected in this study should resample the treatment group better than any other group of independent keratoconus AU8 eyes because of perfect age and gender matching. In addition, because we treated the more advanced eye, respectively, that one with more progression preoperatively, in a comparison of the groups, the effect of the treatment would be rather underestimated than overestimated. Several parameters would have been useful to determine the eye of 2 fellow eyes that needs treatment at first: posterior peak elevation, minimal AU9 corneal thickness, maximal curvature R_{min}, and a combination of these parameters. Only R_{min} is a primary parameter and from the history (with the Orbscan), we learned that deduced parameters of the back surface of the cornea are not as reliable compared with primary parameters. This is the reason why we based the decision of the eye to be treated on R_{min} and its progression.

Although some of the data presented support a stop in progression of the keratoconus, not all parameters do so. The corneal thinning effect was discussed before but also the posterior elevation peak and other keratoconus indices have increased after CXL, indicating progression (Table 2). None of these changes, however, were statistically significant and the standard deviations are up to an order of greater magnitude (Table 3). Nevertheless, only longer follow-up and larger study groups will help to exclude doubts about the efficacy of CXL.

In summary, we could show that a statistically significant corneal flattening occurs within 1 year after CXL compared with the untreated partner eye and compared with the preoperative corneal shape. Optical corneal thickness is reduced after CXL, and during the first year after treatment, the corneal shape changes toward a more regular front surface.

REFERENCES

1. Andreassen TT, Simonsen AH, Oxlund H. Biomechanical properties of keratoconus and normal corneas. *Exp Eye Res*. 1980;31:435–441.
2. Edmund C. Corneal topography and elasticity in normal and keratoconic eyes. A methodological study concerning the pathogenesis of keratoconus. *Acta Ophthalmol Suppl*. 1989;193:1–36.
3. Oxlund H, Simonsen AH. Biochemical studies of normal and keratoconus corneas. *Acta Ophthalmol (Copenh)*. 1985;63:666–669.
4. Seiler T, Spoerl E, Huhle M, et al. Conservative therapy of keratoconus by enhancement of collagen cross-links. *Invest Ophthalmol Vis Sci*. 1996;37:S1017.
5. Spoerl E, Huhle M, Kasper M, et al. Artificial stiffening of the cornea by induction of intrastromal cross-links. *Ophthalmologe*. 1997;94:902–906.
6. Schnitzler E, Spoerl E, Seiler T. Bestrahlung der Hornhaut mit UV-Licht und Riboflavingabe als neuer Behandlungsversuch bei einschmelzenden Hornhautprozessen. *Klin Monatsbl Augenheilkd*. 2000;217:190–193.
7. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
8. Caporossi A, Baiocchi S, Mazzotta C, et al. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen. *J Cataract Refract Surg*. 2006;32:837–845.
9. Kohlhaas M, Spoerl E, Speck A, et al. Eine neue Behandlung der Keratektasie nach LASIK durch Kollagenvernetzung mit Riboflavin/UVA-Licht. *Klin Monatsbl Augenheilkd*. 2005;222:430–436.
10. Hafezi F, Kanellopoulos J, Wiltfang R, et al. Corneal collagen cross-linking with riboflavin/UVA for the treatment of induced keratectasia after LASIK. *J Cataract Refract Surg*. 2007;33:2035–2040.
11. Iseli HP, Thiel M, Hafezi F, et al. UVA/riboflavin corneal cross-linking (CXL) for infectious keratitis associated with corneal melts. *Cornea*. 2008 [accepted]. AU10
12. Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet-A in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34:796–801.
13. Hanna KD, Pouliquen YM, Waring GO III, et al. Corneal wound healing in monkeys after repeated excimer laser photorefractive keratectomy. *Arch Ophthalmol*. 1992;110:1286–1291.
14. Huebscher H, Fink W, Steinbruck D, et al. Scheimpflug records without distortion—a mythos? *Ophthalmic Res*. 1999;31:134–139.
15. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea*. 2006;25:1057–1059.
16. Gherghel D, Hosking SL, Mantry S, et al. Corneal pachymetry in normal and keratoconus eyes. Orbscan II versus ultrasound. *J Cataract Refract Surg*. 2004;30:1272–1277.
17. Ucakhan OO, Ozkan M, Kanpolat A. Corneal thickness measurements in normal and keratoconic eyes: Pentacam comprehensive eye scanner versus noncontact specular microscopy and ultrasound pachymetry. *J Cataract Refract Surg*. 2006;32:970–977.
18. Koller T, Iseli HP, Donitzki C, et al. Topography-guided surface ablation for forme fruste keratoconus. *Ophthalmology*. 2006;113:2198–2202.
19. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. *Cornea*. 2007;26:891–895.
20. Forrester JV, Dick AD, McMenamin P, et al. *The Eye*. London, United Kingdom: WB Saunders; 1996:17. AU11
21. Wollensak G, Spörl E, Reber F, et al. Corneal endothelial cytotoxicity of riboflavin/UVA treatment in vitro. *Ophthalmic Res*. 2003;35:324–328.
22. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin crosslinking of the cornea. *Cornea*. 2007;26:385–389.
23. Caporossi A, Mazzotta C, Baiocchi S, et al. Therapia para-chirurgica mediante cross-linking del collagene corneale con riboflavina-ultravioletto. In: *Il Cheratocono*. SOI; 2004:223–234. AU12