In Vivo Biomechanical Changes After Corneal Collagen Cross-linking for Keratoconus and Corneal Ectasia: 1-Year Analysis of a Randomized, Controlled, Clinical Trial

Steven A. Greenstein, MD, Kristen L. Fry, OD, MS, and Peter S. Hersh, MD

Purpose: To investigate the in vivo, corneal, biomechanical changes after corneal collagen cross-linking (CXL) using the Ocular Response Analyzer (ORA) in patients with keratoconus and post-laser in situ keratomileusis (LASIK) ectasia.

Methods: Single-center, prospective, randomized, controlled, clinical trial. After CXL (69 eyes, 46 keratoconus and 23 post-LASIK), corneal hysteresis (CH) and corneal resistance factor (CRF) were measured using the ORA and analyzed in a treatment, sham control, and fellow eye control group at baseline and 1, 3, 6, and 12 months.

Results: There were no significant changes in CH (change = 0.05 ± 1.5; $P = 0.78$) or CRF (change = 0.29 ± 1.4; $P = 0.1$) at 1 year compared with preoperative values. Changes in CH and CRF were not correlated with changes in clinical outcomes of uncorrected visual acuity, best spectacle-corrected visual acuity, and maximum keratometry. There were no significant changes in CH in the sham or fellow eye control groups ($P_{sham} = 0.7$; $P_{FE} = 0.3$) or CRF ($P_{sham} = 0.6$; $P_{FE} = 0.72$).

Conclusions: Despite an increase in CRF at one month, there were no statistically significant changes in CH and CRF measurements 1 year after CXL. Development of other in vivo biomechanical metrics would aid in evaluating the corneal response to CXL.

(*Cornea* 2012;31:21–25)

Keratoconus and post-laser in situ keratomileusis (LASIK) ectasia are disease processes in which the cornea deforms in association with thinning and biomechanical weakening.[1,2] An understanding of corneal biomechanics may help to elucidate the cause and natural history of these ectatic processes. The cornea is a viscoelastic structure with both viscous and elastic components.[3] In response to stress, there is an immediate elastic response of the cornea followed by a prolonged, time-dependent, viscoelastic response. Early studies measured a decrease in elasticity in corneas with keratoconus.[4–6] Although the pathogenesis of keratoconus and ectasia currently remains unclear, it seems that a primary event leads to the loss and/or slippage of collagen fibrils and changes to the extracellular matrix in the corneal stroma.[7] These changes are thought to cause biomechanical instability of the corneal stroma with consequent changes in both the cornea's anatomical and topographic architecture.[8]

UVA/riboflavin–mediated collagen cross-linking (CXL) for the treatment of keratoconus and post-LASIK ectasia is thought to increase the biomechanical strength of the cornea. Wollensak et al[9] reported that immediate stress measurements increased by 71.9% and 328.9% in porcine and human corneas, respectively, after CXL. In rabbit corneas, these increases in stress measurements were maintained between 69.7% and 106% at 8 months postoperatively.[10] Such postoperative increases in Young modulus were further demonstrated with collagen hydrogels exposed to UVA/riboflavin therapy.[11]

We reported encouraging results of CXL in a previous randomized, controlled, clinical trial.[12] In that study of 1-year CXL outcomes, patients experienced an improvement in both best spectacle-corrected visual acuity (BSCVA) and uncorrected visual acuity (UCVA), and maximum keratometry (K_{max}) and average keratometry. Despite laboratory and clinical findings, however, to date it has been difficult to quantify the actual biomechanical changes effected by CXL in vivo.[13,14]

The Ocular Response Analyzer (ORA; Reichert, Inc, Buffalo, NY) is a commercially available device designed to obtain in vivo measurements of corneal biomechanical properties.[15] Two core metrics are used to describe the biomechanical strength of the cornea: corneal hysteresis (CH) and corneal resistance factor (CRF). CH is a measurement of the viscous dampening in corneal tissue, and CRF is a measurement of the entire viscoelastic response of the cornea, both in response to a graded and time-dependent applanation pressure applied by the ORA. To measure CH and CRF, a tube is automatically aligned with the patient's eye and an air puff is released of a specific time and pressure gradient. Concomitant with the air pulse, the ORA measures 2

applanation pressures: the first pressure is measured when the cornea is moving inward, and the second pressure is measured as the cornea recoils to its native position. In addition, a waveform of this temporal corneal deformation is captured. Measurements derived from the waveform signal such as peak amplitudes, timing of peaks, width of peaks, and others have been used to characterize the biomechanical properties of individual corneas.[16–19]

In this study, in an effort to elucidate corneal biomechanical changes in vivo after CXL, ORA measurements of CH and CRF were analyzed over a 1-year period after the CXL procedure and also were correlated with visual acuity and topographic outcomes after CXL.

MATERIALS AND METHODS

Patients with progressive keratoconus and ectasia were enrolled as part of a multicenter, prospective, randomized, controlled, clinical trial conducted under the guidelines of the US Food and Drug Administration (ClinicalTrials.gov, NCT00647699 and NCT00674661) and approved and monitored by an investigational review board. This study was compliant with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all patients. Progressive keratoconus or ectasia was defined as one or more of the following changes over a period of 24 months: an increase of ≥ 1 diopter (D) in the steepest keratometry, an increase of ≥ 1 D in manifest cylinder, or an increase of ≥ 0.5 D in manifest refractive spherical equivalent.

CXL was performed according the methodology described by Wollensak et al.[20] Initially, a topical anesthetic was administered and the central epithelium was removed. After topical 0.1% riboflavin administration (0.1% in 20% dextran T-500 solution, Medio-Cross; Peschke Meditrade, GmbH, Zurich, Switzerland) every 2 minutes for a total of 30 minutes, riboflavin absorption was confirmed on slit-lamp examination. Ultrasonic pachymetry was performed. If the cornea was <400 μm, hypotonic riboflavin (0.1% in sterile water, Medio-Cross hypotonic; Peschke Meditrade, GmbH) was administered, after which ultrasonic pachymetry was performed to confirm that the stroma had swelled to >400 μm. The cornea was exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm² (UV-X System; IROC, Zurich, Switzerland), and riboflavin administration was continued every 2 minutes for the duration of the treatment.

ORA AND PENTACAM MEASUREMENTS

Treatment Group

The ORA is a device used to measure in vivo corneal biomechanical properties. Two primary metrics are CH and CRF. CH is a measure of the difference between the 2 applanation pressures measured by the ORA (P1–P2), thought to represent the viscous dampening property of the cornea. CRF is a linear calculation (P1-*k*P2), thought to better account for corneal thickness, that measures both the viscous and elastic properties of the cornea. Three ORA measurements were taken at each study visit, and the measurement with the highest waveform score was used for analysis. CH and CRF

were measured at baseline and 1, 3, 6, and 12 months. To further analyze ORA measurements, the correlation among CH, CRF, and central corneal thickness (CCT) measured on the Pentacam (Oculus, Inc, Wetzlar, Germany) was analyzed at baseline and 1 year. Finally, the changes in CH and CRF at 1 year were correlated with 1-year visual acuity and topographic outcomes.

Control Groups

The sham control group received 0.1% riboflavin ophthalmic solution alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for a total of 30 minutes. After the administration of riboflavin, the cornea was aligned with the UVA light and the light was not turned on. While the patient was under the UVA light, riboflavin was administered topically every 2 minutes for an additional 30 minutes. The sham control patients were followed for 3 months postoperatively at which point the study eye crossed over to the treatment group and received full UVA/riboflavin treatment. ORA measurements were analyzed at 1 and 3 months and compared with the postoperative measurements of the treatment group at the same time points.

In addition, a fellow eye control group was analyzed as well. The fellow eyes of patients who did not undergo CXL treatment bilaterally were analyzed in this group. This group consisted of eyes with frank keratoconus or ectasia that did not undergo CXL, eyes with evidence of disease that did not meet the inclusion criteria of this study, and eyes with no evidence of disease. ORA measurements were analyzed at baseline and 12 months and compared with the postoperative measurements of the treatment group between the same time points. Similar to the treated group, in this control group, CH and CRF also were correlated with Pentacam CCT measurements.

OUTCOME MEASUREMENTS

Visual Acuity Measurements

UCVA and BSCVA were measured at 1 and 12 months postoperatively. Visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity test (2nd ed.) with Sloan letters. The fluorescent tubes in the ETDRS chart light box were 40-W, frosted, cool, white bulbs and were replaced annually. New tubes were kept on for 96 hours. Room illumination was measured at a level of 50 to 100 foot candles using a photometer held 4 ft from the floor and directed toward the ceiling. Visual acuity was measured at a 4-m distance. If patients could not read any letters at 4 m, they were tested at a 2-m distance. Visual acuity was recorded and analyzed as the logarithm of the minimum angle of resolution value.

Topographic and Pachymetric Measurements

Topographic and pachymetric measurements were obtained using the Pentacam (Oculus, Inc). The Pentacam is a rotating Scheimpflug camera that generates a 3-dimensional model of the cornea and anterior segment. K_{max} and CCT measurements were obtained preoperatively and at 12 months postoperatively.

Statistical Analysis

Statistical analysis was performed using PASW Statistics 18 (SPSS, Inc, Chicago, IL). A paired 2-tailed Student *t* test was performed to analyze the postoperative ORA changes over time and compared with baseline. An independent *t* test was performed to compare the differences in postoperative changes between the treatment and control groups and the keratoconus and post-LASIK ectasia groups. To analyze the possible correlation of CCT, CXL outcomes, and ORA measurements, Pearson correlation coefficients were used. A *P* value of 0.05 was used as significance level.

RESULTS

A total of 69 eyes (46 keratoconus and 23 ectasia) of 56 patients underwent CXL and were followed for 1 year. The fellow eye and sham control groups each comprised 35 eyes of 35 patients (23 keratoconus and 12 ectasia).
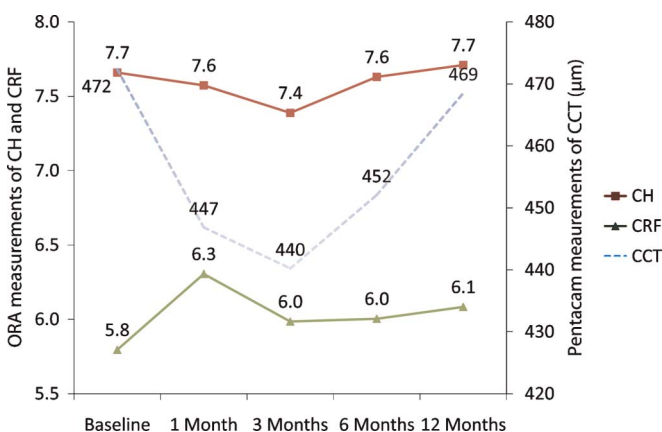
CH and CRF

Preoperative CH was 7.66 ± 1.16 and at 1 year postoperatively remained unchanged at 7.71 ± 1.77 ($P = 0.78$). Preoperative CRF was 5.80 ± 1.31 and at 1 year was 6.08 ± 1.77 ($P = 0.10$).

Postoperative Time Course of CH and CRF

The postoperative changes in CH were -0.09 ± 1.46, -0.18 ± 1.66, 0.24 ± 1.7, and 0.08 ± 1.79 between baseline and 1 month, 1 and 3 months, 3 and 6 months, and 6 and 12 months, respectively. All of these changes failed to reach statistical significance ($P_{0-1} = 0.6$, $P_{1-3} = 0.4$, $P_{3-6} = 0.2$, and $P_{6-12} = 0.7$) (Fig. 1, Table 1).

Initially, there was a significant increase in CRF between baseline and 1 month (0.5 ± 1.42; $P = 0.004$). After this increase in CRF, there were changes in CRF between 1 and 3 months (-0.32 ± 1.36), 3 and 6 months (0.02 ± 1.42), and 6 and 12 months (0.08 ± 1.40). All of these changes failed to reach statistical significance ($P_{1-3} = 0.05$, $P_{3-6} = 0.9$, and $P_{6-12} = 0.6$) (Fig. 1).

FIGURE 1. Change in CH (top line) and CRF (bottom line) versus time in patients with keratectasia. The dashed line represents the change in CCT over time.

Difference Between Keratoconus and Ectasia Eyes

There was no significant difference between patients with keratoconus and post-LASIK ectasia when the change in CH ($P = 0.39$) and CRF ($P = 0.84$) between baseline and 1-year follow-up was analyzed.

Control Eyes

In the sham control group, CH and CRF changed by 0.12 ± 1.1 ($P = 0.5$) and -0.05 ± 1.0 ($P = 0.8$) between baseline and 1 month and by 0.08 ± 1.0 ($P = 0.6$) and -0.07 ± 0.91 ($P = 0.6$) between baseline and 3 months, respectively. All of these changes failed to reach statistical significance.

In the fellow eye control group, CH and CRF changed by 0.17 ± 1.1 ($P = 0.4$) and 0.09 ± 1.0 ($P = 0.6$) between baseline and 12 months. All of these changes also failed to reach statistical significance.

Control Versus Treated Patients

When the change in CRF between baseline and 1 month was compared there was a significant difference between the sham control and treatment groups ($P = 0.04$); in the treatment group, there was a significant increase in CRF, whereas in the sham control group, there was no significant change. There was no significant difference between treated and control patients when the change in CH or CRF between baseline and 3 months ($P_{CH} = 0.14$, $P_{CRF} = 0.26$) and baseline and 1 year ($P_{CH} = 0.68$, $P_{CRF} = 0.93$) was analyzed.

Correlation Between ORA Measurements and CCT

CH and CRF at baseline and 12 months were significantly correlated with CCT at baseline and 12 months, respectively ($CH_{baseline}$ with $CCT_{baseline} = 0.56$, $P < 0.001$; CH_{12} with $CCT_{12} = 0.42$, $P < 0.001$; $CRF_{baseline}$ with $CCT_{baseline} = 0.63$, $P < 0.001$; and CRF_{12} with $CCT_{12} = 0.51$, $P < 0.001$). Similar to the treated group, in the fellow eye control group, CH and CRF at baseline and 12 months were significantly correlated with CCT at baseline and 12 months, respectively ($CH_{baseline}$ with $CCT_{baseline} = 0.60$, $P < 0.001$; CH_{12} with $CCT_{12} = 0.68$, $P < 0.001$; $CRF_{baseline}$ with $CCT_{baseline} = 0.62$, $P < 0.001$; and CRF_{12} with $CCT_{12} = 0.74$, $P < 0.001$).

Correlation Among ORA, Visual Acuity, and Topographic Measurements

In the entire cohort, UCVA, BSCVA, and K_{max} were significantly improved 1 year after CXL (Table 2). The changes in CH and CRF between baseline and 1 year were not correlated with the changes in UCVA ($r_{CH} = -0.06$, $P = 0.6$; $r_{CRF} = -0.10$, $P = 0.4$), BSCVA ($r_{CH} = 0.03$, $P = 0.8$; $r_{CRF} = 0.01$, $P = 0.9$), or K_{max} ($r_{CH} = -0.02$, $P = 0.8$; $r_{CRF} = 0.02$, $P = 0.9$).

DISCUSSION

CXL is a promising new treatment for the stabilization and strengthening of the cornea in keratoconus[20] and post-LASIK ectasia.[21,22] CXL is thought to cause cross-linking

TABLE 1. ORA Measurements Over Time [All (69 Eyes), Keratoconus (46 Eyes), and Ectasia (23 Eyes)]

	ORA Measurements	Preoperatively	1 Month	3 Months	6 Months	12 Months	P Value Change From Baseline to 12 Months (KC vs Ectasia)	P Value Change From Baseline to 12 Months (Tx vs FE)	P Value Change From Baseline to 3 Months (Tx vs Sham)
All	CH	7.66 ± 1.16	7.57 ± 1.9	7.39 ± 1.58	7.63 ± 1.96	7.71 ± 1.77	0.4	0.7	0.1
	CRF	5.80 ± 1.31	6.31 ± 1.63*†	5.99 ± 1.44	6.00 ± 1.64	6.08 ± 1.77	0.8	0.9	0.3
KC	CH	7.76 ± 1.10	7.89 ± 2.04	7.48 ± 1.33	7.72 ± 1.84	7.91 ± 1.68	—	0.5	0.1
	CRF	5.89 ± 1.36	6.52 ± 1.66*†	5.99 ± 1.34*	6.04 ± 1.60	6.20 ± 1.64	—	0.8	0.8
Ectasia	CH	7.48 ± 1.29	6.95 ± 1.50*†	7.21 ± 2.02	7.45 ± 2.23	7.31 ± 1.93	—	0.8	0.6
	CRF	5.62 ± 1.21	5.88 ± 1.50	5.98 ± 1.66	5.94 ± 1.77	5.86 ± 1.95	—	0.7	0.09

Data were considered to be significant at $P < 0.05$.
*Significant change compared with baseline measurements.
†Significant change compared with previous visit measurement.
KC, keratoconus; FE, fellow eye; Tx, treatment.

through the formation of reactive oxygen species, leading to the production of covalent cross-links between collagen molecules, with consequent stiffening of the stromal tissue.[23] This strengthening of the corneal stroma slows the progression of keratoconus and ectasia and, in many cases, improves patients' visual, refractive, and topographic outcomes,[12,24–26] with a low reported rate of complication.[27,28] Indeed, in our previous report of the 1-year clinical results of CXL, we found an average K_{max} flattening of 1.7D and improvement in BSCVA from 20/45 to 20/34 and improvement in a number of corneal topographic indices.[12,29]

In this study, the in vivo biomechanical measurements, CH and CRF remained unchanged 1 year after CXL. The lack of significant changes in CH and CRF is consistent with previously reported ORA results.[13,14,30] Interpreting these results is challenging because postoperative changes to either the viscous or elastic component of the cornea may be too subtle for these ORA metrics to capture and may in part contribute to the lack of significant results.[31,32] Moreover, the surface optical irregularity of these ectatic corneas may introduce error and variability into the ORA signal that may prevent meaningful quantitative comparison of preoperative and postoperative CH and CRF (Fig. 1).[26,33] It is also possible that the biomechanical changes after CXL are inherently different than those measured by CH and CRF, and therefore, these metrics may not capture the true biomechanical effect of CXL over time.

In this study, the treatment group was compared with a 3-month sham control group and a 12-month fellow eye control group. Ideally, all fellow eyes would have been compared with treatment eyes. However, the protocol for this trial allowed fellow eye CXL treatment 3 months after the first eye treatment. Therefore, the treatment patients were compared only with the fellow eyes of the patients who had unilateral treatment and 12-month follow-up in their fellow eyes. Some of the fellow eyes in this study had no topographic or visual signs of keratoconus or ectasia. Thus, disease progression would be expected to be minimal.

In the sham and fellow eye control groups, there were no significant changes in CH or CRF between baseline and 1 year. At 1 month, there was a significant difference between the mean increase in CRF in the treatment group (an increase in biomechanical strength) and the mean decrease in CRF in the sham control group (a decrease in biomechanical strength). This could be a result of an increase in corneal biomechanical strength that occurs 1 month after CXL. Of note, this is concomitant with the significant corneal thinning that is seen 1 month after CXL. Thinner corneas seem to be correlated with lower CRF values. This suggests that the increase in CRF is, indeed, an indication of corneal strengthening at 1 month. In previous work, we defined the postoperative time course of corneal haze after CXL,[34] a clinical analog to the post-CXL healing process. Thus, the increase in CRF that we observed at 1 month could also be a finding incidental to the epithelial and stromal remodeling process.

In this study, the ORA metrics of CH and CRF did not significantly change over a time course of 1 year after CXL. Ongoing development of interpretive models of the waveform itself may better capture the true biomechanical properties of the cornea after CXL. Indeed, such waveform analysis has been shown to identify and grade different clinical stages of keratoconus.[17,18] Further clinical studies

TABLE 2. Visual Acuity and Topographic Measurements (All 69 Eyes)

	Preoperatively	1 Year	Significance ($P < 0.05$)
Uncorrected visual acuity (logMAR)	0.84 ± 0.34	0.77 ± 0.38	$P = 0.02$
Best spectacle visual acuity (logMAR)	0.35 ± 0.23	0.22 ± 0.19	$P < 0.001$
K_{max}, D	58.4 ± 9.1	56.9 ± 8.1	$P = 0.001$

logMAR, logarithm of the minimum angle of resolution.

using such analytic algorithms may help elucidate the in vivo, corneal, biomechanical changes consequent to the CXL procedure.

REFERENCES

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related non-inflammatory corneal thinning disorders. *Surv Ophthalmol*. 1984;28: 293–322.
2. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297–319.
3. Roberts C. The cornea is not a piece of plastic. *J Refract Surg*. 2000;16: 407–413.
4. 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.
5. Edmund C. Corneal elasticity and ocular rigidity in normal and keratoconic eyes. *Acta Ophthalmol (Copenh)*. 1988;66:134–140.
6. Nash IS, Greene PR, Foster CS. Comparison of mechanical properties of keratoconus and normal corneas. *Exp Eye Res*. 1982;35:413–424.
7. Meek KM, Tuft SJ, Huang Y, et al. Changes in collagen orientation and distribution in keratoconus corneas. *Invest Ophthalmol Vis Sci*. 2005;46: 1948–1956.
8. Gefen A, Shalom R, Elad D, et al. Biomechanical analysis of the keratoconic cornea. *J Mech Behav Biomed Mater*. 2009;2:224–236.
9. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg*. 2003;29:1780–1785.
10. Wollensak G, Iomdina E. Long-term biomechanical properties of rabbit cornea after photodynamic collagen crosslinking. *Acta Ophthalmol*. 2009; 87:48–51.
11. Ahearne M, Yang Y, Then KY, et al. Non-destructive mechanical characterisation of UVA/riboflavin crosslinked collagen hydrogels. *Br J Ophthalmol*. 2008;92:268–271.
12. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:149–160.
13. Goldich Y, Barkana Y, Morad Y, et al. Can we measure corneal biomechanical changes after collagen cross-linking in eyes with keratoconus?— a pilot study. *Cornea*. 2009;28:498–502.
14. Vinciguerra P, Albe E, Mahmoud AM, et al. Intra- and postoperative variation in ocular response analyzer parameters in keratoconic eyes after corneal cross-linking. *J Refract Surg*. 2010:1–8.
15. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg*. 2005;31: 156–162.
16. Kerautret J, Colin J, Touboul D, et al. Biomechanical characteristics of the ectatic cornea. *J Cataract Refract Surg*. 2008;34:510–513.
17. Fry KL, Luce D, Hersh P. Integrated ocular response analyzer waveform score as a biomechanical index of keratoconus disease severity. *Invest Ophthalmol Vis Sci*. 2008;49:4343.
18. Gatinel D, Luce D. Corneal hysteresis and waveform analysis in the normal fellow eye of patients with newly diagnosed keratoconus. *Invest Ophthalmol Vis Sci*. 2009;50:1750.
19. Lam AK, Chen D, Tse J. The usefulness of waveform score from the ocular response analyzer. *Optom Vis Sci*. 2010;87:195–199.
20. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
21. Hafezi F, Kanellopoulos J, Wiltfang R, et al. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2007; 33:2035–2040.
22. Vinciguerra P, Camesasca FI, Albe E, et al. Corneal collagen cross-linking for ectasia after excimer laser refractive surgery: 1-year results. *J Refract Surg*. 2009:1–12.
23. Kohlhaas M, Spoerl E, Schilde T, et al. Biomechanical evidence of the distribution of cross-links in corneas treated with riboflavin and ultraviolet A light. *J Cataract Refract Surg*. 2006;32:279–283.
24. 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.
25. 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;34:796–801.
26. Vinciguerra P, Albe E, Trazza S, et al. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. *Ophthalmology*. 2009;116:369–378.
27. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea*. 2007;26:385–389.
28. Greenstein SA, Shah VP, Fry KL, et al. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:691–700.
29. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. In press.
30. Fournie P, Galiacy S, Arne JL, et al. Corneal collagen cross-linking with ultraviolet-A light and riboflavin for the treatment of progressive keratoconus [in French]. *J Fr Ophtalmol*. 2009;32:1–7.
31. Touboul D, Roberts C, Kerautret J, et al. Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. *J Cataract Refract Surg*. 2008;34:616–622.
32. Glass DH, Roberts CJ, Litsky AS, et al. A viscoelastic biomechanical model of the cornea describing the effect of viscosity and elasticity on hysteresis. *Invest Ophthalmol Vis Sci*. 2008;49:3919–3926.
33. Shah S, Laiquzzaman M, Cunliffe I, et al. The use of the Reichert ocular response analyser to establish the relationship between ocular hysteresis, corneal resistance factor and central corneal thickness in normal eyes. *Cont Lens Anterior Eye*. 2006;29:257–262.
34. Greenstein SA, Fry KL, Bhatt J, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *J Cataract Refract Surg*. 2010;36:2105–2114.