

Complication and failure rates after corneal crosslinking

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PURPOSE: To evaluate the complication rate of corneal crosslinking (CXL) for primary keratectasia and to develop recommendations for avoiding complications.

SETTING: Institut für Refraktive und Ophthalmo-Chirurgie, Zurich, Switzerland.

METHODS: In a prospective study, eyes with verified progressive keratectasia had standard CXL. Preoperative and 6- and 12-month postoperative examinations included corrected distance visual acuity (CDVA), slitlamp evaluation, applanation tonometry, and Scheimpflug imaging (Pentacam). Statistical analysis included analysis of variance and the Mann-Whitney *U* test to detect risk factors for complications.

RESULTS: The study evaluated 117 eyes of 99 patients; approximately 90% completed the 12-month follow-up. The complication rate (percentage of eyes losing 2 or more Snellen lines) was 2.9% (95% confidence interval, 0.6%-8.5%). The failure rate of CXL (percentage of eyes with continued progression) was 7.6%. Age older than 35 years and a preoperative CDVA better than 20/25 were identified as significant risk factors for complications. A high preoperative maximum keratometry (K) reading was a significant risk factor for failure. Sterile infiltrates were seen in 7.6% of eyes and central stromal scars, in 2.8%.

CONCLUSIONS: Results indicate that changing the inclusion criteria may significantly reduce the complications and failures of CXL. A preoperative maximum K reading less than 58.00 diopters may reduce the failure rate to less than 3%, and restricting patient age to younger than 35 years may reduce the complication rate to 1%.

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More than 10 years ago, corneal crosslinking (CXL) by means of riboflavin and ultraviolet light (UV) was proposed as a therapeutic approach to improve the biomechanical and biochemical properties of the cornea¹ (Seiler T, et al. IOVS 1996; 37:ARVO Abstract 4671). The first reports of clinical experience with this treatment for corneal melting appeared in 2000.²

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In 2003, a halt in the progression of keratectasia after CXL was shown in eyes with documented progression before the treatment.³ The authors found a decrease in maximum keratometry (K) readings and an improvement in visual acuity during the first postoperative years. This finding was confirmed in 2006 by Caporossi et al.⁴ in a 3-month follow-up after CXL as well as in 2008 by Wittig-Silva et al.⁵ and in 2009 by Koller et al.⁶ in controlled prospective studies with a completed 1-year follow-up. Other applications of CXL include iatrogenic keratectasia after LASIK^{7,8} and infectious keratitis.⁹ All these studies found CXL to be efficacious in stopping the progression of keratectasia. However, they had small cohorts that did not allow estimations of complication or failure rates. Also, none gave a list of indications or contraindications.

This prospective study of a large group of eyes with primary keratectasia evaluated the complication and failure rates of CXL during the first postoperative year.

PATIENTS AND METHODS

Study Design

This study enrolled eyes with progressive keratectasia. Progression of keratectasia was verified by repeated Scheimpflug imaging over at least 6 months (range 6 months to 2 years). Progression was accepted if the increase in the maximum K reading exceeded 1.00 diopter (D), which equals 3 standard deviations (SD).⁶ Second eyes were treated no earlier than 6 months after first eyes. Only eyes with mild to moderate keratoconus (maximum K value <65.00 D; corneal thickness >400 μm) were included. Because of the broad overlap of the diagnoses of pellucid marginal degeneration and keratoconus, no distinctions were made between the 2 clinical entities. Eyes with preoperative corneal opacities were not accepted because Scheimpflug photography may give false results in such cases. Additional exclusion criteria were ocular pathology other than keratectasia, especially the cornea guttata or other endothelial irregularities, history of recurrent erosions, age younger than 18 years, actual or intended pregnancy, not available for follow-up examinations for 1 year, and connective tissue disease. The Ethikkomitee des Kantons Zürich approved the study protocol. All patients provided informed consent.

Examinations

Patients were examined preoperatively, in the early postoperative period (at 1 to 3 days [until epithelial healing]) and 1, 6, and 12 months postoperatively. At all follow-up visits except the early postoperative, a standard examination was performed consisting of autorefractometry and autokeratometry (Humphrey Model 599, Carl Zeiss Meditec), corneal topography (Keratograph C, Oculus), Scheimpflug imaging (Pentacam 70700, Oculus), manifest refraction using the fogging technique, uncorrected (UDVA) and with spectacles corrected (CDVA) distance visual acuity, applanation tonometry, and slitlamp evaluation of the anterior and posterior segments of the eyes. The haze in the anterior stroma was graded on a scale used after photorefractive keratectomy (PRK).¹⁰ This scale was used even though corneal opacity after CXL is not located strictly subepithelially but also extends into deep stroma. At the 1-month follow-up examination, the depth of the demarcation line was estimated at the slitlamp as the percentage of central corneal thickness (CCT).¹¹ The maximum K reading was recorded as the mean of 3 Scheimpflug measurements. The threshold of significant difference for the Scheimpflug maximum K readings was 1.00 D (3 SD of the reproducibility).⁶ To calculate the mean values and for comparisons, visual acuities were converted to the logMAR scale.

The complication rate was defined as the percentage of eyes with a loss of 2 or more Snellen lines of CDVA at the 12-month follow-up compared with preoperatively. The failure rate of CXL was defined as the percentage of eyes with an increase in the maximum K reading of more than 1.00 D over the preoperative value.

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

Surgical Technique

Topical anesthesia of the cornea was obtained using oxybuprocaine and tetracaine drops, alternating every 3 minutes

for 15 minutes. After a lid speculum was inserted, a 9.0 mm diameter corneal abrasion was made. Then, riboflavin 0.1% drops were instilled every 3 minutes for 30 minutes. The riboflavin drops were prepared immediately before treatment by mixing aqueous riboflavin 0.5% solution with dextran T-500 20% solution. Next, central corneal pachymetry was performed using ultrasound. In eyes with a CCT (without epithelium) less than 400 μm , additional riboflavin 0.1% drops without dextran (hypoosmotic drops) were applied until the thickness exceeded 400 μm . The eyes were then inspected at the slitlamp to ensure that the riboflavin had penetrated the aqueous (blue light). After this, the eye was irradiated for 30 minutes with ultraviolet-A light with an irradiance of 3 mW/cm^2 (UV-X, Peschkemed Meditrade). During irradiation, the cornea was moistened every 3 minutes with riboflavin 0.1% drops and oxybuprocaine drops at the patient's discretion. At the end of the procedure, ofloxacin 0.3% ointment 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 2 times a day for 1 week. For eyes with sterile infiltrates during the early postoperative phase, dexamethasone drops were prescribed 5 times a day for 1 week, after which the drops were tapered over the following 2 weeks.

Statistical Analysis

All calculations were performed with WinSTAT for Excel (R. Finch Software). Variables were described as the mean, SD, and 95% confidence interval (CI). A 1-factor analysis of variance (ANOVA) was performed and included the following variables: age, preoperative maximum K reading, change in the maximum K reading between preoperatively and 12 months postoperatively (change in maximum K reading), preoperative CDVA, and change in CDVA (lines lost) between preoperatively and 12 months postoperatively. The ANOVA was followed by multiple comparisons using the Scheffé test. The same variable was compared between different follow-up times using the Wilcoxon rank-sum test. Comparison of a variable between 2 groups (eg, preoperative CDVA in the total group and in the failure group) was by the Mann-Whitney *U* test. The odds ratio (OR) of a risk factor and its CI were calculated using the standard algorithm for a 2×2 table. A *P* value less than 0.05 was considered statistically significant.

RESULTS

One hundred seventeen eyes of 99 patients were evaluated. The demographic data showed a strong skew toward male patients (62.2%) and left eyes (58.1%). Of the 117 eyes enrolled in the study, 105 completed the 1-year follow-up, yielding a dropout rate of 10.3%.

Epithelial healing was complete within a mean of 3.25 ± 1.4 days (range 1 to 8 days; 95% CI, 2-6). At the 1-month examination, virtually all eyes had anterior stromal haze with a mean grade of 0.78 ± 0.42 (range 0 to 2); the mean grade decreased to 0.18 ± 0.28 at 6 months and 0.06 ± 0.18 at 12 months. The demarcation line in the deeper stroma was visible at the 1-month examination in 84% of eyes at a mean depth of $62\% \pm 17\%$ of CCT (range 25% to 100%; 95% CI, 32%-93%). The mean preoperative corneal thickness over the pupil

Table 1. Analysis of variance post hoc multiple comparisons ($P < .05$, Scheffé test).

Variable	CDVA		Change in Max K	Age	Preop Max K
	CDVA	Lost			
CDVA	—	—	—	—	—
CDVA lost	No	—	—	—	—
Change in max K	No	No	—	—	—
Age	Yes	Yes	Yes	—	—
Preop max K	Yes	Yes	Yes	Yes	—

CDVA = corrected distance visual acuity; Max K = maximum keratometry reading

center determined by Scheimpflug imaging was $483 \pm 36 \mu\text{m}$ (95% CI, 424-540). There was no statistically significant difference between applanation tonometry preoperatively and the value 1 year after CXL.

The 1-factor ANOVA showed a highly statistically significant interaction between the variables of age, preoperative maximum K reading, change in maximum K reading, preoperative CDVA, and lines of CDVA lost. The post hoc multiple comparisons showed the influence of the preoperative maximum K reading and age on all other parameters (Table 1).

Of the 105 eyes, 3 lost 2 Snellen lines of CDVA from preoperatively to 1 year postoperatively, yielding a complication rate of 2.9% (95% CI, 0.6%-8.5%). Although initial comparison of the complication subgroup and the total group indicated that age, preoperative CDVA, and preoperative maximum K reading were predictive parameters, the only statistically significant differences between the 2 groups were in mean age (37.7 years versus 29.2 years; $P = .029$) and preoperative CDVA (0.98 versus 0.53; $P = .012$). An age older than 35 years and a preoperative CDVA better than 20/25 were identified as risk factors. The OR was 13.14 for age and 18.18 for CDVA and the 95% CI, 1.3-132.7 and 1.78-185.8, respectively. Introducing an age limit of 35 years as an inclusion criterion would have reduced the complication rate in these patients to 1.04% (95% CI, 0.03%-5.40%). No morphologic or optical reason for the visual loss could be determined.

Regarding efficacy, 8 eyes (7.6%; 95% CI, 3.3%-14.7%) had an increase in the maximum K reading of 1.00 D or more during the first postoperative year (Table 2), indicating failure of the CXL treatment. There were differences between the failure subgroup with the total group in sex (women: 62.5% versus 38.8%; $P = .048$), preoperative CDVA (0.39 versus 0.55; $P = .16$), and preoperative maximum K reading (61.30 D versus 55.00 D; $P = .04$); however, only the differences in the preoperative maximum K reading and sex were statistically significant. The OR for the risk factor of maximum K reading greater than 58.00 D was 5.32 (95% CI, 1.19-23.79) and for female

Table 2. Progression versus regression 1 year after CXL.

Status	Change in Max K (D)	Eyes, n (%)
Progression	< -1.00	8 (7.6)
Unchanged	-1.00 to $+1.00$	58 (55.2)
Regression	$> +1.00$	39 (37.1)

Max K = maximum keratometry

sex, 3.11 (95% CI, 0.7-13.7). Changing the inclusion parameter for maximum K reading from less than 65.00 D to less than 58.00 D would have reduced the failure rate to 2.8% (95% CI, 0.6%-8.5%).

Sterile infiltrates occurred in 7.6% of eyes. A stromal scar developed in 3 eyes (2.9%) (Figure 1). The sterile infiltrates resolved within 4 weeks with treatment of dexamethasone 4 times a day. None of the complications resulted in a significant loss of CDVA. In all 3 cases with stromal scars, the UDVA increased significantly. The scars faded appreciably within the first postoperative year, and the corresponding flattening in topography decreased (Figure 2). No parameter evaluated was identified as a predictor of these complications. There were no other complications requiring medical or surgical intervention.

DISCUSSION

Since the introduction of CXL in 1996,^{1,2} several clinical studies have found the treatment to be efficacious in stopping the progression of keratectasia (Seiler T, et al. IOVS 1996; 36:ARVO Abstract 4671).²⁻⁴ However, the patient groups in these studies were too small to allow conclusions about the real efficacy and safety of the

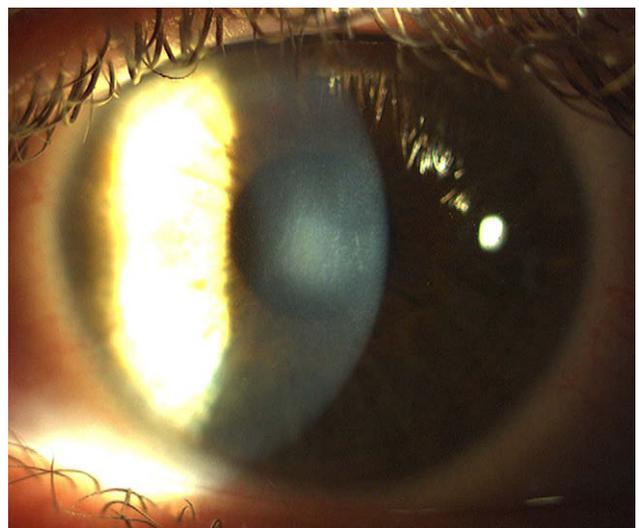


Figure 1. A stromal scar 2 months after CXL. The scar extends to approximately the anterior 50% of stromal depth and is paralleled by significant flattening of the cornea.

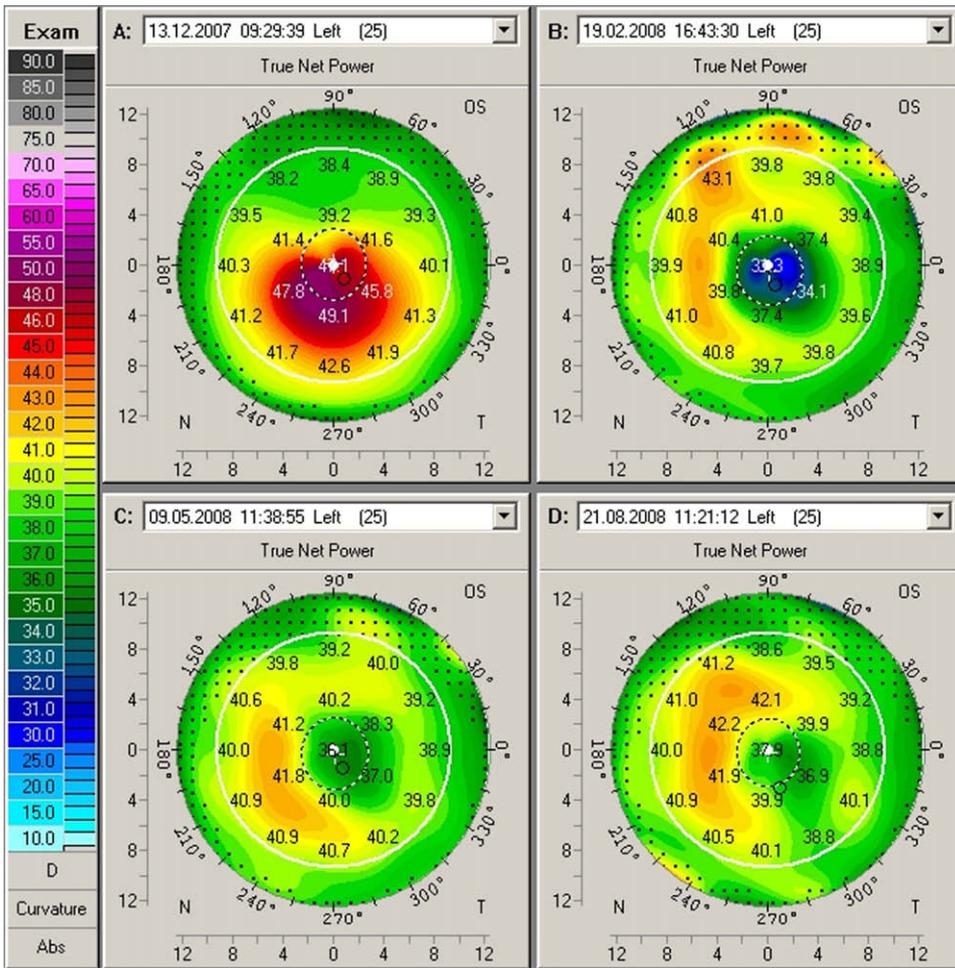


Figure 2. Regression of the flattening effect during 12 months after CXL.

procedure. Single cases with complications after CXL in the literature¹²⁻¹⁴ are important but do not allow an estimation of the complication rate.

In refractive surgery, a complication is defined as a loss in CDVA of 2 or more Snellen lines¹⁵ at an appropriate time after surgery (6 months or 1 year). A refractive surgical procedure is considered safe if this complication rate is lower than 5%.¹⁶ In our study, the complication rate was 2.9% but with a relatively high 95% CI (0.6%-8.5%) because of the small group size (N = 105). Refractive surgery is elective; therefore, a high safety standard is mandatory and appropriate. However, because at present CXL is the only option for halting or reversing the progression of keratectasia, the treatment should no longer be considered elective.

Risk factors for visual loss after CXL seem to be (1) age over 35 years and (2) a CDVA of 20/25 or better. Fortunately, these parameters do not characterize the typical CXL patient because most candidates are in the third decade of life and are motivated to have the treatment because of substantial visual loss. From a strategic viewpoint, it may be that the earlier CXL is performed, the better for the patient because the treatment's

primary aim is to stop the progression of keratectasia. A CDVA of 20/25 or better as a risk factor contradicts this strategy because at this early stage, CDVA is usually still good; thus, the patient will not risk losing visual acuity. In contrast, the other risk factor—age over 35 years—is not a strategic obstacle because patients older than 35 years have usually known about their disease for many years. In addition, in the future, such patients may have CXL much earlier in life. Establishing an upper age limit of 35 years would have reduced the complication rate in this study to 1.04% (95% CI, 0.03%-5.40%), a rate that characterizes a very safe procedure. (Compare this with the 3% adverse reaction rate for general anesthesia in children.¹⁷)

Although failures are not considered complications, they may have an impact on the complication rate. In our study, the only identified risk factor for failure was a maximum K reading greater than 58.00 D. Indeed, limiting the preoperative maximum K reading to 58.00 D or less would have reduced the failure rate to 2.8%. Such a limitation would have had no effect on the complication rate. The 2.8% failure rate is significantly higher than rates for CXL reported in the literature, which range from 0%^{3,4} to 1%.¹⁸

There has been discussion of whether haze is a normal finding after CXL and whether the haze affects vision.¹⁴ Although haze occurs after CXL, it usually decreases from grade 0.78 to 0.06 during the first postoperative year. The haze after CXL differs from the haze after PRK in stromal depth. Whereas haze after PRK is strictly subepithelial, haze after CXL extends into the anterior stroma to approximately 60% depth, which is on average equal to an absolute depth of 300 μm . The nature of this haze is unclear but we associated it with the depth of CXL and loss of keratocytes.^{11,13} Evaluation of the depth of sufficient CXL may become important in the future in terms of a potential surface ablation treatment to regularize irregular astigmatism.¹⁹ More studies, including confocal microscopy, are necessary to elucidate this.

None of our patients had a severe complication; however, several presentations at professional meetings report such complications. In cases of corneal infection after CXL, contact with the infectious agent likely occurred during the early postoperative period rather than during surgery because CXL not only damages keratocytes, it also kills bacteria and fungi. This effect is used to advantage when CXL is performed for infectious keratitis.⁹ In our study group, epithelial healing took up to 8 days; it may take longer in some cases, for example in patients with atopic disease. During epithelial healing, the cornea is vulnerable to infection and melting. The use of amnion in addition to bandage contact lenses may shorten the time to healing. One complication in our study—central stromal scarring—had a beneficial aspect; that is, it resulted in significant flattening of the cornea and a large improvement in UDVA. During the follow-up, the strong flattening effect regressed as the scar faded.

In summary, CXL appears to be a safe treatment that would yield a complication rate of approximately 1% if certain inclusion parameters (eg, patient age less than 35 years, CDVA <20/25) were respected. Also, the efficacy of CXL would likely increase if the treatment were limited to eyes with a maximum K reading of less than 58.00 D. More studies are necessary to identify rare complications and to establish a list of indications regarding patient age, diagnosis (pellucid marginal degeneration versus keratoconus), and the stage of keratectasia.

REFERENCES

- Spörl E, Huhle M, Kasper M, Seiler T. Erhöhung der Festigkeit der Hornhaut durch Vernetzung. [Artificial stiffening of the cornea by induction of intrastromal cross-links]. *Ophthalmologie* 1997; 94:902–906
- Schnitzler E, Spörl E, Seiler T. Bestrahlung der Hornhaut mit UV-Licht und Riboflavingabe als neuer Behandlungsversuch bei einschmelzenden Hornhautprozessen, erste Ergebnisse bei vier Patienten. [Crosslinking of the corneal collagen by UV-radiation with Riboflavin for the mode of treatment melting ulcers of the cornea, first results of four patients]. *Klin Monatsbl Augenheilkd* 2000; 217:190–193
- Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol* 2003; 135:620–627
- Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen; preliminary refractive results in an Italian study. *J Cataract Refract Surg* 2006; 32:837–845
- Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *J Refract Surg* 2008; 24:S720–S725
- Koller T, Isele HP, Hafezi F, Vinciguerra P, Seiler T. Scheimpflug imaging of corneas after collagen cross-linking. In press, *Cornea* 2009.
- Kohlhaas M, Spoerl E, Speck A, Schilde T, Sandner D, Pillunat LE. Eine neue Behandlung der Keratektasie nach LASIK durch Kollagenvernetzung mit Riboflavin/UVA-Licht. [A new treatment of keratectasia after LASIK by using collagen with riboflavin/UVA light cross-linking]. *Klin Monatsbl Augenheilkd* 2005; 222:430–436
- Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. 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
- Isele HP, Thiel MA, Hafezi F, Kampmeier J, Seiler T. Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts. *Cornea* 2008; 27:590–594
- Hanna KD, Pouliquen YM, Waring GO III, Savoldelli M, Fantes F, Thompson KP. Corneal wound healing in monkeys after repeated excimer laser photorefractive keratectomy. *Arch Ophthalmol* 1992; 110:1286–1291
- Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea* 2006; 25:1057–1059
- Eberwein P, Auw-Hädrich C, Birnbaum F, Maier PC, Reinhard T. Hornhauteinschmelzung nach Cross-Linking und tiefer lamellärer Keratoplastik ("DALK") bei Keratokonus. [Corneal melting after cross-linking and deep lamellar keratoplasty in a keratoconus patient]. *Klin Monatsbl Augenheilkd* 2008; 225:96–98
- Mazzotta C, Balestrazzi A, Baiocchi S, Traversi C, Caporossi A. Stromal haze after combined riboflavin-UVA corneal collagen cross-linking in keratoconus: in vivo confocal microscopic evaluation [letter]. *Clin Exp Ophthalmol* 2007; 35:580–582
- Herrmann CIA, Hammer T, Duncker GIW. Haze-Bildung nach Vernetzungstherapie bei Keratokonus. [Hazeformation (corneal scarring) after cross-linking therapy in keratoconus]. *Ophthalmologie* 2008; 105:485–487
- Stulting RD, Carr JD, Thompson KP, Waring GO III, Wiley WM, Walker JG. Complications of laser in situ keratomileusis for the correction of myopia. *Ophthalmology* 1999; 106:13–20
- U.S. Food and Drug Administration. Center for Devices and Radiological Health. Checklist of information usually submitted in an investigational device exemptions (IDE) application for refractive surgery. www.fda.gov/cdrh/ode/2093.html. Accessed April 2, 2009
- Murat I, Constant I, Maud'huy H. Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. *Paediatr Anaesth* 2004; 14:158–166
- Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg* 2008; 34:796–801
- Kanellopoulos J, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK; a temporizing alternative for keratoconus to penetrating keratoplasty. *Cornea* 2007; 26:891–895