

# Progression of Keratoconus and Efficacy of Corneal Collagen Cross-linking in Children and Adolescents

Nico Chatzis, DDS; Farhad Hafezi, MD, PhD

## ABSTRACT

**PURPOSE:** To study the progression rate of keratoconus and assess the clinical outcome of corneal collagen cross-linking (CXL) with riboflavin and ultraviolet A light in children and adolescent patients up to 3 years after treatment.

**METHODS:** Fifty-nine eyes from 42 children and adolescents (aged 9 to 19 years) with confirmed keratoconus were included in this retrospective interventional cohort study. Refraction, slit-lamp examination, Placido-based corneal topography, and Scheimpflug imaging were performed bilaterally in all patients preoperatively and at 6 and 12 months postoperatively. Maximal keratometry readings (Kmax), corrected distance visual acuity (CDVA), corneal thickness, and the keratoconus index (KI) were analyzed. Follow-up was up to 36 months (mean follow-up: 26.3 months [range: 12 to 36 months]).

**RESULTS:** Fifty-two of the 59 eyes enrolled in this study showed progression, corresponding to a progression rate of 88%. Forty-six eyes were treated by CXL. Maximal keratometry, CDVA, and KI showed significant changes over the follow-up period. However, significant Kmax reduction observed up to 24 months after CXL lost significance at 36 months.

**CONCLUSIONS:** Cross-linking seems to be safe in children and adolescents. Progression of keratoconus occurred in 88%. We propose that awaiting documentation of progression is not mandatory and CXL in children and adolescents should be performed as soon as the diagnosis has been made. However, the effect of arrest of disease progression might not be as long-lasting as in adults and longer follow-up is needed to verify this trend. [*J Refract Surg.* 2012;28(11):753-758.] doi:10.3928/1081597X-20121011-01

**C**orneal collagen cross-linking (CXL) with riboflavin and ultraviolet A (UVA) light is a method to surgically increase the rate of cross-links within and between collagen fibers using photopolymerization.<sup>1</sup> Initially, the method was developed for progressive keratoconus.<sup>2-4</sup> Subsequently, CXL was modified to treat postoperative corneal ectasia, far progressed keratoconus with thin corneas, bullous keratopathy, and even infectious melting keratitis.<sup>5-13</sup> Cross-linking is also applied in combination with other procedures with the goal of reduction of irregular astigmatism while maintaining biomechanical stability.<sup>14,15</sup> Currently, CXL devices are in clinical use in 107 countries (Rudolf Peschke, PeschkeMed, personal communication, April 2012).

Progressive keratoconus still represents the main indication for CXL. Typically, the disease starts in the teenage years and shows the most aggressive progression in the second and third decade of life.<sup>16,17</sup> The majority of studies published to date have focused on CXL in adult corneas. In this study, we investigated the rate of keratoconus progression and the clinical outcome of CXL in children and adolescents.

## PATIENTS AND METHODS

### DEFINITION OF CHILDHOOD AND ADOLESCENCE

Childhood, as defined by the United Nations High Commissioner of Human Rights, is the period before 18 years of age, whereas the United Nations Children's Fund (UNICEF) defines adolescence as young people between age 10 and 19 years.<sup>18,19</sup>

*From the Department of Ophthalmology, Geneva University Hospitals, Geneva, Switzerland (Chatzis, Hafezi); and the University of Southern California, Doheny Eye Institute, Keck School of Medicine, Department of Ophthalmology, Los Angeles, California (Hafezi).*

*The authors have no financial interest in the materials presented herein.*

*The authors thank Joerg Sommerhalder, PhD, for the statistical analysis of the data.*

*Correspondence: Farhad Hafezi, MD, PhD, Geneva University Hospitals, Rue Alcide-Jentzer 22, 1211 Geneva, Switzerland. Tel: 41 22 382 83 60; Fax: 41 22 382 84 33; E-mail: farhad.hafezi@unige.ch*

*Received: March 8, 2012; Accepted: September 11, 2012*

TABLE  
**Median Change in Recorded Values After Collagen Cross-linking**

Follow-up (mos)	Median Change (25%/75%)			
	Kmax (D)*	CDVA (logMAR)*	KI†	Pachymetry (µm)*
3 (n=43)	-1.0 (-1.6/0.2)‡	0.00 (-0.14/0.00)	-0.010 (-0.020/0.020)	-41 (-65/-26)‡
6 (n=43)	-0.5 (-1.4/0.1)‡	0.00 (-0.17/0.00)‡	-0.010 (-0.020/0.010)	-23 (-41/-7)‡
12 (n=44)	-1.1 (-2.4/-0.2)‡	-0.14 (-0.24/0.00)‡	-0.010 (-0.040/0.010)	-10 (-20/-3)‡
24 (n=23)	-0.7 (-1.7/0.1)	-0.08 (-0.21/0.00)‡	-0.020 (-0.060/0.000)‡	-5 (-20/3)
36 (n=11)	0.5 (-0.1/1.0)	-0.13 (-0.20/0.00)‡	0.000 (-0.010/0.010)	-4 (-11/13)

*Kmax = maximal keratometry, CDVA = corrected distance visual acuity, KI = keratoconus index*  
*A significant influence of time was found on all four measures (Kruskal-Wallis one way analysis of variance on ranks)—\*P<.001, †P=.01.*  
*‡Values that are significantly different from zero (preoperative value, Dunn’s method, P<.05).*

**PATIENTS**

Fifty-nine eyes from 42 children and adolescents (29 boys, 13 girls) with confirmed keratoconus were included in this retrospective interventional cohort study between March 2005 and July 2010. Of these, 52 eyes showed progression, as defined by an increase of maximal keratometry (Kmax) readings of the anterior corneal surface, at 3.0 mm from the apex, of at least 1.00 diopter (D) in corneal topographies over a maximum of 12 months. Maximal keratometry ranged from 46.30 to 69.80 D (keratoconus grade I to IV according to Amsler-Krumeich<sup>20</sup>) and mean Kmax was 55.90 D. Patient age ranged from 9 to 19 years (mean: 16.6 years, min: 9.4; max: 18.7). All patients were operated at the Institute for Refractive and Ophthalmic Surgery (IROC) in Zurich, Switzerland.

**DIAGNOSIS OF KERATOCONUS**

For the diagnosis of keratoconus, corneal topography (Keratograph C; Oculus Optikgeräte GmbH, Wetzlar, Germany) and Scheimpflug imaging (Pentacam 70700, Oculus Optikgeräte GmbH) were used. To verify progression of keratoconus and for postoperative follow-up, Scheimpflug imaging (Pentacam) was used. To improve accuracy of measurements, only measurements with more than 95% of the 500 elevation points measured (“OK” sign) were included. Pentacam automatic release mode was used to ensure the correct focus.<sup>21</sup>

**PREOPERATIVE EXAMINATIONS AND FOLLOW-UP**

Only corneas that showed minimal stromal thickness >400 µm, as measured by ultrasound pachymetry (Tomey SP-2000; Tomey Corp, Nagoya, Japan) were included in the treatment group. Patients using rigid contact lenses were asked to remove them at least 2 weeks prior to the preoperative examination and each follow-up examination.

Patients were examined preoperatively, early postoperatively (1 to 3 days until healing of the epithelium) and at 1, 3, 6, 12, 24, and 36 months after surgery. Preoperatively and at every follow-up, except early postoperatively, corrected distance visual acuity (CDVA) using a Snellen chart, slit-lamp examination of the anterior and posterior segment, Goldmann applanation tonometry, corneal topography, corneal thickness (as measured by ultrasound), and Scheimpflug imaging were performed. The keratoconus index (KI) is calculated from a portion of the 500 elevation points measured on the cornea, comparing the keratoconus sector with a normal sector, provided by the Pentacam software.

**CXL AND POSTOPERATIVE CARE**

Cross-linking was performed using isoosmolaric riboflavin solution as described previously.<sup>22</sup> After treatment, antibiotic ointment (ofloxacin 0.3%) was given and a bandage contact lens soaked with preservative-free antibiotic (ofloxacin 0.3%) was applied until complete healing of the corneal epithelium, followed by application of fluorometholone eye drops twice daily for 2 weeks.

**STATISTICAL ANALYSIS**

Changes in the parameters investigated (Kmax, CDVA, corneal thickness, and KI) were statistically analyzed. In the absence of a normal distribution (Shapiro-Wilk), the non-parametric Kruskal-Wallis one way analysis of variance on ranks was used to analyze the influence time on medians. Post-hoc comparisons to zero (preoperative value) were performed using Dunn’s multiple comparison test.<sup>23</sup> All calculations were performed with Sigmaplot 11.0 (Systat Software Inc, Chicago, Illinois).

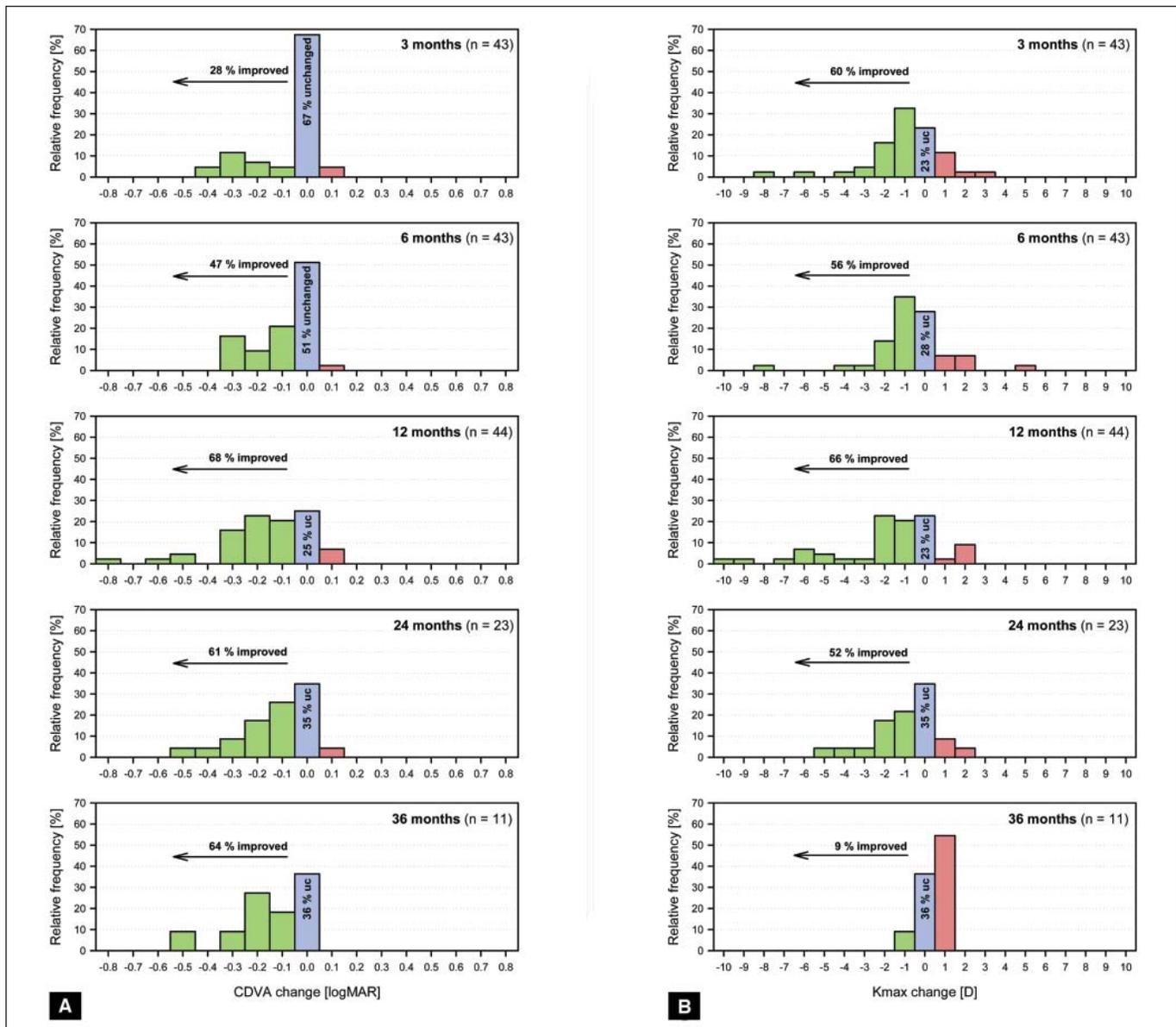


Figure 1. Change in A) corrected distance visual acuity (CDVA) and B) maximum keratometry (Kmax).

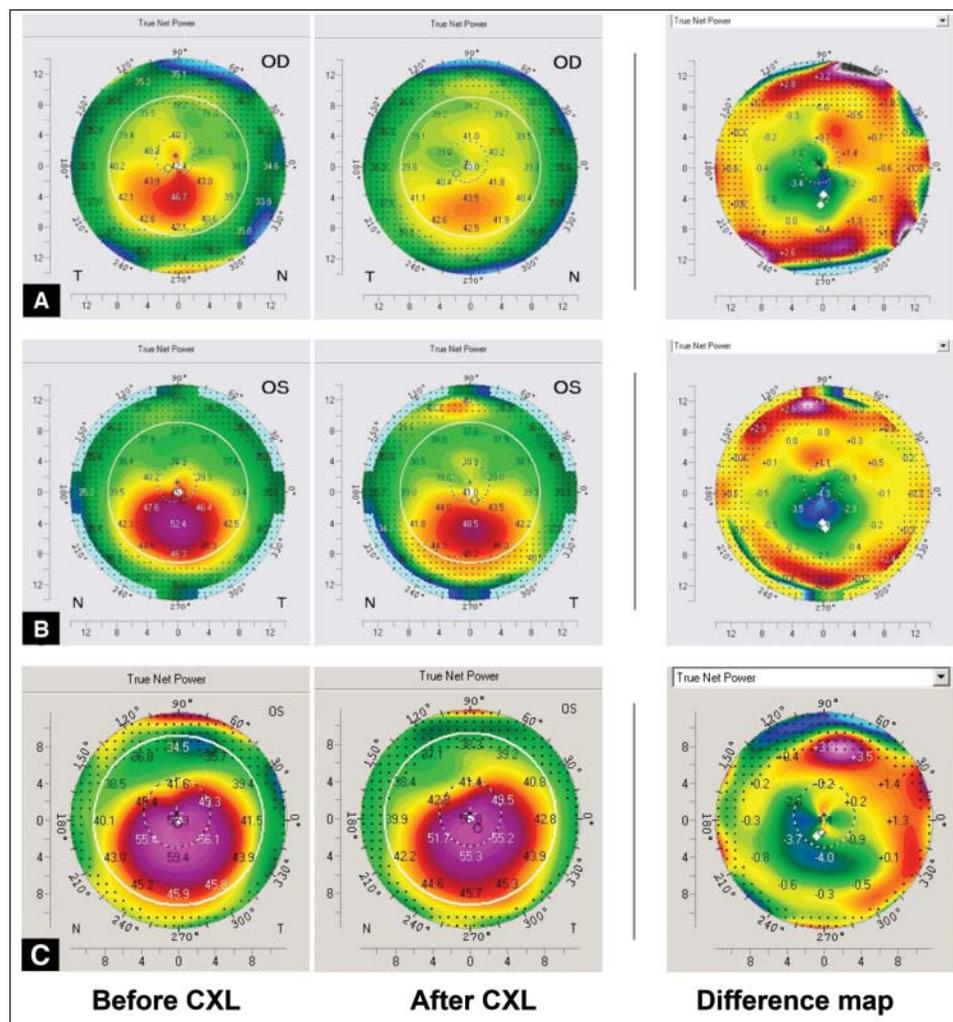
**RESULTS**

Between March 2005 and July 2010, all children and adolescents seen in our setting and presenting with keratoconus (42 individuals, 59 eyes) were followed for progression. Progression was defined as an increase of Kmax of the anterior corneal surface of at least 1.00 diopter (D) over a period of 12 months, as demonstrated by corneal topography (Keratograph C) or Scheimpflug imaging (Pentacam 70700). Progression of keratoconus occurred in 52 (88%) of the 59 eyes investigated. Cross-linking was performed in 46 of 52 eyes, as the parents did not agree to treatment in the remaining 6 eyes. Examinations were

performed daily until complete healing of the corneal epithelium and at 1, 3, 6, 12, 24, and 36 months after treatment.

No complications were noted in the postoperative period, except for 2 eyes with delayed epithelial healing that occurred within 8 days.

The Table summarizes the median changes in recorded values after CXL. At 3 months after CXL, Kmax and ultrasound pachymetry decreased significantly, CDVA remained unchanged, and KI showed no significant changes. At 6 and 12 months after CXL, Kmax and pachymetry showed significant decreases, CDVA showed significant improvement, and



**Figure 2.** Flattening effect of corneal collagen cross-linking in adolescent patients. Preoperative Scheimpflug imaging is depicted on the left side and the postoperative examination is depicted in the middle. The image to the right demonstrates the difference map. **A)** 18-year-old male patient before and 12 months after CXL. **B)** 17-year-old female patient before and 12 months after CXL. **C)** 13-year-old male patient before and 12 months after CXL.

KI changes were not significant. At 24 months after CXL, Kmax and pachymetry decreased in a statistically significant manner, whereas KI did not change significantly. At 36 months after treatment, Kmax and pachymetry were not statistically significant from baseline measurements, but CDVA still showed a significant improvement.

**CHANGE IN CORRECTED DISTANCE VISUAL ACUITY**

Postoperative values are compared to the values measured immediately before the procedure (Fig 1). Specifically, at 3 months after CXL, CDVA improved at least 1 Snellen line in 12 (28%) eyes and remained unchanged in 29 (67%) eyes. Two (5%) eyes lost 1 Snellen line. At 6 and 12 months after CXL, CDVA

improved in 20 (47%) and 30 (68%) eyes, and remained unchanged in 22 (51%) and 11 (25%) eyes, respectively. One Snellen line was lost in 1 (2%) eye at 6 months and 3 (7%) eyes at 12 months after CXL. At 24 months after CXL, 14 (61%) eyes improved and 8 (35%) eyes remained unchanged. One (5%) eye lost 1 Snellen line. One year later, at 36 months after CXL, values were similar with 7 (64%) eyes that improved and 14 (36%) eyes that remained unchanged.

**CHANGE IN KMAX**

At 3 months after CXL, flattening of  $\geq 1.00$  D occurred in 26 (60%) eyes and remained unchanged in 10 (23%) eyes. Kmax readings were increased by  $>1.00$  D in 7 (17%) eyes. At 6 months after CXL, flattening of  $>1.00$  D occurred in 24 (56%) eyes and remained unchanged in 12 (28%) eyes. Kmax readings were increased by  $>1.00$  D in 7 (16%) eyes. At 12 months, flattening of  $>1.00$  D occurred in 29 (66%) eyes and remained unchanged in 10 (23%) eyes. Kmax readings were increased by  $>1.00$  D in 5 (11%) eyes. At 2 years after

CXL, Kmax values were not significantly different from baseline values with 22 (52%) eyes showing flattening and 15 (35%) eyes remaining unchanged. At 3 years after CXL, only 1 (9%) eye showed flattening, 4 (36%) eyes remained unchanged, and 6 (55%) eyes showed an increase in Kmax values of  $>1.00$  D (Figs 1 and 2).

Three patients had a history of extensive eye rubbing, showing a strong side preference and bilateral keratectasia. Of these, an 11-year-old boy who did not cease extensive rubbing after CXL showed progression of 1.90 D at 12-month follow-up and CXL was repeated. With a second follow-up of 11 months after repeat CXL and a distinct change in his eye rubbing behavior, this patient was stable.

## DISCUSSION

This study was performed to investigate two clinical questions: the safety and efficacy of CXL for progressive keratoconus in children and adolescents and the rate of keratoconus progression during clinical follow-up in a population of children and adolescents who were diagnosed with keratoconus. These individuals were preselected, as they were seen by ophthalmologists for a recent decrease in visual acuity or because another family member was affected by keratoconus.

We observed that CXL in children and adolescents shows a safety profile similar to that of adults over the whole duration of the study.<sup>24</sup> We compared the safety, efficacy, and clinical outcome of our data with two recently published studies.<sup>25,26</sup>

Little is known about the efficacy and long-term outcome of CXL in keratectasia complicated by or due to excessive eye rubbing. Extensive eye rubbing was observed in 3 patients (3 eyes, 6%). Of these, keratectasia showed progression at 12-month follow-up in 1 eye and CXL was repeated. Prolonged healing was observed in 2 cases where the epithelium took up to 10 days for full closure. No other complications were noted.

The analysis of Kmax values, CDVA, pachymetry, and KI in the entire study population revealed interesting findings. The Kmax values were significantly reduced as early as 3 months after treatment and up to 24 months after CXL. These findings are in agreement with 3-month follow-up in adults published by Caporossi et al in an earlier study and by recent data on children published by Caporossi's group.<sup>25,27</sup> At 36 months after CXL, the flattening effect seemed to halt and Kmax showed a tendency for progression. This might indicate that although the juvenile cornea reacts to CXL-induced improvement in the short-term, the effect might not be strong enough to show arrest of keratoconus progression at longer follow-up. Corrected distance visual acuity shows a similar effect, but with a much greater latency: a significant improvement takes longer to occur, and even after 36 months, when the flattening effect on the cornea came to an arrest, CDVA was still significantly better than before CXL. Similarly, the KI had a greater latency to react and the typical reduction of corneal thickness had no lasting effect after CXL.

Recently, two studies have been published investigating the effect of CXL in pediatric patients.<sup>25,26</sup> Caporossi et al<sup>25</sup> investigated the effect of CXL in 152 patients aged 10 to 18 years, with 36-month follow-up. Vinciguerra et al<sup>26</sup> analyzed the outcome of CXL in 40 eyes of patients aged 9 to 18 years with 24-month follow-up. Although neither of these studies precisely followed the widely accepted definitions of childhood (8 to 15 years) and

adolescence (10 to 19 years),<sup>18,19</sup> they are comparable to the age group investigated in our study.

We therefore compared the results of the three studies: in all studies, Kmax showed a significant decrease between 3- and 24-month follow-up.<sup>25,26</sup> However, at 36-month follow-up, Kmax values were significantly reduced in the study by Caporossi et al,<sup>25</sup> but not significantly different from preoperative values in our study. Vinciguerra et al<sup>26</sup> did not have data for 36-month follow-up. Corrected distance visual acuity showed a similar behavior in all groups over the entire follow-up period, with a significant increase in all studies up to 24-month follow-up. This increase in CDVA remained significant at 36-month follow-up in the Caporossi et al study and in our study.

We suggest making efforts to document the progression of CXL prior to treatment, because CXL is not yet globally practiced and remains a surgical technique that carries certain risks.<sup>24,28</sup> Before treating a child or an adolescent, we need to ensure the medical necessity of the treatment by documenting progression of the disease. We therefore investigated how many eyes initially diagnosed with keratoconus in this study showed progression. We found that 52 (88%) of 59 eyes were progressive within 12 months. This might not reflect the total keratoconus population, as our study group consisted of preselected patients who were seen by an ophthalmologist for either a decline in visual acuity/quality or because another family member had keratoconus. Nevertheless, this progression rate represents a high number. These findings are in agreement with the fact that keratoconus is most active in the young cornea,<sup>16</sup> and we recommend that CXL be performed at the earliest age possible to arrest disease progression in its beginnings. However, our patient sample does not allow for analysis of subgroups. A higher number of eyes must be treated to provide detailed insight into this question.

Corneal collagen CXL for progressive keratoconus in children and adolescents is a procedure with a safety profile similar to the one observed in adults. However, the effect of CXL might not last as long as in adults, and we recommend careful follow-up to detect a decrease of the CXL-induced effect. A study investigating the long-term effects (>3 years) is needed to clarify the eventual progression of keratoconus.

We also recommend not waiting for documented progression in children and adolescents. Once the individual risk-benefit analysis has been performed and once the patient and legal guardian have received in-depth information and enough time for consideration, treatment should be performed as soon as an unambiguous diagnosis is made.

**AUTHOR CONTRIBUTIONS**

Study concept and design (F.H.); data collection (N.C., F.H.); analysis and interpretation of data (N.C., F.H.); drafting of the manuscript (N.C., F.H.); critical revision of the manuscript (N.C., F.H.); administrative, technical, or material support (N.C., F.H.); supervision (F.H.)

**REFERENCES**

1. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res.* 1998;66(1):97-103.
2. Coskunseven E, Jankov MR II, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. *J Refract Surg.* 2009;25(4):371-376.
3. 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(5):796-801.
4. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135(5):620-627.
5. Ehlers N, Hjortdal J, Nielsen K, Sondergaard A. Riboflavin-UVA treatment in the management of edema and nonhealing ulcers of the cornea. *J Refract Surg.* 2009;25(9):S803-S806.
6. Gatzoufas Z, Seitz B. Riboflavin-UVA treatment for nonhealing ulcers of the cornea. *J Refract Surg.* 2010;26(5):312.
7. Hafezi F, Dejica P, Majo F. Modified corneal collagen crosslinking reduces corneal oedema and diurnal visual fluctuations in Fuchs dystrophy. *Br J Ophthalmol.* 2010;94(5):660-661.
8. 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(12):2035-2040.
9. 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(4):621-624.
10. Iseli 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(5):590-594.
11. Martins SA, Combs JC, Noguera G, et al. Antimicrobial efficacy of riboflavin/UVA combination (365 nm) in vitro for bacterial and fungal isolates: a potential new treatment for infectious keratitis. *Invest Ophthalmol Vis Sci.* 2008;49(8):3402-3408.
12. Moren H, Malmsjo M, Mortensen J, Ohrstrom A. Riboflavin and ultraviolet a collagen crosslinking of the cornea for the treatment of keratitis. *Cornea.* 2010;29(1):102-104.
13. Schrier A, Greebel G, Attia H, Trokel S, Smith EF. In vitro antimicrobial efficacy of riboflavin and ultraviolet light on Staphylococcus aureus, methicillin-resistant Staphylococcus aureus, and Pseudomonas aeruginosa. *J Refract Surg.* 2009;25(9):S799-S802.
14. Coskunseven E, Jankov MR II, Hafezi F, Atun S, Arslan E, Kymionis GD. Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus. *J Cataract Refract Surg.* 2009;35(12):2084-2091.
15. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. *Cornea.* 2007;26(7):891-895.
16. Olivares Jimenez JL, Guerrero Jurado JC, Bermudez Rodriguez FJ, Serrano Laborda D. Keratoconus: age of onset and natural history. *Optom Vis Sci.* 1997;74(3):147-151.
17. Rabinowitz YS. Keratoconus. *Surv Ophthalmol.* 1998;42(4):297-319.
18. Office of the United Nations High Commissioner of Human Rights. Convention on the rights of the child. United Nations Human Rights Web site. <http://www2.ohchr.org/english/law/crc.htm#part1>. Accessed October 10, 2012.
19. The state of the world's children 2011—adolescence: an age of opportunity. UNICEF Web site. <http://www.uis.unesco.org/Library/Documents/state-world-children-adolescence-age-opportunity-education-2011-en.pdf>. Accessed October 10, 2012.
20. Alio JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg.* 2006;22(6):539-545.
21. Koller T, Iseli HP, Hafezi F, Vinciguerra P, Seiler T. Scheimpflug imaging of corneas after collagen cross-linking. *Cornea.* 2009;28(5):510-515.
22. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea.* 2006;25(9):1057-1059.
23. Dunn OJ. Multiple comparisons using rank sums. *Technometrics (American Statistical Association).* 1964;6(3):241-252.
24. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg.* 2009;35(8):1358-1362.
25. 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(3):227-231.
26. 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(3):520-526.
27. 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(5):837-845.
28. Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. *J Refract Surg.* 2009;25(9):S824-S828.