UMC Utrecht

Corneal crosslinking for pediatric keratoconus: Long term results

CXL Experts Meeting, Zurich, December 3rd 2016

Robert Wisse, MD PhD
Daniel Godefrooij, MD
Nienke Soeters, PhD
Saskia Imhof, MD PhD

Financial disclosure

Unrestricted grant from the Dr. Fischer foundation

Introduction

- Effectiveness of crosslinking for progressive keratoconus in adults has been demonstrated in three randomized controlled trials [1-3]
- No trials for CXL in children have been performed to date
- Numerous case series and retrospective observations available
- Keratoconus progression in children can be rapid and devastating[4]
- In the Netherlands no contraindication to treat <18yo

CLINICAL SCIENCE

Corneal Cross-Linking for Pediatric Keratoconus: Long-Term Results

Daniel A. Godefrooij, MD, Nienke Soeters, PhD, Saskia M. Imhof, MD, PhD, and Robert P.L. Wisse, MD, PhD

Published in Cornea 2016;35:954-8

Systematic literature overview

Table 3. Overview of studies on pediatric keratoconus patients treated with crosslinking. Results of the last follow-up visit are shown.

Author, year	Type of CXL	Patients (eyes)	Age range	Follow-up time	UDVA	CDVA	Kflat	Ksteep	Kavg	Kmax	Corneal Thickness
Ozgurhan, 2014	Accelerated	38 (44)	9-18	24	Better	Better	Better	Better	Better	NA	NA
Shetty, 2014	Accelerated	18 (30)	11-14	24	Better	Better	Better	Better	NA	NA	NA
Arora, 2012	Epi-off	15 (15)	10-15	12	Better	Better	≈	≈	≈	Better	NA
Caporossi, 2011	Epi-off	NA (77)	10-18	36	Better	Better	Better	NA	Better	Better	Better
Chatzis, 2012	Epi-off	NA (11)	9-19	36	NA	Better	NA	NA	NA	≈	≈
Kodavoor, 2014	Epi-off	24 (35)	9-16	12	NA	Better	NA	NA	NA	Better	Worse
McAnena, 2015	Epi-off	14 (25)	13-18	12	≈	Better	≈	NA	≈	≈	≈
Peyman, 2015	Epi-off	37 (64)	NA	12	Better	Better	Better	Better	NA	Better	Worse
Soeters, 2014	Epi-off	NA (31)	12-17	12	Better	Better	≈	≈	Better	Better	Worse
Uçakhan, 2015	Epi-off	40 (40)	10-18	48	Better	Better	Better	Better	Better	Better	Worse
Vinciguerra, 2012	Epi-off	40 (40)	9-18	24	Better	Better	Better	≈	Better	NA	≈
Viswananthan, 2014	Epi-off	18 (25)	8-17	20.1	NA	≈	Better	Better	NA	NA	NA
Magli, 2012	Epi-off	19 (23)	12-18	12	≈	≈	Better	NA	Better	Better	NA
Magli, 2012	Transepithelial	10 (14)	12-18	12	≈	≈	Better	NA	Better	Better	NA
Buzzonetti, 2012	Transepithelial	13 (13)	8-18	18	NA	Better	Worse	Worse	Worse	NA	≈
Salman, 2013	Transepithelial	22 (22)	13-18	12	Better	≈	NA	NA	≈	Better	≈
Buzzonetti, 2015	Iontophoresis	14 (14)	10-18	15	NA	Better	≈	≈	≈	≈	≈
Magli, 2015	Iontophoresis	13 (13)	11-18	18	≈	Better	NA	≈	NA	Worse	Better

Year = year in which the study was published; CXL = corneal crosslinking; Patients (eyes) = number of patients and number of eyes at the last follow-up visit; Follow-up time = (mean) follow-up time in months; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; Kflat = keratometry in the flattest meridian; Ksteep = keratometry in the steepest meridian; Kavg = average keratometry; Kmax = maximum keratometry; Accelerated = accelerated crosslinking with epithelium removal; Epi-off = standard epithelium-off crosslinking; Transepithelial = transepithelial crosslinking; Iontophoresis = transepithelial crosslinking with iontophoresis; Better = significant improvement ($P<0.05$); Worse = significant deterioration ($P<0.05$); ≈ = no significant change; NA = data were not available.

Methods 1/2

- Data retrieved from ongoing prospective treatment cohort, initiated in 2010
- 54 eyes of 36 children treated with CXL
  - 370 nm at 3 mW/cm^2
- Longest follow up five years
- Outcome measures:
  - Uncorrected Distance Visual Acuity (UDVA)
  - Corrected Distance Visual Acuity (CDVA)
  - Average Keratometry (K_{avg})
  - Maximum Keratometry (K_{max})

Methods 2/2

- Outcomes compared to baseline values
  - Paired samples t-test

- Subgroup analyses:
  - Topographic progression after CXL was defined as a change in K_{avg} and/or K_{max} of ≥1.0 D at last follow-up visit
  - Comparison of baseline parameters
  - Cause of progression analysis through multivariable logistic regression

Results

- K_{avg} and K_{max} better at all follow up moments
  - K_{max} significant at all follow up moments
  - K_{avg} significant at 3 and 4 years

- UDVA and CDVA better at all follow up moments
  - Although not significant at 4 years and 5 years

	UDVA	*P-value*	CDVA	*P-value*	Kmax (D)	*P-value*	Kavg (D)	*P-value*	n
Baseline	0.33		0.61		59.0		59.0		54
Δ 1 year	+0.13	*<0.001**	+0.22	*<0.001**	-1.65	*0.001**	-0.27	*0.16*	54/54
Δ 2 years	+0.07	*0.01**	+0.19	*<0.001**	-1.13	*0.02**	-0.18	*0.39*	46/54
Δ 3 years	+0.09	*0.02**	+0.24	*<0.001**	-1.94	*0.001**	-0.60	*0.001**	25/37
Δ 4 years	+0.06	*0.17*	+0.19	*0.01**	-2.14	*0.01**	-1.38	*0.03**	18/23
Δ 5 years	+0.05	*0.38*	+0.08	*0.18*	-2.06	*0.01**	-0.65	*0.09*	9/9

Results (subgroup analysis)

- In twelve eyes (22%) of nine children (25%), keratoconus had progressed by ≥1.0 D at the last follow-up visit
  - K_{avg} progressed (range 1.0 - 4.2 D)
  - K_{max} progressed (range 1.0 – 7.2 D)
    - Very limited effect on visual acuity

- Cause of progression analysis
  - More decentralized cones more likely to progress (*P*=0.03)
  - UDVA, CDVA, K_{avg}, K_{max}, corneal thickness and age (within this cohort) not significantly related to progression

Conclusion

- Epi-off CXL is effective in the prevention of progression in peadiatric keratoconus up to 5 years (at group level)

- Progression occurred in 25% of the children
  - In adults progression 2-10%[5,6]
  - Visual acuity was hardly affected however
  - No comparative data available
  - Decentralized cones more likely to progress

UTRECHT
CORNEA
RESEARCH
GROUP

Contact: d.a.godefrooij@umcutrecht.nl

Discussion 1/2

- Relative high percentage of topographic treatment failure warrants attention

- Chatzis et al. suggested that the CXL effect might not be long lasting in children, concerning K_{max}[7]
- Caporossi et al. found a regression of treatment effects (VA, topography) at 24 mo after TE-CXL[8]
- Vinceguerra et al. found no progression in any patient eye at 24 mo after CXL[9]
  - All treated eyes were graded Amsler-Krumeich stage II

Discussion 2/2

- Amsler-Krumeich classification did not seem to alter the chance of progression in our data
- All patients were instructed to stop rubbing their eyes
- Comparative data is lacking. We did not regard these cases as treatment failures since VA stabilized and the extent of progression without treatment is unknown
- Is the immunological process underlying KC development in these cases more outspoken?
  - A role for biological markers of disease activity

References

1. O'Brart DPS, Chan E, Samaras K, et al. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. Br J Ophthalmol 2011;95:1519–24.

2. 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.

3. Wittig-Silva C, Chan E, Islam FM a, et al. A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus: Three-Year Results. Ophthalmology 2014;121:812–821.

4. Soeters N · van der Valk R· Tahzib NG. Corneal Cross-linking for Treatment of Progressive Keratoconus in Various Age Groups. J Refract Surg 2014

5. 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.

6. Wittig-Silva C, Chan E, Islam FM a, et al. A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus: Three-Year Results. Ophthalmology 2014;121:812–821

7. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric corneal collagen cross-linking in children and adolescents. J Refract Surg 2012;28:753–8

8. Caporossi A, Mazzotta C, Baiocchi S, et al. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea 2012;31:227–31

9. Vinciguerra P, Albé E, Frueh BE, et al. Two-Year Corneal Cross-Linking Results in Patients Younger than 18 Years with Documented Progressive Keratoconus. Am J Ophthalmol 2012;154:520–526