Keratoconus

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Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study

• „CLEK Study subjects with keratoconus exhibited a slow but clear decrease in BCVA during follow-up, with low-contrast acuity deteriorating more rapidly than high-contrast.“
• „The 5-year incidence of scarring is 13.7% for the overall sample and 38.0% for those eyes with corneal curvature greater than 52 D that wore contact lenses.“

Davis LJ, Schechtman KB, Wilson BS et al. Longitudinal changes in visual acuity in keratoconus. IOVS 2006; 47: 489-500
Lifetime economic burden of keratoconus

- **compared to the** expected **cost of the treatment of myopia**: included costs of clinic visits, fitting fees, contact lenses, surgical procedures and complications: 25 168 US$
- the factors that most influenced the lifetime cost were the probability of initial corneal transplant and a subsequent regraft
- the average **annual cost** for individual **routine vision care** is 200 US$, but for patients with **keratoconus**, it is 653 US$
- combined with the significantly impaired vision-related quality of life and the relatively young onset of disease, the economic burden of the treatment of keratoconus represents a significant public health concern

Management

- Glasses
- Contact lenses
- Collagen Cross-linking with Riboflavin/UVA
- Intracorneal rings
- Corneal transplant

Global Consensus on Keratoconus and Ectatic Diseases

José A. P. Gomes, MD, PhD,* Donald Tan, MD, PhD,† Christopher J. Rapuano, MD,‡
Michael W. Belin, MD,§ Renato Ambrósio, Jr, MD, PhD,¶ José L. Guell, MD,||
François Malecaze, MD, PhD,** Kohji Nishida, MD,†† and Virender S. Sangwan, MD‡‡, the Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases.

CXL is currently available and is performed by the majority of the panelists (83.3%) for keratoconus, using a variety of techniques. The panelists who do not have current access to CXL were willing to use this technique once it becomes available. In addition, it was recognized that the
Indication for CXL

- PROGRESSION !:
  - K-Value
  - Astigmatism
  - Pachymetry
  - Visual acuity
PROGRESSION

- $K_{\text{max-apex}} \geq 1.0\text{D in 1 y.}, \downarrow VA, \uparrow \text{CL fitting frequency}$
- $\uparrow D_{\text{ph}} \text{ and/or } D_{\text{cyl}} \geq 3\text{D in 6 mo.}, \text{ or }$
  $\uparrow K_{\text{max}} \geq 1.5\text{D}, \text{ or mean } \downarrow CT \geq 5\% \text{ in 3 consecutive measurements in 6 mo.}$
- $\uparrow K_{\text{max}} \geq 1\text{D, or } \uparrow D_{\text{cyl}} \geq 1\text{D, or } \uparrow D_{\text{ph}} \geq 0.5\text{D in 24 mo. (FDA study)}}$

Indication for CXL:
Medical history

- Age, gender
- Sport: body-building, weight-lifting, yoga (upside down standing, pressure breathing)
- Playing wind-instrument
- Pregnancy
- Hormonal therapy (contraceptives, anabolics)
- Thyroid gland dysfunction
- Allergy (Neurodermitis, Steroids)
- Smoking
- Diabetes mellitus
Keratoconus in children

- rapid progression (high risk group)
- Age: 10-18 y.
- Incidence M:F = 4:1
- prompt indication for CXL!

Progression (F/U 6 mo.)
Epi-off

Standard Treatment Parameters

- Treatment time: 30 min
- Abrasion corneae
- Thickness of stroma: >400 µm, <400 µm
  - isoosmolar with Methylhydroxypropylcellulose
  - hypoosmolar (without Dextran)
- Singlet-Oxygen
- Irradiance: 3 mW/cm²
- Wavelength: 370 nm
- Diffusion time: 30 min
- Riboflavin: 0.1%
CXL: Riboflavin + UVA / „Epi-off“

- Topical anaesthesia
- Epithelium removal
- Pachymetry
- 0.1% Riboflavin: 2 Min for 20 Min, Ø Speculum
- Pachymetry
- UVA (370nm): 3mW/cm² (5.4J/cm²) for 30 Min.
- CL, ATB, lubricants till epithelialisation
- Steroid drops
Epi-off


• prospective, nonrandomized, open trial
• 44 eyes
• Age: 10-40 y.
• Follow-up: Ø 52.4 mo. (48-60 mo.)
• multicenter, prospective, randomized controlled clinical trial (FDA trial)
• 49 eyes (KCN), 22 eyes (post-LASIK ectasia)
• Age: ≥ 14 y.
• prospective, unmasked, randomized controlled trial
• 94 eyes: 48 eyes – control group, 46 eyes – treatment group
• Age: between 16 and 50 years
CONCLUSIONS: At 36 months, there was a sustained improvement in Kmax, UCVA, and BSCVA after CXL, whereas eyes in the control group demonstrated further progression.
• 49 papers included: 8 reported 4 RCTs, 29 prospective, 12 retrospective studies

• the majority of evidence graded as „low“ (trial design, no comparator, large drop-out rate, incomplete reporting)

• „…uncertainty remains about duration of benefit…”
• retrospective, non-randomized
• 34 eyes/24 pat.
• ♀:6, ♂:18
• Age: 28.4 ± 7.3y.
• F/U: 131.91 ± 20.13 mo.
Ten-year results

![Graphs showing mean values and visual acuity changes over 10 years.](image.png)
CXL – F/U: 10 y.

BDCVA: RE: 0.9  LE: 0.8
Complications after CXL

Corneal scars

Scars
Corneal scar development after CXL:

- Risk factors: ↑K-values, ↓corneal thickness
- Advanced keratoconus: ↑Risk for scar development
Thin corneas
CXL and corneal thickness < 400µm

- local anaesthesia
- Epithelium removal
- Pachymetry
- hypoosmolar 0.1% riboflavin solution:
  2 Min/30 Min, Ø speculum
- Pachymetry
- UVA (370nm): 3mW/cm² (5.4J/cm²)/30 Min.
- CL, ATB, Lubricant
- Steroids
Thin corneas

- 29 eyes
- Pat.: 29
- 20♂, 9♀
- Age: 27.4±9.4J.
- Follow-up: 1y.

CXL and hypoosmolar 0.1% riboflavin solution

![Graph showing corneal thickness in μm for different conditions: with epithelium, without epithelium, and without epithelium with swelling. The values are 400.8 ± 41.9 μm, 347.0 ± 51.9 μm, and 451.8 ± 46.7 μm, respectively.]
Kapex, CDVA
CXL and hypoosmolar 0.1% riboflavin solution in thin corneas

• No scars
Does Corneal Collagen Cross-linking Reduce the Need for Keratoplasties in Patients With Keratoconus?

Gunhild Falleth Sandvik, MPhil,* Andreas Thorsrud, MD,* Marianne Råen, MPhil,* Atle E. Østern, MD, PhD,* Marit Sæthre, MD, PhD,* and Liv Drolsum, MD, PhD*†

FIGURE 1. The annual number of CXL treatments from 2007 to 2015 (blue line), and the number of keratoplasties for keratoconus in period 1 (2005–2006) and period 2 (2013–2014).
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Conclusions: The frequency of keratoplasty for keratoconus has been more than halved in our department over the last decade. There is reason to believe that this reduction is for a great part caused by the introduction of CXL treatment.
Purpose

The objectives of this study are to evaluate the safety and efficacy of corneal collagen cross-linking performed with riboflavin ophthalmic solution compared to placebo in impeding the progression of, and/or reducing, maximum corneal curvature.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Keratoconus</td>
<td>Drug: riboflavin; 0.12% riboflavin ophthalmic solution</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Drug: placebo; 0.00% riboflavin ophthalmic solution</td>
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Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment
Primary Outcome Measures:
- Change in Kmax from baseline [Time Frame: 12 months] [Designated as safety issue: No]
  - The primary endpoint is the mean change from baseline to 12 months in maximum corneal curvature (Kmax) between [ ] treatment group and the Placebo control group.
- Safety Endpoints [Time Frame: 12 months] [Designated as safety issue: Yes]
  - Loss of BSCVA (Best Spectacle-Corrected Visual Acuity) beginning at the 6 month follow-up examination, specifically, the percentage of eyes that have a loss of 15 or more letters in BSCVA on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart as compared to baseline
  - The incidence of serious ophthalmic adverse events

Estimated Enrollment: 200
Study Start Date: November 2013
Estimated Study Completion Date: December 2016
Primary Completion Date: March 2016 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Area</th>
<th>Assigned Interventions</th>
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| Experimental: 0.12% riboflavin opthalmic solution | Drop riboflavin: 0.12% riboflavin opthalmic solution with the [ ]
  Subjects will receive 0.12% riboflavin opthalmic solution [ ] followed by irradiation with the [ ] at 30mW/cm² intensity for 8 minutes with an on/off cycle of 1 second UVA on/1 second UVA off, for a total radiant exposure of 7.2 J/cm². |
| Placebo Comparator: Placebo 0.0% riboflavin opthalmic solution | Drop placebo: 0.0% riboflavin opthalmic solution with the [ ]
  Subjects will receive 0.0% rboflavin opthalmic solution (Placebo) followed by irradiation with the [ ] at 30mW/cm² intensity for 8 minutes with an on/off cycle of 1 second UVA on/1 second UVA off, for a total radiant exposure of 7.2 J/cm². |

Eligibility
- Ages Eligible for Study: 12 Years and older (Child, Adult, Senior)
- Genders Eligible for Study: Both
- Accepts Healthy Volunteers: No
Accelerated CXL

- shortens the illumination time by increasing the illumination intensity (Bunsen-Roscoe law of reciprocity)
- reduces the overall treatment time
• The ex vivo results in porcine corneas show that the Bunsen-Roscoe reciprocity law is only valid for illumination intensities up to 40 to 50 mW/cm² and illumination time of more than 2 min.

Wernli J, Schumacher S, Spoerl E et al. The efficacy of corneal cross-linking shows a sudden decrease with a very high intensity UL light and short treatment time. IOVS 2013; 54: 1176-1180
Accelerated CXL

- The biomechanical effect of CXL decreased significantly when using high irradiance/short irradiation time settings. Intrastromal oxygen diffusion capacity and increased oxygen consumption associated with higher irradiances may be a limiting factor leading to reduced treatment efficiency.

Hammer A, Richoz O, Mosquera SA et al. Corneal biomechanical properties at different corneal CXL irradiances. IOVS 2014; 55: 2881-2884
Accelerated CXL


Accelerated CXL

- Studies comparing the demarcation line depth between conventional and accelerated CXL showed that the demarcation line was consistently deeper with the "traditional" protocol.
Accelerated CXL

- summarizing all studies on accelerated CXL, no consistent findings could be concluded regarding its effect in the treatment of keratoconus
- this could be explained by the different riboflavin preparation, different CXL protocols, variable total energy of irradiation and different stage of disease