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 devastating4

• In the Netherlands no contraindication to treat <18yo
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
Table 3. Overview of studies on pediatric keratoconus patients treated with crosslinking. Results of the last follow-up visit are shown.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of CXL</th>
<th>Patients (eyes)</th>
<th>Age range</th>
<th>Follow-up time</th>
<th>UDVA</th>
<th>CDVA</th>
<th>Kflat</th>
<th>Ksteep</th>
<th>Kavg</th>
<th>Kmax</th>
<th>Corneal Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatzis, 2012</td>
<td>Epi-off</td>
<td>NA (11)</td>
<td>9-19</td>
<td>36</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kodavoor, 2014</td>
<td>Epi-off</td>
<td>24 (35)</td>
<td>9-16</td>
<td>12</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Peyman, 2015</td>
<td>Epi-off</td>
<td>37 (64)</td>
<td>NA</td>
<td>12</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
</tr>
<tr>
<td>Viswanathan, 2014</td>
<td>Epi-off</td>
<td>18 (25)</td>
<td>8-17</td>
<td>20.1</td>
<td>NA</td>
<td>=</td>
<td>Better</td>
<td>Better</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
</tr>
<tr>
<td>Magli, 2012</td>
<td>Epi-off</td>
<td>19 (23)</td>
<td>12-18</td>
<td>12</td>
<td>NA</td>
<td>=</td>
<td>Better</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Magli, 2012</td>
<td>Transepithelial</td>
<td>10 (14)</td>
<td>12-18</td>
<td>12</td>
<td>NA</td>
<td>=</td>
<td>Better</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Buzzonetti, 2012</td>
<td>Transepithelial</td>
<td>13 (13)</td>
<td>8-18</td>
<td>18</td>
<td>NA</td>
<td>=</td>
<td>Better</td>
<td>NA</td>
<td>Better</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Salman, 2013</td>
<td>Transepithelial</td>
<td>22 (22)</td>
<td>13-18</td>
<td>12</td>
<td>Better</td>
<td>=</td>
<td>NA</td>
<td>NA</td>
<td>Better</td>
<td>Better</td>
<td>NA</td>
</tr>
<tr>
<td>Buzzonetti, 2015</td>
<td>Iontophoresis</td>
<td>14 (14)</td>
<td>10-18</td>
<td>15</td>
<td>NA</td>
<td>Better</td>
<td>=</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Magli, 2015</td>
<td>Iontophoresis</td>
<td>13 (13)</td>
<td>11-18</td>
<td>18</td>
<td>NA</td>
<td>=</td>
<td>Better</td>
<td>NA</td>
<td>NA</td>
<td>Worse</td>
<td>Better</td>
</tr>
</tbody>
</table>

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.
• Data retrieved from ongoing prospective treatment cohort, initiated in 2010

• 54 eyes of 36 children treated with CXL
  – 370 nm at 3 mW/cm²

• 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)
• Outcomes compared to baseline values
  – Paired samples t-test

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

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

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

<table>
<thead>
<tr>
<th>Baseline</th>
<th>UDVA P-value</th>
<th>CDVA P-value</th>
<th>$K_{\text{max}}$ (D) P-value</th>
<th>$K_{\text{avg}}$ (D) P-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.33</td>
<td>0.61</td>
<td>59.0</td>
<td>59.0</td>
<td>54</td>
</tr>
<tr>
<td>$\Delta$ 1 year</td>
<td>+0.13 &lt; 0.001*</td>
<td>+0.22 &lt; 0.001*</td>
<td>-1.65 0.001*</td>
<td>-0.27 0.16</td>
<td>54/54</td>
</tr>
<tr>
<td>$\Delta$ 2 years</td>
<td>+0.07 0.01*</td>
<td>+0.19 &lt; 0.001*</td>
<td>-1.13 0.02*</td>
<td>-0.18 0.39</td>
<td>46/54</td>
</tr>
<tr>
<td>$\Delta$ 3 years</td>
<td>+0.09 0.02*</td>
<td>+0.24 &lt; 0.001*</td>
<td>-1.94 0.001*</td>
<td>-0.60 0.001*</td>
<td>25/37</td>
</tr>
<tr>
<td>$\Delta$ 4 years</td>
<td>+0.06 0.17</td>
<td>+0.19 0.01*</td>
<td>-2.14 0.01*</td>
<td>-1.38 0.03*</td>
<td>18/23</td>
</tr>
<tr>
<td>$\Delta$ 5 years</td>
<td>+0.05 0.38</td>
<td>+0.08 0.18</td>
<td>-2.06 0.01*</td>
<td>-0.65 0.09</td>
<td>9/9</td>
</tr>
</tbody>
</table>
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 pediatric 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
• 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 $K_{\text{max}}$.

• Caporossi et al. found a regression of treatment effects (VA, topography) at 24 mo after TE-CXL.

• Vinceguerra et al. found no progression in any patient eye at 24 mo after CXL.
  – All treated eyes were graded Amsler-Krumeich stage II.
• 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


