Protocol ID: CRXL

**Study title:**
Treatment of Keratoconus With Advanced Corneal Crosslinking

**Study Start:**
October 2009

**Estimated study completion:**
June 2017

**Sponsor:**
Umeå University

**Responsible Party/Principal Investigator:**
Professor Anders Behndig  
Dept. of Clinical Sciences/Ophthalmology  
Umeå University Hospital  
SE-901 85 Umeå  
Sweden

**Review Board approval status:**
Approved.  
Approval Number: 09-044M  
Board Name: Regional Ethical Board in Umeå, Sweden  
Board Affiliation: Umeå University  
Phone: +46907867252  Email: tanja.gylden@umu.se

**Data Monitoring:**
No

**Oversight Authorities:**
Swedish Regional Ethical Review Board
Study Description

**Brief Summary:**
The purpose of this study is to determine whether mechanical compression of the cornea during corneal crosslinking for keratoconus using a sutured rigid contact lens can improve the optical outcomes of the treatment.

**Detailed Description:**
The study is designed as a prospective, open label, randomized controlled trial involving patients aged 18-28 years of both genders with uni- or bilateral keratoconus planned for routine corneal crosslinking (CXL) at the Department of Clinical Sciences / Ophthalmology, Umeå University Hospital, Umeå, Sweden. The study involves 30+30 eyes with keratoconus, which are randomized to receive either conventional corneal crosslinking (n=30) using the Dresden protocol, or a modified treatment - corneal reshaping and crosslinking (n=30), where a rigid, semiscleral contact lens is sutured to the cornea during the treatment, aiming to flatten the corneal curvature and potentially improve the optical outcome after the treatment. Patients are randomized utilizing a computer list of unique random numbers between 1 and 60; an even number will be treated with CXL and an uneven number with CRXL. The study also involves 60 eyes of healthy age- and sex-matched control subjects. All patients and control subjects are informed about the procedures and provide oral and written consent before inclusion in the study.

At baseline, before treatment, each eye is evaluated with autorefractometer measurement (Oculus Parc®), best spectacle-corrected LogMAR visual acuity, Pentacam HR® Scheimpflug photography, Goldmann applanation tonometry and biomicroscopy. For the Pentacam HR® rotating Scheimpflug camera, each eye is photographed using the “25 pictures” program under standardized, mesopic light conditions. Multiple variables will be analyzed, and individual photographs will be analyzed manually for light backscatter and for the occurrence of a demarcation line, by a masked observer. The corneal biomechanical characteristics are assessed with applanation resonance tonometry (ORA) and the ocular response analyzer (ART). The investigations are repeated at 1 month, 6 months, 2 years and 5 years after the treatment.

**Conditions:**
Keratoconus

**Study Type:**
Interventional

**Primary Purpose:**
Treatment

**Study Phase:**
Phase 2

**Intervention Model:**
Parallel Assignment

**Number of Arms:**
**Masking:**
Open label

**Allocation:**
Randomized

**Endpoint Classification:**
Efficacy Study

**Enrollment:**
120
### Arms and Interventions:

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental:</strong></td>
<td><em>Procedure/Surgery:</em> Corneal reshaping/crosslinking (CRXL)</td>
</tr>
<tr>
<td>Corneal reshaping/crosslinking (CRXL)</td>
<td>The keratoconus cornea is treated with epithelial debridement in local anesthesia, is soaked in Riboflavin by repeated topical application during 30 minutes. A flat, semiscleral rigid contact lens is sutured to the cornea and is then irradiated with ultraviolet light 5.4 J/cm² during 30 minutes. Riboflavin is repeatedly injected with a blunt cannula under the contact lens every 5 minutes during the irradiation. The contact lens is left in place for 2 hours and is then removed.</td>
</tr>
<tr>
<td>Corneal crosslinking with compression of the cornea using a sutured semiscleral rigid contact lens during the treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Active Comparator:</strong></td>
<td><em>Procedure/Surgery:</em> Corneal Crosslinking (CXL)</td>
</tr>
<tr>
<td>Corneal crosslinking (CXL)</td>
<td>The keratoconus cornea is treated with epithelial debridement in local anesthesia, is soaked in Riboflavin by repeated topical application during 30 minutes. The cornea is then irradiated with ultraviolet light 5.4 J/cm² during 30 minutes. Riboflavin is repeatedly applied topically every 5 minutes during the irradiation.</td>
</tr>
<tr>
<td>Standard corneal crosslinking using the Dresden protocol.</td>
<td></td>
</tr>
<tr>
<td><strong>No Intervention:</strong></td>
<td><em>Control group to CRXL</em></td>
</tr>
<tr>
<td>Healthy subjects, age- and sex-matched to the CRXL group.</td>
<td></td>
</tr>
<tr>
<td><strong>No Intervention:</strong></td>
<td><em>Control group to CXL</em></td>
</tr>
<tr>
<td>Healthy subjects, age- and sex-matched to the CXL group.</td>
<td></td>
</tr>
</tbody>
</table>
Outcome Measures:

Primary Outcome Measure:

1. *Change from baseline in refraction*
   Time Frame: 1, 6, 24 and 60 months after the treatment
   Safety Issue: No
   Description: Change from baseline in refractive errors, including lower and higher order aberrations in the cornea.

Secondary Outcome Measures:

1. *Change from baseline in ETDRS LogMAR visual acuity*
   Time Frame: 1, 6, 24 and 60 months after the treatment
   Safety Issue: No
   Description: Changes from baseline in uncorrected and best spectacle corrected visual acuity assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, graded in logarithmic values of the minimal angle of resolution.

2. *Change from baseline in corneal biomechanical stability measured with ORA*
   Time Frame: 1, 6, 24 and 60 months after the treatment
   Safety Issue: No
   Description: Change from baseline in biomechanical stability assessed with the Ocular Response Analyzer (ORA).

3. *Change from baseline in corneal biomechanical stability measured with ART*
   Time Frame: 1, 6, 24 and 60 months after the treatment
   Safety Issue: No
   Description: Change from baseline in biomechanical stability assessed with the Applanation Resonance Tonometer (ART).

4. *Change from baseline in corneal biomechanical stability measured with GAT*
   Time Frame: 1, 6, 24 and 60 months after the treatment
   Safety Issue: No
   Description: Change from baseline in biomechanical stability assessed with the Goldmann applanation tonometer (GAT).
5. Change from baseline in corneal densitometry

**Time Frame:**
1, 6, 24 and 60 months after the treatment

**Safety Issue:**
No

**Description:**
Change from baseline in corneal light reflectivity (back scatter) assessed with the Pentacam HR® rotating Scheimpflug camera. The densitometry will be registered in different zones and different depths of the cornea.
Eligibility:
Minimum Age: 18
Maximum Age: 28
Gender: Both
Accepts Healthy Volunteers?: Yes

Criteria:

Inclusion Criteria:
1. Patients planned for corneal crosslinking.
2. Progressive keratoconus documented with Scheimpflug photography using the Pentacam Scheimpflug camera and/or repeated subjective refraction and keratometry.
3. A keratoconus diagnosis based on the Amsler-Krumeich grading and the "Total Deviation" KC quantification value from the "Belin-Ambrosio enhanced ectasia" measurements of the Pentacam HR® Scheimpflug camera, and an altered red reflex and/or an irregular cornea seen as distortion of the keratometric mires.
4. Minimum corneal thickness of 400 µm at the thinnest point after epithelial removal.
5. 18-28 years of age
6. No ocular abnormalities except keratoconus
7. No previous ocular surgery
8. No cognitive insufficiency interfering with the informed consent.

Exclusion Criteria:
1. Age under 18 or over 28
2. Any corneal abnormalities except keratoconus
3. Previous ocular surgery
4. Cognitive insufficiency

Contacts/Locations:

Study Officials:
Principal investigator: Professor Anders Behndig
Dept. of Clinical Sciences/Ophthalmology
Umeå University Hospital
SE-901 85 Umeå
Sweden
Statistical analysis plan

Comparisons between treatments:
Student’s unpaired T-test will be used for statistical comparisons of the primary and secondary outcomes for normally distributed variables. For variables where a normal distribution is lacking, Wilcoxon signed-rank test will be used for comparison of two samples, and independent samples Kruskal-Wallis test will be used for multiple groups. A P-value of <0.05 will be considered statistically significant. Data will be presented as mean ± standard deviation (SD) or ± standard error of the mean (SEM) for normally distributed data, and median ± interquartile range (IQR) for non-normally distributed data.

Comparisons between different time points:
Student’s paired T-tests will be used for statistical comparisons of the primary and secondary outcomes between different time points for normally distributed variables. For variables lacking normal distribution, the Friedman test will be used. A P-value of <0.05 will be considered statistically significant. Data will be presented as mean ± standard deviation (SD) or ± standard error of the mean (SEM) for normally distributed data, and median ± interquartile range (IQR) for non-normally distributed data.

Correlations:
Correlations will be assessed with Pearson’s bivariate correlation analysis for normally distributed variables. For variables where a normal distribution is lacking, Spearman’s rho correlation will be used. A P-value of <0.05 will be considered as a statistically significant correlation.

Power analyses:
The study design will allow for detection of the following differences between the treatments and between different time points, respectively (Alpha = 0.05; Power = 0.80):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference between treatments</th>
<th>Difference between time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best spectacle-corrected visual acuity (BSCVA; LogMAR)</td>
<td>0.20</td>
<td>0.09</td>
</tr>
<tr>
<td>Spherical equivalent, D</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>K1, D</td>
<td>2.3</td>
<td>0.68</td>
</tr>
<tr>
<td>K2, D</td>
<td>2.9</td>
<td>0.76</td>
</tr>
<tr>
<td>Kmax, D</td>
<td>3.8</td>
<td>0.63</td>
</tr>
<tr>
<td>Corneal densitometry (RLU)</td>
<td>3.1</td>
<td>0.65</td>
</tr>
<tr>
<td>CH – ORA</td>
<td>0.95</td>
<td>0.44</td>
</tr>
<tr>
<td>CRF - ORA</td>
<td>1.1</td>
<td>0.42</td>
</tr>
<tr>
<td>CH – ART</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>IOP – GAT (mm Hg)</td>
<td>2.0</td>
<td>0.79</td>
</tr>
</tbody>
</table>