Corneal Collagen Cross Linking Updates

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Disclosure Statement:
• No financial interest in any products discussed

CXL Is In The Fisheye Lens of FDA
• Currently under investigation
• No timeline on approval
• Insurance will not cover it
• Is approved in all European Union Countries
• We can save vision, especially in the pediatric community
• There is a race against time

The many names...
• Corneal Collagen Cross Linking
• Collagen Cross Linking
• CXL
• Holcomb C3R
• CCL
• Ophthalmology Tanning Bed
• Sun

CXL: Indications
• Goal: prevent corneal ectasia from progressing to penetrating keratoplasty
• Indications:
  – Keratoconus
  – Pellucid Marginal Degeneration
  – Post-Refractive Surgery ectasia
  – Corneal melting
  – Infectious keratitis

Patient Selection: Contraindications
• Under age 8
• Corneal thickness < 300-350 um
• Pregnancy or nursing
• Severe central corneal opacities
• Severe dry eye
• Collagen vascular disease
• Prior Herpetic infection
• Poor wound healing
• Autoimmune disease
  – Relative contraindication
  *differ per study
Pre-Operative Evaluation

• Testing:
  – UCVA
  – Biomicroscopy
  – MRx
  – Penta/Topo
  – BCVA
  – IOP
  – DFE
  – Contact Lens Hx
    • Type
    • When last worn
  *differs per study

Patient Education

• Legal obligation: 10-25% KC corneal transplantation
• Earlier treatment = better for the patient
• Preventing > fixing problems
• Pts. usually still need specs and/or CLs, will need to be refit postop

Research: landmark paper, 1997

● Studied since 1994
  ● University of Dresden
    ● Theo Seiler
    ● Eberhard Spoerl
    ● Gregory Wollensak

Diabetes and CXL

- DM + KC = rare
- Spoerl and Seiler, Journal of Refractive Surgery 1999
- Aldehyde sugars in diabetics form natural cross-links but only after prolonged time

Who Is The Best Candidate?

• Mild to Moderate Phase of Keratoconus
  – Little to no corneal scarring
  – BCVA better than 20/40 with best optical device
  – Young
    • Typically the younger and earlier in the disease, the better
• Post RK refractive fluctuations
• Post LASIK ectasia with refractive fluctuations

History of Corneal Cross Linking

• Theo Seiler, MD
  – Studied Medicine, Mathematics and Physics
• Professor of Physics and Ophthalmology
  – University of Dresden
  – University of Zurich
• Early 1990’s
• Uses UV light and a photosensitizer (typically riboflavin, Vitamin B2) to strengthen bonds in the cornea
• The Dentist
Corneal Cross-linking (CXL)

- Strengthens/stiffens corneas with UV light and riboflavin drops
- 98-99% effective*

*CXL Stiffened Cornea
Rigid Cornea Sections
Untreated Cornea
Floppy Cornea Sections

Methods Of Stiffening the Cornea

- Avedro - USA
- CXLUSA - USA
- Peshke
- IROC Innocross
- Sooft
- Vega X-Link

Web-links are on the www.ocxls.org site

Riboflavin Absorption Spectrum

Different Devices

- Avedro - USA
- CXLUSA - USA
- Peshke
- IROC Innocross
- Sooft
- Vega X-Link

Web-links are on the www.ocxls.org site

Real World UV

All Exposed Tissues:
- 170-200 J/cm²/day in 3-4 hrs outdoors
- ~ 60 J/cm²/day of solar UVA
- Cornea:
  - 5 J/cm² in 15-20 min in Summer
  - CXL exposure=3 mJ/cm²
Basics in Cross Linking

1. Riboflavin (vit. B2) + Ultraviolet radiation

2. Production of oxygen radicals (ROS)

3. Induction of collagen cross-links

How Do We Know UV Ages the Body?

CXL Is Everywhere

We see Collagen Cross Linking EVERYWHERE in our world but NEVER pay attention to it

“What’s the Technique?”

- Anesthetic drops
- Prepare cornea
- Riboflavin drops for 30 mins
- UV light for 30 mins
- Bandage contact lens
- Postop Course: Similar to PRK
Riboflavin 0.1% Drops

UV-A Light 370 nanometer wavelength

Patient’s View of UV Light

So We Know it is Safe
But How Does it Work?

• The collagen in our cornea has links between the layers
• UV light stimulates strengthening between the bonds
  – Takes decades to do it naturally
• We are using UV light activated by riboflavin to stimulate the creation of more cross links

Epi-On vs. Epi-Off

**Epi-On**
- Longer "load time"
- Late stage technique
- More ribo needed
- No epi defect
- Less chance of infection and haze
  - No reported complications

**Epi-Off**
- Shorter "load time"
- Early adopted technique
- Less ribo needed
- Large Epi defect
- Slower recovery
- Higher risk of infection and haze
- Reported Complications

Normal Corneal Epithelium

Barrier to riboflavin penetration of stroma?
Typical Epi-Off CXL

- Worse vision for 3-6 months
- Steeper Ks
- More compact corneas
- Some haze
- SPEs, pseudodendrites if epi-off

Epi-Off CXL for KCN
Keratometry Over Time

Epithelial Migration Pattern in KCN

Epi Migration – Notice the Whirl

Epi off Corneal Ulcer
Other Applications of CXL:

- LASIK and CXL
- PRK and CXL
- Post RK Fluctuations
- Cornea-Plastics
- Scleral CXL
- Optic Nerve Head CXL
- Infection
- Intacs - Which currently do the following:
  - Increased K flattening
  - Increased BCVA
  - Increased UCVA

I've heard that Vitamin C can't be used before CXL?

Vitamin C Supplements

- Vitamin C naturally strengthens collagen
- Scurvy is a disease where the lack of Vitamin C leads to an enzymatic breakdown of collagen
- A surplus will possibly be an extra building block for collagen
- Vitamin C therefore will have a synergistic effect
- Many studies do not want their data affected by the addition of Vitamin C
- It is advisable to have your KCN patients that do not have CXL to take daily Vit C

"Moving Pictures" of CXL

Riboflavin + UVA Effect

Anterior View

Posterior View

Riboflavin + UVA vs. Riboflavin alone, 30min treatment

Asota, Fant, Edelhauser, and Stulting, unpublished

"Moving Pictures" of CXL

LASIK AND CXL

LASIK AND CXL

CXL AND INTACS

CXL WITH CK

CORNEAPLASTICS
“Moving Pictures” of CXL
RK FROM COLOMBIA c. 1988 FELLOW EYE POST GRAFT

UNEVEN RIBO DISTRIBUTION CXL WITH CK

Post-operative Patient management

Post-Operative Care
• Schedule:
  – 1 day
  – 3-7 days (optional)
  – 1 month (optional)
  – 3 months
  – 6-9 months
  *differs per study

Post-Operative Care
• Testing:
  – UCVA
  – Biomicroscopy
  – MRx (3 d→)
  – Penta/Topo (3 d→)
  – BCVA (1 mo→)
  – IOP (1 mo→)
  *differs per study

Literature Review:
CXL Complications Uncommon

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Complication</th>
</tr>
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<tbody>
<tr>
<td>Polhammer M</td>
<td>CRS July 2008</td>
<td>1 Corneal Uker - E Coli</td>
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<tr>
<td>Romesh I</td>
<td>CRS March 2009</td>
<td>1 Sterile Infiltrate &amp; Melt</td>
</tr>
<tr>
<td>Kymionis G</td>
<td>CRS Nov 2007</td>
<td>1 HSV Keratitis</td>
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Complications

- Infection
  - Epi-off only reported
- Corneal Haze and Scarring
  - Epi-off only reported
- Progression of disease
- Intraocular Inflammation
- Worsening of refraction
- Inability to tolerate contact lenses
- Need for PKP

Post-cxl
visual correction

Postoperative Management Strategies

- Spectacles
  - Be careful with refraction!
    - Often different axis vs. preop Rx
    - Have patient rotate dial of axis in phoropter
- Contact Lenses
  - Most patients

Post-CXL CL Pearls

- Wait 2 wks-4 mos po prior to fitting (study and surgeon dependent)
  - Combination procedures (CK-CXL, Intacs-CXL) less stable initially
- Healthy anterior segment (many have been wearing CL p CXL)
- Patient Ed: refits may be required
- Always begin with a new refraction, topo, and Ks
  - Fitting should be no different than non-CXL

Contact Lens Design and Material

- Soft
  - Sphere
  - Toric
  - KC-specific designs (NovaKone, Alden, Kerasoft IC, B+L)
- Hybrid
  - ClearKone or UltraHealth (SynergEyes, Inc.)
- GP
  - Small diameter for KC
  - Large corneal for KC, post-RS, PKP
  - Scleral

Scleral Contact Lenses after CXL
Scleral Lens Fitting

- Vaults the cornea entirely, resting on the bulbar conjunctiva/scleral
  - Improved comfort, stability and retention
- Topography helpful, but not mandatory
- Most designs specify 1st BC/sag to insert
  - Your own gross subjective impression: steep, flat or moderate and adjust BC from there
- Fill lens with nonpreserved AT/saline AND NaFL
  - Let lens settle for 20-30 minutes

Scleral Lens Terminology

<table>
<thead>
<tr>
<th>Lens Style</th>
<th>Alternative Names</th>
<th>Diameter (mm)</th>
<th>Boating</th>
<th>Tear Reservoir</th>
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</thead>
<tbody>
<tr>
<td>Corneal</td>
<td></td>
<td>8.0 to 13.5</td>
<td>All lens boating on the cornea</td>
<td>No tear reservoir</td>
</tr>
<tr>
<td>Corneal-Scleral</td>
<td></td>
<td>12.5 to 15.0</td>
<td>Lens down boating on the cornea and the sclera</td>
<td>Limited tear reservoir capacity</td>
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<tr>
<td>Full (Scleral)</td>
<td></td>
<td>15.0 to 25.0</td>
<td>All lens boating is on the sclera</td>
<td>Somewhat limited tear reservoir capacity</td>
</tr>
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Summary

- David P S O’Brart1, Tsong Q Kwong1, Parul Patel1, et al.
- Long-term follow-up of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linking to halt the progression of keratoconus
- Abstract
  - To determine long-term efficacy of riboflavin/ultraviolet A corneal cross-linking (CXL).
  - Methods Thirty patients (30 eyes) who had undergone CXL following epithelial removal 4–6 years previously were examined.

Summary

- 1 Year
  - Spherical equivalent error (SEQ) increased by +0.72 dioptres (D) (p<0.002)
  - Corrected distance visual acuity (CDVA) improved (p<0.05)
  - Mean simulated keratometry (Sim K) reduced by 0.27D (p<0.04)
  - Cone apex power (CAP) reduced by 0.4D (p<0.02)
  - Secondary astigmatism improved (p<0.01) compared with preoperative values.

- 4-6 Year
  - SEQ increased by +0.82D (p<0.001), CDVA improved (p<0.03), mean Sim K reduced by 0.84D (p<0.0001), CAP reduced by 1.3D (p<0.003), and root mean square (RMS) (p<0.0001), coma (p<0.0001), secondary astigmatism (p<0.01) and pentafoil (p<0.05) decreased.

Results

- No treated eyes progressed.
- None lost >1 line of CDVA.
- Seven untreated fellow eyes progressed.
Thank you from your Nation’s Capital