Controversies In Crosslinking

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Disclosures

Dr. Rubinfeld has intellectual property in corneal strengthening technology and financial interests in CXLO and CXLUSA.
There are known knowns; there are things we know that we know. There are known unknowns; that is to say there are things that, we now know we don't know. But there are also unknown unknowns – there are things we do not know, we don't know. 2/12/02
US Multicenter, Physician-Sponsored IRB Study
Actively Recruiting Patients since 10/09

- 8 or older
- FFKC, KCN or PMD
- Postop Ectasia
- Post RK with Visual Fluctuations
- Cornea at least 300 microns thick
- At least 6 mo since last corneal Sx
CXLUSA US Study Centers

14 centers
38 Investigators

Marwa Adi, MD                   Chevy Chase, MD
Neil Martin, MD                  Chevy Chase, MD
Roy Rubinfeld, MD                Chevy Chase, MD
Jodi Luchs, MD:                  Long Island, NY
Richard Lindstrom, MD           Minneapolis, MN
William Trattler, MD            Miami, FL
Parag Majmudar, MD              Chicago, IL
Lance Forstot, MD               Littleton, CO
Sandy Feldman, MD               San Diego, CA
Jay Schwartz, MD                Phoenix, AZ
Ty McCall, MD                   Dallas, TX
John Talamo, MD                 Boston, MA
Ranjan Malahotra, MD            St. Louis, MO
Gregg Berdy, MD                 St. Louis, MO
David Wallace, MD               Los Angeles, CA
Dan Goodman, M D                San Francisco, CA
So Many CXL Myths
<table>
<thead>
<tr>
<th>Epi-Off is Better</th>
<th>Epi-On is Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium removal is needed to load the stroma with riboflavin</td>
<td>See pictures</td>
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15 Min Epi-On CXLO (~20 y/o pt)
Cobalt Blue Light SL Pix
Epi-on Flare
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<td>With Epi-On CXL, the riboflavin only loads the epithelium and this blocks the UVA so limits the CXL</td>
<td>See picture</td>
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15 Min Epi-On CXLO
White Light SL Pix (18 y/o Pt)
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<td>Epithelium off CXL is more effective than epi-on</td>
<td>See graphs</td>
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Clinical Experience - Keratoconus

Vision Improvement (>= 1 line of vision)
CXLUSA vs. Hersh/Avedro

N = 177  N = 48  N = 49  N = 48  N = 177  N = 49

% improved UCVA
3 months  52.30%  N = 177
1 year  51.20%  N = 48
Hersh/Avedro  31%  N = 49

% Improved BSCVA
3 months  42.30%  N = 177
1 year  46.80%  N = 48
Hersh/Avedro  45%  N = 49

C/o William Trattler, MD
Treatment Failures
Epi-On vs. Off

- 5% in this Epi-Off report
- CXLUSA
  ~31 out of 2200 epi-on eyes (0.01%) identified so far
What Does CXL Usually Do?

- Stop progression of vision loss and corneal steepening
- **Mild** improvement in vision and corneal topo/tomos (some patients have “strong response”)
- CXL is great for early KCN
How Effective is CXL in this case?

Preop

Postop 3 M

William Trattler, MD  Epi-ON case
2.8 D Steeper
3.8 D Flatter

Preop

Postop 3 Mo

Difference Map

c/o William Trattler, MD
RESULTS

### Pre Operative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Strong</th>
<th>Non-Strong</th>
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<tr>
<td>Number of Eyes</td>
<td>101</td>
<td>232</td>
</tr>
<tr>
<td>Pre-Op Avg ultrasound pachymetry</td>
<td>480 microns</td>
<td>470 microns</td>
</tr>
<tr>
<td>Average age at time of surgery</td>
<td>34.9</td>
<td>35.81</td>
</tr>
<tr>
<td>Gender</td>
<td>68% male</td>
<td>66% male</td>
</tr>
<tr>
<td>Average Pre-Op MRSE</td>
<td>-4.12D</td>
<td>-5.35D</td>
</tr>
<tr>
<td>Average Pre-Op Penta Pach Thinnest Point</td>
<td>470 microns</td>
<td>460 microns</td>
</tr>
</tbody>
</table>
| Average Pre-Op Penta K Astig | 4.80D | 4.71D      

**Average Change in K Max at 6 months**

- **Strong Responders** (n=101) -0.58
- **Non Strong Responders** (n=232) -0.72
Preop

Difference Map

2 Mo Postop

9 D Flatter

3+ D Steeper
Kmax Reproducibility with Pentacam: 3 scans of 1 Eye at same sitting (c/o William Trattler, MD)

Kmax range: 69.2 to 71.6 = 2.4D
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<td>Epithelium off CXL is safer than epi-on</td>
<td>See pictures</td>
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Delayed Epithelial Healing and Infiltrate after Epi-Off CXL

OS
Courtesy of W. Trattler, MD

Zymar & polytrim Q2 hrs started; BCTL removed
Punctal plugs placed

Postop Day 2
OS

Postop Day 5
Perforation after Epi-Off CXL
Epi-off CXL AEs


- Complication and failure rates after corneal crosslinking. Koller, Seiler, et. al. JCRS 2010;36(1):185

Epi-off CXL AEs (cont.)

- Corneal melting in both eyes after simultaneous corneal cross-linking in a patient with keratoconus and Down syndrome. Ophthalmologe. 2010 Oct; 107(10):951-5
- Corneal melting corneal collagen cross-linking for keratoconus: A case report. Labiris. Journal of Medical Case Reports 5:15 2012
Haze after Epi-Off CXL
“White Cornea” after High Irradiance CXL
Corneal “Deposits” after High Irradiance Epi-Off CXL

c/o Robert Fintelman, MD
Phoenix, Arizona
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<td>Well, maybe ribo can load stroma but it takes too long or needs iontophoresis</td>
<td>See pictures</td>
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Transepithelial Riboflavin Loading @12 min
Have You Ever Prescribed?

- Tobramycin ophthalmic solution
- Prenisolone acetate ophthalmic suspension
- Erythromycin ophthalmic solution
- Olopatadine hydrochloride ophthalmic solution
Wouldn’t You Want to Have Your CXL Procedure Without Removing Your Corneal Epithelium?
Clear Cornea- Epi-On CXL POD 1
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<th>UVA is the rate limiting factor in CXL</th>
<th>Oxygen is the rate limiting factor in CXL</th>
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<td>Therefore high UV irradiance speeds CXL</td>
<td>Google “Chemistry of crosslinking”</td>
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It’s All About the Oxygen

UVA

Riboflavin

Hydrogen Peroxide

Singlet Oxygen

Safe, Effective, Controlled CXL

3-4 mW

Adequate Oxygen

Cell Death, Scarring, Limited CXL

High UVA

Low Oxygen

TOXIC HAZARD
High Radiation CXL

• Higher irradiance = faster crosslinking?

30 mW/cm² X 3 min = 3 mW/cm² X 30 min
300 degrees for 30 min = 3000 degrees for 3 min

Roy Rubinfeld, MD
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<td><strong>Epi-on CXL does not produce a “demarcation line” which shows epi-on does not work</strong></td>
<td><strong>See picture</strong></td>
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Thank You
Galileo (1633) vs. Common Knowledge
`I, Galileo, being in my seventieth year, being a prisoner and on my knees, ...abjure, curse, and detest the error and the heresy of the movement of the earth.'
“Vatican Science Panel Told By Pope: Galileo Was Right” - NY Times 11/1/92

Pope John Paul II declared the ruling against Galileo was an error resulting from "tragic mutual incomprehension."
Controversies and “Known Knowns”