CORNEAL CROSS-LINKING (CXL)

J. Bradley Randleman, M.D.
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Presenter Introduction

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CORNEAL CROSS-LINKING

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SLACK Incorporated
Corneal cross-linking

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OVERVIEW

• CXL Basic principles
• Primary Indications: Ectatic corneal disorders
• CXL Protocols
• Complications & Controversies
• Patient Selection: Beginning & Advanced
Corneal cross-linking

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\textbf{ABSTRACT}

Since its inception in the late 1990s, corneal cross-linking has grown from an interesting concept to a primary treatment for corneal ectatic disease worldwide. Using a combination of ultraviolet-A light and a chromophore (vitamin B2, riboflavin), the cornea can be stiffened, usually with a single application, and progressive thinning diseases such as keratoconus arrested. Despite being in clinical use for many years, some of the underlying processes, such as the role of oxygen and the optimal treatment times, are still being worked out. More than a treatment technique, corneal cross-links represent a physiological principle of connective tissue, which may explain the enormous versatility of the method. We highlight the history of corneal cross-linking, the scientific underpinnings of current techniques, evolving clinical treatment parameters, and the use of cross-linking in combination with refractive surgery and for the treatment of infectious keratitis.

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Crosslinking for keratoconus (KC)

- Non-enzymatic collagen stiffening with riboflavin and UVA light

CX: CLINICAL RESULTS

Wittig-Silva JRS 2008
Goals for CXL in Ectasias

- Stabilize ectatic process
- Reduce corneal steepening
- Improve CTL fitting
- Provide alternatives for visual rehabilitation
  - Intracorneal ring segments
  - PRK

Avoid corneal transplantation!
Avedro Receives FDA Approval for Photrex® Viscous, Photrex® and the KXL® System for Corneal Cross-Linking

Photrex Viscous (riboflavin 5’-phosphate in 20% dextran ophthalmic solution) 0.146%, Photrex (riboflavin 5’-phosphate ophthalmic solution) 0.146%, and the KXL system are the first and only FDA-approved therapeutic treatment for progressive keratoconus

Waltham, Massachusetts, USA, Apr 18, 2016
CXL:

STEP BY STEP
Procedure: Standard Dresden Technique

- 9 mm epithelial removal
- Riboflavin 0.1% drops x 30 min
- Riboflavin 0.1% drops x 30 min with 30 minutes 365 nm UVA (3mW/cm²)
- UV-X, Peschke Meditrade, Zurich
CXL IN THE US

KXL System

Avedro’s KXL System, the only FDA approved cross-linking device, offers:

- UVA Irradiation: 30 minutes at 3 mW/cm²
- Laser alignment for patient positioning
- Wireless control for beam alignment in the X, Y and Z axes
- Fully-integrated stable delivery platform
- Touch screen operation
- Self-calibration of UVA irradiation intensity
CXL IN THE US

Photrex Formulations

Photrex Viscous
(riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%

Photrex
(riboflavin 5'-phosphate ophthalmic solution) 0.146%

Technical Information:
Formulation: 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical ophthalmic use

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Formulation: 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution for topical ophthalmic use
CXL FOR CORNEAL ECTASIAS
Emory University data (unpublished)
Corneal Thickness (Pentacam)

- Emory University data (unpublished)
Uncorrected Distance Visual Acuity

- Ectasia
- Keratoconus

Emory University data (unpublished)
Best Spectacle Corrected Visual Acuity

CDVA (ETDRS Letters)

- Ectasia
- Keratoconus

Emory University data (unpublished)
Eyes Achieving UDVA 20/40 or Better

Emory University data (unpublished)
Eyes Achieving BSCVA 20/40 or Better

Emory University data (unpublished)
MEASURING CXL CHANGES: CHALLENGES

Difference Maps
ORA changes with crosslinking in post-LASIK ectasia

Corneal Collagen Cross-Linking Complications and Their Management

J. Bradley Randleman, MD and Karolinne Maia Rocha, MD, PhD
CXL COMPLICATIONS

• Corneal Damage
• Infectious Keratitis
• Lack of efficacy
• Failed remodeling
COMPLICATIONS

- CXL: potential complications
  - UVA Exposure
    - Endothelium Damage
    - Temporary Stromal Edema
  - Wound Healing Response
    - Temporary or Permanent Haze
    - Corneal Scarring
  - Epithelial Removal
    - Sterile Infiltrates
    - Keratitis (e.g., infectious)
DELAYED HEALING
CORNEAL MELT
PERIPHERAL INFILTRATES
PERIPHERAL INFILTRATES
ENDOTHELIAL DAMAGE
UVA Corneal Absorption in Presence of Riboflavin

<table>
<thead>
<tr>
<th>Depth (microns)</th>
<th>Irradiance</th>
<th>Damage Threshold</th>
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<tbody>
<tr>
<td>0</td>
<td>3.00 mW/cm²</td>
<td>Keratocytes: 0.5 mW/cm²</td>
</tr>
<tr>
<td>100</td>
<td>1.49 mW/cm²</td>
<td></td>
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<tr>
<td>200</td>
<td>0.74 mW/cm²</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>0.36 mW/cm²</td>
<td></td>
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<tr>
<td>400</td>
<td>0.18 mW/cm²</td>
<td>Endothelium: 0.3 mW/cm²</td>
</tr>
<tr>
<td>500</td>
<td>0.09 mW/cm²</td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>0.06 mW/cm²</td>
<td></td>
</tr>
</tbody>
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Soosan Jacob MS, FRCS, DNB; Dhivya Ashok Kumar, MD; Amar Agarwal, MS, FRCS, FRCOphth; Sushanth Basu, DO; Pratheek Sinha, BOptom; Ashvin Agarwal, MS


Figure 2. Intraoperative anterior segment optical coherence tomography image showing the soft contact lens on the cornea. Note: The contact lens and riboflavin film contributed the additional 108 µm of treatment zone.

Figure 3. The postoperative stromal demarcation line seen at 1 month after contact lens-assisted corneal cross-linking as seen with anterior segment optical coherence tomography.
Figure 2. Intraoperative anterior segment optical coherence tomography image showing the soft contact lens on the cornea. Note: The contact lens and riboflavin film contributed the additional 108 μm of treatment zone.
In Vivo Confocal Microscopy After Contact Lens-Assisted Corneal Collagen Cross-linking for Thin Keratoconic Corneas

Cosimo Mazzotta, MD, PhD; Soosan Jacob, MS, FRCS, DNB; Amar Agarwal, MS, FRCS, FRCOphth; Dhivya Ashok Kumar, MD

Figure 1. (A) Contact lens immersed in riboflavin 0.1% during contact lens-assisted corneal collagen cross-linking. (B) Riboflavin 0.1% solution application under and above the contact lens during contact lens-assisted corneal collagen cross-linking treatment.
Figure 3. In vivo confocal microscopy analysis performed 3 months after treatment. Scan A shows regular basal epithelium mosaic and cell borders. Scan B shows corneal reinnervation with the presence of subepithelial cluxus fibers (blue arrows). Scan C shows initial keratocyte nuclei repopulation of the anterior stroma at 100 μm with progressive edema reduction. Scan D shows edema reduction of the deep stroma followed by gradual keratocyte repopulation and hyperreflective microbands of high molecular weight collagen (white arrow). Scan E shows demarcation line with the presence of activated repopulating keratocytes. Scan F shows regular endothelium mosaic.
COMPLICATIONS

Failed Remodeling
EPI-OFF CXL
Epithelium MUST be removed for efficacy
In Vivo Imaging of Riboflavin Penetration During Collagen Cross-linking With Hand-held Spectral Domain Optical Coherence Tomography

Chintan Malhotra, MS; Rohit Shetty, DNB, FRCS (Glasgow); Rajesh S. Kumar, MS; Himabindu Veluri, MS; Harshe Nageraj, MS; V. Bhujang Shetty, MS

**Graph:**
- **Group 1:** Epithelium removed completely
- **Group 2:** Epithelium removed in grid pattern

- **30 minutes**
- **60 minutes**
In Vivo Imaging of Riboflavin Penetration During Collagen Cross-linking With Hand-held Spectral Domain Optical Coherence Tomography

Chintan Malhotra, MS; Rohit Shetty, DNB, FRCS (Glasgow); Rajesh S. Kumar, MS; Himabindu Veluri, MS; Narsa Nagaraj, MS; K. Bhujang Shetty, MS
EPITHELIUM ON OR OFF?

- Epithelium must be removed for efficacy

Epi Off

Epi On
A Standard

B Iontophoresis

248 μm nella cornea

240 μm nella cornea
Biomechanical Characterization of Keratoconus Corneas Ex Vivo With Brillouin Microscopy

Giuliano Scarcelli,1,2 Sebastien Besner,1,2 Roberto Pineda,3 and Seok Hyun Yun1,2,4

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Biomechanical Characterization of Keratoconus Corneas Ex Vivo With Brillouin Microscopy

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^3Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, United States
^4Harvard-MIT Health Sciences and Technology, Cambridge, Massachusetts, United States
Brillouin Microscopy of Collagen Crosslinking:
Noncontact Depth-Dependent Analysis of Corneal Elastic Modulus

Giuliano Scarcelli, Sabine Kling, Elena Quijano, Roberto Pinuela, Susana Marcos, and Seok Hyoung Yun

(Invest Ophthalmol Vis Sci 2013:54:1418-1425)
The Efficacy of Corneal Cross-Linking Shows a Sudden Decrease with Very High Intensity UV Light and Short Treatment Time

Jeremy Wernli,1 Silvia Schumacher,1 Eberhard Spoeri,2 and Michael Mrochen1


Figure 3. Young’s moduli at 10% strain for the control and different treatment groups. Box-plot whiskers indicate the fifth and the 95th percentiles, crosses (x) indicate the first and the 99th percentiles and dashes (--) indicate the minimum and maximum values within the groups.
Equivalence of Biomechanical Changes Induced by Rapid and Standard Corneal Cross-linking, Using Riboflavin and Ultraviolet Radiation

Silvia Schumacher, Lydia Oestiger, and Michael Mrochen

(Invest Ophthalmol Vis Sci. 2011;52:9048-9052)
Corneal Biomechanical Properties at Different Corneal Cross-Linking (CXL) Irradiances

Arthur Hammer,1 Olivier Richoz,1 Samuel Arba Mosquera,2 David Tabibian,1 Florence Hoogewoud,1 and Farhad Hafezi1,3

1Department of Ophthalmology, Geneva University Hospitals, Geneva, Switzerland
2SCHWIND eye-tech-solutions, Kleinostheim, Germany
3Doheny Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, California, United States

CXL PROTOCOLS

- Epi-Off
  - Standard (30 min x 3mW/cm²)
  - Accelerated
    - 10 min x 5mW/cm²
    - 5 min x 18 mW/cm²
    - 3-4 min x 30mW/cm²

- Epi-on
  - “regular”
  - iontophoresis
PATIENT SELECTION

- Progressive keratoconus/ectasia
  - high risk for progression
    - adolescents
    - signs of progression
    - history of changing vision
- Issues with current visual correction
PROTOCOL

• Follow the evidence:
  • Epithelium-off
  • Standard protocol
CONCLUSIONS

• Complications can arise after CXL
  • Requires diligence early postoperative
  • Affects screening for CXL
  • Affects patient and surgeon acceptance of protocols
CONCLUSIONS

• Variations in clinical protocols occurring faster than research into these protocol variations

• Variability in comparative results depending on the metric followed

• Best metrics to follow still undetermined
Thank You