Corneal Cross-Linking: A New Treatment for Corneal Ectasia

November 4, 2017
Matthew J. Kauffman, OD, FAAO, FSLS

Financial Disclosures

- STAPLE Program Speaker
- Soft Toric and Presbyopic Lens Education Speaker
- Gas Permeable Lens Institute (GPLI) Speaker
- Visionary Optics Speaker
- NIH/NEI R01EY019105 (RAA and JDM) Funding

Corneal Ectasia

Keratoconus Pellucid Marginal Degeneration

Corneal ectasia

- Collagen matrix proteoglycan difference (normal vs. keratoconic)
- Increase of lysosomal and proteolytic enzymes
- Decrease of protease inhibitors
- Configuration of stromal collagen lamella modified

Treatment options

Corneal cross-linking (CXL) Methodology

0.1% Riboflavin (Vitamin-B2)
Ultraviolet A (UV-A) 3 mW/cm²
Increased stromal strength and stability
History

- University of Dresden (German) – late 1990s
- Cross-linking
  - Fibrin = blood clot formation
  - Tendons = increased tensile strength
- Non-enzymatic cross-linking of collagen (glycation)
  - Age-related
- Cornea – parallel collagen fibers

Defining Progression

- United States
  - Increase steep K by > 1.00 D
  - Increase in manifest refraction astigmatism > 1.00 D
  - Myopic shift in spherical equivalent > 0.50

Contraindications

- Corneal thickness < 400 µm
- History of herpetic infection
- Corneal scarring/opacification
- Poor epithelial healing
- Ocular surface disease
- Immune disorders
- Pregnancy/breast feeding
- Age: 14-65 year old

Dresden Protocol

- Aka: Epithelium-off ("epi-off")
- Topical anesthesia
- Standard aseptic technique
  - Epithelium removed (central 9 mm)
  - Riboflavin saturations (stroma)
    - Photoxa viscous (riboflavin 5'-phosphate in 20% dextra ophthalmic solution)
  - Absorption peak = 366 nm
  - Administered in 2 minute intervals ± 30 minutes

- Ensure proper stromal saturation after 30-minute uptake phase
- Yellow flare in anterior chamber
- Minimum corneal thickness after debridement = 400 µm
- Ultrasound pachymeter
- Hypotonic Photexa riboflavin (5-10 seconds)

Riboflavin

- Functions
  - Photosensitizing agent to propagate chemical reactions
  - Protective effect by reducing UV transmittance beyond treatment depth
### Chemical reaction

- **Aerobic phase**
  - Riboflavin excited to single or triplet state
  - Stromal proteins undergo photosensitized oxidation with reactive oxygen species
- **Anaerobic phase**
  - Stromal interacts with reactive radical ion species
  - Photochemical reaction produces increase of corneal rigidity, collagen fiber thickness, and resistance to enzymatic degradation

### FDA Classification

- **Approval**
  - Label
  - Approved indications and procedure by FDA
  - Directions for use
- **Off-label**
  - Use of approved product in manner not described on the label
- **Unapproved**
  - Use of unapproved product that has no label

### CXL FDA Approval (April 2016)

- **14 – 65 years old**
- **Indication**
  - Progressive keratoconus
  - Corneal ectasia following refractive surgery
- **Drug-device combination**
  - KXL UV System
  - Photrexa and Photrexa viscous
  - Epithelium off (“epi-off”) technique

### KXL System

- **Only approved FDA CXL device**
- **UVA irradiation:** 3 mW/cm²
- **Laser alignment**
  - Wireless control for beam alignment
  - Fully-integrated stable delivery platform
- **Touch screen operation**
- **Self-calibration UVA intensity**

### Photrexa

- **Photrexa viscous**
  - 1.46 mg/ml riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical administration
  - 3.0 mL volume
- **Photrexa**
  - 1.46 mg/ml riboflavin 5'-phosphate ophthalmic solutions for topical administration
  - 3.0 mL volume

### FDA Approval – Health Insurance

- **Not currently covered by insurance**
- **Epi-off most likely only procedure accepted in future**
- **Potential liability going “off-label”**
- **Under approved study**
- **Institutional Review Board (IRB) approved study**
Treatment and Management

Post-operative treatment

- Bandage contact lens
- 3-5 days
- Epithelium healed
- Topical antibiotic (1 week)
- Topical corticosteroid (2-3 weeks)
- Do not rub eyes for first couple days

Post-op expectations

- Vision may worsen first month
- Returns to baseline by 3 months
- Possible vision improvement 3-6 months
- Increase in Kmax first month
- Keratometry, pachymetry, and corneal haze
  - Worse 1st month, improves after 3rd month

Complications

- Eye pain
- Epithelial abrasion
- Corneal haze
- Microbial keratitis
- Sterile infiltrates
  - Corneal edema (1-2%)
  - Corneal opacity and tear (1-2%)

Eye pain

- Discomfort first night post-op
- Possible light absorption by nerves
- Worse on day of surgery and 1 day post-op
- Oral pain medication
- Cold compresses
- PF refrigerated artificial tears

Corneal haze

- Most common
  - 90% of patients
- Decreases naturally 3-12 months
  - Recent study noted haze after 10 year follow-up
- Most likely different cellular mechanism as PRK
  - Increased density - extracellular matrix
Keratitis

- Infectious keratitis
  - Gram (+) bacteria
  - Gram (-) bacteria
  - Fungi
  - Herpes simplex virus
- Sterile infiltrates
  - 7.6% incidence rate
  - Resolved after 4 weeks topical corticosteroid

Reduced epithelial healing

- 3-8% of cases
- Higher risk of additional complications
- Potential corneal melt
- Reduced rate of healing due to conical shape of cornea

Corneal edema

- 2.9% cases had corneal edema day 1
  - Half did not improve
  - Possible corneal endothelial damage

Endothelial decompensation

- Minimal corneal thickness = 400 µm
- Hypo-osmolar riboflavin
- Customized epithelial debridement

Contact Lenses

- Majority will still need contact lens
  - Epithelium-off
    - Resume wear 4 weeks post-op
    - Redo lens in 6 months
  - Epithelium-on
    - Resume 1-2 weeks
- Re-epithelization is key
  - Cornea may change shape over the year following surgery
  - Eyes get steeper for a month, then get flatter over next year

- Kmax, Kmin, Kapex significantly decreased
- Mean astigmatism significantly reduced
  - 5.7 D to 4.0 D
- 2 eyes required repeat
  - 5 years
  - 10 years
  - Kvalues increased and VA worsened (one case)
**Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: Ten-year results.**

- Mean corrected distant VAs significantly improved by 0.14 logMAR
- Complications absent after 10 years
  - Permanent stromal scar (one eye)
  - Persistent haze (13 eyes)
- No long-term endothelial cell deterioration

**Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: Ten-year results.**


**140 eyes analyzed (s/p Lasik or PRK)**

**Results:**
- No significant difference in Kmax and Kmin values after CXL
- CDVA improved significantly after CXL
- UCVA did not differ statistically
- Endothelial cell count and corneal thickness did not deteriorate

**Conclusion:** CXL promising treatment to stabilize ectasia post-refractive surgery.

**A review and meta-analysis of corneal cross-linking for post-laser vision correction ectasia.**


- Most parameters continuously decreased
- Statistically significant improvement in all higher order aberrations (HOA) parameters
- All values significantly decreased
- CXL effective in improving HOAs

**Pediatric populations**

- 52 eyes
- Epi-off
- Significant decrease Kmax
- Improvement uncorrected VA
- BCVA improvement
- < 14 y/o – “off label”

**Summary of changes**

**Corneal topography**

- Kmax steepening occurs first month
- K values flatten 2 D on average

**Corneal thickness**

- Mild thinning immediate post-op
- Progression halted 98% of cases
Alternative CXL applications

Epithelium-on
- AKA “epi-on,” trans-epithelium (TE-CXL)
- Fewer associated complications
- Quicker recovery
- Lower CXL efficacies
- Brian Wachler (Beverly Hills, CA)
  - Holcomb C3-R Crosslinking

Epi-on
- 26 eyes
- Modified riboflavin
- Accelerated UVA irradiance
  - 9 mW/cm² for 10 min.
  - Total dose: 30 mW/cm²
- Thin corneas < 400 µm
- Uncorrected and corrected distance VAs, spherical equivalent, astigmatism = significant improvement
- Kmax and pachymetry = significant reduction over baseline

CXL with Lasik
- Long-term results (high refractive errors) variable
  - Requires enhancement procedure
  - Corneal weakening
  - Reduced biomechanical strength with flap creation and stromal ablation
  - CXL induces flattening effect
  - Hyperopic shift
  - Haze formation.
- Lasik with concomitant half-fluence CXL

CXL with Lasik
- Lasik XTRA procedure
  - 0.25% riboflavin applied prior to stromal ablation (90 sec)
  - Flap repositioned
  - UVA (30 mW/cm² for 90 sec = 2.7 J/cm²)
- Hyperopic eyes
  - Significantly lower regression in Lasik XTRA group
- High myopes (-8.00 to -15.00 D)
  - Greater refractive accuracy in XTRA group at 3 months

CXL and PRK – “Athens Protocol”
- Corneal cross-linking performed in conjunction with PRK
  - Improvement in:
    - Spherical equivalent
    - Defocus equivalent
    - Uncorrected VA
  - Better corrected VA
  - Higher order aberrations
  - Kmax
CXL and intracorneal rings

- Perform CXL and intracorneal ring
- Several studies (Duration 7-12 months)
  - Improvement in:
    - UCVA
    - BCVA
    - Refraction
    - Kmax
  - Another study: no difference

Iontophoresis (I-CXL)

- Increase riboflavin penetration during “epi-on” CXL
- Electrical current utilized to enhance delivery of charged molecules
- Riboflavin = negatively charged
- Five minute process achieves adequate stromal riboflavin concentration
- Initial studies promising results
- Keratometric regression was lower compared to epi-off
- Demarcation line depth lower with TE-CXL

Infectious keratitis

- UV irradiation antimicrobial
- Disinfect air, tears, and surfaces
- Photochemical riboflavin has antimicrobial effect
- Antimicrobial effect on agar plates
  - Pseudomonas aeruginosa
  - Staphylococcus aureus
  - Staphylococcus epidermidis
  - Streptococcus pneumoniae
  - Candida albicans
- Treatment of resistant bacterial and HSV keratitis
  - 8 patients underwent CXL
    - 6 bacterial
      - Good response and rapid epithelization and resolution (4/6 eyes)
    - 2 HSV
      - One patient exhibited good response
      - Others – recurrence
- Conclusion: May/may not be effective

Pseudophakic bullous keratopathy

- Corneal resistance to swelling increased with cross-linking
- More difficult for stromal edema formation to occur
- CXL = increase in interfiber collagen connections
- CXL has potential to:
  - Reduce ocular scarring
  - Improve visual acuity
  - Delay necessity for penetrating keratoplasty
  - Significant improvement corneal transparency, corneal thickness, ocular pain after 1 month
  - Effects did not last greater than 6 months

Customized CXL

- Biomechanical changes in keratoconus are focal
- Great efficacy of small diameter treatment zones
- UV-A delivered in customized treatment pattern
- KXL II (Avedro)
  - Advanced pupillary tracking mechanism
  - Customized CXL
Customized CXL

- Patterns
  - Toric
  - Asymmetric arcuate
  - Concentric circles
- Advantages
  - Superior vision results
  - Impact of haze formation less due to decentration
  - Decreased risk of infection
  - Improved post-op comfort

- UV-A custom toric pattern (TE-CXL)
- Treatment centered on steepest area of cornea
- 0.8 D reduction in mean keratometry
- UCVA 20/40 to 20/25 after 6 months

Photorefractive intrastromal CXL

- High-fluence CXL for low myopia
- CXL for refractive correction
- Mosaic device (Avedro)
- Kanellopoulos et al.
- UV-A (12 J/cm²) custom treatment
- 6 month follow-up
  - Avg corneal flattening at 1 week = 2.3 D
  - Regression and stabilization = 1.4 D at 1 month

Pulsed CXL

- Pulsed UV-A irradiance delivery with on/off pattern
- Peyman et al.
  - 1 sec on/1 sec off vs. 4 min continuous UV-A irradiation
  - Deeper demarcation line
- Moramarco et al.
  - 60 eyes
  - Average demarcation depth: 213 ± 47.38 µm
  - 149.31 ± 47.36.06 µm (continuous)

Accelerated corneal cross-linking

- Decrease irradiation timeframe
- Bunsen-Roscoe law of photochemical reciprocity
- Ultraviolet UV devices
  - 43 mW/cm²
  - 2 minute treatment time required
- Study results
  - Procedure safe and effective in halting progression
  - No long-term dose
  - Protocol variability

- Kanellopoulos
  - 7 mW/cm² for 15 min.
  - 42 eyes
  - 46 month follow-up
  - Similar efficacy and refractive effect
  - No adverse effects
- Multiple studies
  - 9 mW/cm² for 10 min.
  - Significant improvement in visual acuity and keratometric values
Accelerated 15 mW pulsed-light crosslinking to treat progressive keratoconus: Two-year clinical results

- Mazzotta et al.
- Epithelium removed
- 15 mW/cm² pulsed-light accelerated CXL: 6 min (1 sec on/1 sec off)
- Total exposure = 12 min at 5.4 J/cm²
- 132 eyes
- UDVA and CDVA significantly improved
- Corneal values improved significantly

Scleral cross-linking

- Beneficial for axial length elongation
- Photosensitizer and blue light
- Prevent progression of axial length
- Kwok et al.
- Induced scleral cross-linking in porcine eyes
- Significant increase in Young's modulus

Financial Aspects of CXL

- Annual cost
  - Routine care: $20
  - Keratoconus care: $653
- Corneal transplant: $13,-27,000/transplant
- Lifetime cost of keratoconus treatment: $25,168 ± $16,247
- Initial corneal transplant and subsequent regraft
- Gofundme.com
  - Keyword: Keratoconus and cross-linking

Avedro sponsored patient assistance

- ARCH Program
  - Patient Assistance Program
  - Uninsured patients
- Prescription Assistance Program
  - Commercially insured patients
  - Federal coverage excluded

Financial costs of keratoconus

- Annual cost
  - Routine care: $20
  - Keratoconus care: $653
- Corneal transplant: $13,-27,000/transplant
- Lifetime cost of keratoconus treatment: $25,168 ± $16,247
- Initial corneal transplant and subsequent regraft
- Gofundme.com
  - Keyword: Keratoconus and cross-linking

Billing and coding

- CXL is medically necessary
  - Should be covered by 3rd party payers
- Many patients delay CXL due to financial reasons
  - Vision at risk if delay occurs
  - Wait until insurance provides coverage
Billing and coding

- Insurance coverage (As of May 2017)
  - Aetna, Kaiser Permanente
  - Blue Cross Blue Shield (BCBS) Dental coverage
  - Cigna (considers CXL experimental)
  - BCBS of North Carolina (considers CXL experimental)
  - BCBS of Massachusetts (believes CXL not FDA approved)

- CPT Code: 0402T (Collagen cross-linking of cornea)
- J3490 (unclassified drug): Protrexa viscous and Protrexa
- Procedure: 1.5 – 2 hours total time

Co-management

- Surgeon co-management
- Co-management fees
- Can be difficult to manage with out-of-town surgeon
  - Numerous follow-up visits required

Conclusion

- CXL is a new FDA approved treatment for progressive keratoconus and post-refractive surgery ectasia
- FDA approved protocol is epi-off
- Optometrist plays important role in management
- May reduce life-time financial burden of keratoconus

THANK YOU!

mjkauffm@central.uh.edu