COLLAGEN CROSSLINKING: WHERE ARE WE NOW?

Kevin T. Lavery, MD
TLC Eye Care and Laser Centers

Keratoconus

A degenerative non-inflammatory disease of the cornea where the central or paracentral cornea undergoes progressive thinning and steepening causing irregular astigmatism.

Etiology

- Unknown
- Two Hit Hypothesis
- Hereditary pattern plus another “hit” such as eye rubbing, sleep apnea and Floppy Eyelid Syndrome
- Associated disorders include Down’s Syndrome, Atopy, Ehler’s Danlos, Leber’s congenital amaurosis
- Incidence is approximately 1 in 2000
Classification based upon K’s

- **Mild:** Less than 45.00 D
- **Moderate:** 45.00-52.00 D
- **Advanced:** 52.00-62.00 D
- **Severe:** More than 62.00 D

Classification based on Shape

- **Nipple Cones** (small size 5mm)
- **Oval Cones** (larger 5-6mm ellipsoid)
- **Globus cones** (larger than 6mm)
Pathophysiology

- Breaks or absence of Bowman’s layer
- Collagen disorganization
- Scarring
- Thinning

Primary Prevention

- No preventive strategy has been proven effective to date
- Avoiding Eye Rubbing or Pressure (i.e., Sleeping with hand against eye)
- Avoidance of allergens may decrease eye rubbing

A Normally Seen (20/20) Parking Sign
Parking Sign: Mild Keratoconus

Parking Sign: Advanced Keratoconus

Forme Fruste Keratoconus

- Occurs 10 times more often than progressive keratoconus
- If remains stable, no treatment is needed
Future Research

- Better understanding of the biochemical and molecular changes and genetic influences that occur in KC corneas
- Leukocyte common antigen related protein (LAR) expression plays a role in Apoptosis
- KC corneas have an increased amount of nitrotyrosine staining
- In the KC cornea there is decreased activity of Aldehyde Dehydrogenase (ALDH) which detoxifies aldehydes

Treatments

- Spectacles
- Soft contact lenses
- Hard contact lenses
- Intacs
- Scleral contact lenses
- Corneal Transplantation

Corneal Cross-linking for Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery

First and Only FDA Approved Therapeutic Treatment for Progressive Keratoconus
Corneal Cross-linking: Mechanism of Action

- First studied in Europe at the University of Dresden in the late 1990s
- Corneal collagen cross-linking is a medical procedure that combines the use of ultra-violet (UV) light and riboflavin (vitamin B2) drops
- The absorption of UVA by riboflavin generates radical riboflavin and singlet oxygen to form cross-links
- Cross-linking creates new corneal collagen cross-links
- Results in a shortening and thickening of the collagen fibrils
- Leads to the stiffening of the cornea

Where do cross-links occur?

- Collagen fibrils within lamellae are regulated by an interconnecting network of proteoglycans.
- Cross-linking with UVA/riboflavin has no effect on any collagen structural parameter measured by x-ray scattering except uniformity of nearest neighbor interfibrillar spacing.
- Therefore, it is believed that cross-links are formed predominantly at fibril surfaces and within the protein network surrounding the collagen.

AVEDRO FDA APPROVED PRODUCTS

Photrex Viscous, Photrex and the KXL System are the First and Only FDA-approved Therapeutic Treatment for Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery
Treatment Protocol

- 9 mm epithelium removal
- Photrexa Viscous: 1 drop topically every 2 min for 30 min
- Check for riboflavin flare in anterior chamber
  - If yellow flare not detected, add 1 drop of Photrexa Viscous every 2 minutes for an addl 2 to 3 drops. Recheck for flare.
  - Repeat as necessary.
- Ultrasound pachymetry:
  - If <400 µm, 2 drops Photrexa every 5-10 sec until >400 µm.
  - Irradiation should not be performed unless 400 µm is met
- 30 minutes UV exposure with KXL System
  - 365 nm UV, 3mW/cm²
  - Continue Photrexa Viscous every 2 min

US CLINICAL STUDY DATA OVERVIEW

Phase III Study Design

- Avedro's NDA submission encompassed data from three prospective, randomized, parallel-group, open-label, placebo-controlled, 12-month trials conducted in the United States to evaluate the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing corneal collagen cross-linking.
- The trials included:
  - 205 patients with progressive keratoconus.
  - 179 patients with corneal ectasia following refractive surgery.
- Schedule of Assessments:
  - Screening/baseline, Day 0 (randomization/treatment day), 1 day, 1 week, and 1, 3, 6, and 12 months after treatment.
- Primary Endpoint was Kmax as measured by keratometry.
Efficacy Analysis: Progressive Keratoconus

- In clinical studies, the CXL treated eyes showed increasing improvement in Kmax from month 3-12, while in untreated, Sham eyes, Kmax demonstrated steepening.

- Progressive keratoconus patients had an average Kmax reduction of 1.4 diopters in Study 1 and 1.7 diopters in Study 2 in the CXL treated eyes while the sham eyes had an average increase of 0.5 diopter in Study 1 and 0.6 diopter in Study 2 at Month 12.

Post-baseline missing data were imputed using last available Kmax value. For the sham study eyes that received CXL treatment after baseline, the last Kmax measurement recorded prior to receiving CXL treatment was used in the analysis for later time points.

Patients should be monitored for resolution of epithelial defects as ulcerative keratitis can occur.

Efficacy Analysis: Corneal Ectasia Following Refractive Surgery

- In clinical studies, the CXL-treated eyes showed increasing improvement in Kmax from month 3-12, while in untreated, Sham eyes, Kmax demonstrated steepening.

- For corneal ectasia patients, at Month 12, the CXL treated eyes had an average Kmax reduction of 1.0 diopter in Study 1 and 0.5 diopter in Study 2, while the sham eyes had an average increase of 1.0 diopter in Study 1 and 0.5 diopter in Study 2.

Post-baseline missing data were imputed using last available Kmax value. For the sham study eyes that received CXL treatment after baseline, the last Kmax measurement recorded prior to receiving CXL treatment was used in the analysis for later time points.

Patients should be monitored for resolution of epithelial defects as ulcerative keratitis can occur.

Efficacy Analysis: Mean Change from Baseline Kmax, CXL and Sham
CONTRAINDICATIONS

None

ADVERSE REACTIONS

corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, corneal ulcer, eye pain, reduced visual acuity, blurred vision, corneal striae, dry eye, eye pain and photophobia.

Treatment Adverse Events

- The majority of adverse events resolved during the first month
- Corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye and eye pain, and decreased visual acuity took up to 6 months to resolve. Corneal opacity or haze took up to 12 months to resolve
- In 1-5% of patients, corneal epithelium defect, corneal edema, corneal opacity and corneal scar continued to be observed at 12 months

Haze after CXL
Haze after CXL is different in clinical character from haze after other procedures, such as excimer laser photorefractive keratotomy. The former is a dust-like change in the corneal stroma or a midstromal demarcation line, whereas the latter has a more reticulated subepithelial appearance. Similarly, the mechanisms leading to haze formation may be different.

Scheimpflug image densitometry

Theories for haze

**After CXL**
1. Concomitant changes in the corneal lamellar array and spacing may lead to an increase in light scatter and a decrease in transparency.
2. A significant increase in collagen fibril diameter, with decreased spacing between collagen fibrils, after CXL. This may also play a role in decreased corneal transparency.
• 3) CXL leads to an almost immediate loss of keratocytes in the corneal stroma
• Activated keratocytes repopulate the corneal stroma,
• It is possible that these activated keratocytes contribute to the development of CXL associated corneal haze.

Haze, is it a problem?
1) Mild haze is considered a normal finding in most of cases and even a sign of success and usually doesn’t affect vision
2) Mild Haze is usually paracentral in position and regressing in course with topical steroids
2) Risk factors for severe haze include advanced keratoconus and Epi-off CXL.

Severe haze
PATIENT EDUCATION & CO-MANAGEMENT

Patient Selection/ Treatment Criteria

- Screening exams for early diagnosis to identify patients and monitor for progression of keratoconus or development of corneal ectasia following refractive surgery
- Pediatric Use
  - 14 years of age and older
- Geriatric Use
  - No subjects enrolled in the clinical studies were 65 years of age or older

Current Protocol

- Epithelium Off procedure following the Dresden Protocol
- Unilateral treatment to begin
- $2500 per eye
- Currently not reimbursed by insurance
Pre-Operative Patient Education

- Set the expectation that cross-linking is not refractive surgery
- Contact lenses and/or spectacles still required
- Educate patients regarding the time course of the post-operative healing process.
- On average, steepening of Kmax is observed at 1 month postoperatively, followed by flattening through 12 months.
- In 1-2% of patients, corneal epithelium defect, corneal edema, corneal opacity and corneal scar continued to be observed at 12 months.

Post-Operative Management

- Post-operative Care
  - Post-operative regimen similar to care after PRK
  - Care of epithelial debridement
  - Bandage contact lens
- Expected outcomes
  - Initial steepening followed by gradual flattening
- Contact Lens Refitting

Post-Operative Patient Counseling

- Do not rub their eyes.
- May be discomfort in the treated eye and that sunglasses may help with light sensitivity.
- Contact us if the bandage contact lens falls out or becomes dislodged.
- Slow process
Purpose

Stop keratoconus progression by increasing corneal strength

Relative portion cross-linked determines overall strength

Cross-linking larger corneal tissue volume

How to maximize cross-linked volume?

Goal:
More effective CXL

How to maximize cross-linked volume?

Cross-linking depth

50 µm deeper CXL → 30% higher intensity
Maximize cross-linking volume

Effect parallel to posterior corneal surface
Effect parallel to anterior corneal surface

Future treatment options

• “EPI–ON” will be a game changer but epithelium is lipophilic and Riboflavin is lipophobic.
• Newer agents to help get across the epithelium
• Newer treatment protocols requiring less time

Epi-Off vs. Epi-On CXL

Epi-Off CXL
• Established surgical procedure
• Long term data showing stabilization
• New CXL applications continually advancing: Shorter treatment time etc.

Epi-On CXL
• Less painful for patient
• Reduced risk of infection
• Suitable for thinner corneas (<400µm)
The problem

Epi Off CXL

• During standard DRESDEN protocol for CXL, the corneal epithelium is mechanically removed after surface anesthesia and prior to riboflavin application.

Epi On CXL

• The intact corneal epithelium, with its tight junctions, is considered the most significant barrier to riboflavin permeability resulting in less effective riboflavin diffusion.

Oxygen and CXL

Review Of Epi-On Cases
In-Vitro Studies:

• 20% biomechanical effect compared to Epi-Off
• Reduction in riboflavin absorption without epithelial debridement


Possible solutions
Modified formulations:
- Benzalkonium chloride (BAC)
- Tetracaine, pilocarpine
- EDTA
- Ribomycin drops containing gentamycin,
- EDTA and BAC with Oxybuprocaine drops

Modified applications
- Iontophoresis
- Micro-needle injections
- FS - laser pockets

Preoperative Pentacam

Post Operative Exam
This is about maintaining our patient’s quality of life and functionality

Pleased to offer your patients the latest technologies
• This is not a money maker
• TLC believed that this was in the best interest of your patients
• That is why we committed to acquire the technology

Thank You
Summary

• Avedro products and protocol:
  • First and Only FDA-approved Therapeutic Treatment for Progressive Keratoconus and Cornea Ectasia Following Refractive Surgery

• Clinical Outcomes Review
• Typical Adverse Events
• Proper Patient Selection
• Pre and Post Op Counseling

Thank you!

Diffusion Findings


Trans-epithelium results

In Vivo Studies:

• Improvement in corneal curvature at 3 and 6 months post-op

• Stability ONLY up to 12 months

• Increase in K-max from baseline and loss of UDVA in 12-24 months

• No modifications to corneal morphology after treatment under confocal microscope


Patient Background and Previously Unmet Medical Need

- Keratoconus is a bilateral, progressive corneal ectasia resulting in irregular astigmatism and loss of visual function, with onset in teenage years.
- Affects 1 in 2000 people.
- KXL for the treatment of keratoconus granted orphan designation in the US by FDA due to rare nature.
- Keratoconic Cornea

Use in Specific Populations

- Pregnancy Risk Summary
  - Animal development and reproduction studies have not been conducted with the PHOTREXA VISCOUS/PHOTREXA/KXL™ system. Since it is not known whether the corneal collagen cross-linking procedure can cause fetal harm or affect reproduction capacity, it should not be performed on pregnant women.

- Lactation Risk Summary
  - There are no data on the presence of PHOTREXA VISCOUS or PHOTREXA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for the PHOTREXA/KXL corneal collagen cross-linking procedure and any potential adverse effects on the breastfed infant from the PHOTREXA/KXL corneal collagen cross-linking procedure or from the underlying maternal condition.
Good anterior chamber flare

Clinical Experience - Keratoconus
Vision Improvement (≥ 1 line of vision) CXLUSA vs. Hersh/Avedro

Clin William Trattler, MD
From our short experience in Sohag Future Center for Corneal surgeries

A 32 y old male with keratoconus grade (1)
Subjected to Epi-on CXL,
Preoperative refraction:
-5 Ds -5Dc @74 with BCVA : 6/48

Post.Epion CXL Pentacam after 3 weeks only

Postoperative refraction

-5 Ds -3Dc @ 72 with BCVA : 6/24

Avg K: Decrease by 2 Ds
Cylinder: Decrease by 2 Dc