Corneal Collagen Cross-linking

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Disclosures

- Abbott Medical Optics
- Alcon
- Avedro
- Calhoun
- Euclid Systems
- EyeBrain Medical
- Forsight
- AcuFocus
- Ophtec
- Ocuvee
- Wavetec
- Zeiss
- Mynosys
- LRG
- Equinox
- Precision Lens
- ORA
- Amaken
- EXCELLens

EyeWorld Breaking News

Joint panel recommends FDA approval for drug-device combination for CXL for 2 ophthalmic diseases

A joint panel of the Ophthalmic Effectiveness and Safety and Ophthalmic Drug Review Committees recommended approval of a drug-device combination of riboflavin (ophthalmic solution) and UV light for cross-linking for both progressive keratoconus and keratoconus astigmatism.

Yesterday, the panel voted on the question “Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Prokera Mesosil and Prolensa (ophthalmic solution) and the KXL Sytem (UV light to support approval)?” Issues regarding progressive keratoconus and cross-linking corneal collagen have been discussed extensively at recent meetings of the EyeWorld Ophthalmic Product Advisory Committee. The panel recommended approval, stating that the benefit outweighs the risk. Results for the corneal crosslink following refractive surgery were also presented, and it was not favorable.

The panel heard testimony from both the sponsor and the FDA before moving on to public testimony. Concerns were expressed from the panel members regarding the study protocol and data.
Keratoconus is a bilateral, asymmetric, progressive corneal ectatic disease that leads to corneal thinning, irregular astigmatism, and loss of BCVA.

Current treatments aim to provide temporary visual rehabilitation, but do nothing to stop the progression of the disease.

Substantial impact on quality of life.

Financial burden: lost productivity & lost scholastic/career opportunities.

Psychological burden: feeling of helplessness at the inevitability of further visual loss.

Frustration for both patients and doctors after finally achieving an acceptable contact lens fit, only to have the disease progress, and the fitting process begin again.

Eventual corneal transplantation in as many as 20% of cases.
In 2003, Wollensak et al published the results of a study of 23 eyes of 22 patients treated with CXL. The goal was to evaluate the effect of cross-linking on patients with moderate or advanced keratoconus.

Results showed the progression of keratoconus was halted.

Follow-up of 3 to 47 months showed flattening of the K Max readings by 2.01 D and reduction of the refractive error by 1.14 D in 70% of cases. No serious adverse events were noted.

Cross-linking Procedure

Corneal collagen crosslinking is not approved in the United States.
Corneal epithelium is debrided, as is done in PRK.

Riboflavin eye drops (vitamin B2) are applied to the cornea.

The riboflavin film is maintained with reapplication of drops at ~2 minute intervals until the stroma is saturated (20 minutes).

UVA light (365nm) is shined on the eye for 30 minutes (conventional technique).

A bandage lens is placed. Follow-up care is similar to PRK.

Radical riboflavin and reactive oxygen species are thought to interact with corneal proteins (such as tyrosine and tryptophan) to create chemical bonds within or between collagen fibrils: "cross-links"
Collagen Fibril
Collagen Molecule
GAG
Proteoglycan
Core Protein

1 Collagen molecule (Intramolecular)
2 Collagen-Collagen Molecule (Intermolecular)
3 Within Proteoglycan core proteins
4 Proteoglycan – Collagen molecule (Fibril surface)
5 Proteoglycan-Proteoglycan (Inter Proteoglycan)

Research Required to Optimise Crosslinking

Mechanisms
Photochemistry
Biomechanics
Safety
Efficacy

How Can We Modify Cross-linking

UV Power/Time/Energy
Soak Time
Riboflavin Concentration
Trans Epithelial
Topographic Application

Photochemistry

Combination

O* O* O* 10%
RF* RF* RF* 90%
Cross-linking Procedure

- Cross-linking improves the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma

LOCF = Last Observation Carried Forward
Improvement met the definition of success (i.e., a difference between treatment groups of ≥1D in the mean change in $K_{max}$ from baseline) at Months 3, 6, and 12.

The difference between treatment groups statistically significant at month 12 ($p<0.0001$).

"LOCF = Last Observation Carried Forward"
Patient Education

• Primary goal is to stabilize the cornea
  • Visual improvement or topographic flattening is a “bonus”
  • Contact lenses and/or spectacles still required

• Possible complications
  • Risk of reduced BCVA
  • Risks associated with epithelial removal

In Our Clinics

• Early diagnosis and referral
  • Incorporating routine screenings for keratoconus & ectasia

• Post-operative Care
  • Post-operative regimen
  • Expected outcomes

• Contact Lens Refitting
  • Time course of the corneal curvature changes that occur after cross-linking
  • Initial steepening followed by gradual flattening
  • Remember the long term goal of cross-linking is to stabilize the cornea (~12-24 months)

In Our Clinics

• Options for visual rehabilitation remain limited in the United States; early diagnosis and treatment is critical

• Corneal cross-linking is the first procedure we can offer patients to stabilize progression of their keratoconus

• Patients must be educated to have realistic expectations and understand the goal of the procedure: stabilization
Options for visual rehabilitation remain limited in the United States; early diagnosis and treatment is critical.

Corneal cross-linking is the first procedure we can offer patients to stabilize progression of their keratoconus.

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Outside of the US, treatment of keratoconus continues to advance

- Accelerated procedures, modified riboflavin formulations
- Customized, topography guided cross-linking techniques

Combination procedures may offer visual management
- Topography guided PRK + CXL


Corneal cross-linking (CXL) was first introduced in the late 1990s as a treatment for progressive keratoconus.

- Laboratory and clinical studies have demonstrated that CXL stiffens the cornea (alters corneal biomechanics)
- PiXL is the application of CXL using a customized treatment pattern consisting of the zone-specific application of UVA
- The goal of PiXL is to introduce controlled corneal shape change using only patterned UVA CXL, without ablation


Simulation of standard 9mm-diameter CXL produced decreases in corneal curvature resembling clinical outcomes. Simulated topographic flattening was greatest with cone-localized CXL simulations.

The FEA model demonstrates that in order to achieve controlled corneal shape change, modifications to the conventional CXL technique are needed.
**PIXL Requirements**

- Sharply defined edges
  - Eye Tracking
- Complex patterning
  - Digital Micromirror Device (DMD)
- More stiffening than standard CXL technology
  - Pulsed Illumination
  - Higher Energy Doses

*Image Courtesy: Vicente Rodriguez, MD*

The KXL II System is not approved for sale in the United States

**Keratoconus Treatment Example: Pre-operative**

*Image Courtesy: Vicente Rodriguez, MD*

The KXL II System is not approved for sale in the United States
Inferior Flattening + Superior Steepening = Normalization

Keratoconus Treatment Example: Post-Operative

3 Months Pre-OP

Keratoconus Treatment Example: Post-Operative

Greater flattening of K Max relative to conventional cross-linking

Treatment of Keratoconus With KXL II

Normalization of the Cornea: flattening steep zones, steepening flat zones

PiXL for refractive correction

• Specific UVA patterning is applied to the center (myopia), the periphery (hyperopia), or a bowtie shaped region (astigmatism) of the riboflavin-soaked cornea

• Focal stiffening is induced in the cross-linked regions, resulting in “bulging” of the cornea in untreated regions in response to the normal intraocular pressure

Images Courtesy: Professor John Marshall, MBE, PhD
PiXL for Myopia Case Example: Preoperative

- 23 year old Female, Pseudophakia OD
- MR: -1.25-0.25 x 180
- BCVA 20/20
- UCVA 20/200

Case from Dr. Pavel Stodulka

PiXL for Myopia: 9 Month Post-Op

- MR: -0.50 sphere, UCVA: 20/25, BCVA: 20/20

Case from Dr. Pavel Stodulka

Photorefractive Intrastromal Cross-linking

- Theoretical and clinical results demonstrate potential to produce greater "normalization" of corneal shape in patients with keratoconus than in conventional cross-linking.
- Preliminary studies in patients with normal corneas show predictable, persistent changes in corneal curvature and refractive error of clinically significant magnitude.
- PiXL shows potential as the first corneal refractive procedure that works by strengthening the cornea, without requiring relaxation, degradation, or removal of tissue.

LASIK + Corneal Cross-Linking: Lasik Xtra

Key Points

- What do we know:
  - LASIK weakens the cornea
  - Cross-linking stiffens the cornea

- What Do We Need to Know?
  - Can we safely add cross-linking to LASIK?
  - Can we achieve predictable refractive outcomes with Lasik Xtra?
  - Can Lasik Xtra improve corneal stability?

LASIK Weakens the Cornea

Chart showing changes in corneal thickness before and after LASIK procedure.
Refractive Regression Can Occur

LASIK Weakens the Cornea

Resurgence in interest in maintaining corneal strength

Dan Reinstein concludes that by maintaining corneal strength, indications for refractive surgery may be broadened to larger corrections and thinner corneas.
Laboratory studies: demonstrate stiffening as a function of CXL dose

Cross-linking Strengthens the Cornea


Recent advances in laser vision correction—incorporating improved technologies, patient selection criteria, surface ablation strategies, and analyzing changes in higher order aberrations (HOAs) have allowed for better treatments and outcomes.

"Despite the improved outcomes, the limitation includes the inability to measure and render all HOAs with current technology. The inability to predict the surgically induced aberrations, the inability to perfectly position the treatment on the corneal plane, and the inability to perfectly reposition the treatment on the corneal plane.

Other important considerations include biomechanical changes and the wound healing effects that take us in the opposite direction from that desired."

Important needs requiring improvement are the need to prevent ectasia, increase corneal rigidity and stability after LASIK, have large optical zones to preserve the intended HOA correction, and have large optical zones to reduce glare and halos.

"These can be accomplished by macroparticle cross-linking performed at the time of LASIK.

Recent advances in laser vision correction—including improved technology, patient selection, surface ablation, and wavefront-guided custom LASIK—have allowed for better treatments and outcomes.

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Other important considerations include biomechanical changes and the wound healing effects that take us in the opposite direction from that desired."

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"These can be accomplished by collagen crosslinking performed at about the time of LASIK."


Lasik Xtra: Safety

Published studies to date indicate:

- No endothelial cell loss, no increase in adverse events


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Adjunctive Collagen Crosslinking of the Residual Stromal Bed in LASIK: Finite Element Analysis of Impact on Refractive Outcome and Surgically Induced Keratometric Changes

<table>
<thead>
<tr>
<th>LASIK 15MMHG</th>
<th>LASIK + CXL 15MMHG</th>
<th>LASIK 30MMHG</th>
<th>LASIK + CXL 30MMHG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 194 183 263 271</td>
<td>2 206 195 219 276</td>
<td>3 205 194 218 274</td>
<td>4 270 254 347 516</td>
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</tbody>
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P<0.05

RESULT: LASIK with CXL of the RSB employing a 50% increase in anterior RSB stiffness contributed less than 0.25D of hyperopic effect to the postoperative refractive error and significantly reduced corneal displacements after LASIK.

Lasik Xtra: Predictability

In vivo confocal laser microscopy of morphologic changes after simultaneous LASIK and accelerated collagen cross-linking for myopia. One-year results.
In vivo confocal laser microscopy of morphologic changes after simultaneous LASIK and accelerated collagen crosslinking for myopia: One-year results.

Lasik Xtra: Predictability

Spherical Equivalent Refractive Accuracy LASIK vs. LASIK Xtra at 3 Months

Jerry Tan, MD. Submitted Paper
Lasik Xtra: **Predictability**

Spherical Equivalent Refractive Accuracy
LASIK vs. LASIK Xtra at 3 Months

Lasik Xtra: **Stability**

In vivo confocal laser microscopy of morphologic changes after simultaneous LASIK and accelerated collagen crosslinking for myopia: One-year results

Minoru Tomita, MD, PhD, Yuko Yoshida, BA, Yusuke Yamamoto, MD, Mariko Mita, MD, PhD, George Waring IV, MD. J CATARACT REFRACT SURG - VOL 40, JUNE 2014

Lasik Xtra: Stability

LASIK + Corneal Cross-Linking: Lasik Xtra
Key Points

• What do we know:
  • LASIK weakens the cornea
  • Cross-linking stiffens the cornea
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Would you offer Lasik Xtra to your LASIK patients?
**Brillouin Spectroscopy**

for Assessment of Corneal Biomechanics

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**Goal:** Develop a technique to directly map corneal stiffness properties in a clinical setting

**Potential Applications:**
- Measure Effect of Cross Linking
- Measure Effect of Cross Linking
- Early Diagnosis of Ectasia
- Pre-Op Screening of Refractive Patients
- Assessment of other tissues

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**Measuring Corneal Cross-linking**

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**Clinical Measurement of Corneal Biomechanics**

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Brillouin scattering, named after Léon "Marcel" Brillouin, was discovered in 1922.

Brillouin scattering is created by the interaction between photons and acoustic phonons in a material.

Phonons: quantum of the vibration of the crystalline lattice of the material.

The photon may lose energy (Stokes process) or gain energy (anti-Stokes process) from this interaction.

**Brillouin Scattering Spectroscopy**

The change in energy of the photon from the interaction with the crystalline lattice of the material corresponds to a shift in frequency in the Brillouin spectrum.

This shift is related to the elastic modulus ($M'$) of the material where, $\rho = \text{mass density}, \lambda = \text{wavelength}, \Omega = \text{frequency of phonon}, n = \text{refractive index}$.

$$M' = \rho \lambda^2 \Omega^2 / 4n^2$$


Elastic modulus ($M'$) is related to Young's modulus ($E'$) 
\[ M' = E'(1 - \sigma) \frac{1 + \sigma}{1 - 2\sigma} \]

Shown empirically:
\[ \log(M') = a \log(E') + b \]
where $a$ and $b$ are material dependent coefficients.

Brillouin Scattering Measurements
- Single wavelength laser reflected off cornea, focused on different locations and/or depths
- Spacing between stokes and anti-stokes peaks used to calculate the elastic modulus of the measured region

Brillouin Spectroscopy: Attenuation of Rayleigh Peak
- The Rayleigh peak is significantly brighter than the stokes and anti-Stokes peaks, and 'washes out' the Brillouin signal
- The rubidium cell has a characteristic absorption peak around 780nm. The laser in the system used to illuminate the eye is tuned to this peak and therefore is attenuated.
- By changing the temperature of the cell, the amount of attenuation is controlled to help isolate the Brillouin peaks and make them more easily detected.
Scarcelli et al measured differences in treated and untreated porcine corneas that were in agreement with Avedro laboratory findings for the same doses. They also demonstrated that Brillouin Spectroscopy could show effects as a function of depth and was sensitive enough to detect differences between crosslinking protocols.

Potential Applications:
- Pre-Op Screening of Refractive Patients
- Early Diagnosis of Ectasia
- Measure Effect of Crosslinking

Future Applications:
- More Accurate IOP Measurement
- Assessment of Other Tissues
- Lens, Lamina, Retina...?