Overview

Disclosures

US FDA Approval for Avedro
Epi On vs. Epi Off
Accelerated Cross Linking
Contact Lens Assisted CXL (CACKL)
Iontophoresis

Disclosures

- Member, AOA Evidence Based Optometry Committee Member
- Member, US Centers for Medicare & Medicaid Services Ophthalmologic Disease Management Clinical Subcommittee
- Subject Matter Expert, US Department of Defense/Veterans Affairs Vision Center of Excellence
- Founder, PinkEye Health and Oculsive

Disclosures

- All information in this presentation is my opinion only based on peer-reviewed information and was gained through the public domain.
- I have no financial interests regarding anything discussed in this presentation.
- All information presented is the opinion of Andrew Morgenstern, OD FAAO and NOT the opinion of the US Government, Department of Defense, Department of Veterans Affairs, Army, Navy, Air Force, Vision Center of Excellence or any other US Government organization, US Government Contractor or Booz Allen Hamilton.
Disclosures

- Alcon
- Allergan
- American Optometric Association
- Boston University Deans Advisory Board Member
- Bruder EyeCare
- Bruns Eye Communications
- CXL USA
- Glaukos
- International Keratoconus Academy
- Oasis
- Oculus
- Science Based Health
- Sun Ophthalmics
- TLC Laser Eye Centers

Why is Corneal Cross Linking So Important?

“Progression Rate of 88%”

This is Why We Need To Identify Ectatic Disease Early

Belin Ambrosio Display

Results: Fifty-two of the 54 eyes enrolled in this study showed progression, corresponding to a progression rate of 96%. Forty-six eyes were treated by CXL. Measured keratometry, CTDI, and IF showed significant changes over the follow-up period. However, significant improvement observed after 24 months after CXL test significance at 36 months.
Flaws of a Placido Disc Image

What Is a Topography?

Rotational Camera

United States
Food and Drug Administration (FDA)
Corneal Cross Linking Approval

What is Approved by the FDA?

Corneal Cross Linking
Food and Drug Administration (FDA) Approval
Summary

- Corneal cross-linking with the KXL system, Photrexa and Photrexa Viscous is now FDA approved for treatment of progressive keratoconus and corneal ectasia following refractive surgery.
- Patients with progressive keratoconus or corneal ectasia following refractive surgery should be educated regarding risks and benefits of CXL.
- Optometrists will play a critical role in ensuring early diagnosis, monitoring, appropriate referral and co-management of these patients.

Pre-Operative Patient Education

Set the expectation that cross-linking is not refractive surgery. Contact lenses and/or spectacles still required. Regular post-operative examinations needed to monitor keratoconus.

Indications

- PHOTREXA® VISCOS and PHOTREXA® are indicated for use in corneal collagen cross-linking in combination with the KXL System for the treatment of:
  - Progressive keratoconus
  - Corneal ectasia following refractive surgery.

Who Has Observed a CXL Procedure?
Dosage and Administration

- Using topical anesthetic, debride the epithelium to a diameter of approximately 9 mm using standard aseptic technique.
- Post epithelial debridement, instill 1 drop of Photrexa Viscous topically on the eye every 2 minutes for 30 minutes.
- At the end of the 30 minute soaking period, examine the eye under the slit lamp for the presence of a yellow flare in the anterior chamber.

Dosage and Administration

- If the yellow flare is not detected, instill 1 drop of Photrexa Viscous every 2 minutes for 30 minutes until the corneal thickness increases to at least 500 microns.
- Once the yellow flare is observed, perform ultrasound pachymetry. If corneal thickness is less than 400 microns, instill 2 drops of PHOTREXA every 5 to 10 seconds until the corneal thickness increases to at least 400 microns.
- Irradiation should not be performed unless this 400 micron threshold is met and the yellow flare is seen.

- Irradiate the eye for 30 continuous minutes at 3mW/cm² at a wavelength of 365 nm, centered over the cornea, using the KXL System as per the instructions in the KXL manual.
- During irradiation, continue topical instillation of Photrexa Viscous onto the eye every 2 minutes for the 30 minute irradiation period.

PHOTREXA VISCOUS and PHOTREXA are for use with the KXL system only.

Appointment Slots Were 30 Minutes Apart

NDA Dosage Forms and Strengths

PHOTREXA VISCOUS
- 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical administration.

PHOTREXA
- 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution for topical administration.

Contraindications

None Reported in NDA
Adverse Reactions

- In progressive keratoconus patients, the most common ocular adverse reactions in any CXL-treated eye were corneal opacity (haze), corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision.
- In corneal ectasia patients, the most common ocular adverse reactions were corneal opacity (haze), corneal epithelium defect, dry eye, eye pain, punctate keratitis, photophobia, reduced visual acuity, and blurred vision.

Warnings & Precautions

- Ulcerative keratitis can occur. Monitor for resolution of epithelial defects.

Clinical Pharmacology & Mechanism of Action

- Riboflavin 5’-phosphate sodium (Vitamin B2) is the precursor of two coenzymes, flavinadenine dinucleotide and flavin mononucleotide, which catalyze oxidation/reduction reactions involved in a number of metabolic pathways.
- Under the conditions used for corneal collagen cross-linking, riboflavin 5’-phosphate functions as a photo-enhancer and generates singlet oxygen which is responsible for the cross-linking.

Carcinogenesis, Mutagenesis and Impairment of Fertility

- Animal studies have not been conducted to determine the carcinogenic potential of photo-excited riboflavin. Photo-excited riboflavin has been shown to be genotoxic in the Ames Salmonella reverse mutation assay and in the SOS/umu test system.
- Animal studies to determine the effects of the PHOTREXA/KXL corneal collagen cross-linking procedure on fertility were not conducted.

Limitations of Usage

- The safety and effectiveness of CXL has not been established in pregnant women, women who are breastfeeding, patients who are less than 14 years of age and patients 65 years of age or older. Photrexa Viscous and Photrexa should be used with the KXL System only.

United States Phase III Studies

- 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 phosphate solution/UVA irradiation for performing corneal collagen cross-linking.
US Phase III Studies

- Study eye randomized into one of two groups
  - CXL treatment
  - Sham Control
- At Month 3 or later:
  - Non-randomized fellow eyes could receive CXL treatment
  - Control eye could receive CXL treatment
- The primary efficacy parameter evaluated over time was corneal curvature, as measured by corneal keratometry
- Study success was defined as a difference of at least 1 diopter in the mean change in Kmax following changes over a period of 24 months or less:
  - A myopic shift (decrease in the spherical equivalent) of ≥ 0.50 D on retinoscopic manifest refraction
  - A decrease ≥ 0.1 mm in the BOZR (Back Optical Zone Radius) in rigid contact lens wearers where other information is not available.

Progressive Keratoconus: Clinical Study Definition

Progression of keratoconus was defined as one or more of the following changes over a period of 24 months or less:

a. An increase of ≥ 1.00 D in the steepest keratometry value (or simK)

b. An increase of ≥ 1.00 D in regular astigmatism evaluated by subjective manifest refraction

c. A decrease ≥ 0.1 mm in the BOZR (Back Optical Zone Radius) in rigid contact lens wearers when other information is not available.

Progressive Keratoconus Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Pooled Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXL Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Received Randomized Treatment</td>
<td>%</td>
<td>100</td>
</tr>
<tr>
<td>Completed</td>
<td>n (%)</td>
<td>93 (93.1)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Mean</td>
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<tr>
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<td>Female: n (%)</td>
<td>27 (26.5)</td>
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<td>Male: n (%)</td>
<td>75 (73.5)</td>
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<tr>
<td>Kmax</td>
<td>Mean (SD)</td>
<td>60.9 D (+/- 9.14)</td>
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Pentacam

Key Inclusion and Exclusion Criteria

- Eyes classified as either normal, astigmatic normal, or keratoconus consistent with contact endothelial
- For progressive keratoconus, a history of previous corneal surgery or the insertion of lenses in the eye(s) to be treated
- Increased probability of the screening mean Kmax value ≥ 47.00 D, as determined by the lettering keratometric reflex, or < 300 microns when the riboflavin had been used is to be used or < 100 microns when the riboflavin had been used, as to be used
- A history of chemical injury or delayed epithelial healing in the eye(s) to be treated
- Exclusion of participants with keratoconus on any other condition that will have高空 or be used during the CXL treatment or other diagnostic tests

Clinical Studies (cont)

- Approximately 56% and 89% of the sham study eyes in patients with progressive keratoconus received CXL treatment by Month 3 and Month 6, respectively. The average age of keratoconus patients was 43 years and the average baseline Kmax value was 64 dioptries. For corneal ectasia patients in Study 1 and Study 3, approximately 90% of the sham study eyes received CXL treatment by Month 3 and Month 6, respectively. The average age of corneal ectasia patients was 33 years and the average baseline Kmax was 55 dioptries. A majority (93%) of the corneal ectasia patients had LASIK only, 3% patients had photorefractive keratectomy (PRK) only, and 8% patients had both LASIK and PRK.

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Post-Operative Patient Counseling

- Patients should be advised not to rub their eyes for the first five days after their procedure.

- Patients may be sensitive to light and have a foreign body sensation. Patients should be advised that there may be discomfort in the treated eye and that sunglasses may help with light sensitivity.

- If patients experience severe pain in the eye or any sudden decrease in their vision, they should be advised to contact their physician immediately.

- If the bandage contact lens that was placed on the patient’s eye on the day of treatment falls out or becomes dislodged, the patient should be advised not to replace it and to contact their physician immediately.

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Epi On Vs. Epi Off

The War is On!

The Opposition to the “Dresden Protocol”
The CXLUSA Group and Roy Rubinfeld, MD

“Epi-On is THE Way to Go”
“Is this Even a Question?”

Roy Rubinfeld, MD, MA
Clinical Associate Professor, MedStar Georgetown University/Washington Hospital Center, Washington, D.C.
Medical Director, Re-Vision, Washington, D.C.
Financial Disclosures

- CurveRight, LLC: Equity Owner
- CXL Ophthalmics, LLC: Equity Owner
- CXLUSA, LLC: Equity Owner

This lecture discusses non-FDA approved techniques and technology which are not yet commercially available.

Traditional vs. Laparoscopic Cholecystectomy

Why Was the Epithelium Removed in Dresden?

Extracap vs. Microincision Phaco

Epi-off Complications

Advantages of Effective Epi-On

1. Major risk/benefit shift so weekly watch-prior VA
2. Treat thinner; thinner, younger corneas,
3. Return to preop VA; work at 100% 1st or 2nd 5-day wk
4. 1 day of discomfort
5. Decreased K/VA as indication for PK (dermatomal), D. Aita (Arts, 2012)
CXL Photochemistry

UVA Light
Energy Source

Riboflavin
Energy Transfer

Oxygen
Rate Limiting Reagent

Why Hasn’t TE CXL Worked?

Epithelium can block:
• Ribo stromal loading
• UVA
• Oxygen

Until Now

Ex Vivo Rabbit Cornea SL Photos

Paracel™-VibeX Xtra™
At 20 min

CXLUSA/CXLO Formulation
At 10 Min

Riboflavin Concentration: Chromatography

15 Minute Human Study: Excellent Stromal Loading with No Visible Epithelial Loading
Extensive Human Clinical Data

- Binkhorst Lecture, ASCRS, New Orleans 2016, International CXL Congress, Zurich 2016, Doyle Stulting, MD, PhD
- 592 treated eyes; 269 male, 99 female; 512 with post LASIK ectasia; 80 with post-LASIK ectasia
- 5 measures improved: UCVA, CDVA, Kmax, HOA, coma
- No eyes (0/592) progressed >1 D Kmax and >1 line lost BSCVA. (Dresden Epi-Off disease progression postop is reported at 2.3-7.6%, Seiler, et.al.)
- 88% (43) of 49 eyes of patients ≤ 18 yo, should have progressed in 12 months (Charis et al., JRS 2012;28:753)

Have we gone from “No Transepithelial CXL is Effective” to “All TE CXL is Effective”? ABSOLUTELY NOT

No other TE CXL System Has Been Shown to Be Effective in Large, Long Term Trials

Accelerated Cross-Linking

- Original CXL studies at the Dresden Technical University in the late 90s were conducted with 3mW/cm² irradiance, requiring UV treatment time of 30 minutes.
- The Bunson Roscoe Law of Reciprocity states that the photochemical biological effect of ultraviolet is proportional to the total energy dose delivered, regardless of the applied irradiance and time.
- The energy delivered by a UV source is the product of the irradiance of the light source and the delivery time:
  \[ \text{Irradiance (mW/cm}^2\text{)} \times \text{Time (seconds)} = \text{Dose (J/cm}^2\text{)} \]

Accelerated CXL Clinical Outcomes

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<tr>
<th>Study</th>
<th>Methodology</th>
<th>Results</th>
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<tr>
<td>Hafezi: JRS 2013</td>
<td>6 months outcomes: 18 mW/cm² for 5 minutes (5.4 J/cm²) (CXL-365 Vario)</td>
<td>No adverse events, no delay in epithelial healing, no endothelial cell loss.</td>
</tr>
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Epi-On vs. Epi-Off

For the appropriate and qualified patient, any cross-linking is better than no cross-linking. - Morgenstern

Accelerated Cross-Linking

- For the appropriate and qualified patient, any cross-linking is better than no cross-linking. - Morgenstern

Accelerated CXL Clinical Outcomes

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<td>Kanellopoulos: CO 2012</td>
<td>7mW/cm² irradiation for 15 minutes (6.3 J/cm²), 3mW/cm² irradiation for 30 minutes in the contralateral eye (5.4 J/cm²).</td>
<td>Delayed epithelial healing in 4 aCXL and 5 cCXL Eyes, Complete Closure by 9 days.</td>
</tr>
<tr>
<td>Mita: JCRS 2014</td>
<td>30mW/cm² irradiation for 3 minutes for a dose of 5.4 J/cm²</td>
<td>No endothelial cell loss.</td>
</tr>
</tbody>
</table>
| Tomita: JCRS 2014   | 30mW/cm² irradiation for 3 minutes (KXL, Avedro) vs 3mW/cm² for 30 minutes (CCL-365 Vario) | No differences between groups in UDVA or CDVA. Statistically significant improvement UDVA and decrease in Kmax; significant flattening of average keratometry at 3, 6 and 12 months was observed in both groups. Trend towards decreased Kmax at 1 year, significant in cCXL.
Accelerated CXL - Morphology

- 21 eyes treated with conventional or accelerated CXL
- 9mW/cm² for 10 minutes vs 3mW/cm² for 30 minutes (CCL-365, Peschke Meditrade).
- A corneal stromal demarcation line was identified in both groups, observed at a statistically significant greater depth in eyes treated with conventional CXL (350.75±49.34 µm) vs accelerated CXL (288.46±42.37 µm).

Tomita: Journal of Cataract and Refract Surgery 2014
- 30 eyes treated with aCXL and 18 eyes treated with cCXL
- Mean demarcation line depth 294.38±60.57 µm in the accelerated group and 380.78±54.99 µm in the conventional group, though this difference was not statistically significant.

Touboul: Journal of Refractive Surgery 2012
- Complete obliteration of keratocytes in the anterior stroma 1 month after conventional (3mW/cm²) and Accelerated (30mW/cm²) CXL. Keratocyte repopulation was similar in both groups.
- The demarcation area was more pronounced and more anteriorly located in patients treated with accelerated vs conventional CXL.

Pediatric Accelerated Epi-Off CXL
Cornea 12/2017

- Accelerated Epi-On Versus Standard Epi-Off Corneal Collagen Cross-Linking for Prognostic Keratoconus in Pediatric Patients
- Mean age: 16.4 years, 54.5 years, 78.8 years, 54.5 years
- Mean demarcation depth 294.38±60.57 µm in the accelerated group and 380.78±54.99 µm in the conventional group, though this difference was not statistically significant.

Contact Lens Assisted Corneal Cross Linking (CACXL)

- Epi OFF Treatment
- For Corneas less than 400 microns after debridement

CONCLUSIONS: CACXL technique was effective and safe in performing cross-linking in corneas less than 400 µm after epithelial ablation and appeared effective based on stromal demarcation line depth.

Iontophoresis
Iontophoresis

Iontophoretic corneal collagen crosslinking (I-CXL) is a new, promising technique that uses low-intensity electric current to facilitate the penetration of riboflavin, a low molecular weight substance electronegatively charged, through the intact corneal epithelium.

Deeper penetration of riboflavin into the corneal stroma than the transepithelial CXL, producing histological changes and resulting in corneal stiffening comparable with standard CXL.

Clinical studies have demonstrated the efficacy and safety of iontophoretic crosslinking in both adults and the pediatric population, in halting the disease progression in most cases, with a rapid vision recovery and virtually with no side effects.


Pre Cross Linking Concerns

David DiMarco
January 23 at 10:16am

Sending a patient for crosslinking post laski ectasia... getting by with 20/70 corneal gas but lots of bearing... I am going to set patient up for cross linking... should I fit with scleral now or wait?

Virgin Cornea Required