Corneal Crosslinking: Diagnosis, Care and Treatment Options for the Keratoconus Patient

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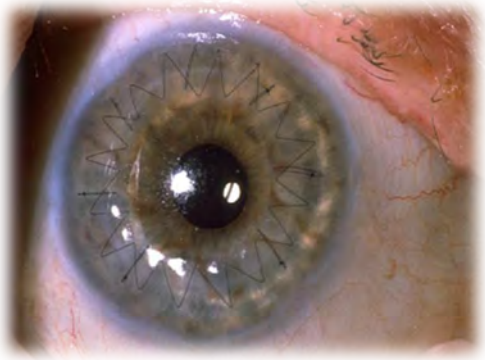
Corneal Crosslinking: Diagnosis, Care and Treatment Options for the Keratoconus Patient

December 2, 2021

I HAVE NO FINANCIAL DISCLOSURES RELATED TO ANY TOPICS IN THIS LECTURE

Overview of Progressive Keratoconus



- Keratoconus is a bilateral, progressive corneal ectasia resulting in irregular astigmatism and loss of visual function, with onset in teenage years[1]
- Affects 1 in 2000 people in the US[2]
- As of 2016, keratoconus was the most common indication for penetrating keratoplasty in the United States. [4]
- Eye Bank Association of America noted ~6,195 transplants/year in patients with keratoconus.[4]
- Predicted 73% of grafts fail within 20 years; 98% at 30 years[3]
  - Potential for multiple transplants

Signs & Symptoms of Keratoconus

Look out for warning signs in medical history

- History of eye rubbing
- Family & genetic predispositions[1]

Look out for visual complaints

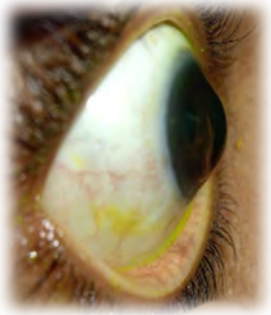
- Blurred vision
- Distortion of images

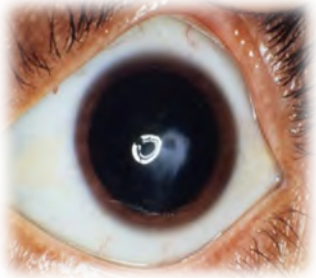
Look out for refractive anomalies

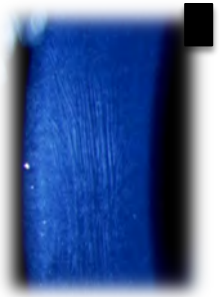
- Distortion of mires on keratometry
- Error messages on autorefractors
- Unsatisfactory attempts at vision correction & progressive loss of UCVA & BCVA
- Increasing astigmatism

Slit-lamp biomicroscopy

- Vogt's Striae
- Fleisher's Ring
- Munson's Sign
- Scarring







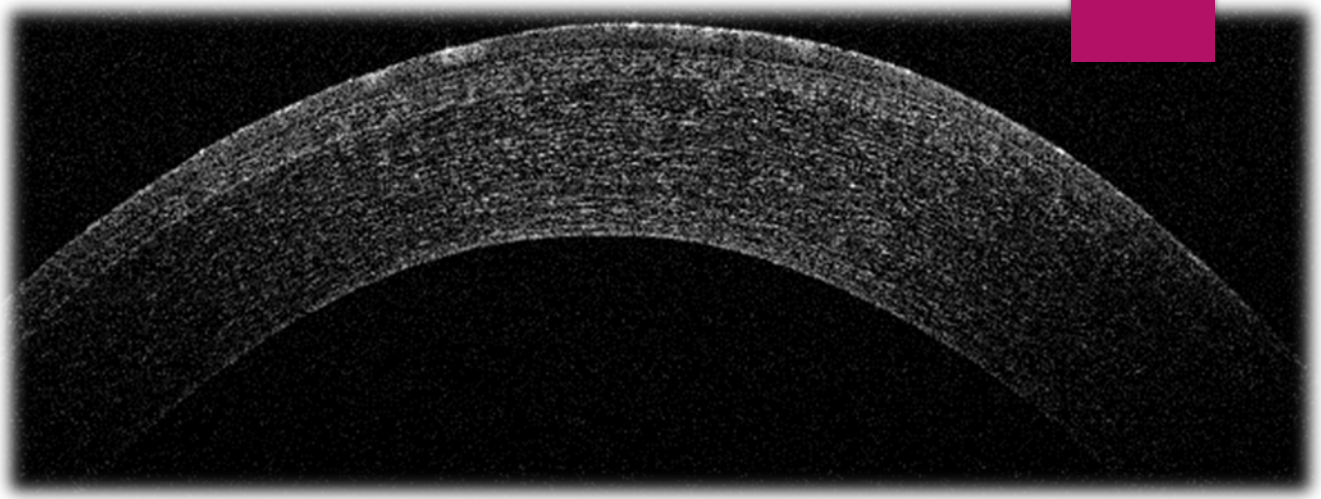
Patient Selection and Diagnosis

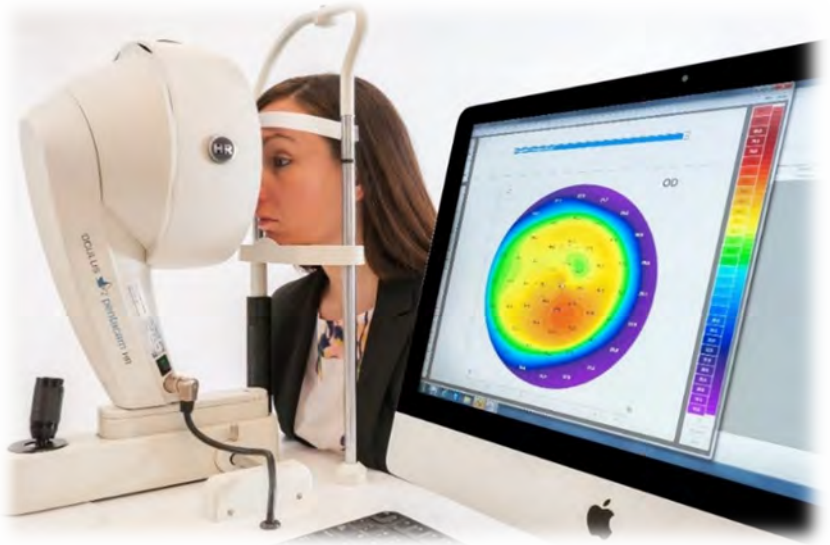
Diagnosis and Monitoring of Progression

- Advanced diagnostic equipment
  - Placido Topographer
  - Scheimpflug Tomographer
    - Analyze front and back surface of cornea
  - Anterior Segment OCT
    - Detailed cross-section of cornea

Referring Patients

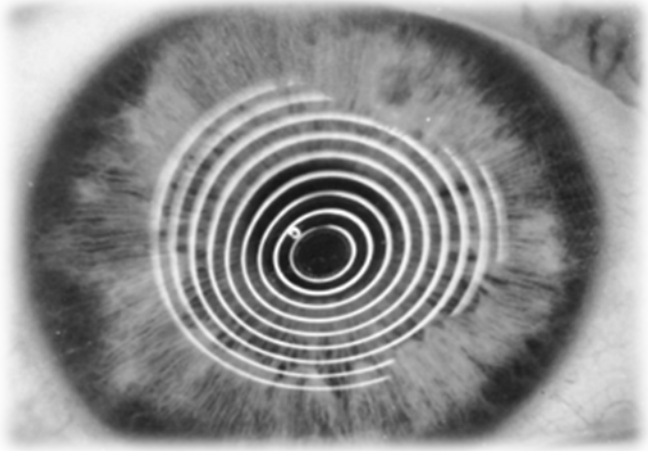
- Patients suspected with signs of KC should be referred for further evaluation if necessary equipment is not available
- Patients will require to be monitored with post-op care and contact lens fitting even after CXL





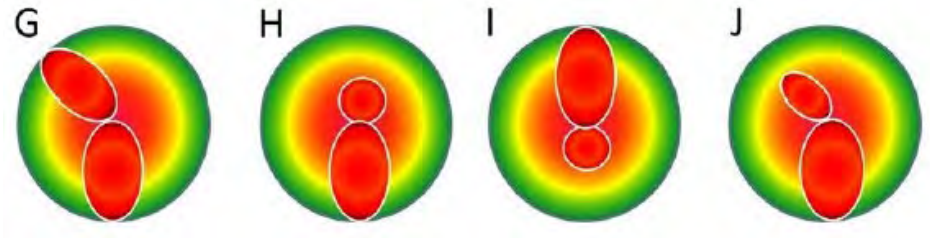
Early Diagnosis

Irregular Placido (egg-shaped) Topography



Early signs of keratoconus may include:

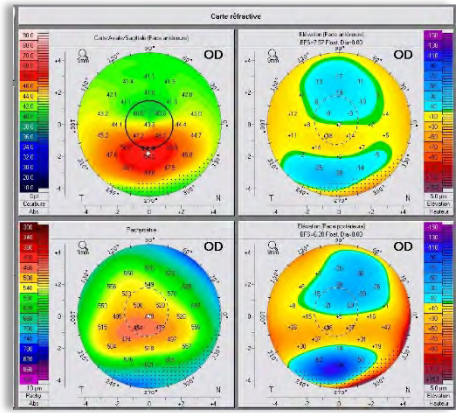
- Skewed radial axis of astigmatism
- Asymmetric or truncated bow-tie



- As keratoconus progresses, it becomes more challenging to manage
- Keratoconus can be easily overlooked in patients who are currently functioning well in spectacle lenses
- Important to diagnose and educate patients before visual function is lost

Diagnostic Imaging

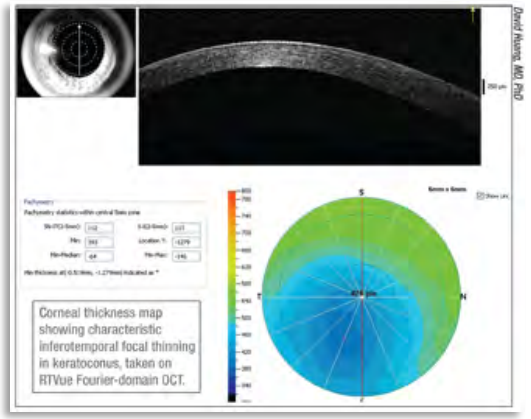
Irregular Topography/Tomography



Additional signs of keratoconus may include:

- Astigmatism variance between eyes
- Stromal and epithelial thickness changes
- Posterior elevation changes

Focal thinning on OCTs[1]



- Wavefront aberrations
- Topographic changes
  - Inferior steepening
  - Irregularity indices

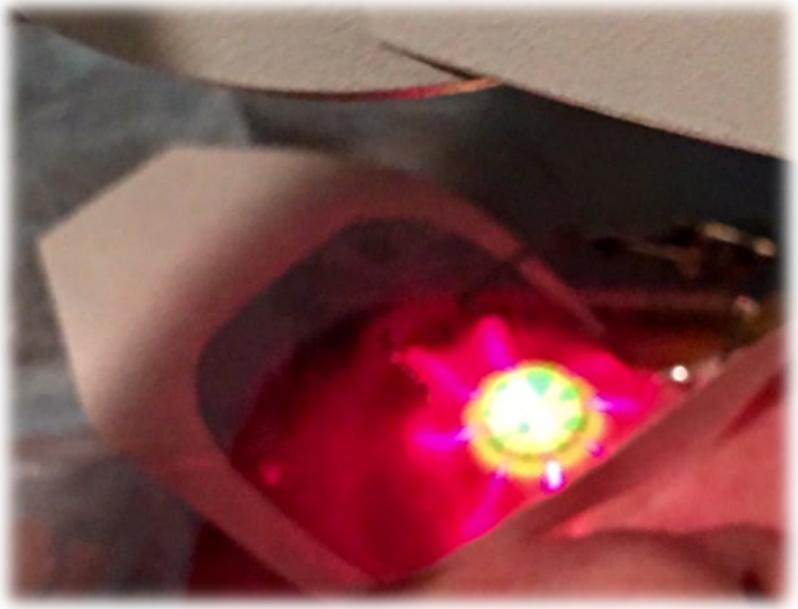
Treatment Options: Corneal Crosslinking

CORNEAL CROSSLINKING OVERVIEW

FDA-APPROVED PRODUCTS

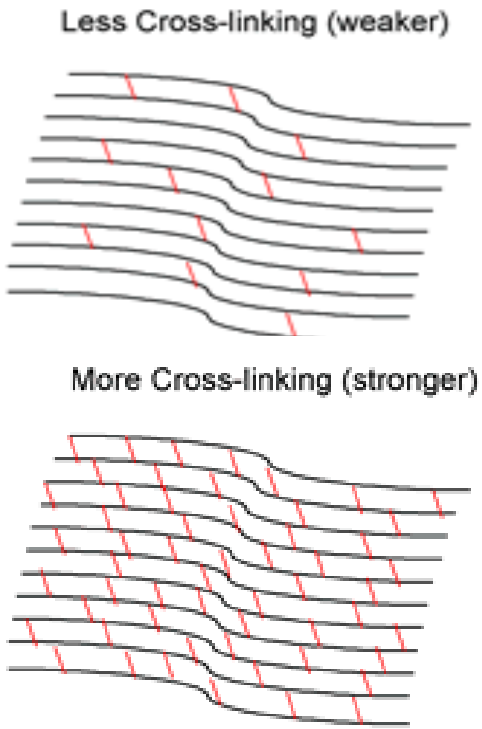
TREATMENT PROCEDURE

SAFETY INFORMATION



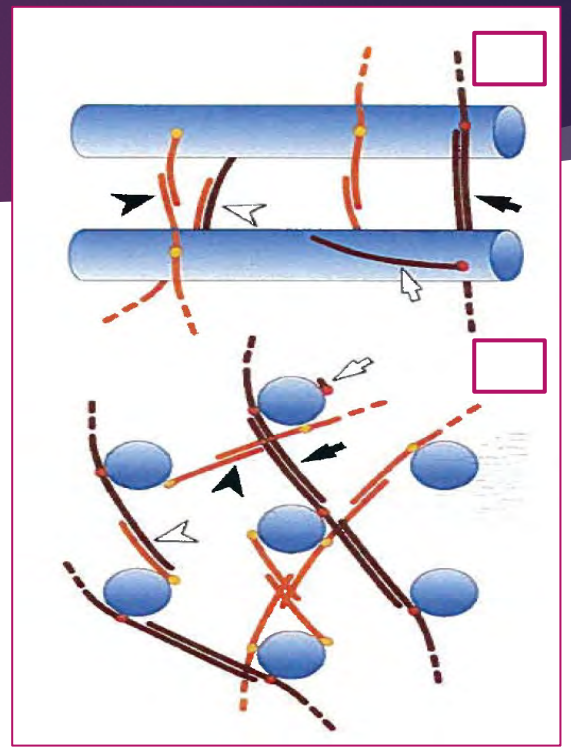
Corneal Cross-linking: Overview

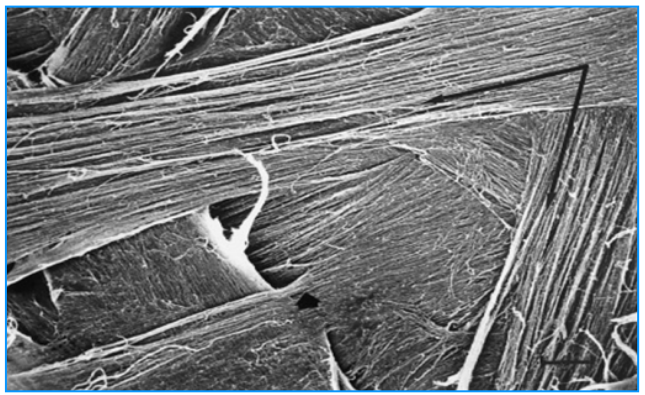
- **Corneal cross-linking is the only treatment that is FDA Approved to stop the progression of Keratoconus and corneal ectasia**
- During the procedure, the affected eye is saturated with riboflavin (vitamin B2) and exposed to UV light to strengthen the cornea through the creation of new collagen bonds.
- Cross-linking[2]:
  - Creates new corneal collagen cross-links
  - Results in a shortening and thickening of the collagen fibrils
  - Leads to the stiffening of the cornea
- Created by Dr. Theo Seiler in 1997; Dresden Protocol



Where do cross-links occur?

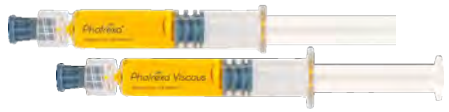
- Collagen fibrils within lamellae are regulated by an interconnecting network of proteoglycans.[1]
- Cross-linking with UVA/riboflavin has no effect on any collagen structural parameter measured by x-ray scattering except uniformity of nearest neighbor interfibrillar spacing. [2]
- Therefore, it is believed that cross-links are formed predominantly at fibril surfaces and within the protein network surrounding the collagen.[2]





1. Meek, K.M. & Boote, C., 2009. The use of X-ray scattering techniques to quantify the orientation and distribution of collagen in the corneal stroma. *Progress in Retinal and Eye Research*, 28(5), p.369-392
2. Meek, K.M. & Hayes, S., 2013. Corneal cross-linking - a review. *Ophthalmic and Physiological Optics*, 33(2), p.78-93.
3. Meek, K.M. et al., 2005. Changes in collagen orientation and distribution in keratoconus corneas. *Investigative Ophthalmology and Visual Science*, 46(6), p.1948-1956.
4. Lewis, P.N. et al., 2010. Structural Interactions between Collagen and Proteoglycans Are Elucidated by Three-Dimensional Electron Tomography of Bovine Cornea. *Structure*, 18(2), p.239-245.

FDA-Approved Products



In April 2016, the FDA approved Photrexa Viscous, Photrexa and the KXL System as the **First and Only** Therapeutic Treatment for Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery

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

Two available protocols for CXL

1. Epithelium-OFF (Epi-OFF)

- In this method, about 8 mm of the central corneal epithelium is removed under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma.

2. Epithelium-ON (Epi-ON)

- Epithelium-on CXL (also known as “epi-on” or transepithelial): In this method, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

Currently, the only CXL treatment approved by the FDA is the epithelium-off method. There are no FDA-approved CXL treatments using the epithelium-on method. CXL is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery.

Access to Cross-Linking in the U.S.

FDA APPROVED & ON-LABEL

Use of Photrexa® Viscous & Photrexa® with the KXL® system for the treatment of progressive keratoconus or corneal ectasia following refractive surgery

(On-label use of a legally marketed drug)

OFF-LABEL

Use of Photrexa Viscous & Photrexa with the KXL system for any indication other than progressive keratoconus or corneal ectasia following refractive surgery

(Off-label use of a legally marketed drug)

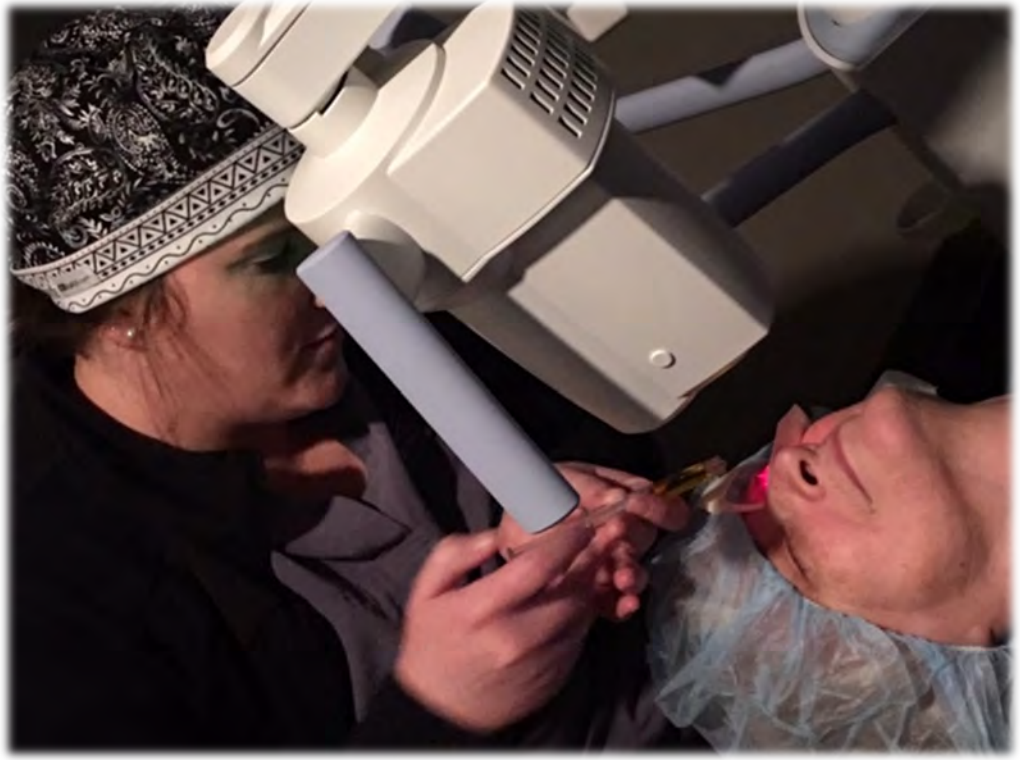
UNAPPROVED

Use of any other drug, device, or procedural protocol (i.e., epi-on) for cross-linking

(Except as part of an investigational new drug (IND) study)

DOSAGE AND ADMINISTRATION
Epi-OFF 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/cm^2
  - Continue Photrexa Viscous every 2 min



Important Safety Information

INDICATIONS

- Photrexa® Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) and Photrexa® (riboflavin 5'-phosphate ophthalmic solution) are indicated for use with the KXL System in corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.

LIMITATIONS OF USE

- 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.

WARNINGS AND PRECAUTIONS

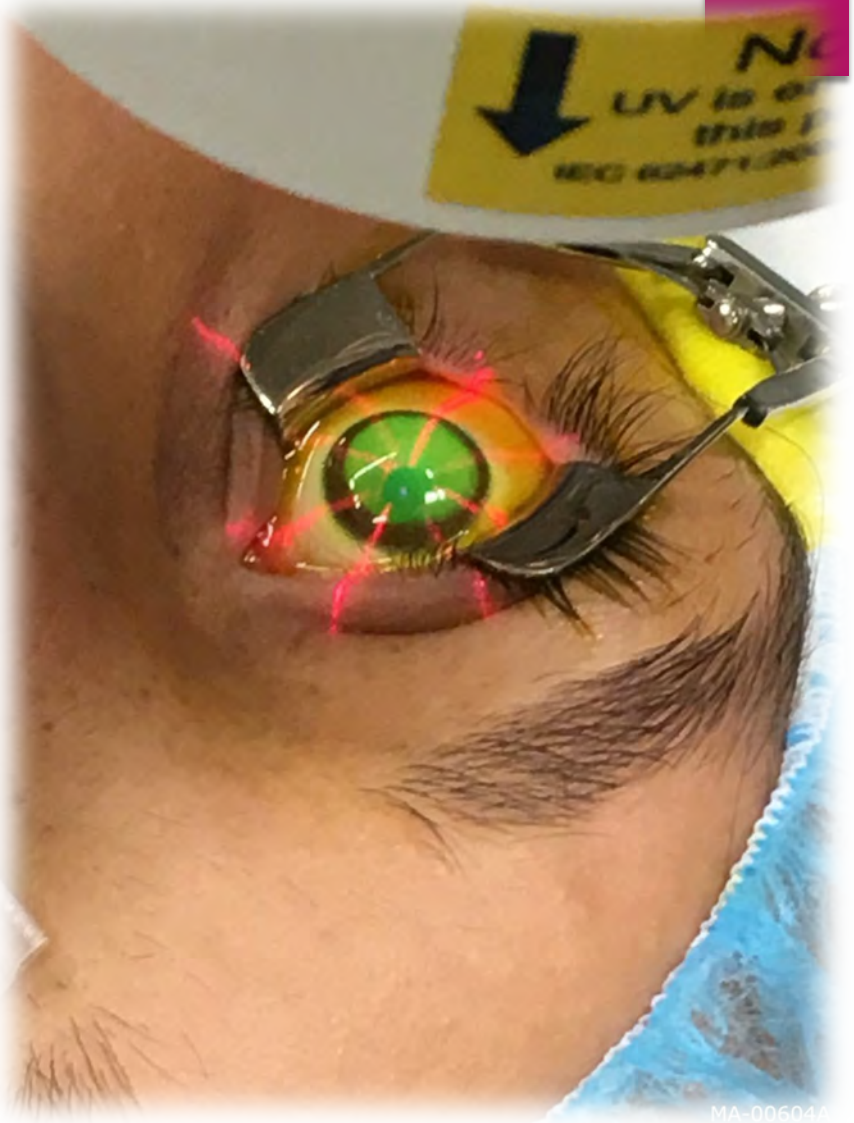
- Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects.

ADVERSE REACTIONS

- In progressive keratoconus patients, the most common ocular adverse reactions in any CXL treated eye were corneal opacity (haze), punctate keratitis, corneal striae, 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, corneal striae, dry eye, eye pain, punctate keratitis, photophobia, reduced visual acuity, and blurred vision.
- These are not all of the side effects of Photrexa® Viscous, Photrexa® and the CXL treatment. For more information, see Prescribing Information.

You should report an adverse event to Avedro by calling 1-844-528-3376, Option 1 or you should contact the U.S. Food and Drug Administration (FDA) directly at 1-800-FDA-1088.

SETTING PATIENT EXPECTATIONS



When should patients consider CXL?

Many doctors now believe that since CXL stops the progression of KC, it is best to treat patients as early as possible so that no further vision will be lost.

Pros:

- Can stabilize the cornea and allow a patient to maintain good VA
- Can lead to positive corneal remodeling that may help avoid or delay a corneal transplant
- If a transplant is needed in the future, early CXL may highly increase the chance of a successful surgery

Cons:

- FDA Approval only for *Progressive* KC/ectasia
- If a patient does not have documentation of progression, they will likely not be able to obtain insurance coverage for CXL

Patient Education
Defining treatment goals

Establish that cross-linking is **not refractive surgery**

- Treatment is not intended to eliminate or reduce dependence on refractive correction
- Contact lenses and/or spectacles still required
- Regular eye exams still needed to monitor disease state

Define the objective of the procedure

- Aim is to stiffen cornea to limit progression of the disease

Educate patients regarding the post-operative healing process.

- On average, **steepening of K_{max} 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

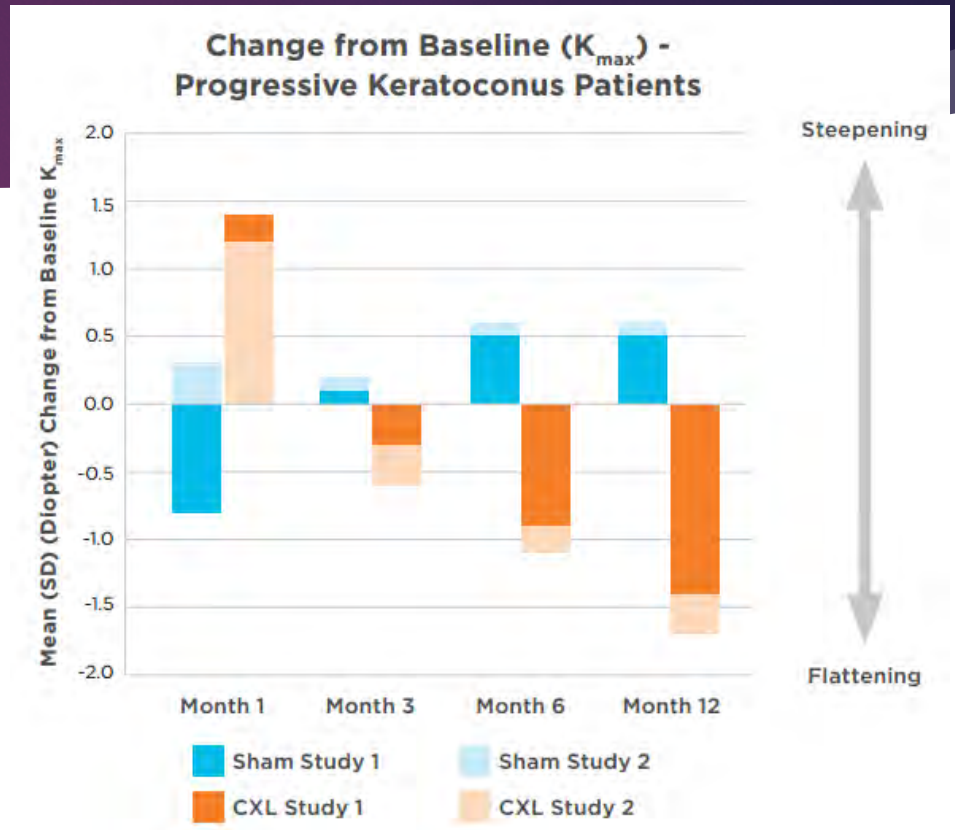
Helping patients understand why early treatment is important:

It's like calling the fire department as soon as you smell smoke, not after your house is halfway burned down. Firefighters are able to prevent more damage if they fight the fire sooner.

Efficacy Analysis: Progressive Keratoconus

- In clinical studies, the **CXL-treated eyes showed increasing improvement in K_{max}** from month 3-12,while in untreated, **Sham eyes, K_{max} demonstrated steepening**.

- **Progressive keratoconus patients had an average K_{max} reduction of 1.4 diopters in Study 1 and 1.7 diopters in Study 2 at Month 12** 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.



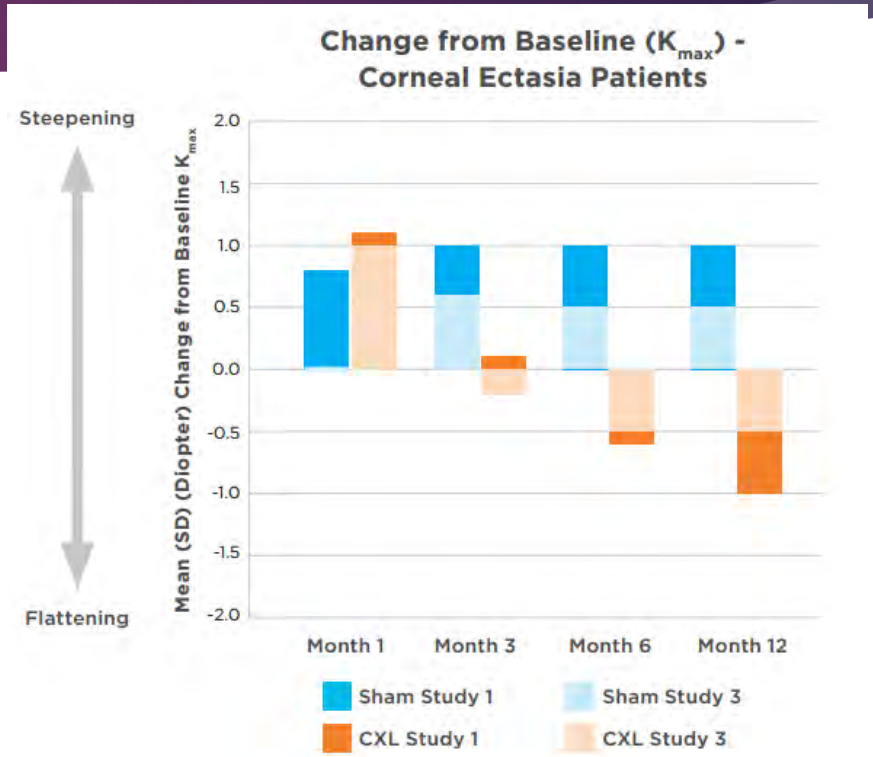
Post-baseline missing data were imputed using last available K_{max} value. For the sham study eyes that received CXL treatment after baseline, the last K_{max} measurement recoded prior to receiving CXL treatment was used in the analysis for later time points.

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 K_{max}** from month 3-12,while in untreated, **Sham eyes, K_{max} 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 3 while the sham eyes had an average increase of 1.0 diopter in Study 1 and 0.5 diopter in Study 3.



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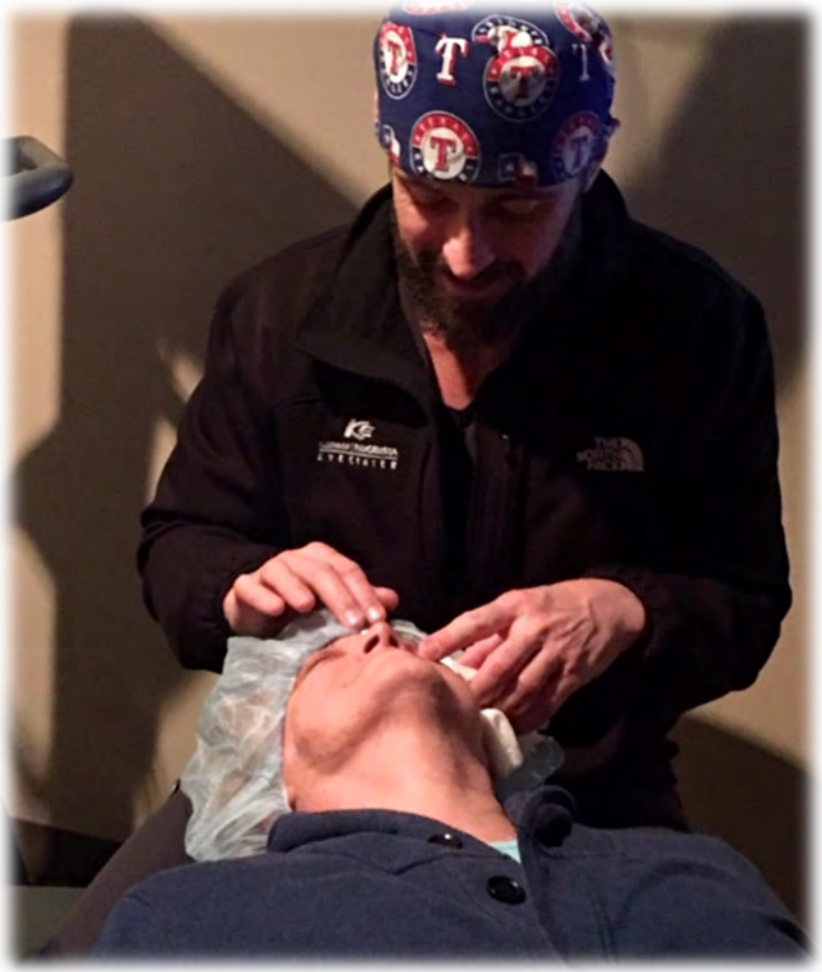
Post-Op Management: Drops protocol

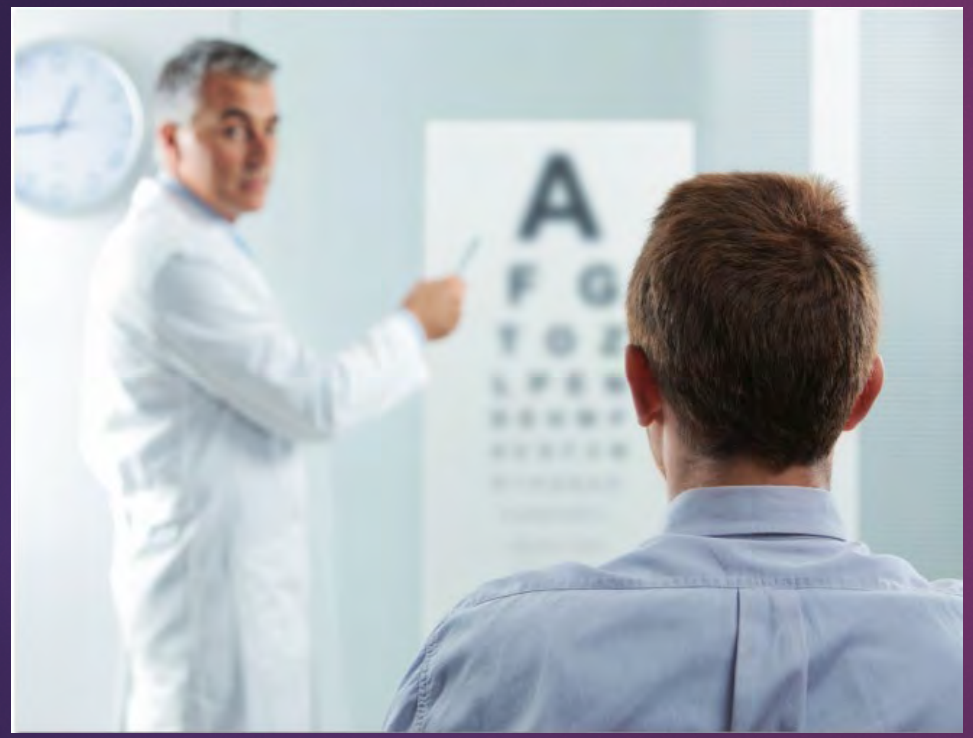
Pred-Gati-Brom ophthalmic solution	Prednisolone 1%
Week 1: One drop 4 times a day	Week 3: One drop 2 times a day
Week 2: One drop 3 times a day	Week 4: One drop 1 time a day

Corneal Cross-linking Post-Procedure Instructions

- 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



- 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.

Post Procedure Visits

Day 1	• Topical antibiotic, steroid/NSAID • Frequent lubricants • No eye rubbing Remove BCL once epithelium heals
Week 1 (3-7 day)	• Topical antibiotic, steroid/NSAID • Frequent lubricants • No eye rubbing • Remove BCL once epithelium heals
Month 1	• Topography imaging • Refraction • Vision assessment
Month 3, 6, 12	• Continues evaluation utilizing topography • Vision assessment • Refraction Contact lens evaluation

Treatment Emergent Adverse Events (TEAEs)

- The most common ocular adverse reactions reported in the CXL-treated eye were:

Progressive Keratoconus

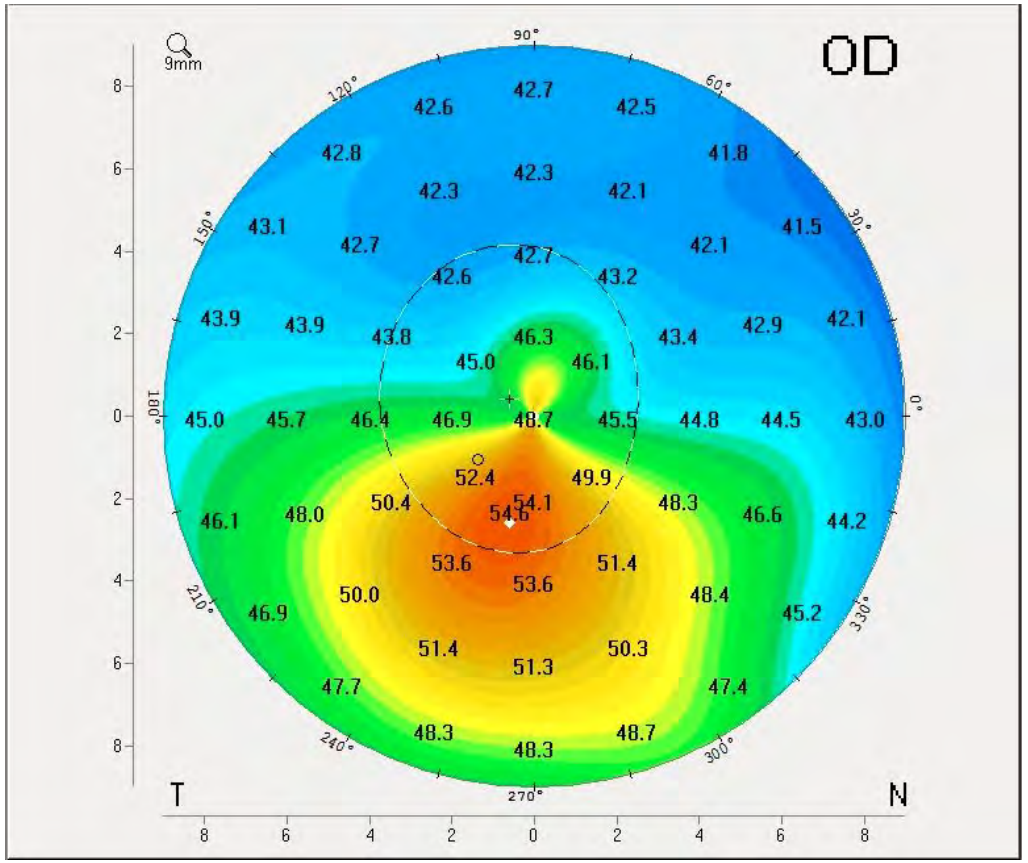
- corneal opacity (haze)
- punctate keratitis
- corneal striae
- corneal epithelium defect
- eye pain
- reduced visual acuity
- blurred vision

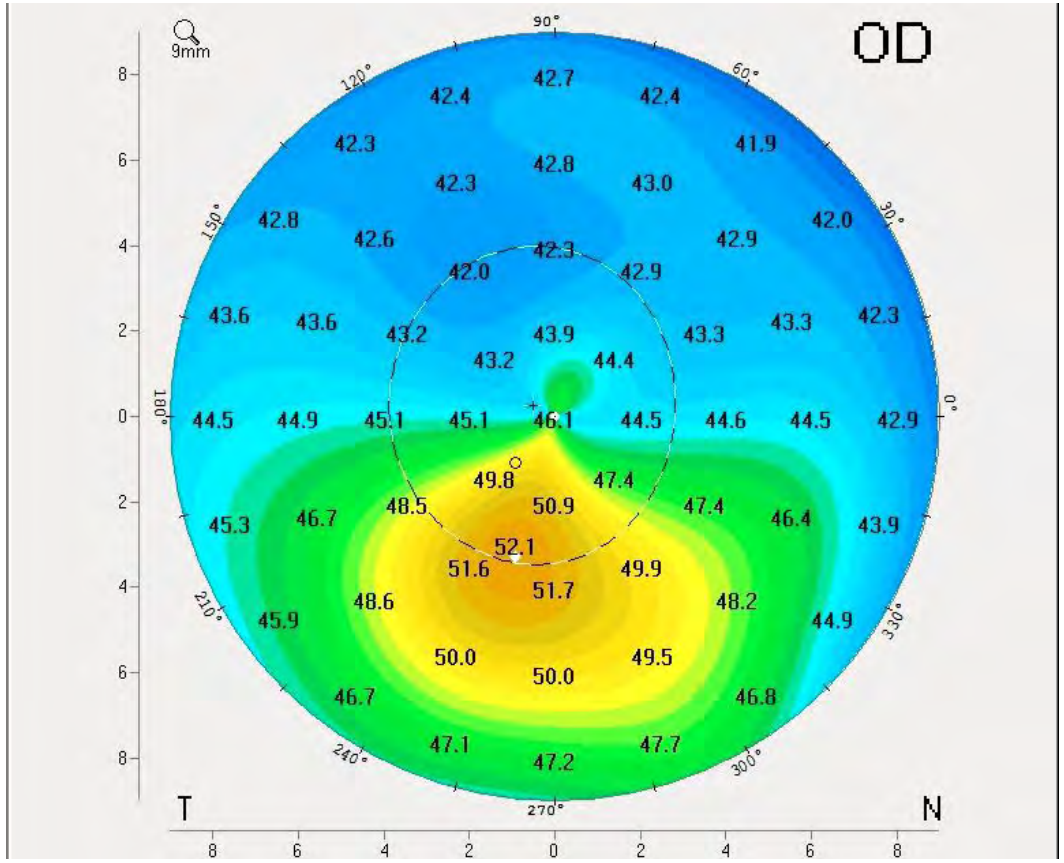
Corneal Ectasia

- corneal opacity (haze)
- corneal epithelium defect
- corneal striae
- dry eye
- eye pain
- punctate keratitis
- photophobia
- reduced visual acuity
- blurred vision

- The majority of adverse events reported 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 1-2% of patients, corneal epithelium defect, corneal edema, corneal opacity and corneal scar continued to be observed at 12 month

PATIENT EXAMPLES – PRE and POSt CXL





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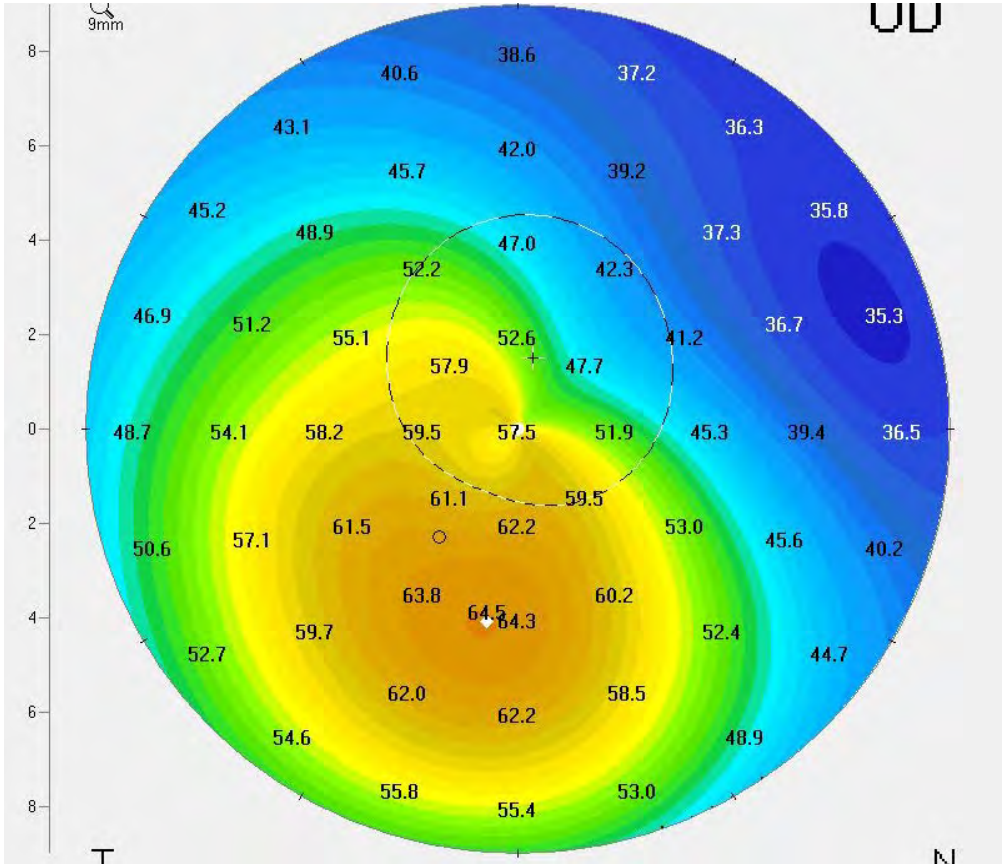
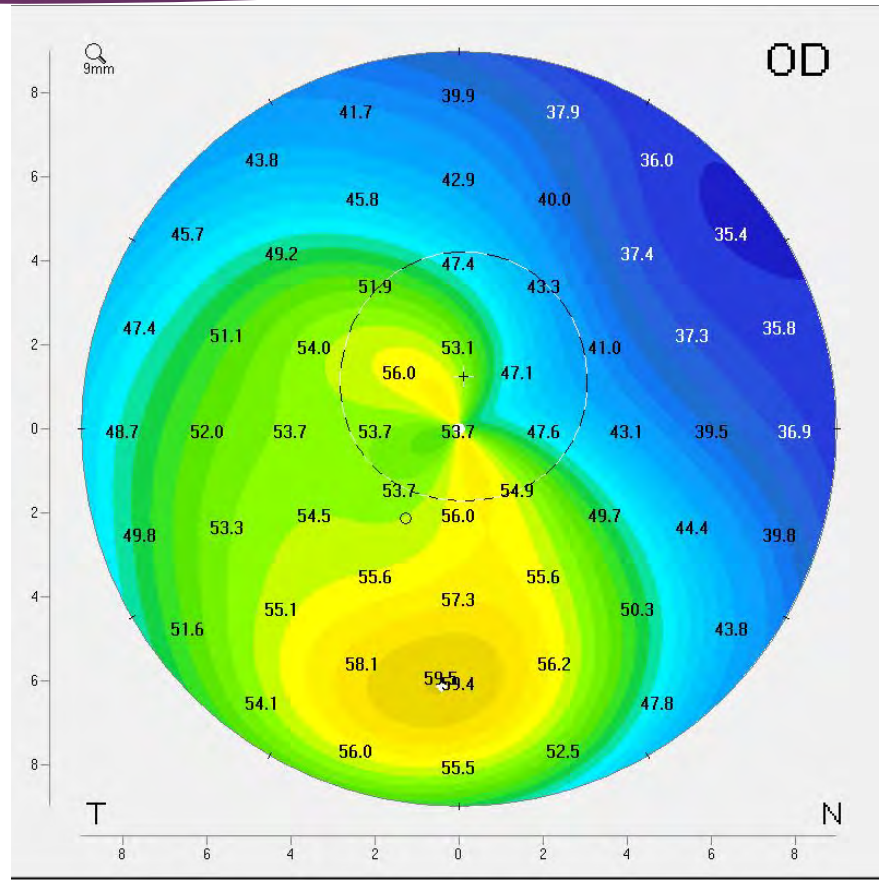




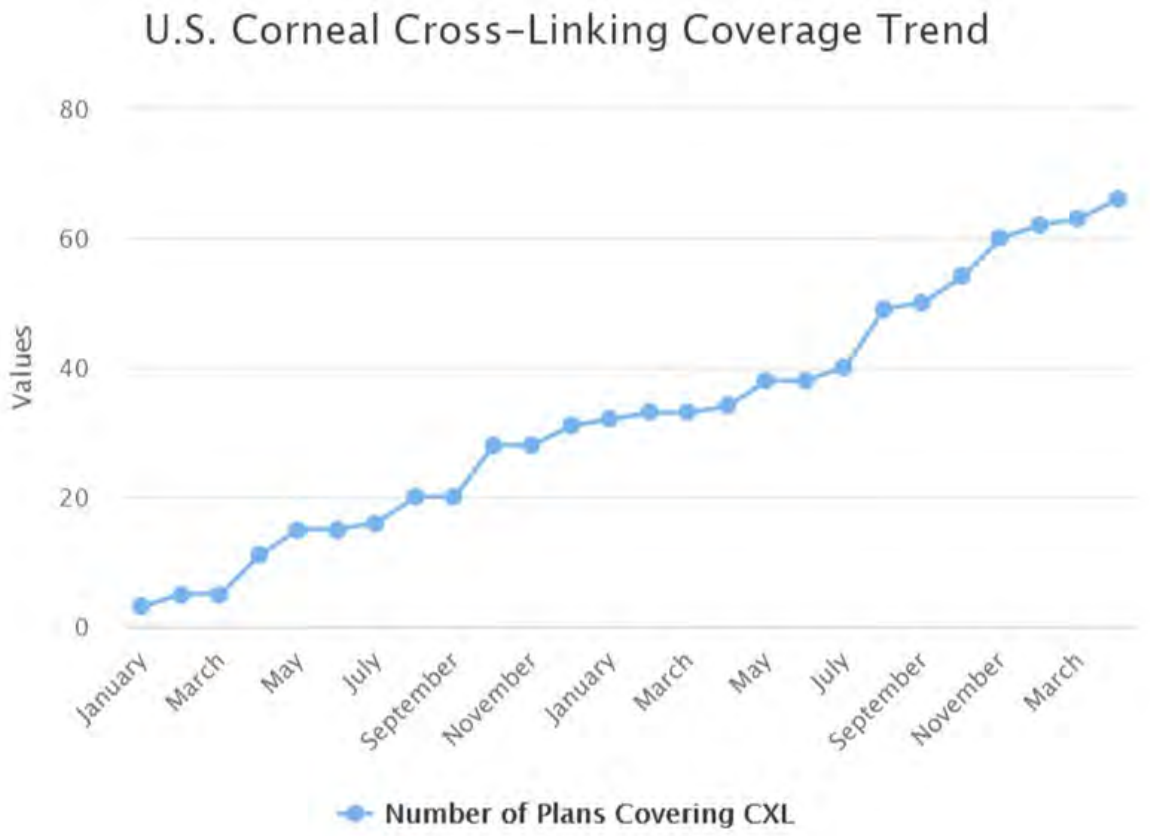
Does Insurance Cover FDA-Approved Cross-linking?

Insurance coverage for FDA approved cross-linking with Photrexa® Viscous, Photrexa® and the KXL® System is now widely available.

In 2017, 3 plans covered the procedure and now, greater than 95% of the commercially insured population has access to this potentially sight-protecting treatment.

Commercial Insurance Coverage for FDA-Approved Cross-Linking in the U.S.

**data on file*



Progressive keratoconus or corneal ectasia is defined as 1 or more of the following:

***Defined progression according to the clinical trial criteria**, is often required for insurance coverage. Insurance companies may mandate documentation of specific criteria demonstrating progression of keratoconus.*

- AN INCREASE OF 1 DIOPTER (D) IN THE STEEPEST KERATOMETRY VALUE
- AN INCREASE OF 1 D IN REGULAR ASTIGMATISM EVALUATED BY SUBJECTIVE MANIFEST REFRACTION
- A MYOPIC SHIFT (DECREASE IN THE SPHERICAL EQUIVALENT) OF 0.50 D ON SUBJECTIVE MANIFEST REFRACTION,
- A DECREASE ≥0.1 MM IN THE BACK OPTICAL ZONE RADIUS IN RIGID CONTACT LENS WEARERS WHERE OTHER INFORMATION WAS NOT AVAILABLE

Does insurance cover non-FDA approved products?

- Generally, insurance does not typically cover products and procedures that have not received FDA approval. As an example, the Blue Cross and Blue Shield Association's Technology Evaluation Center (Premera BCBS Technology Review) lists as part of their new technology evaluation criteria:*"1. The technology must have final approval from the appropriate governmental regulatory bodies."*
- Does insurance cover epi-on procedures?
  - The only FDA-approved products for cross-linking are from Avedro, and performed epi-off. Many insurance policies have details about the fact that the epi-off procedure is the only FDA approved treatment for progressive keratoconus that is being covered, while epi-on is not.

Corneal collagen cross-linking using riboflavin and ultraviolet A is considered experimental, investigational and/or unproven for all other indications and is therefore not covered

Future Advances

- Newer and better imaging modalities
- LASIK with CXL: thinner corneas, less risk of ectasia?
- Topography-guided PRK with CXL for FF KC or KC
- Newer treatment protocols

Conclusion

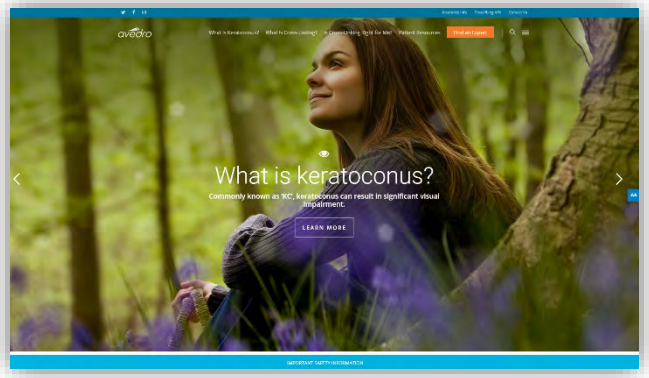
- Patients with progressive keratoconus should be educated regarding risks and benefits of CXL.
- Optometrists play a critical part in ensuring early diagnosis, monitoring, and continuing care of these patients.
- Financial hurdles are preventing some patients from treatment. Thankfully, the insurance landscape is rapidly changing with an increased number of insurers covering treatments.

Online Resources for Patients

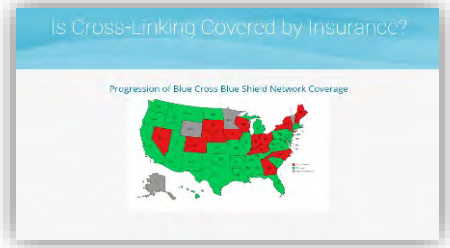
NKCF Website

Available at **www.NKCF.org/patient-packets**

Living with KC Website



Available at
www.livingwithkeratoconus.com



Patient Brochures (English and Spanish)