Financial Disclosure

- Bill Tullo, OD has no financial interests in any of the products or companies discussed in this program.

Corneal Ectasia – Causes

- Naturally-existing Corneal Pathology
  - Forme Fruste Keratoconus
  - Keratoconus
  - Pellucid Marginal Degeneration

- Surgically induced Pathology
  - Mechanical Instability
    - Post- LASEK ectasia
    - Post-PRK ectasia
  - Abnormal Collagen fibrils vs biomechanical destabilization
Keratoconus

Progressive corneal steepening and thinning in the absence of refractive surgery

Keratoconus

- Adolescent onset
- Progresses over 10–20 years
- Incidence
  - 1/2,000 in general population
- Prevalence: 1/430
  - 2% in patients seeking surgical correction of refractive errors
- About 20% of patients with KC require corneal transplantation
  - KC is the indication for 5000 (15%) corneal transplants performed each year in the US

Characteristics of Keratoconus

- Reduced corneal rigidity in eyes with keratoconus – Corneal Hysteresis


2006 EBAA Eye Banking Statistical Report

Reduced corneal rigidity in eyes with keratoconus – Corneal Hysteresis
Who is NOT at Risk?

- Reduced likelihood of keratoconus progression with age (physiological cross-linking)³
- Diabetes protects against development of keratoconus – glycation²
- Cigarette smoking protects against development of keratoconus – unknown toxins in cigarette smoke protects against development of keratoconus⁴

Risks of Post–Surgical Ectasia

- Flap Thickness/Diameter
- Ablation Depth
- Irregular topography

Post–Surgical Ectasia – Tomography
Methods of Stiffening the Cornea

- **Glutaraldehyde**
  - Crosslinking (prosthetic heart valves)
- **Formaldehyde**
  - Crosslinking (pathology specimens)
- **Aldehyde sugars**
- **UVA**-induced crosslinking (dentistry)

Riboflavin Absorption Spectrum

**Basics in Cross Linking**

1. Riboflavin (vit. B2) + Ultraviolet radiation
2. Production of oxygen radicals (ROS) \( \text{O}_2^* \)
3. Induction of collagen cross-links
Pretreatment 30 Days Post Treatment

70% reduction of K readings by 2.01 D
1.14D reduction of refractive error
65% improvement in Visual Acuity (3.6 lines Caprorossi et al)
Important Questions

- Does it really work?
- Is it really safe?
- How long does the effect last?
- Does the epithelium have to be removed?
- What is the best protocol?

Cross-Linking and Keratoconus Keratometric Change

Cross-Linking and Keratoconus Keratometry Over Time


Clinical Studies

- 687 Peer-reviewed literature citations
- 96% of eyes show topographic stability
- Average flattening 1.7D of max-K
- Flattening effect reduced max-K > 54D

Dresden Protocol

- UVA dosage 3 mW/cm² for 30 minutes
- 0.1% riboflavin

Remove Epithelium
Riboflavin 0.1% Drops

1 drop q2 min x 30 min

Fluorescence in Anterior Chamber

UV–A Light 370
UV Light for 30 Minutes

Bandage Contact Lens

CXL – Possible Side Effects

- Endothelial Cell Loss
- Crystalline lens opacity
- Pain
- Infection
- Delayed Epithelial healing
- Retinal damage
- Stromal Haze
Haze

Confocal Microscopy

- Apoptosis 300 µm deep after CXL
- Repopulation takes 6 months

6 m postop

Minimal Corneal Thickness

- 400 microns when using 3.0 mW/cm² and Dextran based Riboflavin
- Thicken a thin cornea with hypoosmotic riboflavin not safe¹
- Stromal haze peaks at 1 month post–op and decreases significantly between 3 and 12 months²

**Conclusions – CXL**

- Halts progression of ectatic corneal diseases
  - Decreases corneal curvature and thickness
  - Regularizes corneal surface
  - Improves UCVA and BSCVA
  - Effect lasts indefinitely
- Offers safe and effective treatment for conditions with no currently available treatment and may avoid
  - 15% of corneal transplants
  - Disability, cost, loss of productivity, CTL

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**Regulatory Status**

- International
  - CE Mark since 2006
  - Distributed internationally
- United States
  - Investigational
  - Combination product
  - Device: UVA light source
  - Drug: Riboflavin

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**CXL FDA Studies**

- > 27 total FDA studies
- 13 US studies

- FDA Grants Riboflavin Orphan Drug Status
  - 10/10
  - Avedro – 7 years of exclusive rights
  - 1/12 FDA Expedited Review Request
Ideal CXL Study Candidate
Young patients with good history expected to progress if untreated

- Age ≤ 35 yr
- Kmax ≤ 56 D
- Pachymetry > 400 microns
- Health History Non-smoker/Non-diabetic
- Corneal signs Scissoring or Thinning
  - No or few Vogt’s striae
  - No or little scarring
- Keratoconus/Ectasia History Rapidly progressive disease
  - At least 3 months of topographic history preferred

ACOS CXL Study

- Multicenter (100 sites), randomized
- Keratoconus and Ectasia after Refractive Surgery
  - > 12 yrs old and evidence of KC on topography
- Minimum Pachymetry > 375 microns
- 3 treatment groups
  - Epi-removal – 15 mW/cm² x 8 minutes
  - Epi-removal – 30 mW/cm² x 4 minutes
  - Epi-removal – 45 mW/cm² x 2 min 40 sec

Normal Corneal Epithelium
Barrier to riboflavin penetration of stroma
Riboflavin

- Epithelium-OFF
  - 0.1% Riboflavin with 20% Dextran
  - Vibex Rapid – 0.1% riboflavin with hydroxypropyl methylcellulose
  - Reduced corneal thinning allow treatment of corneas as thin as 325 microns
- Epithelium-ON (Transepithelial)
  - Paracel – BAC opens epithelial junctions
  - Vibex Xtra – 0.1% riboflavin

Transepithelial Epi-On CXL

- Mechanical Disruption
  - Daya Disruptor
- Chemical Disruption
  - BAK
  - Tetracaine
  - EDTA
  - 20% Alcohol
- Permeability Enhancers
  - Cellulose or sodium phosphate
- Iontophoresis

Epi-on ParaCel Protocol

1. Apply topical anesthetic to the cornea.
2. Insert lid speculum using standard clinical techniques.
3. Apply 2–4 drops of ParaCel to coat the cornea. Apply an additional drop every 90 secs for a total soak of 4 mins.
4. Rinse cornea completely with Vibex XtraTM.
5. Apply sufficient Vibex Xtra to coat the cornea and repeat this procedure every 90 secs for a total of 6 mins.
6. Initiate UV treatment using the KXL SystemTM for 2 mins 40 secs at 45mW/cm², applying 1–2 drops of BSS as needed during irradiation.
7. Rinse cornea completely with BSS.
8. Remove speculum using standard clinical techniques.
Trans-epithelial CXL – CXL-USA

- Riboflavin 1% with gum cellulose Q2 min:
  - From local compounding pharmacies
- Topical Tetracaine with BAK provided Q2 to 5 min
- Corneal Protector sponge used
- 60–80 minutes of Riboflavin drops required

SUMMARY EPI-ON CXL

Benefits:
- Faster visual recovery & less pain
- Reduced risk of pain & haze
- Reduced risk of infection & slow re-epithelialization
- Very good clinical results
  - Even in keratoconus patients in their 50’s and 60’s

Downside:
- Longer procedure (30–50 min longer)
- Insufficient Riboflavin penetration can lead to UVA over-exposure and damage to ocular structures.
- Can not combine with simultaneous topo-guided PRK

Intacs with Sequential CXL

- Effects of both treatments are synergistic
  - Increased K flattening
  - Increased BCVA
  - Increased UCVA

**CLX & PRK**

- Simultaneous CXL & PRK more effective than sequential CXL & PRK
- PRK before CXL better than PRK after CXL


**Athens Protocol**

- Topographically Guided Transepithelial PRK
  - Treat 70% corneal astigmatism
- 0.02% Mitomycin-C 20 seconds
- 0.1% riboflavin sodium phosphate x 10 minutes
- 370nm 3.0 mW/cm² x 30 minutes

**LASIK Xtra**

- Use of modified CXL protocol for LASIK patients
- All LASIK patients vs. “at risk”
  - Thin corneas
  - Irregular topography
  - High myopia
- Stabilize hyperopic LVC?
LASIK Xtra Shinagawa Protocol

- 1. After ablation, sufficient VibeX Xtra™ is applied to coat the stromal bed
- 2. Following a 90 second soak, VibeX Xtra is thoroughly flushed from the eye using BSS
- 3. The flap is carefully replaced, and the cornea is irradiated with the KXL® device at 45mW/cm² for 90 seconds

Keratoconus in Younger Patients

- Poorer prognosis
- Faster progression
- Increased probability of PK
- Higher risk of PK rejection

**MUST DIAGNOSE KERATOCONUS AS EARLY AS POSSIBLE!!**

Keratoconus Treatment

- **Early Keratoconus** - progressive topography or tomography minimal reduced BCVA
  - CXL as soon as Dx confirmed
- **Moderate Keratoconus** - progressive topography or tomography moderate reduced BCVA
  - Consider CXL / Intacs
- **Advanced Keratoconus** - pachymetry less than 400 microns
  - Intacs if stable with CL refit
  - PK as last resort
Future Directions

- Transepithelial CXL
- High Irradiance CXL
- Oxygen Enhanced CXL
- Accelerated CXL with Pulsed Illumination
- Intrastral CXL
- LASIK Xtra & PRK Xtra
- Topographic Guided – CXL
- Alternative Agent CXL
- Selective CXL

CXL Myths

- Wait till ectasia progresses before CXL
- Older patients don’t benefit from CXL
- Insurance will pay for CXL soon
- The epithelium must be removed for CXL
- CXL effect is temporary
- CXL not approved because it’s dangerous
- Epithelium has to be removed for CXL

“The Mission”:

- Comprehensive KC Education for ECP’s
- Resource for all KC Patient’s Needs
- Provide Comprehensive Care for KC Patients in Conjunction with Affiliated ECP’s
- Advancement of Knowledge re-KC Through Clinical Research Leading to Ongoing Improvement in the Care of KC Patients

NKCI
National Keratoconus Institute
THANKS!