Epithelium on Cross-linking and Iontophoresis

Professor David O'Brart MD FRCS FRCOphth
Consultant Ophthalmic Surgeon, St. Thomas' Hospital, London
Professor of Ophthalmology and Corneal Science, King's College, London

Financial disclosures related to this lecture: Fight for sight small grant award 2014

Epithelium-off Riboflavin CXL

- Wollensak *AJO 2003;135:620*
- Multiple published case series
- 6-24 mth follow-up, 100s treated eyes
- Including advanced KC*,paediatric cases**, PMD ***
  - Caporossi *JCRS 2006;32(5):837-45.*
  - Vinciguerra *Ophthal 2009;116(3):369-78.*
  - Coskunseven *JRS 2009 ;25(4):371-6.*
  - Agrawal *Indian J Ophth 2009;57(2):111-4.*
  - Arbelaez *Oman J Ophth 2009 ;2(1):33-8.*
  - Vinciguerra *Arch Ophth 2009;127(10):1258-65.*
  - Fournié *J Fr Ophtalmol. 2009 Jan;32(1):1-7.*
  - Henriquez *Cornea 2011;30(3):281-6*
  - Kampik *Klin Monbl Augen 2011;228(6):525-30.*
  - Goldich *Cornea. 2012;31(6):609-14.*
  - Asri *JCRS. 2011;37(12):2137-43.*
  - Hersh *JCRS 2011;37(1):149-60.*
  - Arora *JRS 2012;28(11):759-62* *
  - Vinciguerra *Am J Ophth 2012;154(3):520-6.* *
  - Ivarsen *Cornea. 2013;32(7):903-6.* **
  - Spadea *JRS 2010;26(5):375-7* ***
  - Hassan *Indian J Ophth 2013 10* ***
  - Bayraktar *Case Rep Ophthalmol Med. 015:840687* ***
- Stabilization in 90-95%
- Few complications
- Typically significant improvements in
  - Vision/Topographic indices
  - Higher order aberrations

Epithelium off CXL: Randomized Controlled Studies

O'Brart *Br J Ophth 2011;95:1519*

- Bilateral RCT,18mth f-u, 22 patients
- Treated - Improved CDVA, reduced SimK, astig, RMS, coma, Sph Ab, 2nd astig, pentafoil ($p<0.05$)
- Untreated Eyes - Worsening of refractive astigmatism $p<0.005$

Wittig-Silva *JRS 2008;24:S720-5, Ophth 2014;121:812-21.*

- 46 Treated eyes- Reduction in Kmax $p<0.001$, Improvement in UCVA, CVDA $p<0.0$
- 48 Control eyes, 3 yr f-u - Increase Kmax $p<0.001$ cylinder $p<0.02$, Decrease in UCVA $p<0.05$

Lang *BMC Ophthalmol. 2015;15:78*

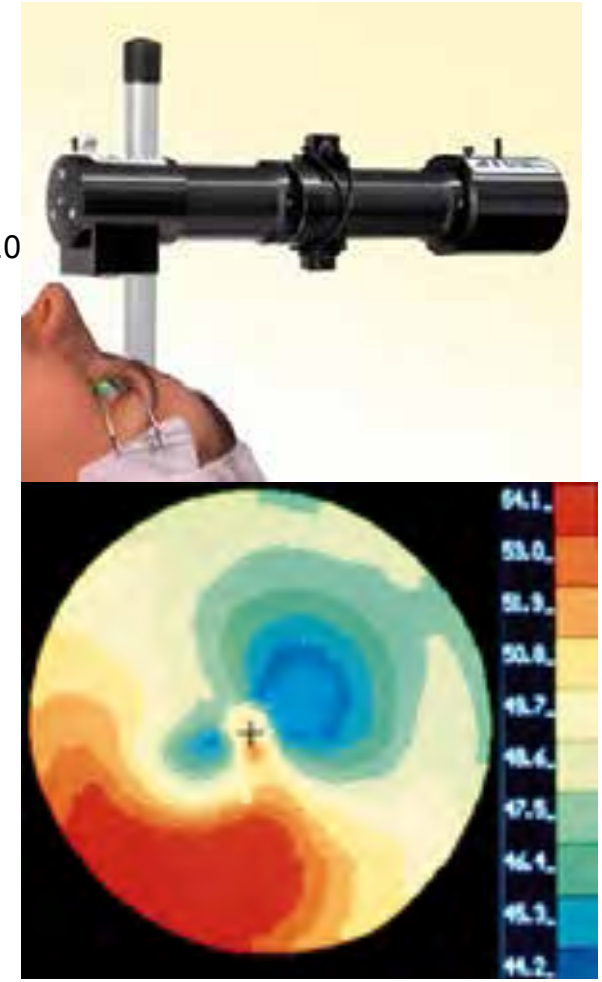
- 29 eyes, 15 treated, avg f-u 3 years
- Treated - Ref power reduced by 0.35 +/- 0.58 D/yr.
- Untreated eyes - Increase of 0.11 +/- 0.61 D/yr - significant difference $p<0.02$

Seyedian *Middle East Afr J Ophthalmol. 2015;22(3):340*

- Bilateral, RCT 26 eyes, 12 mth f-u
- Treated - K-max reduced by 0.22D, CDVA improved
- Untreated - Kmax increased by 0.41 D, CDVA decreased - ($P < 0.02$)

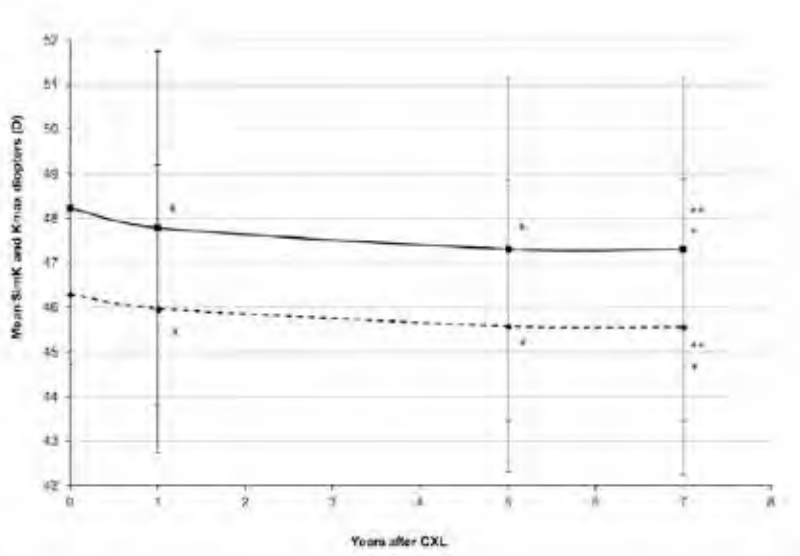
Sharma *Int Ophthalmol. 2015 Feb 24*

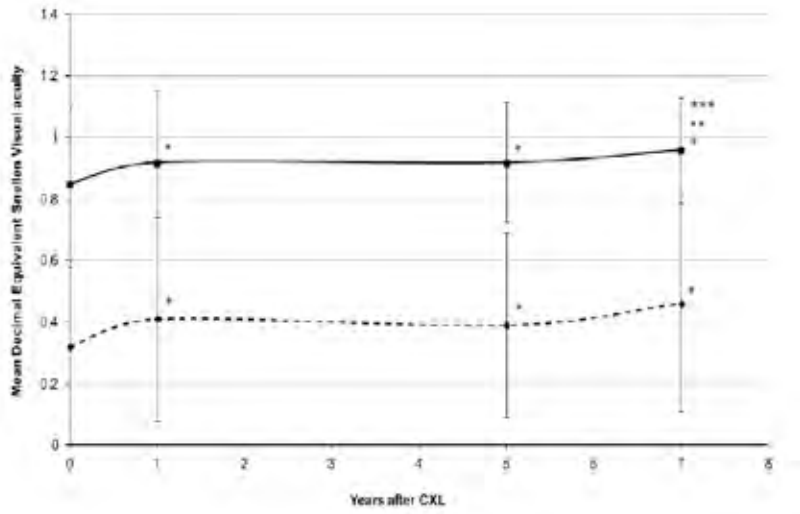
- RCT with sham treatment control, 43 eyes, treatment (23), sham (20), 6mth f-u
- Improvements in UDVA, Ref Cyl, Kmax ($p<0.01$)
- Sham group no changes.



Epithelium off CXL: 7-10 year follow up

- Theuring *Ophthalmologe 2015;112(2):140*
  - 30 eyes 20 patients 10yr f-u
  - Kapex -7D ($p<0.001$), Kmax -4D ($p<0.001$), Kmin -3D($p<0.001$)
  - BCVA -0.13 LogMAR ($p<0.005$)
  - 2 eyes progressed
  - No long-term loss of transparency
- O'Brart *AJO 2015 160(6):1154-63*
  - 36 eyes 36 pts 7yr fu
  - KC stabilized in 100%
  - Kmax -0.9D ($p<0.0001$), Kmean -0.74DD ($p<0.0001$)
  - UCVA/CDVA improved ($p<0.001$)
    - 4 eyes (11%) lost 1 line of UCVA
    - 22 (61%) gained 1-4 lines of UCVA
    - 3 eyes (8.5%) lost 1 line CDVA
    - 15 (42%) gained 1-4 lines of CDVA
  - SEQ +0.78D ($p<0.005$) 8 eyes (22%) >+2.0D
  - RMS, Coma, 2^0 Astig improved ($p<0.005$)
  - No sight threatening complications
  - 24% untreated eyes progressed
  - 7 year compared to 5 year
  - Improvements in CDVA ($p<0.01$), trefoil ($p<0.05$)

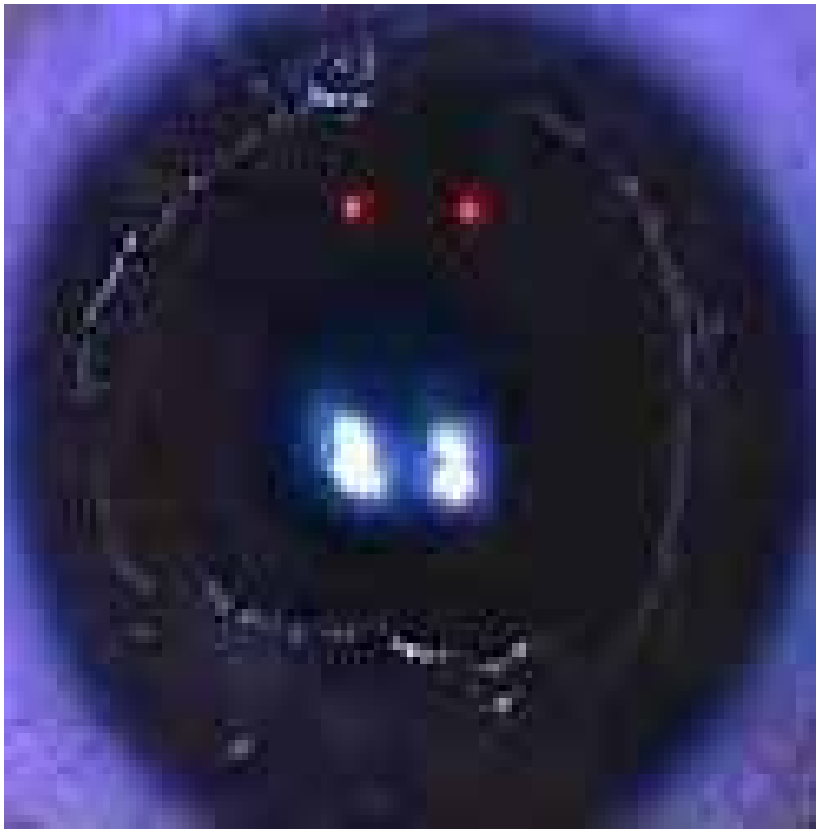




Epithelium-off CXL:
Post-operative Recovery and Complications

But

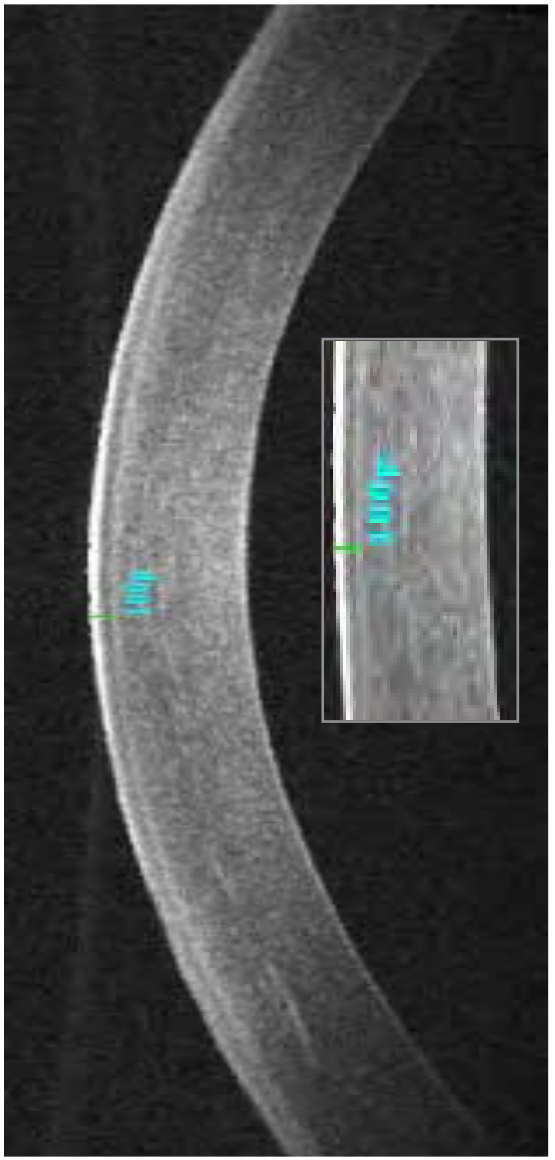
- Severe post-operative pain +++
  - 24-48 hours
- Blurred vision
  - 2-4 weeks
  - Worse at 1mth, return 3mth
- No contact lens wear
  - 3-4 weeks
- Sight-threatening complications
  - Haze, Scarring
  - Infectious, non-infectious keratitis
  - Persistent corneal oedema
  - Excessive flattening



Epithelium On CXL

- Less pain
- Faster visual recovery
- Less risk of infection
- ? Reduced risk of:
  - Stromal scarring/corneal melt
    - Reduced epithelial/stromal cytokine interaction
  - Stromal oedema/Endothelial damage
    - Thicker overall corneal thickness
    - Reduced peri-operative dehydration/thinning

- Riboflavin- poor lipid solubility
- Pre-clinical and clinical studies
  - Epithelium removed
  - Facilitates riboflavin stromal absorbtion



Epithelium On CXL

- Modification of Epithelial permeability
  - Mechanical
    - Partial epithelial disruption
  - Chemical
    - Local anaesthesia, BACS, EDTA, TASS, channel forming peptides
  - Electrical
    - Iontophoresis
- Modification of Riboflavin Solution
  - Without dextran
  - Hypo-osmolar
  - Higher concentration
- Modification of application
  - Increase application time
  - Remove riboflavin from epithelium
- Modification of UV dosage
  - Increase due to epithelial absorption

Epithelium-on CXL: Chemical Enhancement
Comparative Studies: Against

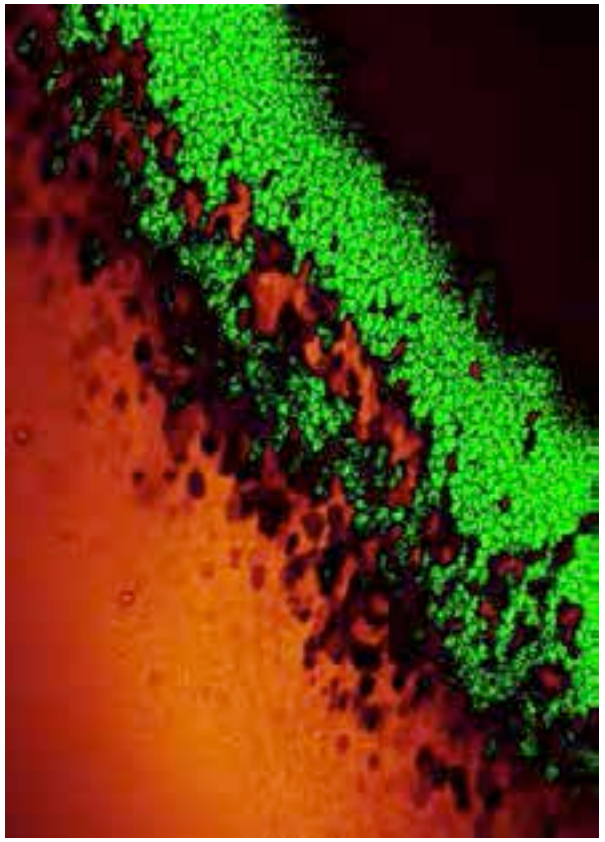
Al Fayez *Cornea. 2015; ;34 Suppl 10:S53*

- •RCT, 70 pts, 3 yr f-u
- •Epi-off: Kmax decreased ave 2.4 D, no progression
- •Epi-on: Kmax increased ave 1.1 D, 55% progression

Yuksel J *Ocul Pharm Ther 2015;31:296*

- •78 eyes epithelial signs and pain scores
- •Longer epithelialisation in epi-on ($p<0.001$)
- •Pain scores higher in epi-on day1 ($p<0.001$)

- •Gatzioufas,Hafezi, Raiskup, Speorl, O'Brart *JRS 2016 Jun 1;32:372*
  - •Medicross TE (Ribflavin 0.25%, BACS 0.01%)
  - •(47.6%) epithelial defect
  - •5 (23.8%) severe punctate keratopathy



Epithelial cell lysis observed with Paracel

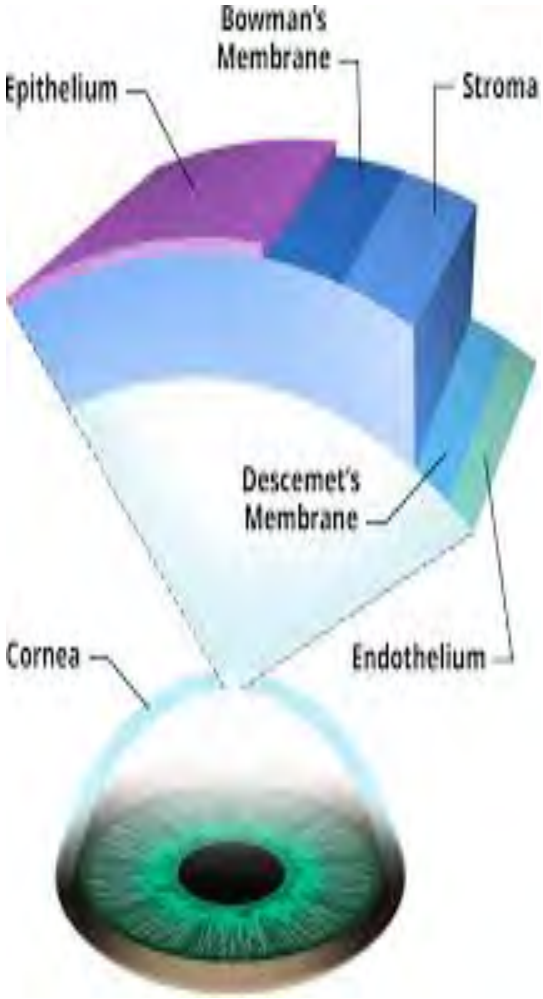
Epithelium-on CXL: Chemical Enhancement Comparative Studies: Against

Soeters *AJO 2015;159:821*

- •RCT
- •Ricolin TE 35 eyes, Epi-off 26 eyes 1yr f-u
- •Reduction Kmax epi on, no diff epi-off
  - •Significant difference between groups ($p<0.05$)
- •Better improvement in CDVA in epi-on ($p<0.05$)
- •23% progression epi-on (Kmax >1D)
- •15% epi-off complcations (scarring, HSK, infltrates)

Kocak *J Fr Ophtalmol. 2014;37:371*

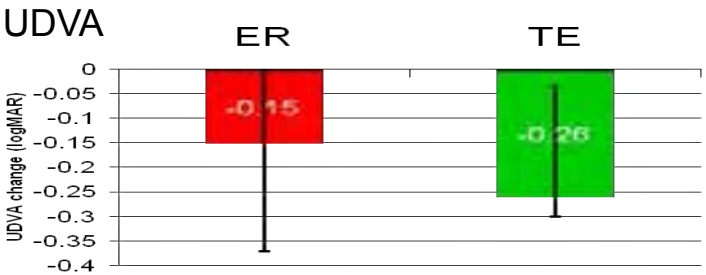
- •Retrospective study, 12+ mth Follow-up
- •Greater flattening of cone apex in epi-off eyes ($p<0.0005$)
- •Progression (>1D apical K) in 65% epi-on eyes compared to 11% in epi-on ($p<0.0001$)
- •Epi-off self-limiting corneal oedema

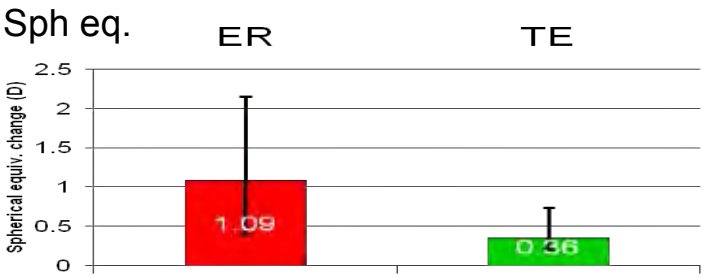


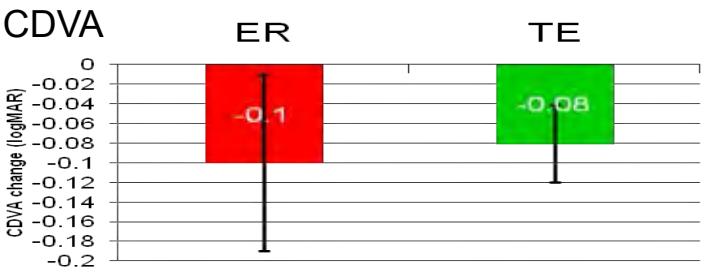
Epithelium-on CXL: Chemical Enhancement Literature Review Studies: Against

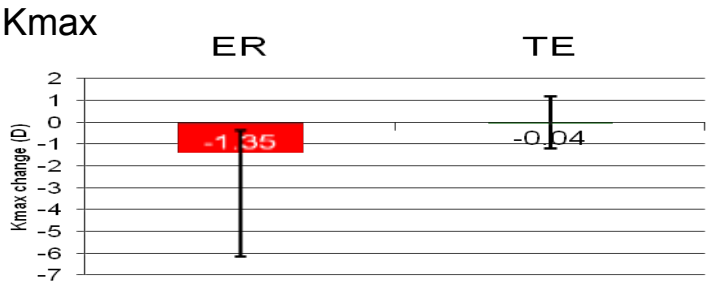
Shalchi *Eye 2015;29:15*

Literature review, 44 epi-on, 5 epi-off studies analyzed







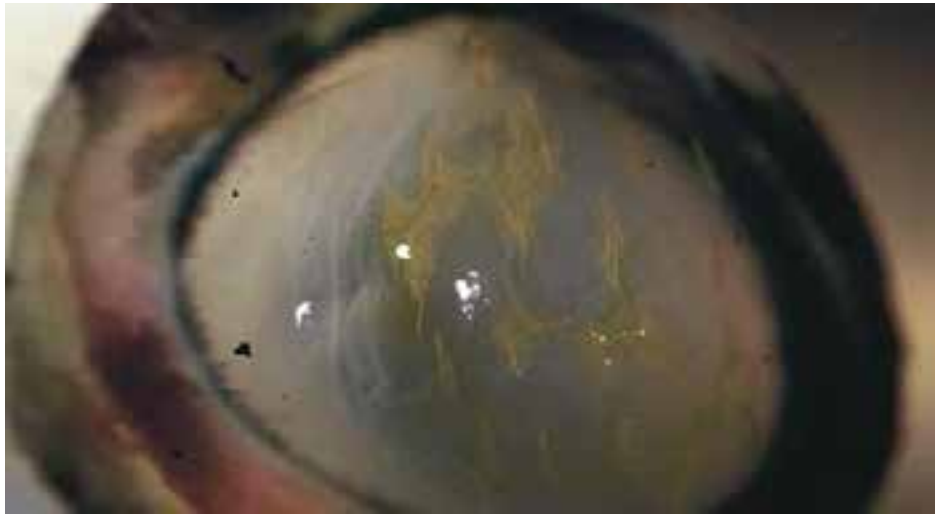


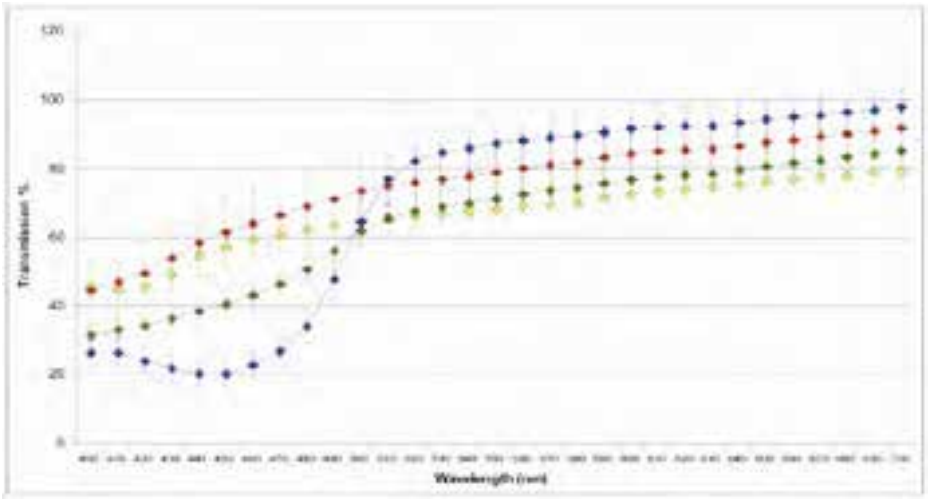
	Epithelial removal	Transepithelial
Scar formation	0 – 8.6%	0%
Infection	0 – 2.9%	0%
Loss of CDVA	0 – 27%	0%

CXL: Partial Epithelial Disruption
Comparative studies

Hashemi *J Refract Surg. 2015;31:110*
- Retrospective comparative study
- 80 eyes 65 patients, 12mth f-u
- No diff in improvements in UDVA, SEQ
- Better improvement in CDVA in partial group ($p<0.001$)
- Less reduction in Kmax , Mean K in partial group ($p<0.05$)
- Greater reduction in pachymetry in complete group ($P<0.01$)

Razmjoo *Adv Biomed Res 2014;3:221*.
- RCT 44 eyes 22 patients
- No diff in haze, refraction, visual acuity
- Total removal improvement of K-max/Q-value ($P<0.01$)
- Partial removal better improvement of CDVA ($P<0.01$)

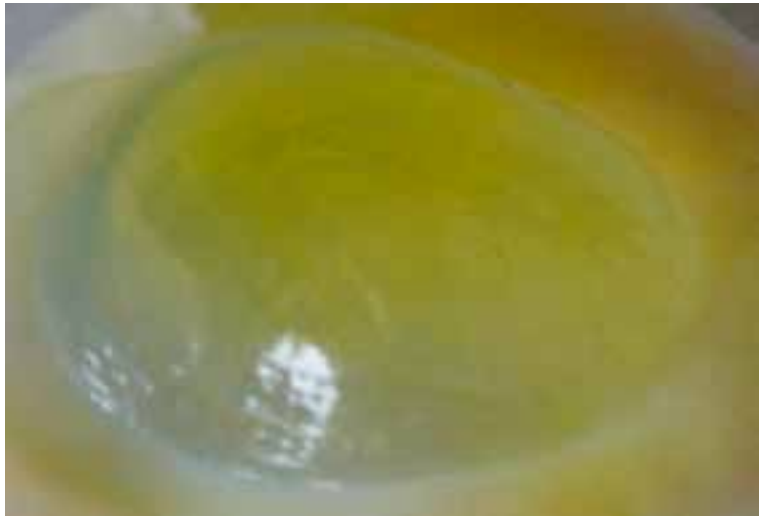


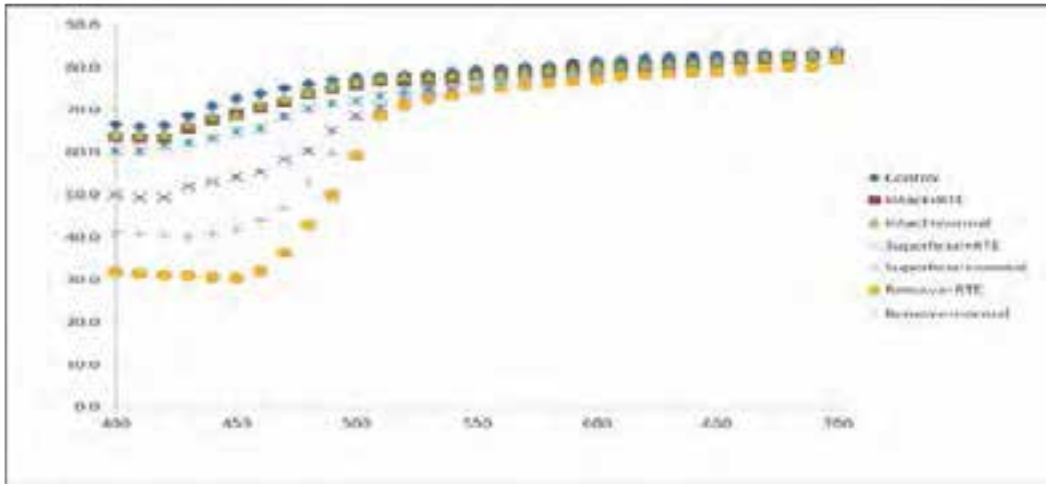


Samaras, O'Brart *JRS 2009;25:771-5*

O'Brart et al,18 month outcomes of CXL using grid-pattern epithelial scratches and Ricrolin TE ®

- 28 eyes, 26 KC, 2 post-LASIK
- 18-24mth follow-up
- Pain 24-48 hours, epithelial closure by 1 wk
- Contact lens wear 2-3 weeks
- KC stabilized in 25 eyes (89%)
- UCVA/CDVA improved ($p<0.05$)
- Apex power reduced 1.3D ($p<0.0005$)
- High order aberrations improved ($p<0.05$)
- No eyes lost >1 line CDVA
- But 5 failures >2 years

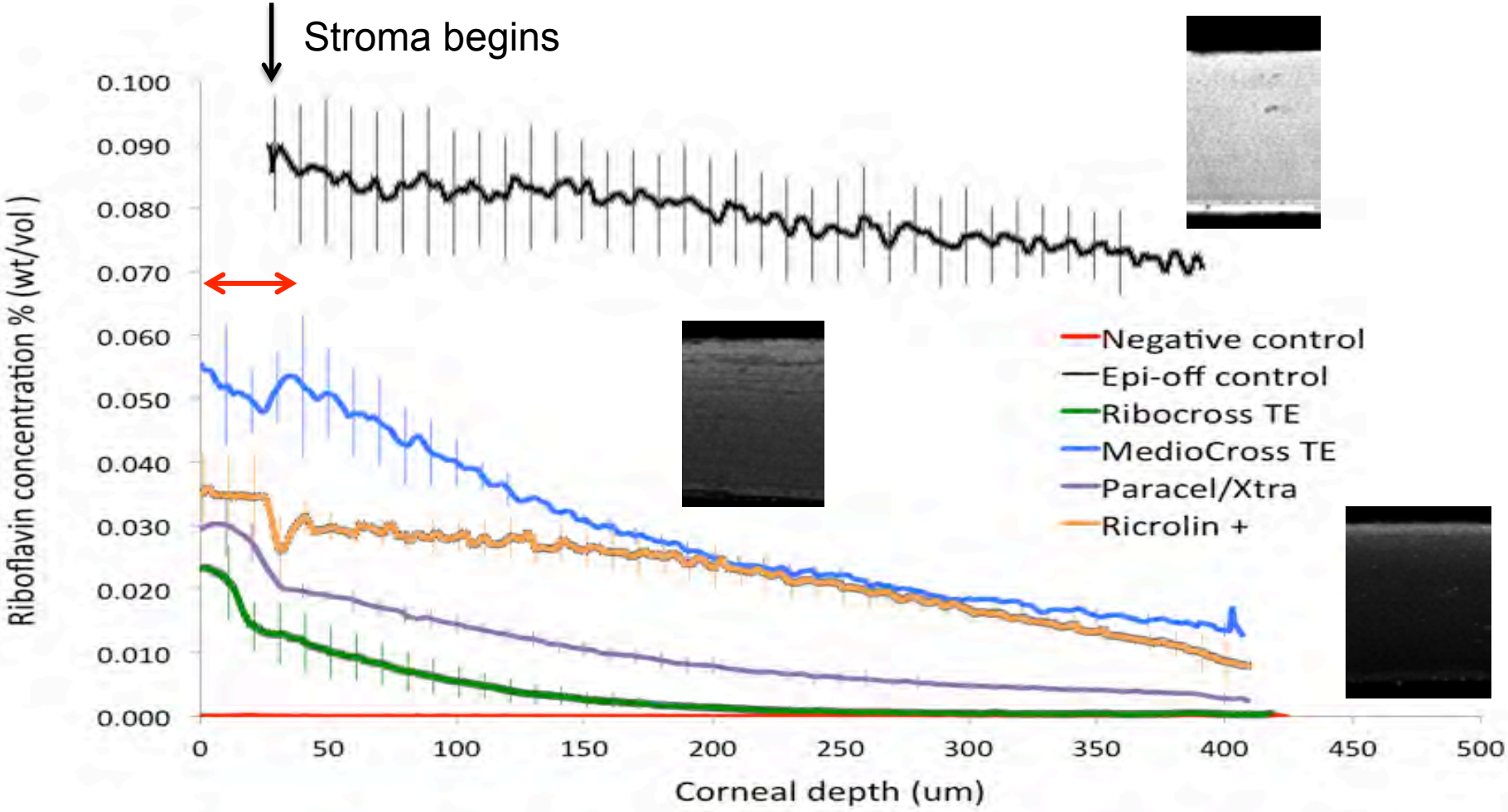




Alhamad, O'Brart JCRS 2012;38:884.

Epithelium-on CXL: Limited Riboflavin Absorption

2-photon fluorescence microscopy: ex-vivo rabbit model



Transepithelial Riboflavin Absorption in an Ex Vivo Rabbit Corneal Model

Gore DM, O'Brart D, French P, Dunsby C, Allan BD IVOS 2015 Jul 1;56(8):5006-11

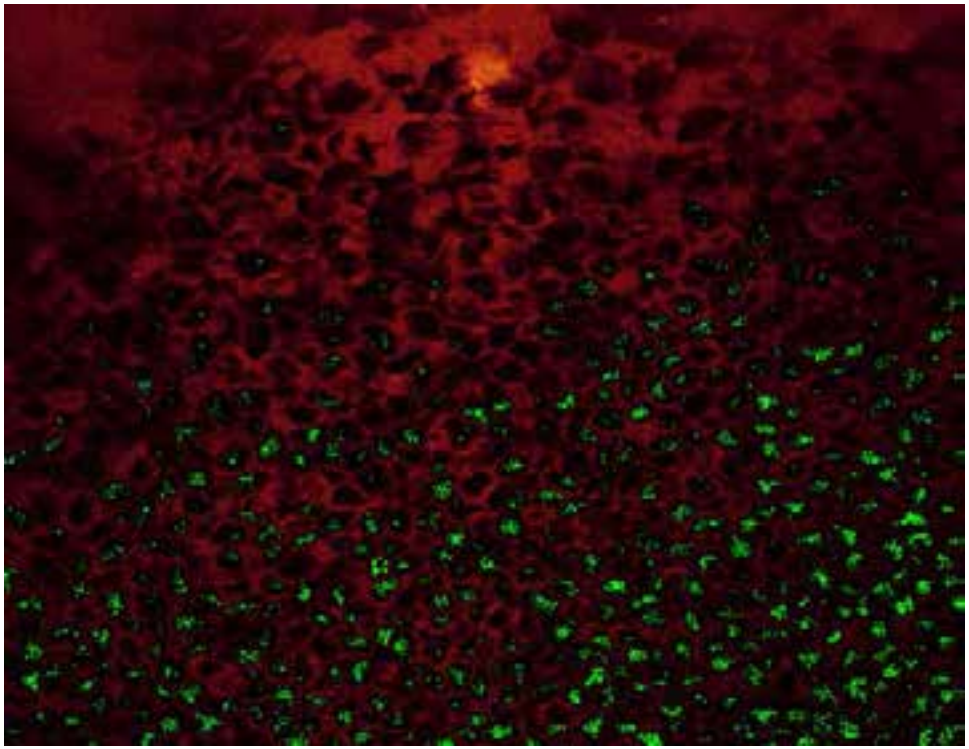
Epithelium On CXL: UVA and the Epithelium

Epithelial absorption of UV

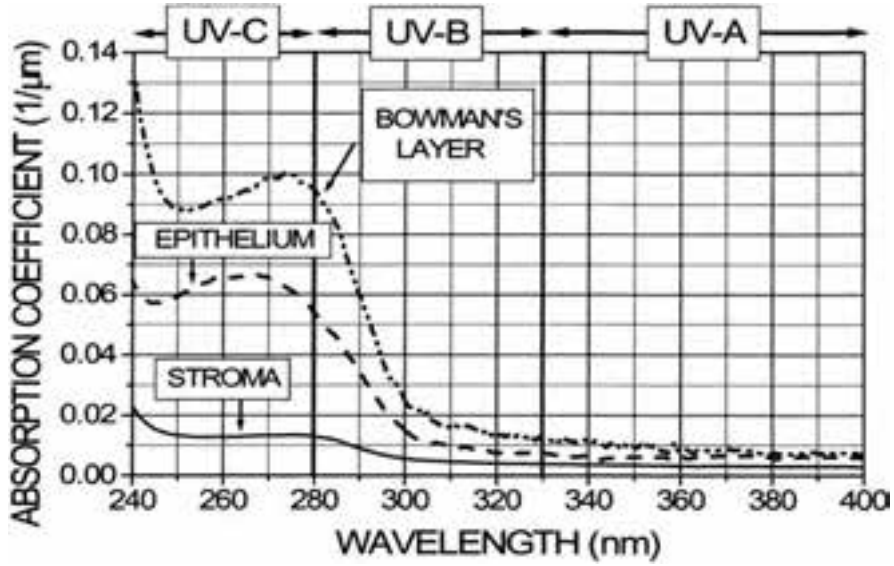
- Kolozsvári *IVOS 2002;43:2165-8*

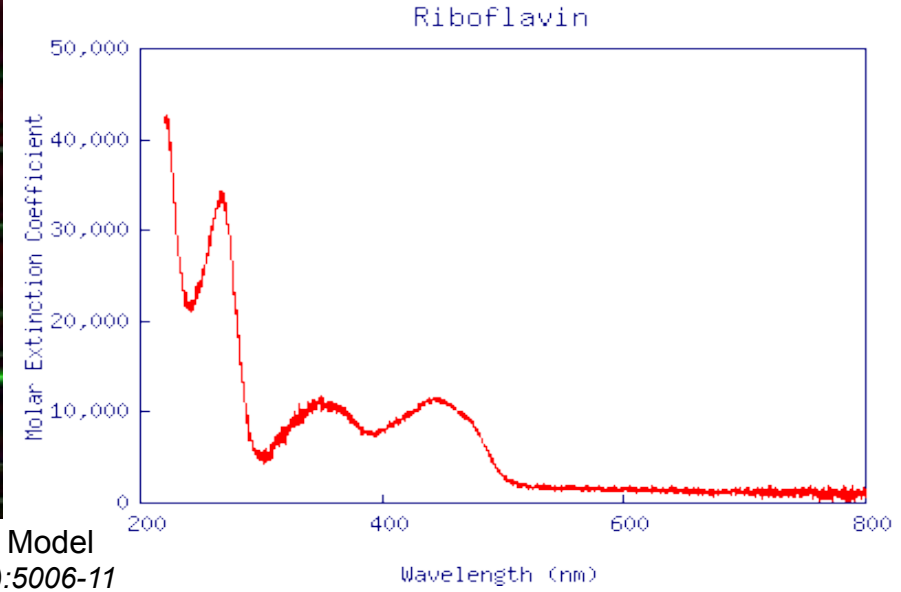
UVA absorption of Riboflavin within epithelium

- Will mask UVA stromal absorption
- Impair effiacy of CXL
- increased UVA engery/exposure time (?20%)
- Optimum BSS epithelial wash out protocol



Transepithelial Riboflavin Absorption in an Ex Vivo Rabbit Corneal Model
Gore DM, O'Brart D, French P, Dunsby C, Allan BD *IVOS 2015 Jul 1;56(8):5006-11*





Epithelium-on CXL: Iontophoretic Delivery
Clinical Studies

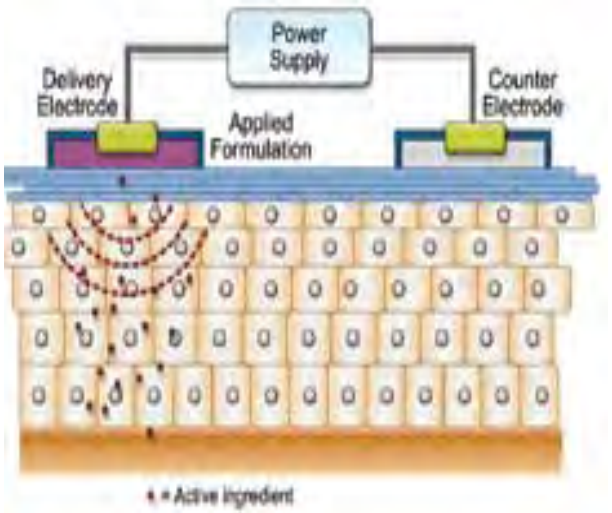
Riboflavin suitable for iontophoresis
- •Water soluble
- •Negatively charged at physiological pH

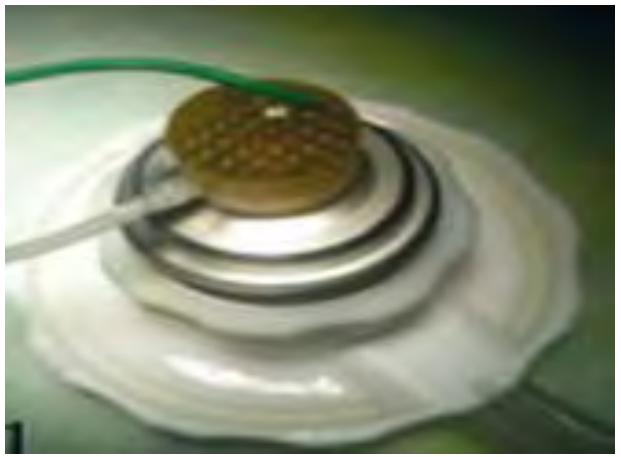
Bikbova *Acta Ophthalmol 2014:92:e30-4.*
- •22 eyes 10 min 1mA
- •12 mths 22 eyes of 19 pts
  - •Kmax reduced by 2D (p<0.005)
  - •Kmean reduced by 2.35D (p<0.005)

Vinciguerra *JRS 2014;30;746*
- •20 eyes (20 pts) 12 mth f-u, 5min 1.0mA 0.1% riboflavin
- •CDVA improved (p<0.05)
- •Stable Keratometry, HoAs, pachymetry, ECC

Li *Eye Sci. 2014;29(3):160.*
- •11 pts (15 eyes), 6 mths f-u, 0.1% riboflavin, 5 min 1mA
- •Improved visual and topo parameters
- •Corneal demarcation line 288µm

Buzzonetti *Cornea 2015 ;34:512*
- •14 paediatric eyes (14 pts) 15mth f-u
- •CDVA improved (p<0.005)
- •Demarcation line 180um

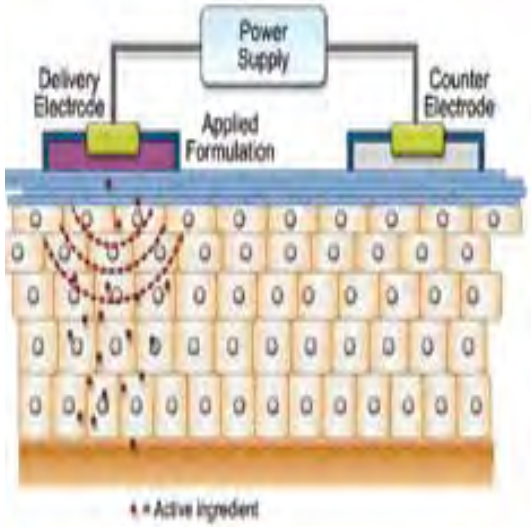


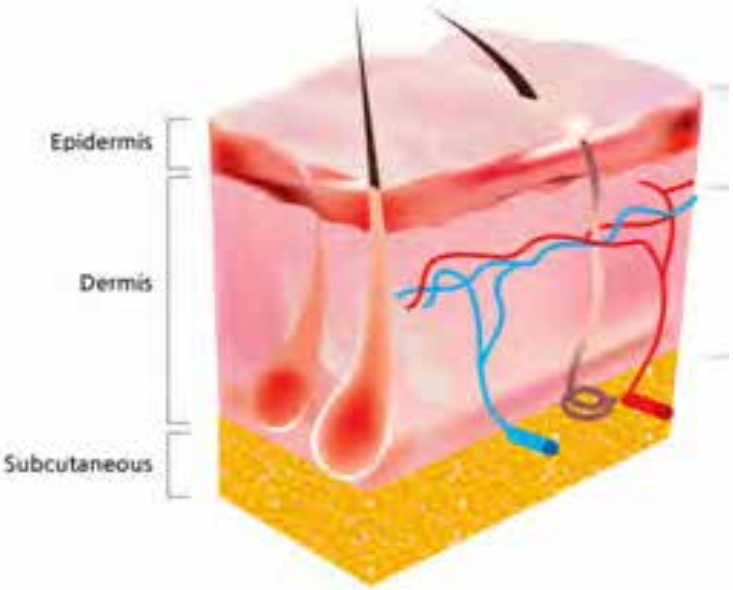


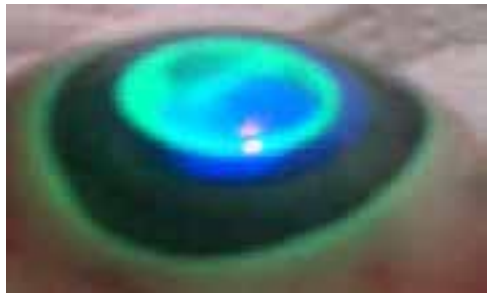
Epithelium-on CXL: Iontophoretic Delivery

- Current protocols
  - Riboflavin 0.1% and 1mA for 5-10min

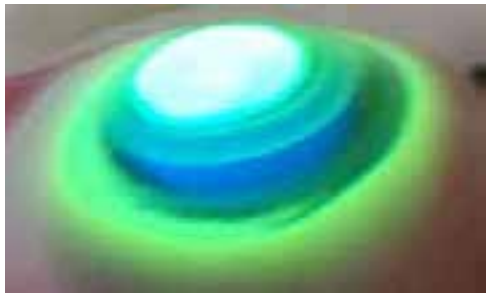
- Two stage procedure
- Drug deposition - Epidermis/epithelium
- Drug diffusion
  - Concentration gradient
    - Novruzlu *Cornea. 2015;348:932*
      - 0.2% Riboflavin 1mA 10min rabbit eyes
      - Better absorption than chemical enhancement
  - Time dependent
  - Chemical enhancement of Iontophoresis
    - Fang *J Control Release 1998;54:293*
    - Enhancement of iontophoresis with BACS







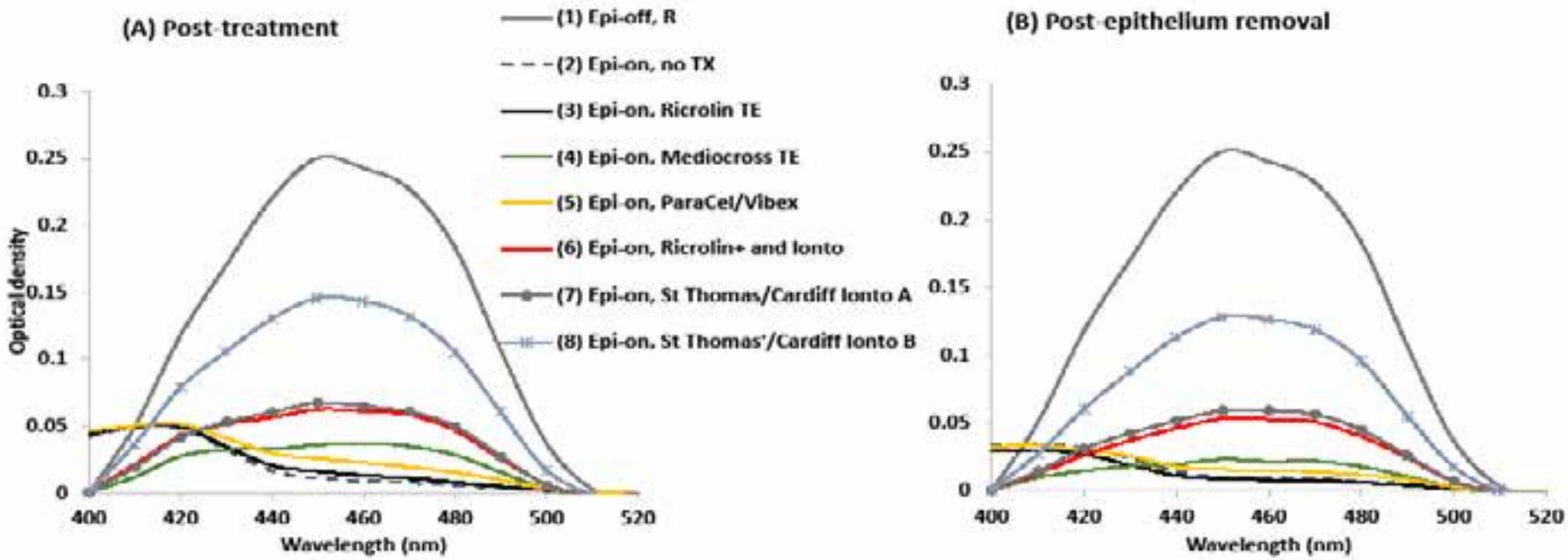
0.1% 5min 1mA



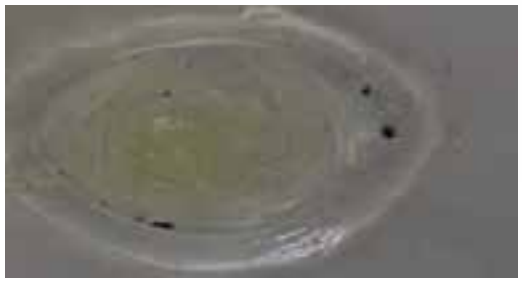
Increased time and concentration

Stromal riboflavin absorption using new and existing delivery protocols for corneal cross-linking

Morgan S, Hayes S, O'Brart D P, O'Brart N, Meek KM. *Acta Ophthalmalogica 2016;94:e109.*



Epithelium–off CXL

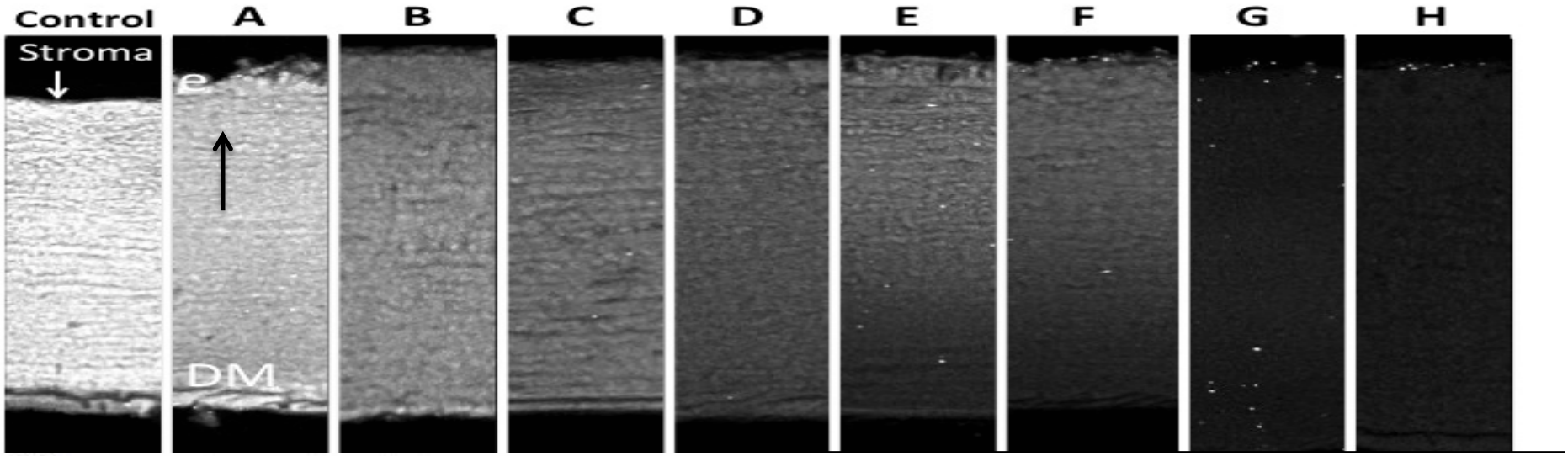


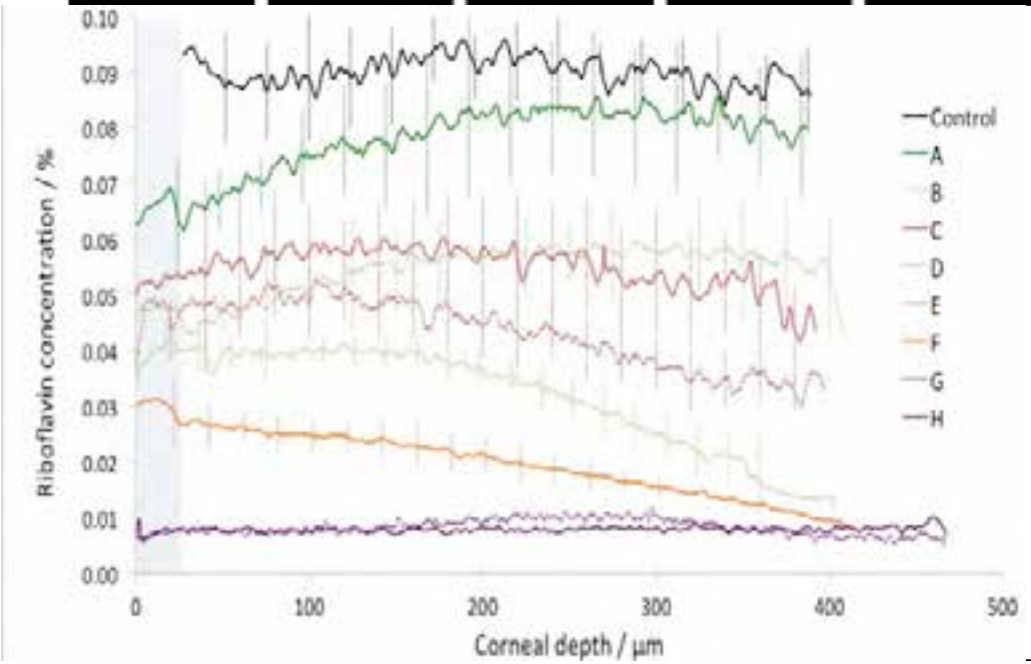
Epi–on CXL BACS,TASS,EDTA

Iontophresis extended protocol

Comparison of different iontophoresis protocols for transepithelial corneal cross-linking using two-photon fluorescence microscopy

Gore, O'Brart, Allen et al IVOS 2015;56(13):7908





Control	Vibex Rapid	-	30 min	-	-	-
A	MedioCross TE	1mA 5 min	5 min	0.5 mA 5 min	5 min	
B	MedioCross TE	1mA 5 min	15 min	-	-	1 min
C	Ricrolin+ 0.25%	1mA 5 min	5 min	0.5 mA 5 min	5 min	5 min
D	Ricrolin+ 0.25%	1mA 10 min	-	-	-	5 min
E	MedioCross TE	1mA 5 min	-	-	-	1 min
F	Ricrolin + 0.1%	1mA 5 min	-	-	-	1 min
G	Vibex Rapid	1mA 5 min	-	-	-	1 min
H	Vibex Rapid	1mA 5 min	5 min	0.5 mA 5 min	5 min	5 min

Epithelial on CXL:Iontophoresis

Modified Iontophoresis protocol RCT

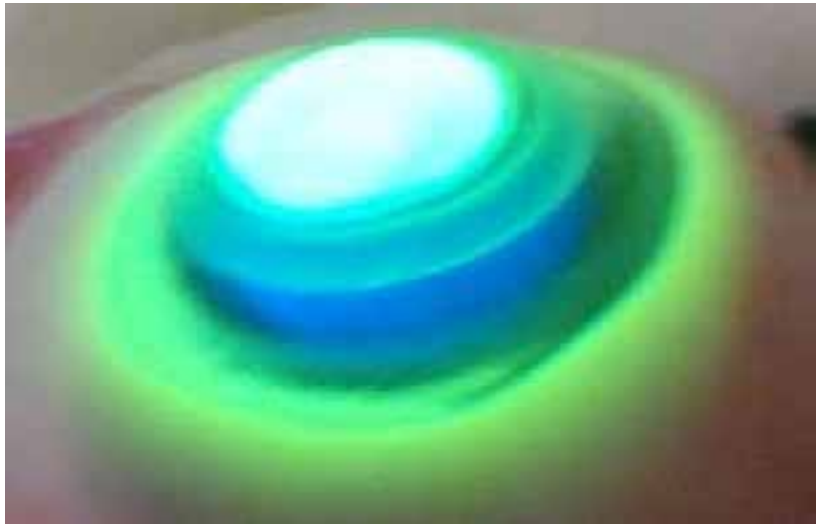
- Fight for Sight Grant
- Randomized bilateral study
- 46 patients (92 eyes)
- Epi off vs iCXL (modified extended protocol)
- Accelerated CXL 9mw/cm2 for 11min
- ISRCT No: 04451470

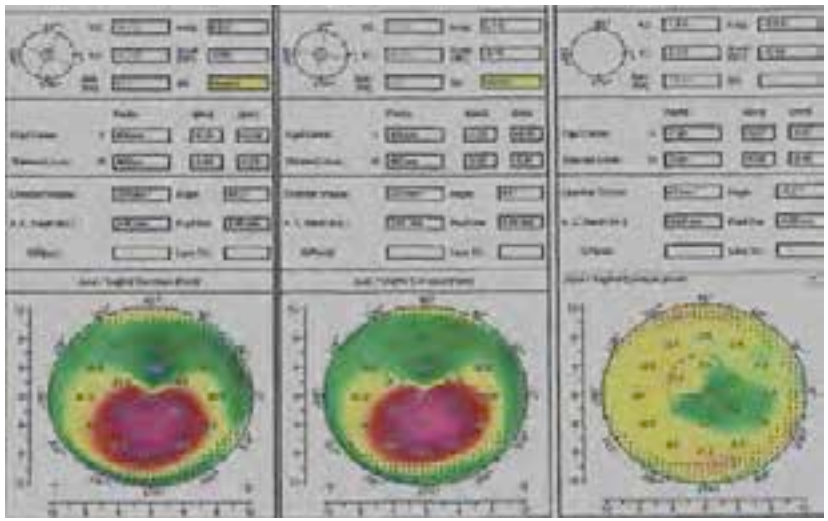
- 49% epithelial defect in iCXL
  - No BC/L
  - (Cacicol, Amnion)

- **12 months**
- 34 iCXL, 37 epi-off
- UCVA, CDVA, SEQ, Cyl, K1, K2, Astig
  - No diff between treatments

- Except reduced pach in Epi-off ($p<0.01$)
  - Not in iCXL

- Trend to greater reduction steepest K in iCXL
  - -0.36D vs -0.17D
- Tend to greater Reduction in Tomographic Astig in iCXL

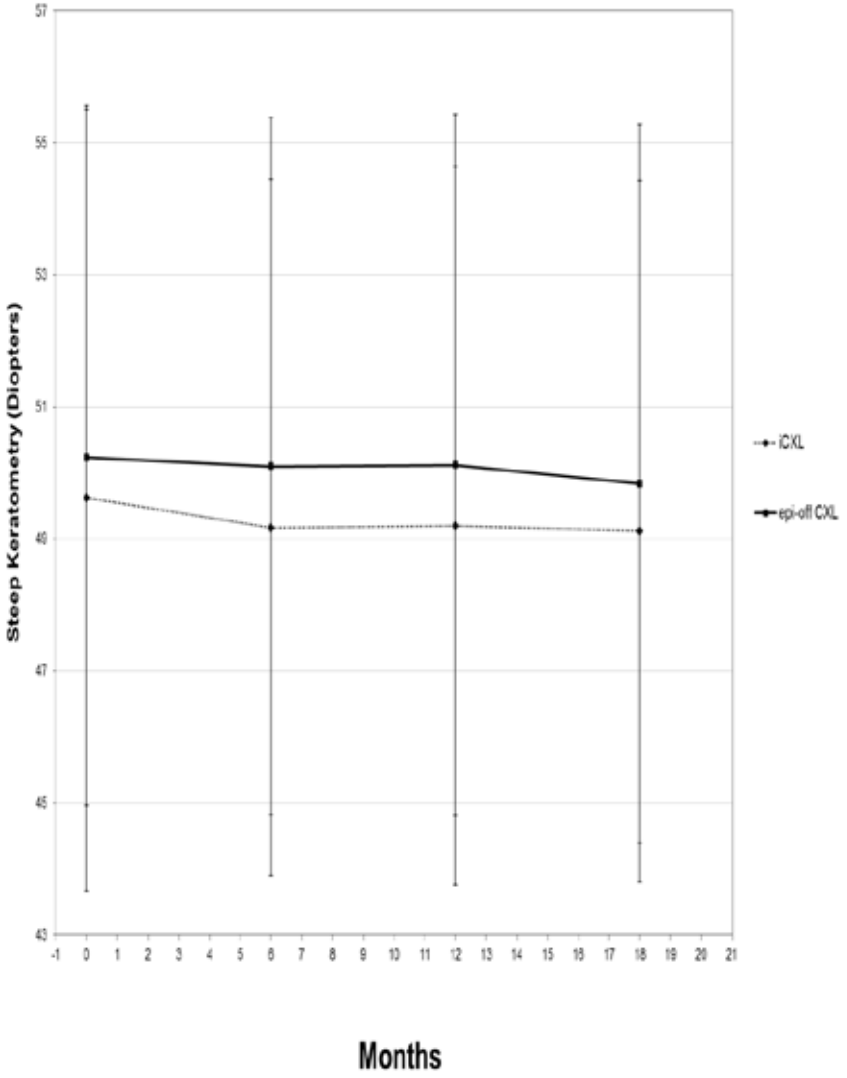




Epithelial on CXL:Iontophoresis

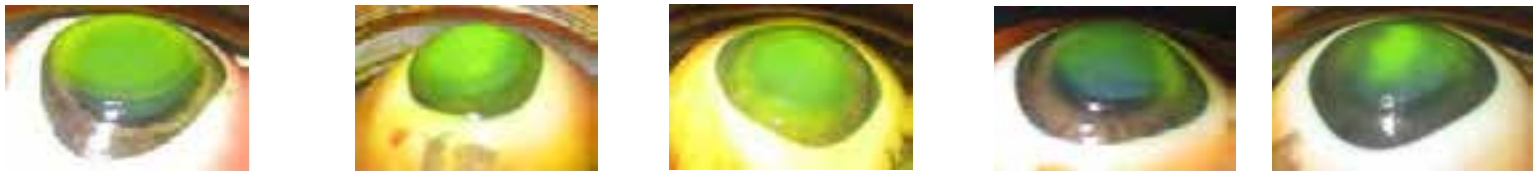
Modified Iontophoresis protocol RCT

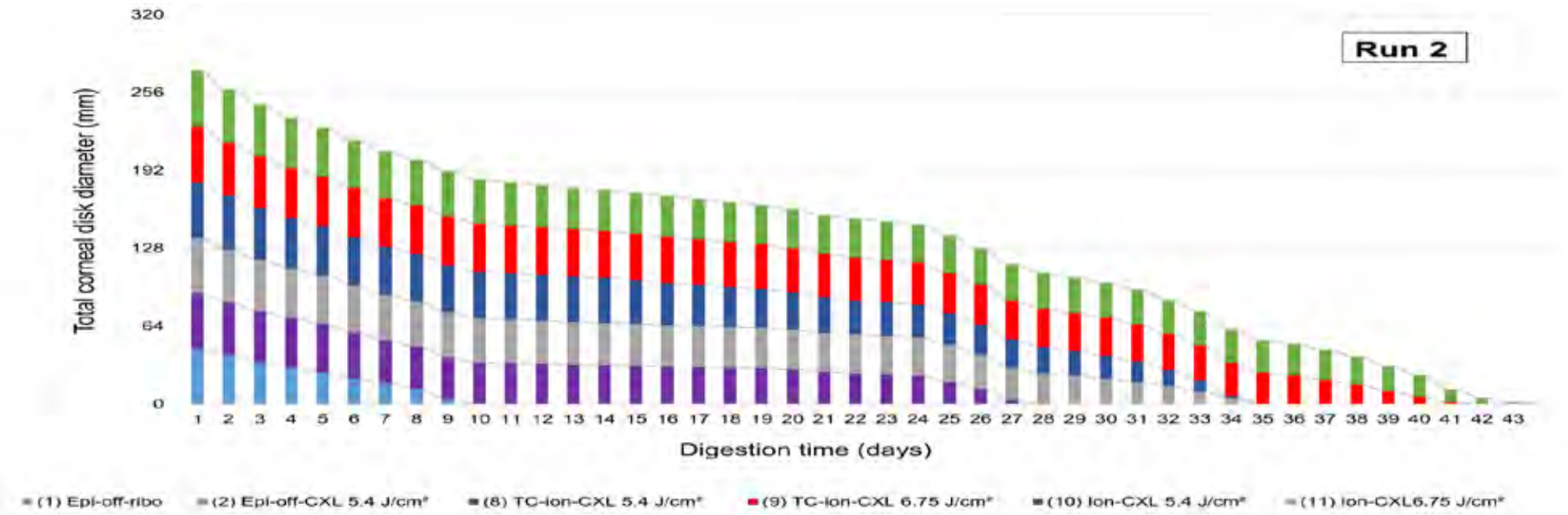
- 18 month follow-up
- 29iCXL, 25 epi-off
- **iCXL**
  - -0.5D reduction Steepest K (p=0.1)
  - -1.2 reduction in Kmax (p<0.03)
  - Reduction in Topographic astig -0.52D (p<0.04)
  - No eye progressed (Kmax >1.5D) (none >1.0D)
  - Index of Height Decentration improved (p<0.0005)
  - Index of vertical asymmetry reduced (p<0.03)
  - Central pach no diff,
  - Thinnest pach reduced (p<0.05)
- **Epi-off**
  - -0.4D reduction Steepest K (p<0.02)
  - -1.0D reduction in Kmax (p=0.002)
  - ?One eye progressed (Kmax increased by 2.0D, mean K only 0.45D)
  - ISV, IVA, IHD, KI improved (p<0.02)
  - Reduced central and thinnest pachymetry (p<0.02)



Aldahlawi, Hayes, O'Brart *Exp Eye Res. 2016 Oct 17.*

Epi-off-ribo | Epi-off-CXL 5.4 J/cm² | TC-ion-CXL 5.4 J/cm² | TC-ion-CXL 6.75 J/cm² | Ion-CXL 5.4 J/cm² | Ion-CXL 6.75 J/cm²





Epithelial on CXL: Conclusions

- Comercially avaialable protocols
  - Limited efficacy compared to epi-off
- Efficacy limited by
  - Stromal riboflavin absorption
  - Epithelial riboflavin masking UV absorption
- Chemical enhancers
  - Associated with epithelial damage
  - Limited stroma Riboflavin uptake
- Modified iontophoretic protocols
  - Increased stroma absorption
  - Up to 80% epi-off
  - Encouraging results with RCT
- Optimization of epi-on protocols
  - Accurate methodology to assessing CXL efficacy
  - Optimal riboflavin stroma concentration
  - Optimum stromal UVA dosage