

Higher Fluence CXL

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School of Medicine

Kanellopoulos, MD

LaserVision.gr
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Financial Interests:

- Alcon/Wavelight
- Bausch & Lomb
- Revision Optics
- Ocular Therapeutix
- Avedro



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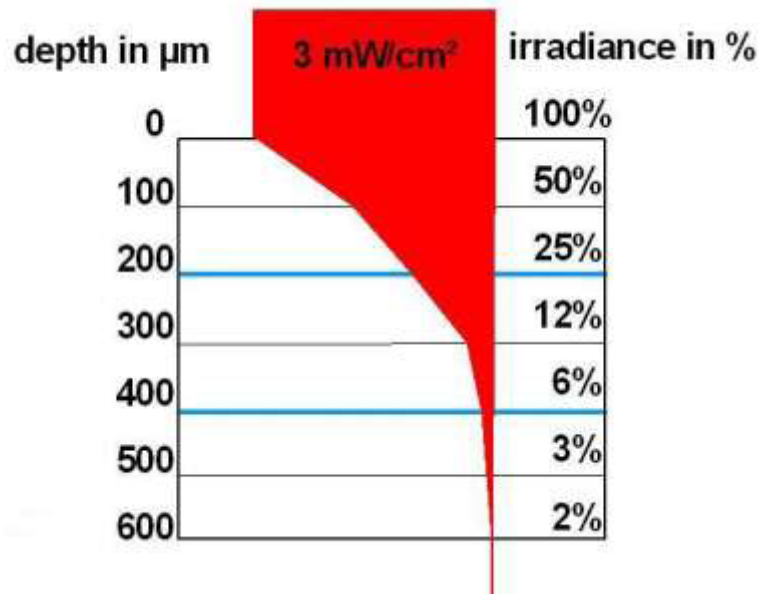
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Decrease of UV-intensity

courtesy E. Spoel MD



3.00 mW/cm²

1.49 mW/cm²

0.74 mW/cm²

0.36 mW/cm²

0.18 mW/cm²

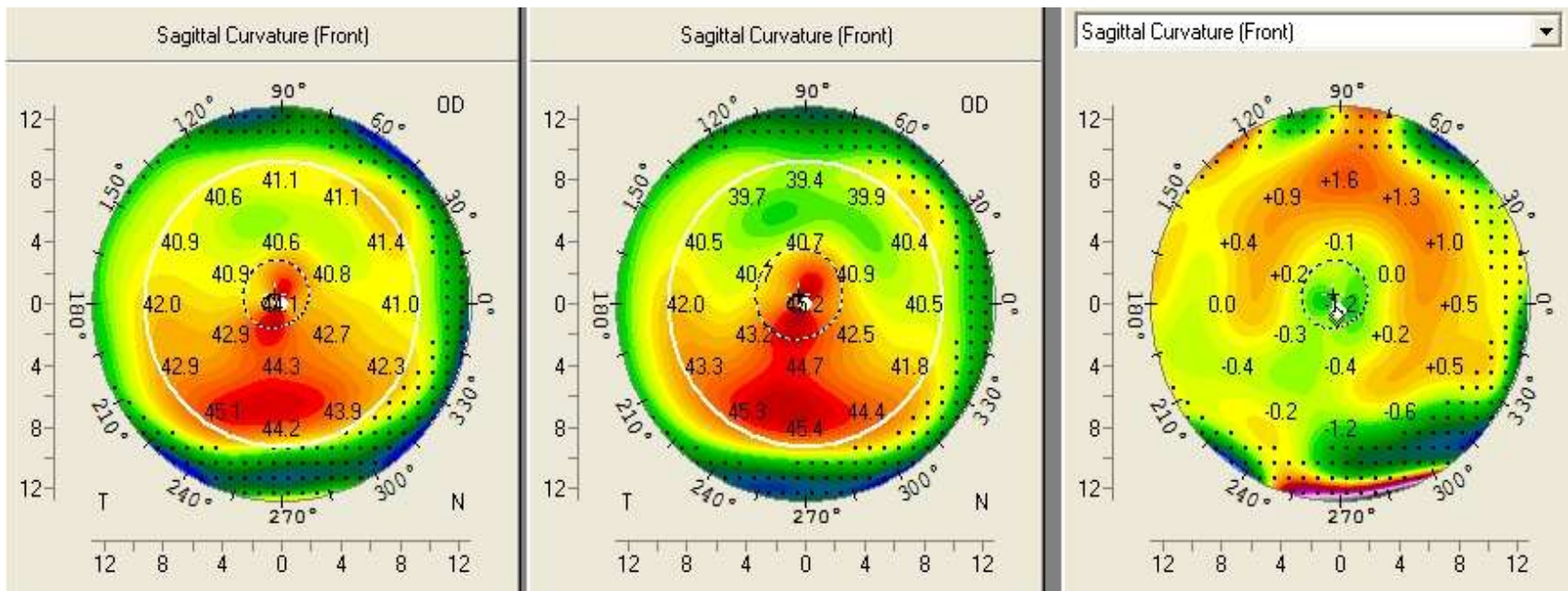
0.09 mW/cm²



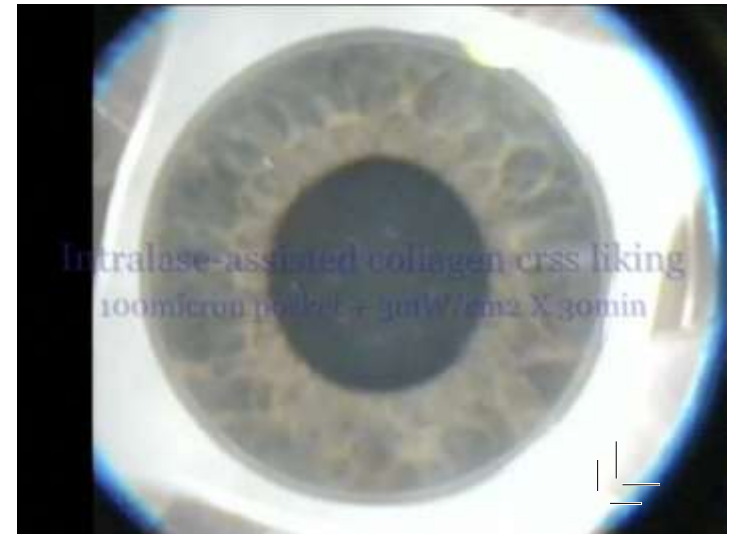
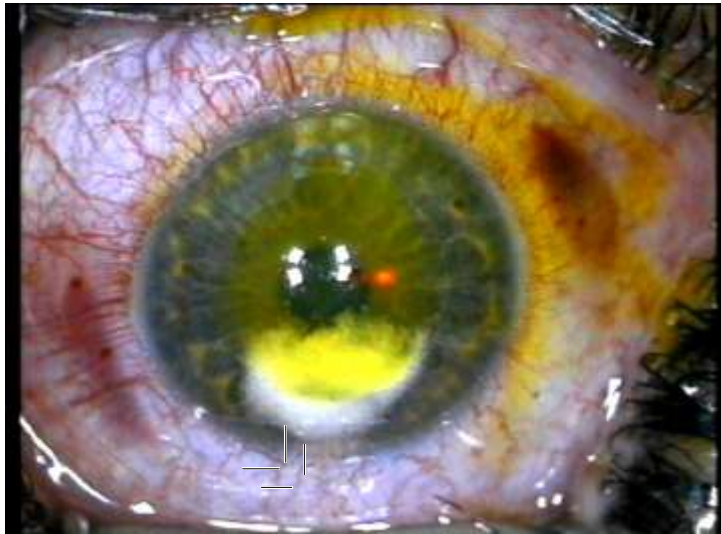
Dresden protocol 3mw/cm²

Post-LASIK ectasia: -1 -1.75@ 75. Pach 445, Treated with epi-on CXL (C3R) 3mW/cm² for 30' in 2005.

Same case seen 3 years later with ectasia progression



Introduction of riboflavin in a femto-pocket CXL with 10mW/cm² for 10 minutes



NEW TECHNIQUE





Collagen Cross-linking in Early Keratoconus With Riboflavin in a Femtosecond Laser-created Pocket: Initial Clinical Results

Anastasios John Kanellopoulos, MD

We introduced: Higher fluence CXL: 6 mW/cm²

AAO 2008:
CXL for 15
minutes
utilizing
7mW/cm²
fluence




Shorter duration, higher ultraviolet A irradiation (UVA) fluence collagen cross-linking (CCL) for keratoconus (KCN)

A. John Kanellopoulos, MD

From the: New York University School of Medicine, Manhattan Eye, Ear and Throat Hospital, New York, NY, USA
Laservision.gr Institute, Athens, Greece



Laservision.gr

Background:
We have presented our experience over the last 6 years in using this entity in its standard form in past AAO meetings. With goal to shorten the duration and potentially increase efficacy we opted to study a model of CCL of higher UVA light intensity (from 3mW to 7 mW/cm²) and the same adjunct 0.1% topical riboflavin sodium phosphate solution.

Objective: To evaluate the safety and efficacy of higher UVA fluence and shorter duration for collagen cross-linking in KCN.

Design: Prospective, randomised comparative case series.

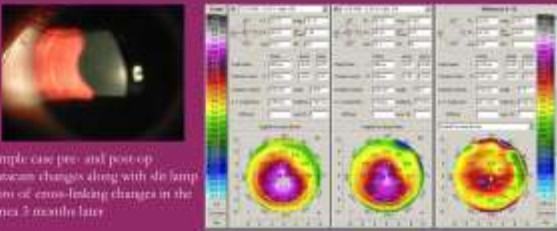
Methods: 15 patients with bilateral keratoconus were studied. All cases were evaluated for UCVA, BSCVA, refraction, keratometry changes (K), topography changes, endothelium cell changes and cornea clarity. All eyes received CCL with topical 0.1% riboflavin solution drops and in regard to UVA they were randomized for each patient; 15 eyes were CCL with 7mW/cm² for 15 minutes and the 15 contra lateral eyes with 3mW/cm² for 30 minutes. Mean follow up was 1.5 years.

	UCVA	BSCVA	Sph. EQ change	Cylinder change	ECC change	Topo change *	Complications
7mW	0.2	0.3	1.5D	2.2D	100	2.3	0
3mW	0.2	0.3	1.4D	2D	200	2.1	0

Results:
The mean improvement of UCVA was 0.2 to 0.4, BSCVA improved from 0.4 to 0.7, The average change of spherical equivalent was 1.5D reduction in myopia, the average change in cylinder was 2.1D reduction, The average highest keratometry was 51.2D pre-op and changed to 48.5D post-op. There was no statistical difference in the means in the 2 groups.

Conclusions:
Shorter duration, higher UVA fluence CCL appears to be as safe and as effective in stabilization of ectasia in KCN. It may cause less cell toxicity due to lesser cornea dehydration (less time) and shorter exposure of keratocytes and endothelial cells to UV light along with riboflavin. Further studies are needed to validate this data.

Figure: Example case pre- and post-op. Between changes along with 40 lamp photo of cross-linking changes in the cornea 3 months later.




Zurich 2007: CXL for PBK: 2 femto pockets and CXL with 10mW/cm²

Staged Intrastromal Delivery of Riboflavin With UVA Cross-linking in Advanced Bullous Keratopathy: Laboratory Investigation and First Clinical Case

Ronald R. Krueger, MD, MSE; Jerome C. Ramos-Esteban, MD; A. John Kanellopoulos, MD

UVA Cross-linking in Advanced Bullous Keratopathy/Krueger et al

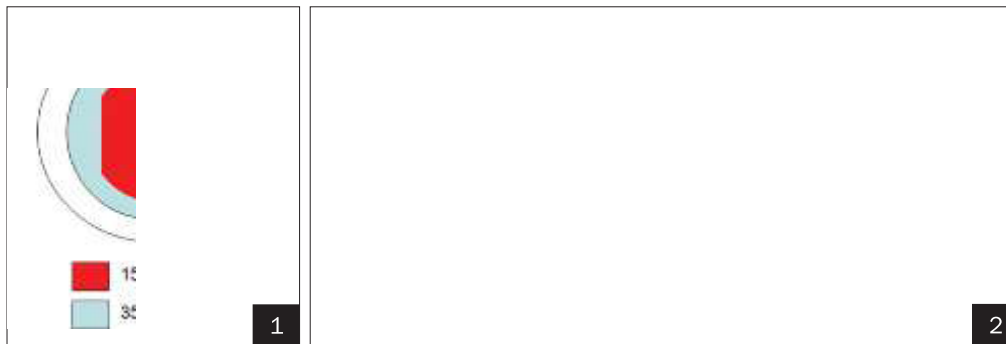


Figure 1. Schematic representation of the pockets created during staged intrastromal injection of 0.1% riboflavin and UVA cross-linking. **Figure 2.** Staged intrastromal injection of 0.1% riboflavin and UVA cross-linking.

WITH UVA Cross-linking in Advanced Bullous Keratopathy: Laboratory Investigation and First Clinical Case

Ronald R. Krueger, MD, MSE; Jerome C. Ramos-Esteban, MD; A. John Kanellopoulos, MD

Abstract

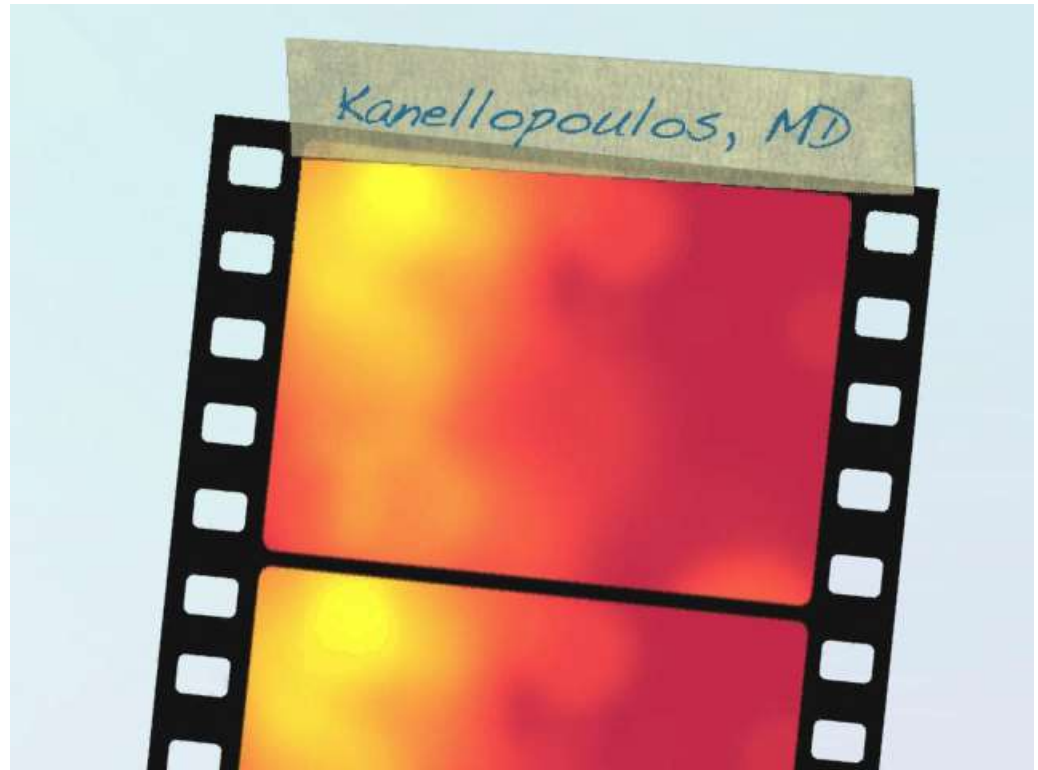
PURPOSE: To evaluate the safety and efficacy of staged intrastromal 0.1% cross-linking riboflavin combined with UVA cross-linking in eyes with advanced bullous keratopathy.

DESIGN: In vitro cornea studies for 10 days and 100 days in a porcine model without and with UVA cross-linking (cross-linking riboflavin). The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes. The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes. The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes.

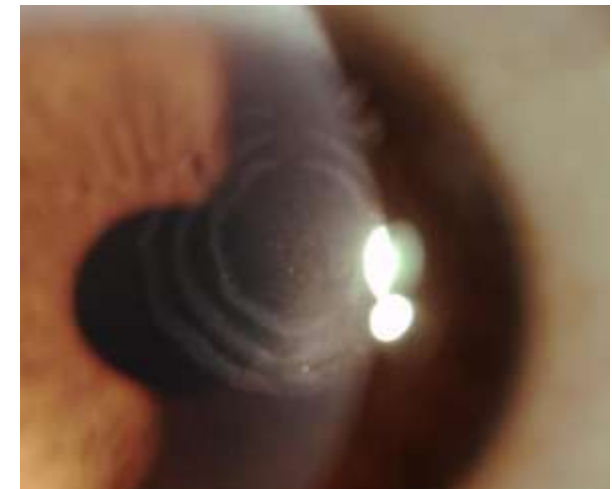
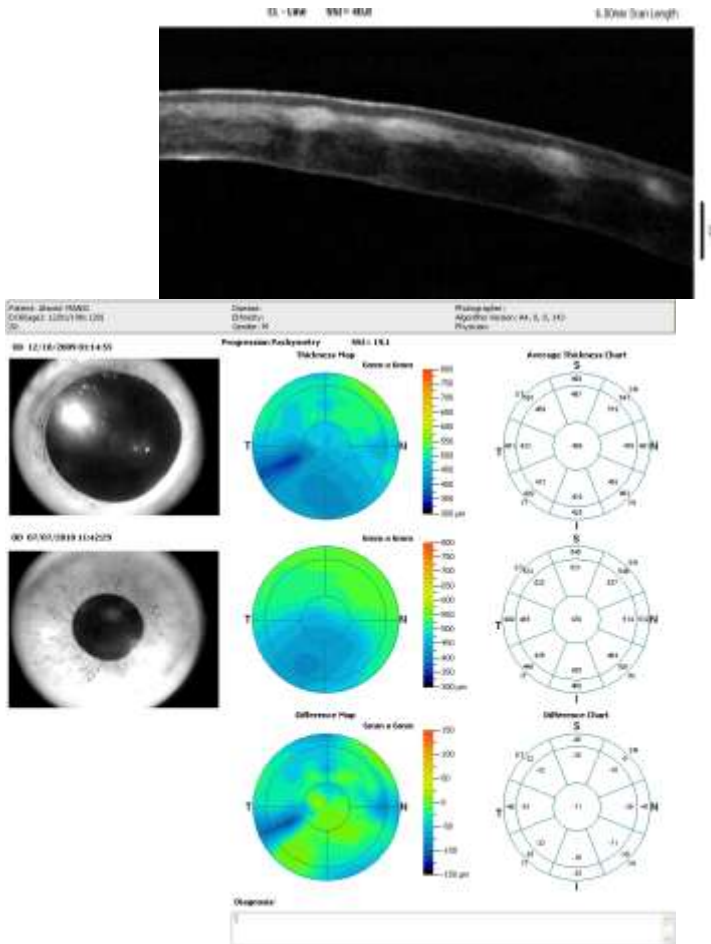
RESULTS: In vitro cornea studies for 10 days and 100 days in a porcine model without and with UVA cross-linking (cross-linking riboflavin). The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes. The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes. The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes. The cornea was stained with 0.1% and 0.2% riboflavin and exposed to UVA cross-linking (300-400 nm) for 10 and 20 minutes.

Cornea remodeling without tissue removal shrinkage + CXL (10mW/cm² x 10')

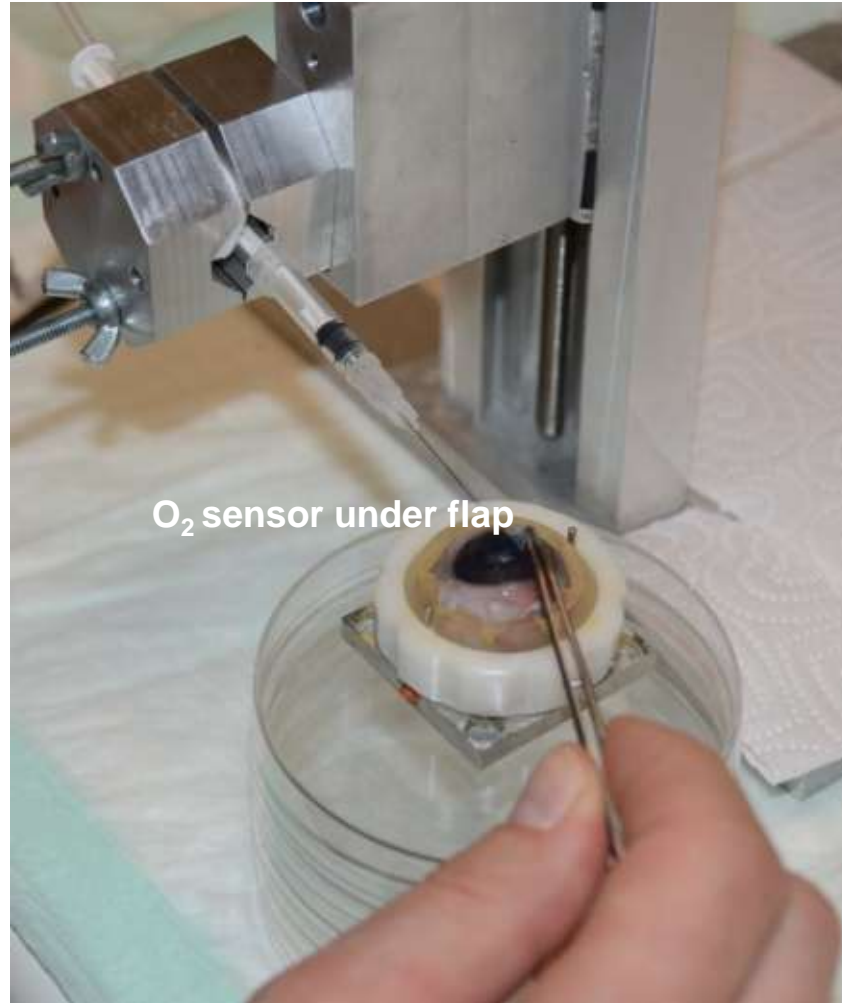
- Avedro,
Keraflex first
reports
- Kanellopoulos,
Herakar:TRXL



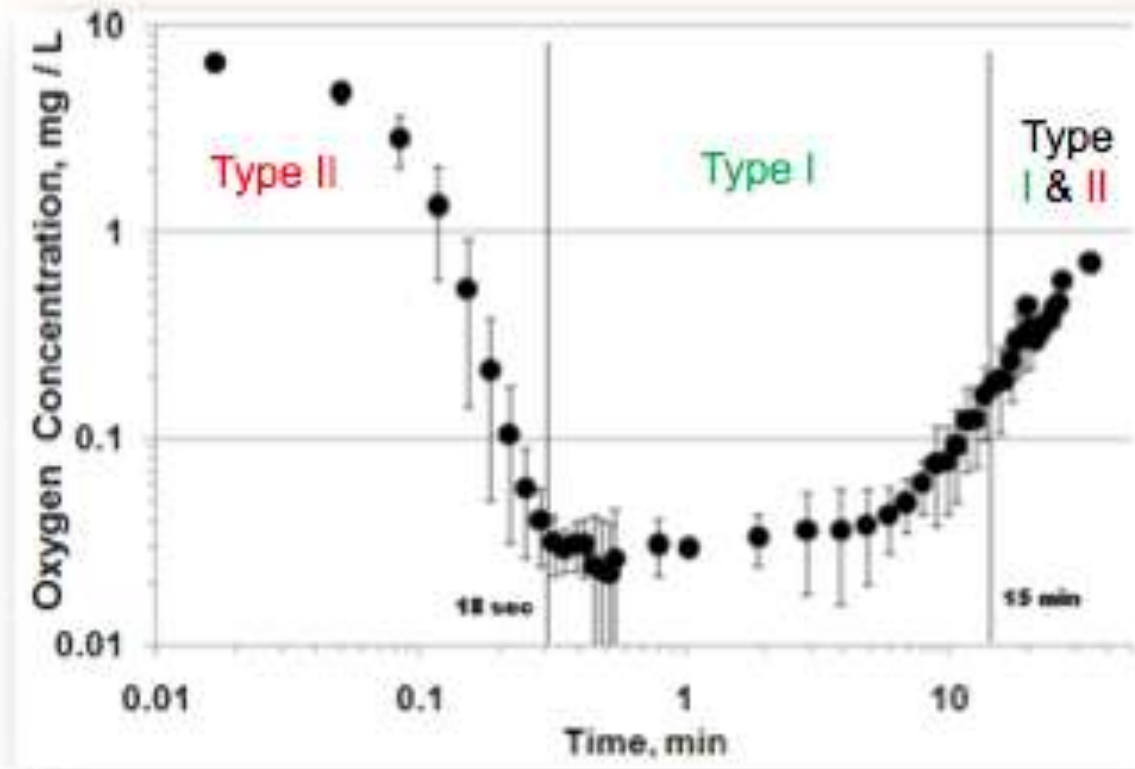
10 minute postop-Cornea OCT -8 months follow-up No regression of the flattening effect!



Experimental setup



Oxygen Depletion Over 30 Minutes



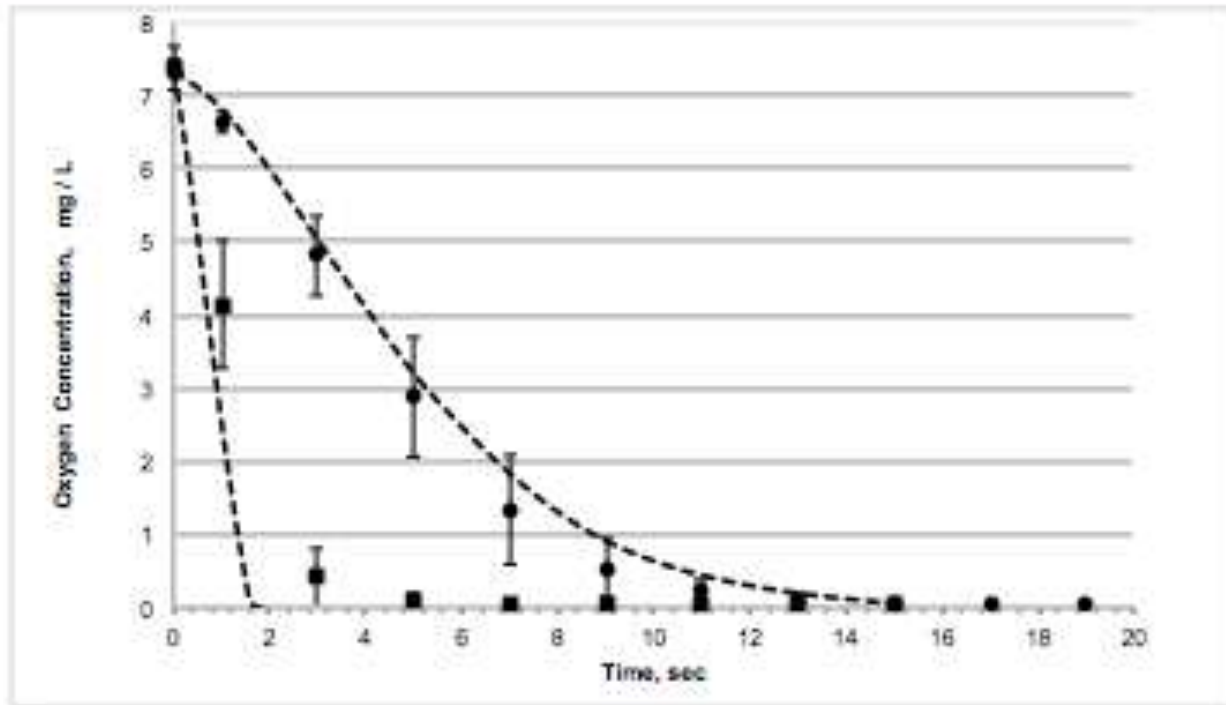
Depletion and gradual replenishment of dissolved oxygen below a 100 μm thick corneal flap, saturated with 0.1% RF during 3 mW/cm^2 UVA irradiation at 25 $^{\circ}\text{C}$.

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Theoretical Model vs Experimental Data



Depletion of dissolved oxygen below a 100 μm thick corneal flap, saturated with 0.1% RF during 3 mW/cm^2 (•) and 30 mW/cm^2 (■) UVA irradiation at 25 $^{\circ}\text{C}$. Dashed lines are the modeled results.

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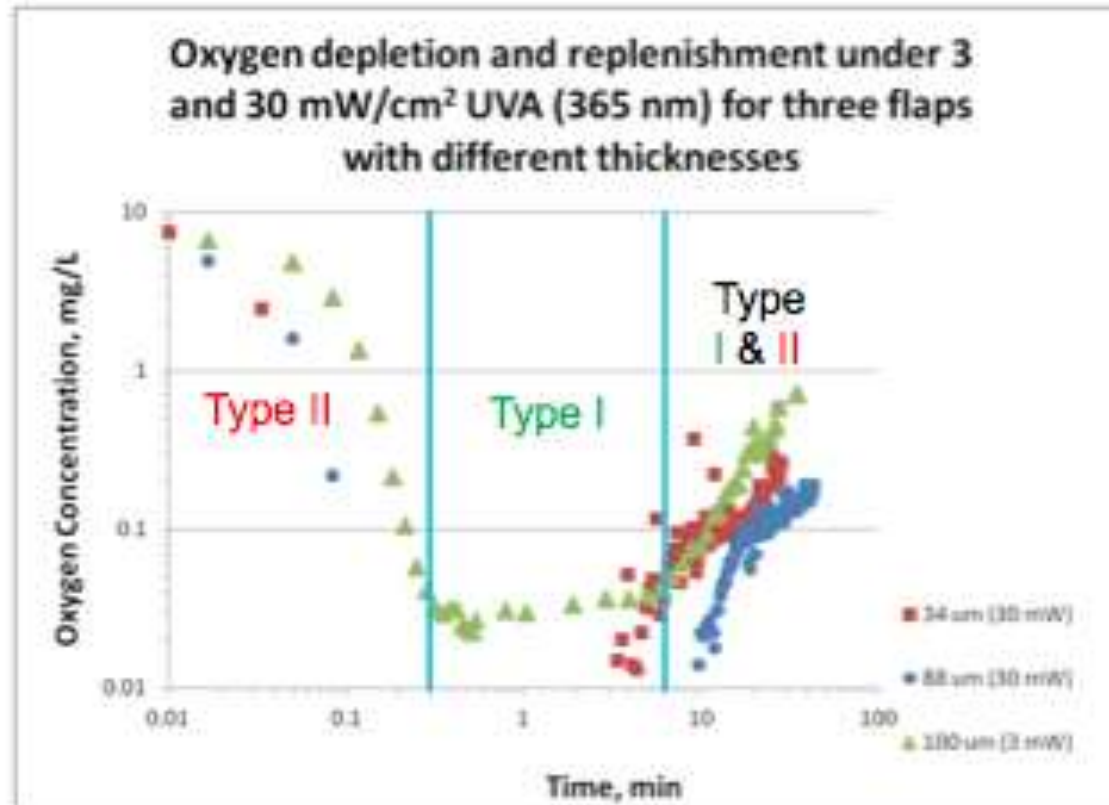
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Oxygen Depletion Over 30 Minutes



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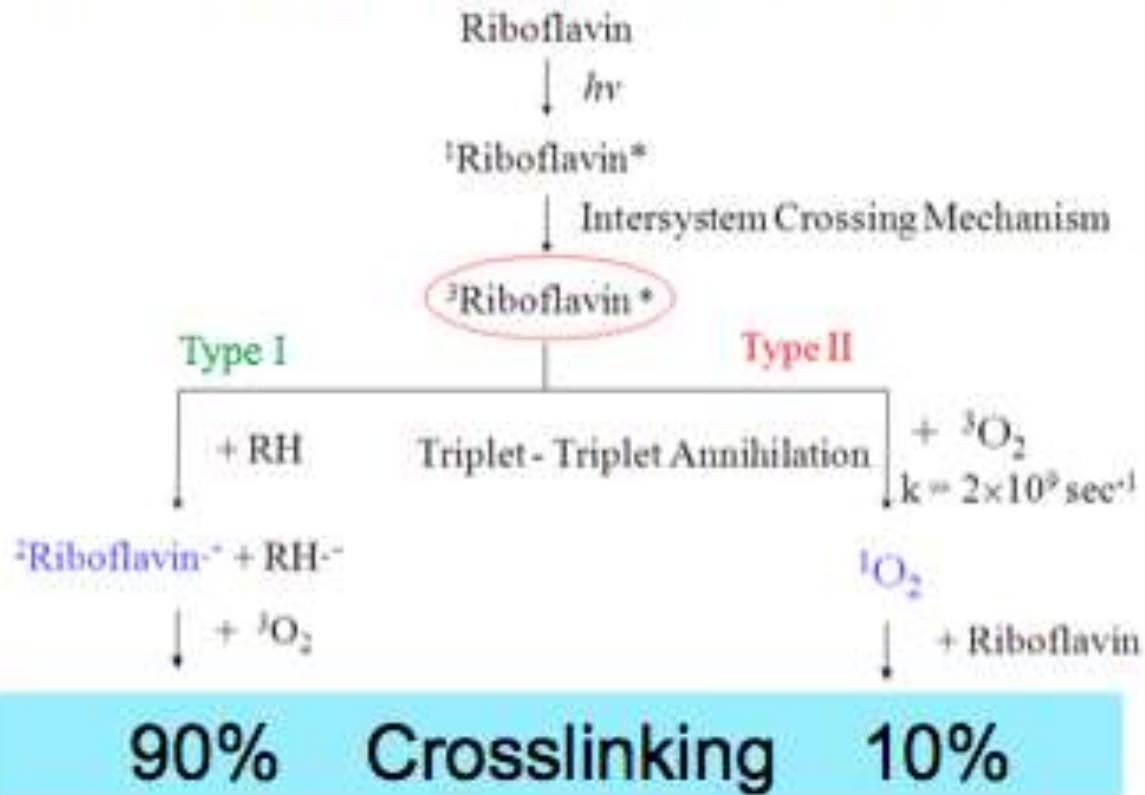
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Theoretical Model for Cross-linking

2 General Paths For Riboflavin And Oxygen Reactions



?lumiflavins
1DFR
5DFR
DMRF
iprRF

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The Athens Protocol: topo-guided PRK+6mW/cm² CXL x15'

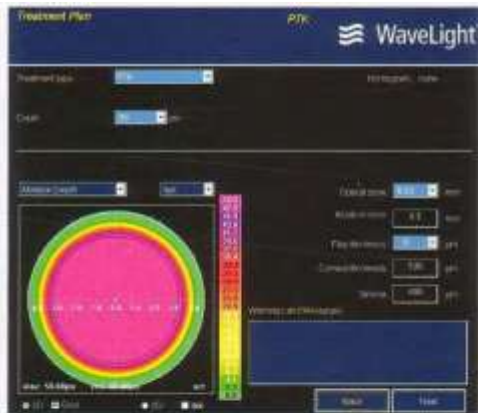


Figure 4.1: Epithelium removed with 50 micron PTK



Figure 4.3: Topography-guided PRK to correct part of the refractive error (TCAT treatment plan) maximal thickness removal 50 microns

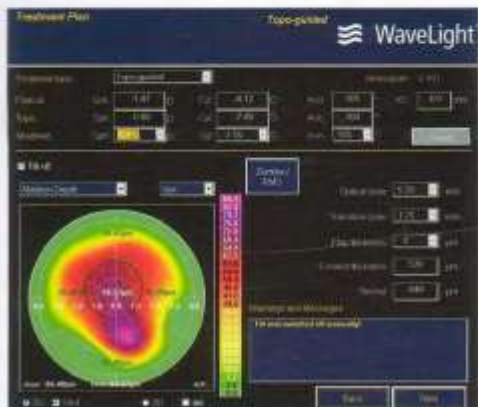


Figure 4.2: TC at treatment plan

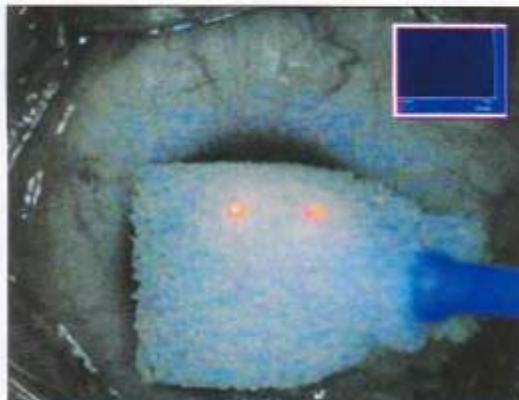
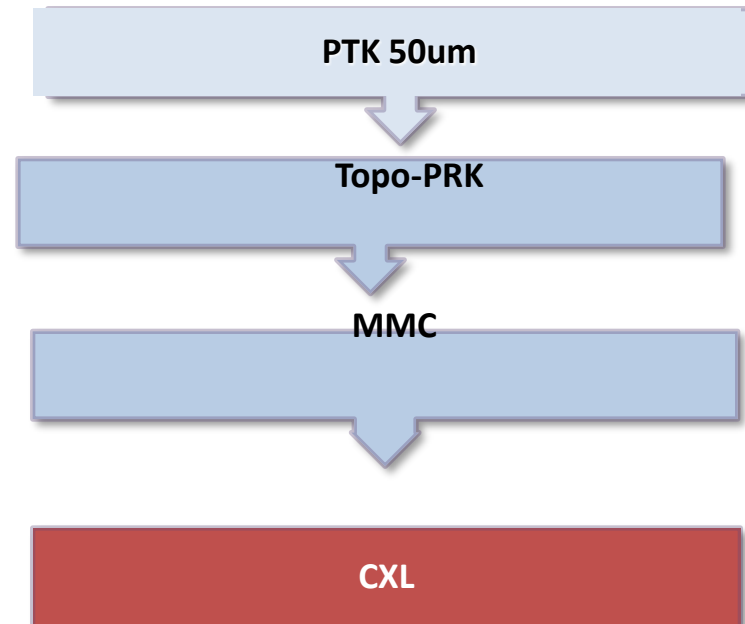
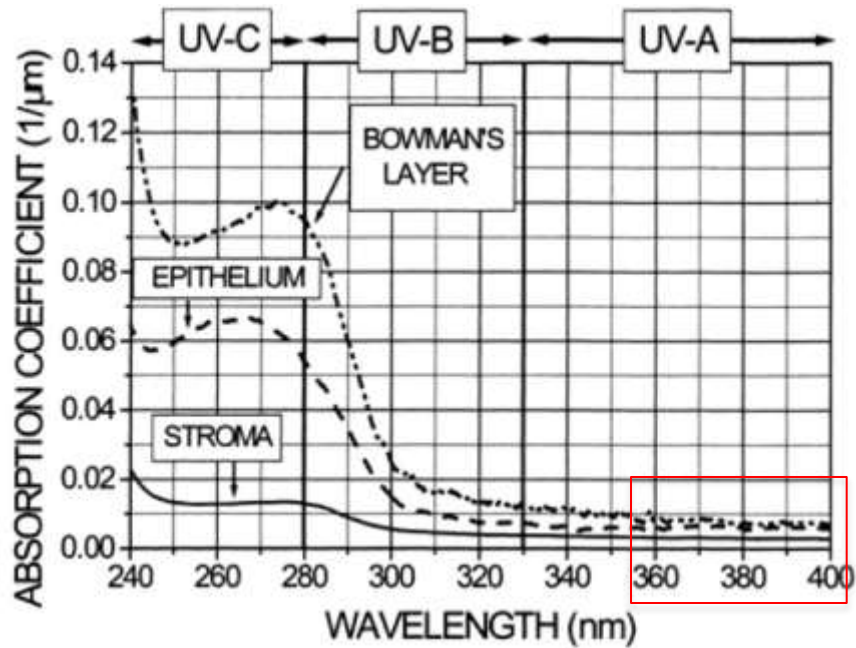


Figure 4.4: MMC solution 0.02% for 20 seconds



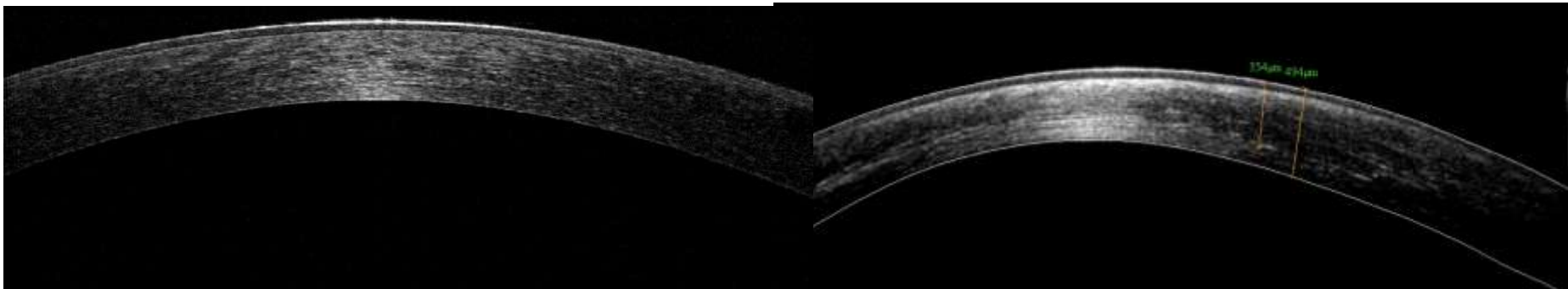


Comparison of Sequential vs Same-day Simultaneous Collagen Cross-linking and Topography-guided PRK for Treatment of Keratoconus

Anastasios John Kanellopoulos, MD

JRS Sept 2009

Kolozsvári et al
IOVS 2002;43:2165-2168



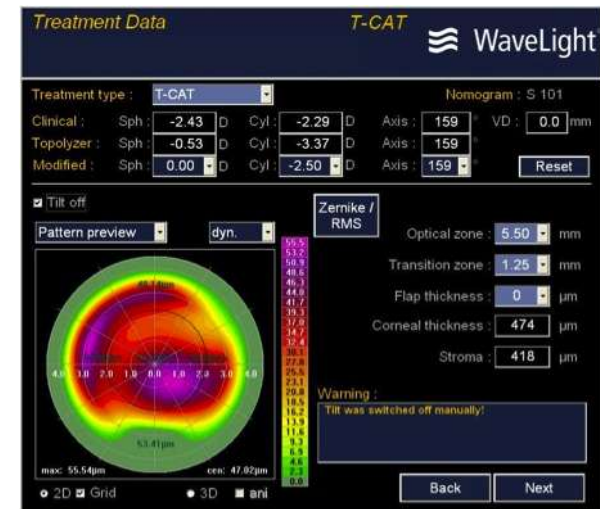
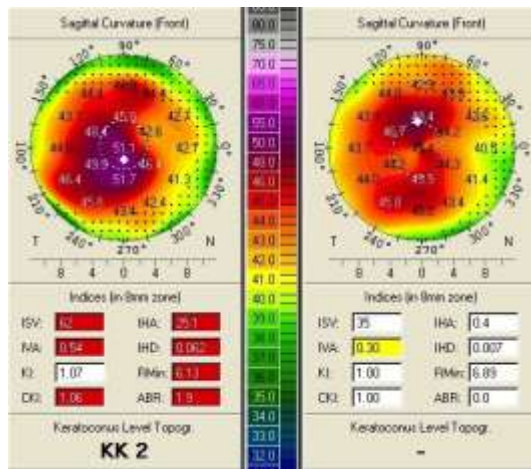
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The Athens Protocol: Simultaneous surface ablation and CXL for correction of Refractive error in eyes with early keratoconus

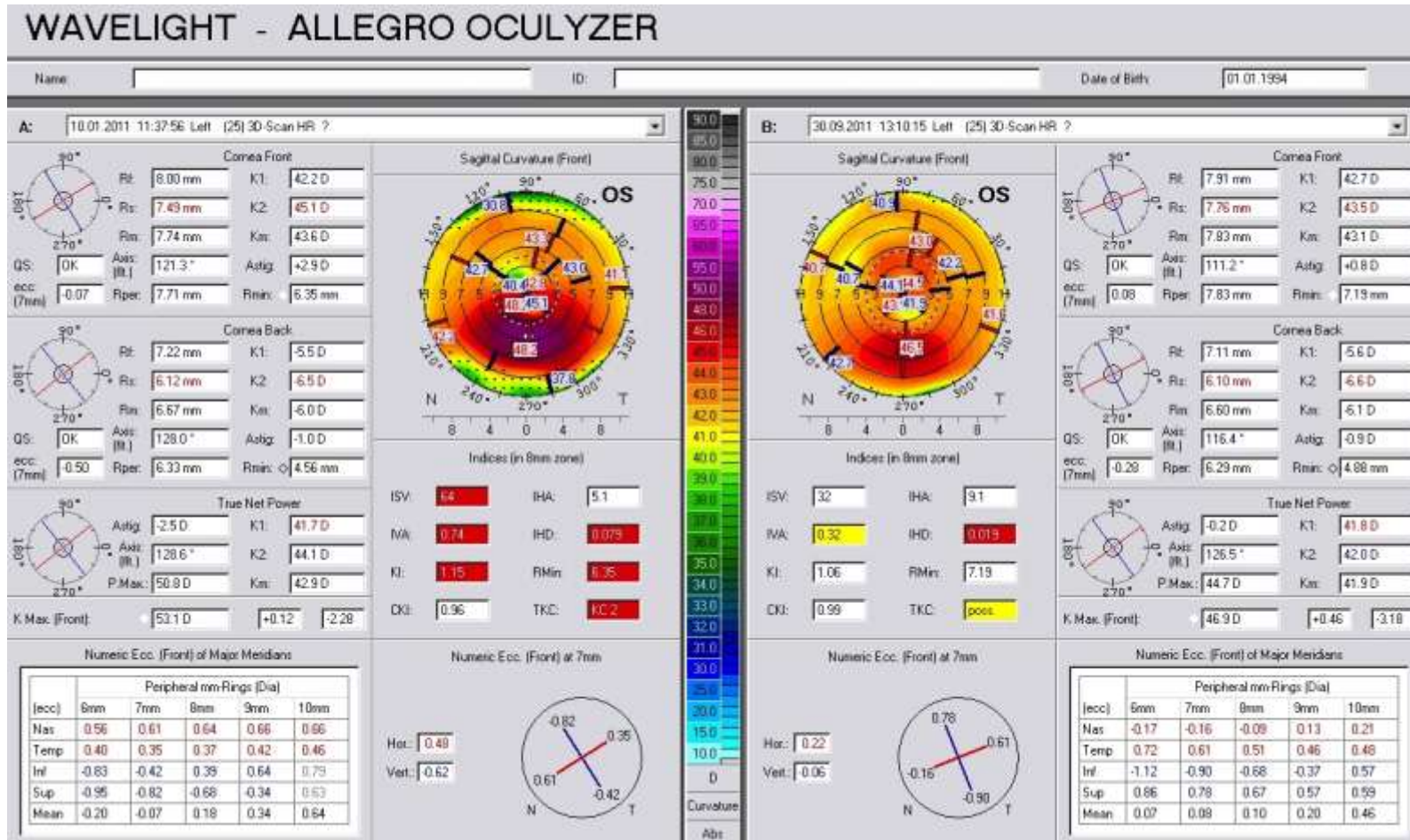


ISRS/AAO keynote



Topometric improvement: Significant reduction in IHD Myopia induction!:

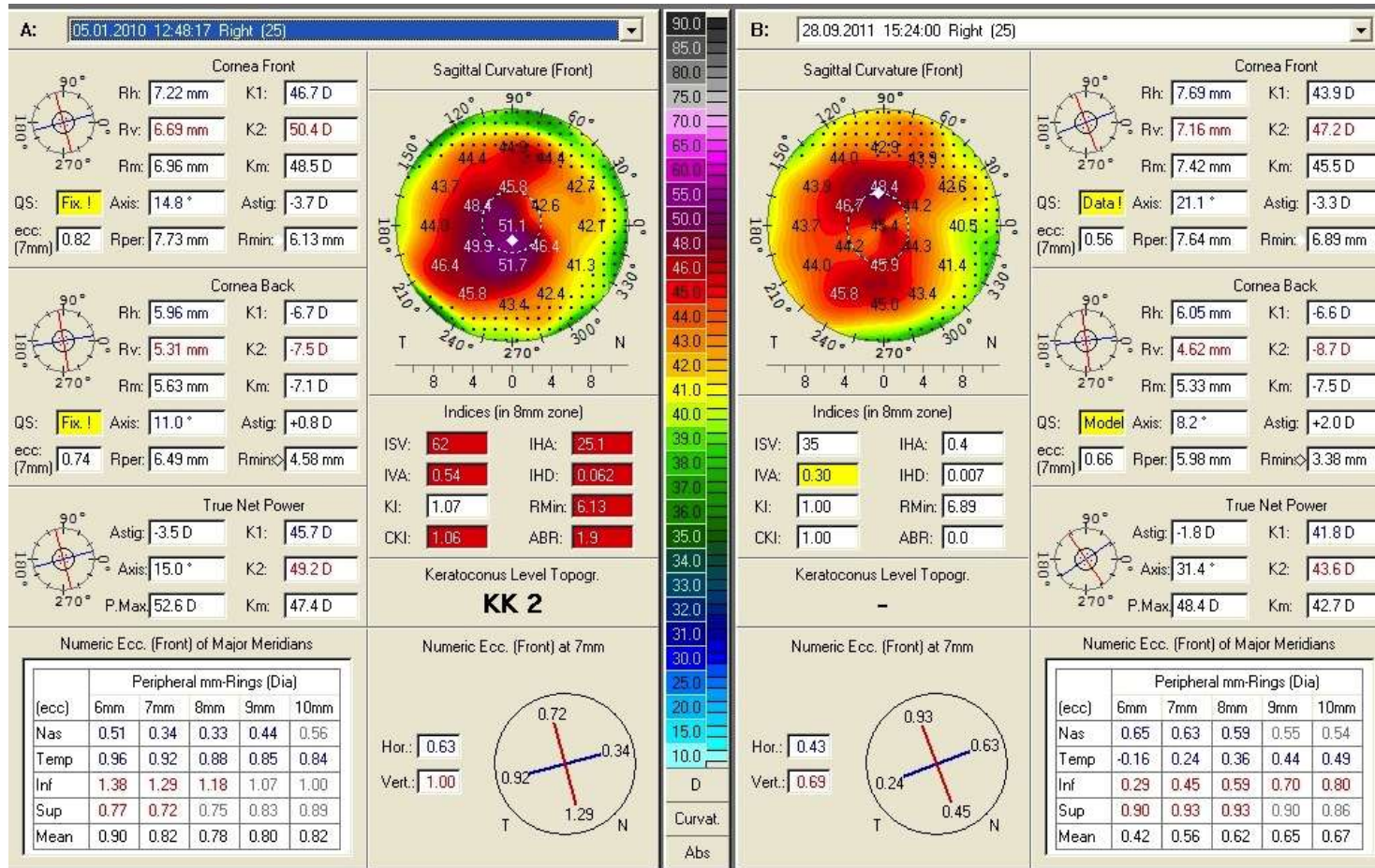
Refraction from +0.75-3.50@10 (20/60) to -0.75-0.75@170 (20/20) due to improvement of the topometric parameters



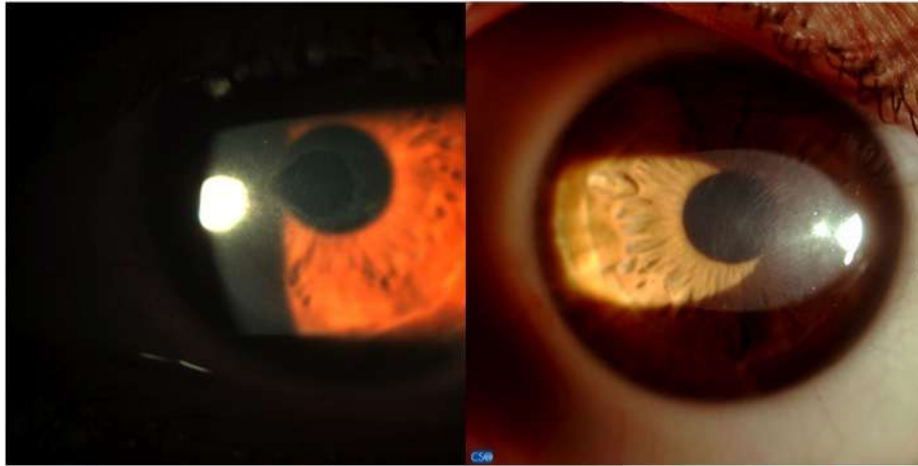
2 year follow up in a 15 y/o

Topometric improvement:

Significant reduction in IHD (Index of Height Decentration)



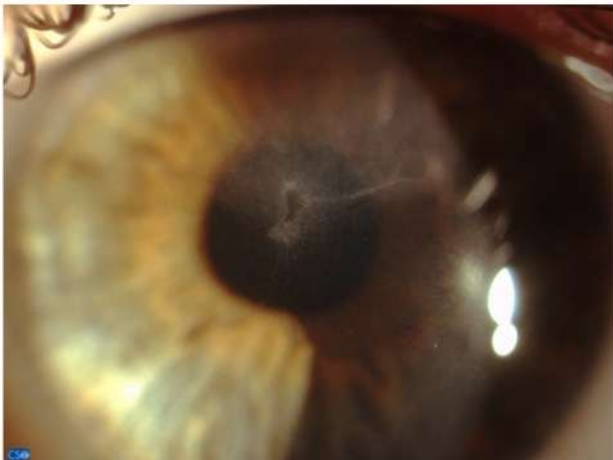
Healing delay-day4-ok on 1 month



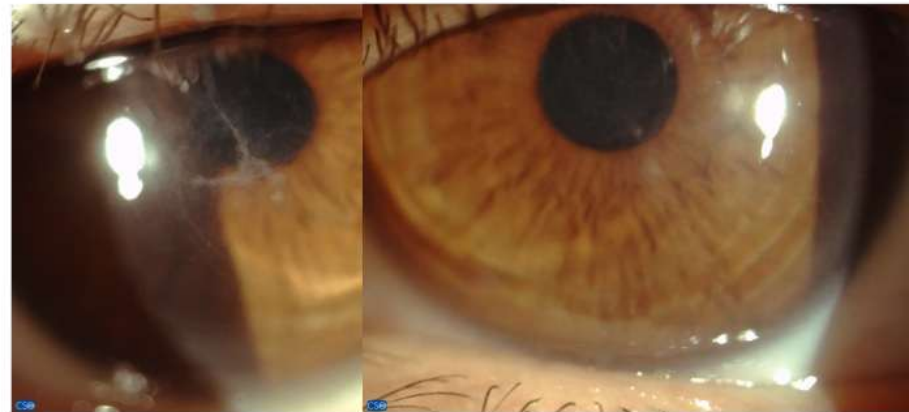
PRK-like haze 1 year after, in heavy sunbathing improved with steroids



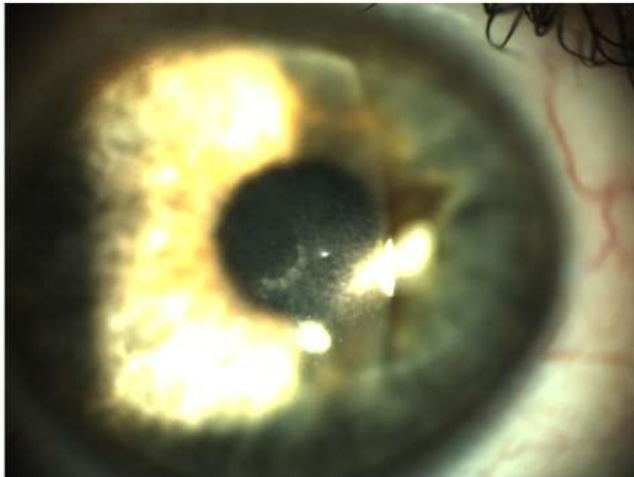
Week 2



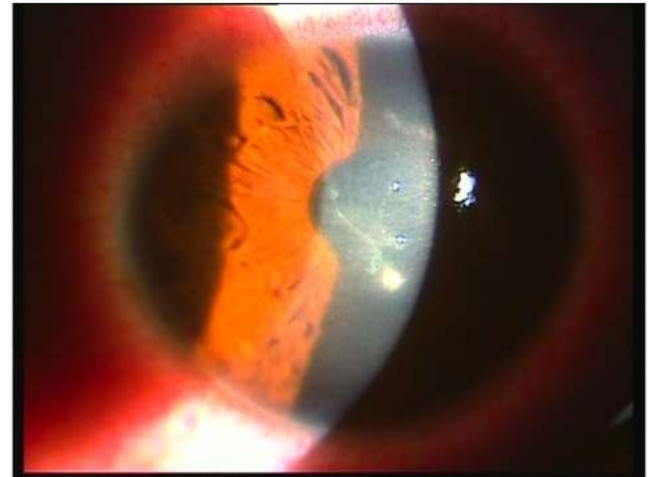
Week 2



Salzman's-like nodule(s) can persist to 3 months postop



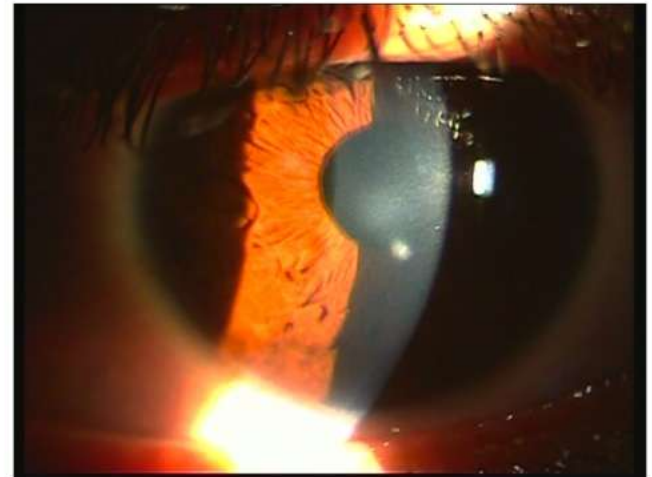
Delayed epithelial healing with white spots



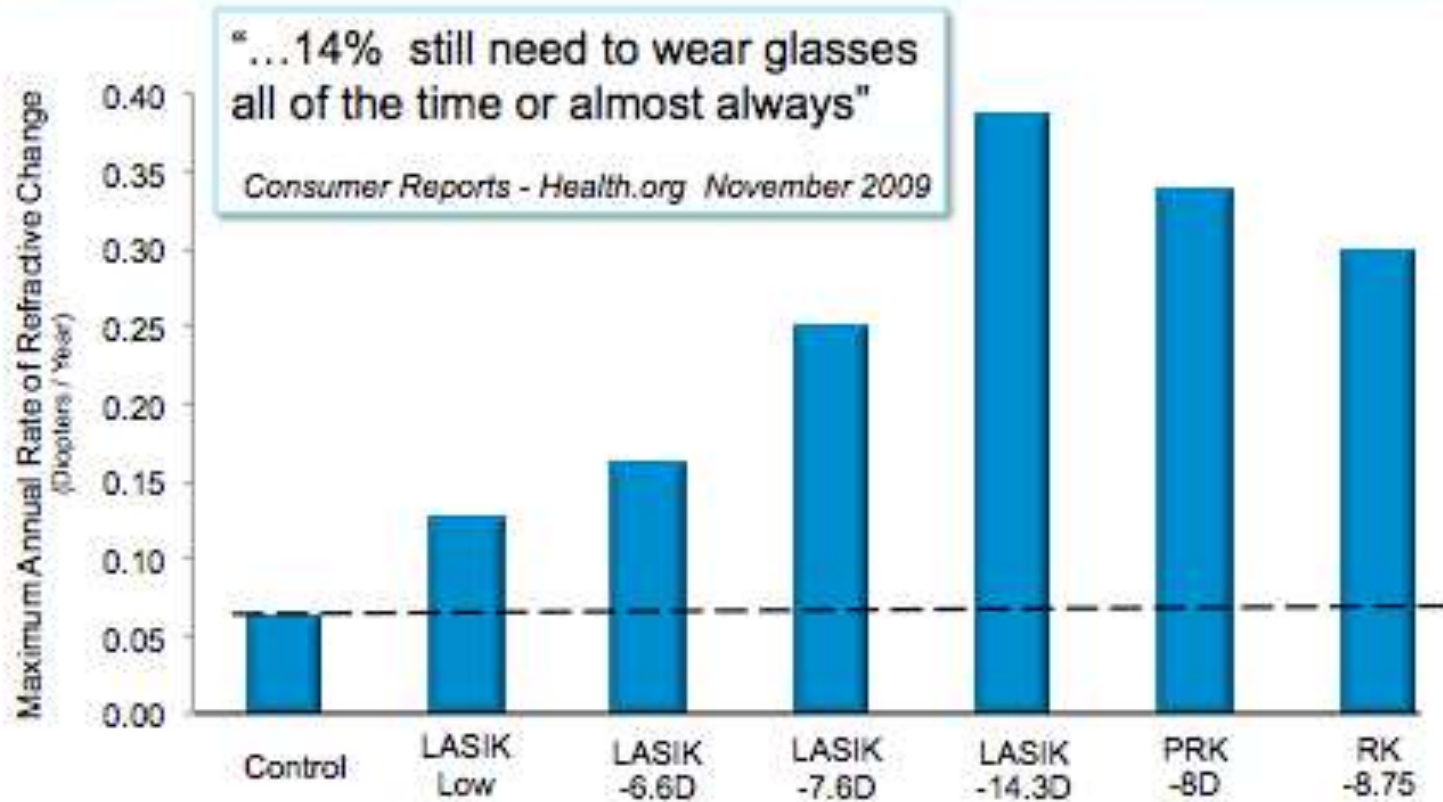
Haze



Faint Scar and white spot



Long term LASIK regressions:



AAO/ESCRS 2008 Prophylactic CXL in LASIK



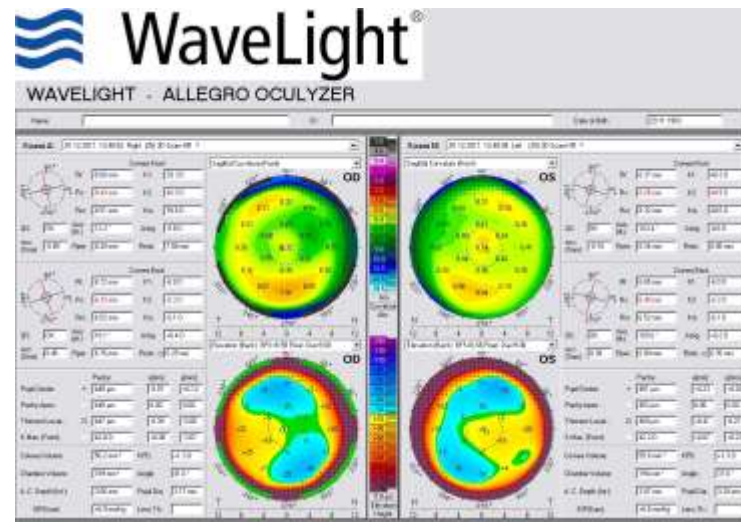
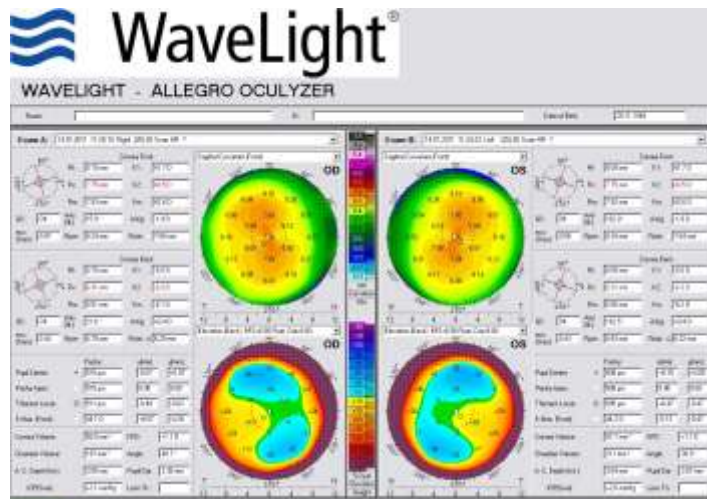
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www.brilliantvision.com
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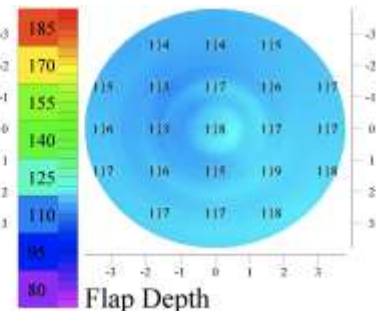
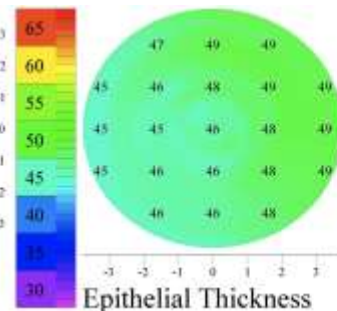
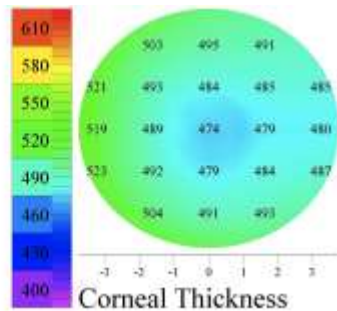
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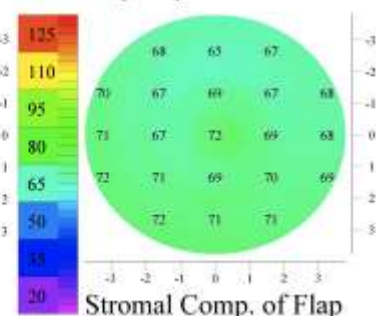
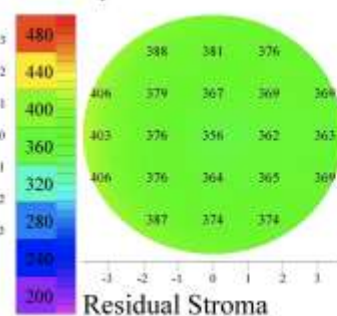
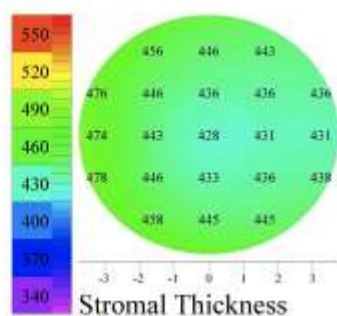
Every day practice LASIK Xtra



Mean Epithelial Thickness Overall	47um
Minimum Stromal Thickness	427um
Minimum Corneal Thickness	473um
Mean Corneal Thickness @ 0-3 mm	478um
Mean Corneal Thickness @ 3-6 mm	489um



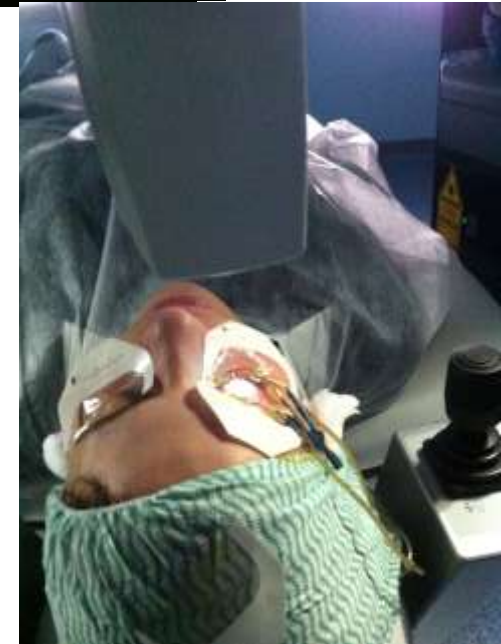
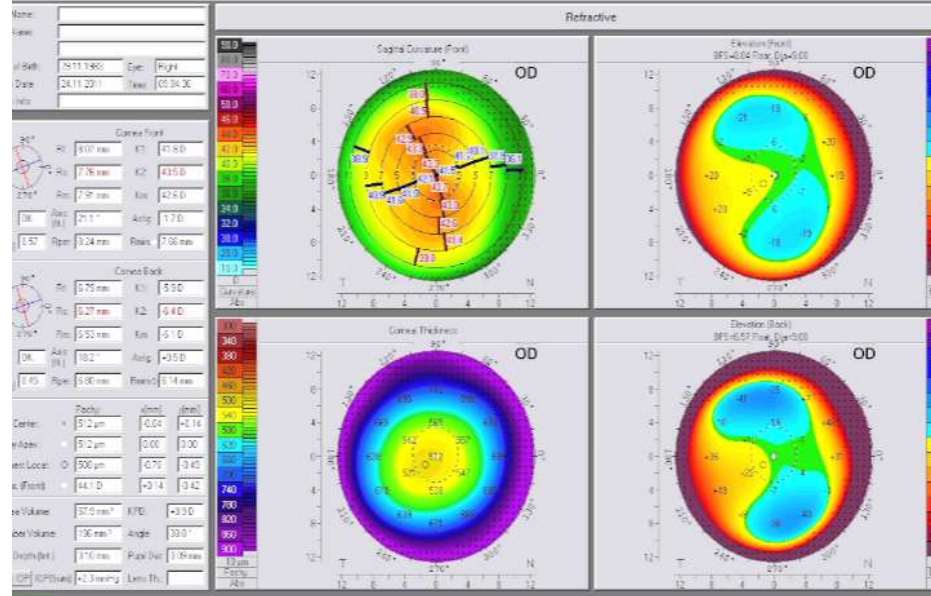
Minimum Residual Stroma	354um
Mean Stromal Component of Flap	69um
Mean Flap Depth Overall	116um
Mean Flap Depth @ 0-3 mm	117um
Mean Flap Depth @ 3-6 mm	116um



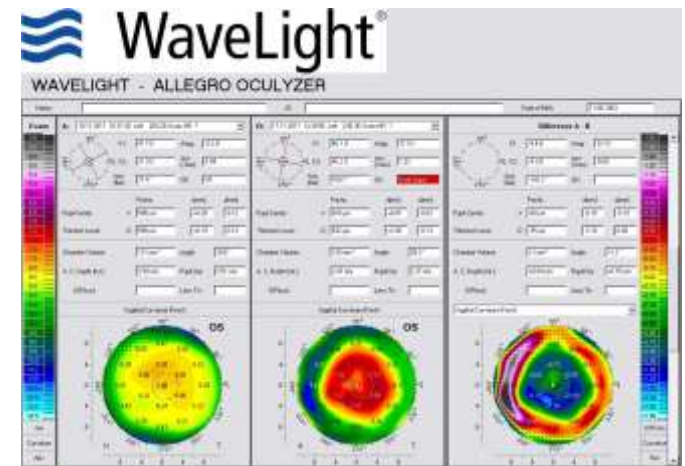
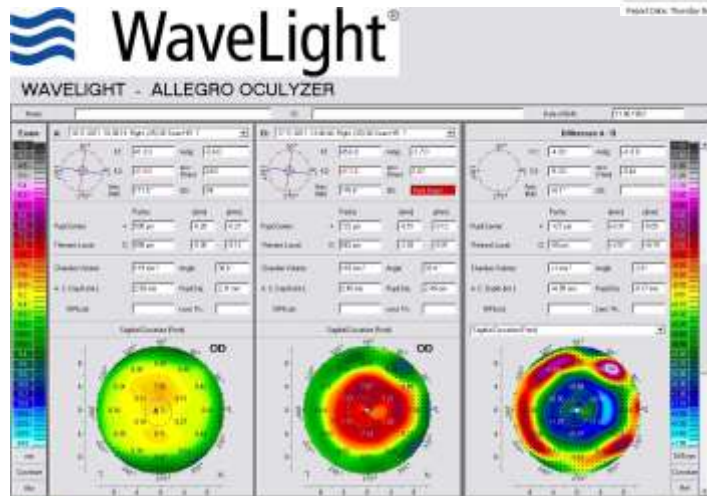
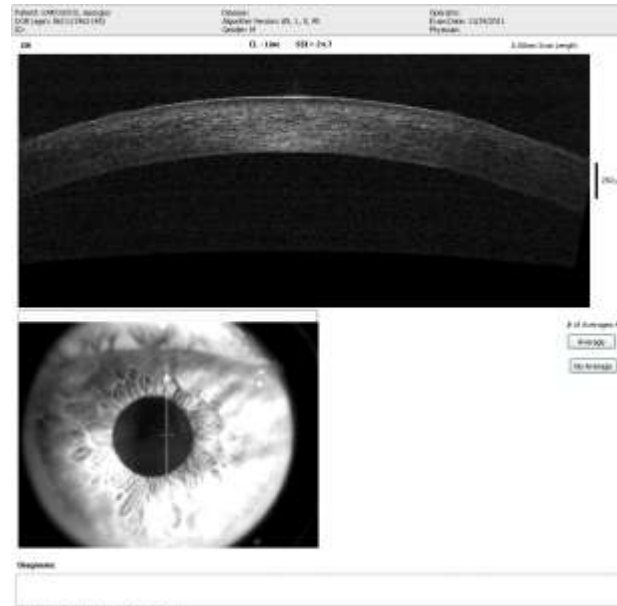
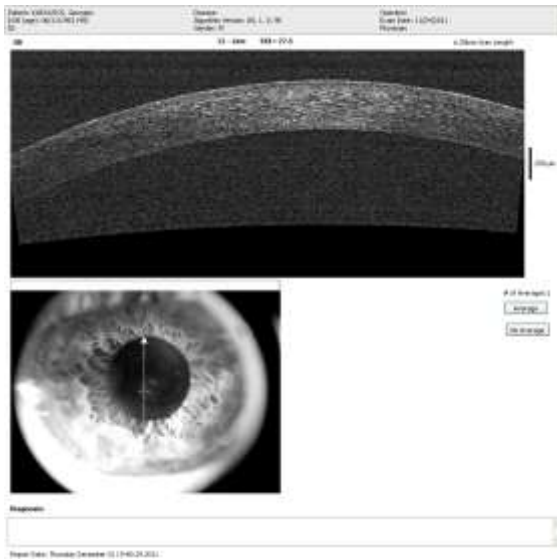
LASIK Xtra within the Alcon Refractive Suite



WAVELIGHT - ALLEGRO OCULYZER



Hyperopic LASIK xtra



- **CXL and long term Hyperopic LASIK stability. Initial clinical findings in a contralateral eye study**

Purpose: The evaluation of the safety and efficacy of the application of intrastromal CXL in a contralateral eye study in routine hyperopic LASIK

Methods: 27 consecutive hyperopic and hyperopic astigmatic bilateral topography-guided LASIK patients were randomized to receive 5 minutes of 10mW/cm² CXL after in-the-flap administration of a single drop of 0.1% sodium phosphate riboflavin solution. All cases were treated with the Allegretto 400Hz Eye-Q excimer laser and femtosecond laser flap creation. Peri-operative refractive error, keratometric, topographic and topometric measurements were evaluated with a mean follow-up of 23 months (22-35).

Results: Mean sphere was +3.25D, Cyl: -1.75D. The CXL cases demonstrated a mean regression from treatment of +0.22D (diopters), the non-CXL cases: + 0.72 D, showing a very strong statistically significant difference even in the first 6 patients despite the expected flattening effect of CXL.

Conclusions: These preliminary data suggest that the combination of CXL in hyperopic LASIK may offer a very significant synergy in efficacy, suggesting that hyperopic LASIK long term regression may be more related to cornea biomechanical changes, than just residual accommodation.

High Fluence Transpethelial CXL early findings

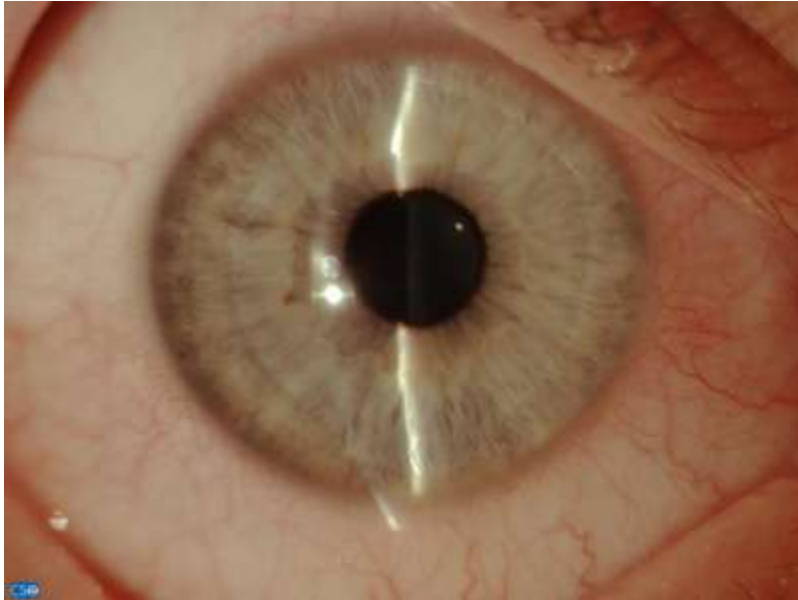
There is significant CXL effect

The epithelium does not seem to absorb significant riboflavin

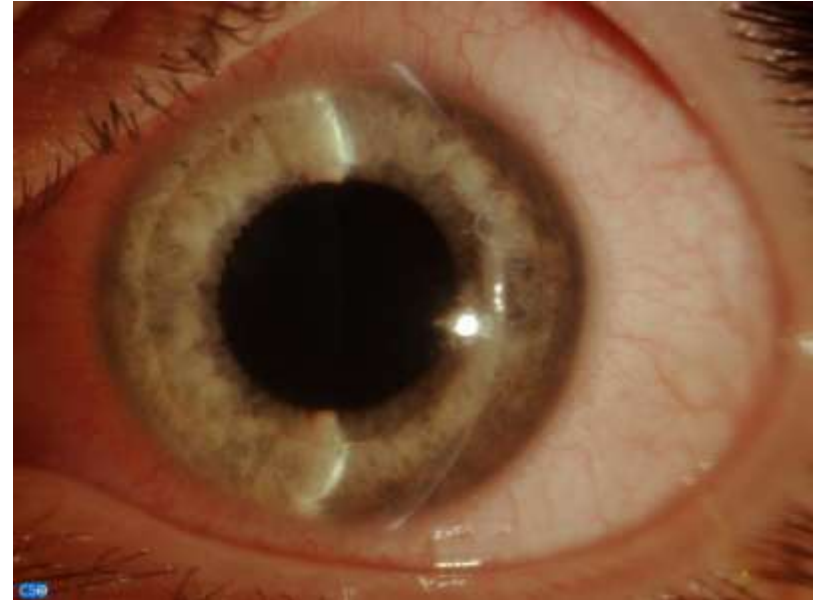
Extremely comfortable, no recoup time

Long term data necessary

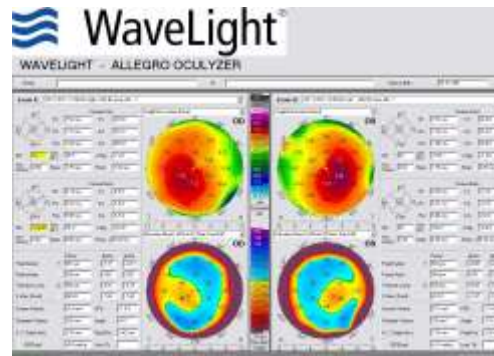
Trans epi 0.25% Ribo + 30mW X 3 min



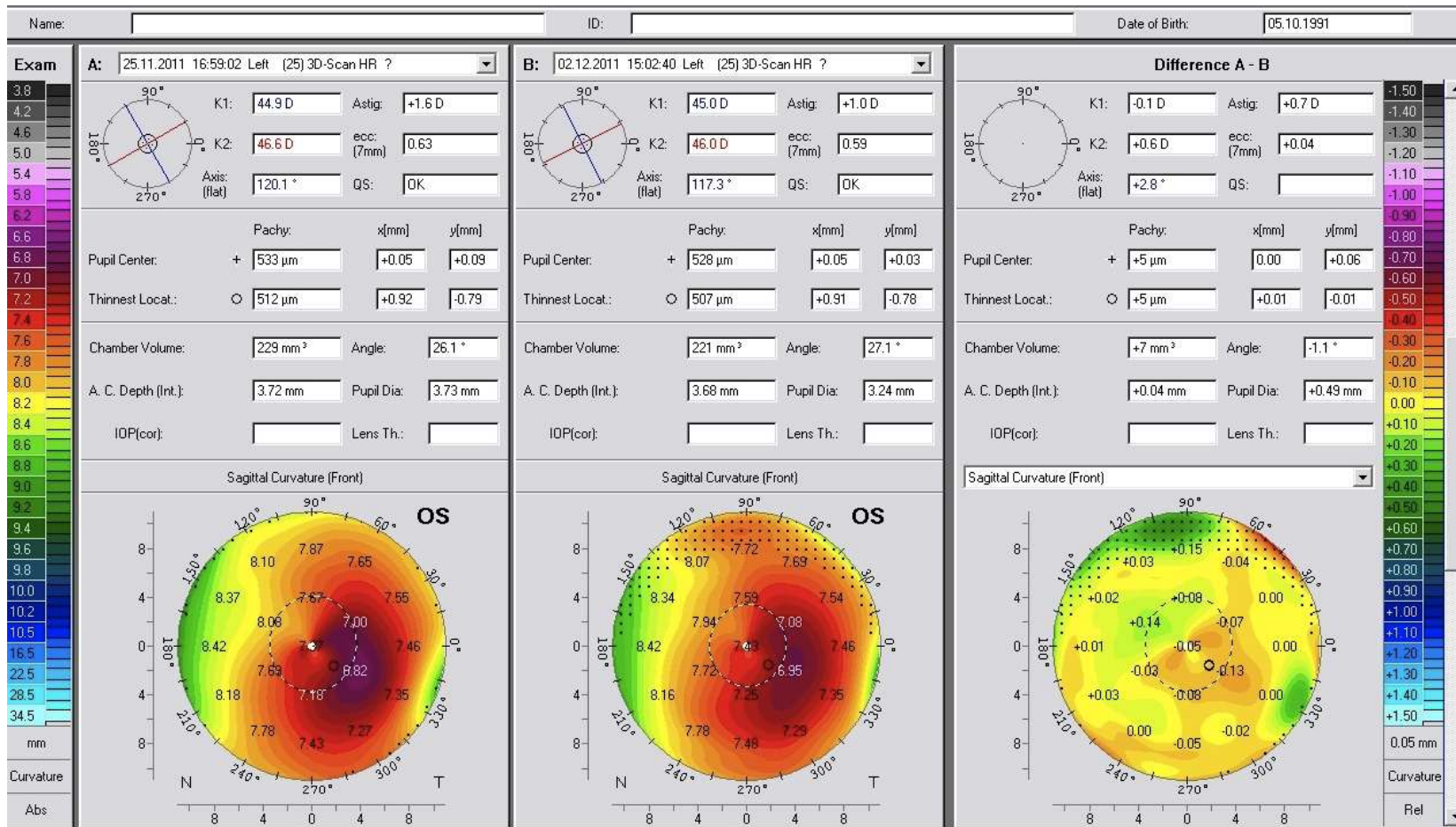
Untreated



Treated



Transepi 30mW X 3' + 0.25% ribo 1 week!



Conclusions higher fluence CXL

Our current protocols

1-Athens Protocol: topoPRK +10'x $10\text{mw}/\text{cm}^2$

2-LASIK Xtra: 1' (60") $45\text{mW}/\text{cm}^2$

2-PRK Xtra: 1' (60") $30\text{mW}/\text{cm}^2$

3-Transepithelial CXL: 0.25% riboflavin +
 $30\text{mW}/\text{cm}^2$ X 3' (180")

3-Infection: 0.25% riboflavin + $45\text{mW}/\text{cm}^2$ x 5
minutes



Conclusions higher fluence CXL

Appears to be more effective if **Type I** model of CXL holds true

Customised fluence and riboflavin concentration may personalize CXL as a biomechanical stromal modulator for many applications:

May prevent regression in hyperopia

LASIK Xtra appears to have only potential advantages

May become the standard of care for PRK (reduce scarring, epithelial hyperplasia)



Conclusions higher fluence CXL

CXL can sterilize the stroma higher fluence and higher riboflavin % may be useful

The apoptosis of keratocytes may have unknown benefit to epithelial hyperplasia and risks

Potential endothelial toxicity

Potential limbal cell cell and/or goblet cell toxicity from collateral Rib⁺ interaction

CXL may prove to be the standard collagen stabilizer and adjunct disinfectant in LASIK, PRK and **even cataract surgery**



AAO/ISRS meeting in Athens!

December 17th

The ISRS didactic
course

Live surgery and
commentary in LASIK
Xtra, Athens Protocol,
CXL and femto cataract
surgery

Please contact:

Helen@laservision.gr



Kanellopoulos MD

