Anterior Segment Disease Therapy: A Look Into The Future

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Autologous Serum – The How

- More aptly called Eye-Platelet Rich Plasma (EPRP)
- Eyedrops created from patient's own blood
- Blood is drawn and spun down
- WBC and RBC are all removed by centrifugation; platelets and growth factors remain
- Plasma is placed in sterile eyedrop bottle

Autologous Serum

- 100% Platelets
- No Preservatives, No additives

Autologous Serum – The Why

- Autologous plasma is rich in platelets and growth factors
- Growth factors enhance proliferation and wound healing
- Effective on hard and soft tissues
- Growth factors restore damaged ocular surface by inducing mesenchymal and epithelial cells to migrate and proliferate

Autologous Serum – The What For?

- Severe Dry Eye
- Corneal Ulcers (especially if dormant)
- LASIK complications
- Chronic Dystrophies (EBMD)

Autologous Serum Studies

- Alio – Ophthalmology 2007

- E-PRP improved symptoms – photophobia, pain, inflammation
- E-PRP facilitated re-epithelialization
- E-PRP promoted wound healing
- Improved VA
- ".. In the majority of the patients in the study."

Kojima study – Am J Ophthalmol, 2005

- E-PRP for Dry Eye
- Conclusion- Autologous plasma is superior to conventional treatment for improving ocular surface health and subjective comfort
- E-PRP improved tear stability and vital staining scores (RB)

Autologous Serum
What Does it Really Mean?

- Autologous Serum brings growth factors directly to compromised eye.
- Diseased eye is not getting nutrients to help healing
- Diseased eye is undergoing chronic tissue breakdown
- E-PRP breaks that cycle

Autologous Serum – Clinical Questions

- What is the dosage?
- Who keeps the bottle?
- Where should it be kept?
- When should it be Rx'd?

Tear Film Osmolarity

- High tear film osmolarity (>308) is a leading indicator for dry eye
- Changes in osmolarity precedes symptoms
- May allow for earlier, more successful treatment
- May allow doctors to monitor treatment success more quantifiably
- Positive correlation between ocular surface condition and tear film osmolarity

New DES Pathology Data

- Lemp- 1/06 *Refractive Eyecare*
  - 2 alterations occur on the tear film
    - Increased electrolyte concentration, which leads to elevated osmolarity
    - Destabilization of structure of POTF
  - These lead to global changes on the surface, namely:
    - Increased evaporation
    - Increased surface tissue damage

Dry Eye Disease Pathology

- Chronic dry eye patients have hyperosmolar tears, so what…..!

- Hyperosmolar tears have direct dessicating effects
- Actively stress kinase enzymes
- Leads to further cellular breakdown, POTF disruption and more inflammation.

The Device

- Tear Lab Osmolarity System
  - 50 nL of tears collected from inferior lateral tear meniscus (5-6 secs)
  - Does this via electrical impedance
  - Calculates osmolarity of tear film (20 secs)

TEARLAB™ COLLECTION GUIDE

A

PATIENT PREPARATION

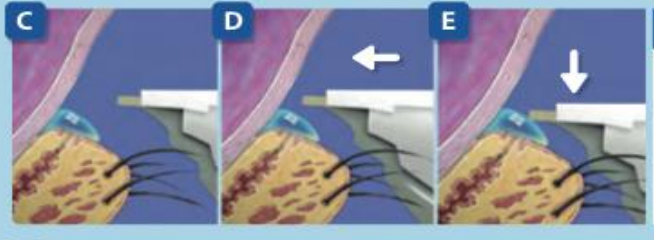
- Seat patient with head back and eyes upward towards the ceiling (A).
- **IMPORTANT: Do NOT pull the eyelid away from the eye; moving the lid down will break the tear lake and make collection difficult.**

B

SAMPLE COLLECTION

- Move Pen into place, then ask patient to open their eyes.
- Lower the Pen allowing the bottom of the tip to come into contact with the lower eyelid and the line of moisture along the inner eyelid margin (B).

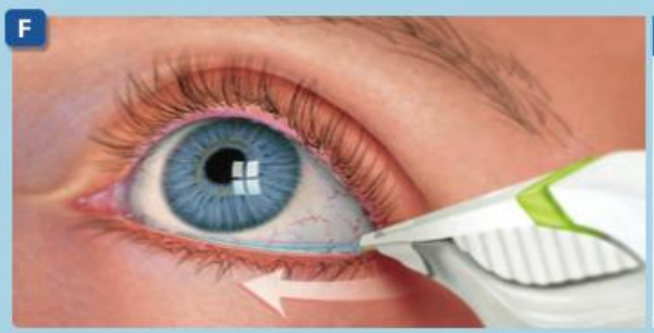
C D E



COLLECTION TECHNIQUE

- Move the tip beyond the eyelashes near the corner of the eye (C & D).
- Avoid touching the white of the eye.
- Press down lightly on the eyelid to collect tears (E).
- Fluid is collected at the **bottom** tip of the test card.

F



IF COLLECTION IS DIFFICULT

- Make sure to avoid pulling down the lid when collecting.
- Allow patient to blink normally.
- If there is not enough tear to collect immediately, **do not peck.**
- Lightly brush the Pen back and forth along the outer 1/3rd of the lid (F).
- In the rare case where there just isn't enough tear on the surface of the eye, a Below Range error may result.

FOR MORE INFORMATION, PLEASE CONTACT: TearLab Corp., San Diego, CA USA, +1-858-455-6006, info@tearlab.com, www.tearlab.com

TearLab™

Tear Film Osmolarity

- Test seems to be more sensitive in mild and moderate dry eye
- Slightly less sensitive in severe dry eye (94.7%)
  - TFBUT has 98.7% sensitivity in severe dry eye
- High osmolarity results in a very unstable tear film thus the osmolarity levels may vary

Clinically what do we know?

- Osmolarity may vary from day to day
- There may be intereye differences
  - 8-10 mOsms/L difference is suspicious
- Mild-moderate disease shows greater variability – may be a hallmark of early disease
- Normals or severes show less fluctuation

So….

- If tear osmolarity high – Dry Eye

- If tear osmolarity varies – mild to moderate Dry Eye
- If tear osmolarity different between 2 eyes – mild to moderate Dry Eye
- If osmolarity consistently low – not dry eye
  - MGD or Allergy

Tear Film Osmolarity Testing

- CPT code – 83861
- Reimbursement connotates that facility must have a moderate complex CLIA certificate

InflammaDry

- Detects elevated levels of MMP-9 in tear fluid
- 10 minute in-office results
- Easy to use – can be performed by technicians or nurses
- Disposable – no additional equipment required

Limit of Detection: the normal level of MMP-9 in human tears ranges from 3-41 ng/ml

- **Positive test result = MMP-9 ≥ 40 ng/ml**
- **Negative test result = MMP-9 <40 ng/ml**

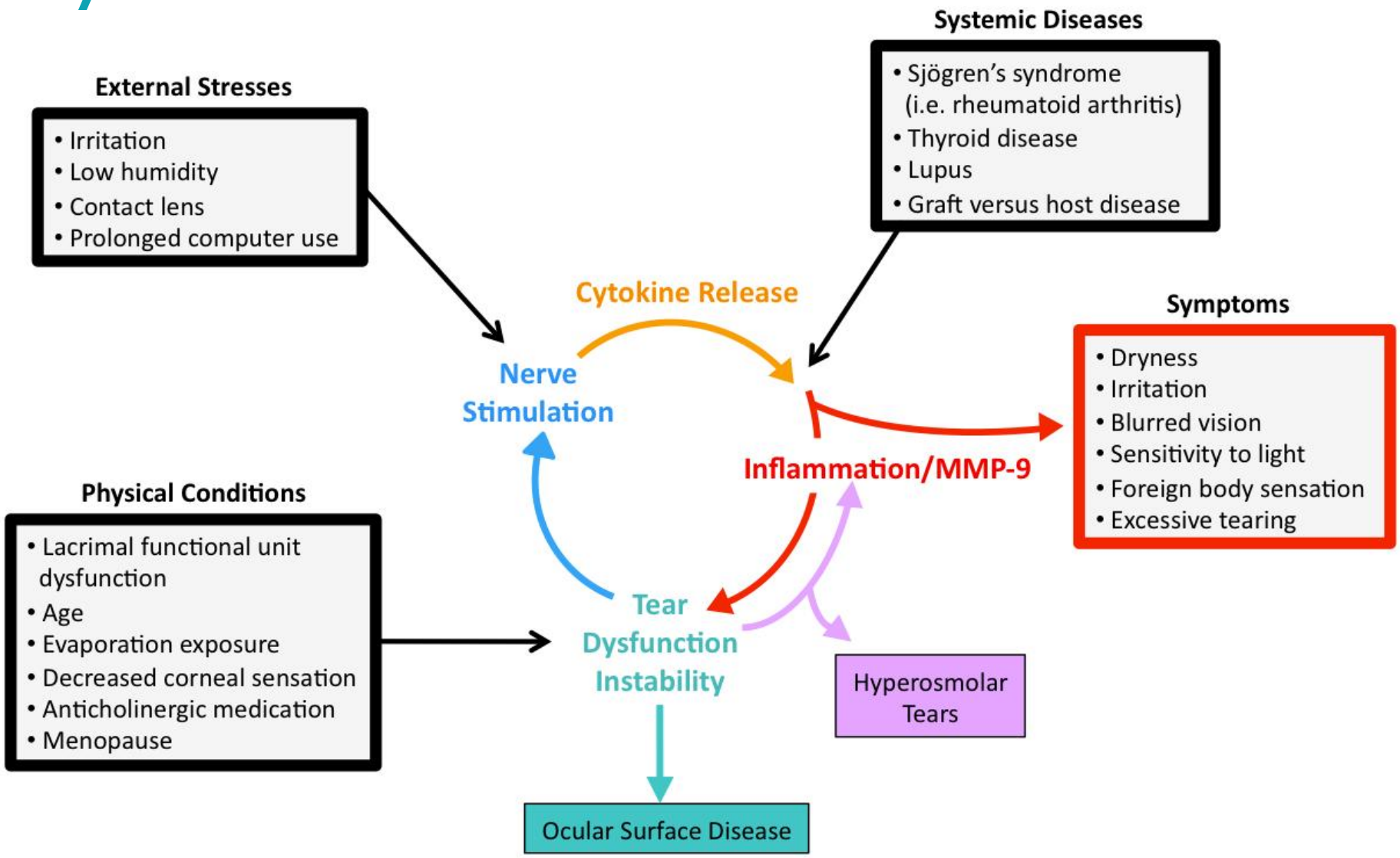
InflammaDry is CE Marked and commercially available in Europe. At this time InflammaDry is pending 510(k) review by FDA and is not commercially available in the U.S.

What is MMP-9?

- Matrix metalloproteinases (MMP) are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface [1]
- Non-specific inflammatory marker
- More sensitive diagnostic marker than clinical signs [1]
- Correlates with clinical exam findings[1]
- Normal range between 3-41 ng/ml
- Ocular surface disease (i.e. dry eye) demonstrates elevated levels of MMP-9 in tears[1]

[1] Chotikavanich S, de Paiva CS, Li de Quan, et al. Invest Ophthalmol Vis Sci 2009; 50(7): 3203-3209.

Cycle of Inflammation



Normal Levels of MMP-9

Literature supports that the normal levels of MMP-9 (ng/ml) in human controls range from 3-41 ng/ml

Study	Normal Controls	Average MMP-9 Levels (ng/ml)	Standard Deviation (ng/ml)	Upper Range (ng/ml)
Acera et al 2008	18	23.6	17.4	41.0
Chotikavanich et al 2009	16	8.4	4.7	13.0
Solomon et al 2001	17	7.2	2.1	9.0
Leonardi et al 2003	10	10.5	0.2	11.0
Lema et al 2009	20	6.9	1.4	8.0
Honda et al 2010	28	22.7	14.0	37.0
Markoulli et al 2010	38	11.6	15.2	N/A
Total/Avg/Range	**147**	**12.9 ng/ml**	**–**	**41.0 ng/ml**

MMP-9 and Dry Eye Severity[1]

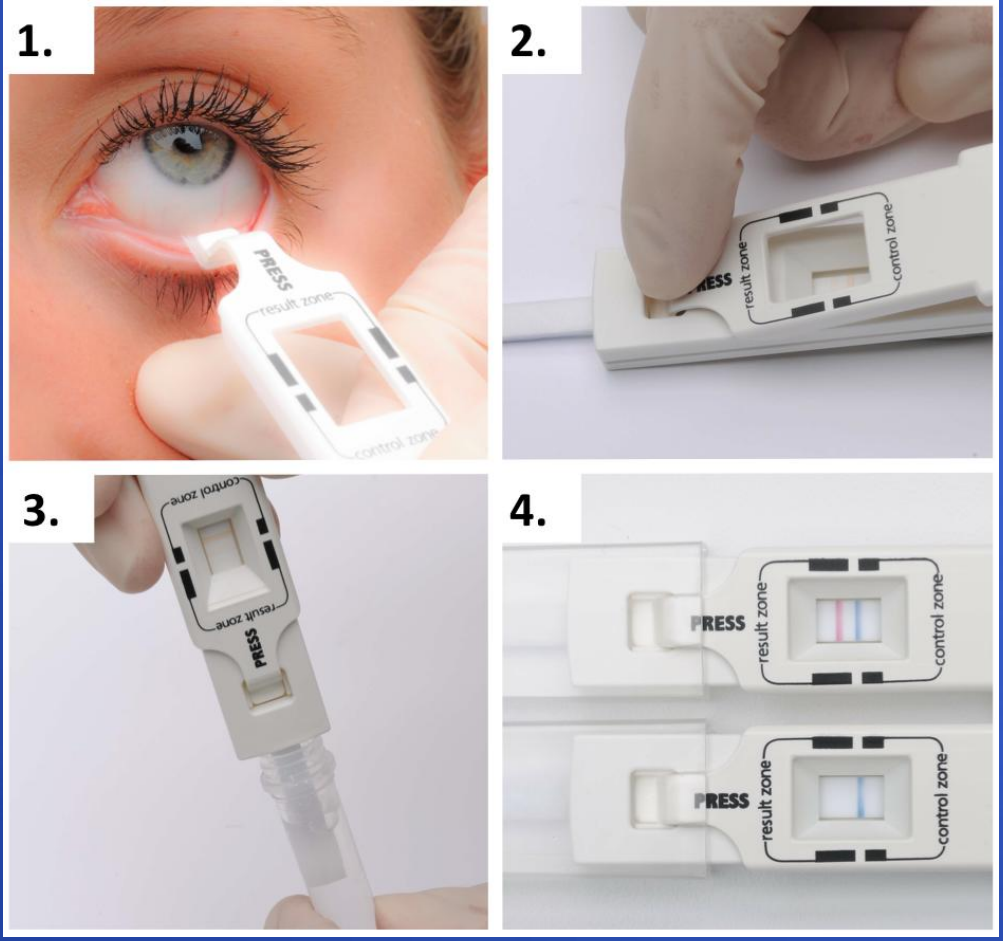
Patient's Dysfunctional Tear Syndrome Level	Average MMP-9 Level	Statistical Significance vs Normal
Normal (n=18)	8.39 ng/ml	NO
Severity Level 1 (n=15)	35.57 ng/ml	NO
Severity Level 2 (n=11)	66.17 ng/ml	YES
Severity Level 3 (n=9)	101.42 ng/ml	YES
Severity Level 4 (n=11)	381.24 ng/ml	YES

Positive Result = Chronic Dry Eye

≥ 40 ng/ml

[1] Chotikavanich S, de Paiva CS, Li de Quan, et al. Invest Ophthalmol Vis Sci 2009; 50(7): 3203-3209.

How to Use InflammaDry: Four-step Process



1. Gently dab the Sample Collector in 6-8 locations on the palpebral conjunctiva (lower eyelid) to collect a tear sample. Do not use a dragging motion.
2. Snap the sample collector into the test cassette and press firmly where indicated.
3. Dip the test cassette into the provided buffer vial for 20 seconds. Replace the cap.
4. Read the results: 2 lines (1 red, 1 blue) = positive, 1 line (blue) = negative

InflammaDry Clinical Trial

N = 206		Clinical Criteria	
		+	–
InflammaDry	+	121	4
	–	22	59
Sensitivity		85% (121/143)	
Specificity		94% (59/63)	
Overall Agreement		87% (180/206)	

Other Methods for Dry Eye Diagnosis[1]

Dry Eye Testing Method	Sensitivity	Specificity
Schirmer Tear Test	42%	76%
Tear Break Up Time	92%	17%
Corneal Staining	63%	89%
Questionnaire	89%	72%
TearLab Osmolarity[2,3]	64-73%	71-92%

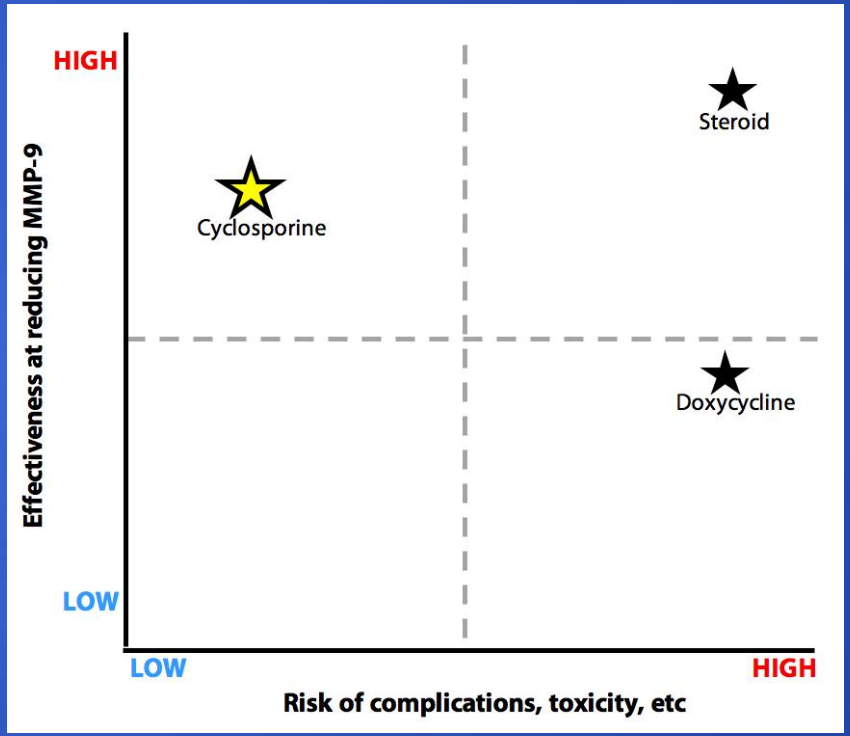
InflammaDry Sensitivity **85%** Specificity **94%**

[1] Versura P, Frigato M, Cellini M, et al. Diagnostic performance of tear function tests in Sjogren's syndrome patients. Eye (Lond). 2007;21:229-37. **[2]** TearLab Performance Data – 510(k) Clearance. **[3]** Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol 2011;151:792-798.

Treatment of Dry Eye

Treatment of Dry Eye

- Elevated MMP-9 may predict which patients will respond to anti-inflammatory therapy
- Patients who test positive can be treated with one of the following:[1-3]
  - Cyclosporine, Steroid, or Doxycycline

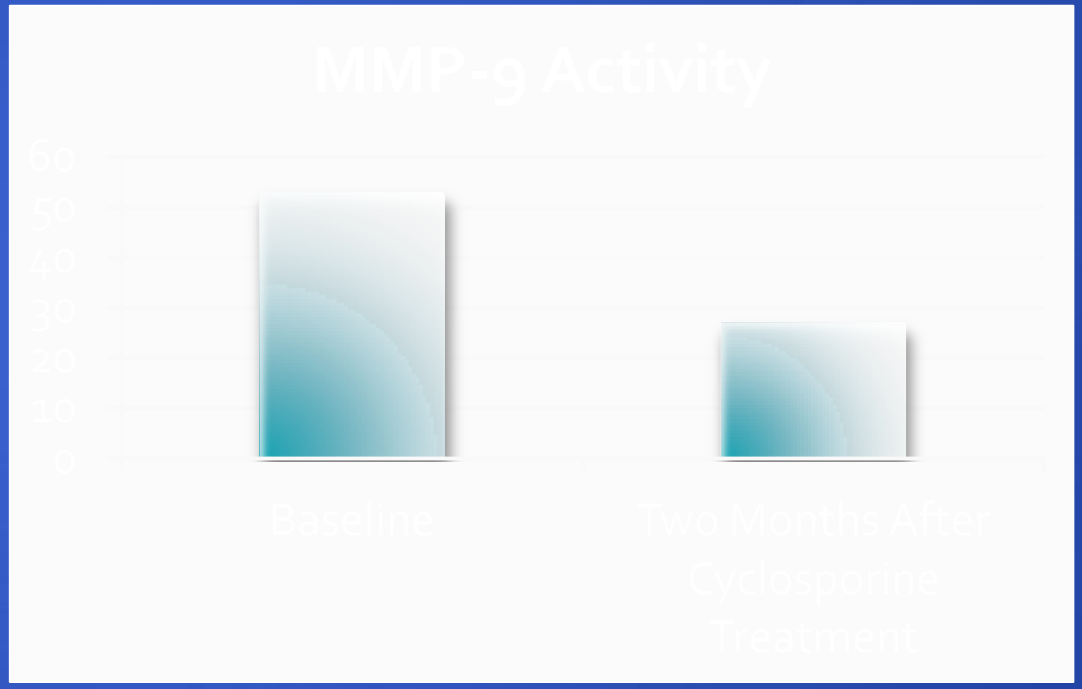


[1] De Paiva CS, Corrales RM, Villarreal AL, et al. Exp Eye Res 2006; 83(3): 526-535. **[2]** Gurdal C, Genc I, Sarac O, et al. Current Eye Research 2010; 35(9): 771-777. **[3]** Li DQ, Zhou N, Zhang L, et al. Invest Ophthalmol Vis Sci 2010; 51(11): 5623-5629.

Cyclosporine and MMP-9

MMP-9 expression was evaluated by immuno-histochemistry. The mean percentage of MMP-9 expression of the conjunctival epithelial cells was significantly decreased.

MMP-9 expression was evaluated semi-quantitatively by measuring cytoplasmic staining for MMP-9.



N=24 eyes of patients with thyroid orbitopathy-related dry eye

Gürdal C, Sarac O, Can I, et al. Ocular surface and dry eye in Graves' disease. Curr Eye Res 2011; 36: 8-13.

Corneal Collagen Cross-Linking

- Clinical Indications
  - Keratoconus
  - Forme-fruste keratoconus
  - Post-LASIK ectasia
  - Post-RK
  - Pelliucid Marginal Degeneration

CCXL- How It Works

- Cornea is saturated with riboflavin
- Cornea is exposed to UV light
- Photosensitization occurs, singlet oxygen released
- The molecular oxygen causes extra cross-linking of corneal collagen fibers and extracelluilar matrix proteins
- This causes corneal stiffening

CCXL – The Procedure

- Debridement of central 7-9mm of epithelium
- Riboflavin 0.1% is applied and allowed to saturate cornea for 30 minutes
- Cornea is irradiated with 370-nm wavelength light for 30 minutes, riboflavin is reapplied every 5 minutes throughout the procedure
- Topical antibiotic ointment and bandage CL applied
- Monitor post-op healing closely

CCXL Post –op Process

- Much like PRK post-op
- Watch for infection – antibiotic
- Mitigate corneal haze – steroid
- Moderate pain- NSAID
- Final result may not be seen until 18 months out, so refraction may vary

Some CCXL Particulars

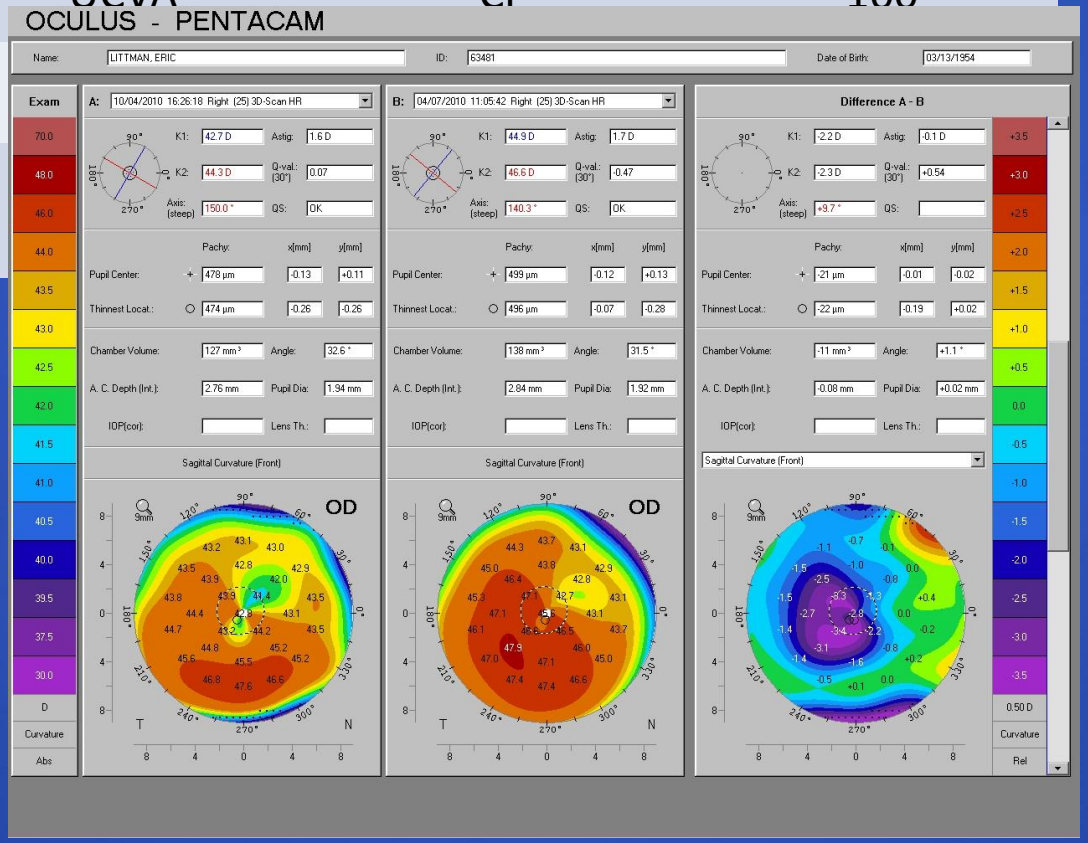
- Cornea must be saturated before UV light application
- 90% of the UV light absorbed within the anterior 400 microns of K
- Riboflavin blocks deeper light penetration thus avoiding cytotoxicity at endothelium or lens capsule
- Effect is not immediate, 3-6 months for new keratocytes to repopulate and remodel cornea
- Improvement continues over 15 month period

CCXL Benefits

- Improved regularity to corneal shape
- Decreased apical scarring
- Improved UCVA and BCVA
- Decreased astigmatism
- Improved ability to wear CL
- Improve outcomes with secondary ICCL
- *CCXL definitely works better on early diagnosed keratoconic pxs!*

56 yr old male with Keratoconus: Epi-On CXL OS

	Pre Op	3 months Post Op
UCVA	CF	100



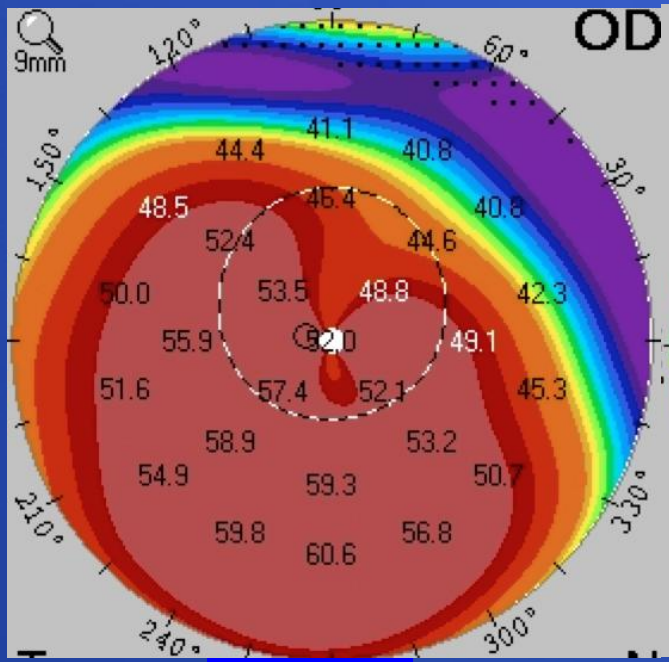
6 months

Preop

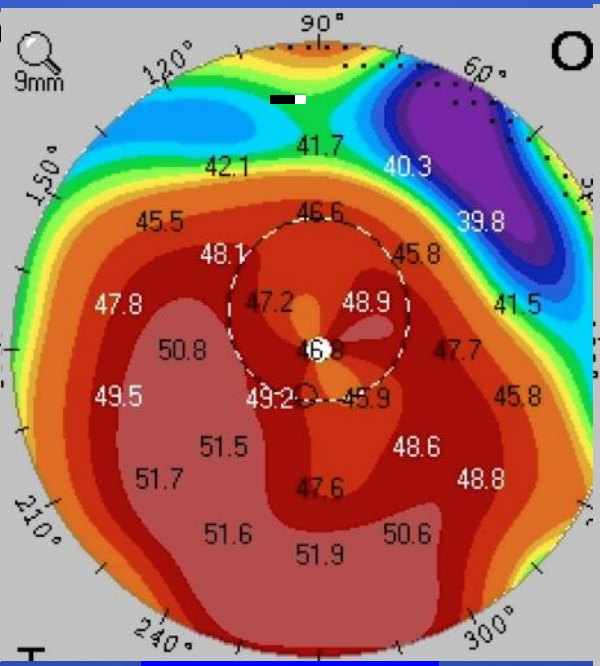
Difference Map

58 yr old female with Keratoconus: Epi-On CXL OD

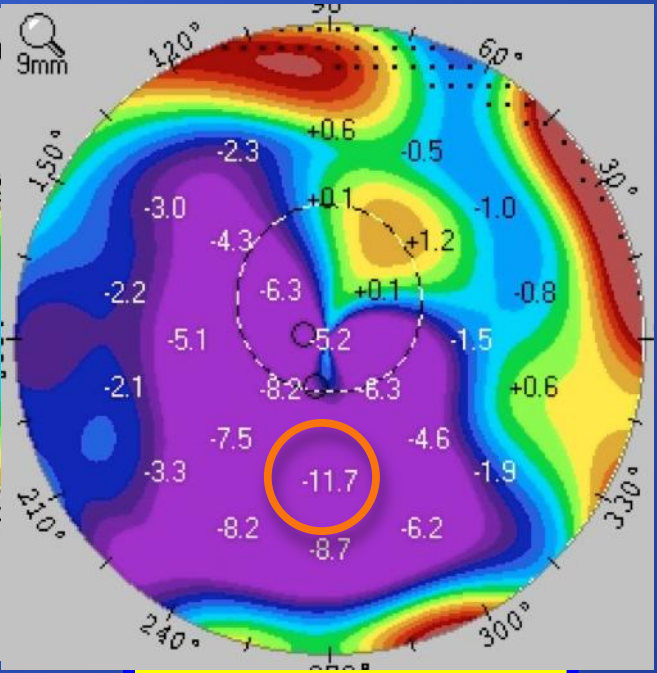
OD	Pre Op	12 months Post Op
UCVA	CF	20/200
BSCVA	20/400	20/50
Refraction	-10.25+5.25 x 175	-10.00+2.50X175



Preop



12 months

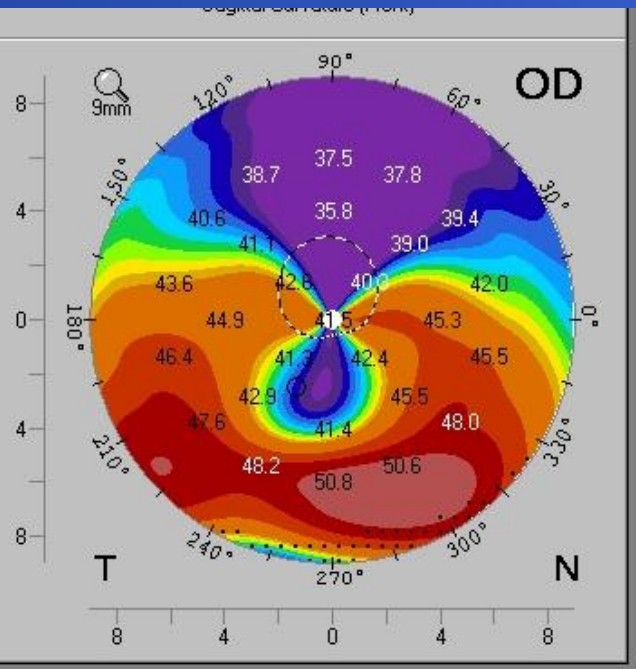


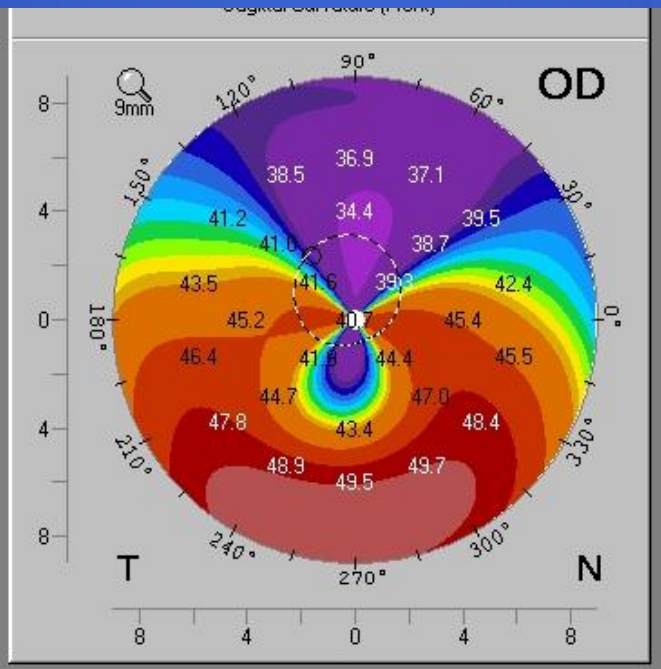
Difference Map

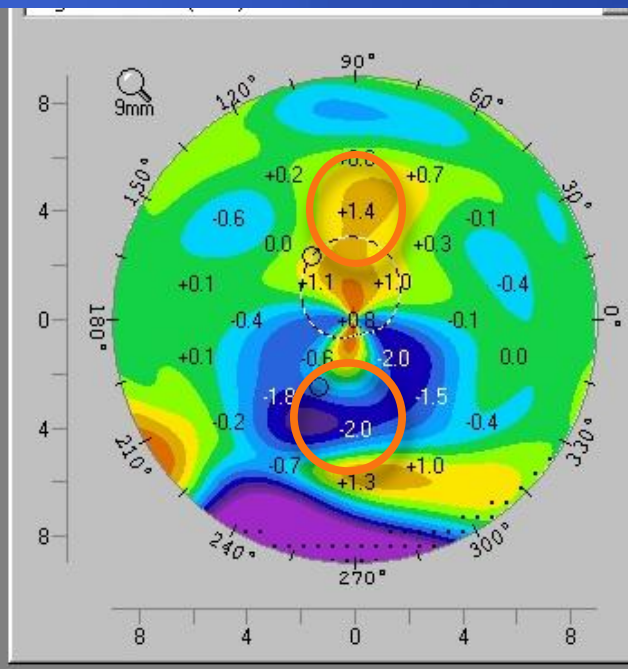
Cliff Salinger & William Trattler,

Epi-On Crosslinking for Ectasia
38 year-old male with post-Lasik ectasia

OD	UCVA	Refraction	BSCVA
Pre Op	200	-3.50+6.50x180	30
3 Months	50	-0.75+1.75x175	25







Post Op 3 Months | Pre Op | Difference Map

CCXL ADVERSE EFFECTS

- Treatment failure
  - Risk factors for treatment failure are:
  - Age 35 or older
  - BCVA 20/25 or better
  - K reading > 58.00D
- Post-op infection
- Stromal haze
- Increased IOP

CCXL – 2 years later

- Epi-On can be as effective as Epi-Off
  - Technique differences can explain differences in results
- Age is not a major factor
  - Older patients can benefit from crosslinking
- Progression is not required for successful results with crosslinking
  - Non-progressive patients can achieve improvement in corneal shape, UCVA, and BSCVA

Summary of Epi-ON

- EPI-On CXL
  - Benefits:
    - Faster visual recovery/less pain
    - Reduced risk of pain/haze
    - Very good clinical results
      - Even in keratoconus patients in their 50’s and 60’s
  - Downside:
    - Longer procedure (30-50 min longer)
    - Can not combine with simultaneous topo-guided PRK

The future for Collagen Cross-Linking

- Treatment of recalcitrant bacterial corneal ulcers
  - Esp if in anterior 250 microns
- Corneal melts
- EBMD
- As an adjunct to Orthokeratology!!

Pre-Medicated Punctal Plugs

- Antibiotic containing intracanalicular punctal plug
- Used for sustained drug release
- Safety and feasibility was demonstrated
- 95% retention rate through day 10

Moxifloxacin Punctum Plug (Ocular Therapeutix)

- Polyethylene glycol plug – dissolvable
- Moxifloxacin-encapsulated microspheres
- Dimensions that swell or shrink to conform to punctum
- 2 Phase I Prospective Single Arm Studies
  - Implanted at cataract surgery
  - Followed for 30 days post-operatively

Safety and Feasibility Studies

- Study 1 –
  - 90% Retention rate through Day 10
  - All plugs absent by Day 30
- Study 2 –
  - Adjusted study for more stringent tear sample collection
  - Higher levels of available moxi were found
  - 100% retention rate at Day 10

Study Goals

- Reaching therapeutic level of moxifloxacin in tears
  - Drug levels were well above MIC-90 levels needed for staph aureus, staph epi., strep pneumoniae
- Safety
  - No adverse effects
  - Overall ease of use noted
- Specifically did not look at clinical outcomes

Is this clinically significant?

- Therapeutic success has not been proven , but if that can be shown then…
  - Much more than just post-op therapy opens up
    - Corneal ulcers
    - Uveitis
    - 30 day implant for glaucoma
    - Allergic eye disease

Novel Drug Delivery Systems- the next frontier

- Drug Eluting Punctal Plugs
  - QLT – latanoprost
  - 75% -80% retention rate
  - Results- 3-4mm drop in IOP
- Ocular Therapeutix – Intracanalicular latanoprost
  - Good sustained release of drug but doesn't lower IOP as good as topical Xalatan
- SOOOO????

Intravitreal/Intracameral Injections

- Intracameral seems to be preferred
- Less likely to stay on cornea
- Most of drug stays in AC
- Little is transferred to vitreous

- Brimonidine DDS (Biodegradable Drug Delivery System)
  - Polymer breaks down into H_2O and CO_2
  - Duration and effect are in question

Implantable Devices for Glaucoma

- 27 g needle used to place implant intracamerally (either in front of or posterior to iris)
- PLGA polymer used
- Different implants allow the concentration and delivery rate of drug to be altered
- Lasts up to 6 months
- Great for compliance, ?? IOP drop
- Consequences for optometry

Injectable Glaucoma Therapy

- Anecortave acetate
  - Angiostatic cortisene
  - Cortisol derivative
  - Lacks glucocorticoid activity, thus:
    - No anti-inflammatory properties
    - No cataractogenic properties
  - Insoluble so works very well near its delivery site

Transdermal Testosterone Therapy

- 5% transdermal testosterone cream
- Applied to eyelid BID
- Increases tear production
- Increases meibomian gland secretion

Transdermal testosterone

- Clinical Indications
  - Dry Eye
  - CL intolerance
  - Chronic surface disorders
  - Exceptional effective on females

Transdermal testosterone

- Connor study – ARVO 2010
  - TFBUT increased from 2.6 to 6.5 seconds
  - Average CL wear time increased from 1 hour to 10.5 hours
  - All patients were female, 80% post-menopausal

Anti- VEGF Therapy

- Vascular Endothelial Growth Factor (VEGF) promotes angiogenesis
  - Increases venous permeability
  - Induces vascular endothelial cell mitosis and migration

VEGF is found in great concentrations

- Corneal epi- and endothelium
- Limbal vessels
- Scar tissue
- Choroid
- Ciliary Body

- So Anti-VEGF therapy should affect these tissues

Topical anti-VEGF therapies

- Bevacizumab, ranbizumab and sunitunib have all been investigated for topical treatment of

- Diabetic macular edema
- Corneal neovascularization
- CNVM

- Results?
- Potential?

Lipi View and Lipi Flow