Basics To Biologics: Selecting Drops For Dry Eye

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DED and Drops

- Addressing meibomian gland dysfunction, and blepharitis is key to suppressing the inflammatory nature of dry eye disease (DED).
- However, artificial tears still play a pivotal role in managing the condition.
- Drops a provide symptomatic relief to patients
- Especially during flare-ups.

When do we use Artificial Tears?

- Patients should use tears regularly “like a lip balm”
- They shouldn’t wait until symptomatic
- Or until the ocular surface is compromised

DED is Non-Binary

- It can’t easily be categorized in a classification of evaporative or aqueous deficient

- TFOS DEWS II found up to 70% of sufferers have a mix of the two.

Not just Symptomatic Relief

- Artificial tears can reduce inflammation and help prevent epithelial cell death.
- When chosen carefully, eye drops can play a significant role in the management of dryness.

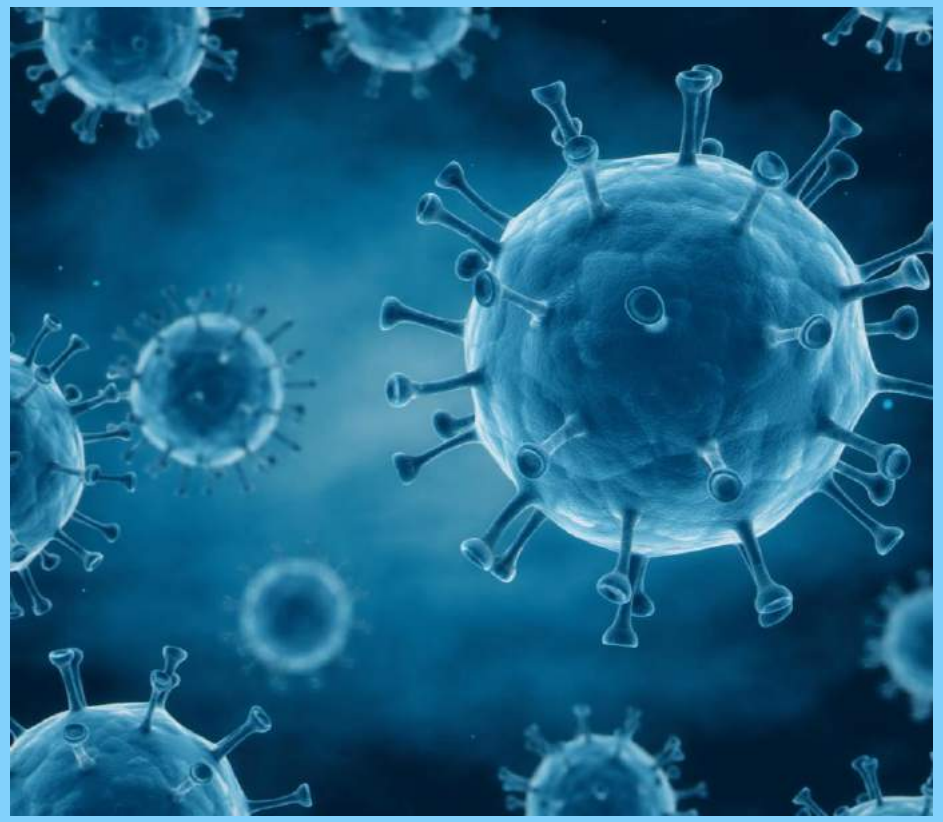
The amount of eye drops available can make selection overwhelming for a doctor (let alone a patient).

Let’s explore some favorite drops

→Clarify when they are most appropriate.

→Simplify when to turn to biologics

Preservatives



- Preservatives in multi-dose bottles:

-a **necessary evil** to contain bacterial replication

-minimize contamination.

- **Counterproductive** to treating the condition.

- An **irritant** is being **introduced** to a **compromised** tear film and **ocular surface**.

Preservatives

- Preservative-free formulations are generally superior
- Highly recommended for those using drops more than four times a day.
- BAK and thimerosal formulations should be avoided at all costs.

Selecting Viscosity

- Tear osmolarity can be used as a guideline for selecting AT viscosity.
- Moderate to severe DED needs a thicker drop.
- Viscosity increases→ the duration of effect increases…
- But so does the potential for blurred vision.

Systane Ultra Hydration (Alcon)

- A relatively **inexpensive** and **effective** option for mild to moderate DED

- It's a **moderately viscous** drop with the coating power of **hyaluronate**.

HP-Guar (Hydroxypropyl-guar)

- **Forms a gel layer** (acting as a mucomimetic), **compensating for a compromised tear layer** and **reducing friction** during blinks.
- (HP-Guar) interacts with the blinking motion prolonging the contact time on the eye.
- HP-guar molecules bind to compromised areas of the cornea

Systane Ultra Non Preserved

- Systane Ultra also comes in a single dose non-preserved option
- It is substantially more expensive
- Highly recommended if using drops more than four times a day

Hylo Dual Intense (CandorVision)

- A premium **multi-dose preservative-free** option for more advanced dry eye
- The unique multi-dose pump does not allow air to penetrate the interior
- Keeping it **safe for six months** (once opened).
- When compared head-to-head with single dose non-preserved options, this product's cost becomes more defensible.

- A **higher viscosity** level (produced by a **high concentration** of **heavier** molecular weight sodium **hyaluronate**)

- Does not blur vision.

Hylo Dual Intense Contains Ectoine

- A natural anti-allergy and anti-inflammatory agent
- Effective in patients suffering from DED and allergic conjunctivitis.
- It has even been shown to accelerate wound healing post-op.

Thealoz Duo Gel (Labtician- Thea)

- A single unit preservative-free thicker gel
- Excellent bedtime option.
- Does not blur vision
- Not oily.
- Trehalose (osmoprotectant) designed to guard dried epithelial cells and stabilize their membranes.

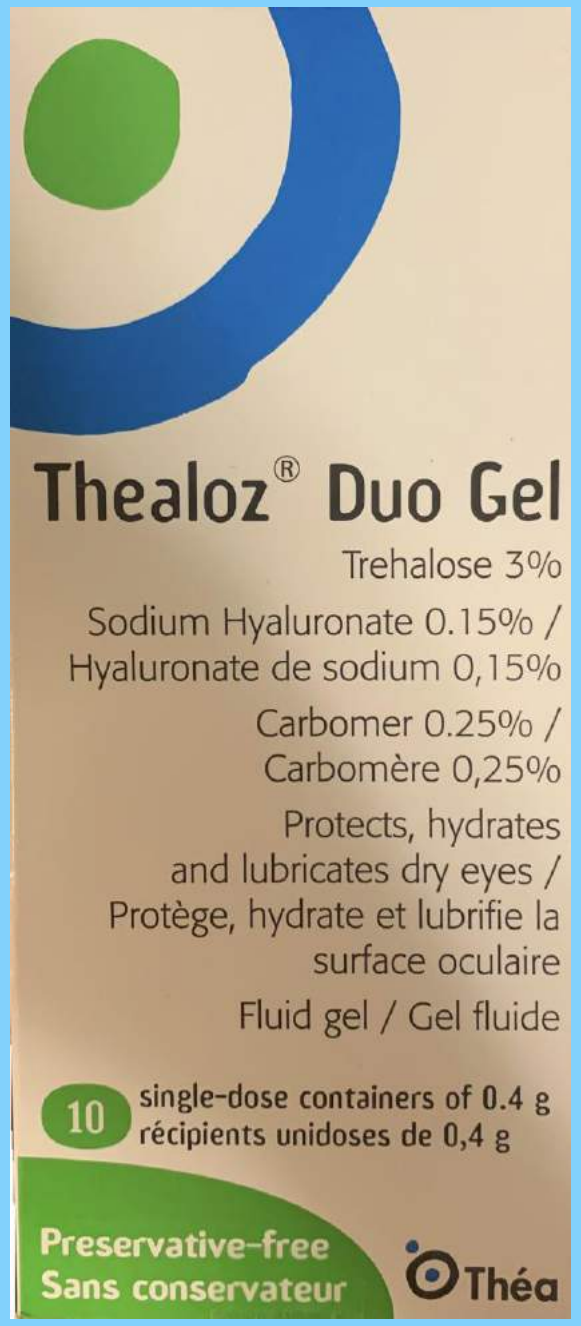
Thealoz Duo Gel (Labtician- Thea)

- Trehalose protects against the destructive inflammatory cascade of DED.
- Sodium hyaluronate enhances viscosity.
- Carbomer increases viscosity

Carbomer

- Also maintains the hyaluronic acid and trehalose together in contact with the ocular surface
- For six hours
- Without being sticky.

- The single unit dose nature of the product does make it a more expensive option



Thealoz Duo (Labtician- Thea)

- Same ingredients as the gel minus the Carbomer
- Preservative free
- Good for 3 months

Calmo spray (CandorVision)

- A unique product for MGD
- Preservative-free.
- It is used with the eyes closed which allows it to seep into the eye slowly
- Replicating meibomian gland secretions (using liposomes)

Calmo spray (CandorVision).

- It’s also an excellent option for people who hate putting drops into their eyes.
- Dexpanthenol (pro-vitamin B5), which moisturizes the eye and surrounding skin.
- Good for six months once opened.

Optase Hylo Night (Scope Health) AKA Ocunox

- Nighttime ointment that uses vitamin A to speed up epithelial healing.
- Preservative-free
- It is also phosphate free

- A bit oily but not greasy
- Minimal blur to vision

Refresh Lacri-Lube ointment (Allergan)

- The go-to for very thick overnight coverage.
- **M**ineral oil base that allows **M**elting at body temperature
- White petroleum which serves as a lubricant.

- Patients need to be warned that it will blur them out for a sustained duration if inserting the ointment in both eyes.

- Ideally, they should already be sitting in bed when inserting it for safety.

The Liposic (Bausch + Lomb)

- A reasonably priced option for decades.
- While MGD patients don't always respond best to oil replenishment drops
- This particular product has endured in both drop and ointment form (for nighttime use).

- The drops contain carbomer, sorbitol, medium chain triglycerides (Myritol 318) and cetrimide as a preservative.

- Liposic gel has sodium hydroxide,

→which closely mirrors the PH of tears at 7.4,

→and attempts to replicate all three tear layers.

Refresh Optive Mega-3 (Allergan)

- Single dose preservative-free drop.
- Contains omega-3 from flaxseed oil.
- Studies show that eye drops using emollients can increase the lipid layer thickness (LLT) of the tear film

- Omega-3 fatty acids are actually found in the normal tear film.
- Formulated for minimal blur
- Does not require shaking.
- It is designed to replenish all three tear layers
- Targeted towards MGD patients (like Systane complete and Retane).

- These drops may be most helpful for patients with prolonged screen time
- (a lifestyle that decreases blinking and meibum secretion).
- Its lubricants include glycerin 1%, CMC (carboxymethylcellulose sodium) 0.5% and polysorbate 80 (0.5%).

AT Drops Summary

- There are many other excellent products on the market for DED.
- There is no magic formula or perfect drop for every patient
- A careful case history helps

- There will be some trial and error in finding the right combination of products
- Both doctor and Patient need to understand this and work together

51 YOF – INTERIOR DECORATOR

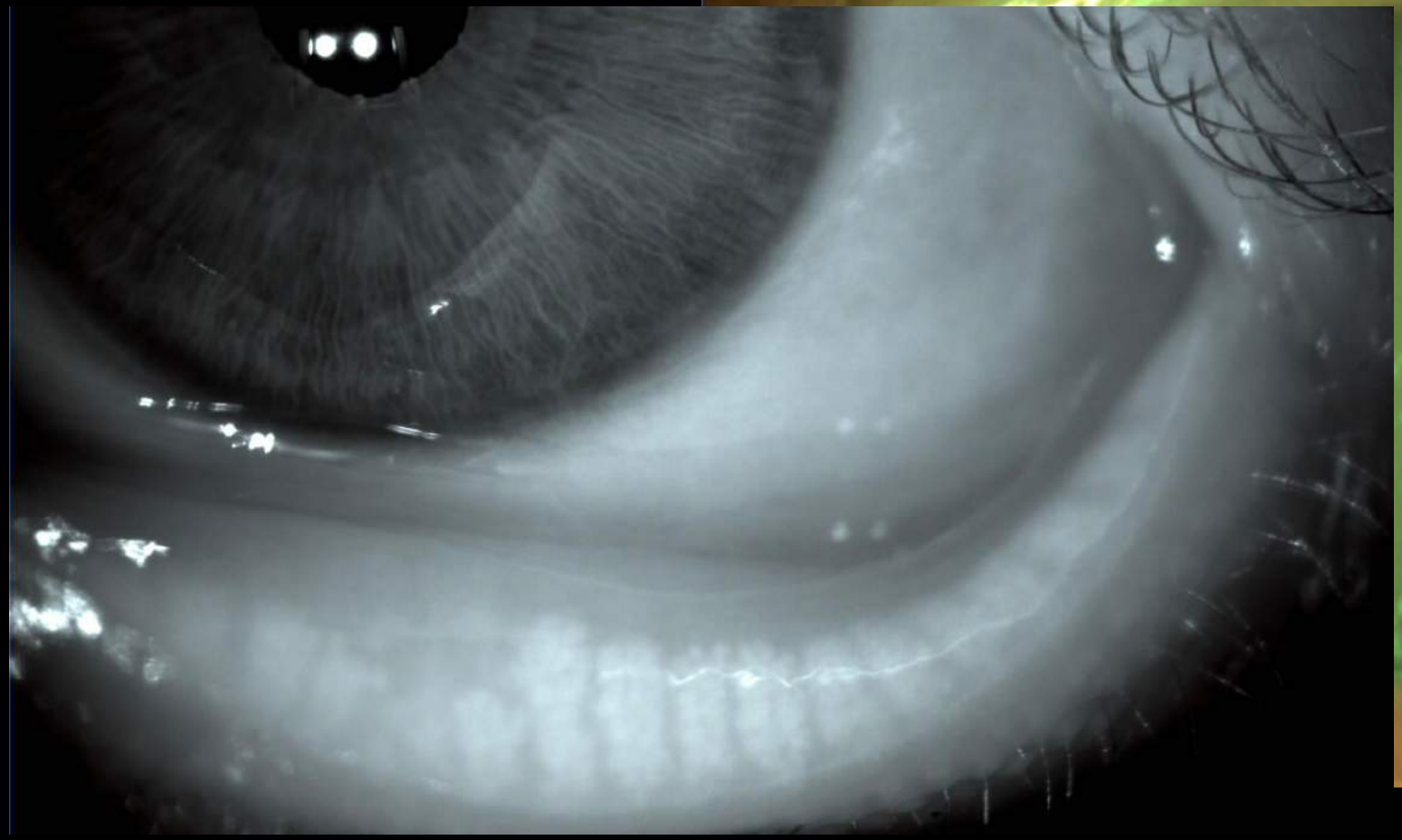
- CC: Referred for dry eyes
- Burning, redness, sand, gravel in the eyes
- Constantly using drops

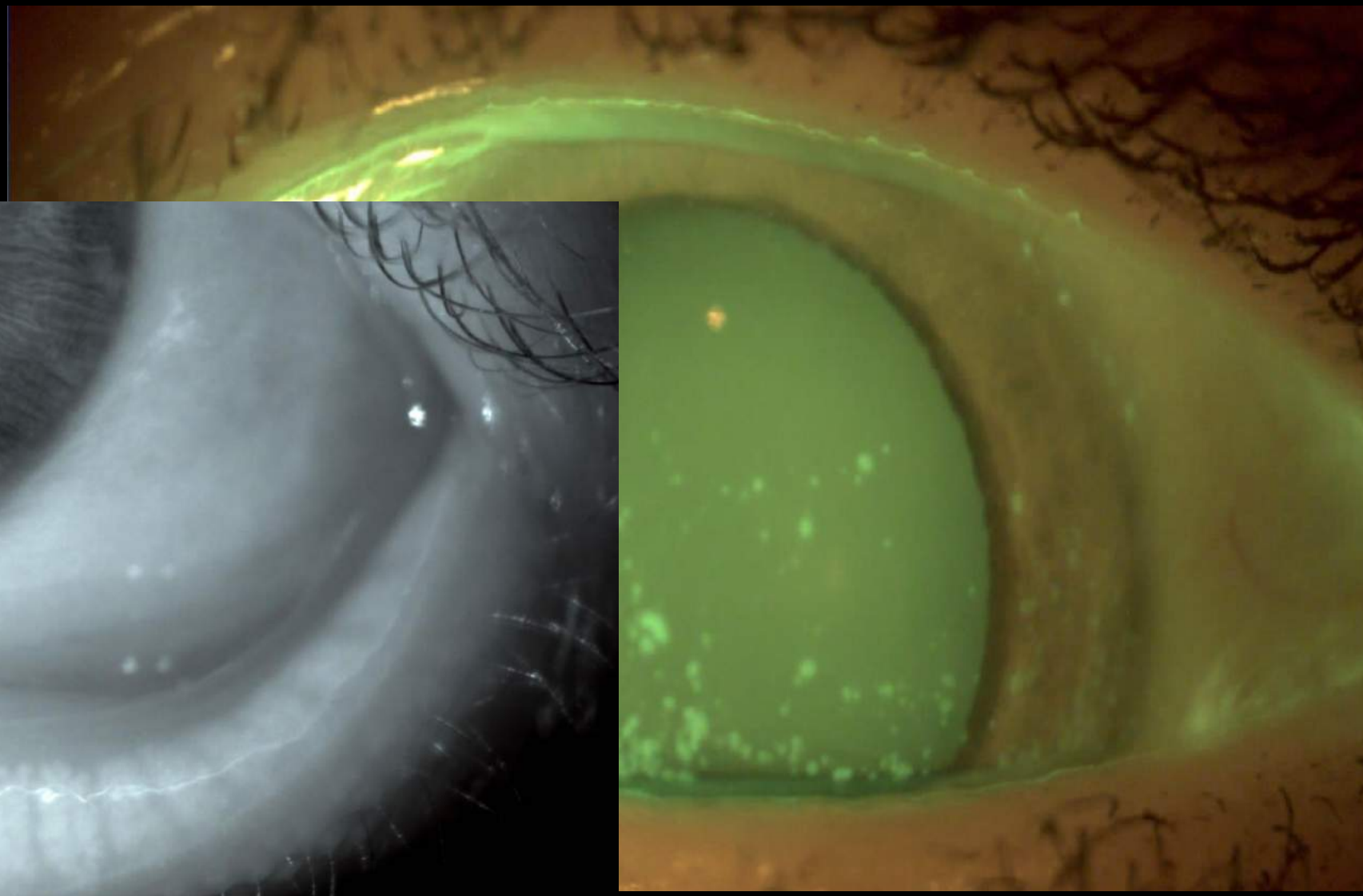
51 YOF – HISTORY

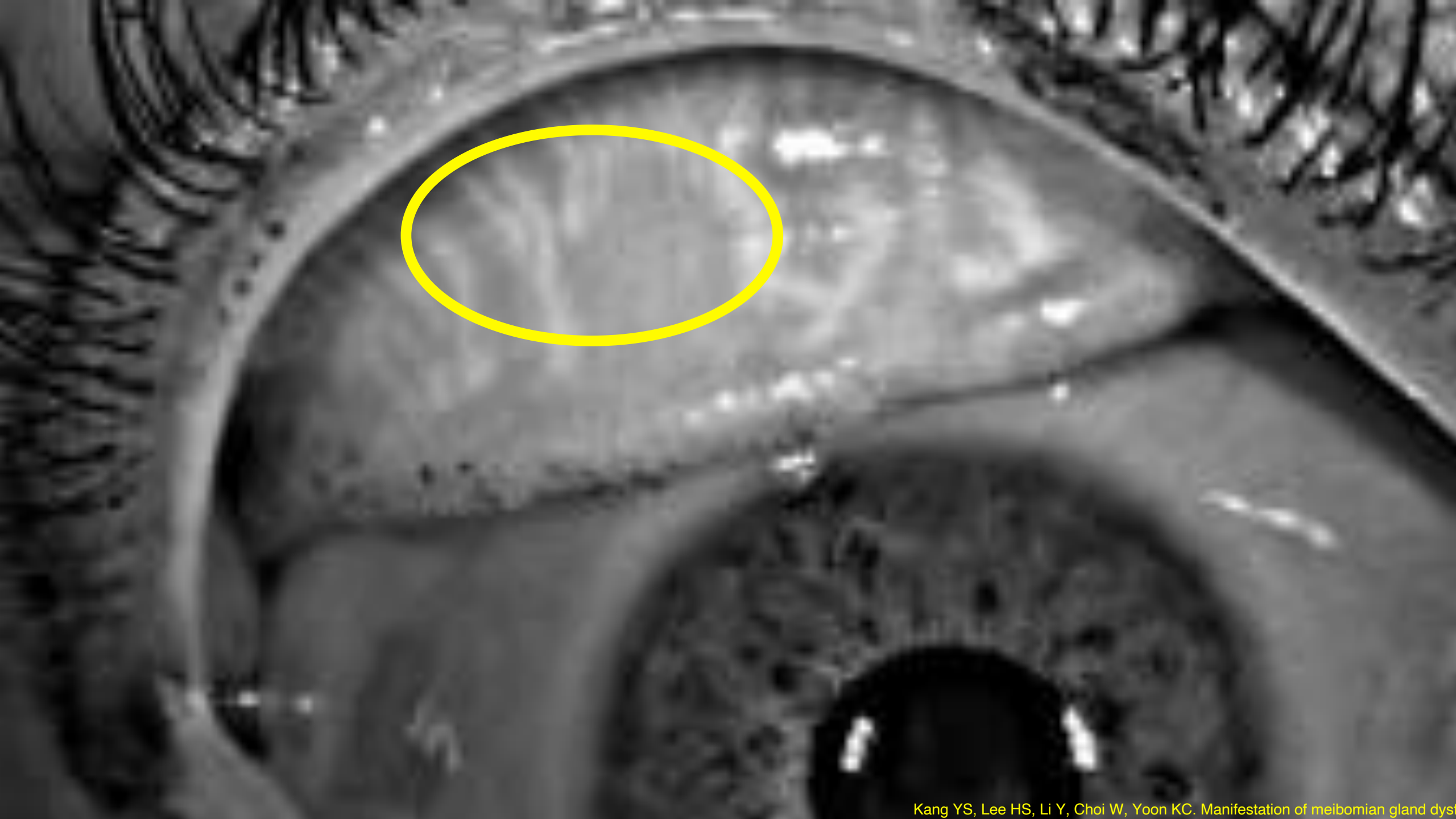
- Trehalose & hylournic gel Q2h
- Liftigrast BID
- Omega 3/hot compresses
- Moisture goggles

- <u>Medical:</u>
- Sjogren's Syndrome
- Breast Cancer
- Sarcoidosis (no Tx)

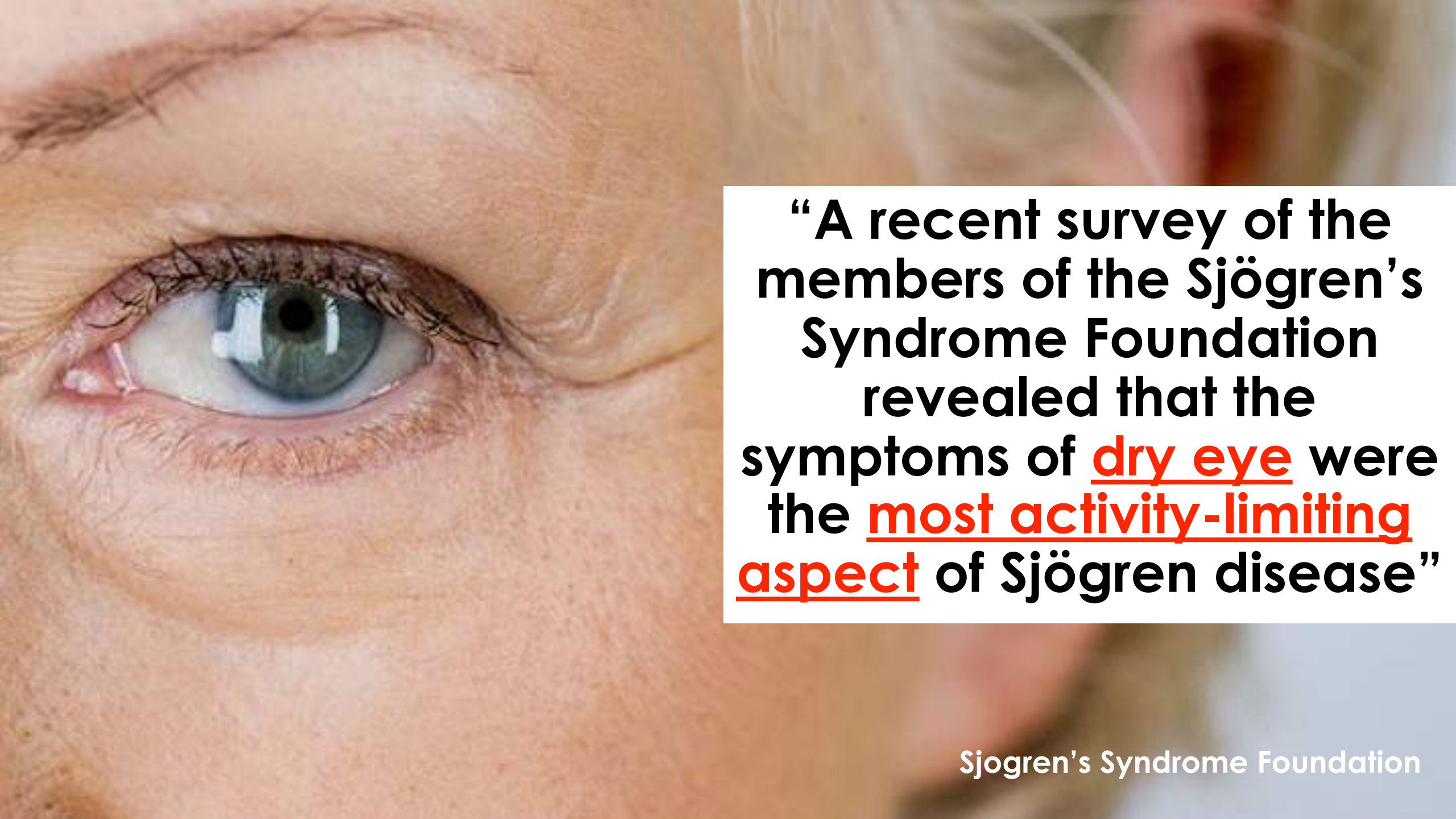
51 YOF – INTERIOR DECORATOR







Kang YS, Lee HS, Li Y, Choi W, Yoon KC. Manifestation of meibomian gland dysf



"A recent survey of the members of the Sjögren's Syndrome Foundation revealed that the symptoms of dry eye were the most activity-limiting aspect of Sjögren disease"

Sjogren's Syndrome Foundation

"Multifactorial disease of the ocular surface characterized by a loss of **homeostasis** of the **tear film**"

Ophthalmology. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276-83.

DRY EYE TREATMENT

- Lifestyle changes
- Modify risk factors
- AT, Omega 3
- Lid hygiene, hot compresses

- Topical steroids,
- PFAT, Gel drops
- Lifitegrast/Cyclosporin
- Topical/Oral antibiotics
- Punctal Plugs,
- Eyelid treatments

- Autologous Serum/PRP
- Recombinant GF
- Amniotic Fluids
- Oral Secretagogues
- Bandage CL/Amniotic Membrane
- Scleral CL

- Steroids long term
- Amniotic graft
- Surgical

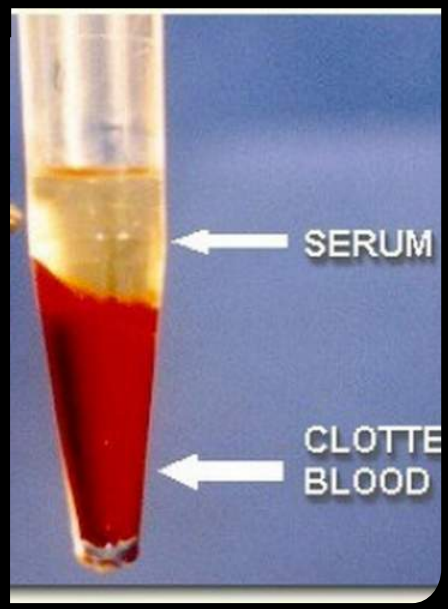
HOW IT ALL STARTED?

- The Ebers Papyrus 1534 BC - first reference of a blood use in the eye.
- In 1975, Ralph et al. used it in dry eye
- In 1984, Fox et al. used AS as treatment for DED

BLOOD BIOLOGICS TO THE RESCUE

AS, PRP, PRGF, PRF, L-PRF, PRL

- All made by centrifugation of blood
- All contain different amounts of growth factors



In almost every form of DED, a lubricating drop is needed

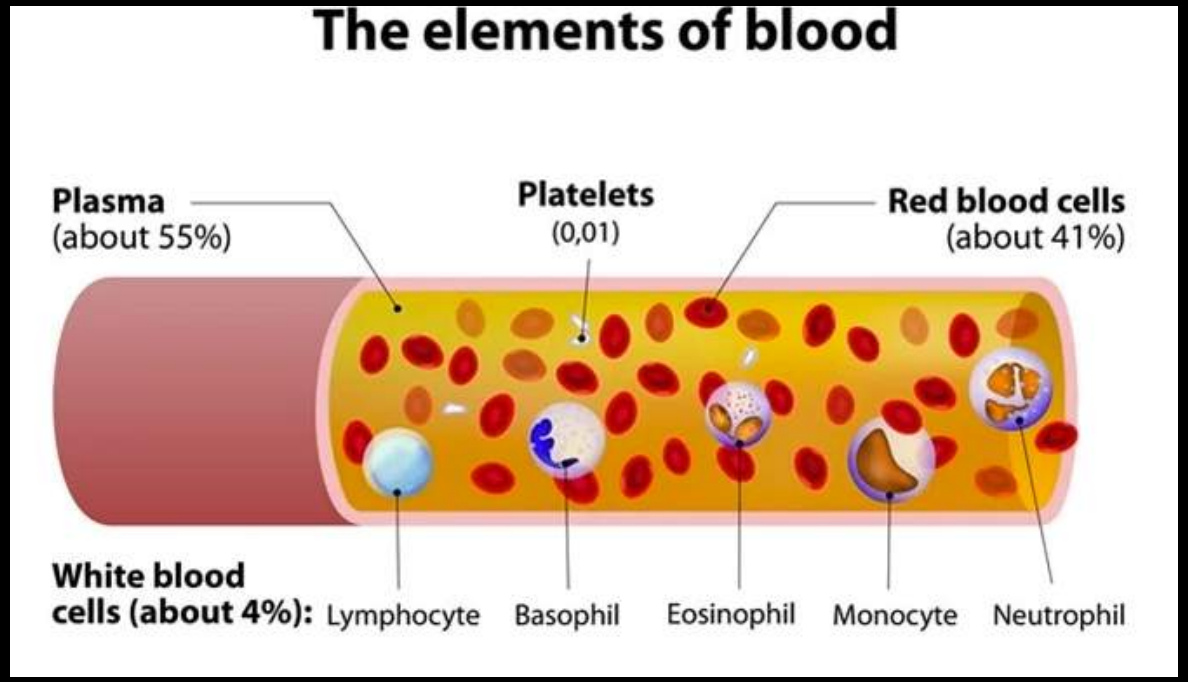
WHAT IS A GOOD EYE DROP?

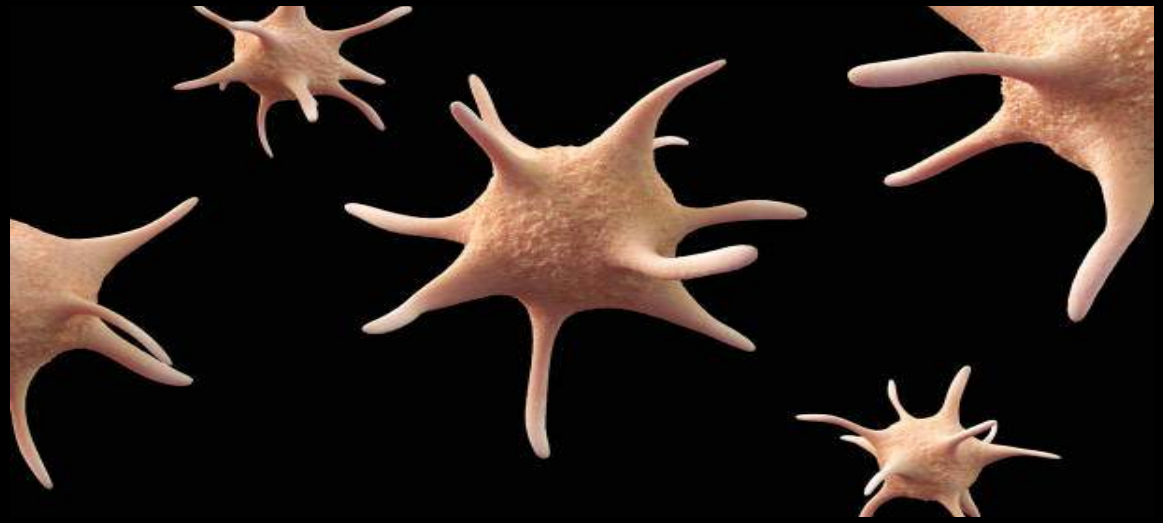
HUMAN TEAR: 1800 KNOWN MOLECULES

- Perfect lubricant
- Antimicrobial activity
- Anti-inflammatory activity
- Nourishing
- Maintain clarity of cornea
- Epitheliotropic – support proliferation, migration, and differentiation of corneal and conjunctival cells

Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II Tear Film Report. Ocul Surf. 2017;15(3):366-403

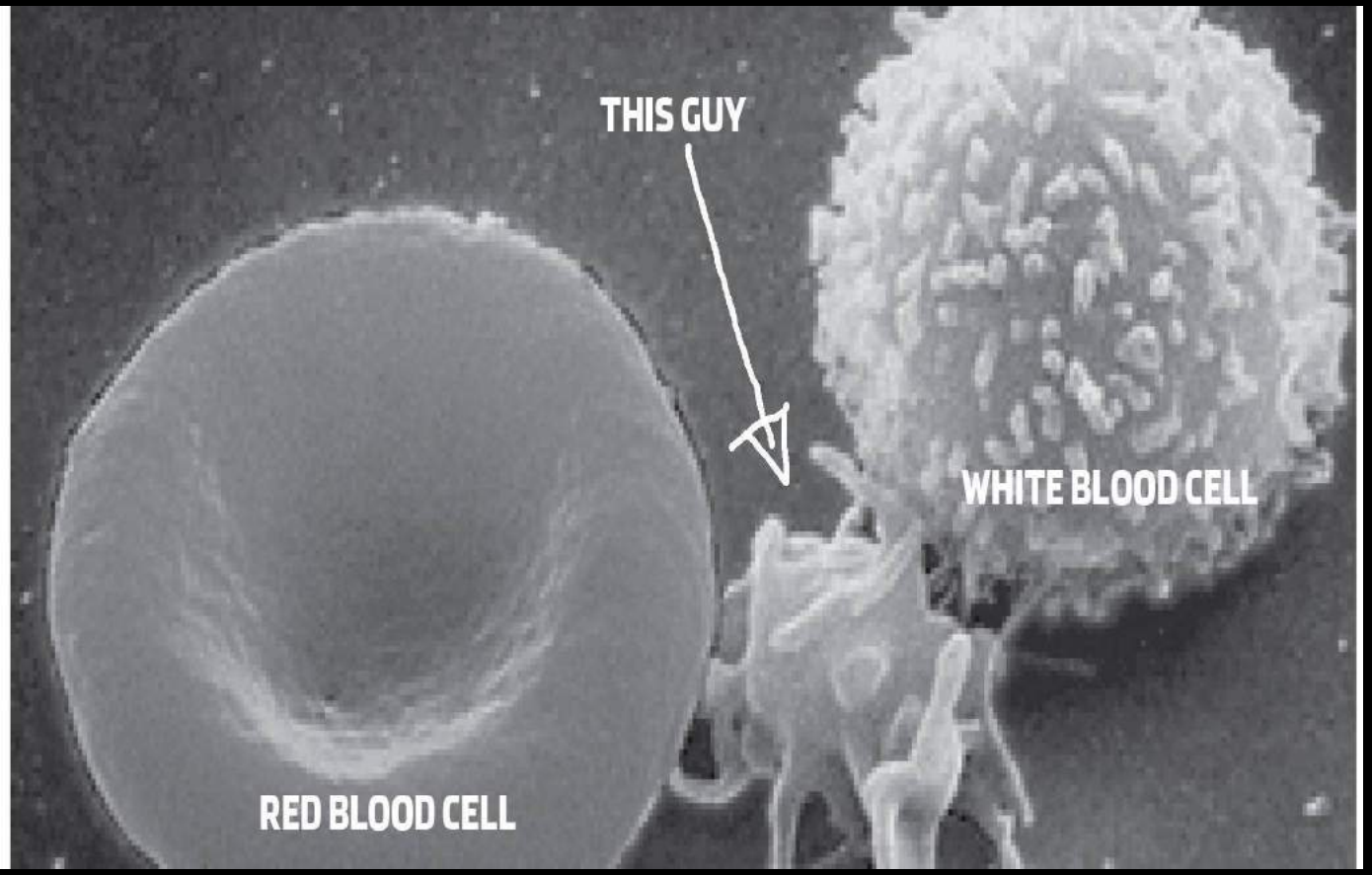
WHAT IS PRP?

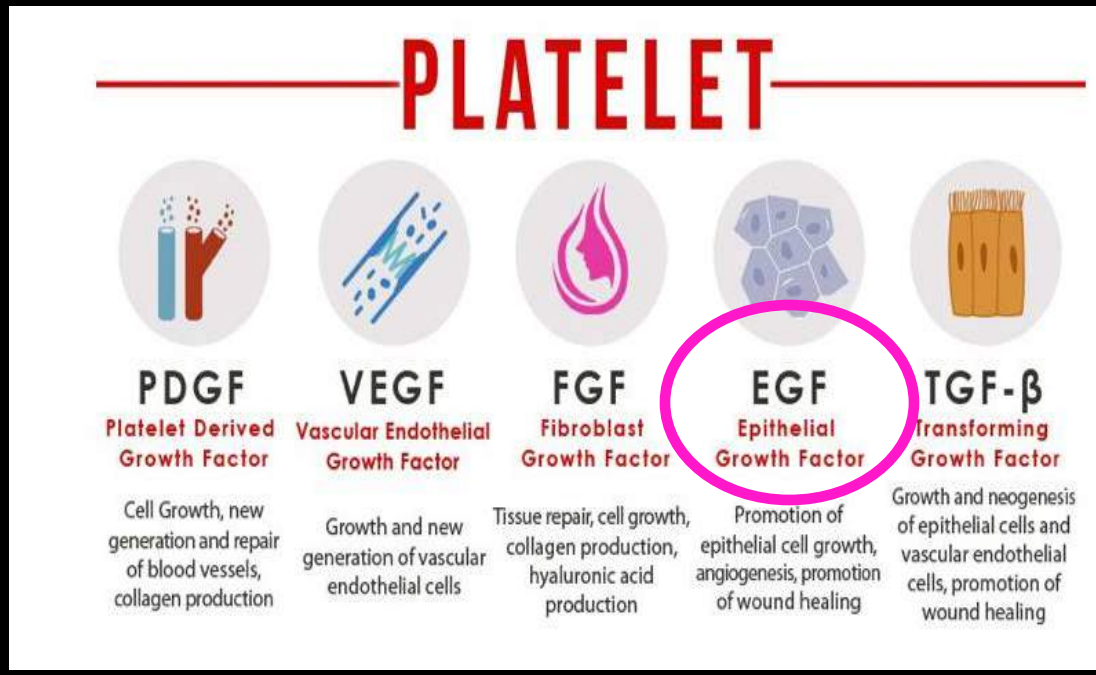




PRP – 3-5x platelet concentration than whole blood

PLATELETS -- GROWTH FACTORS





Growth Factors support wound healing by promoting proliferation, migration and differentiation of damaged cells

PLASMA

- Makes up 55% of blood
- Proteins- albumin/fibrinogen
- Immunoglobulins – fight infections
- Electrolytes – maintain cell function

- Over 600 molecules to support cellular healing

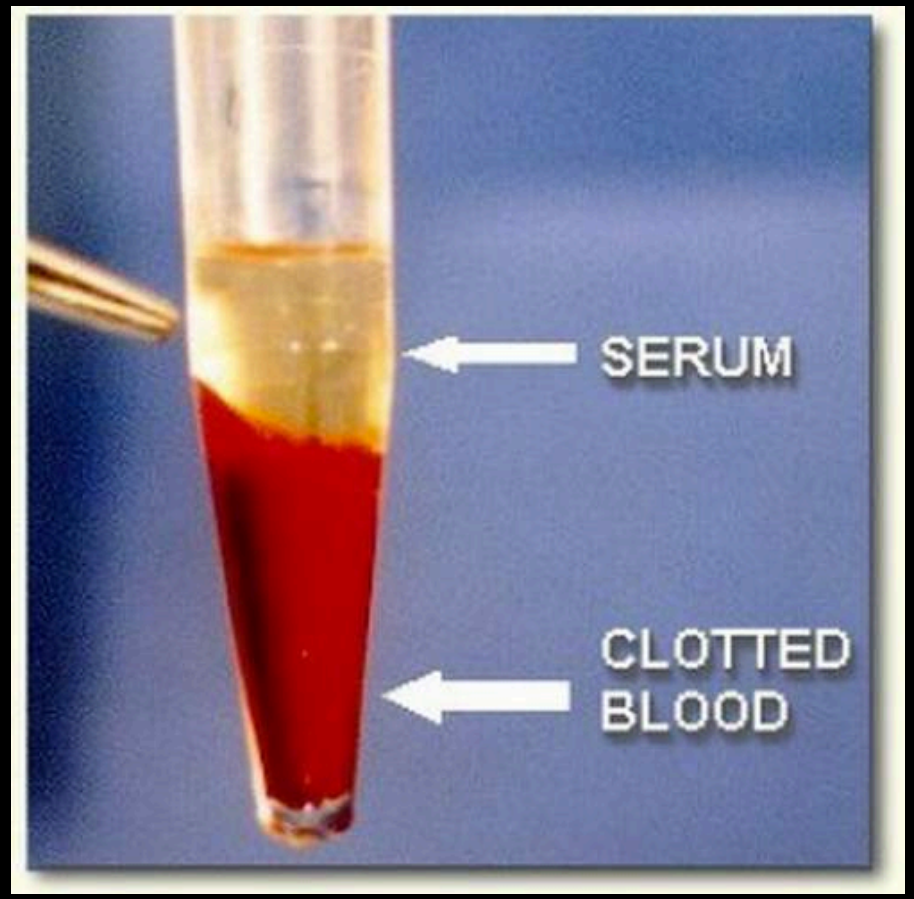
PRP - composition

GROWTH FACTORS	Key role in tissue repair Epitheliotrophic - Support proliferation/migration/differentiation of corneal/conjunctival cells
VITAMINS	Important for maturation of epithelium
FIBRONECTIN	Promotes cell migration and adhesion of epithelium to stroma Has "clearing" responsibilities to remove infectious agents/cellular debris.
CYTOKINES LYSOZYMES	Anti-inflammatory cytokines to reduce tissue inflammation and natural analgesia
ALBUMIN/ IMMUNOGLOBULINS CLOTTING FACTORS	Has anti-apoptotic activity Reduces degradation of cytokines and growth factors in areas of tissue injury

	TEARS	PRP	
Physico-chemical parameters (33, 57)			
Osmolality, mosm/l	302	300	Maintains physiological osmolality and pH
pH	7.2–7.4	7.2–7.4	
Proteins (33, 55, 56, 74)			
Total proteins, mg/mL	7.37	60–70	Support tear surface tension, physiological hydration of the ocular surface, and ocular homeostasis
Albumin, mg/mL	0.05	35–40	Anti-apoptotic activity, detoxification
Fibronectin, µg/mL	21	200–300	Adhesion protein supporting wound healing
IgG, mg/mL	0.032	8–12	Anti-microbial
IgA, mg/mL	0.41		Anti-microbial
IgM, mg/mL	–	0.5	Endotoxin binding
IgD, µg/mL	–	3–300	
IgE, µg/mL	–	0.25–0.7	
Alpha 2-macroglobulin		2.6	Anti-collagenase
Complement system			Anti-microbial; bacteriostatic
Lactoferrin, mg/mL	1.51	–	Anti-microbial and anti-inflammatory
Transferrin, mg/mL	–	2–3	Iron-carrier; anti-microbial
Lysozyme, mg/mL	1.4	6	Iron carrier; anti-microbial
Growth factors (33, 55–57, 61)			
TGF-β1, ng/mL	2–10	6–50	Epithelial and stromal repair processes
PDGF, ng/mL	0.09–1.7	30–100	Enhances mitosis and scarring
EGF, ng/mL	0.2–3	0.5–1	Accelerates the migration of epithelial cells; anti-apoptotic
HGF, ng/mL	0.2–0.5	0.1–1	Supports corneal epithelial cells
VEGF, ng/mL	0.019	1–5	Supports conjunctival endothelial permeability
Vitamins (33)			
A, ng/mL	16–20	800–1000	Prevents squamous metaplasia and helps maintain the normal histology in the conjunctiva
C, µg/mL	117	7–20	Antioxidant
Antioxidants (33)			
Tyrosine, µM	45	77	
Glutathione, µM	107	ND	
Electrolytes (33)			
Na+, mEq/L	145	135–146	
K+, mEq/L	24.1	3.5–5.0	
Ca^{2+}, mM	1.5	1.1	
Cl^-, mM	128	96–108	
HCO_3^- mM	26	21–29	
NO_3^- mM	0.14	0.19	
PO_4^{3-} mM	0.22	1.42	
SO_4^{2-} mM	0.39	0.53	

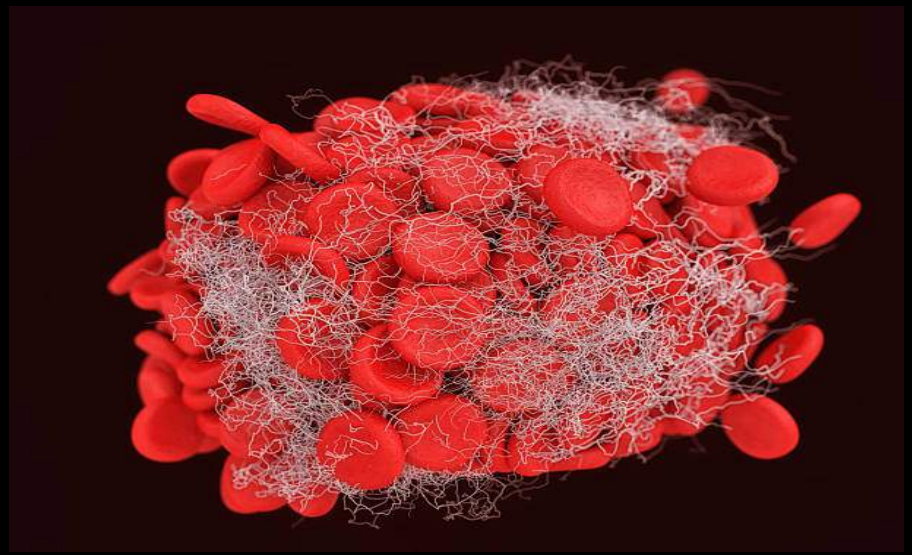
PREPARATION – AUTOLOGOUS SERUM

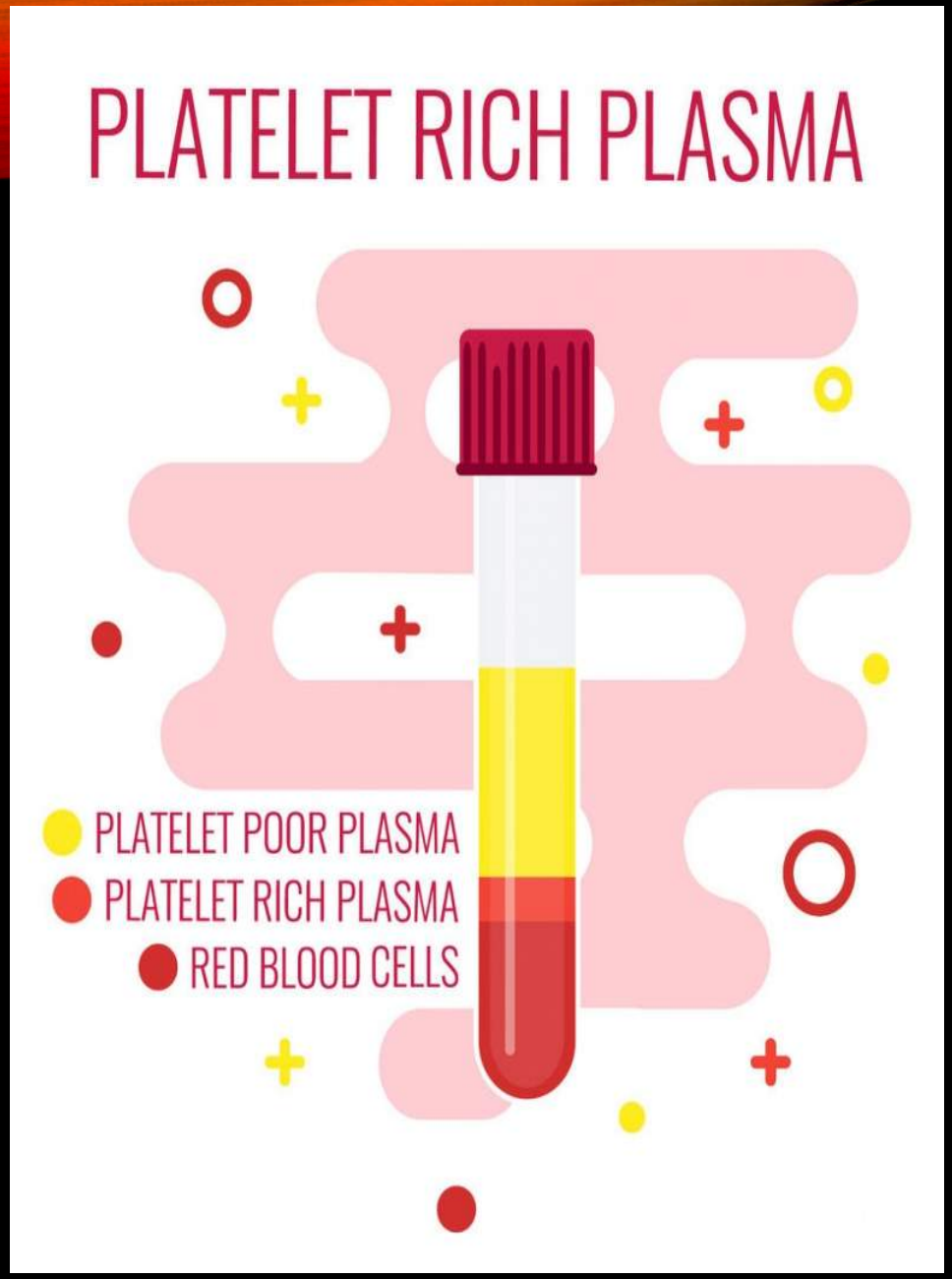
Uses Clotted Blood



Autologous Serum

Clotted blood with platelets





PREPARATION – PRP

Uses Un-clotted Blood

Keeping platelets in their true form

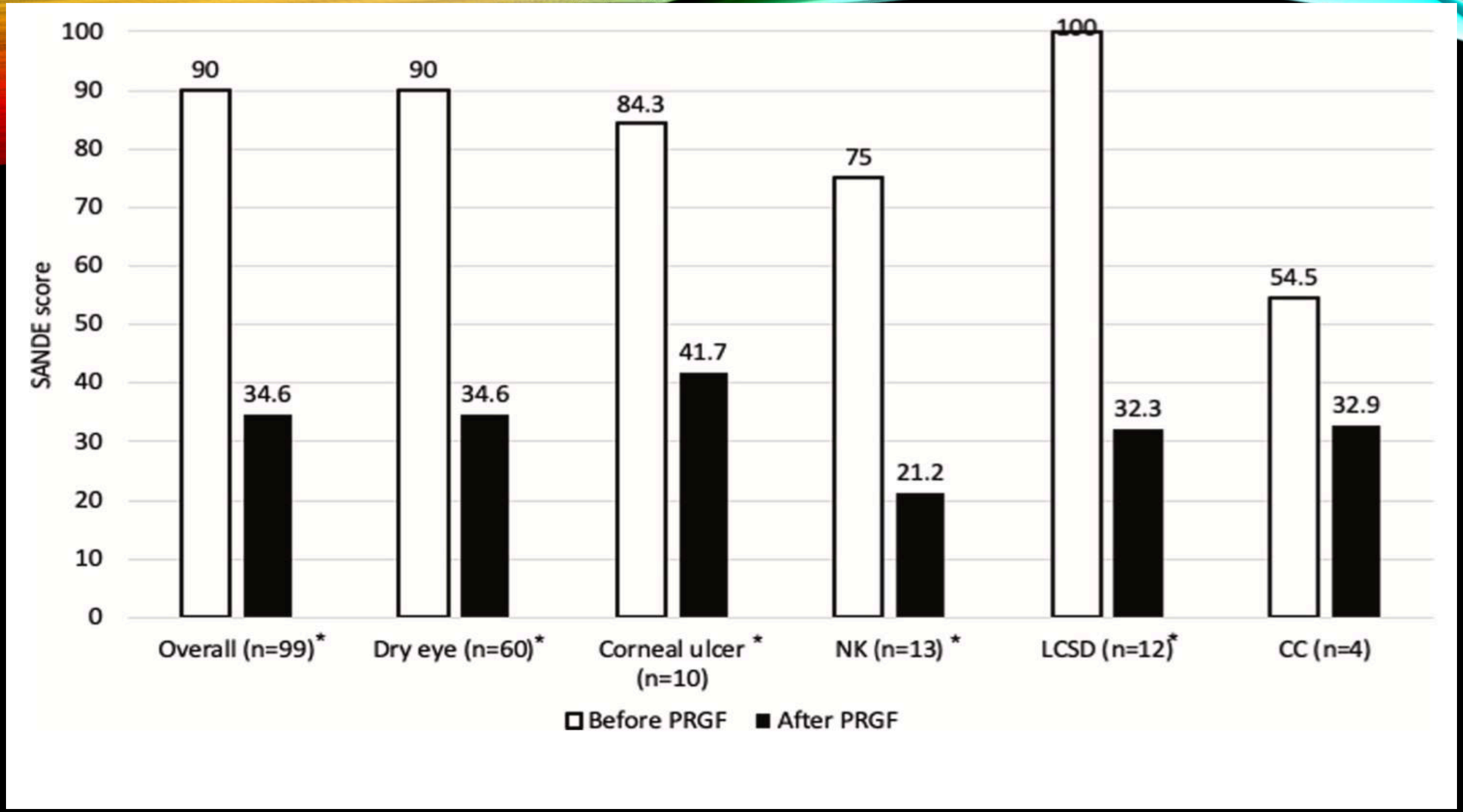
AS VS PRP

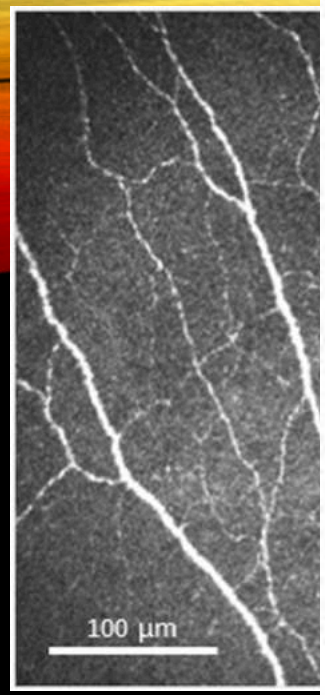
AS

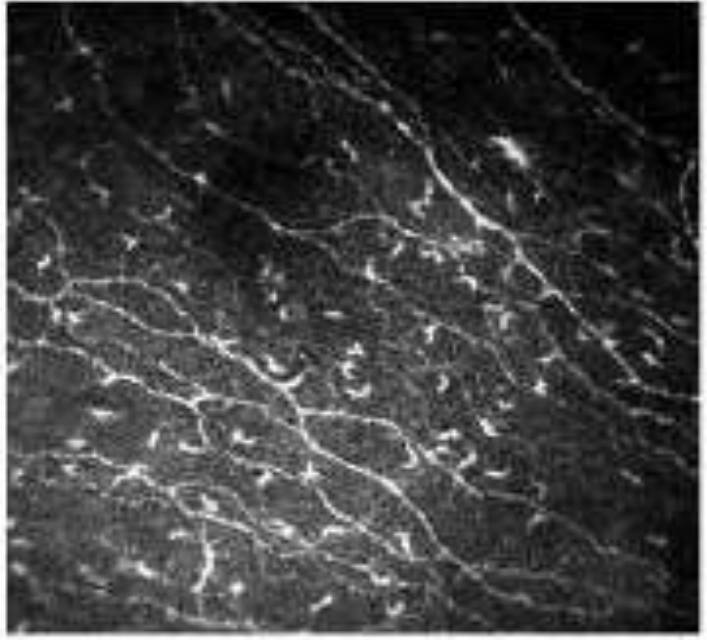
- Does NOT contain platelets
- Less concentration of GF/Plasma factors
- Serum is not plasma
- Has inflammatory cytokines from monocytes and leukocytes
- Contains high amounts of TGF-Beta – can suppress wound healing
- Often diluted with saline (20-50%) to reduce inflammatory cytokines (further dilutes GF)

PRP

- Contains Platelets
- High Concentration for GF and Plasma Factors
- GF released in a biologically relevant ratio
- No inflammatory cytokines
- Not diluted
- Dispensed 100%
- Considered superior to AS
- Used in medicine


SANDE score
100
90
80
70
60
50
40
30
20
10
0
90
34.6
90
34.6
84.3
41.7
75
21.2
100
32.3
54.5
32.9
Overall (n=99)*
Dry eye (n=60)*
Corneal ulcer (n=10) *
NK (n=13) *
LCSD (n=12)*
CC (n=4)
Before PRGF
After PRGF





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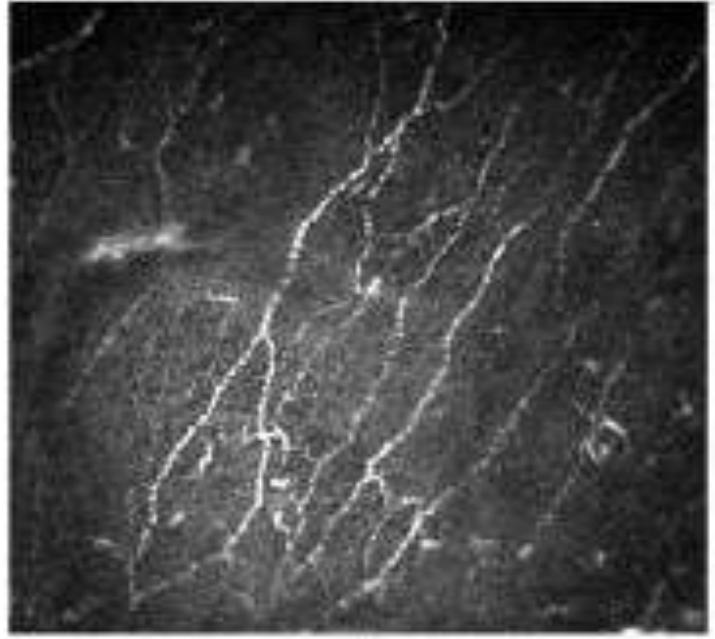

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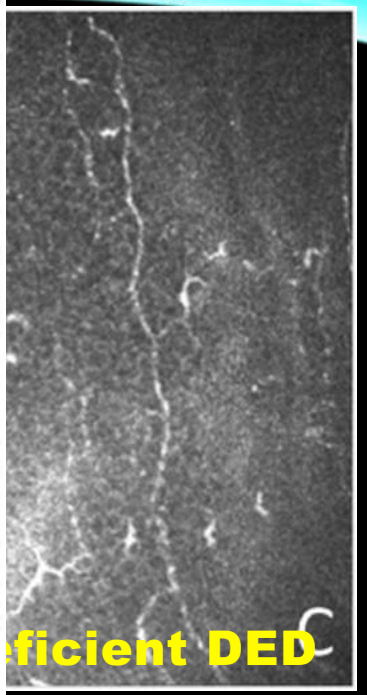
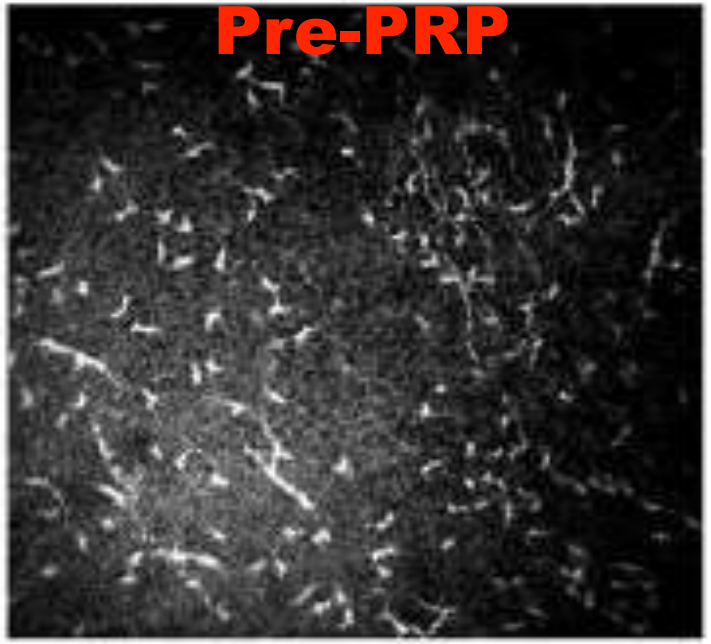


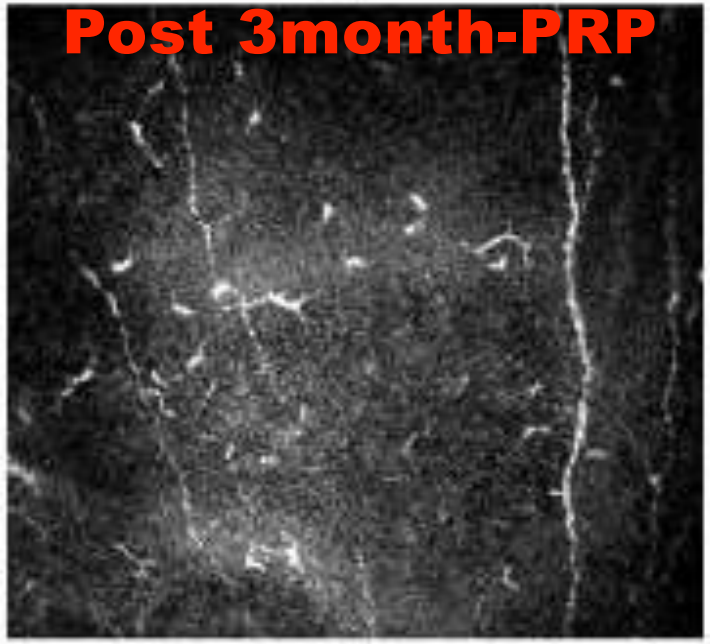
eficient DED

Pre-PRP



(c)

Post 3month-PRP



(d)

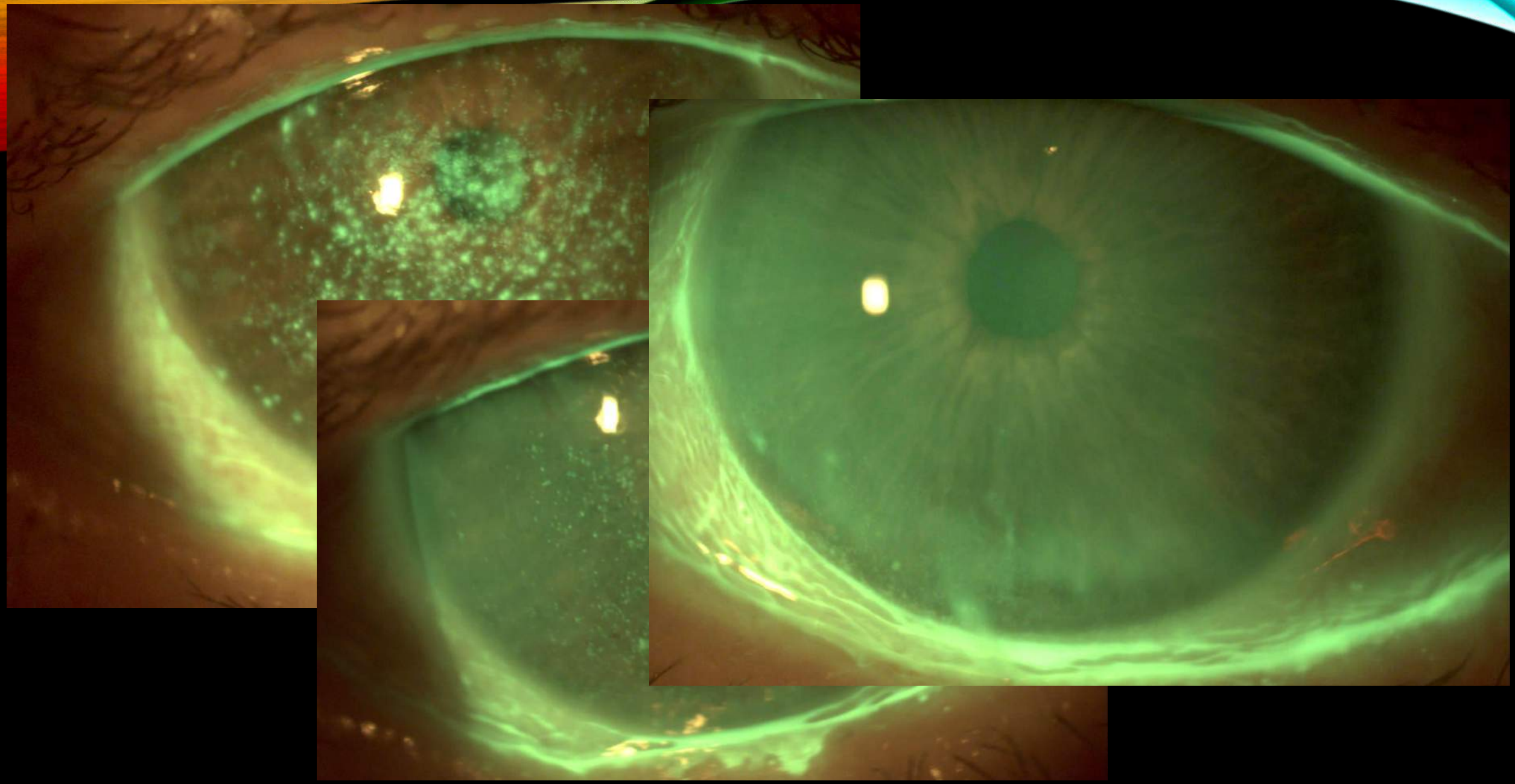
Autologous Platelet Lysate Eye Drops: An In Vivo Confocal Microscopy Study. Biomed Res Int.

WHO CAN BENEFIT FROM BIOLOGICS?

- Mild/moderate/severe DED
- Aqueous and Evaporative
- LASIK/PRK induced
- Neuropathic/Neurotropic
- Corneal ulcers/RCE
- Persistent Epi defects
- Autoimmune (SS) dry eye
- Patients who want natural options

	Conventional treatment group (n = 20)	PRP treatment group (n = 27)	*p*-value*
Follow-up (mon)	15.2 ± 17.4 (6-64)	14.6 ± 12.0 (6-42)	0.900
BCVA at final visit	0.84 ± 0.14	0.87 ± 0.14	0.400
Recurrences (total no. of episodes)			
Major	23	7	0.001
Minor	50	10	0.001
Mean frequency of recurrences	0.39 ± 0.24	0.06 ± 0.08	0.003

Lee JH, Kim MJ, Ha SW, Kim HK. **Autologous Platelet-rich Plasma Eye Drops in the Treatment of Recurrent Corneal Erosions**. *Korean J Ophthalmol*. 2016;30(2):101-107. doi:10.3341/kjo.2016.30.2.101

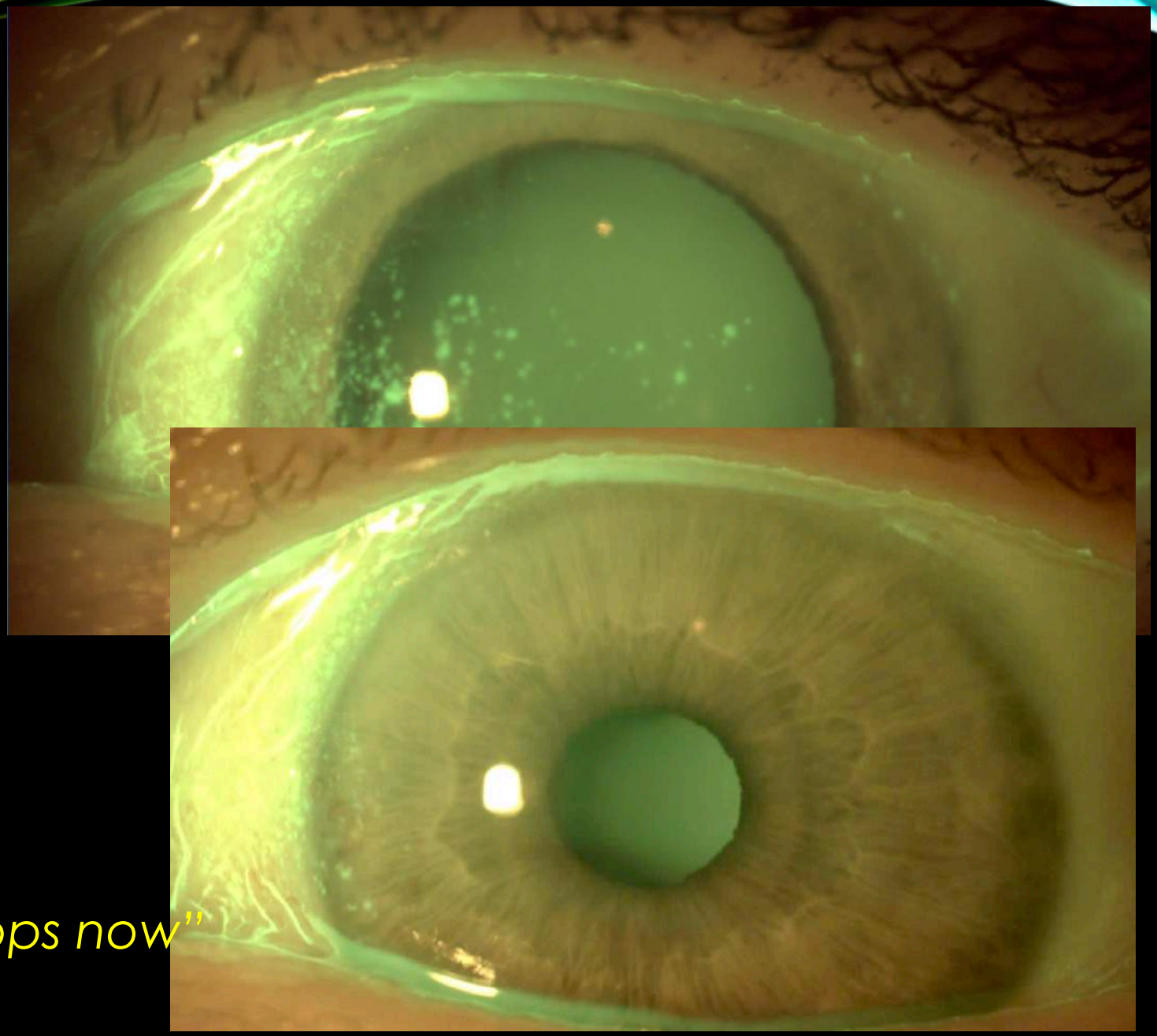


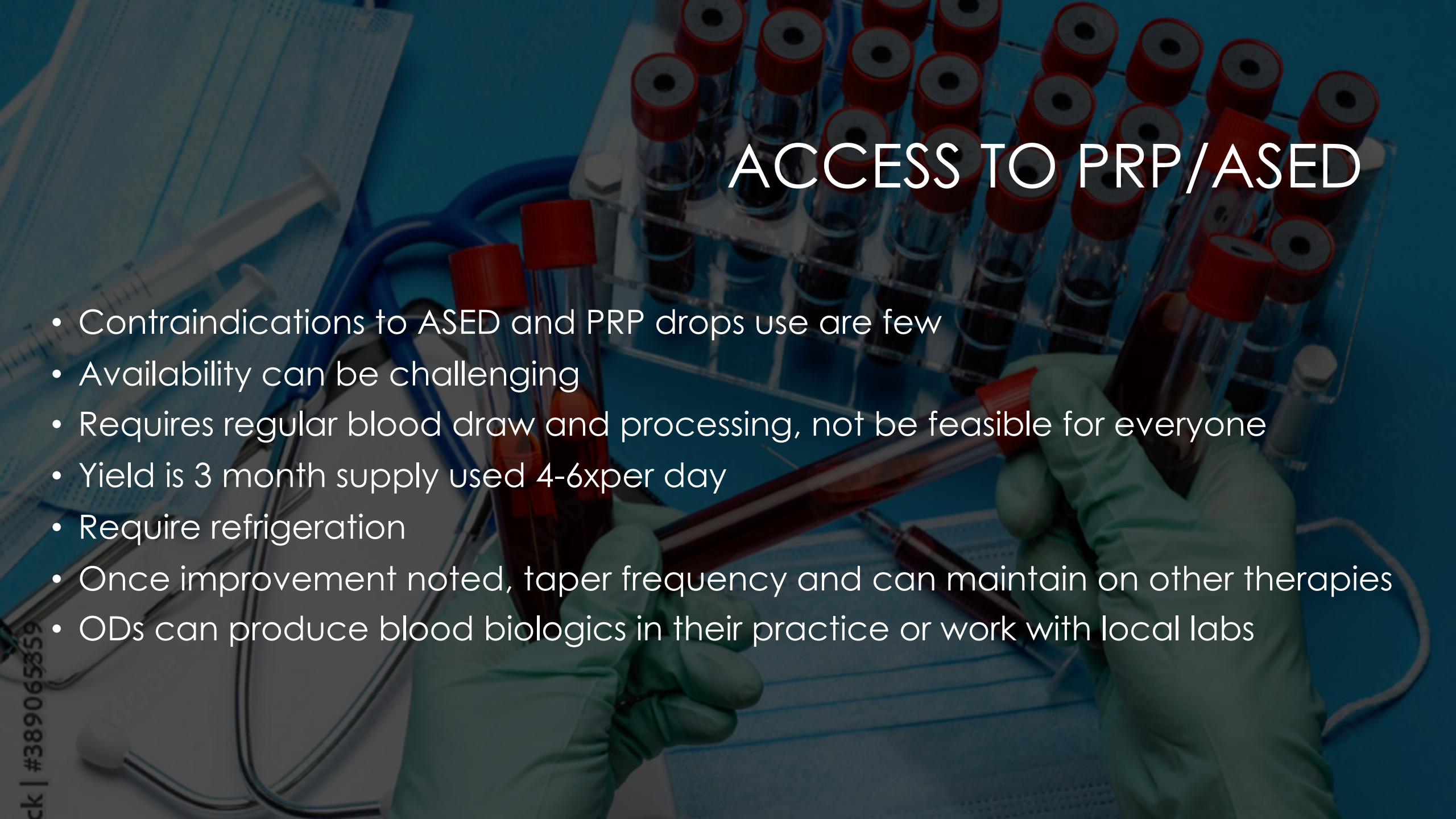
51 YOF – INTERIOR DECORATOR

- 4 IPL treatments
- PRP QID x 3 months

- Maintain:
- Trehalose & hylournic drops BID
- Cyclosporine 0.09% BID
- PRP using every other week
- Omega 3
- Collagen punctal plugs
- Lid hygiene

"I sometimes forget to use my drops now"





ACCESS TO PRP/ASED

- Contraindications to ASED and PRP drops use are few
- Availability can be challenging
- Requires regular blood draw and processing, not be feasible for everyone
- Yield is 3 month supply used 4-6xper day
- Require refrigeration
- Once improvement noted, taper frequency and can maintain on other therapies
- ODs can produce blood biologics in their practice or work with local labs

AMNIOTIC FLUID DROP

- Made from donor human amniotic fluid or placental tissue
- Contain cytokines and GF to aid healing
- Mild to severe dry eyes
- Found to reduce pain and inflammation and promote re-epithelialization in ocular chemical burns

- StimulEyes (M2 Biologics) and Regener-Eyes (Regener-Eyes)

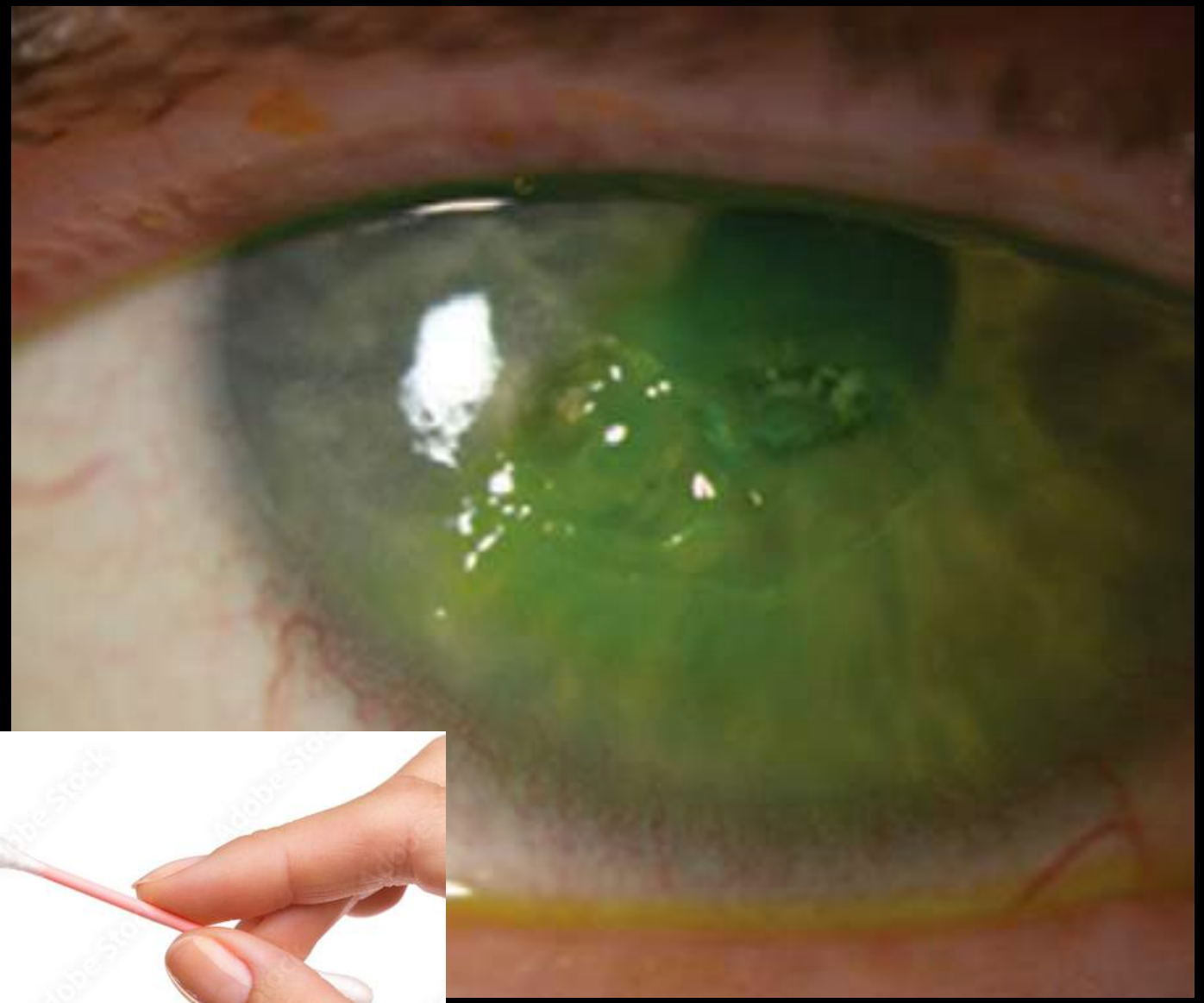
Liang L, Li W, Ling S, et al. Amniotic membrane extraction solution for ocular chemical burns. Clin Exp Ophthalmol. 2009;37(9):855–863

NEUROTROPIC KERATITIS (NK)

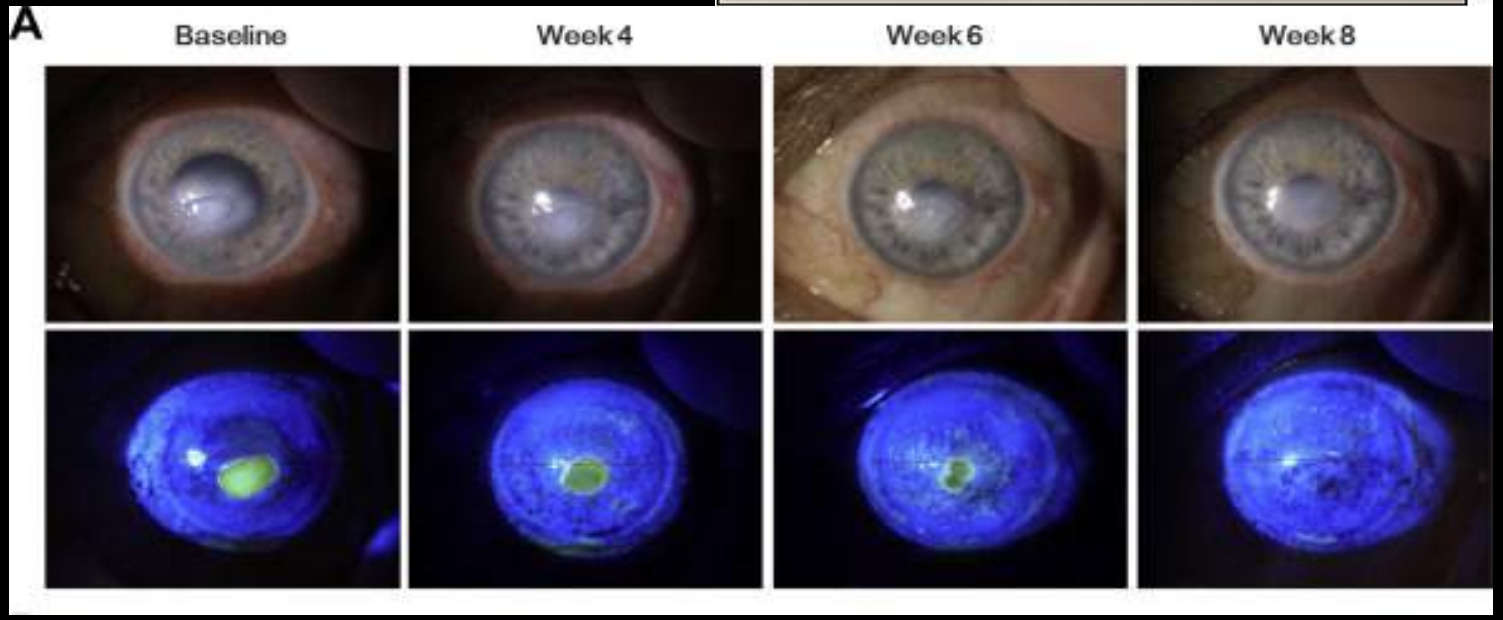
- Degenerative disease due to lack of cornea's ability to heal
- Cornea is the most densely innervated tissue
- Damage to nerves leads to partial or total loss of corneal sensation
- Leads to non healing defects

NEUROTROPIC KERATITIS – STAIN BUT NO PAIN

- Orphan disease
- Causes: injury, surgery, infections, systemic conditions
- Test corneal sensitivity



OXERVATE (CENEGERMIN OPHTHALMIC SOLUTION 0.002% DOMPE)



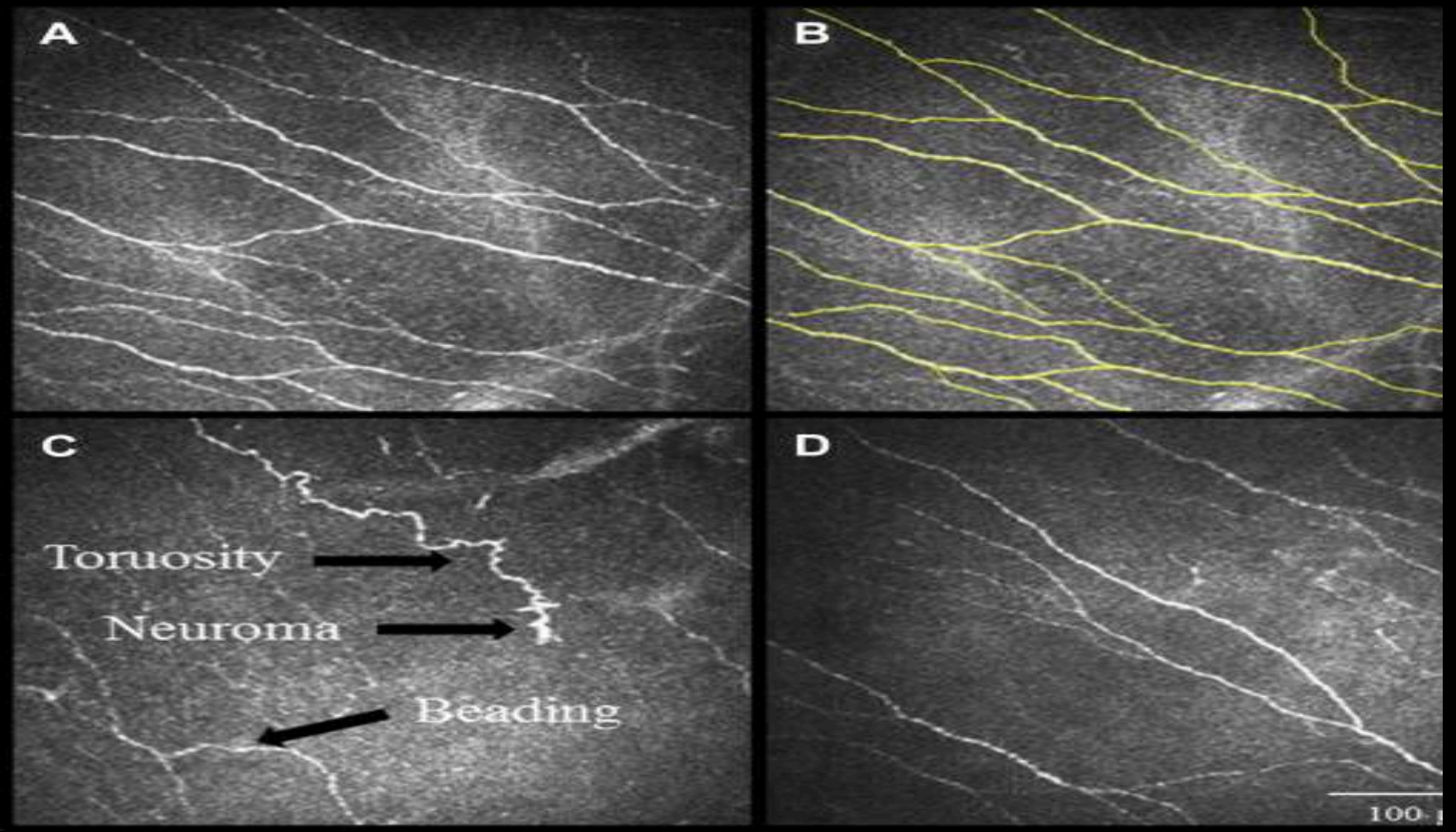
- Recombinant NGF - promotes corneal healing in a neurotrophic cornea
- PF, sterile drop, use 6x/day for 8 weeks.
- Significant improvement noted in the cenegermin group
- Orphan drug

Bonini S et al., for the REPARO Study Group. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology. 2018 Sep;125(9):1332-1343

NEUROPATHIC PAIN: PAIN WITH NO BENEFIT

- Insult to the nociceptive system
- Heightened pain
- Burning, stinging
- Eye-ache
- Photoallodynia
- Insignificant findings

PAIN IS FELT, NOT SEEN – UNTIL NOW



Damaged corneal nerves on confocal microscopy

NEUROPATHIC PAIN TREATMENT

- Multi-treatment approach
- Reduce Inflammation
- Optimize the ocular surface

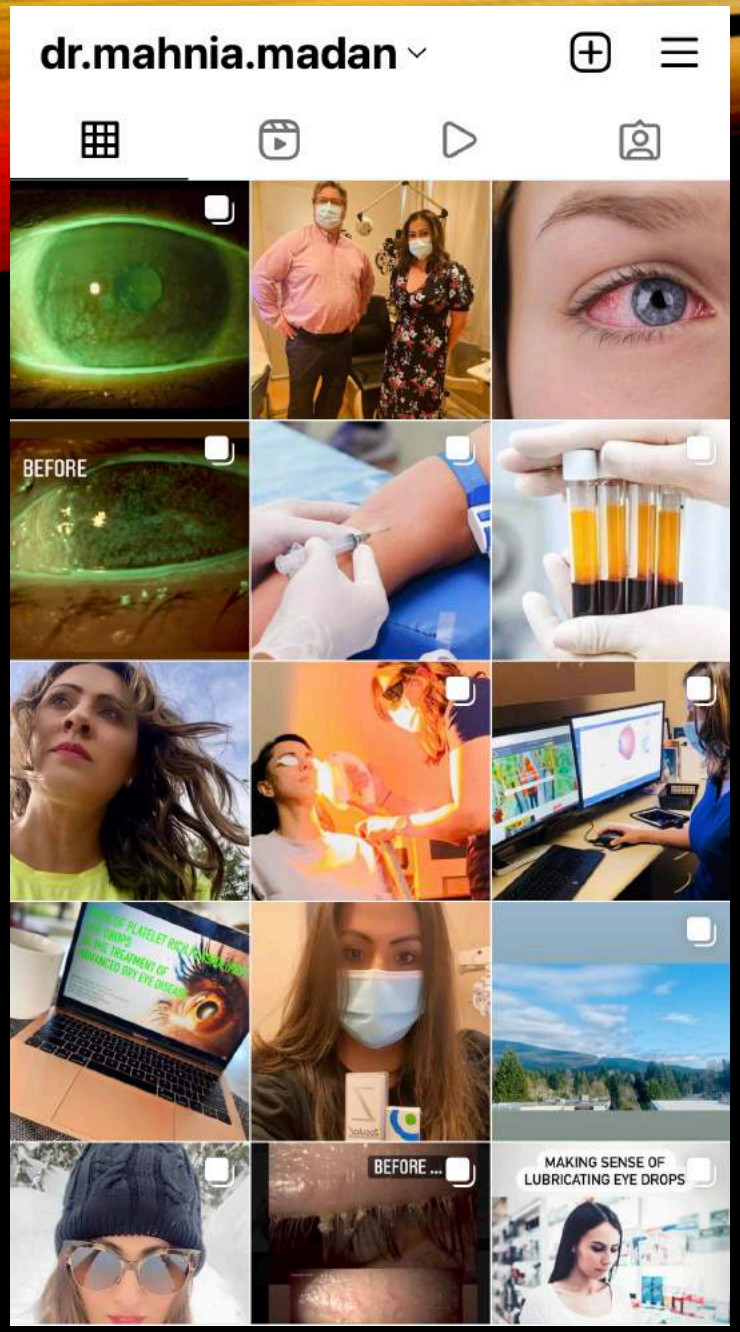
Goyal S, Hamrah P. Understanding neuropathic corneal pain—gaps and current therapeutic approaches

Systemic Pharmacotherapy for Pain

1. TCAs like Nortriptyline, amitriptyline
2. Carbamazepine
3. GABAergic drugs (gabapentin
4. SNRI like duloxetine and venlafaxine
5. Opioids like Tramadol
6. Class 1B sodium channel blocker Mexiletine

Alternative measures

1. Acupuncture
2. Transcranial Magnetic Stimulation
3. Scrambler Therapy
4. Implantable neuromodulators
4. Cardio- Exercise
5. Omega-3 rich diet



THANK YOU!
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