# Dry Eye: Current & Future Treatment Options

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## Disclaimers

- Have been on speaker's bureaus for :
  - Allergan
  - Tear Science
  - Bausch & Lomb

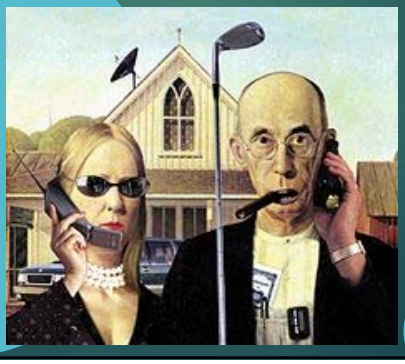
*The art of medicine consists of amusing the patient while nature cures the disease.*

*—Voltaire, 1694-1778*

French enlightenment writer, philosopher

- Dry eyes is out of synch with the modern world

*—Cassandra Wong, Allergan representative*



# Approach to the Dry Eye Patient

DED affects multiple aspects of the functional lacrimal unit

- Lids & Meibomian glands
- Lacrimal glands
- Goblet cells
- Other ocular surface cells

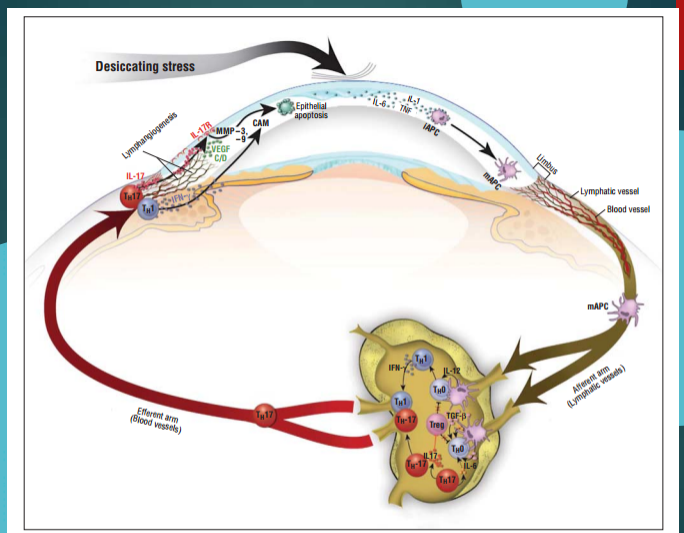
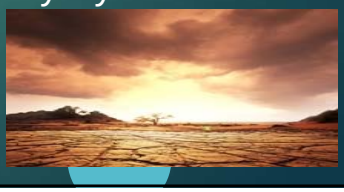



**Figure 1.** Immunoinflammatory pathways. Desiccating stress induces tear hyperosmolarity, activating intracellular signaling pathways that initiate the production of proinflammatory cytokines (eg, interleukin [IL] 1, tumor necrosis factor [TNF], and IL-6). This proinflammatory milieu facilitates the activation and maturation of immature antigen-presenting cells (iAPC). Mature APCs (mAPC) migrate through the afferent lymphatics to draining lymph nodes, where they induce effector helper T cell 1 ($T_H1$) and $T_H17$ cells that subsequently migrate through efferent blood vessels to the ocular surface. The $T_H17$ cells antagonize regulatory T cell (Treg) functions and lead to further expansion of T effectors in the draining lymph nodes. Effector $T_H1$-secreted interferon (IFN) -γ and $T_H17$-secreted IL-17 exert their pathogenic effects by promoting the production of proinflammatory cytokines, chemokines, matrix metalloproteinases (eg, MMP-3 and MMP-9), cell

# Approach to the Dry Eye Patient

Determine if Chronic DED vs Acute DED exacerbation


- If acute dry eye, put out the fire
- Most patients have chronic dry eye



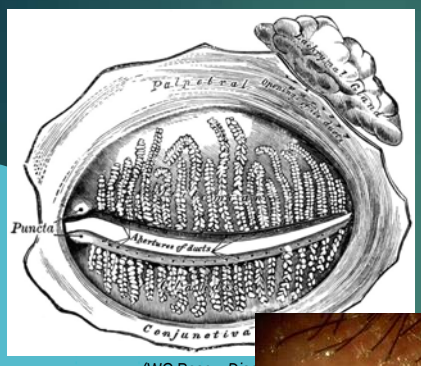

- I'm going to use all my tools, my God-given ability, and make the best life I can with it

*—LeBron James, NBA great (1984-)*

# Selected current and future treatment strategies

- **MGD treatments** (don't neglect anterior blepharitis/ demodex)
  - Physical Lid therapies
  - Topical therapies
  - Systemic therapies
- Lacrimal gland treatments
  - Corticosteroids
  - Cyclosporine & other calcineurin inhibitors
  - Lifitegrast
- Goblet cell treatments
  - Cyclosporine
  - Rebamipide?
  - Diquafosol

# TREATING MEIBOMIAN GLAND DYSFUNCTION




(WC Posey, *Dise*

*If I had known I was going to live this long I would have taken better care of myself*

—Mae West, American actress

1893-1980

# Meibomian Gland Dysfunction

(Posterior blepharitis)

Wide array of disease processes

- Gland drop out & obstruction/keratinization of orifices
- Alterations of lipid composition
- Seborrheic dermatitis/ keratinization
- Rosacea common contributor
- Closely interwoven with dry eye

Mathers "Meibomian gland disease" in Dry Eye & Ocular Surface Disorders 2004

# MGD Treatment

- **Lid hygiene**
- Meibomian gland expression
  - Manual
  - Lipiflow
  - IPL
- Topical therapies
- Systemic therapies

--Should consider using something from **each modality** to control this chronic progressive condition

# MGD Treatment

- Lid hygiene
  - Warm paks ~10 minutes bid-qid standard of care
  - Time consuming
  - Should follow with lid massage or scrub
  - Patient compliance usually poor unless highly motivated

## MGD Treatment

- Lid hygiene
- **Meibomian gland expression**
  - Manual
  - Lipiflow
  - IPL
- Topical therapies
- Systemic therapies

--Should consider using something from **each modality** to control this chronic progressive condition

## MGD Treatment

- Meibomian gland expression
  - Manual
    - Generally inconvenient for physician
    - Painful
    - Bruising


- I make impact plays. I make game-changing plays

  —*LeBron James, NBA great (1984-)*

## MGD Treatment

- Meibomian gland expression
  - Automated Vectored Thermal Pulsation
    - Lipiflow System

Donald R. Korb, OD

Boston, MA

## LipiFlow® Thermal Pulsation System

**LipiFlow® safely and effectively treats Meibomian gland obstruction in both upper and lower eyelids simultaneously**

**— in-office procedure,**

**—treats both eyes simultaneously**

**—takes only 12 minutes**

TearScience®

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## LipiFlow® Uses Heat and Pressure to Liquefy and Evacuate Obstructed Glands

### Disposable Activator

**Air Bladders**
*Composed of inflatable silicon pneumatic bladders*

**Lid Warmer**
*Composed of a heater, eye insulation, and vaulted shape*

TearScience®

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## Meibomian Gland Dysfunction

Clinical Results With LipiFlow®

TearScience®

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## LipiFlow® Clinical Data

**Open-label, Randomized, Controlled, Multicenter Trial of the LipiFlow® System as Compared to Warm Compress Therapy for the Treatment of MGD**

**Study reviewed by FDA to obtain clearance**

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## Meibomian Gland Evaluator™

- Allows Meibomian gland secretions to be evaluated through a slit lamp biomicroscope
- Applies consistent, moderate pressure
  - Between 0.8-1.2 g/mm$^2$

| Grade | Secretion Characteristics |
|---|---|
| 3 | Clear liquid oil |
| 2 | Colored/cloudy liquid |
| 1 | Inspissated (toothpaste consistency) |
| 0 | No secretion (includes capped orifices) |

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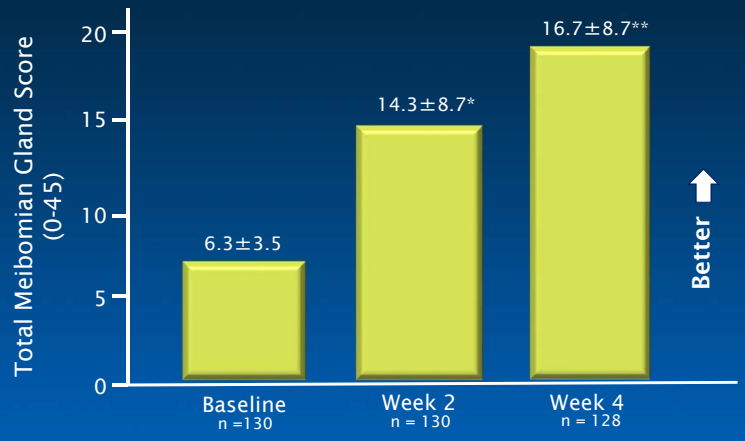
## LipiFlow® Treatment Increased Mean Meibomian Gland Secretion Score




*P<0.0001 vs baseline; **P<0.0001 vs warm compress at week 2.
Mean scores are provided with their standard deviation.

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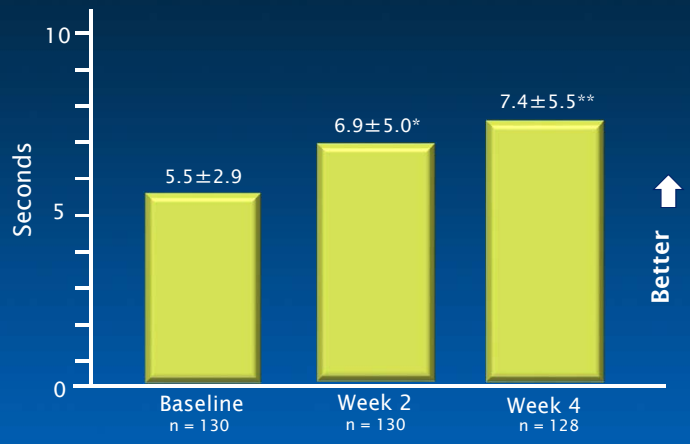
## LipiFlow® Treatment Significantly Improves Mean Tear-Film Break-up Time




*P<0.0001 vs baseline; **P<0.0001 vs warm compress at week 2.
Mean scores are provided with their standard deviation.

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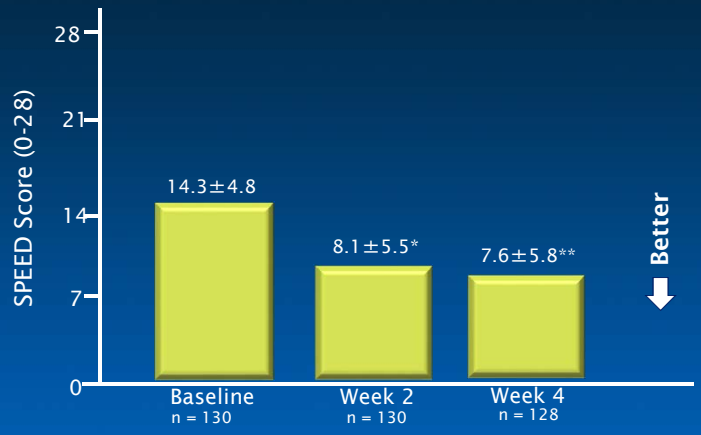
## LipiFlow® Decreases the Frequency and Severity of Dry Eye Symptoms Post Treatment




*P<0.0001 vs baseline; **P<0.0001 vs warm compress at week 2.
Mean scores are provided with their standard deviation.

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## LipiFlow® - A Primary Treatment for MGD

- **90%** of patients had total Meibomian gland score improvement
- **79%** of patients reported improvements in overall Dry Eye symptoms

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## LipiFlow® Follow-up Patient Survey[1]

- 465 LipiFlow® patients
  - –71 practices, across 49 states

- 75% had previously tried >4 therapies
- 73% are hindered at leisure and work
- Average 3 physicians seen for dry eye
- Average spend = $64 per month
- 82% would recommend LipiFlow®
  - – (15% noted too early to tell)

TearScience®

1 TearScience study. Data on file.

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## MGD Treatment: Other Studies

- **3 & 6 month study** (Dusseldorf)

  Prospective randomized observer masked trial

  - Compared 1 Lipiflow Tx with 3 months of warm paks/massage bid
    - 1&3 months Lipiflow group had significant OSDI improvement compared with lid hygiene group
    - Expressible meibum was equivalent both groups
    - Trend for improved lipid layer thickness & TBUT with Lipiflow
    - 6 months: OSDI, Lipid layer thickness, # expressible glands, cchalasis, bulbar redness all improved only with Lipiflow;
      - The more gland atrophy (dropout), the less symptom improvement

Finis, et al. The Ocular Surface Apr 2014 12(2) (Dusseldorf)

Finis et al. Cornea 2014 Dec; 33(12)1265-70

1 year study ASCRS 2015

# Long-term Effectiveness of a Single Thermal Pulsation Treatment for Meibomian Gland Dysfunction and Evaporative Dry Eye

PARAG MAJMUDAR, MD

**Financial Interest Disclosure Statement:**

The author of this presentation has received research funding from TearScience

## Methods: Randomization and Treatment

- Subjects randomized to:
  - Single 12-minute thermal pulsation treatment (Treatment group)
  - Twice daily conventional therapy using over-the-counter warm compresses and lid scrubs for 3 months (Control group)
- Control group subjects received crossover thermal pulsation treatment at 3 Months (Crossover group)
- All subjects followed at 3, 6, 9 and 12 Months
- Subjects with inadequate symptom relief could receive additional prescribed MGD or dry eye therapy based on physician's discretion
  - after 3 months in the Treatment group
  - after 6 months in the Crossover group

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## 12-Month Follow-up of Single Treatment Group

- Of the 101 subjects (202 eyes) randomized to Treatment group:
  - 94 subjects (95% of randomized subjects) followed to 12 Months
    - 81 Treatment Group subjects (86% of subjects at 12 Months) had received only one thermal pulsation treatment & no additional prescribed MGD/dry eye treatment at 12 Months
- Of the 99 subjects (198 eyes) randomized to Control group:
  - 93 subjects (94% of randomized subjects) followed to 12 Months
    - 82 Crossover group subjects (89% of subjects at 12 Months) had received only one thermal pulsation treatment & no additional prescribed MGD/dry eye treatment at 12 Months

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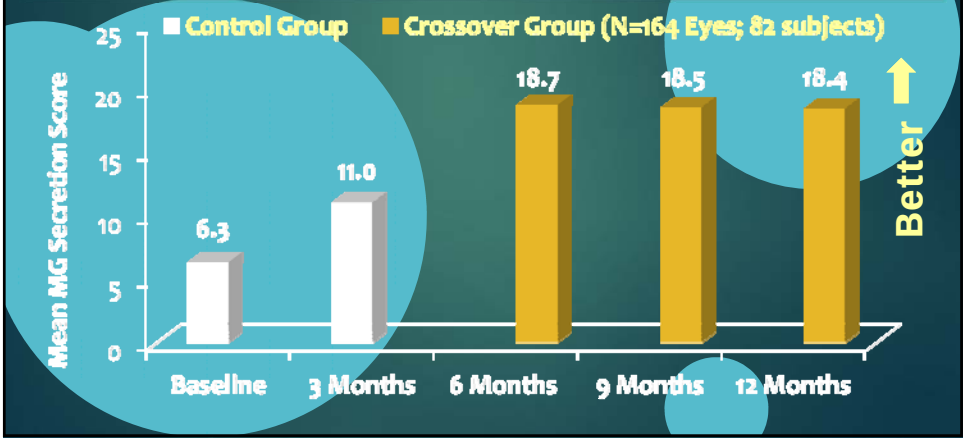
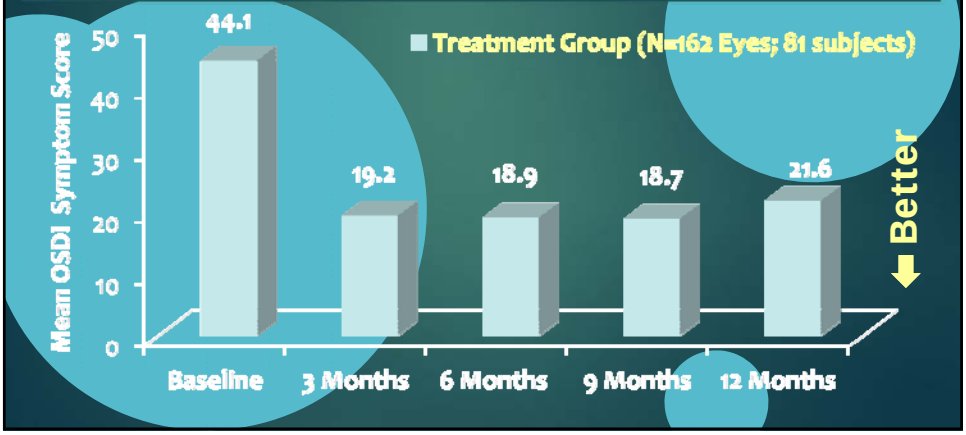
## Results: Mean MG Secretion Score

For the 89% of Crossover group subjects who received one thermal pulsation treatment, a sustained mean improvement in MG secretion score was observed from Baseline (6.3 ± 3.6) to 12 Months (18.4 ± 11.1) ($p<0.0001$) (9 Months post-treatment)



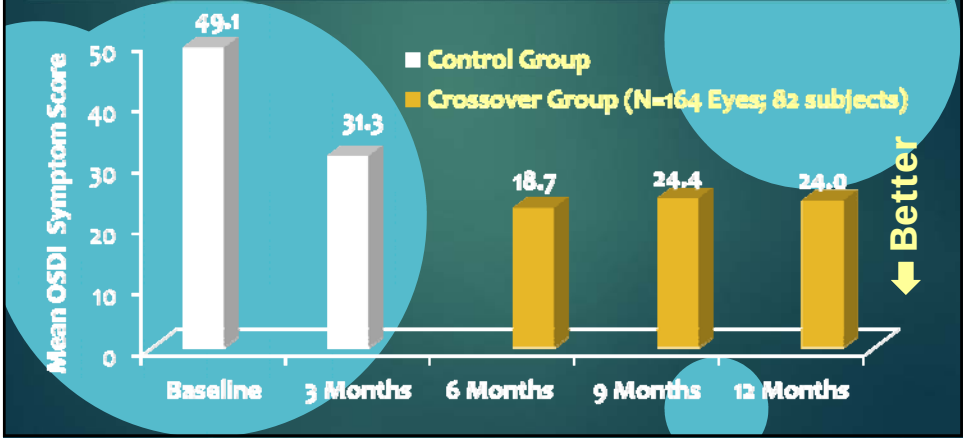
# Results: Mean Dry Eye Symptom OSDI Score

For 86% of Treatment group subjects who received only one thermal pulsation treatment, a sustained mean improvement in dry eye symptom score was observed from Baseline (44.1 ± 20.4) to 12 Months (21.6 ± 21.3) (p<0.0001)




# Results: Mean Dry Eye Symptom

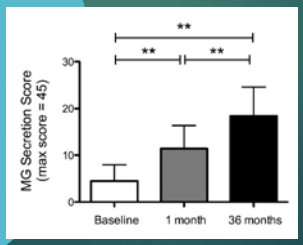
For 89% of Crossover group subjects who received only one thermal pulsation treatment, a sustained mean improvement in dry eye symptom score was observed from Baseline (49.1 ± 21.0) to 12 Months (24.0 ± 23.2) (p<0.0001) (9 Months post-treatment)



# MGD Treatment: Other Studies

**3 year study**

- Prospective 3 year open label randomized multicenter trial
- 20 patients, 1-12 minute Lipiflow treatment
  - MG secretion score and SPEED symptoms score significantly improved at 3 years.




Greiner. AAO Poster presentation 2012. Eye & Contact Lens Apr 13, 2015

# MGD Treatment

- Lid hygiene
- Meibomian gland expression
  - Manual
  - Lipiflow
  - IPL
- Topical therapies
- Systemic therapies

--Should consider using something from each modality to control chronic progressive condition

# MGD Treatment

- Meibomian gland expression
  - IPL—Intense Pulse Light therapy


# MGD Treatment

- IPL—Intense Pulse Light therapy Study
  - Prospective double masked placebo control
  - 28 patients
  - Treatment at 1, 15 and 45 days
  - Statistically improved lipid layer & non invasive TBUT
  - 86% of patients noted improved symptoms

Craig, Chen, Turnbull IOVS 2015 Feb12:56(3):1965-70

- Some reports utilized meibomian gland expression

# MGD Treatment

- Lid hygiene
- Meibomian gland expression
  - Manual
  - Lipiflow
  - IPL
- **Topical therapies**
- Systemic therapies

--Should consider using something from each modality to control chronic progressive condition

# MGD Treatment

**Topical therapies**

- Currently no FDA approved topical MGD treatment
- Off label therapies:
  - Corticosteroids for MGD/ inflammation
  - Azithromycin (Asasite)
  - Cyclosporine (Restasis) for long term maintenance
  - ASED's
  - Topical omega 3s in study

# MGD Treatment

Topical therapies

- Corticosteroids for MGD/ inflammation

# MGD Treatment

Topical therapies: Steroids for inflamed ocular rosacea

Randomized Loteprednol (LE) trial for moderate and severe MGD

- Topical LE + lid hygiene vs. lid hygiene X 2 months
- Results: group LE
  - Decreased interleukins
  - Decreased TBUT, corneal and conjunctival staining
  - Improved Meibum quality & expressibility
  - MGD stage reduction (improvement)--Results manifest as early as 1 month

Lee et al AJO 2014 Aug 13

## MGD Treatment

- Topical therapies
  - Azithromycin (Asasite)


## MGD Treatment

- Topical therapies

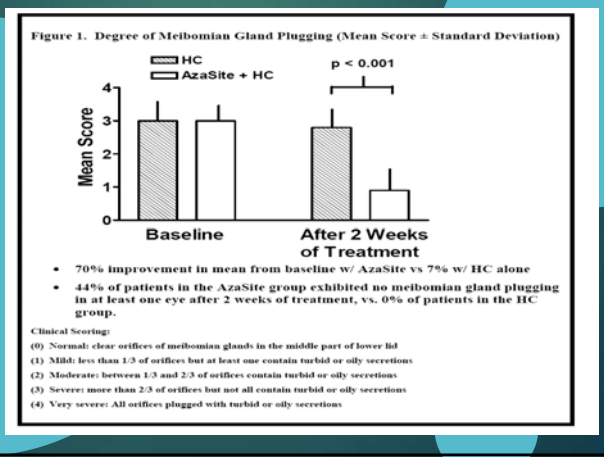

- Azithromycin (Asasite)

  Acts directly on MG epithelial cells to:
  - stimulate differentiation
  - enhance quality & quantity of lipid production
  - promote holocrine secretion

  JAMA Ophthalmology Dec 2013; Liu, Kam, Ding, Sullivan

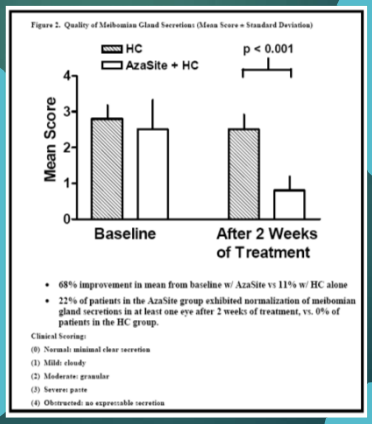
# MGD & Topical Azithromycin/Durasite
## Hot compresses +/- Azasite

- 20 patient study, open label, randomized




.Inspire, Inc

# MGD & Topical Azithromycin/Durasite
## Warm paks vs Azasite




.Inspire, Inc

## MGD & Topical Azithromycin/Durasite

Systemic doxcycyline vs topical Azasite

- 37 ocular rosacea patients
- 12 systemic doxy, 16 topical Azasite, 9 controls
- 1 month treatment

**Significant improvement of both tx groups**

--33% GI upset with doxycycline

--Mild burning with Azasite common

Mantelli et al Ocul Immunol Inflamm 2013 Oct;21(5):371-7

Another similar study showed oral doxycycline or topical Azasite restores carotenoids in MGD meibum improving TBUT

- Each appears to act by a different mechanism

Foulks et al Cornea 2013 Jan;32(1):44-53

## MGD Treatment

Topical therapies

- Cyclosporine (Restasis) for long term maintenance

# Cyclosporine & MGD

33 patient study with symptomatic MGD

Randomized to topical CsA vs placebo x 3 months

Results:

- 26 patients completed study
- CsA group symptoms improved more than placebo, but not statistically significant
- P<0.05 improvements included vascular injection, tarsal telangiectasias, FL staining
- P<0.001 decreased meibomian gland inclusions

Perry, et al Cornea. **2006** 25(2):171-5

# Cyclosporine & MGD

Double masked randomized 3 month trial

- 37 patients
- Lid margin telangiectasias, MG inspissation, lid fullness, corneal changes
- Results:
  - Increased Schirmer (p<0.001)
  - Improved TBUT (p<0.001)
  - Reduced corneal staining (p<0.001)
  - Improvement of OSDI score (p=0.022)

Schechter, Katz, Friedman Adv Ther 2009 Jun 23 Epub

# Cyclosporine & MGD

Double masked randomized 3 month trial

70 patients, 3 months CsA bid

- Significant improvement of
  - Noninvasive Tbut
  - Lid margin inflammation
  - MG expressability
  - Tarsal injection
  - OSDI

Prabhasawat et al Cornea 2012 De;31(12):1386-93

# MGD Treatment

- Topical therapies
  - Steroids for MGD/ inflammation
  - Azithromycin (Asasite)
  - Cyclosporine (Restasis) for long term maintenance
  - **Topical omega 3s in study**

## MGD Treatment

- Topical therapies
  - Omega-3's

## MGD Treatment

### Omega-3's

Preliminary studies: **topical** & **systemic** improve DES signs and symptoms

- Reduce dry eye inflammation
- Regenerate damaged corneal nerves
  - A-LA (alpha lipoic acid)
  - DHA derivatives (resolvin E1, neuroprotectin D1)

Stay Tuned!

## MGD Treatment

- Lid hygiene
- Meibomian gland expression
  - Manual
  - Lipiflow
  - IPL
- Topical therapies
- **Systemic therapies**

--Should consider using something from each modality to control chronic progressive condition

## MGD Treatment

- Systemic Therapies
  - Antibiotics
    - Doxycycline
    - Minocycline
    - Erythromycin
    - Referral to dermatologist
  - Nutritional Therapies
    - Omega 3's

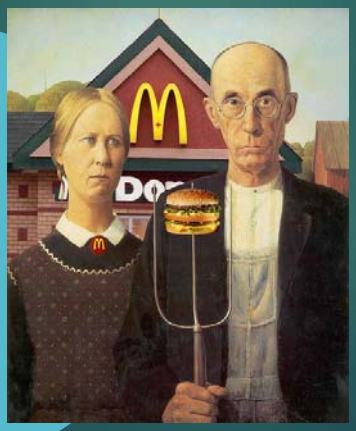
## MGD Treatment

- Systemic Therapies
  - Antibiotics
    - Doxycycline
    - Minocycline
    - Erythromycin
    - Referral to dermatologist
  - Nutritional Therapies
    - Omega 3's

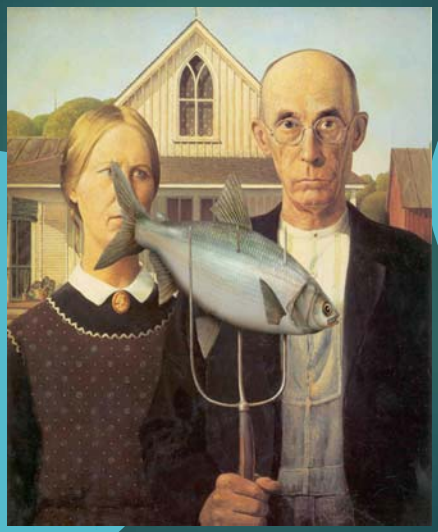
## Theories of Omega-3 Actions

# Dry Eyes and Omega-3, Omega-6 Fatty Acids

American diet appears to be a principal contributor to MGD



# The Solution?

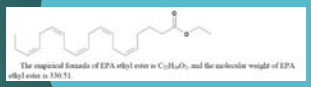


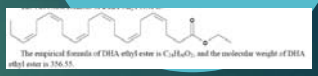
# Omega-3 & Omega-6 Fatty Acids

What are Omega-3's?:

Very long chain PUFA's associated with reduced cardiovascular disease risk, neural & retinal development

- EPA eicosopentanoic acid
  - Source of antioxidant resolvins
- DPA docosapentanoic acid
- DHA docosahexanoic acid (24 carbon)



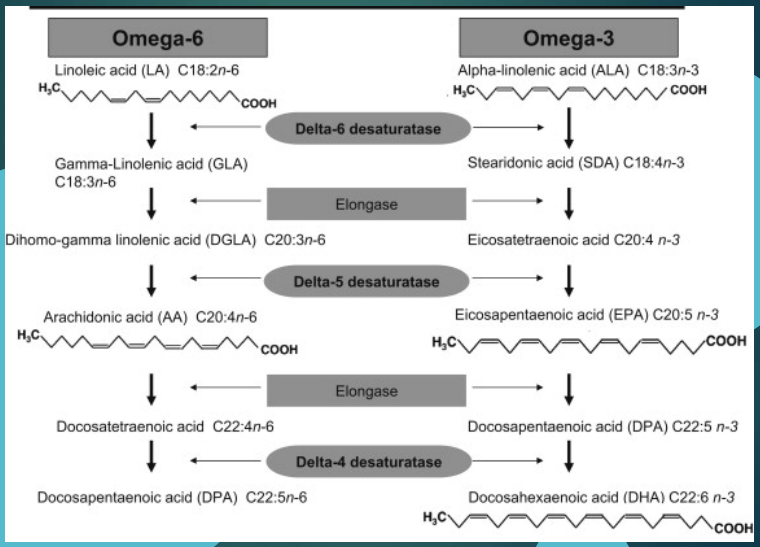


8-carbon A-LA alpha linolenic acid "essential"

Reesterified triacylglyceride form provides a 10-15% improvement of red cell membrane DHA+EPA (vs alcohol ethyl ester form); may be absorbed more effectively

- E.g. Nordic Naturals, Carlson's

# EPA & DHA



# Omega-3 & Omega-6 Fatty Acids

- Omega-6 interferes with DHA accretion (accumulation)

In general:

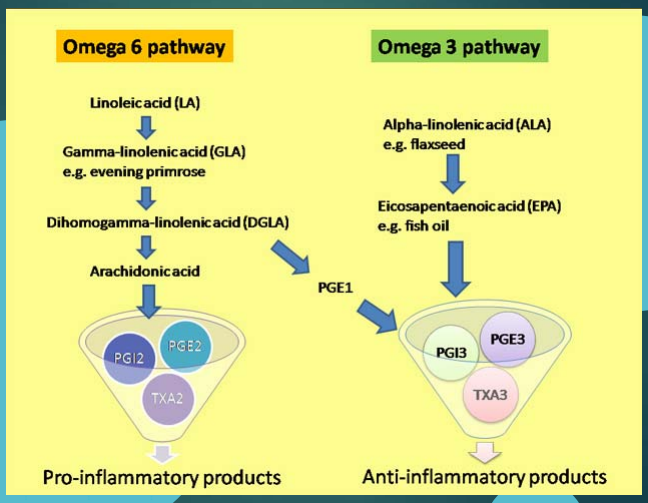
- Omega-6 such as AA promote inflammation
- Omega-3's dampen inflammation

# Omega-3 Fatty Acids

- Omega-3 and Omega-6 PUFA's are precursors of lipid mediators/regulators of inflammation
- Omega-3's inhibit formation of n-6 derived eicosanoids e.g. PGE(2) & LTB(4)
- Omega-3's form anti-inflammatory lipid mediators (e.g. resolvins, protectins)
- Reduce enzymes & cytokines including Cox-2, (TNF)-alpha, (IL)-1beta

.Subcell Biochem 2008:49:133-43

# A-LA, EPA & DHA




# Dry Eyes and Omega 3 Fatty Acids

- Women's health study
- 32,470 women age 45-84
- 4.7% reported Dry Eye Syndrome
- Assessed FA intakes using validated food-frequency questionnaire
- Adjusted for demographics, HRT, total fat intake

.Miljanovic, Trivedi, Dana, Gilbard, Buring, Schaumberg Am J Clin Nutr **2005** Oct;82(4):887-93

# Dry Eyes and Omega-3 Fatty Acids

Women's health study (cont)

Results:

Higher ratio of n-6 to n-3 FA consumption associated with increased risk of DES

Tuna consumption inversely associated with DES p =0.005

.Miljanovic, Trivedi, Dana, Gilbard, Buring, Schaumberg Am J Clin Nutr **2005** Oct;82(4):887-93

# Dry Eyes and Omega-3 Fatty Acids

Randomized double-masked; MGD

- 3 months of treatment 1.5G/day
  - OSDI, TBUT, lid inflammation, MG expression significantly improved
  - Schirmer significantly improved ($p<0.01$)

Miljanovic, Trivedi, Dana, Gilbard, Buring, Schaumberg Am J Clin Nutr **2005** Oct;82(4):887-93

# Dry Eyes and Omega-3 Fatty Acids

- Contact lens study
- Double masked multicenter
- 496 patients
- 6 months of omega 3's or placebo
- Results:
- Symptoms/ CL comfort highly improved in omega 3 group ($p<0.0001$)
- Significant improvement of other parameters ($p<0.0001$)

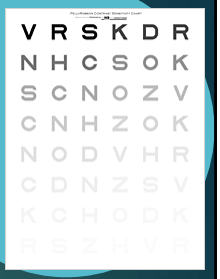
Bhargava, Kumar. Cornea. 2015 Feb 18

# Dry Eyes and Omega-3 Fatty Acids

- Computer Vision Syndrome related Dry Eye
- Double masked multicenter
- 478 patients
- 3 months of omega 3's (180mg EPA, 120 mg DHA) or placebo
- Results:
- Symptoms, TBUT and impression cytology significantly improved in omega3 group

Bhargava, Kumar P, Phogat, Kumar M. Cont Lens Anterior Eye 2015 Feb 16

# Dry Eyes and Omega-3 Fatty Acids




Contrast Sensitivity Study

- Prospective study
- 60 patients
- 3 months of omega3's (1.2 g) vs placebo
- Results:
- Photopic & scotopic CS improved significantly in Omega3 group

Malhotra, Singh, Chakma, Jain Cornea 2015 Apr 23

# Fish Oil or Krill Oil?



Fish oil (FO): mostly TG form of FA's

Krill oil (KO): phospholipids + di- and tri-glycerides, non-esterified FA's

- Studies to date: inadequate intake controls to compare KO & FO
- No evidence of greater bioavailabilitiy of KO over FO

Lipids health Dis. 2014 Aug 26;13:137

# Fish Oil: Cheap or Expensive?

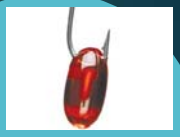
Reesterified triacylglyceride form provides a 10-15% improvement of red cell membrane DHA+EPA (vs alcohol ethyl ester form); may be absorbed more effectively

- E.g. Nordic Naturals, Carlson's

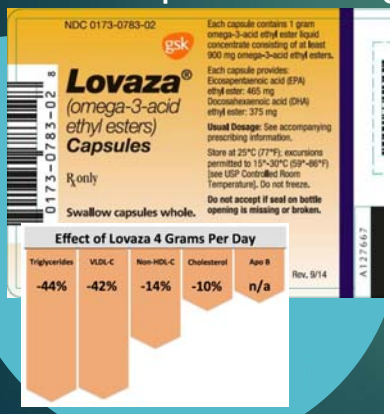
OMEGA-3
Ethyl Ester
vs.
Triglyceride

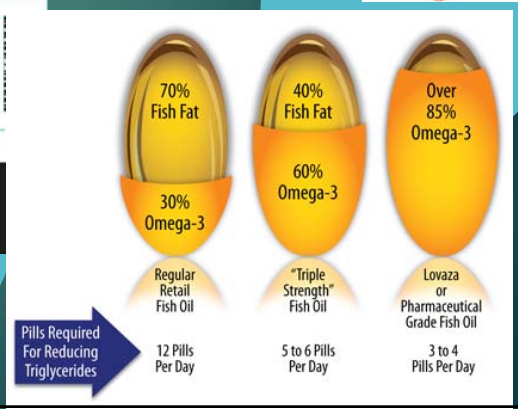
**The 'EE vs TG' discussion refers only to fish oil supplements that have been concentrated and specifically refers to EE and rTG form, not the nTG form.**

# Fish Oil: Cheap or Expensive?



## Prescription Strength



# What Do I do for MGD?

- Encourage Lipiflow treatment for Grade 1-2 or worse MGD
- Lid hygiene, including warm paks and lid scrubs
- Initiate long-term omega-3's
  - Fish oil per mfg recommendation (2-4/day depending on brand) (2000 mg EPA+DHA)
  - Flax seed oil 1000 mg male /2000mg female

  +/- low-dose doxycycline (20-50 mg bid for 4 months)
- ~2 months of loteprednol gel drops bid
- Add in cyclosporine (Restasis), or azithromycin (Azasite) as loteprednol is tapered

# What Do I do for MGD?

- Lid hygiene including warm paks and lid scrubs

*Caveat*

- Warm paks should be warm and not hot
  - Warm, moist, fresh wash cloth
- +/-Microwavable gel paks
- Self-activated warming units
- 10 minutes generally bid


# What Do I do for MGD?

(cont) Lid hygiene including warm paks and lid scrubs

*Caveat (cont):*

Lid scrubs should not contain toxic soaps

Example: 2/3 of 28 baby shampoo products contained chemicals such as dioxane

82% contain formaldehyde

(cancer, skin condition links)

# What Do I do for MGD?

- Lid hygiene including warm paks and lid scrubs

*Caveat*

No data on toxicity:


# What Do I do for MGD?

- Lid hygiene including warm paks and lid scrubs

*Safe Alternative:*

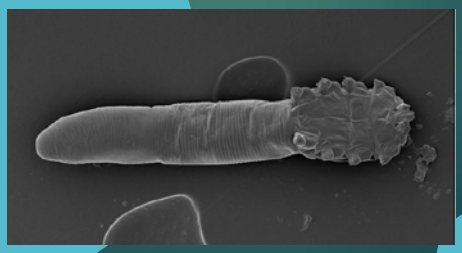
- Artificial tears
- Avenova
  (I-lid scrub)

Old name


New name


# What should I do for MGD?

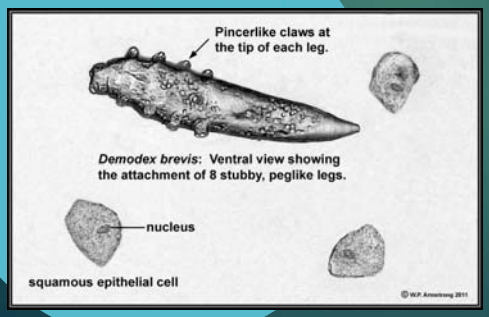
- Remember ocular Demodex infestation (demodicosis)
- Potential cause of ocular surface inflammation
- *Demodex folliculorum* (anterior blepharitis)
- *Demodex brevis* (posterior blepharitis, MGD, recurrent chalazia, refractory keratoconjunctivitis)



*D. brevis*

# What should I do for MGD?

- ***Demodex brevis*** (posterior blepharitis, MGD, recurrent chalazia, refractory keratoconjunctivitis)
- Likes the fat of skin pores, Meibomian glands
- In vivo confocal microscopy can detect (or scrapings)




Terpinen-4-ol


# Approach to the Dry Eye Patient

DED affects multiple aspects of the functional lacrimal unit

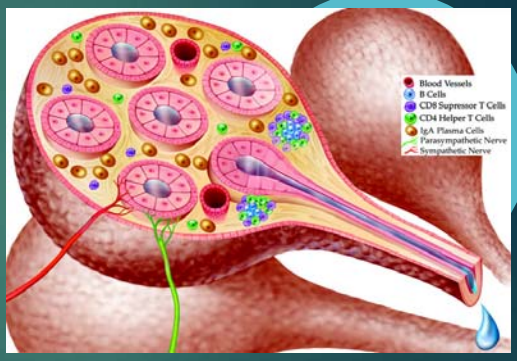
- Lids & Meibomian glands
- Lacrimal glands
- Goblet cells
- Other ocular surface cells

# Selected current and future treatment strategies

- MGD treatments (don't neglect anterior blepharitis/ demodex)
  - Physical Lid therapies
  - Topical therapies
  - Systemic therapies
- **Lacrimal gland treatments**
  - Corticosteroids
  - Cyclosporine & other calcineurin inhibitors
  - Lifitegrast
- Goblet cell treatments
  - Cyclosporine
  - Rebamipide?
  - Diquafosol

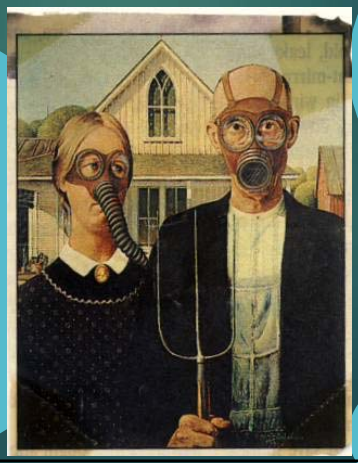
# Lacrimal Gland Treatments

- Corticosteroids
- Cyclosporine
- Lifitegrast
- Diquafosol



## Lacrimal Gland Treatments

- First eliminate preservatives as best as possible!



## Lacrimal Gland Treatments

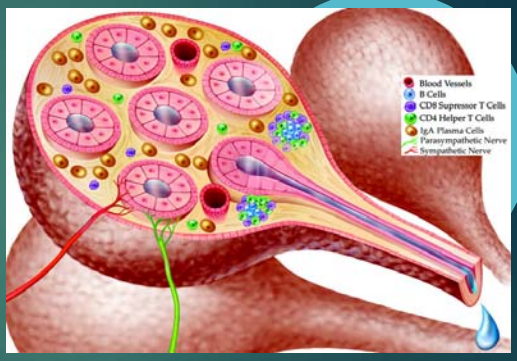
First eliminate preservatives as best as possible!

- Treatment with preservative free drops is effective against DES (vs preserved)
- Study in 100 pts moderate to severe DES
- Preservative free drops more effective:
  - in decreasing inflammation
  - increasing antioxidant contents in tears of patients with DES

Jee, Park, Kim, Kim; IOVS 2014 Jul 3

# Lacrimal Gland Treatments

- Corticosteroids
- Cyclosporine
- Lifitegrast
- Diquafosol




# Lacrimal Gland Treatments: Corticosteroids

Studies in environmentally induced ocular surface disease (dessicating environment)

- Corticosteroid eye drops mitigate acute adverse effects of experimental low humidity challenge
- Likely suppress stress-activated inflammation

Moore, Paiva, Pflugfelder AJO 2015 Apr 10

# Lacrimal Gland Treatments: Corticosteroids

Severe Dry Eye associated with Sjogren's

- Retrospective 2 year study
- Loteprednol 0.5% n=66
- Fluorometholone 0.1% n=67
- Improvement over baseline both groups
  - Schirmer
  - Keratoepitheliopathy
  - Symptoms scores
  - TBUT
- Loteprednol with lower risk of IOP elevation

Jung, et al. Chonnam Med J 2015 Apr;51(1):26-32

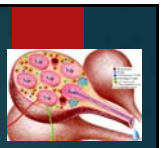
# Lacrimal Gland Treatments: Corticosteroids

Corneal Confocal Microscopy in Dry Eye Treated with Corticosteroids

- 50 pts, Moderate to Severe DES
- Loteprednol 0.5% topical suspension qid
- OSDI, Central Corneal LSCM
- Results:
  - Significant decrease OSDI & dendritic cell density (DCD)
  - Suggest *predictive value of DCD* for clinical response to topical steroids

Villani et al. Optom Vis Sci 2015 Apr 23

# Graft vs. Host Disease: Dry Eye Model



Following allogeneic bone marrow transplantation

Chronic condition leads to:

--K sicca

--Cicatricial lagophthalmos

--Sterile conjunctivitis

--Corneal epithelial defects

--Corneal ulceration and melting


# Lacrimal Gland Treatments: Corticosteroids

Graft vs Host Disease after hematopoetic stem cell Transplantation

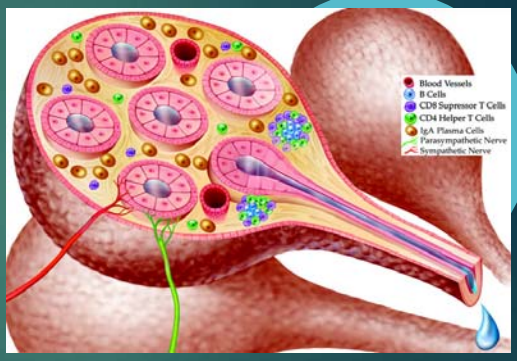
1 year study, 75 patients

- Randomized to receive either LE or CsA pre-hsct
- Results
  - **90%** development of DES in CsA group, **79% LE**
  - **38%** DES progression CsA, **26% LE**
  - No IOP elevations >10mmHg in either group

Boynton, et al Cornea 2014 Apr 4

# Lacrimal Gland Treatments

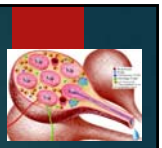
- Corticosteroids
- **Cyclosporine**
- Lifitegrast
- Diquafosol




# Question

Do Calcineurin inhibitors such as Cyclosporine (Restasis) work?

# Do Calcineurin Inhibitors Work?



Cyclosporine, tacrolimus (FK-506) et al

- Bind to immunophilins, blocking calcineurin phosphatase
- Result in ***failure to activate genes*** *required for:*
  --B-cell help (e.g. IL-4, CD40 ligand production)
  --T-cell proliferation (e.g. IL-2 production)
  --Causes altered T-and B-lymphocyte function
- Induce apoptosis (programmed cell death) of **T-lymphocytes** responsible for perpetuating chronic inflammation

Currently known therapeutic and toxic effects are due to inhibition of calcineurin phosphatase

# Calcineurin inhibitors (CNIs)

Inhibit enzyme calcineurin phosphatase (CaN)

- CaN ubiquitously found in cell cytoplasm

CNIs

--reversibly suppress T-cell activation and proliferation

--prevent release of pro-inflammatory cytokines (by mast cells, eos, epithelial cells)

## Mechanism of Cyclosporin A Action in Inflammatory Diseases

- Prevents T-cell activation
  - Activated T cells produce inflammatory cytokines that lead to:
    - Tissue damage
    - Recruitment of more T cells
    - Production of more inflammatory substances

## CNIs (cont)

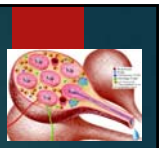
Potential Uses:

{Cyclosporine A, FK-506 (tacrolimus), LX-211}

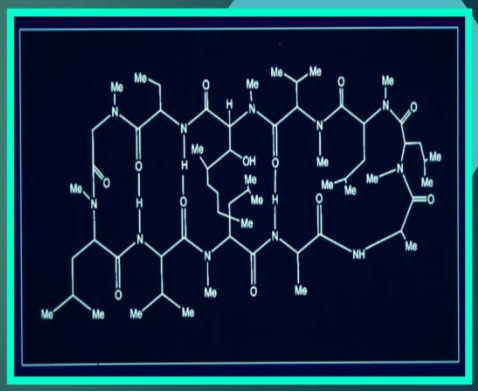
- Immune mediated eye diseases such as
  - --uveitis
  - --dry eye syndrome
  - --inflammatory blepharitis/ MGD
  - --corneal graft rejection

Anglade, Yatscoff, Foster, Grau: Next-generation calcineurin inhibitors for ophthalmic indications; Expert Opin Investig Drugs **2007** Oct 16(10):1525-40

## Topical Cyclosporin A (CsA)

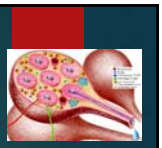


- Well-known macrolide immunomodulatory agent
- Systemic uses:
  - Prevent organ transplant rejection
  - Treat inflammatory diseases (psoriasis, rheumatoid arthritis)

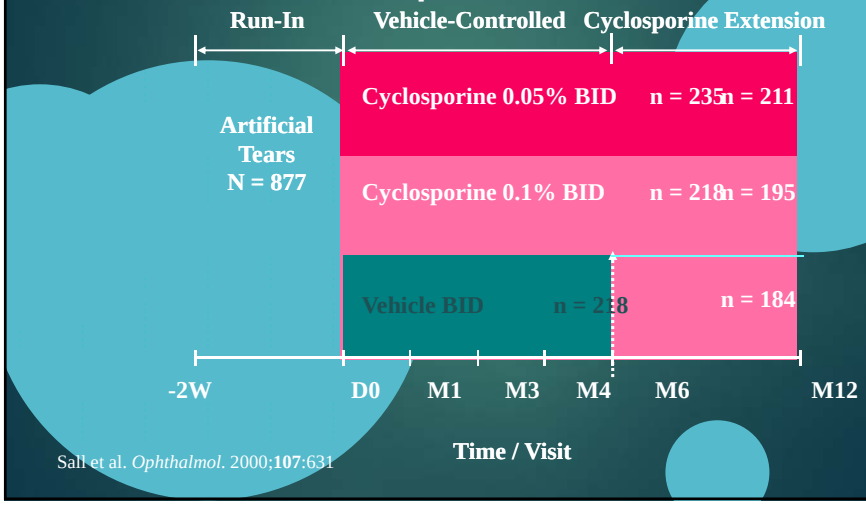


## Restasis studies (cyclosporine 0.05%)

# Phase III US Study Design

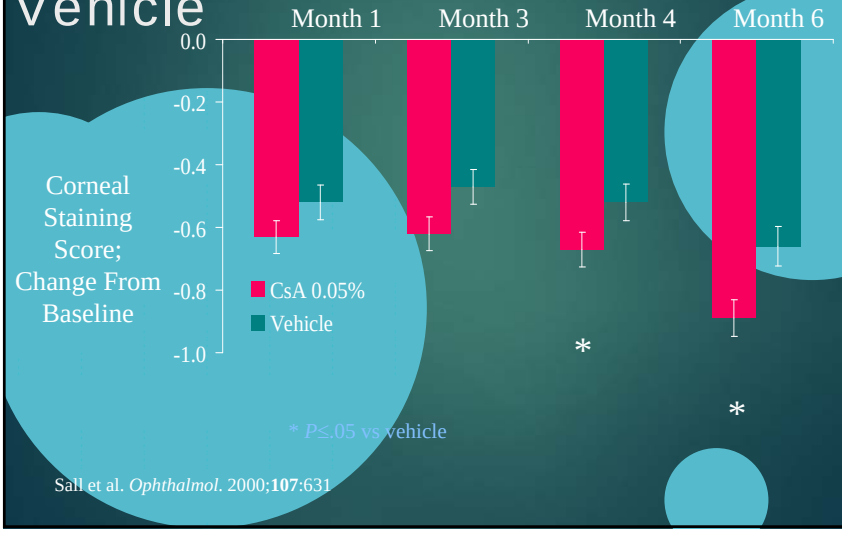


- **Multicenter, double-masked, randomized, parallel**




Sall et al. *Ophthalmol.* 2000;**107**:631

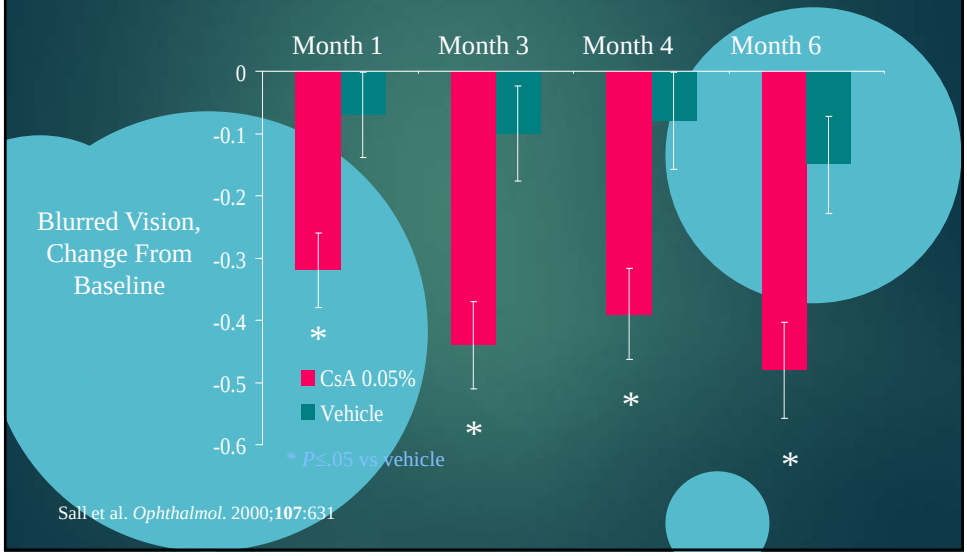
# Clinical Correlation Improved Corneal Staining vs Vehicle




* $P \leq .05$ vs vehicle

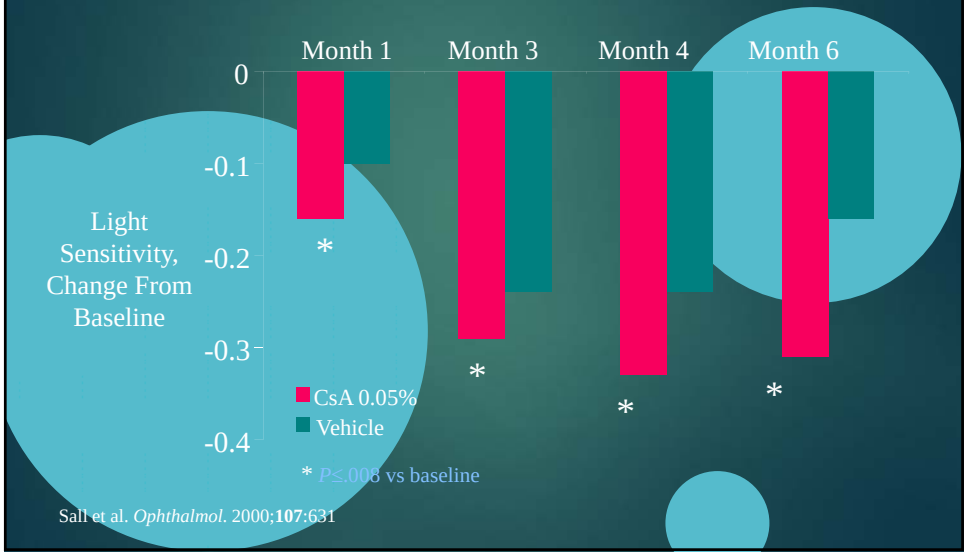
Sall et al. *Ophthalmol.* 2000;**107**:631

# Improved Blurred Vision vs Vehicle

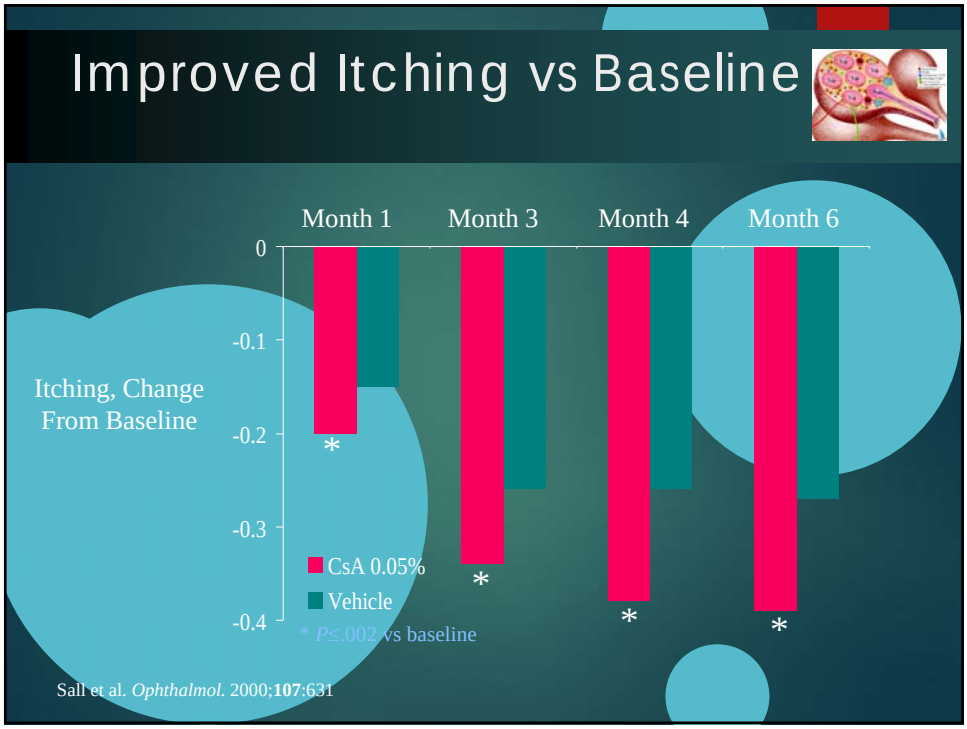


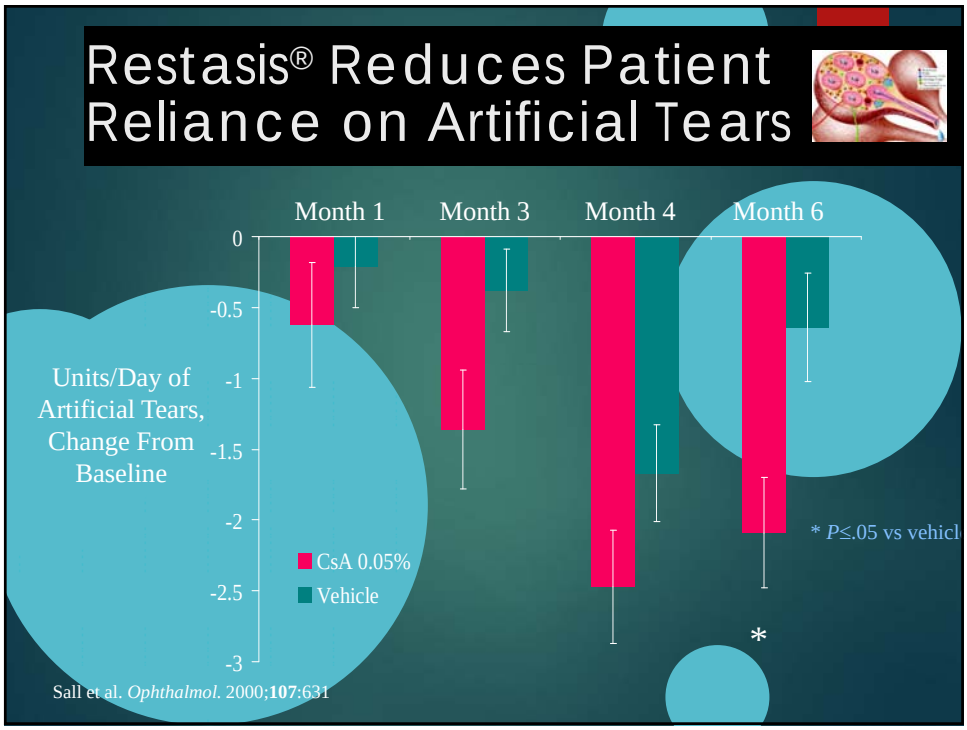

Sall et al. *Ophthalmol*. 2000;**107**:631

# Improved Light Sensitivity vs Baseline

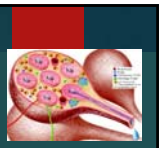


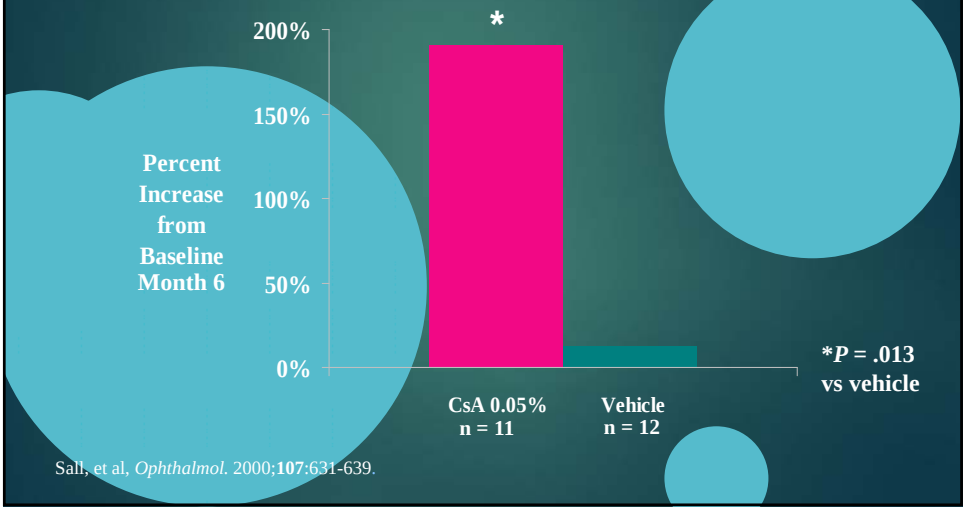

Sall et al. *Ophthalmol*. 2000;**107**:631


Improved Itching vs Baseline
Month 1
Month 3
Month 4
Month 6
0
-0.1
-0.2
-0.3
-0.4
Itching, Change From Baseline
CsA 0.05%
Vehicle
* P≤.002 vs baseline
Sall et al. Ophthalmol. 2000;107:631


Restasis® Reduces Patient Reliance on Artificial Tears
Month 1
Month 3
Month 4
Month 6
0
-0.5
-1
-1.5
-2
-2.5
-3
Units/Day of Artificial Tears, Change From Baseline
CsA 0.05%
Vehicle
* P≤.05 vs vehicl
Sall et al. Ophthalmol. 2000;107:631

## Increased Goblet Cell Density Vehicle

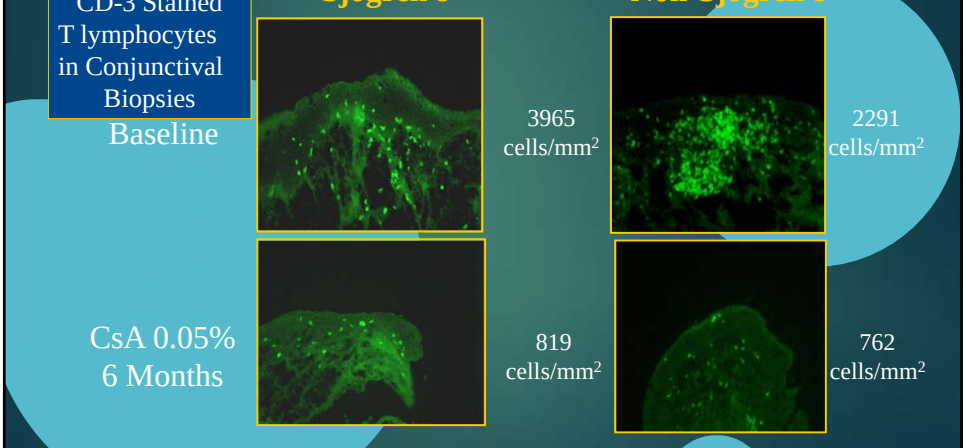





Sall, et al, *Ophthalmol.* 2000;**107**:631-639.

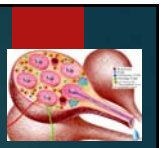
## Decreased T-Cells Demonstrated in Sjögren's & Non-Sjögren's Patients

CD-3 Stained T lymphocytes in Conjunctival Biopsies




Kunert et al, *Arch Ophthalmol.* 2000;**118**:1489

## Conclusions



- Cyclosporine 0.05% treatment was superior to vehicle
- At month 6, increased natural tear production resulted in statistically significant improvements in Schirmer wetting scores
- Clinical correlation with improvement in
  - Patient symptoms
    - Dryness, itching, blurred vision, photophobia
  - Corneal staining
- Cyclosporine reduces indicators of inflammation

## Other Cyclosporine Studies

Outline:

- Experimental Dry Eyes
- KCS Clinical Patient Studies
- Special Cases ("Models" of Dry Eye)

--Graft vs. Host Disease

--Contact Lens Wear

--LASIK

--LASIK and Primary Sjogren's Syndrome

## **Corticosteroids** and **Cyclosporine** tolerability

Prospective randomized placebo controlled multicenter trial

- 118 patients 27-80 yrs old
- Group AT—qid tears x 2 weeks,
  —bid tears + bid CsA 0.05% wk 3-8
- Group LE—qid LE x 2 weeks
  —bid LE + bid CsA 0.05% wk 3-8
- Evaluated Va, IOP, OSDI, global self assessment, FL and LG staining, slit lamp exam, Schirmer

Sheppard, Donnenfeld ARVO abstract 99 2008

## Corticosteroids and cyclosporine tolerability (cont)

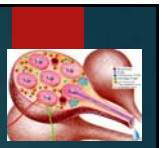
Results:

- LE reduced stinging p<0.05%
- LE/CsA and AT/CsA improved OSDI
- LE/CsA improved OSDI more than AT/CsA p<0.05%
- Both treatments improved most parameters
- LE/CsA superior to AT/CsA for
  --Schirmers
  --FL staining
  --LG staining

Thus **LE induction** can increase number of patients who can benefit from longer- term CsA maintenance therapy

Sheppard, Donnenfeld ARVO abstract 99 2008

# Lacrimal Gland Treatments: Corticosteroids & cyclosporine



Steroids used routinely to initiate Dry Eye Treatment with topical cyclosporine: "Loteprednol induction"

# Newer CNIs for Dry Eye

- Tacrolimus 0.02-0.03 % (FK506)

  --alternative to cyclosporine 0.05%

  Berdoulay, English, Nadelstein Vet Ophthalmol **2005** 8(4):225-32

- LX211 (Luveniq—voclosporin/oral version in posterior uveitis trial) compared with Cyclosporine 0.05%

  --less irritating than Restasis formulation

  Mitra, Natesan, Hariharan et al ARVO abstracts **2008**

# Newer CNIs for Dry Eye

Tacrolimus 0.03 % Treatment of Sjogren's syndrome DED

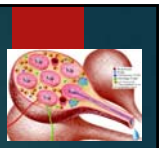
- Prospective double-blind randomized study
- 48 eyes, 24 patients
- Bid treatment vs vehicle 90 days
- Statistically improved: fluorescein staining, rose Bengal scores, Schirmer I and BUT values by 28 days

Moscovici et al Cont Lens Anterior Eye 2015 MAY 5 s1367

# What do I do regarding steroids and cyclosporine?

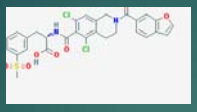
- If considering cyclosporine treatment
  - Begin Restasis bid—commit patient to 3-6 months of treatment for adequate eval.
  - Induce treatment with loteprednol gel or ungt 0.05% 2-4 x/ day for 6-8 weeks (preservative-free steroid if preservative intolerant)
- If Cyclosporine intolerant:
  - Begin Loteprednol gel or ungt 0.5% 2-4x/day and taper to once daily or less

# Lacrimal Gland Treatments



- Corticosteroids
- Cyclosporine
- **Lifitegrast**
- **Diquafosol**


# Lacrimal Gland Treatments



**Lifitegrast**

- Currently in FDA review
  - Lifitegrast binds to integrin lymphocyte function-associated antigen (LFA-1)
  - Blocks LFA-1 interaction with ICAM-1 preventing T-cell activation and migration to target tissue

Restasis CsA only works on newly formed T-cells that live 3.5 months

Lifitegrast has much earlier onset of action

Both might be used together for greater effectiveness

# Lacrimal Gland Treatments

**Lifitegrast**

- Currently in FDA review
- OPUS-1 Phase 3 Study
- 5% Lifitegrast bid vs placebo in 588 DED patients—84 days
- Results
  - Lifitegrast significantly improved
    - Corneal fluorescein staining
    - Conjunctival lissamine green staining
    - Improved OSDI

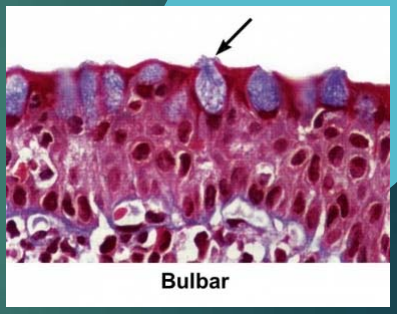
Ophthalmology 2013 Nov 26

# Selected current and future treatment strategies

- MGD treatments (don't neglect anterior blepharitis/ demodex)
  - Physical Lid therapies
  - Topical therapies
  - Systemic therapies
- Lacrimal gland treatments
  - Corticosteroids
  - Cyclosporine & other calcineurin inhibitors
  - Lifitegrast
- **Goblet cell treatments**
  - Cyclosporine
  - Rebamipide?
  - Diquafosol

# Goblet Cell Treatments

- Cyclosporine
- Rebamipide
- Diquafosol




# Lacrimal Gland and Mucin (Goblet cell) Treatments


Cyclosporine

6 patients--12 week study

CsA vs Artificial tears

- AT's: no improvement
- CsA: significantly improved goblet cell density
- TGF-beta2 positive goblet cells increased (immunoregulatory factor)

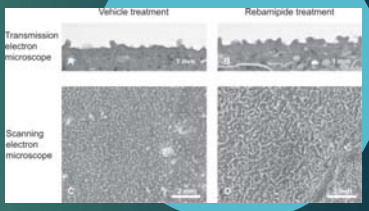
Pflugfelder et al Cornea, **2008** Jan;27(1):64-9

# Mucin (Goblet cell) Treatments

Rebamipide


Clinically used for years in Japan for gastric ulcers, gastritis—improves mucus

also used in ophthalmology




US Study


Treats:

- Tear deficiency
- Mucin-associated corneal epithelial damage
- Restore microstructure responsible for tear stability
- Suppress inflammation

Kashima et al Clin Ophthalmol 2014 8:1003-10

# Mucin (Goblet cell) Treatments


Rebamipide in moderately severe dry eye

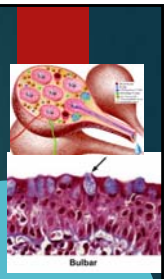
Study: 2% rebamipide qid x 4 weeks

Results:

- Improved fluorescein and lissamine green staining (wk 2)
- TBUT improvement (wk 4)
- Symptoms significantly improved, more so with punctal occlusion

Arimoto et al Cornea 2014 Aug;33(8):806-11

# Lacrimal Gland and Mucin (Goblet cell) Treatments




**Diquafosol**

- P2Y2 receptor agonist
- Promotes tear fluid and mucin secretion
- Approved in Japan and S. Korea for DES treatment
- Failed repeated FDA review


# Lacrimal Gland and Mucin (Goblet cell) Treatments


**Diquafosol**

**"**Comparison of Topical Cyclosporine and Diquafosol in Dry Eye"

- Prospective NON-randomized comparative study
- 60 eyes of 60 patients; mod to severe DED
- CsA 0.05% vs DQS 3% [+AT's]; 3 months
- No significant difference p>0.05 @3 months
- Earlier improvement with DQS at 1 month

Yang et al Optom Vis Sci 2015 Jun 23

# Lacrimal Gland and Mucin (Goblet cell) Treatments

**Diquafosol**

Literature Review

- 8 randomized clinical trials (RCT's)
- 1516 patients
- Symptoms significantly improved in 75% (6 of 8) RCT's
- No adverse reactions at [0.5-5%]
- Heterogeneity of studies prevented meta-analysis
- Authors conclude topical use beneficial in improving integrity of epithelial cell layer & mucin secretion in DES

Wu et al. Cornea 2015 Apr 23

# Dry Eye Treatment Success


Dry Eye: Current & Future Treatment Options
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