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
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
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 packs ~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
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
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

Meibomian Gland Dysfunction
Clinical Results With LipiFlow®
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

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/mm²

<table>
<thead>
<tr>
<th>Grade</th>
<th>Secretion Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Clear liquid oil</td>
</tr>
<tr>
<td>2</td>
<td>Colored/cloudy liquid</td>
</tr>
<tr>
<td>1</td>
<td>Inspissated (toothpaste consistency)</td>
</tr>
<tr>
<td>0</td>
<td>No secretion (includes capped orifices)</td>
</tr>
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</table>
**LipiFlow® Treatment Increased Mean Meibomian Gland Secretion Score**

![Graph showing increases in meibomian gland secretion scores over time.](image)

- Baseline: 6.3 ± 3.5
- Week 2: 14.3 ± 8.7*
- Week 4: 16.7 ± 8.7**

*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**

![Graph showing improvements in tear-film break-up time over time.](image)

- Baseline: 5.5 ± 2.9
- Week 2: 6.9 ± 5.0*
- Week 4: 7.4 ± 5.5**

*P < 0.0001 vs baseline; **P < 0.0001 vs warm compress at week 2.

Mean scores are provided with their standard deviation.
LipiFlow® Decreases the Frequency and Severity of Dry Eye Symptoms Post Treatment

- Baseline: 14.3 ± 4.8
- Week 2: 8.1 ± 5.5*
- Week 4: 7.6 ± 5.8**

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

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
LipiFlow® Follow-up Patient Survey

• 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)

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, c chalasis, 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
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
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

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)

Better

Results: Mean Dry Eye Symptom OSDI Score

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)

Better
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 Feb 12:56(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

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**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

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)

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

Figure 1. Degree of Meibomian Gland Plugging (Mean Score ± Standard Deviation)

- 30% improvement in mean from baseline w/ Azasite vs 7% w/ HC alone
- 48% of patients in the Azasite group exhibited no meibomian gland plugging in at least one eye after 2 weeks of treatment, vs. 4% of patients in the HC group.

Clinical Scoring:
1) Vertical or oblique slit-like meibomian glands in the middle part of lower lid
2) Meibos less than 2.5 of wellness but at least one exam 24 hr before visit
3) Meibos between 2.5 and 3.0, if score exists marked as 3.0 presence
4) Score of 3.0 or more, but not all exam 24 hr before visit
5) Score of 3.0 or more, but not all exam 24 hr before visit
6) Score of 3.0 or more, but not all exam 24 hr before visit

Inspire, Inc

Figure 1. Quality of Meibomian Gland Function (Mean Score ± Standard Deviation)

- 90% improvement in mean from baseline w/ Azasite vs 15% w/ HC alone
- 72% of patients in the Azasite group exhibited no meibomian gland plugging in at least one eye after 2 weeks of treatment, vs. 4% of patients in the HC group.

Clinical Scoring:
7) No normal structure
8) Meibos less than 2.5
9) Meibos 2.5-3.0
10) Meibos 3.0 or more
11) Meibos 4.0 or more
MGD & Topical Azithromycin/Durasite

Systemic doxycycline 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


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


Cyclosporine & MGD
Double masked randomized 3 month trial

- 37 patients
- Lid margin telangiectasias, MG inspissation, lid fullness, corneal changes

Results:
- Increased Schimmer (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 Dec;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

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 eicosapentanoic 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

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<table>
<thead>
<tr>
<th>Omega-6</th>
<th>Omega-3</th>
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<tr>
<td>Linoleic acid (LA) C18:2n-6</td>
<td>Alpha-linolenic acid (ALA) C18:3n-3</td>
</tr>
<tr>
<td>Δ6 desaturase</td>
<td>Stearidonic acid (SDA) C18:4n-3</td>
</tr>
<tr>
<td>Δ6 desaturase</td>
<td>Eicosapentaenoic acid C20:5n-3</td>
</tr>
<tr>
<td>Δ6 desaturase</td>
<td>Docosapentaenoic acid (DPA) C22:5n-3</td>
</tr>
<tr>
<td>Δ4 desaturase</td>
<td>Docosapentaenoic acid (DPA) C22:5n-3</td>
</tr>
<tr>
<td>Imidazolone</td>
<td>Resolvins</td>
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</table>
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Diagram showing the metabolic pathways of EPA and DHA.
Omega-3 & Omega-6 Fatty Acids

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, Gilbaid, 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 omega 3 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 omega 3’s (1.2 g) vs placebo

Results:
Photopic & scotopic CS improved significantly in Omega 3 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 bioavailability 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

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

Effect of Lovaza 4 Grams Per Day

<table>
<thead>
<tr>
<th>Triglyceride</th>
<th>HDL-c</th>
<th>Non-HDL-c</th>
<th>Cholesterol</th>
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<tr>
<td>idle</td>
<td>-44%</td>
<td>-42%</td>
<td>-34%</td>
</tr>
<tr>
<td>rTG</td>
<td>40%</td>
<td>60%</td>
<td>60%</td>
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Each capsule contains 1 gram omega-3 acid ethyl ester lipid concentrate containing at least 70% docosahexaenoic acid and at least 10% eicosapentaenoic acid. Each capsule provides: 4.47 g total omega-3 fatty acids (510 mg DHA, 360 mg EPA); 2.24 g total eicosapentaenoic acid (265 mg); 8 mg vitamin E (0.5 mg alpha-tocopherol). Use only as directed. Avoid use if tamper-evident cap is open or if you are pregnant. Consult your doctor before use in children or if you have a specific medical condition.

Pills Required for Reducing Triglycerides

<table>
<thead>
<tr>
<th>Fish Fat</th>
<th>Omega-3</th>
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</thead>
<tbody>
<tr>
<td>12 Pills Per Day</td>
<td>70%</td>
</tr>
<tr>
<td>5 to 6 Pills Per Day</td>
<td>40%</td>
</tr>
<tr>
<td>2 to 4 Pills Per Day</td>
<td>85%</td>
</tr>
</tbody>
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Lovaza®
(omega-3 acid ethyl esters)
Capsules

Rx only

Smaller capsule volume.
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

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 packs 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 packs and lid scrubs
Caveat
No data on toxicity:
What Do I do for MGD?

- Lid hygiene including warm packs and lid scrubs

Safe Alternative:
- Artificial tears
- Avenova (I-lid scrub)

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)
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!

- 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

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 AJ O 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

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)
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

Run-In
Vehicle-Controlled
Cyclosporine Extension

Artificial Tears N = 877

Cyclosporine 0.05% BID n = 235 n = 211
Cyclosporine 0.1% BID n = 218 n = 195
Vehicle BID n = 218 n = 184


Clinical Correlation
Improved Corneal Staining vs Vehicle

Corneal Staining Score; Change From Baseline

Month 1 Month 3 Month 4 Month 6

CsA 0.05%
Vehicle

*S P<0.05 vs Vehicle

Improved Blurred Vision vs Vehicle

Blurred Vision, Change From Baseline

-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0

Month 1
Month 3
Month 4
Month 6

* P<.05 vs Vehicle

* P<.005 vs baseline


Improved Light Sensitivity vs Baseline

Light Sensitivity, Change From Baseline

-0.4
-0.3
-0.2
-0.1
0

Month 1
Month 3
Month 4
Month 6

* P<.05 vs baseline

**Improved Itching vs Baseline**

Itching, Change From Baseline

- CsA 0.05%
- Vehicle

*P* ≤ .002 vs baseline

**Restasis® Reduces Patient Reliance on Artificial Tears**

Units/Day of Artificial Tears, Change From Baseline

- CsA 0.05%
- Vehicle

*P* ≤ .05 vs vehicle

Increased Goblet Cell Density vs Vehicle

*Percent Increase from Baseline Month 6*

- CsA 0.05%: n = 11
- Vehicle: n = 12

*P = .013 vs vehicle*


Decreased T-Cells Demonstrated in Sjögren’s & Non-Sjögren’s Patients

- **Sjögren’s**
  - Baseline: 819 cells/mm²
  - CsA 0.05% 6 Months: 3965 cells/mm²

- **Non-Sjögren’s**
  - Baseline: 762 cells/mm²
  - CsA 0.05% 6 Months: 2291 cells/mm²


CD-3 Stained T lymphocytes in Conjunctival Biopsies Baseline
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%

- LX211 (Luveniq—voclosporin/oral version in posterior uveitis trial) compared with Cyclosporine 0.05%
  -- less irritating than Restasis formulation
  Mitra, Natesan, Harhara et al ARVO abstracts 2008
Newer CNIIs 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

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


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

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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