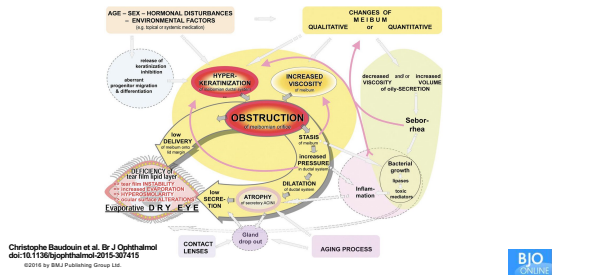


The Inflammatory Components of Dry Eye Disease

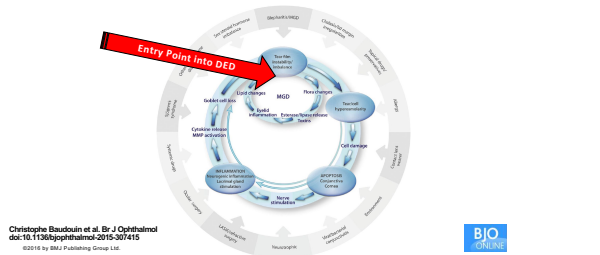
Whitney Hauser, OD



Pathways Involved in the Pathophysiology of MGD (2011 International Workshop on MGD)

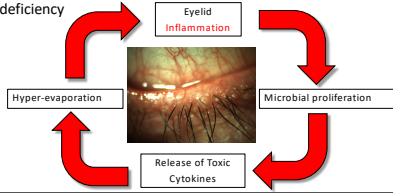


Proposed Vicious Circle of the Pathology of Dry Eye Disease

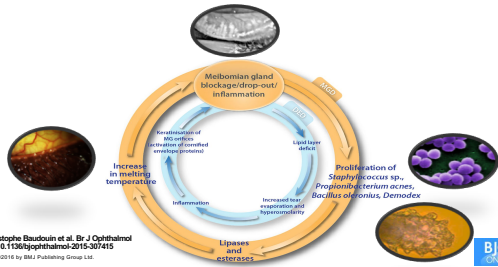


Meibomian Gland Dysfunction

- Pathological mechanisms of MGD:
 - Inflammation
 - Microbial factors
 - Lipid deficiency



MGD in the Vicious Circle of the Pathology of DED



Think Beyond the Eye for DED



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MGD & The Skin

- There is a clear association between MGD and skin inflammatory diseases occurring in close proximity to the eyelids
- A common example is facial skin rosacea

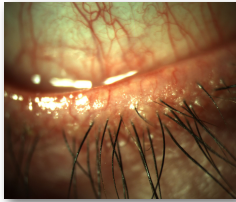
1:10 people are affected by this skin condition, with >80-90% of these patients having concomitant MGD.



Photo: Whitney Hauser, OD

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MGD & The Skin



In 20% of cases, ocular signs precede skin rosacea – possibly suggesting that skin rosacea could already exist in a subclinical forms

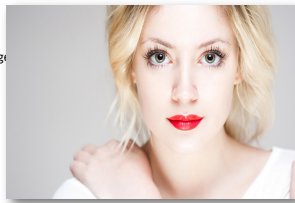
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MGD & The Skin

RISK FACTORS

- Female > Male
- Fair skin, particularly if it has been damaged by the sun
- > age 30
- Smoke
- Family history of rosacea



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MGD & The Skin

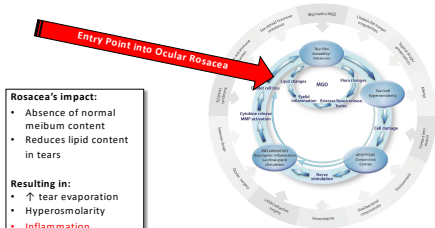


TRIGGERS

- Hot drinks and spicy foods
- Alcohol
- Temperature extremes
- Sunlight or wind
- Emotions
- Exercise
- Cosmetics
- Drugs that dilate blood vessels, including some blood pressure medications

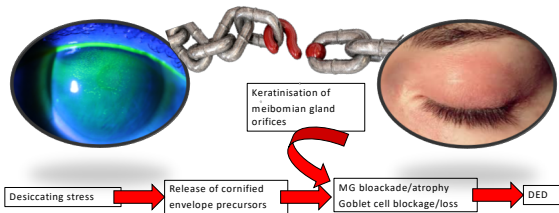
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MGD & The Skin



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MGD & The Skin



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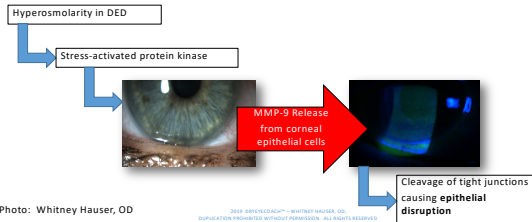
MGD & The Skin



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Matrix Metalloproteinase-9

- Enzyme important for tissue remodeling in wound healing



Matrix Metalloproteinase-9

- ↑ MMP-9 production due to hyperosmolar conditions
- Resulting in corneal barrier disruption
- Rises with increasing levels of DE severity
- MMP-9 is present in a wide range of ocular surface conditions

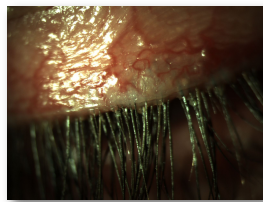


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Matrix Metalloproteinase-9

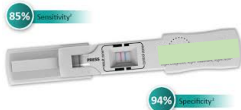
Elevated in:
MGD
Conjunctival hyperemia
Lid hyperemia
Skin rosacea
Corneal ulcers



http://medscape.com/matrix-metalloproteinase-9/
http://www.drugmonks.com/medications/matrix-metalloproteinase-9/
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Diagnostic Testing

- InflammDry® (Quidel, San Diego, CA)
 - Rapid, immunoassay test for the visual, qualitative, *in vitro* detection of elevated levels of the MMP-9



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Diagnostic Testing

- InflammDry® has strong correlation with:
 - Survey scores
 - Fluorescein staining
 - Fluorescein TBUT



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Diagnostic Testing

Tear MMP-9 Activity in Normal Control and DTS Groups	
Group	MMP-9 Activity (ng/ml)
Normal (n = 18)	8.39 ± 4.70
DTS1 (n = 15)	35.57 ± 17.04
DTS2 (n = 11)	66.17 ± 57.02
DTS3 (n = 9)	101.42 ± 70.58
DTS4 (n = 11)	381.24 ± 42.83

Positive Result
= Chronic Dry
Eye ≥ 40ng/ml

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Diagnostic Testing

Collecting the tear sample



A Instruct the patient to look up.

B Gently lower the eyelid to expose the palpebral conjunctiva.

C Dab the sampling fessce in multiple locations along the conjunctiva, releasing the lid after every 2-3 dabs.

D Allow the patient to blink.

E After completing a minimum of 8 dabs along the conjunctiva, allow the sampling fessce to rest on the conjunctiva for an additional 15 seconds, to ensure saturation.

F Inspect the sampling fessce. The fessce will glisten when an adequate tear sample is collected. Depending on the patient's tear composition, the fessce may also turn pink or color. If the fessce is NOT glistening, repeat the entire process.

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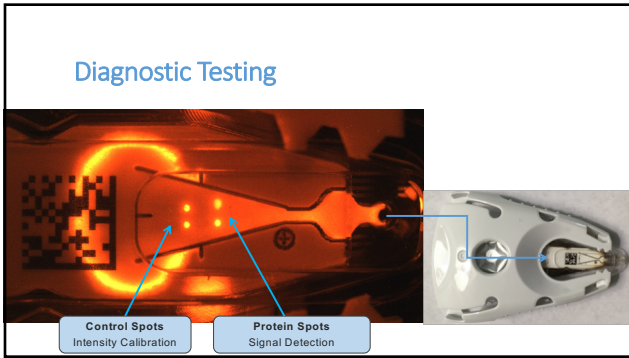
Diagnostic Testing

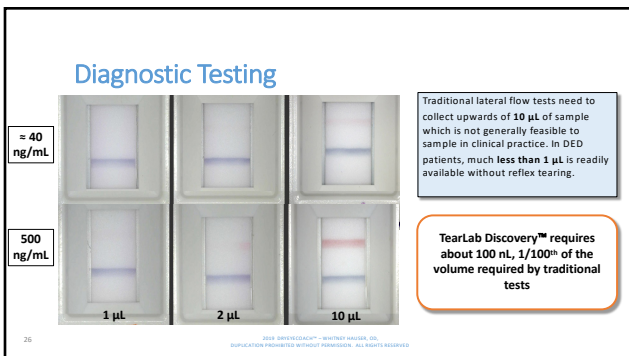
TearLab Discovery™ Assay Platform

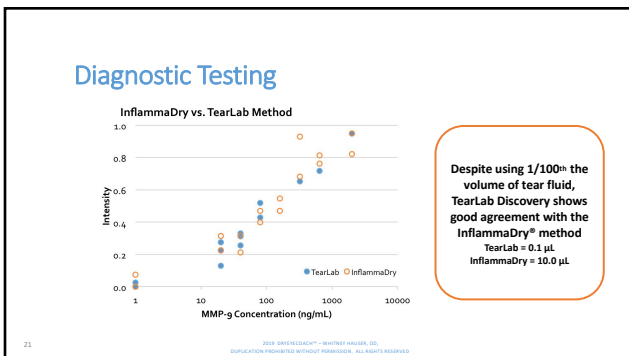
- Panel Testing of Tear Fluid Biomarkers
 - Tear osmolarity plus inflammatory marker
 - Capable of quantitative measurement
 - Single 100 nanoliter tear collection
- Fluorescent Immunoassay
- Rapid < 2 minutes from collection to result



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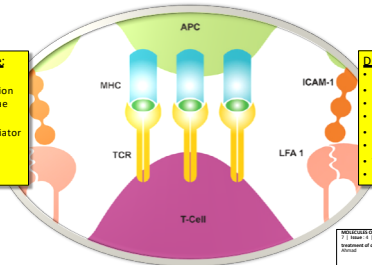
Diagnostic Testing



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Therapeutics for Inflammation

Dry eye patients have:
↑ CD4+ T cells
↑ HLA-DR expression in their conjunctivae
↑ levels of inflammatory mediator expression like ICAM-1



Dry eye patients have:
• IL-2
• IL-4
• IL-5/IL-6
• IL-8
• IL-10
• IL-17
• TNF-α
• IL-6

Journal of
Pharmacology &
Pharmacotherapeutics

Journal of Pharmacology & Pharmacotherapeutics, 2012, 3, Volume 11, Number 11, Page 1010-1016 (http://dx.doi.org/10.1177/1099700212456614)
Statement of dry eye disease: [http://dx.doi.org/10.1177/1099700212456614](#)

Therapeutics for Inflammation

- Mice were subjected to:
 - Low humidity environment
 - Given scopolamine
- T-cell mediated inflammation developed on the ocular surface resembling dry eye in humans
- Researchers induced a similar response in nude mice by adoptively transferring CD4(+) cells from



Wardrop et al. et al. 2006

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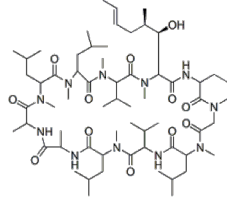
Therapeutics for Inflammation

• **Restasis, ophthalmic emulsion (cyclosporine A, 0.05%, Allergan PLC)**

- Immunosuppressant
- Used in organ transplant
- Suspension/emulsion

- Interferes with:
 - Activity of T-cells
 - Growth of T-cells

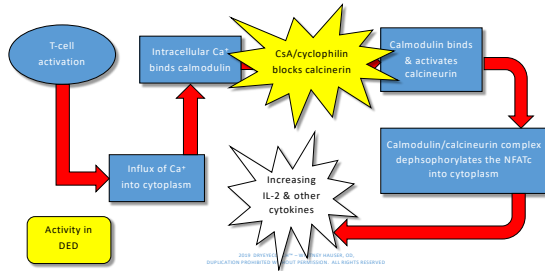
• Note: Higher doses have been compounded



http://www.penguin.com/...
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Therapeutics for Inflammation



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Therapeutics for Inflammation

• Many studies report a positive effect of CsA

• Improvements have been found in:

- Symptom scores
- Ocular staining
- Schirmer scores
- Goblet cell density
- Corneal sensitivity
- Tear meniscus height and volume

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Therapeutics for Inflammation

INDICATIONS AND USAGE
RESTASIS® is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs. (1)

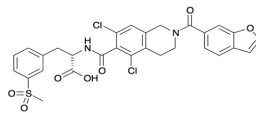
Four multicenter, randomized, adequate and well-controlled clinical studies were performed in approximately 1,200 patients with moderate to severe keratoconjunctivitis sicca. RESTASIS® demonstrated statistically significant increases in Schirmer I wetting of 10 mm versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of RESTASIS® ophthalmic emulsion-treated patients versus approximately 5% of vehicle-treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

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Therapeutics for Inflammation

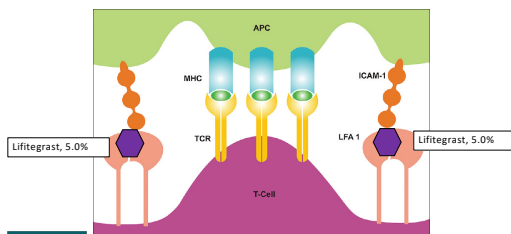
• Xiidra, ophthalmic solution (lifitegrast, 5.0%, Shire PLC)

- Discovered in rational design process
- Identifying amino acid side chains vital for LFA-1 and ICAM-1 binding



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Therapeutics for Inflammation



Journal of
Pharmacology &
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Therapeutics for Inflammation

INDICATIONS AND USAGE
Xidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1,401 patients received at least 1 dose of lifitegrast (1,287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity.

The safety and efficacy of lifitegrast for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multi-center, double-masked, vehicle-controlled studies. Patients were randomized to Xidra or vehicle (placebo) in a 1:1 ratio and dosed twice a day. Use of artificial tears was not allowed during the studies. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Enrollment criteria included, minimal signs (i.e., Corneal Fluorescein Staining (CFS) and non-anesthetized Schirmer Tear Test (STT)) and symptoms (i.e., Eye Dryness Score (EDS) and Ocular Discomfort Score (ODS)) severity scores at baseline.

Therapeutics for Inflammation

• Summary of Study Data

- Four separate trials completed
- One safety study
- Assessed Eye Dryness Score was seen at Week 2
- Measured Intraocular Inflammation (4-coalescent)
- 2,133 subjects enrolled
- Over 1200 received Xidra™ (lifitegrast 5%)

Improvement was noted in EDS in all 4 studies by Week 6
Improvement was noted in ICS in 3 out of 4 studies by Week 12

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Therapeutics for Inflammation

- Cequa (cyclosporine A, 0.09%, ophthalmic solution, Sun Pharmaceutical Industries)
- Novel nanomicellar formulation
- Clear, preservative-free aqueous solution

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Therapeutics for Inflammation

- 12 week, multi-center, randomized, double-masked, vehicle controlled, Phase 3 confirmatory study
- 744 subjects enrolled
- At 12-week endpoint, OTX-101 showed statistically significant improvement in the primary endpoint Schirmer test scores versus vehicle (measurement of tear production)
- The demonstration of efficacy at the 12 week point is earlier than other drugs in the same class
- Previous Phase 2b/3 studies with 455 subjects enrolled also found side effects to be mild to moderate, and with earlier onset of action relative to other drugs in class

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