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

MGD & The Skin

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

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

https://newswing.press/Get-White-milk-skin-in-a-day...

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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

Rosacea's impact:
- Absence of normal meibum content
- Reduces lipid content in tears

Resulting in:
- ↑ tear evaporation
- Hyperosmolarity
- Inflammation

MGD & The Skin
MGD & The Skin

Inflammation

Matrix Metalloproteinase-9

- Enzyme important for tissue remodeling in wound healing
- Hyperosmolarity in DED

Hyperosmolarity in DED

Matrix Metalloproteinase-9 Release from corneal epithelial cells

Cleavage of tight junctions causing epithelial disruption

Matrix Metalloproteinase-9

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

Photo: Whitney Hauser, OD
Matrix Metalloproteinase-9

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

Diagnostic Testing

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

• InflammaDry® has strong correlation with:
  • Survey scores
  • Fluorescein staining
  • Fluorescein TBUT
### Tear MMP-9 Activity in Normal Control and DTS Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>MMP Activity (ng/mL)</th>
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<tbody>
<tr>
<td>Normal (n = 18)</td>
<td>8.39 ± 4.70</td>
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<tr>
<td>DTS1 (n = 15)</td>
<td>35.57 ± 17.04*</td>
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<tr>
<td>DTS2 (n = 11)</td>
<td>66.17 ± 57.02</td>
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<tr>
<td>DTS3 (n = 9)</td>
<td>101.42 ± 70.58* †</td>
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<tr>
<td>DTS4 (n = 11)</td>
<td>381.24 ± 42.83* ‡</td>
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</tbody>
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*P < 0.008 Compared with normal.
†P < 0.003 Compared with normal and DTS1.
‡P < 0.001 Compared with normal and the other DTS severity groups.

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**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
Traditional lateral flow tests need to collect upwards of 10 µL of sample which is not generally feasible to sample in clinical practice. In DED patients, much less than 1 µL is readily available without reflex tearing.

TearLab Discovery™ requires about 100 nL, 1/100th of the volume required by traditional tests.

Despite using 1/100th the volume of tear fluid, TearLab Discovery shows good agreement with the InflammaDry® method:

- TearLab = 0.1 µL
- InflammaDry = 10.0 µL
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
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

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
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
Therapeutics for Inflammation

- **Summary of Study Data**
  - Four separate trials completed
  - One safety study completed
  - Assessed Eye Dryness Score (0=no discomfort to 100=maximal discomfort)
  - Measured Inferior Corneal Staining (0=no staining to 4=coalescent)
  - 2,133 subjects enrolled
  - Over 1200 received Xiidra™ (lifitegrast 5%) Improvements were noted in EDS in all 4 studies by Week 6. Improvement was noted in ICS in 3 out of 4 studies by Week 12.
  - In two out of the four studies (Study 3 and Study 4), an improvement in the Eye Dryness Score was seen at Week 2.

Therapeutics for Inflammation

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