The Dry Eye Story... 
“A Real Tear Jerker”

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Overview
• Dry Eye
  – Definition & Prevalence
  – Diagnostic techniques
• Rx Treatment
  – Cyclosporine-A: Restasis
  – Lifetigrast: Xiidra
• Amniotic Membrane
  – Cryo-preserved

Disclosures
• University of Houston
  College of Optometry
• nJoy Vision Center
• BioTissue, Inc.
• OCuSOFT, Inc.
• Shire Pharmaceuticals

NEI Definition of Dry Eye
• Dry eye is:
  – Disorder of tear film
  – Due to tear deficiency or
  – Excessive evaporation,
    • Causing damage to the ocular surface and
    • Associated with symptoms of discomfort.

Prevalence of Dry Eye
• Results from Gallup Poll
  – Projects an increase in the number of adults who frequently experience Dry eye.
  – Over 26.4 million Americans Suffer from signs and symptoms of Dry Eyes

Visits to Eye Care Professionals

PhysPulse® Study 2005.
Higher Incidence of Dry Eye

- Women aged 50 or older¹
  - Peri-menopausal females
  - Patients on Post-menopausal Hormone Replacement Therapy²
- Patients with ocular comorbidities³
  - Glaucoma, Diabetics or HTN retinopathy etc.
  - Contact lens wearers³
  - Smokers⁴
  - Users of artificial tears ≥ 3 times/day


Multiple Factors in Dry Eye

- Factors:
  - Transient discomfort
  - Fluctuating vision
  - May be stimulated by environmental conditions¹
  - Inflammation and ocular surface damage
  - Altered tear film composition²


Altered Tear Film Composition

- An Additional Component of Dry Eye
  - The tear film is either compromised or lacking
- Many cases of dry eye have an inflammatory component
  - Leads to an imbalance of tear components and
  - Increased inflammatory factors in tears¹,²


Healthy Tear Film

- Lipid Layer - prevents evaporation
  - Secreted by meibomian glands
  - Stabilizes tear film and reduces evaporation

- Aqueous Layer - a complex mixture of proteins, mucins, electrolytes
  - Secreted by main & accessory lacrimal glands
  - 90% of tear film¹
  - Salts, minerals, anti-microbial agents and organic materials hydrate cornea and flush out contaminants²

- Mucins - provide viscosity and stability during the blink cycle
  - Help spread aqueous layer over cornea and conjunctiva
  - Create stable base for tears
  - Coat and flush out foreign objects easier by blinking

¹Lipid: Meibomian Glands
  - The lipid layer restricts evaporation to 5–10% of tear flow
  - Also helps lubricate the eyes by stabilizing tear film

²Healthy Tear Film Image from Dry Eye and Ocular Surface Disorders, 2004

Lipid: Meibomian Glands

- Meibomian glands
- Transillumination of meibomian glands

Aqueous: Lacrimal Glands

- Secretions from acinar cells:
  - Converge into excretory ducts, then to ocular surface
- Lacrimal glands secrete:
  - Aqueous component
  - Most tear proteins
  - Similar architecture for main and accessory glands
  - Androgens important for glandular homeostasis
  - Sullivan et al, 1998

Healthy Tear Film Image from Dry Eye and Ocular Surface Disorders, 2004

Image from Dry Eye and Ocular Surface Disorders, 2004
**Mucin: Goblet Cells**

- Superficial layer of bulbar conjunctiva. Goblet cells violet, epithelial cells blue
- 10% of conjunctival epithelial cells are mucin-producing goblet cells
- Soluble mucins essential for viscosity of the normal tear film
- Helps resist thin spots and tear break-up

**Healthy Tears**

- A complex mixture of proteins, mucins, and electrolytes:
  - Antimicrobial proteins: Lysozyme, lactoferrin
  - Growth factors & suppressors of inflammation: EGF, IL-1RA
  - Soluble mucin 5-AC secreted by goblet cells for viscosity
  - Electrolytes for proper osmolality

**Functions of Healthy Tear Film**

- Optical clarity, refractive power
- Ocular surface comfort, lubrication
- Protection from environmental & infectious insults
  - Antibacterial proteins, antibodies, complement
  - Reflex tears flush away particles
- Trophic environment for corneal epithelium
  - Necessary electrolytes maintain pH
  - Protein factors for growth and wound healing
  - Antioxidants

**Tears in Chronic Dry Eye**

- CDE Tears:
  - Decrease in many proteins
  - Decreased growth factor concentrations
  - Altered cytokine balance promotes inflammation
  - Soluble mucin 5-AC greatly decreased
- Due to goblet cell loss
- Impacts viscosity of tear film
- Proteases activated
- Increased electrolytes

**Healthy vs. Dry Eye Tears**

**Consequence of Altered Tears**

- Altered tears of ocular surface tissues has:
  - Increased osmolality
  - Imbalanced growth factors and cytokines fail to promote normal epithelial growth
  - Poor viscosity can cause thin spots in tear film and tear break-up – Lubrication compromised
  - Ocular surface damage
  - Loss of corneal epithelial integrity
  - Squamous metaplasia of conjunctival epithelium
Conclusion: CDE vs. Healthy Tears

- **Chronic Dry Eye Tears:**
  - Altered composition
  - Poor viscosity
  - Provide unfavorable environment, leading to ocular surface damage

- **Artificial tears:**
  - Provide temporary palliative relief of symptoms

- **Natural, healthy tears:**
  - Complex mixture of proteins, mucins, other factors
  - Essential for optical clarity, ocular comfort
  - Provide environment supporting health of ocular surface tissues

Identifying Dry Eye Patients

- **Yes**
  1. Do your eyes feel dry, painful, or sore?
  2. Do you experience episodes or periods of blurred vision?
  3. How often are your eyes sensitive to light?
  4. Do you have problems with your eyes when you are working on a computer, watching TV, or reading?
  5. Do you use artificial tears three or more times a day?

- **No**

Diagnosing Dry Eye Disease

- **Questionnaire:**
  - Patients who answer “yes” to any one of the questions should be evaluated for dry eye disease.
  - Many clinicians use clinical tests
  - Plus symptoms and patient history to diagnose

Current Testing for Dry Eye

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moder-ly Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Conjunctival Staining</td>
<td>Mild</td>
<td>Moderate</td>
<td>Marked</td>
<td>Severe</td>
</tr>
<tr>
<td>Corneal Staining</td>
<td>--</td>
<td>Mild punctate</td>
<td>Marked punctate central</td>
<td>Severe punctate erosions</td>
</tr>
<tr>
<td>Tear Film</td>
<td>--</td>
<td>Visual signa</td>
<td>Filamentary keratitis</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lissamine Staining</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tear Film Breakup Time</td>
<td>&lt; 12</td>
<td>5-7</td>
<td>&lt; 3</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Schirmer’s Score</td>
<td>&gt; 10</td>
<td>6-10</td>
<td>&lt; 5</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

Diagnostic Testing: Osmolarity

- **Definition of Osmolarity**
- **Impact on Ocular Surface Health**
- **Impact on Visual Stability**
- **Device use and Patient Prep**

What Is Osmolarity?

Osmolarity is the concentration of solutes in the tear film.
In any form of dry eye, abnormal osmolarity is an early indicator of DED.

Abnormal osmolarity is defined by:
- An elevated reading >305 mOsm/L, indicating loss of homeostasis - OR-
- When the inter-eye difference >8 mOsm/L, indicating instability of the tear film.

Abnormal osmolarity will decrease with effective treatment.

Abnormal osmolarity leads to: epithelial cell death & visual fluctuations.
As Inflammation and Tear Film Instability Resolve...

• Corneal staining improves¹
  – Improved ocular surface integrity
• Blurred vision improves¹
  – Moisture balance of corneal epithelial cells
• Goblet cells increase¹
  – Normalization of ocular surface


TearLab Osmolarity: How it works

Lab ‘On-a-Chip’:
  – Gold chip located on the underside of the test card
  – 50nL of tear fluid is collected & analyzed.
  • TearLab analyzer:
    – Test card with the pen
    – Contains all the technology for nano-fluidic collection and analysis.
  • Each system actually has two analyzers (pens) that work independent of each other.

Patient Preparation

• Patient Preparation:
  • Always perform a TearLab test FIRST before any other diagnostic examinations.
  • No procedure that alters the tear fluid should be performed within 2 hours prior to TearLab testing, including:
    – Tonometry: Goldmann, Air Puff
    – Ocular Surface Staining
    – Schirmer’s testing
    – Tear Break Up Time (TBUT)
    – Slit lamp exam

Patient Preparation

• Patient Preparation:
  – YOU CAN TEST with contact lenses on.
• Patients that are currently being treated with:
  • Punctal plugs
  • Oral meds – ex: Omega-3s
  • Eye drops may have reduced osmolarity.
  • Patient may still present with symptoms of dry eyes.

Collecting Tears

• Collecting Tears:
  – Seat the patient with their head tilted back, looking up and away
  • Collect sample from lower eyelid margin at the lateral tear lake
    – Avoid corneal contact
    – Tip should be lowered onto the tear meniscus
  • Do NOT pull the lower lid away from the globe
    – This will reduce the tear meniscus height and may prevent tear collection
Summary: Tear Osmolarity

- Dry eye is a prevalent yet underdiagnosed disease ranging from mild to severe, episodic or chronic
  - Episodic dry eye can be due to external factors
  - Chronic dry eye can be a progressive disease with underlying pathophysiology of inflammation and altered tear composition
- For dry testing with osmolarity:
  - Remember:
    - Over 308 mOSm/l - OR -
    - A difference of 8 between the both eyes is NOT great!

Pathophysiology of Dry Eye Disease

Healthy Tear Film

Lacrimal Glands

Secretomotor Nerve Impulses

Tears Support and Maintain Ocular Surface

Ocular Surface Neural Stimulation

Dry Eye Disease: Immune-Mediated Inflammation

Lacrimal Glands:
- Neurigenic inflammation
- T-cell activation
- Cytokine secretion into tears

Interrupted Secretomotor Nerve Impulses

Tears Inflamed Ocular Surface

Cytokines Disrupt Neural Arc

Inflammation in Dry Eye Disease

Conjunctiva

T-Cell Infiltrations
(Dark-stained cells; Canine biopsy)

Lacrimal Gland

Symptoms of Ocular Surface Disease

Triggers of Dry Eye Disease

- Environment
- Medications
- Contact Lens
- Surgery
- Allergens
- Rheumatoid Arthritis
- Lupus
- Sjögren’s
- Graft vs Host
- Postmenopausal women
- Meibomian Gland Disease
Summary: Pathophysiology of Dry Eyes

• Immune-mediated inflammation of lacrimal glands and ocular surface
  – Cytokines in tears, altered tear composition
• Inflammation
  – Disrupts normal neuronal control of tearing
  – Multiple triggers and predisposing factors

What Is Cyclosporine?

• Mechanism of Action:
  – Anti-inflammatory & Immuno-modulating agent
    • Inhibits proliferation of inflammatory cells
    • Inhibits activation of T-cell-mediated immune response

What Is Restasis™?

• Restasis™
  – Indication:
    • Increases tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with:
      KCS – Kerato-Conjunctivitis Sicca
    – Prevents T-cell activation:
      (Kunert et al, Arch Ophthalmol. 2000;118:1489)
      • Activated T-cells produce inflammatory cytokines that result in:
        – Recruitment of more T-cells
        – More cytokine production

Dry Eye Disease: Immune-Mediated Inflammation

Lacrimal Glands:
  – Neurogenic inflammation
  – T-cell activation
  – Cytokine secretion into tears

Inflammation disrupts normal neuronal control of tearing

FYI: The Restasis™ Vehicle

• Oil-based ophthalmic emulsion
• Designed to solubilize cyclosporine
  – Ensures penetration into surface tissue at low cyclosporine concentrations
• Vehicle formulation was the basis for Refresh Endura™
Clinical Variables for FDA Approval

**Primary**
- **Objective**
  - Corneal and Conjunctival staining
  - Schirmer with anesthesia
- **Subjective**
  - Blurred vision
  - Artificial tear reliance

**Secondary**
- **Subjective**
  - Photophobia
  - Sandy / gritty feeling
  - Burning / stinging
  - Itching
  - Dryness
  - Pain

**Tertiary**
- **Objective**
  - Conjunctival biopsies
  - Presence of inflammatory mediators
  - Number of T-cells
  - Goblet Cell Density

Clinical Presentation Varies in Severity

**Mild**
- Slit lamp
- Fluorescein Dye Stain

**Severe**
- Slit lamp
- Fluorescein Dye Stain

Schirmer’s Testing

- **Reflex Tearing**
  - Without anesthesia
  - Measures reflex tear secretion
- **Basal Tearing**
  - With anesthesia
  - Eliminates stimulated tearing

Restasis™ Improves Schirmer Test Scores vs Vehicle

<table>
<thead>
<tr>
<th>Improvement from Baseline in Schirmer scores</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10 mm</td>
<td>40%</td>
</tr>
<tr>
<td>3-9 mm</td>
<td>44%</td>
</tr>
<tr>
<td>&gt; 15% increase with Restasis™ vs 5% with vehicle</td>
<td></td>
</tr>
</tbody>
</table>

Restasis™ Safety: Ocular Adverse Events (%)

<table>
<thead>
<tr>
<th>Ocular Adverse Events</th>
<th>Restasis™ 0.05% Cyclosporine</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning upon instillation</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Stinging</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Discharge</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Foreign-body sensation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epiphora</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Decreased Inflammation in Sjögren’s and NonSjögren’s Pts.

**CD-3 Stained T Lymphocytes in Conjunctival Biopsies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Sjögren</td>
<td>2291 cells/mm²</td>
<td>819 cells/mm²</td>
</tr>
<tr>
<td>Sjögren</td>
<td>3965 cells/mm²</td>
<td>762 cells/mm²</td>
</tr>
</tbody>
</table>


Restasis™ improves Schirmer test scores vs Vehicle


Restasis™ Safety: Ocular Adverse Events (%)

Data on file, Allergan
Restasis™ Candidate Profile

Restasis™ is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS – Kerato-Conjunctivitis Sicca.

Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

### Most Common Symptoms of Restasis™ Candidates

- **Occasional Symptoms**
  - Frequent to Chronic Symptoms
  - Frequent Tear Users
  - Years used 34 times daily
- **Non-functioning Lacrimal Glands**

### Prescribing Restasis™

**Restasis Ophthalmic Emulsion 0.05%**

**Sig:** i q t q 12h OU

**Disp:** One 30-vials per eye (60 vials/co-pay)

- **Inform pts. not use “as needed” like traditional drops**
- **Concomitant aqueous tears**
  - Non-preserved tears were used in clinical trials
  - Allow 15-minute interval between instillations
  - Additional emulsion may be poorly tolerated
- **Contact lens users**
  - Administer Restasis™ before placing lenses in the eye, and wait 15 minutes and then repeat at end of day post-CL removal.

### Prescribing Restasis™

- **Follow-up in 4 to 6 weeks to:**
  - Note improvement
  - Subjective vs. objective findings
- **Treat for minimum 6 mos.**
  - Life Span of T-cell
    - 164 days
- **Initiate artificial tears therapy concomitantly**

### Expectations for the First Months of Restasis™ Therapy

- **Patients begin to notice reduced symptoms**
- **Key signs continue to improve**
- **Significant improvement in signs and symptoms**
- **Improvement maintained with continued therapy**

- **One Month**
- **Three Months**
- **Six Months**

### Efficacy Conclusions

- **At 6 months, increased tear production resulting in statistically significant improvements:**
  - Schirmer’s wettability
  - Corneal / Conjunctival staining
  - Patient symptoms: confirmed with CDE Questionnaire

- **Significant reduction in T-cell infiltration and inflammatory cytokines**
Lifitegrast™

Latest in Dry Eyes: Lifitegrast 5%

Progression of Dry Eye:
- A receptor on the surface of T-cells is called ICAM-1 (Inter-Cellular Adhesion Molecule-1) binds to LFA-1.
- ICAM-1 may be overexpressed in the corneal and conjunctival tissues in Dry Eye Disease patients
- This interaction can result in T-cell activation and migration to target tissues

What Lifitegrast Does:
- IIDRA blocks the interaction of ICAM-1 to LFA-1

Mechanism of Action

By binding to LFA-1, Lifitegrast blocks the ICAM-1 & LFA-1 interaction.

In vitro studies demonstrated that Lifitegrast may inhibit T-cell adhesion to ICAM-1 and the secretion of pro-inflammatory cytokines.

The exact mechanism of action of Lifitegrast in Dry Eye Disease is not known.

Study Overview

Evaluated for safety and efficacy
- Four randomized, double-masked, 12-week trials with total of 2133 patients.
- Assessed by improvement in:
  - Signs: measured by Inferior Corneal Staining Score
  - Symptoms: measured by Eye Dryness Score (N=2,133)
- Vehicle consisted of a sterile buffered solution with:
  - pH range of 7.0-8.0
  - Osmolality range of 200-330 mOsmol/kg

Study: Symptoms Assessed

Each of the 4 studies assessed the effect of Xiidra vs. Vehicle (saline) on:
- Both the signs and symptoms of Dry Eye at: baseline and weeks 2, 6, and 12.
- Assessment of symptoms was based on change from baseline in patient-reported Eye Dryness Score (EDS):

Mechanism of Action Video

https://www.xiidra-ecp.com/mechanism-of-action?gclid=CKvUudWDmM8CFUlfgoDE6UPXg
Study: Symptoms Assessed

- **EDS Evaluation Scale:**
  - 0-100 point scale
    - 0 = no discomfort, 100 = maximal discomfort
    - The average baseline EDS was between 40 and 70.

- In addition, the VAS (Visual Analog Scale) was used to assess other symptoms:
  - burning/stinging, itching
  - foreign body sensation
  - blurred vision, photophobia, and pain

Overview of Study Designs

<table>
<thead>
<tr>
<th>Study</th>
<th>Study 1 (OPUS 1)</th>
<th>Study 2 (OPUS 2)</th>
<th>Study 3 (OPUS 3)</th>
<th>Study 4 (OPUS 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>230</td>
<td>588</td>
<td>718</td>
<td>711</td>
</tr>
<tr>
<td>Study Arms</td>
<td>Vehicle</td>
<td>Lifitegrast 5%</td>
<td>Lifitegrast 5%</td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>BID for 12 wks.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms assessed</td>
<td>EDS – Eye Dryness Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs assessed</td>
<td>ICSS – Inferior Corneal Staining Score</td>
<td>(measured in 0.5 increments from 0-4 (no staining to coalescent ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criterion</td>
<td>Change in Inferior Corneal Staining Score &gt;/+ &gt; pre-to-post control adverse environment</td>
<td>Inferior Corneal Staining Score &gt;0.5 at baseline</td>
<td>EDS &gt; 40 at baseline</td>
<td>Recent History of Artificial Tears</td>
</tr>
</tbody>
</table>

Study 1: Symptoms SONATA Study

- **Study 1:**
  - **Arm 1:** Dose ranging study.
    - Study arms consisted of vehicle, lifitegrast 5% (Xiidra), lifitegrast 1%, and lifitegrast 0.1%
  - **Arm 2:**
    - Used Lifitegrast 5% to compare to vehicle.
    - Assessed 230 DED patients
  - **Arm 3:**
    - Additionally, Xiidra versus vehicle was evaluated in a 1-year safety study: SONATA (N=331)

STUDY 3&4: Symptoms OPUS 2&3

- **Study 3** assessed 718 DED patients
- **Study 4** assessed 711 DED patients
  - In Study 3 and Study 4, an improvement in the Eye Dryness Score was seen at Week 2.

Study 2: Symptoms OPUS 1

**Mean Change (SD) from Baseline and Treatment Difference (Xiidra – Vehicle) in Eye Dryness Score in 12-Week Studies in Patients with Dry Eye Disease**

- Study arms for Study 2, Study 3, and Study 4 were vehicle and Lifitegrast 5% (Xiidra)²
- Study 2 assessed 588 DED patients
  - Xiidra when compared to vehicle had a larger reduction in Eye Dryness Score at week 6 and 12.


Symptoms Results

- In all four studies, a larger reduction in eye dryness was observed with Xiidra versus vehicle at week 6.
**Study: Signs - Corneal Staining**

- **Assessment of signs was measured by:**
  - Inferior Corneal Staining Score (ICSS)
  - On a scale of 0 to 4 in increments of 0.5.

<table>
<thead>
<tr>
<th>Inferior Corneal Staining Score (ICSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
</tr>
</tbody>
</table>

- The average baseline ICSS was approximately 1.3 in Studies 1 and 2 and 2.4 in Studies 3 and 4.

**ICSS: Study 1 & 2**

- **Mean change (SD) from baseline and Treatment Difference (Xiidra – Vehicle) in Inferior Corneal Staining Score**

**ICSS: Study 3 & 4**

- In 3 of the 4 studies, at day 84 (after 12 weeks) a larger reduction of Inferior Corneal Staining was noted in Xiidra patients compared to vehicle.

- In three out of the four studies (Study 1, Study 2, and Study 4), a larger reduction in inferior corneal staining was observed with Xiidra versus vehicle at week 12.

**Let There Be Light…NOT?**

- **Instructions:**
  - Take a foil pouch out of the Xiidra box.
  - Pull off 1 single use vial.
  - Put the remaining strip of single use containers back in the pouch and fold the edge to close the pouch.

- **Storing Xiidra**
  - Store at room temperature between 68°F to 77°F (20°C to 25°C).
  - Store in the original foil pouch to protect it from light.
  - Do not open the foil pouch until you are ready to use.
  - Return unused single use containers to their original foil pouch to protect from excessive light exposure.

**What’s So Hot?**

- **Fast acting:**
  - relief of symptoms in 2 to 4 weeks
- **Great for patients with:**
  - Sjogren’s Syndrome
  - Severe KCS
  - Inflammatory tears
- **Allows for patients to:**
  - Decrease use of concomitant tears
  - Decrease use of adjunctive steroids
And What’s Not So Hot?

- **Dysgeusia** – “FUNKY” taste
  - tastes like heavy metal – “iron man”
- **Burning upon instillation**
  - Phlegm in throat days to weeks of use
- **Blurred vision**
  - Lasts 30min to 2 hrs.
- **Increased Lacrimation**
  - “Floods” eyes with reflex tearing
  - Unable to “blink away” excess tearing

Important Safety Information

- In clinical trials, the most common adverse reactions reported in 5 to 25% of patients:
  - instillation site irritation,
  - dysgeusia and
  - reduced visual acuity.
- Other adverse reactions reported in 1% to 5% of the patients:
  - Blurred vision, increased lacrimation
  - conjunctival hyperemia, eye irritation,
  - headache, eye discharge, eye discomfort,
  - eye pruritus and sinusitis.

My Patient Instructions

- Use drop in the morning
  - Pinch nose and tilt head downward
  - This will prevent burning and drainage to back of throat
- Do not drink or eat anything for 30 min post-instillation
  - This will lessen “metallic” taste
  - Brush your teeth post-gtt Instillation
  - Shower afterwards, if blurring of vision occurs.
- Wait 15 min before inserting SCLs

Texas Eye: Clinical Results

Latest in Dry Eyes: Lifitegrast 5%

- **FDA Indication**:
  - For the treatment of the “signs & symptoms” of Dry Eye Disease
- **Dosage**:
  - Used twice daily
- **LFA-1 Antagonist Medication**:
  - Lymphocyte Functioning-associated Agonist-1 (LFA-1) Antagonist
  - New drug class

Cryo-Preserved Amniotic Membrane
Dry Eye Disease (DED) is:
- One of the most commonly encountered conditions in our practice.
- Common denominator is:
  - Tear film instability and ocular surface inflammation


Benítez et al. (2004) An in vivo confocal masked study on corneal epithelium and subbasal nerves in patients with dry eye. IOVS

Corneal nerves play a significant role in the maintenance of corneal sensation and ocular surface health

Lacrimal Glands

Secretomotor Nerve Impulses

Tears Support and Maintain Ocular Surface

Ocular Surface Neural Stimulation

Although there is an inflammatory component:
- Not all patients respond to topical anti-inflammatory specifically when the nerves are compromised.
- To the best of our knowledge, there is no current treatment for nerve degeneration.

Hypothesis

Cryopreserved Amniotic Membrane (CAM)
- Rich in nerve growth factor
- Possesses a potent anti-inflammatory effect
- Successfully used to treat DED with ocular surface involvement
- Therefore CAM may help corneal nerve regeneration.
- To prove this hypothesis a Randomized Clinical Trial was designed.


Study: Corneal Nerve Regeneration after Self-Retained Amniotic Membrane Use for Dry-Eye Disease (ASCRS 2016)

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Objectives

• To evaluate:
  – Efficacy of cryopreserved self-retained amniotic membrane in restoring corneal nerve density and
  – Improving corneal sensitivity in patients with dry eye disease (DED).

Study Design

A prospective, controlled study to compare:

– Self-retained amniotic membrane
– Conventional treatment in patients with moderate to severe DED (DEWS 2, 3, 4).

20 subjects were enrolled and randomized to receive:
– CAM – Cryopreserved AM (Study Group) or
– Conventional maximum medical treatment (control group).

ITF-DEWS: International Task Force Dry Eye Work Shop

Discussed Treatment Without Lab High Disease

Observations: evaluated at baseline, 1 month, and 3 months

– Changes in clinical signs & symptoms,
– Corneal topography,
– Corneal sensitivity, and
– Corneal nerve density (using in vivo confocal microscopy)

Testing and Results

• 20 Patients enrolled
  – 17 Patients completed the 1 and 3 months follow-up visits

• Dry eye signs and symptoms testing:
  – SPEED 
    "Standard Patient Evaluation of Eye Dryness Score"
  – Pain score
  – Fluorescein staining
  – TBUT
  – DEWS grading

• Significant improvement in the study group compared to no change in the control group.

SPEED Questionnaire
Results: SPEED Score
- Statistically significant decrease:
  - SPEED score compared to control group at:
    - 1 month ($p<0.0001$, $n=17$)
    - 3 months ($p<0.0001$, $n=12$)

Results: Corneal Staining
- Less Corneal Staining:

Results: Pain Scoring
- Pain was graded 0 to 10, 10 being the most severe pain score.
- Study showed statistically significant decrease in these parameters from baseline to:
  - 1 month ($p<0.005$, $n=9$)
  - Pain score showed statistical significant decrease from 1 month to 3 month ($p<0.05$, $n=7$)

Results: DEWS Scoring

Results: Corneal Sensitivity
- Significant increase in corneal sensitivity:
  - from $3.25 \pm 0.6$ to $5.2 \pm 0.5$ at 1 month
  - $5.6 \pm 0.4$ cm at 3 months ($p<0.001$)
Results: Confocal Microscopy

- **BASELINE**
- **1 MONTH**
- **3 MONTHS**

Results: Corneal Nerve Density

- **Significant increase in corneal nerve density:**
  - from $12,241 \pm 5083$ to $16,364 \pm 3734 \ mu/mm^2$ at 1 mo.
  - $18,827 \pm 5453 \ mu/mm^2$ at 3 months, $p=0.015$.

Results: Corneal Topography

- **Corneal Topography showed:**
  - Consistent improvement of total aberrations,
  - Wavefront error, and
  - Cylinder values in the PKS group and
  - Remained unchanged in the control group.

<table>
<thead>
<tr>
<th>Data</th>
<th>Parameter</th>
<th>Control</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Map Pattern</td>
<td>Fairly similar regular astigmatism</td>
<td>Reduction in irregular astigmatism to a more regular pattern</td>
<td></td>
</tr>
<tr>
<td>Artificial Steepness</td>
<td>Possible increase in artificial steepening</td>
<td>Reduction in artificial steepness (presumed from ocular surface)</td>
<td></td>
</tr>
<tr>
<td>GPO Pattern</td>
<td>Negligible change</td>
<td>More regular control pattern with less change in aberration</td>
<td></td>
</tr>
<tr>
<td>Wavefront Error</td>
<td>Streeter pattern, change within measurement error</td>
<td>Reduction in WF error</td>
<td></td>
</tr>
<tr>
<td>Zernike Graph Total Aberration</td>
<td>Mild increase in aberration, within measurement error</td>
<td>Reduction in total aberration</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>No significant change</td>
<td>Ocular surface more optimized</td>
<td></td>
</tr>
</tbody>
</table>

Results: Superficial Punctate Keratitis

- **55-year-old Caucasian Female from Texas**
  - History of Dry Eye Syndrome, GP BF Lens wearer
  - Oc Meds: Restasis bid OU, Preservative Free Artificial Tears qid OU
  - Eyes hurt all the time, tired of pain/dryness especially with computer
- Wants to try alternative treatment for condition
- Starts CAM-Prokera Slim

Superficial Punctate Keratitis

- **Day 1**
- **Day 14**
Study Conclusion

- Placement of Cryopreserved amniotic membrane is a:
  - Promising therapy for corneal nerve regeneration AND
  - Accelerated recovery of the ocular surface health in patients with Dry Eye Disease.
  - It effectively suppresses inflammation, promotes regenerative healing with a lasting effect and helps avoid further deterioration.

Summary

- **Rx Treatment**
  - Cyclosporine-A: Restasis
  - Lifetigrast: Xiidra
- **Amniotic Membrane**
  - Cryo-preserved tissue
- **What’s Next…**
  - Neural Stimulation !!!

The Dry Eye Story...
“A Real Tear Jerker”

Thank You!