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How Will Novel Mechanisms of New and Emerging Treatments Address the Signs and Symptoms of Dry Eye?
This continuing medical education activity is provided by VINDICO medical education®.
This activity is supported by an educational grant from Oyster Point Pharma, Inc.
TFOS DEWS II Management and Therapy Report

Aim of DED management is to restore homeostasis

- “Algorithm is not a rigid stepwise approach”
- “Heterogeneity that exists in the DED patient population precludes an overly formulaic approach”
  - Considers both disease etiology and severity
  - Risk/benefit and cost considerations contribute to treatment choices

“In summary, the management of DED remains something of an art, not easily lending itself to a rigid, evidence-based algorithm that accommodates all patients....”

DED = dry eye disease; DEWS = Dry Eye Workshop; IPL = intense pulsed light; MGD = meibomian gland dysfunction; TFOS = Tear Film and Ocular Surface Society.
Treatment Strategies

- Less common to be purely aqueous deficiency (<10%)
- Meibomian gland dysfunction involved in >80% of DED
- Targeted strategies
  - Based on disease severity
  - Etiology
  - Treat signs and symptoms

Dry Eye Treatment BEFORE Drops

- Exacerbating medications should be eliminated when possible.
- Cigarette smoking is associated with dry eye.
  - Adverse effects on the lipid layer and tear proteins
- Humidifying ambient air and avoiding air drafts by using shields and by changing the characteristics of airflow at work, at home, and in the car may be helpful.
- Lowering computer screens below eye level to decrease lid aperture, scheduling regular breaks, and increasing blink frequency may decrease the discomfort associated with computer and reading activities.

Dry Eye Treatment BEFORE Drops

• Dry eye symptoms may have many contributory factors.
• Tear replacement is frequently unsuccessful when used as the sole treatment if additional causative factors are not concomitantly addressed.
• It is imperative to treat any causative factors that are amenable to treatment.
  – Lid malposition – entropion/ectropion, lagophthalmos
  – Trichiasis
  – Blepharitis, meibomianitis/MGD
  – Medications

## Treatment Strategies

### Lubricants
- Tears (emulsions, solutions), gels, ointments, sustained-release formulation
- Ingredients
  - Hyaluronic acid
  - Methylcellulose
  - Lipid based

### Nutrition
- Oral essential fatty acids
  - DREAM study
- Vitamin A ointment

Treatment Strategies

Anti-inflammatory agents:

- Topical cyclosporine A emulsion (CSA), 0.05%, 0.09%
- Topical corticosteroids
- Oral doxycycline
- Topical azithromycin
- Combination topical antibiotic and steroid
- Topical lifitegrast, 5%

Serum tears

Amniotic membrane therapy¹

- Self-retaining
- Drops/gels (eg, ACE)

Surgical treatment - tarsorrhaphy

ACE = amniotic cytokine extract.
Lid Margin Disease Management

- Warm compresses and lid massage
  - Difficult to maintain adequate temperature; poor compliance
- Lid scrubs
  - Commercial soap scrubs (eg, hypochlorous acid)
  - Tea tree oil for *Demodex* mite infestation
- In-office lid margin cleansing and meibomian gland expression for anterior blepharitis and posterior blepharitis
  - Motorized/mechanical devices
  - Thermal pressure and thermal pulsation
  - Intraductal probing
  - IPL

Lid Margin Disease Management

- Thermal pulsation
  - Heats posterior lid and then compression of lid
- IPL, with meibomian gland expression
  - Series of monthly treatments
- Microblepharoexfoliation
  - Removal of bacterial biofilm obstructions are key to successful MGD management
  - Exfoliation of the eyelid margin unroofs the meibomian glands

New Dry Eye Therapy

Cyclosporine

0.09% cyclosporine A

- FDA approval in August 2018 for treatment of dry eye
- Utilizes nanomicellar technology
  - Allows cyclosporine to overcome solubility challenges
  - Better penetration of the aqueous layer and prevents release of the active lipophilic molecule prior to penetration

FDA = US Food and Drug Administration.
## Novel Cyclosporine Formulations

<table>
<thead>
<tr>
<th>Chemical modification of the drug</th>
<th>Prodrug</th>
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<tbody>
<tr>
<td>Novel application of excipients</td>
<td>Cyclodextrins</td>
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<tr>
<td></td>
<td>Semifluorinated alkanes</td>
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<tr>
<td></td>
<td>Positively charged vectors</td>
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<tr>
<td>Novel ophthalmic dosage forms</td>
<td>In situ gelling systems</td>
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<td></td>
<td>Hydrogels</td>
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<td></td>
<td>Lysosomes</td>
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<td></td>
<td>Micelles</td>
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<td>Nanoparticles</td>
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</tbody>
</table>

**Nanomicellar cyclosporine 0.09%**

Nanomicellar Cyclosporine 0.09% (OTX-101): Pooled Analysis of Phase 2b/3 and Phase 3 Studies

OTX-101: N= 523; vehicle: N=525

Greater % of patients with an increase in Schirmer test scores of ≥10 mm at week 12 relative to baseline for OTX-101 versus vehicle

<table>
<thead>
<tr>
<th>Population, %</th>
<th>OTX-101</th>
<th>Vehicle</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>16.6</td>
<td>9.0</td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td>Score &lt;10 mm at baseline</td>
<td>18.7</td>
<td>10.2</td>
<td>P = .0001 (^a)</td>
</tr>
</tbody>
</table>

SANDE score

<table>
<thead>
<tr>
<th>Population, %</th>
<th>OTX-101</th>
<th>Vehicle</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>-29.0</td>
<td>-30.4</td>
<td>P &lt; .3539 (^a)</td>
</tr>
<tr>
<td>Score &lt;10 mm at baseline</td>
<td>-27.3</td>
<td>-31.4</td>
<td>P = .1343 (^a)</td>
</tr>
</tbody>
</table>

\(^a\) P value from the Cochran–Mantel–Haenszel test for general association with day 84/early discontinuation increase at least 10 mm or any lesser increase or decrease versus the treatment group.

\(^a\) P value from the Wilcoxon rank-sum test for differences between treatment groups (2-sided normal approximation).

ITT = intention-to-treat; SANDE = Symptom Assessment in Dry Eye.
Primary Endpoint:
Lissamine Green Staining (Study Eye)

Note: ANCOVA for mITT population, observed values; * p<0.05  ** p< 0.01

ANCOVA = analysis of covariance; mITT = modified intention-to-treat.
Loteprednol Etabonate 0.25%
Mucus-Penetrating Particles (MPP)

- **Only** FDA-approved steroid for short-term treatment of signs and symptoms of dry eye disease
- **Innovation** in drug delivery
- Proprietary **mucous-membrane particle coating** that helps to increase diffusion and penetration of the steroid on the ocular surface

Loteprednol Etabonate 0.25%

- Episodic inflammatory flares occur in **most patients** with chronic DED
- Flares result from **complex inflammatory cascades**
- Example: **asthma**
- Increased understanding of flares may guide management and improve outcomes

Efficacy of Loteprednol 0.25% MPP (KPI-121)

STRIDE 1, 2, and 3 showed significant improvements in ocular discomfort for KPI-121 versus vehicle on Day 8

- NDA w/ STRIDE 1 and STRIDE 2 data received CRL from the FDA in August 2019; additional efficacy data requested.
- Resubmission with STRIDE 3 data was approved by the FDA in October 2020 for short-term treatment of DED (up to 2 weeks)

CRL = complete response letter; NDA = New Drug Application; SD = study day.
Tear Secretion Is Regulated by the Lacrimal Functional Unit

Intranasal Neurostimulation

- Handheld device
- Transmits small electrical pulses to the disposable tip
- Inserted into the nostrils
- Stimulation of trigeminal afferent nerve in the nasal mucosa triggers the nasolacrimal reflex pathway
  - Contributes to both basal and stimulated tear production

Intranasal Neurostimulation: Schirmer Test Score Increases

Significantly greater tear production with intranasal stimulation than with control extranasal or sham stimulation

Study eye (n=48)  Fellow eye (n=35)

*P<0.0001, active versus controls; error bars represent standard error of the mean.
**Tear Neurostimulation: OC-01 (Varenicline)**

- **OC-01 (varenicline)** is a novel compound delivered via nasal spray.
- It is a **highly selective nicotinic acetylcholine receptor agonist** that activates the trigeminal parasympathetic pathway that stimulates the **lacrimal functional unit** to reestablish the natural tear film.

Tear Neurostimulation: OC-01 (Varenicline)

- OC-01 nasal spray demonstrated statistically significant improvement in signs (Schirmer score) by day 28 compared with placebo.
- OC-01 nasal spray demonstrated nominally statistically significant improvement in symptoms (EDS) as early as day 14 and by day 28 compared with placebo.
- No significant changes were seen in mean change from baseline in EDS in the CAE chamber at day 28.

CAE = controlled adverse environment; EDS = eye dryness score.
New Dry Eye Therapy:
Preservative-Free 0.1% Cyclosporine A

- Semifluorinated alkane vehicle
  - Nonaqueous
  - Low viscosity and surface tension allows drug dissipation in minutes
  - Does not impair vision like emulsions, oils, and gels do
- Amphiphilic nature
  - Increases solubility, stability, and tissue penetration of poorly soluble small molecules like cyclosporin A does
- Phase 2 trial showed efficacy equal to cyclosporine 0.05% but with a quicker onset – as early as 14 days
- Currently in clinical development, with anticipated new drug filings in the United States, Japan, and Europe
New Dry Eye Therapy: OCU310 (Brimonidine 0.2% + Loteprednol 0.2%)

- Brimonidine 0.2% + loteprednol 0.2% (OCU310)
  - Plans to begin phase 3
- Brimonidine (OCU300)
  - Nanoemulsion of 0.18% brimonidine
  - Treatment for ocular discomfort and redness in patients with graft-versus-host disease
  - Phase 2 showed 90% of patients with improved symptoms after 6 months, especially reduction of ocular redness

New Dry Eye Therapy: Reproxalap

• Small-molecule reactive aldehyde species (RASP) inhibitor that covalently binds free aldehydes and diminishes excessive RASP levels

Reproxalap Mechanism of Action

Reproxalap Phase 2a Clinical Trial Results: Reduction in Tears

MDA = malondialdehyde; SEM = standard error of the mean.
RGN-259

- Thymosin beta-4
  - Naturally occurring peptide
  - Important in protection, regeneration, and remodeling of damaged tissues
- Treatment of moderate to severe dry eye and neurotrophic keratitis
- Currently in repeat phase 3

New Dry Eye Therapy: TOP1630

- p38α, Syk, Lck, and Src are significantly upregulated in the ocular surface of persons with DED
  - This upregulation is associated with increase in the inflammatory cytokines IL-1β, IL-8, MCP-1, and in the inflammatory mediator MMP-9
- Nonsystemic kinase inhibitors are a novel class of agents that selectively target p38α, Syk, Lck, and Src
  - They produce broad, potent anti-inflammatory effects in vitro and in vivo, exhibiting potent inhibition of cytokine release in cellular assays and mimicking both innate and adaptive immune systems, as well as in vivo models
  - They are small molecules designed for topical administration and demonstrate an exemplary safety profile in preclinical and clinical studies, with very low systemic exposure

IL = interleukin; MCP-1 = monocyte chemoattractant protein-1; Lck = lymphocyte-specific protein tyrosine kinase; MMP = matrix metalloproteinase; Syk = spleen tyrosine kinase; Src = proto-oncogene c-Src.
TOP1630 Phase 2 Results

Safety and tolerability

- 12/61 participants reported TEAEs
  - 7 reported in 6 patients in the TOP1630 group
  - 9 in 6 patients in the placebo group
- All were mild to moderate in severity
- No SAEs reported
- Drop comfort was similar between treatment groups

CAE = controlled adverse environment; SE = standard error; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

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