Ocular Surface Disorders: Diagnosing an Elusive Array

Preeya K. Gupta, MD

Point-of-care (POC) testing has revolutionized the diagnosis of dry eye. Previously, clinicians began an investigation on the basis of patient complaints or late signs, such as corneal staining. Objective data acquired from the tear film now can provide earlier diagnosis and allow earlier treatment, which may improve outcomes. Point-of-care testing can be used to monitor therapeutic response as well as identify masquerading ocular surface disease that is not specifically dry eye.

Dry eye is common in the patient population presenting for cataract surgery. In a prospective study of 120 consecutive cataract surgery patients, 80% had at least 1 abnormal tear test, and 40% had 2 abnormal tests, with positive corneal staining observed in 39%. The series included 46 asymptomatic patients, of whom 85% had at least 1 abnormal tear test.

Several POC tests are available that can provide a comprehensive assessment of the ocular surface (Table). Understanding the rationale, benefits, and limitations of each test can assist clinicians with providing optimal state-of-the-art management of their patients’ ocular surface.

**Osmolarity Testing**

Tear osmolarity can be measured using a Clinical Laboratory Improvement Amendments (CLIA)-waived, in-office–based osmometer. A single-use microchip embedded in a handheld device uses gold electrodes to measure the electrical impedance of a 50-nL tear fluid sample. The osmolarity test should be performed before any drops are instilled in the eye.

Osmolarity ≥308 mOsmol/L in either eye is considered diagnostic for dry eye disease (DED). That cutoff had 88% specificity and 75% sensitivity in mild to moderate disease and 95% sensitivity in severe disease. Inter-eye variability of >8 mOsmol/L is also diagnostic for DED. Inter-eye variability, with repeated osmolarity determinations, is significantly greater in patients with DED compared with controls.

Osmolarity does not distinguish the subtype of DED—abnormal osmolarity can occur in both meibomian gland disease and aqueous-deficient dry eye. Because the test is highly specific for DED, an alternate diagnosis can be pursued if a patient with a suspicion of dry eye has normal osmolarity.

**Matrix Metalloprotease-9 Testing**

Matrix metalloproteinase-9 (MMP-9) is a nonspecific inflammatory enzyme that can interrupt tight junctions in the ocular surface epithelium as well as increase corneal desquamation and surface irregularity when concentrations rise. Measuring MMP-9 has become a POC tool for diagnosing inflammatory dry eye, and a CLIA-waived commercial immunoassay with 85% sensitivity and 94% specificity is available.

As with sampling for osmolarity testing, MMP-9 testing should be performed before administering any agents into the eye. A sampling fleece is patted along the conjunctiva until it glistens, indicating saturation has been achieved. Samples <5 µL will give negative results. The sample and buffer are placed within the test cassette, with the result being available within 10 minutes. A positive outcome, based on an MMP-9 cutoff concentration of 40 ng/mL or greater, produces a red line. Samples with <40 ng/mL MMP-9 produce a blue line, although a faint positive line may be seen between 30 and 40 ng/mL.

Limitations of MMP-9 testing include the nonspecificity of the test for the source of inflammation. Elevation in MMP-9 levels has been observed in patients with Sjogren syndrome, conjunctivochalasis, vernal keratoconjunctivitis, keratoconus, and extended contact lens wear.

A positive result may support initiating anti-inflammatory therapy, such as use of corticosteroids, lifitegrast, or cyclosporine. A recent study included patients with >3 DED criteria (ocular surface disease

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<th>Test</th>
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<td>Osmolarity</td>
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<td>Inflammation: matrix metalloproteinase-9</td>
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<td>Meibomian gland imaging</td>
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<td>Lipid layer thickness</td>
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<td>Lactoferrin/Sjogren syndrome</td>
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<td>Allergy panel</td>
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index [OSDI] score $\geq 12$, tear film breakup time [TBUT] $\leq 10$ seconds, and Schirmer I test result $\leq 10$ mm/5 minutes and/or corneal staining grade $\geq 1$) who were treated with topical cyclosporine ophthalmic emulsion 0.05% twice daily for 1 month. A semiquantitative grading method was used with the commercial test to assign 4 levels of MMP-9 positivity. The subgroup of 17 eyes with positive or strong-positive MMP-9 results at baseline had significantly improved OSDI, TBUT, corneal staining, and Schirmer test at 1 month. These outcomes were unchanged in the subgroup of 14 eyes that were MMP-9–negative at baseline, with 2 eyes becoming positive or strong-positive despite cyclosporine treatment. These observations suggested that increased management benefits may be possible with a quantitative test.

Research to develop improved next-generation devices is underway, including a single device that can measure both osmolarity and MMP-9 quantitatively. In addition to providing more efficient diagnosis, the device is expected to have the potential for disease stratification.

**Dynamic Meibomian Gland Imaging**

Dynamic meibomian gland imaging uses infrared light to observe meibomian gland silhouette morphology. Visualizing meibomian gland morphology can be useful in stratifying disease severity, as significant disease may be overlooked without using this modality. Features such as meibomian gland dilatation and atrophy can be helpful to the eye care provider in associating abnormal structure with dysfunction (Figure 2). Meibography is also useful for patient education, as it is easy to convey the structural damage that is occurring in the form of meibomian gland atrophy as part of meibomian gland disease. Meibography alone may not be adequate to diagnose meibomian gland dysfunction, so the results should be coordinated with clinical examination findings and other testing.

**Lipid Layer Interferometry**

A POC interferometer is available that provides automated measurement of tear film lipid layer thickness (LLT). A significant correlation was observed between expressible meibomian glands and LLT ($P<.0001$) in a retrospective analysis of 199 eyes. Using a cutoff value of $\leq 75$ nm provided 66% sensitivity and 63% specificity for diagnosing meibomian gland dysfunction. At a more severely reduced LLT of $\leq 60$ nm, sensitivity was 48% and specificity increased to 90%. Another study reported a significant inverse linear relationship between LLT and dry eye symptoms ($P=0.0014$)—74% of patients with severe symptoms had an LLT of $\leq 60$ nm, and 72% of patients with no symptoms had an LLT $\geq 75$ nm. Current technology (ie, LipiView II) allows for dynamic meibomian imaging, visualization and quantization of lipid
layer thickness, near-infrared surface imaging, and partial blink detection with a single instrument.¹⁶

**Lactoferrin Testing**
Lactoferrin is a glycoprotein secreted primarily by the lacrimal gland.¹⁷ Lactoferrin in tear film has anti-inflammatory, antioxidant, and antimicrobial activities. Its concentration in healthy tears is approximately 1.4 mg/mL. However, lactoferrin decreases in the presence of some eye pathologies, including aqueous-deficient dry eye, meibomian gland dysfunction, and Sjogren syndrome–associated dry eye, as well as with aging.¹⁷,¹⁸ Using a cutoff of 1.1 ng/mL, lactoferrin levels detected DED with 79% sensitivity and 78% specificity.¹⁹ The commercially available lactoferrin assay uses a 0.5-µL sample and has a 83% sensitivity and 98% specificity, with a <9% coefficient of variation, using a cutoff of 0.9 mg/mL.¹⁸,²⁰,²¹ The test is regulated as CLIA class II; that is, it is of moderate complexity and requires licensing for all persons taking, processing, or reading the laboratory samples.²²

**Sjogren Syndrome Testing**
The nonspecific and variable symptoms associated with Sjogren syndrome contribute to common diagnostic delays.²³ Early diagnosis allows prompt treatment initiation and possible avoidance of other systemic autoimmune conditions. Objective diagnostic factors include the autoantibodies anti-Sjogren syndrome–related antigen A/Ro and antigen B/La, antinuclear antibody, and rheumatoid factor. However, these traditional biomarkers have limited usefulness in early cases. A more recent diagnostic panel (Sjo test) adds detection of salivary gland protein-1, parotid secretory protein, and carbonic anhydrase-6 to the 4 traditional analytes, with a resulting greater specificity and sensitivity for early detection. Blood samples obtained by finger prick can be applied to a card, or a normal blood sample can be sent for laboratory analysis. Dry eye and dry mouth are common presenting complaints in patients with Sjogren syndrome; thus, eye care and dental professionals should work with rheumatologists to provide optimal diagnosis and management.

**Allergy Testing**
Ocular allergies are estimated to affect up to 20% of the population in the United States.²⁴ A commercial POC test that is US Food and Drug Administration–approved is available and in use by many clinicians, including allergists, dermatologists, and primary care physicians.²⁵ The “no needle” test provides results in 15 minutes for the presence of 60 geographically specific antigens. Patients should be given a list of medications to avoid for 48 hours to 5 days, depending on the specific drug, before undergoing the test. They should understand that the test does not need to be done during an allergic episode. Test administration, waiting time, and interpretation are typically completed in 35 minutes. Counseling after allergy testing includes advising the patients to avoid activities that expose them to culprit allergens, with follow-up in 1 month to examine outcomes.

**Immunoglobulin E Levels**
Systemic immunoglobulin E (IgE) antibodies can be detected in most cases of allergic conjunctivitis.²⁵ Point-of-care assessment of IgE levels in tears is now possible, using a 0.5-µL sample, with 80 ng/mL representing the cutoff for allergic conjunctivitis.²⁶ The diagnostic kit for lactoferrin can also determine IgE levels as a CLIA class II test.²⁶ Results can help to determine which patients may benefit from topical antihistamine and/or corticosteroid therapy. For patients with severe allergies, eye care specialists should work with an allergist to facilitate optimum care.

**Systemic and Ocular Medications Associated With DED**
The contribution of systemic medications for the treatment of patients with DED should not be overlooked. Clinicians should carefully review their patients’
medical records for use of systemic or ocular medications that increase the risk of DED. Among the top 100 best-selling systemic drugs in the United States in 2009, 22 were possibly associated with dry eye and dry mouth. Many drugs that are commonly used in the older population have a higher prevalence of dry eye compared with younger persons and are associated with an increased risk of dry eye. Topical ocular drugs, including agents to treat allergies, may also cause or aggravate dry eye. Agents in several drug classes used to treat glaucoma, as well as topical anesthetics, non-stereoidal anti-inflammatory drugs, decongestants, and antiviral agents, can also cause the development or worsening of dry eye. Eye care professionals should pay special attention to caring for the ocular surface in patients with increased risk for DED.

**SUMMARY**
Point-of-care testing facilitates rapid, uncomplicated, and earlier diagnosis of DED. Measuring these “ocular vital signs” can aid clinicians in making an accurate diagnosis and facilitate the timely initiation of appropriate treatment.

**CASE**
A 47-year old man complains of chronic foreign body sensation (FBS) and red eyes. He has been treated with several products over the previous 9 months, including cyclosporine, azithromycin, and doxycycline. He recently discontinued prescription treatments because he did not detect any improvement. He continues with artificial tears as needed and warm compresses. He has no significant past medical history.

A typical ocular work-up was performed. Matrix metalloproteinase-9 was positive in both eyes. Osmolarity was normal (290 mOsmol/L in the right eye and 293 mOsmol/L in the left eye). Dynamic meibomian imaging revealed mild gland atrophy, with 2+ meibomian gland dysfunction. His cornea was clear, although he had some conjunctival injection, with a mild ectropion (Figure 3).

This patient typifies what is often referred to as a “tough dry eye patient.” This type of patient has been to several doctors, has taken several medications, and is frustrated with the lack of results. Point-of-care testing can help assess all ocular surface situations that could be contributing to patients’ complaints. Meibomian gland imaging can identify patients who have atrophy, which was not evident from other diagnostic investigations. Tear chemistry, including osmolarity and MMP-9, provides an indication of the microenvironment bathing the eye. External anatomy examination can comprise assessing lid position and function, including the completeness of the blink and the resulting spread of tear film.

Due to the mild ectropion, the examination continued with eversion of the eyelids, revealing extreme floppy eyelid syndrome (FES) (Figure 4). Ulcerations and...
papillary reaction were evident at the lid margin. Therefore, his FBS was assumed to be due to floppy eyelid-related chronic mechanical trauma from the overriding lids, producing ulceration.

The patient was treated with a topical steroid with taper and initiation of lifitegrast 5% as well as artificial tear ointment at bedtime. At his first follow-up visit, he was 60% improved. He was referred to an oculoplastics specialist for a lid-tightening procedure, which resolved his symptoms completely.

This case also exemplifies the importance of reviewing the patient’s medical record. He had obstructive sleep apnea, which has been noted to be associated with FES.28 Sleep apnea could provide a first diagnostic suspicion, warranting specific FES investigations.

Not all patients’ FBS and redness is DED. Point-of-care testing can provide a more comprehensive assessment that can lead to an accurate diagnosis. As with this case, a multidisciplinary approach is sometimes necessary to resolve symptoms.

References


Dry eye disease (DED) is a symptomatic condition that affects hundreds of millions of people worldwide. Although DED has 2 recognized forms—aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE)—fewer than 10% of patients have isolated ADDE. Meibomian gland dysfunction, a contributor to EDE, is involved in more than 80% of DED cases. Three major management guidelines were recently published, exemplifying the increasing recognition of the importance of ocular surface health and emphasizing the importance of proper diagnosis.

**TFOS DEWS II Management and Therapy Report**

The Management and Therapy Subcommittee of the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS II) published a thorough evidence-based review of current therapies and management options for patients with DED, emphasizing that “diagnosis precedes therapy.” Clinicians should determine the contribution of EDE and/or ADDE, as well as the possible presence of other ocular conditions, before developing a management plan. The ultimate goal of DED management is restoring homeostasis, which may require multiple and long-term treatments to address specific issues with the ocular surface condition.

The complexity of DED and its heterogeneity among patients precludes having a rigid, stepwise management approach and requiring consideration of both disease etiology and severity. The TFOS DEWS II staged management and treatment recommendations begin with conventional low-risk and commonly available therapies for early-stage disease, progressing to more advanced therapies with increasing disease severity (Table 1). Clinicians should use these recommendations as a guide and adapt them as warranted to provide optimal management of their individual patients with DED.

The TFOS Subcommittee acknowledged that due to its heterogeneity, managing patients with DED remains somewhat of an art. Eye care providers must be prepared to use their clinical expertise to judge the significance of the various pathogenic processes that can produce similar symptoms and signs.

**CEDARS Dysfunctional Tear Syndrome: Diagnostic-based Approach**

A panel of experts from the Cornea, External Disease, and Refractive Society (CEDARS) developed a diagnostic-based approach to managing dysfunctional tear syndrome. They defined dysfunctional tear syndrome as a disorder in tear film quality and/or quantity, with a variety of etiologies, resulting in various signs and symptoms. Their management recommendations related to 4 diagnostic subtypes: tear deficiency, goblet cell/mucin deficiency, blepharitis/meibomian gland dysfunction, and exposure keratopathy (Figure 1).

**Dry Eye Syndrome Preferred Practice Pattern**

The American Academy of Ophthalmology updated their Dry Eye Syndrome Preferred Practice Pattern in 2018. Treatment recommendations are divided among mild, moderate, and severe disease (Table 2). As with TFOS DEWS II, the American Academy of Ophthalmology acknowledged that this is not a rigid system and that there can be crossover as clinicians use their experience and expertise together with patient preference to develop optimum management strategies.

**Putting it all Together: Treatment Strategies**

Reports from 3 major professional societies recommended similar approaches for managing DED. Targeted treatment strategies should be based on disease severity, etiology, and patient signs and symptoms. Patients make office visits in response to their symptoms; thus, symptom resolution is a key objective in patient management.

**Pretreatment Strategies**

A patient’s management plan should include identifying contributing factors for which interventions can be made before starting treatment. If relevant changes are not made, treatments may not be successful. Medications that may cause or exacerbate dry eye should be discontinued if possible. Collaborating with the prescribing physician may be warranted to determine whether alternative options for required medications exist. As with all clinicians, eye care specialists should counsel their patients who smoke about quitting.
### Table 1. TFOS DEWS II Staged Management of Dry Eye<sup>a,b,c</sup>

<table>
<thead>
<tr>
<th>Step 1:</th>
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<tbody>
<tr>
<td>Education regarding the condition, its management, treatment, and prognosis</td>
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<tr>
<td>Modification of local environment</td>
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<tr>
<td>Education regarding potential dietary modifications (including oral essential fatty acid supplementation)</td>
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<tr>
<td>Identification and potential modification/elimination of offending systemic and topical medications</td>
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<tr>
<td>Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)</td>
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<tr>
<td>Lid hygiene and warm compresses of various types</td>
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<tr>
<th>Step 2:</th>
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<tbody>
<tr>
<td>If above options are inadequate, consider:</td>
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<tr>
<td>Nonpreserved ocular lubricants to minimize preservative-induced toxicity</td>
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<tr>
<td>Tea tree oil treatment for <em>Demodex</em> (if present)</td>
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<tr>
<td>Tear conservation</td>
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<tr>
<td>Punctal occlusion</td>
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<tr>
<td>Moisture chamber spectacles/goggles</td>
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<tr>
<td>Overnight treatments (such as ointment or moisture chamber devices)</td>
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<tr>
<td>In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)</td>
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<tr>
<td>In-office intense pulsed light therapy for MGD</td>
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<tr>
<td>Prescription drugs to manage DED&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)</td>
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<tr>
<td>Topical corticosteroid (limited-duration)</td>
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<td>Topical secretagogues</td>
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<td>Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)</td>
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<td>Topical LFA-1 antagonist drugs (such as lifitegrast)</td>
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<td>Oral macrolide or tetracycline antibiotics</td>
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<th>Step 3:</th>
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<tr>
<td>If above options are inadequate, consider:</td>
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<tr>
<td>Oral secretagogues</td>
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<tr>
<td>Autologous/allogeneic serum eye drops</td>
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<tr>
<td>Therapeutic contact lens options</td>
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<tr>
<td>Soft bandage lenses</td>
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<td>Rigid scleral lenses</td>
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<th>Step 4:</th>
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<tr>
<td>If above options are inadequate, consider:</td>
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<tr>
<td>Topical corticosteroid for longer duration</td>
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<tr>
<td>Amniotic membrane grafts</td>
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<tr>
<td>Surgical punctal occlusion</td>
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<tr>
<td>Other surgical approaches (eg, tarsorrhaphy, salivary gland transplantation)</td>
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**DED** = dry eye disease; **lymphocyte function-associated antigen-1**; **MGD** = meibomian gland dysfunction.

<sup>a</sup>Potential variations within the disease spectrum are acknowledged to exist between patients and the management options listed above are not intended to be exclusive. The severity and etiology of the DED state will dictate the range and number of management options selected from one or more steps.

<sup>b</sup>One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.

<sup>c</sup>It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

<sup>d</sup>The use of prescription drugs needs to be considered in the context of the individual patient presentation and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.

Source: Reprinted from Jones L, et al<sup>a</sup> © 2017 with permission from Elsevier.
Beneficial environmental changes should also be explored. Ambient air should be adequately humidified, and drafts should be avoided.\(^4\)\(^,\)\(^6\) Shields and/or changing the characteristics of airflow in patients’ cars as well as at work and at home may be helpful.\(^4\)\(^,\)\(^6\)

Computer screens should be below eye level to decrease lid aperture.\(^6\) Reading and computer use should include regular scheduled breaks, attention to increasing blink frequency, and increased use of topical lubrication.\(^6\)

Some eye conditions that contribute to DED can be treated. Clinicians can address lid malposition and abnormalities such as entropion/ectropion and lagophthalmos.\(^4\)\(^,\)\(^6\)

**Lubricants**

Use of lubricants, in the form of artificial tears as emulsions or solutions, gels, ointments, and sustained release formulations, is the usual first therapy.\(^4\)\(^,\)\(^6\) Ingredients can include hyaluronic acid, methylcellulose, and lipids. When possible, benzalkonium chloride preservatives should be avoided.\(^4\)\(^,\)\(^6\)

**Nutrition**

Oral supplementation with essential fatty acids has been widely recommended to relieve dry eye symptoms. Recently, the multicenter DREAM study randomized 349 patients with moderate to severe dry eye to a daily oral dose of 3 g of fish-derived n-3 eicosapentaenoic and docosahexaenoic acid and 186 to an olive oil control.\(^7\) The primary outcome of mean change from baseline in Ocular Surface Disease Index (OSDI) score, based on the mean obtained at 6 and 12 months, was similar in the treatment (-13.9 points) and control (-12.5 points) groups (\(P=0.21\)) and was consistent across all prespecified subgroups.\(^7\) Secondary outcomes were also similar between groups.\(^7\) The authors concluded that supplementation with 3 g of n-3 fatty acids for 12 months did not improve outcomes compared with those who received placebo. However, some argue that both the placebo group and the omega-3 group had significant improvements from baseline in their OSDI scores and objective tests of DED and that the olive oil used as a placebo was not a fair comparator.

Vitamin A has been compounded as a 0.01% all-trans retinoic acid topical ointment and used off-label to treat goblet cell deficiency.\(^5\) However, this treatment has not been studied in robust clinical trials and any investigational use is at the discretion of the clinician.\(^5\)

**Lid Margin Disease Management**

Conventional treatment for lid margin disease includes warm compresses and lid massage.\(^4\)\(^,\)\(^6\) Disadvantages of this approach include difficulty maintaining adequate temperature and poor compliance. Lid scrubs are available, some of which contain...
hypochlorous acid. Tea tree oil scrubs can be used for *Demodex* mite infestation.\(^4\)-\(^6\)

In-office procedures include lid margin cleansing and meibomian gland expression for anterior and posterior blepharitis.\(^4\)-\(^6\) Several devices are available with different mechanisms of action, including microblepharoexfoliation. In addition to motorized mechanical devices, thermal pressure and pulsation, intraductal probing, and intense pulsed light can be used.\(^4\)-\(^6\)

### Anti-inflammatory Agents: Topical Cyclosporine 0.05%

In 2003, a 0.05% cyclosporine emulsion became the first prescription medication approved by the US Food and Drug Administration (FDA) for treating DED.\(^8\) Data from approximately 1200 patients enrolled in 4 randomized trials supported its approval.\(^5\) The primary endpoint—increased Schirmer wetting of at least 10 mm at 6 months—was observed in approximately 15% of cyclosporine-treated patients compared with 5% of vehicle-treated patients.\(^9\)

Treatment with cyclosporine is associated with improved ocular surface health, including increased tear production and decreased activated lymphocytes, with decreased corneal staining and blurred vision.\(^10\),\(^11\) Reductions in artificial tear use suggest improved patient comfort, and tolerability and safety for up to 4 years were demonstrated in clinical trials.\(^12\) Potential additive improvements in artificial tears were observed in patients with concomitant punctal plugs.\(^13\) Contact lens–intolerant patients experienced increased comfort and wear.\(^14\) Patients with dry eye who were undergoing LASIK experienced faster recovery and better outcomes.\(^15\)

The initial cyclosporine formulation was provided in preservative-free, single-use vials.\(^9\) A proprietary sterile, multidose, preservative-free vial is now available, which has a unidirectional valve and air filter.\(^16\)

### Topical Steroids

Topical corticosteroids are used to treat several ocular inflammatory conditions.\(^17\) Although not specifically indicated to treat DED, the loteprednol etabonate 0.5% suspension is indicated for treating steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.\(^18\)

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Management Recommendation</th>
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| **Mild** | • Education and environmental modifications  
• Elimination of offending topical or systemic medications  
• Aqueous enhancement using artificial tear substitutes, gels, and/or ointments  
• Eyelid therapy (warm compresses and eyelid hygiene)  
• Treatment of contributing ocular factors, such as blepharitis or meibomianitis (see Blepharitis Preferred Practice Pattern)  
• Correction of eyelid abnormalities (eg, trichiasis, lid malposition) |
| **Moderate** | In addition to the above treatments:  
• Anti-inflammatory agents (topical cyclosporine and corticosteroids)  
• Lifitegrast  
• Systemic omega-3 fatty acids supplements  
• Punctal plugs  
• Spectacle side shields and moisture chambers  
• Slow-release hydroxypropyl cellulose inserts  
• Intranasal neurostimulation  
• Labial mucous membrane and minor salivary gland transplantations |
| **Severe** | In addition to the above treatments:  
• Systemic cholinergic agonists (pilocarpine and cevimeline)  
• Mucolytic agents (eg, acetylcysteine 10%)  
• Autologous (or allogeneic) serum tears  
• Self-retaining amniotic membrane  
• Permanent punctal occlusion  
• Tarsoorhaphy  
• Contact lenses |

Source: Data from Akpek EK, et al.\(^6\)
Treatment for postoperative inflammation can be given during the first 2 weeks after surgery. Corticosteroids have been reported to decrease ocular irritation and corneal fluorescein staining, which were also observed in a study that provided corticosteroid pretreatment for 2 weeks before punctal occlusion.17

A small study of 64 patients with dry eye and delayed tear clearance compared loteprednol with vehicle administered 4 times daily for 4 weeks.19 The subset of patients with at least moderate clinical inflammation had significant improvement at 2 weeks compared with the vehicle group, which remained numerically but not statistically greater at 4 weeks.19 A significant increase in increased intraocular pressure was not observed in the loteprednol group. A later randomized trial of 118 patients with mild to moderate DED examined the effects of 2 weeks of pretreatment with loteprednol etabonate 0.5% compared with artificial tears, followed by the addition of cyclosporine treatment for an additional 6 weeks.20 Significantly less stinging associated with cyclosporine administration was observed in the loteprednol group. In addition, the loteprednol group experienced superior improvement in Schirmer testing, fluorescein staining, and lissamine green staining, with significantly greater OSDI score improvement compared with the artificial tears group. Intraocular pressure did not increase in either group.20 Nonetheless, patients prescribed corticosteroids for the treatment of DED should be monitored for increased intraocular pressure, corneal melting, and cataract formation.20

Loteprednol suspension requires vigorous shaking before use.18 A nonsettling gel formulation is now available to facilitate administration.21,22 The inverted bottle is shaken once to fill the tip. The formulation includes glycerin and propylene glycol, which have a humectant effect and are expected to contribute to patient comfort by retaining moisture on the eye surface.21

Lifitegrast 5%

The lymphocyte function-associated antigen-1 (LFA-1) antagonist lifitegrast received FDA approval for the treatment of the signs and symptoms of DED in 2016.23 By binding to LFA-1 (a leukocyte cell surface protein), the interaction is blocked between LFA-1 and its cognate ligand, intercellular adhesion molecule-1 (ICAM-1). In DED, ICAM-1 may be overexpressed in the cornea and conjunctiva, with the LFA-1/ICAM-1 interaction contributing to T-cell activation and migration to target tissues.23 Based on in vitro studies, lifitegrast may also inhibit inflammatory cytokine secretion, although its exact mechanism of action in DED is not known.23

Data contributing to the FDA approval of lifitegrast were reported from 4 sequentially designed, 12-week studies that included 1067 patients who received lifitegrast 5% in a phase 2 dose-finding study and the phase 3 OPUS studies.24-26 The primary outcomes for the studies were day 84 status of inferior corneal staining score (ICSS) (phase 2; N=116), change from baseline in ICSS (signs) and the visual-related function subscale of a symptom scale (symptoms) (OPUS-1; N=588), change in ICSS and eye dryness score (EDS) from baseline (OPUS-2; N=718), and change in EDS from baseline (OPUS-3; N=711).24-26

The symptoms endpoint was not met in OPUS-1, which enrolled patients with mild to moderate DED.25 However, a post hoc analysis of the subgroup with more severe symptoms (EDS ≥40) at baseline and prior artificial tear use revealed improved EDS in the lifitegrast group compared with placebo.25

Based on OPUS-1 findings, OPUS-2 eligibility required moderate to severe baseline DED symptomatology.25,26 Although the symptoms primary endpoint was significantly reduced compared with placebo (P<.0001), the signs primary endpoint was not met (P=.6186). Post hoc analyses showed significantly greater EDS change from baseline at days 14 and 42 in the lifitegrast patients compared with placebo.25,26

OPUS-3 was undertaken to confirm the symptom improvement findings in OPUS-2 in additional patients with moderate to severe DED.24 The primary endpoint—EDS change from baseline to day 84—was again significantly improved in the lifitegrast group compared with placebo (P=.0007).24

In 5 clinical trials in which 1287 participants received at least 1 dose of lifitegrast 5%, the most common adverse reactions reported in 5% to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.23 The SONATA 1-year safety study included 220 lifitegrast and 111 placebo patients with DED.27 The primary outcome was percent and severity of treatment-emergent adverse events (TEAEs), with secondary ocular safety measures taken at 7 visits during the 360-day treatment interval. Ocular TEAEs were experienced by 52.6% and 34.2% of lifitegrast and placebo group subjects, respectively.27 Most were mild to moderate, and no serious ocular TEAEs were noted. Discontinuations due to TEAEs were 12.3% and 9.0%, respectively.27 The most common TEAEs were instillation site irritation (15.0% and 4.5%), instillation site reaction (13.2% and 1.8%), reduced visual acuity (11.4% and 6.3%), dysgeusia (16.4% and 1.8%), and dry eye (1.8% and 5.4%).27 The authors concluded that twice-daily lifitegrast was safe and well tolerated. The
safety profile was similar to that observed in the 12-week studies, with no unexpected TEAEs.27

Punctal Occlusion

Punctal occlusion with semipermanent silicone or collagen plugs is widely used to conserve tears. In patients with DED, punctal plugs may decrease the osmolarity of hyperosmolar tears and significantly relieve symptoms.28,29 However, punctal plugs may exacerbate symptoms in eyes with ocular surface inflammation; therefore, they should be used with caution in these patients.3,6

Many studies reported benefits of punctal plugs in the management of patients with DED.30 A review of 2499 patients from 27 qualifying studies determined that level II and III evidence supports that the plugs are well tolerated, improved signs, and resulted in a ≥50% improvement in symptoms of moderate dry eye that are not improved with topical lubrication.31 Epiphora occurred in 9% (range: 1.9% to 36.5%) of patients in 15 trials of punctal plugs. However, a Cochrane review of 18 poorly reported trials (711 participants; 1249 eyes) of collagen or silicone punctal plugs in symptomatic patients concluded that their benefits are inconclusive.32 The authors noted that although the plugs are considered to be relatively safe, there is a risk for epiphora.33,34 Inflammatory conditions, including dacrocytitis, were observed less frequently.3,6

Spectacle Side Shields/Moisture Chambers

Specialized moisture retention eyewear and moisture chambers provide a noninvasive means to treat evaporative dry eye.33,34 Although these may be poorly tolerated because of negative cosmetic effects, new designs of commercially available eyewear may be more acceptable.

Moisture Inserts

Hydroxypropyl cellulose delivered by a dissolvable insert on the ocular surface has been available for more than 30 years.4 However, this is not widely used due to discomfort and poor efficacy. A water-soluble, slow-release, preservative-free device is now available that is placed into the inferior cul-de-sac using a reusable applicator.35 The device dissolves over approximately 12 hours, thickening the precorneal tear film.35 It is indicated for patients with moderate to severe DED, particularly in those who remain symptomatic after an adequate trial of artificial tears.3,5 Once-daily treatment is recommended, although some patients may require twice-daily use. Several studies have supported the efficacy and safety of the insert.36 Patients should be provided with clear administration instructions.36

Secretagogues

Oral cholinergic agonists, including pilocarpine and cevimeline, stimulate salivary and lacrimal gland secretion by activating muscarinic acetylcholine.5 They are not indicated for treating DED, have significant systemic adverse effects, and do not have robust supporting evidence as an effective therapy for DED.5 A small, 12-week, single-center, randomized study of 57 patients with Sjogren syndrome with dry eye symptoms reported significant improvement with pilocarpine compared with artificial tears (P<.001).37 Objective tests revealed significant improvement in rose Bengal staining but not Schirmer test results.37

Two topical secretagogues from other drug classes are available in some countries outside the United States.38,39 Currently, there are no registered US studies of the P2Y2 receptor agonist diquafosol or the quinolinone derivative rebamipide.

Treatment of Filamentary Keratitis

Dry eye disease is the most common cause of filamentary keratitis, where strands of degenerated epithelial cells and mucus attach to the cornea.40 Resulting friction between the filaments and the eyelid can exacerbate the condition, which often becomes chronic and increasingly inflammatory.

Filamentary keratopathy can be treated by debriding the filaments with a cotton-tip applicator, dry cellulose sponge, or jeweler’s forceps.6 Off-label application of topical mucolytic agents, such as N-acetylcysteine 10% 4 times daily may also be effective. Because N-acetylcysteine is not available as an ophthalmic agent, it may be compounded for off-label use. It is also available as a 10% solution, which is indicated for nebulizer use in treating respiratory conditions with abnormal mucus secretion and as an antidote for acetaminophen overdose.41,42

Bandage contact lenses are another recommended treatment of filamentary keratitis. However, they can be poorly tolerated in cases of severe dry eye. Due to infection risk, contact lenses should be used with caution in patients with associated neurotrophic keratopathy.6

Autologous Serum

Autologous serum drops, which mimic the composition of natural tears, have been reported in some studies to improve symptoms and signs of several ocular surface disturbances, including DED, neurotrophic keratitis, persistent epithelial defects, Sjogren syndrome, and inflammatory conjunctivitis such as that associated with graft-versus-host disease.5,6,43 Drops are not commercially available and must be compounded, with associated technological and regulatory challenges.5,6,43 A 2017 updated
Cochrane review included 5 qualifying randomized controlled trials (92 participants) that compared autologous serum with artificial tears in patients with dry eye. The evidence was considered low or very low due to failure to report quantitative data for most outcomes and unclear or high risk of bias. Incomplete outcome reporting and heterogeneity among trials precluded performing a meta-analysis. The authors concluded that results were inconsistent regarding a potential benefit for autologous serum. It may be beneficial compared with artificial tears early in the treatment interval; however, they noted no evidence of an effect after 2 weeks. Conversely, a recent case series from a single center reported significant improvements in signs and symptoms of dry eye in 83 eyes of 47 patients treated with autologous serum for 9.8±15.5 months. Robust randomized controlled trials are warranted to further examine the potential benefit of autologous serum.

**Amniotic Membrane**

Use of amniotic membrane has a long history as an adjuvant for tissue healing. Cryopreserved amniotic membrane (CAM), available as a self-retaining biological corneal bandage that can be left in the eye for 29 days, has been shown to be effective in eyes with DED. The retrospective DREAM study examined the efficacy of CAM in 97 eyes of 84 patients with severe dry eye despite maximal medical treatments. The CAM were in place for 5.4±2.8 days (range: 2 to 11 days) and were removed from 4 eyes (4%) after 2 days due to intolerance. Improved ocular surface was noted in 88% of patients after removal. The dry eye severity score was reduced significantly from 3.25 at baseline to 1.44, 1.45, and 1.47 at 1 week, 1 month, and 3 months (all \( P<.001 \)). Ocular discomfort scores, visual symptom scores, corneal staining scores, and overall corneal signs scores were significantly improved at 3 months (all \( P<.001 \)). Patients continued to use their conventional treatments despite previous treatment failure. Prospective controlled studies are warranted.

Amniotic membrane extract is used in other fields and has recently become commercially available as an eye drop formulation (Figure 2). One commercial amniotic cytokine extract (ACE) eye drop formula comprises a solution of more than 120 active cytokines, growth factors, and anti-inflammatory molecules harvested from amniotic
tissue using a proprietary cryopreservation technique.\textsuperscript{45,48}

The product is covered under Section 361 of the Public Health Service Act and is not FDA regulated.\textsuperscript{45} Therefore, no clearance or premarket approval is required.

Outcomes using the ACE eye drops were examined in a retrospective chart review of 43 patients.\textsuperscript{48} Patients received 1 ACE drop twice daily for 4 weeks in the study eye, identified as the eye with the highest total corneal staining at baseline. Significant improvements were observed between baseline and week 4 in mean eye dryness score (68 vs 41), total corneal staining score (7.2 vs 3.2), and total conjunctival score (6.3 vs 5.1; all $P<.05$).\textsuperscript{48} Another retrospective chart review that included 45 patients who received ACE for 12 weeks also reported positive outcomes.\textsuperscript{49}

**Surgical Treatment for Dry Eye**

Limited tarsorrhaphy may be beneficial in patients with severe dry eye who have not responded to other therapies.\textsuperscript{6} Tear evaporation reduction, resulting from the decreased eye opening, may improve ocular surface homeostasis.\textsuperscript{50}

**SUMMARY**

The approach to treating DED is based on careful assessment of the etiology, signs, symptoms, and severity of the disease. The armamentarium is expanding, and clinicians should be aware of the indications, limitations, risks, and benefits of each treatment option. Before initiating treatment, exacerbating factors should be eliminated when possible. Lubricant eye drops, gels, and ointments are available as first-line therapies. Subsequent treatments are discussed in major reports from professional societies, which provide valuable management recommendations and guidance.

**CASE**

A 54-year-old woman with a long-standing history of rheumatoid arthritis is systemically stable on infliximab. Recently, she complained of decreased vision and severe foreign body sensation, saying it feels as if there are razor blades in her eyes. Eye examination reveals filaments (Figure 3).

Her deformed hands complicated her management of vials for accurately applying eye drops or self-applied inserts. She has no available assistance in the home. A trial of self-retained amniotic membrane was short- and unsuccessful. She self-administers bottled artificial tears approximately 10 times per day.

She was given a short course of compounded topical acetylcysteine 10\% for the filaments and loteprednol 0.5\% gel for the inflammation. She was able to use warm compresses and hypochlorous lid scrubs. She also was capable of using the multidose cyclosporine 0.05\% bottle. Other possible interventions included neurostimulation, moisture chamber, and amniotic extract drops. Other options discussed included bandage contact lenses and tarsorrhaphy.

At the visit, the patient’s filaments were removed with jeweler forceps, and she was seen 2 weeks later for follow-up. She felt better, which most likely was due to the manual removal of the filaments as well as the loteprednol therapy. She was tapered off the acetylcysteine 10\% over 6 weeks and the loteprednol over 3 months. Amniotic extract drops were added, and she has been maintained on the multidose cyclosporine, amniotic extract drops, warm compresses, and hypochlorous lid scrubs for 1 year.

**References**


Increasing research activity that focused on developing treatments for ocular surface disease (OSD) resulted in the US Food and Drug Administration (FDA) approval of topical cyclosporine in 2003 and lifitegrast in 2016.1 Encouragingly, industry involvement in dry eye disease (DED) research is increasing, with more than 20 companies sponsoring ongoing registered phase 1 through phase 3 DED studies in early 2019.2 Several agents with a spectrum of targets are also being investigated in preclinical studies.3 In recent decades, research established DED as a chronic inflammatory disease.1 However, current research and development activities are pursuing agents with noninflammatory mechanisms of action as well as those aimed at resolving inflammation.

**AutoLOGous Serum**

The initial report describing subjective and objective benefits using artificial tears made from 15 autologous serum donors to treat DED was published 35 years ago.4 Between 2015 and 2017, 11 basic research and 21 clinical studies were published on autologous serum and DED.5

The feasibility of using autologous serum is supported by the presence of many essential tear components in serum.6,7 Concentrations of each component are often variable between the 2 fluids—for example, serum contains considerably less lactoferrin and considerably more albumin compared with natural tears. Replacing deficient epidermal growth factor in eyes with an abnormal tear film may promote growth and migration of ocular epithelial cells, supporting corneal epithelial function and morphology. Most studies use 20% autologous serum to closer approximate the concentrations of substances that might not be beneficial at higher concentrations.6,7 Specifically, the high concentrations of transforming growth factor-β in serum may have antiproliferative effects that could suppress ocular surface epithelium healing.

Drops prepared from autologous serum are among available treatment options, starting with second-line therapy recommendations by the Cornea, External Disease, and Refractive Society and the Tear Film and Ocular Surface Society Dry Eye Workshop II and are a recommended treatment option for severe dry eye disease by the American Academy of Ophthalmology.8-10 Limitations to their expanded use include the paucity of evidence from robust randomized trials, challenges in the preparation and preservation of the product, and possible development of new therapies based on specific beneficial serum components.5,7 Some practitioners restrict the use of autologous serum to patients with inflammatory conjunctivitis, which is sometimes observed with Stevens-Johnson syndrome and graft-versus-host disease (GVHD).5,7

**Amniotic Membrane**

Amniotic membrane can be a beneficial adjunct for the patient with persistent epithelial defect or severe dry eye with chronic epitheliopathy. It can be used either as a cryopreserved membrane applied directly to the ocular surface as a temporary graft or a dehydrated graft held in place with a bandage contact lens.11 The fit of the contact lens is critical to the function and retention of the membrane.12 The cryopreserved membrane is indicated for treating inflamed or wounded tissue, whereas the dehydrated graft is approved for wound coverage only.13-15

**Cyclosporine: New Formulations**

**Compounded Preservative-free Cyclosporine 0.1%**

A nonpreserved compounded formulation of cyclosporine 0.1% is available.16,17 The cyclosporine is combined with several lubricants in a chondroitin sulfate emulsion, which may also provide benefits. The product is currently available as a 503(a) compounded drug. That is, clinicians cannot order a supply to keep in stock; rather, they must order it on an individual patient basis.18

**Nonaqueous Preservative-free Cyclosporine 0.1%**

The oil-based emulsions in cyclosporine formulations can be associated with retention time and tolerability issues. Clinical trials are underway, using a proprietary cyclosporine formulation without water, oils, surfactants, and preservatives.19 The technology is based on semifluorinated alkanes, producing a low-viscosity liquid that spreads rapidly over the ocular surface. With a refractive index similar to water, visual disturbances are decreased compared with oil-based formulations.19 In vivo and ex vivo studies have shown
greater local bioavailability compared with standard commercial cyclosporine formulations.

A phase 2 trial showed equivalent efficacy with commercial 0.05% cyclosporine. Improved DED signs with the nonaqueous formulation were observed starting at 2 weeks, which was earlier than the standard formulation. Several outcomes were significantly improved with the new formulation compared with both the vehicle and standard formulations. Symptom scores were similar for the 0.1% nonaqueous and 0.05% standard formulation.

The ESSENCE trial was a pivotal, phase 2/3, vehicle-controlled study of the new formulation in 328 patients at 9 US sites. The sponsor announced that positive topline results were obtained, and complete outcome data are expected in the near future.

Nanomicellar Cyclosporine 0.09%

A 0.09% cyclosporine formulation approved by the FDA in August 2018 is indicated to increase tear production in patients with dry eye. The cyclosporine is in a nanomicellar formulation that allows cyclosporine to overcome solubility challenges, achieving better penetration of the aqueous layer and preventing release of the active lipophilic molecule prior to penetration. In a 12-week, dose-ranging, phase 2/3 trial, both 0.05% and 0.09% doses met the conjunctival staining primary sign endpoint, whereas an approximate 30% decrease in global symptoms from baseline to day 84 was achieved in the 3 study arms, including placebo. Pivotal trial data from a total of 1048 patients with dry eye revealed that approximately 17% of treated patients achieved at least a 10-mm increase from baseline in Schirmer wetting, compared with approximately 9% of vehicle-treated controls.

Dry Eye Flare Treatment Strategy

Dry eye flare is being increasingly encountered by eye care professionals. A dry eye flare is a rapid-onset, inflammation-driven response to environmental triggers that typically cannot be adequately managed with artificial tears or other palliative treatments alone. Episodic flares are common, with approximately 80% of patients suffering from dry eye flares rather than continuous symptoms and experiencing 4 to 6 flares per year. Flares typically subside within a few days to weeks, followed by periods of few or no symptoms. Flares can occur in patients being treated with long-term anti-inflammatory therapies. These patients typically have more severe dry eye and experience more frequent flares than patients with less severe dry eye disease.

Mucus-penetrating Particle DED Drug Delivery

Although mucus performs an important role as part of innate defense mechanisms, it can impair ocular drug delivery. Theoretically, the outer mucin layer may trap and eliminate this foreign material and successfully remove the suspended drug from the ocular surface. Proprietary mucus-penetrating nanoparticles <500 nm, developed using excipients approved by the FDA for ophthalmic use, have been investigated for their ability to more effectively deliver loteprednol into ocular tissues by enhancing its penetration through the tear film mucous layer. The small size is necessary to effectively penetrate the mucin meshwork and overcome the adhesiveness of the ocular mucous layer. The investigational agent KPI-121 was shown in preclinical studies to produce approximately 3-fold higher peak concentrations of loteprednol in ocular tissue following administration of a 0.4% nanoparticle formulation compared with the 0.5% commercial formulation of loteprednol.

KPI-121 1% has been investigated as a twice-daily therapy for postoperative inflammation and pain after cataract surgery. In 2 phase 3 randomized controlled trials, the coprimary efficacy endpoints of complete resolution of ocular inflammation and pain at days 8 and 15 were achieved in significantly more KPI-121 patients compared with controls, and adverse events were reported more frequently in control subjects.

For treating DED, a phase 2 study and the phase 3 STRIDE 1 and 2 studies provided pivotal safety and efficacy data for the October 2018 FDA submission of KPI-121 0.25% for 4-times daily administration. The phase 3 STRIDE 3 study is ongoing, with an estimated completion date in late 2019.

Ocu300: Brimonidine 0.2% + Loteprednol 0.2% Nanoemulsion Combination

Development efforts are also repurposing brimonidine tartrate, an existing glaucoma therapy. Ocu300 is a novel ophthalmic preservative-free nanoemulsion formulation containing brimonidine tartrate, which is being investigated as a potential treatment for ocular GVHD under orphan drug status. After encouraging results in preclinical and early human studies suggesting that Ocu300 0.18% may relieve ocular GVHD signs and symptoms, an ongoing phase 3 study is targeting an enrollment of 60 participants, with completion anticipated in early 2020.

The nanoemulsion Ocu310, which is a combination of brimonidine 0.2% and loteprednol 0.2%, is also being studied for the treatment of DED. The sponsor announced that positive results were obtained in a
28 days. The primary endpoints were change from baseline in corneal fluorescein staining score and ocular discomfort at day 29. However, several secondary endpoints were significantly different in RGN-259 compared with placebo group subjects. The single-center study failed to observe a significant difference between treatment and control groups for the primary efficacy endpoints of ocular discomfort scores and inferior corneal staining at day 29. However, several secondary endpoints were significantly different in RGN-259 compared with placebo group subjects.

In the ARISE 1 phase 2b/3 study completed in 2016, 317 subjects with dry eye were randomized to receive RGN-259 0.05% or 0.1% or placebo 4 times daily for 30 days. The primary endpoints were change from pre-to post-controlled adverse environment in total corneal fluorescein staining score and ocular discomfort score at day 29. Ocular discomfort after controlled adverse environment exposure was significantly improved in both RGN-259 groups compared with the placebo group in a dose-dependent manner. Corneal staining was also significantly improved in both treatment groups compared with placebo.

Safety data from ARISE 1 and the phase 3 ARISE 2, which enrolled 601 subjects and was completed in early 2018, were accepted by the FDA; however, an additional phase 3 trial was required to demonstrate efficacy. The sponsor announced that the study was initiated in February 2019, targeting an enrollment of 700 patients, with completion expected in mid-2020.

Cenegermin: Approval for Topical Treatment of Neurotrophic Keratitis

Neurotrophic keratopathy is a rare disease with orphan status, reported to be associated with many systemic conditions, including herpes virus and diabetes mellitus, as well as ocular conditions, including surgery and use of preserved medications. Historically, treatments with traditional OSD therapies provided nonspecific and often temporary relief. Recently, several new treatments have been investigated, with times to healing ranging from 16 to 61 days and rate of complete healing from 33% to 100%. Nerve growth factor, which is involved in the differentiation and maintenance of neurons to support corneal innervation and integrity, was one of the potential therapeutic agents.

The recombinant human nerve growth factor cenege
ermin is a first-in-class agent that was approved by the FDA to treat neurotrophic keratitis in 2018. Pivotal data supporting its approval were acquired in 2 randomized controlled trials that enrolled 151 patients with neurotrophic keratitis, with treatment applied 6 times daily for 8 weeks. Complete corneal healing was achieved by 65.2% and 16.7% of cenege
ermin and vehicle participants, respectively, in study 0214 and 72.0% and 33.3%, respectively, in study 0212 (P<.01 for both comparisons). In the 2 studies, recurrences after 8 weeks occurred in 14% and 20% of patients, respectively, who achieved healed corneas.

Punctal Plug Delivery System

The use of punctal plugs as a delivery system offers an opportunity to target sustained treatment over weeks or months with several drugs. Development challenges include avoiding eye irritation, excessive tearing, ocular discomfort, and loss of the plug. The devices being developed typically have a drug core that diffuses from a cross-section that is in contact with tears. Their potential for delivering treatments for DED is under development but has not yet been explored in clinical trials.

Glucoma Studies

A latanoprost-releasing plug, designed to provide unidirectional drug flow into the tear film, was reported by the manufacturer to successfully reduce intraocular pressure (IOP) in phase 2 studies at 3 months, with excellent retention. Ten of the 11 completed phase 2 studies investigated the latanoprost-releasing device. The most recent study, completed in December 2018, investigated a nepafenac punctal plug delivery system in 63 post-cataract surgery participants.

Studies are also investigating drug release into the subpunctal canalicula. OTX-TP is a biodegradable intracanalicular implant designed to release preservative-free travoprost for 3 months. A feasibility study of 17 patients with 26 devices showed that IOP reductions from baseline at days 10 and 30 were 24% and 16%, respectively. All plugs were present at 10 days, but
retention had declined to 42% at day 30. The sponsor announced positive results and greater retention at 75 days in phase 2 studies.

**Sustained DED Ocular Drug Delivery**

In December 2018 the FDA approved OTX-DP, a resorbable intracanalicular device that elutes 0.4 mg of dexamethasone for up to 30 days following insertion into the canaliculus for treating ocular pain after ophthalmic surgery. The manufacturer announced that a supplemental new drug application was submitted in January 2019 to extend the indication to treat ocular inflammation following ophthalmic surgery.

The device was also used to treat allergic conjunctivitis in 2 phase 3 studies. A 2016 conference report on a study that enrolled 73 subjects concluded that the device was efficacious and well tolerated. Subsequent reports have not been published. In 2015, the company announced promising topline results from a phase 2 exploratory trial of 43 patients with dry eye. However, the current development status for this indication is not clear.

**Sustained Glaucoma Ocular Drug Delivery**

An ocular insert that provides topical bimatoprost has been studied in patients with open-angle glaucoma and ocular hypertension (Figure 1). A phase 2, multicenter, noninferiority trial of 130 patients compared the active insert plus artificial tears with a placebo insert plus timolol twice daily for 6 months. A clinically relevant reduction in IOP was observed over the 6-month treatment interval, although noninferiority with timolol was met at only 2 of 9 time points. The authors concluded that the insert was safe and well tolerated and may provide an alternative to daily drops to improve adherence and delivery consistency. Studies of DED have not been reported, but other applications of the ring platform for delivering drugs to treat DED, ocular allergy, and postoperative inflammation were noted in the report as being under development.

**Intranasal Neurostimulation to Increase Tear Production**

A small study showed that nasal mucosal anesthesia was associated with a significant decrease in tear production. Subsequent development of an intranasal neurostimulator led to marketing authorization by the FDA in 2017. Two pivotal trials of subjects with aqueous-deficient dry eye included a 1-day crossover study (study 1; N=48) and a single-arm, 180-day, prospective, open-label cohort (study 2; N=89). During the single study 1 visit, participants applied the device intranasally (active application), to nasal skin outside the nares (active control), and sham intranasal stimulation (inactive control). The primary endpoint for study 1 was difference in Schirmer scores during device application compared with 2 control applications. Subjects in study 2 were to use the intranasal tear neurostimulator between 2 and 10 times daily and not exceeding 3 minutes per use. The primary endpoint for study 2 was the acute stimulated tear production at day 180, as measured by the difference between Schirmer test scores during and before stimulation.

In study 1, mean Schirmer scores in the study eye were significantly greater during active intranasal stimulation (25.3 mm) compared with active extranasal (9.5 mm) and sham intranasal stimulation (9.2 mm) application ($P<.0001$ for both comparisons). Similar results were observed in 35 qualifying fellow eyes; that is, eyes that met all inclusion criteria but had less severe dry eye than the study eye.

At day 180, the mean Schirmer score in the study eye was significantly higher during stimulation compared with the unstimulated eye (17.3 vs 9.4 mm; $P<.0001$). Qualifying fellow eyes achieved similar increases in tear production.

A small, randomized, controlled trial was performed in 10 subjects with dry eye and in 5 subjects without signs or symptoms of tear dysfunction to explore the hypothesis that the intranasal tear neurostimulator may stimulate conjunctival goblet cell degranulation and
mucus secretion. After a screening visit, participants were seen for 2 additional visits to perform extranasal and intranasal tear neurostimulator application in randomized order. Anterior segment optical coherence tomography was performed before and immediately after the 3-minute application, and periodic acid–Schiff staining and MUC5AC immunostaining was performed on impression cytology samples obtained from the temporal and inferior bulbar conjunctiva. Preliminary results indicated that intranasal tear neurostimulation induced conjunctival goblet cell degranulation and mucin secretion.

**Lid Margin Disease Management: Thermal Pulsation**

Vectored thermal pulsation treatment aims to simultaneously evacuate the contents of both the upper and lower meibomian glands during a single treatment. Successful use of a device that received FDA clearance in 2011 has been reported in several studies. Recently, its effectiveness as a single treatment was examined in a small pilot study that enrolled 55 soft contact lens wearers with meibomian gland dysfunction (MGD) and evaporative dry eye. Primary effectiveness outcomes were meibomian gland secretion and SPEED (Standard Patient Evaluation of Eye Dryness) scores. The mean change between baseline and 3 months was significant in both efficacy outcomes ($P<.0001$ for both comparisons), with significantly greater improvement in exploratory variables relative to controls. Mean comfortable contact lens wearing time in the treatment group increased 4.0±3.9 hours at 1 month and was sustained at 3 months, with no change observed in the control group. Another randomized controlled trial compared a 12-minute bilateral vectored thermal pulsation procedure with a 3-month course of oral doxycycline in 28 subjects with dry eye symptoms and evidence of MGD. Vectored thermal pulsation was significantly more effective than doxycycline for improving dry eye symptoms and was similar in effectiveness for improving meibomian gland function and associated signs of MGD.

**Lid Margin Disease Management: Intense Pulsed Light**

Intense pulsed light has received widespread use in treating diseases involving facial sebaceous glands and may be more efficient and effective for treating MGD than many routine procedures. Its mechanism is not clear, but it has been hypothesized to be related to a photothermal effect, decreased inflammation, and stimulation of meibomian gland activity. A recent prospective case series included 62 eyes of 31 patients with refractory obstructive MGD. Eligibility criteria included failure of ≥3 standard MGD therapies or objective findings for at least 1 year before study enrollment. Patients underwent 4 to 8 intense pulsed light treatments combined with meibomian gland expression at 3-week intervals. Dry eye symptoms and signs and MGD assessments were significantly improved, except for meiboscore and Schirmer test value.

**Microblepharoexfoliation**

The organized aggregate of microorganisms residing in an extracellular polymeric matrix, or biofilm, is estimated to be associated with approximately one-third of bacterial infections. Bacterial biofilm plays an important role in the pathogenesis of MGD, beginning with its contribution to meibomian gland obstruction. Altered meibum combined with biofilm, often called meibofilm, provides a source of virulence factors and subsequent inflammation as the disease progresses.

Microblepharoexfoliation is an in-office procedure that may unclog meibomian gland orifices. The commercially available device comprises a hand-held unit that spins a disposable microspatula to provide lid margin debridement and exfoliation. The device may be beneficial in removing harmful bacterial biofilms from the eyelids. A randomized controlled trial that compared tea tree wash with commercial lid scrub and lid scrub plus microblepharoexfoliation in 86 subjects with *Demodex* infestation reported similar outcomes in the 3 groups for *Demodex* reduction and symptom improvement.

**Summary**

Considerable advancements are being made in available treatments for ocular surface disease. Recent FDA approvals primarily provide novel delivery systems and devices for existing agents, whereas the recent approval of cenegermin for treating neurotrophic keratitis marks the first approval of a topical ophthalmic biologic medication. In-office procedures supplement the options that clinicians can consider as part of their armamentarium. Research exploring new and improved treatments continues, with many agents under FDA review and in late stages of clinical development.

**Case Presentation**

A 44-year-old woman complains of severe dry eyes that started acutely about 1 year ago (Figure 2). She also has difficulty exercising due to chronic fatigue and aching knees and hips that started shortly before the dry eye symptoms. She complains of dry mouth and thirst. She is emmetropic and never needed vision correction. She has trouble seeing the computer monitor, especially late in the day, when her vision is blurry.
Numerous artificial tears and a short course of topical cyclosporine provided relief of the patient’s symptoms.

Her examination results (Table) warrant a suspicion of Sjogren syndrome. Subsequent tests for Sjogren syndrome A and Sjogren syndrome B antibodies were positive. She was educated about Sjogren syndrome and referred to a rheumatologist for systemic workup and possible systemic therapy. She was also referred to a dentist who had experience managing patients with Sjogren syndrome.

Aggressive treatment was indicated, starting with loteprednol 0.5% 4 times daily, lifitrigast twice daily, and nonpreserved artificial tears. Symptom persistence was followed by insertion of a punctal plug.

If she does not respond to this therapy, a trial of autologous serum drops and intranasal neurostimulation treatment would be recommended. Referral to a rheumatologist for the initiation of disease-modifying antirheumatic drugs should be considered, as they help to slow or stop Sjogren syndrome from getting worse.

In addition to signs and symptoms of dry eye and dry mouth, Sjogren syndrome also presents with salivary gland enlargement and dental caries. Inflammatory mononuclear infiltrates involving the lacrimal and salivary glands lead to glandular destruction and dysfunction. Sjogren syndrome has a 10-fold greater prevalence in women than men and is diagnosed most commonly in the fifth to sixth decade of life.

Sjogren syndrome is not associated with an increase in overall mortality. It can coexist with a variety of other connective tissue diseases (secondary Sjogren syndrome) or exist without a definable connective tissue disease (primary Sjogren syndrome).

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