CME MONOGRAPH

Current Opinions and Modern Approaches in the Diagnosis and Treatment of DRY EYE DISEASE

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This continuing medical education (CME) activity captures content from an expert roundtable discussion held on January 17, 2017, in Koloa, Hawaii.

ACTIVITY DESCRIPTION

Population studies have estimated the prevalence of dry eye disease (DED) in the United States to range between 5% and 35%, depending on the severity of symptoms. Understanding of the pathophysiology has provided a foundation for developments in diagnostic modalities and therapies. The purpose of this activity is to update ophthalmologists on the role of inflammation in the pathophysiology of DED and new diagnosis and new treatment options.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, ophthalmologists will be better able to:

- Diagnose dry eye disease using at least 1 objective test, regardless of symptom severity
- Describe the implications of inflammation in dry eye disease on diagnosis and treatment approaches
- Describe clinically relevant results from clinical trials assessing anti-inflammatory drugs for the treatment of DED
- Select appropriate DED treatment based on individual patient characteristics and an appropriate approach

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Current Opinions and Modern Approaches in the Diagnosis and Treatment of DRY EYE DISEASE

Introduction

The prevalence of dry eye disease (DED) is on the rise. This is due to many factors, including better diagnostics, greater awareness of the disease and its effect on our patients' quality of life, and the modern lifestyle that includes far greater time spent staring at device screens than ever before. New diagnostic and therapeutic tools assist us in dealing with this large and growing problem. In this educational activity, we will provide an update on the pathophysiology of DED, review our current array of tests, discuss new therapies for our patients with DED, and present a series of case studies to illustrate our approach to DED in 2017.

—Kenneth A. Beckman, MD

Epidemiology

Population studies have estimated the prevalence of DED in the United States to range between 5% and 35%, depending on the severity of symptoms. Studies evaluating severe DED symptoms report prevalence in the range of 4.3% to 7.8%[1,2] for men and women aged 49 years and older, whereas studies with less strict case definitions report values in the range of 14.4% to 14.6% in US adults.[3,4] Numerous risk factors for DED are known **(Table 1).**[5] Of these, the most common are aging and female sex. Several aging changes predispose to DED, including a general reduction in corneal sensation leading to decreased blink rate and tear film instability, as well as a reduction in androgen hormones. The latter is particularly important in postmenopausal women, in that it may account in part for the higher prevalence of DED in older women. Other risk factors include environmental stressors such as contact lens wear, wind, pollution, and low humidity; corneal surgery such as LASIK (laser-assisted in situ keratomileusis); autoimmune conditions such as Sjögren syndrome; and the use of some medications. Among the medications that can increase the risk of DED are antihypertensives, anticholinergics, antihistamines, and antidepressants. Concurrent ocular conditions, such as meibomian gland dysfunction (MGD)[6] and blepharitis,[7] can also predispose to DED.

Table 1. Risk Factors for Dry Eye[5]

Level of Evidence		
Mostly Consistent*	**Suggestive†**	**Unclear‡**
Older age	Asian race	Cigarette smoking
Female sex	Medications	Hispanic ethnicity
Postmenopausal estrogen therapy	Tricyclic antidepressants	
Omega-3 and Omega-6 fatty acids imbalance	Selective serotonin reuptake inhibitors	Anti-cholinergics
Medications	Diuretics	Anxiolytics
Antihistamines	Beta-blockers	Antipsychotics
Connective tissue disease	Diabetes mellitus	Alcohol
LASIK and refractive excimer laser surgery	HIV/HTLV1 infection	Menopause
Radiation therapy	Systemic chemotherapy	Botulinum toxin injection
Hematopoietic stem cell transplantation	Large incision ECCE and penetrating keratoplasty	
	Isotretinoin	Acne
Vitamin A deficiency	Low humidity environments	Gout
Hepatitis C infection	Sarcoidosis	Oral contraceptives
Androgen deficiency	Ovarian dysfunction	Pregnancy

* Mostly consistent evidence implies the existence of at least 1 adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data

† Suggestive evidence implies the existence of either: 1) inconclusive information from peer-reviewed publications or 2) inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal

‡ Unclear evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale

Abbreviations: ECCE, extracapsular cataract extraction; HIV/HTLV1, human immunodeficiency virus/human T-cell lymphotropic virus type 1; LASIK, laser-assisted in situ keratomileusis.

Dr Beckman: Historically, DED has been considered to be largely a disease of older women. How has the face of DED changed over time?

Dr McDonald: In my experience, more and more younger people—even college students—are presenting with DED. This is likely related to their use of smart devices—from computer screens to tablets to phones. A recent meta-analysis found that 50% of working-aged people whose job necessitates use of video display terminals report symptoms of DED.[8]

Dr Beckman: I have seen this trend as well. Young people are spending more time staring at screens, which reduces blink rate and predisposes to DED. Other contributing factors in this age group include long study sessions, staying up late, drinking coffee, and contact lens overwear. Together, these factors stress the ocular surface and increase the risk of triggering DED.

Dr O'Brien: While women are statistically more likely than men to be affected by DED, the gender gap is closing, especially among younger patients, in that working men and women may be equally affected in terms of reading speed and lowered productivity in the workplace. In addition to the personal suffering, this loss of productivity exerts considerable economic costs and a significant financial burden.

Update on Pathophysiology of Dry Eye Disease
–Mark S. Milner, MD, FACS

Over the past 20 years, our understanding of DED has changed in 4 important ways. First, we know now that DED is an inflammatory process. In both animal models[9] and human DED,[10] the lacrimal gland and the conjunctiva are infiltrated with T-lymphocytes. Second, DED is no longer considered a static condition, but may be a chronic, progressive disease[11] that can ultimately lead to damage to the ocular surface. Third, we have therapies today that go beyond supportive care to treat the underlying causes of DED.[11] And fourth, we now view DED as not just an abnormal *quantity* of tears, but also as an abnormal *quality* to the tear film.

Any of the 3 layers of the tear film—the lipid layer arising from the meibomian glands, the aqueous layer from the lacrimal and accessory lacrimal glands, or the mucin layer from the conjunctival goblet cells—can become impaired and lead to DED. Together, these 3 layers form an aqueous mucin gel, a complex mixture of proteins, mucin, and electrolytes. The proteins include antimicrobial factors such as lysozyme and lactoferrin, as well as growth factors, inflammation suppression factors, and immunoglobulins. Mucins such as the soluble 5AC mucins provide viscosity to tears, and electrolytes ensure the proper osmosis for optimal tear function.[12]

In the dry eye, this balance of tear components is detrimentally altered.[13-15] Altered cytokine levels may promote inflammation while reduced growth factor levels and protease activation may impair the healing processes of the ocular surface. Loss of goblet cells will reduce levels of soluble mucin 5AC to adversely affect tear viscosity, whereas increased concentrations of electrolytes will raise tear osmolarity and promote desiccation and death of ocular surface cells. Ocular surface damage then becomes cyclical **(Figure 1)**[16]: desiccation stresses the ocular surface and concentrates the tear film, which increases osmolarity and leads to release of cytokines such as interleukin-6, tumor necrosis factor alpha, interleukin-1, and matrix metalloproteinases (MMPs) that can further promote cell damage and hyperosmolarity. These inflammatory factors activate antigen-presenting cells, which migrate into the lymphatic system and recruit T-lymphocytes to the ocular surface, promoting further cytokine release and propagation of the inflammatory response.

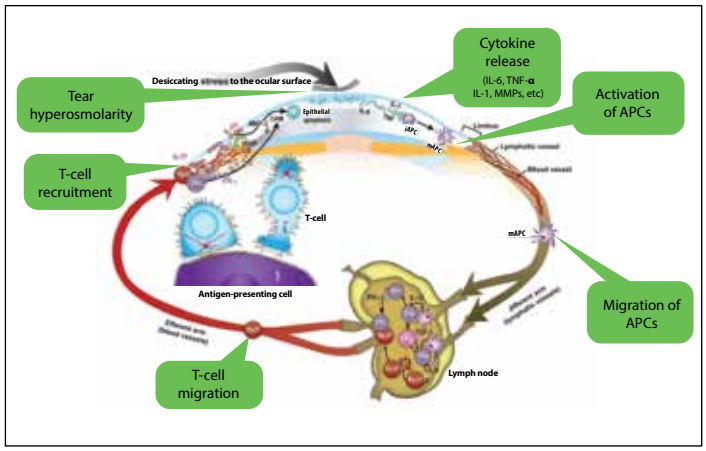

Figure 1. Cyclical nature of ocular surface inflammation in dry eye disease

Abbreviations: APC, antigen-presenting cell; CAM, cell-adhesion molecule; iAPC, immature antigen-presenting cell; IFN, interferon; IL, interleukin; mAPC, mature antigen-presenting cell; MMP, matrix metalloproteinase; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

If left uninterrupted, this cyclic process can lead to worsening DED and, consequently, ocular surface damage. As we understand the inflammatory nature of DED, our treatments have evolved from supportive therapies such as artificial tears to more targeted therapies such as cyclosporine A and lifitegrast, both of which inhibit T-lymphocyte activation through different mechanisms with the common goal of breaking the inflammatory cycle.

What triggers the inflammatory cycle that leads to DED? The risk factors associated with DED have been illustrated above. The interaction of these risk factors and the various mechanisms that contribute to the inflammatory cycle in DED is illustrated in **Figure 2.**

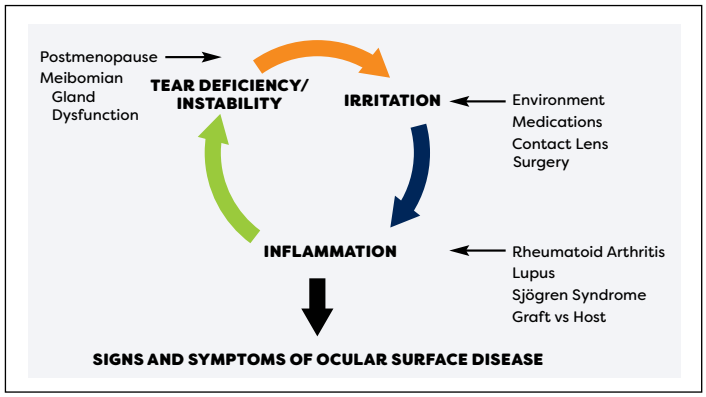

Figure 2. A schematic diagram depicting the interaction and cycle of disease triggers and the various mechanisms of DED

Dr Beckman: How has our appreciation for the inflammatory basis of DED changed our approach to patients with this disease?

Dr O'Brien: There was a time when **"dry eye"** was just that, and ***inflammation*** was the "Emperor's New Clothes"—something we anticipated with great fanfare, but often that which we could not readily identify by conventional examination. Inflammation is no longer a fairy tale in DED, but rather the rule, not the exception. This fundamental awareness has totally changed our entire approach to both diagnosis and therapy.

Dr Matossian: I find it helpful to educate patients on the inflammatory nature of DED. I tell them this is a chronic disease with many different contributing factors. I reinforce to my patients that we are not going to make it better overnight, nor will we be able to cure it. Knowing this helps our patients better understand why the treatment course will be chronic and, potentially, even lifelong.

Dr Beckman: Are there systemic ramifications to inflammation in patients with DED?

Dr McDonald: Many of our patients with DED have other systemic issues that need to be addressed. One example is the perimenopausal woman who presents with DED. She often does not make the connection that her DED is arising in part because of her changing hormone profile. These patients can often benefit from consultation with their gynecologist or an endocrinologist. Our patients with DED associated with Sjögren syndrome clearly have systemic inflammation that can manifest with oral issues such as gum recession, cavities, and halitosis. These were issues we did not consider when we viewed DED as a disease of senescence rather than one of inflammation.

Dr Beckman: As we have become more aware of the inflammatory nature of DED, what effect has it had on our therapeutic approach to the disease?

Dr Wu: Years ago, the first steps in the treatment of mild-to-moderate DED were artificial tear supplementation and punctal plugs. I currently initiate anti-inflammatory therapy much earlier in the clinical management of DED. Also, I use punctal plugs less often, and not as early in the clinical course as I used to.

Table 2. Conditions That Can Mimic Dry Eye Disease[17]

Superior limbic keratoconjunctivitis
Medicamentosa (topical medication toxicity)
Superficial punctate keratitis of Thygeson
Mucus fishing syndrome
Contact lens-related toxicity
Chemical toxicity (eg, hairspray toxicity)
Allergic/Atopic conjunctivitis
Conjunctivochalasis
Floppy lid syndrome
Lagophthalmos, with subsequent exposure keratitis

Dr Milner: A number of unrelated conditions can mimic DED and should be considered when the presentation is atypical for DED or is recalcitrant to DED therapies **(Table 2).**[17] Diagnostic testing can aid in determining which of these types of DED we are dealing with in each individual patient.

New Diagnostic Tools
–Marguerite B. McDonald, MD, FACS

Diagnostic testing for DED focuses on identifying the damage, or the factors causing the damage, arising from the known pathophysiology of the disease. Testing can also identify the underlying factors contributing to DED in each individual patient. There are many tests, each of which provides additive information to help piece together the complex pathophysiology of the disease on a patient-by-patient basis.

Osmolarity. One key aspect of DED pathophysiology is tear film hyperosmolarity. This is the central pathophysiologic mechanism for all forms of DED. Hyperosmolarity causes inflammation and apoptosis of ocular surface cells; this leads to a breakdown of homeostatic control, causing tear film instability, and reduces the ability of mucins to lubricate the ocular surface.[18]

Tear film hyperosmolarity is a global marker of DED, indicating a concentrated tear film. Hyperosmolarity has been added to the definition of DED,[18] and when above 316 mOsm/L, has been shown to have a higher predictive value for diagnosing DED than Schirmer, lactoferrin assay, or rose bengal staining.[19]

As a result of studies in the peer-reviewed literature, dry eyes are said to have either a higher than normal (300 mOsm/L) tear osmolarity or a difference between the 2 eyes of greater than 8 mOsm/L.[20,21] What accounts for this? Healthy eyes have great reserve; the osmolarity does not change, even when the patient is confronted with the many challenges and conditions of modern life. They can take an oral decongestant, drink a glass or 2 of wine, sit outside for hours at a windy football game, work on their computers all day in offices with forced air heating and cooling, and their osmolarity readings are stable and virtually identical in both eyes. Dry eyes have little or no reserve. When confronted with these situations, they decompensate immediately. Their already elevated osmolarity swings wildly, up and down; the 2 eyes no longer have stable and virtually identical osmolarity scores that are within the normal range. That is why dry eye manifests itself with either a higher than normal (300 mOsm/L) tear osmolarity or a difference between the 2 eyes of greater than 8 mOsm/L.

Tear film osmolarity can be easily and noninvasively measured in the office. The only system available for commercial use, TearLab, is a nanofluidics platform using electrochemical detection methodology. The sample volume is 50 nL, the sampling time is 1 second, and results are available in 10 seconds after the handpiece is docked in its station. The device's manufacturer conducted a study demonstrating that a cutoff value of 308 mOsm/L provided 88% specificity and 75% sensitivity in detecting mild-to-moderate DED and 95% sensitivity in detecting severe DED.[22]

MMP-9. Matrix metalloproteinases are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface. Of these, MMP-9 is a nonspecific inflammatory marker. The concentration of MMP-9 in tears becomes elevated in DED. MMP-9 levels correlate with clinical examination findings.[23]

Tear MMP-9 levels can also be measured in the clinic setting using the InflammaDry handheld testing device. The test can be administered by a technician or nurse, and results are available within 10 minutes. Several studies have demonstrated the clinical use of this point-of-care test.[24,25]

Lactoferrin. Lactoferrin is a glycoprotein secreted by the lacrimal gland that plays an important role in regulating ocular surface cell growth, and because it is bacteriostatic, defends against infections.[26] Low tear lactoferrin levels can be a sign of lacrimal gland dysfunction, particularly in those with DED related to Sjögren syndrome.[27]

Conjunctival cell impression cytology. Sampling conjunctival cells for biomarkers of inflammation is a relatively invasive procedure. A new device—EYEPRIM—produces RNA samples comparable to those obtained with traditional impression cytology that are adequate for analysis of inflammatory biomarkers,[28] without the need for topical anesthesia.

Serum biomarkers. Novel early biomarkers for Sjögren syndrome have been identified, including salivary protein-1 (SP-1), carbonic anhydrase (CA-6), and parotid secretory protein (P-SP).[29] These biomarkers are expressed earlier in the disease and have higher sensitivity and specificity than the more traditional biomarkers Ro or La. With earlier detection, there is a better opportunity to prevent complications of Sjögren, such as xerostomia, pulmonary fibrosis, and non-Hodgkin lymphoma.

Lipid layer interferometry. Commercial systems can now provide quantitative and qualitative measures of lipid layer thickness (LLT). The LipiView instrument has documented that LLT values ≤ 60 nm yield a 90% specificity for MGD.[30]

The Keratograph 5M also uses interferometry to measure the thickness of the lipid layer of the tear film[31] using an observable field of 9 mm.

Meibomography. The LipiView, LipiScan, and the Keratograph 5M devices also provide meibomography to visualize gland architecture and reveal pathology such as duct dilation, gland constipation, atrophy, and dropout[32,33] **(Figure 3).**

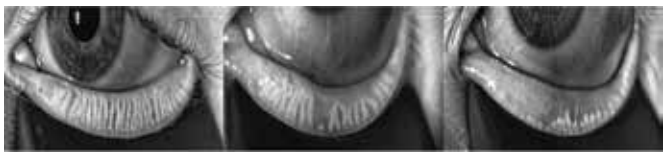

Figure 3. Meibomography with the LipiScan instrument. Early (left), moderate (center), and severe (right) meibomian gland dysfunction. Note the progressive loss of ducts as the disease worsens.

Image Courtesy of Marguerite B. McDonald, MD, FACS

Tear volume. Optical coherence tomography can measure several aspects of tear quantification, including tear meniscus height (TMH), area and volume, as well as the true precorneal tear film thickness. Low TMH values can provide sensitivity of 92% and specificity of 90% for the detection of DED,[34] and values correlate strongly with symptoms.[35]

Tear break-up time (TBUT). Tear break-up time has long been an important metric in the evaluation of DED. An automated measure of noninvasive keratography break-up time (NIKBUT) is now available with the Keratograph 5M.[33]

The result of all the DED tests performed by the Keratograph 5M can be aggregated into the JENVIS Dry Eye Report **(Figure 4).** In this graphical representation of testing data, the shape of the blue hexagon indicates the nature of DED responsible for each individual patient's ocular surface status. These tests include the automated NIKBUT, meibography, the Dry Eye Ocular Surface Disease Index questionnaire, tear meniscus height, LIPCOF (lid parallel conjunctival folds) score, and ocular redness and limbal redness (ciliary flush) scores. The Keratograph 5M also has a Placido-based topographer and the OxiMap for visualizing oxygen permeability, so that a patient with dry eye can be fit with the contact lens that allows for the best oxygen supply to the cornea.[33]

Dr Beckman: With so many new tests to complement our standard tests of the ocular surface—including Schirmer, dye staining, and manual TBUT—what is the optimal workup for a patient with dry eye today?

Dr Matossian: It would be great to perform a full battery of all these tests to more accurately characterize our patients with dry eye, but that is impractical and often unnecessary.

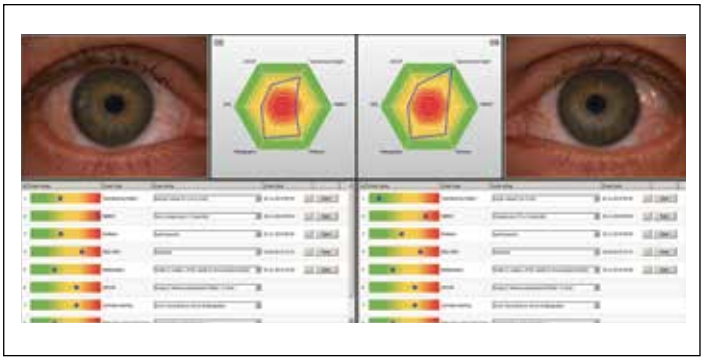

Figure 4. The JENVIS Dry Eye Report summarizing all DED testing from the Keratograph 5M. Values are depicted in green (normal), yellow (borderline), or red (abnormal) zones.

Image Courtesy of Marguerite B. McDonald, MD, FACS

I generally start with a few tests, and the results of these—coupled with the patient's specific history—will guide my further workup. First is tear osmolarity and MMP-9 testing; second is lissamine green staining. I look at the staining pattern of the lid margin and conjunctiva as well as the cornea. Third is meibomography, wherein I focus on the extent of dropout.

Dr Wu: I perform TBUT at the slit lamp after assessing staining patterns. Then I express the meibomian glands with a cotton-tipped applicator to qualitatively assess the consistency of the secretions. If the meibomian gland status appears abnormal, I will obtain meibomography. I do not often do Schirmer testing unless I suspect Sjögren syndrome or autoimmune disease.

Dr McDonald: I agree. I usually perform Schirmer testing only to document epiphora before referring patients to the oculoplastics service or if a study protocol requires it. I do not use it routinely to diagnose dry eye.

Dr Matossian: I have stopped using the Schirmer test routinely.

Dr Beckman: I typically do Schirmer testing once early in the care process to estimate aqueous production. It may help guide my decision to use punctal plugs if I see a low Schirmer result. Otherwise I do not use it routinely.

Dr Milner: I seem to be in the minority of people who still use Schirmer testing routinely. I tend to treat dry eye more according to its underlying cause than its severity. I find that the Schirmer test without anesthesia can be very helpful in distinguishing between aqueous deficiency and evaporative loss as the underlying cause of DED.

Dr Luchs: One of the most important pieces of data that I consider when evaluating dry eye is the patient's clinical history. I have instructed my staff regarding how to take the

history, including soliciting symptoms of DED. Too many of our patients fail to report the classic symptoms—fluctuating vision and sensations of dryness, grittiness, stinging, burning—because they assume those sensations are a normal part of aging. As for diagnostic tests, I test osmolarity routinely. The test is quick and easy to perform.

Dr O'Brien: It is always important to listen to our patients. In DED, moreover, we have to remain aware of the well-documented disconnect between symptoms and signs.[36,37] Validated questionnaires can assist with uncovering symptoms and assessing their severity. As for the examination, I think that a minimum evaluation should include measurement of TBUT with fluorescein to assess tear film instability, grading the severity of ocular surface cellular damage using lissamine green or fluorescein staining, as well as an assessment of tear volume/production with Schirmer testing (I prefer Schirmer I) or anterior segment optical coherence tomography. This information can help classify the DED as aqueous deficient or evaporative, grade severity, and guide management.

Dr McDonald: For the comprehensive ophthalmologist reading this and considering the wide array of tests available, I recommend a simple approach. Start with a good history, then tear osmolarity, because hyperosmolarity is the central pathway by which all ocular surface damage occurs in DED. Testing for osmolarity must be performed early in the examination, before the ocular surface is disturbed. I usually assess MMP-9 at this point as well, especially if the patient has complaints that suggest dry eye, but his or her osmolarity is normal. Then I assess staining with both lissamine and fluorescein. These tests are easy to administer, inexpensive, and will identify most patients with DED. The next level of evaluation would be meibomography to assess the status of the meibomian glands and to look for dropout.

Dr Matossian: I find MMP-9 testing helpful. When the result is positive, I tend to treat more aggressively than if it was negative. One word of caution when introducing tear osmolarity testing into your practice: Staff training is critically important; so is equipment calibration. MMP-9 testing is easy to perform once technicians are trained. Interpretation of the tear osmolarity data can be confusing initially, considering osmolarity fluctuates in hyperosmolar patients. I find trends over time are more informative than isolated readings.

New Treatment Options
–Jodi Luchs, MD

Not so long ago, we considered DED to be a disease primarily of decreased tear production, and our therapies—artificial tears and punctal plugs—aimed to replace or enhance the volume of existing tears. We did not fully appreciate the significance of inflammation in the DED disease process. We tended to reserve anti-inflammatory drugs such as topical steroids for patients with more severe disease. In retrospect, the patients with more severe disease likely would have benefitted from anti-inflammatory therapy much earlier in their disease course. The damage they have suffered to their lacrimal gland and to their ocular surface may have been preventable had the inflammatory cycle been broken earlier in the clinical course.[11]

We know now that DED is not simply a condition of the tear film in isolation, but that it has a complex pathophysiology that offers several potential therapeutic targets and presents in several clinical scenarios. Our goals in therapy are to identify the underlying causes of dry eye in each of our patients and to select therapies that target those specific causes.

Cyclosporine A was FDA approved for the treatment of DED 15 years ago. It is indicated to increase tear production in patients whose tear production is presumed to be suppressed because of ocular inflammation associated with keratoconjunctivitis sicca. Clinical trials have demonstrated increased tear production, reduced corneal staining, reduced use of artificial tears, and increased goblet cell density after 6 months of therapy.[38,39] Cyclosporine A forms a complex with cyclophilin that inhibits the phosphatase activity of calcineurin.[16] This decreases cytokine production and T-cell migration into the tissues of the ocular surface.

In 2016, lifitegrast was FDA approved for DED. This new drug is indicated for the treatment of the signs and symptoms of DED. Three phase 3 clinical trials have been conducted. Improvement in symptoms of eye dryness was noted after 6 weeks of therapy in all 3 studies and after 2 weeks in 2 of the studies[40] **(Figure 5).** In 2 of the 3 studies, improvement in inferior corneal staining was demonstrated after 3 months of therapy.[40-42] The most common adverse event associated with lifitegrast in all 3 studies was discomfort upon instillation. Lifitegrast is an antagonist of lymphocyte function-associated antigen 1 (LFA-1).[43] It prevents binding of LFA-1 to key cell surface receptors, thereby blocking T-cell activation, adhesion, migration, and cytokine release.

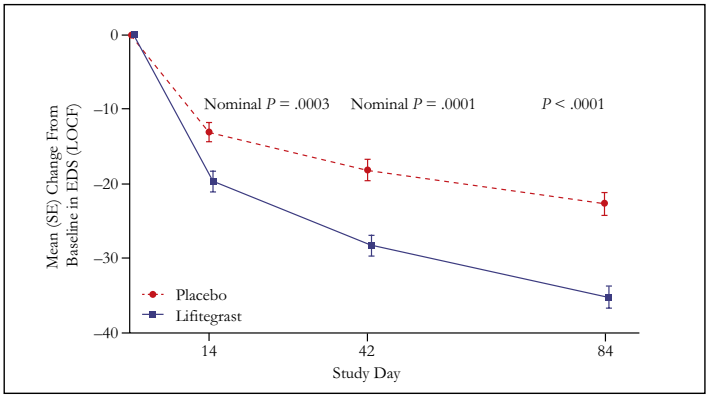

Figure 5. Change from baseline to day 84 in symptom scores in the placebo and lifitegrast groups in OPUS-2. Eye dryness score (EDS) was a coprimary end point.[40]

Abbreviations: LOCF, last observation carried forward; SE, standard error.

Also in 2016, cyclosporine A was approved in a multidose package while remaining preservative free,[44] thus providing increased convenience for patients who might otherwise struggle with the single-dose vials in which cyclosporine A had been previously supplied.

Several new therapies for DED are on the near horizon. One is a novel nanomicellar formulation of cyclosporine A at a 0.09% concentration that was shown in clinical trials to provide improvement in Schirmer scores in as little as 12 weeks.[45]

A novel nonpharmacologic therapy, the TrueTear nasal neurostimulatory device, was recently granted marketing authorization by the FDA.[46] This treatment stimulates production of the aqueous, mucin, and lipid components of the tear film. According to the recent press release, in 2 clinical trials, the primary effectiveness end point of increased tear production measured by Schirmer score was met.[46] There were no serious device-related adverse events reported. The most common nonserious device-related adverse events recorded in the trials were nasal pain, discomfort, or burning (10.3%), transient electrical discomfort (5.2%), and nosebleed (5.2%).[46] Symptom scores and corneal and conjunctival staining were measured in another study in 34 patients who used a prototype of the nasal neurostimulatory device. In that open label non-randomized study, scores from baseline to day 180 were significantly reduced in patients with mild-to-severe DED.[47] This nasal neurostimulatory device might be a reasonable complement to topical pharmacologic therapy.

CASE DISCUSSIONS

CASE 1. Dry Eye Disease and Eye Pain Following Refractive Surgery

—From the Files of Helen K. Wu, MD

A 45-year-old man underwent photorefractive keratectomy (PRK) in 2011 for hyperopia in both eyes. He experienced prolonged pain in both eyes after the procedure. His postoperative uncorrected visual acuity was 20/25 in the right eye and 20/50 in the left; best corrected visual acuity (BCVA) in the left eye was also diminished to 20/30. Slit-lamp examination revealed mild subepithelial haze typical of post-PRK appearance in both eyes, with slightly diminished tear lakes and decreased TBUT in both eyes. There was also mild irregular astigmatism in the left eye.

He was initially treated with lubricants, topical cyclosporine, and topical steroids for several weeks, as well as oral omega-3 supplements for several months. Punctal plugs were placed 6 to 8 weeks after initiating topical anti-inflammatory therapy. Despite these interventions, his pain persisted in both eyes, and the visual acuity remained diminished in the left eye. We attempted rigid gas permeable contact lens fitting, but he was unable to tolerate the lenses because of pain. He was then lost to follow-up for 5 years when he presented with persistent pain in both eyes. His examination was essentially unchanged, with mild dry eye noted. There was no evidence of anterior basement membrane dystrophy, and his ocular pain was mostly—but not completely—improved with topical anesthesia.

At this point we performed confocal microscopy **(Figure 6),** which demonstrated decreased density and

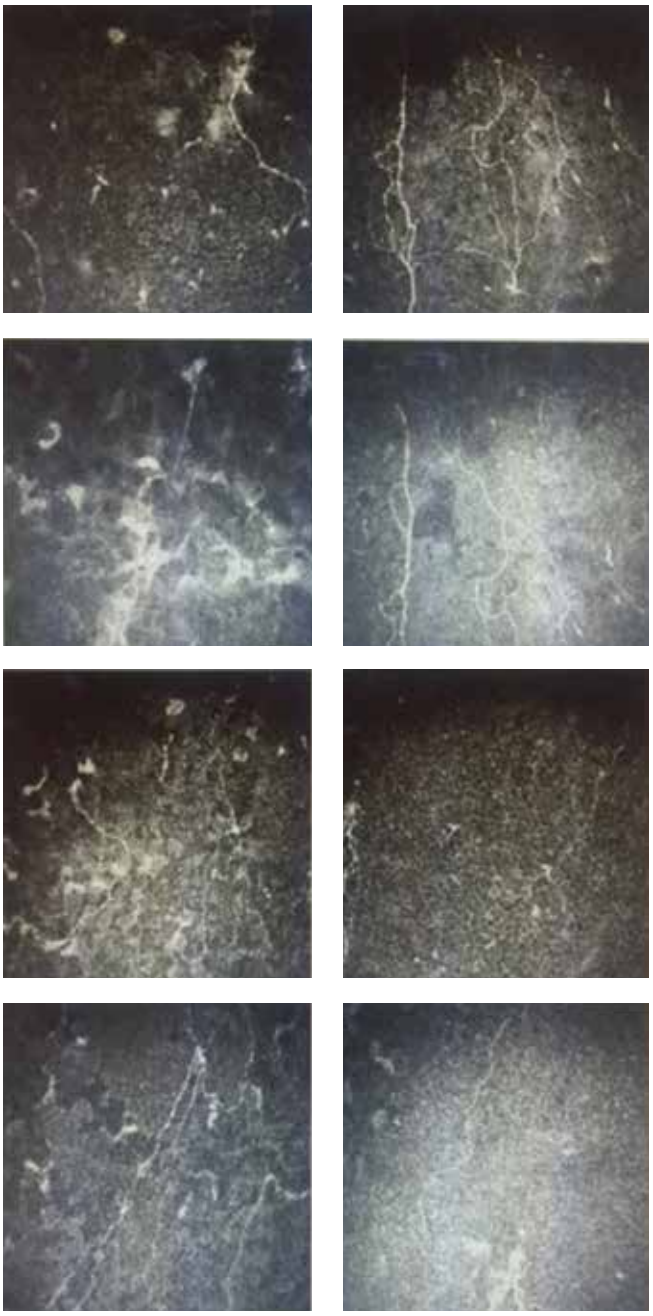

Figure 6. Confocal microscopy of the corneas of the patient presented in Case 1. Top 4 images, right eye; bottom 4 images, left eye. Abnormal nerve regeneration after photorefractive keratectomy in both eyes, with increased neuromas noted in the left eye.

Images Courtesy of Helen K. Wu, MD

increased tortuosity of the nerves in both eyes and neuromas in the left cornea. We continued the current therapies, consisting of topical steroids, cyclosporine, lubricants, and plugs. I added lifitegrast twice daily to both eyes as well as serum tears every 2 hours. He was also fitted for a prosthetic replacement of the ocular surface ecosystem (PROSE) device. This patient has been lost to follow-up since.

Dr Beckman: What are the hallmarks of corneal neuropathic pain?

Dr Wu: Injured neurons may develop after refractive surgery. The terminals of these injured neurons swell, forming what are called endobulbs. Small neuromas form here as the neuron tries unsuccessfully to regenerate itself. These injured nerves can cause classic neuropathic pain, which is characterized by a triad of symptoms: hyperalgesia, allodynia, and spontaneous pain. Allodynia is the sensation of severe pain resulting from seemingly innocuous stimuli such as bright lights or light touch. In the cornea, neuropathic pain might be perceived as irritation, itching, burning, aching, light sensitivity, or grittiness.[48]

Dr Beckman: What clinical features might suggest this diagnosis?

Dr Wu: In these cases, regrettably, standard dry eye testing may be normal. The patient did have diminished TBUT, but normal Schirmer scores. The proparacaine challenge test was informative in that instillation of proparacaine did not completely relieve his symptoms. The gold standard for diagnosis is laser in vivo confocal microscopy.

Dr Beckman: Why do you think the decreased nerve density is associated with the increased pain? We typically think of the nerve loss with laser surgery leading to a desensitized cornea.

Dr Wu: I think what happened is that the peripheral corneal nerves were affected in this case by the PRK. This causes structural changes in the nerves, leading to sensitization of the nerve fibers. These changes are not limited to the peripheral nervous system—they can spread to the central nervous system as well, in which case patients may require systemic pharmacotherapy with agents such as nortriptyline, naltrexone, or even opioids. Some patients turn to acupuncture and other alternative treatments. The point is that such patients can be very difficult to treat.

Dr McDonald: This patient had hyperopic PRK, so he had a large diameter ablation in both eyes that may have damaged the trunk nerves coming in at 3 and at 9 o'clock. A central PRK for myopia damages far fewer of the nerves.

Dr Beckman: Can you address your decision to add lifitegrast to cyclosporine?

Dr Wu: If the patient has a partial response to cyclosporine, I will continue it and add lifitegrast.

Dr Matossian: I also have patients on both agents, and I proceed just as Dr Wu described, adding lifitegrast in patients who show incomplete resolution of symptoms on cyclosporine alone. Each of these 2 T-cell inhibitors work differently. It makes sense to interrupt the inflammatory process at 2 different points along the pathway.

Dr Milner: We all have patients who report definite improvement with cyclosporine or lifitegrast alone, but may still have symptoms, and I too add the other, lifitegrast or cyclosporine, to these patients' regimens. There are no head-to-head studies or additivity studies that show a synergistic effect of the 2 agents. In the absence of such data, it is reasonable to assume that they are additive on the basis of their distinct mechanisms of action on the T-lymphocyte. As are many other diseases, such as glaucoma, I believe that DED is a complex disease that often needs multiagent treatment. Therefore, if I have a patient on either cyclosporine or lifitegrast alone and signs and/or symptoms improve but are not resolved, I will often add the other.

Dr O'Brien: These cases can be among the most challenging to manage, and the role of adjunctive imaging with confocal microscopy to confirm the diagnosis is essential. I agree with Dr Wu's use of the autologous serum tears to try to provide the various nerve growth factors and other humoral substances not present in artificial tears that may accelerate recovery and ameliorate symptoms. Topical nerve growth factor has been suggested and used in other neurotrophic ocular conditions, but is expensive and unapproved, and the dose response is incompletely determined. The judicious off-label use of very dilute topical anesthetics as previously recommended with surface photoablative procedures can be considered and monitored very carefully. Finally, because of not only the local ocular pain, but also the concomitant *central* mechanisms mediating chronic pain, these cases should be referred and comanaged with a reliable expert in pain management.

CASE 2. Dry Eye Disease and Upcoming Cataract Surgery

—From the Files of Cynthia Matossian, MD, FACS, ABES

A 65-year-old woman was seen in consultation for cataract surgery. She was pseudophakic in the right eye and felt that her vision was getting worse in both eyes. Specifically, she reported that she had difficulty driving home from work at night. Her BCVA was 20/25– in the right eye and 20/60 in the left eye. Her external examination is shown in **Figure 7.**

The patient's external examination revealed foamy deposits on the lower lid margins, indicative of MGD. Also, she had

Figure 7. External photographs of the patient presented in Case 2. Note the foamy deposits on the lid margins of both eyes as well as loss of lashes bilaterally.

Images Courtesy of Cynthia Matossian, MD, FACS, ABES

diffuse lash loss in both eyes, so severe that she had lash extensions placed on her upper lids. On the basis of the examination findings, she underwent testing for DED. Her tear osmolarity was 346 and 330 mOsm/L in the right and left eye, respectively, and her MMP-9 was positive in both eyes. Lissamine green and fluorescein dyes revealed staining of the inferior cornea and conjunctiva in both eyes. Corneal topography demonstrated significant irregular astigmatism, and meibomography **(Figure 8)** revealed extensive gland dropout.

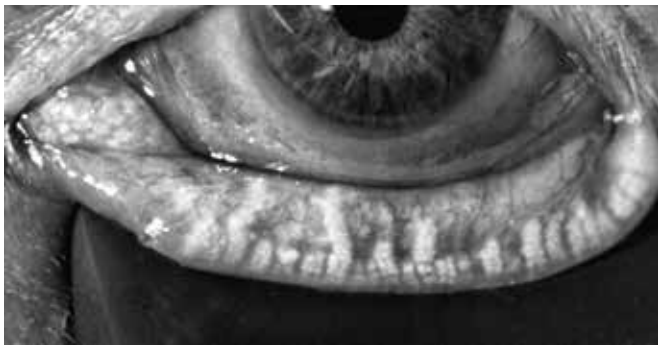

Figure 8. Meibomography of the left eye of a patient with meibomian gland dysfunction. Note the diffuse loss of glands throughout the lower lid.

Image Courtesy of Alice Epitropoulos, MD

Dr Beckman: What is the significance of the foamy tears in this patient?

Dr Luchs: The finding is typical of MGD. There are abnormal lipids in the tear film, which are being acted upon by bacterial lipases and turned into soaps. This can cause significant discomfort for the patient.

Dr Beckman: This patient now wants cataract surgery in her second eye. What did you do to prepare her ocular surface for surgery?

Dr Matossian: Her primary problem is her lids. I started with lid hygiene, which included scrubs and a microwaveable-heated mask to help soften secretions. I also performed vectored thermal pulsation treatment using the LipiFlow system. I then prescribed high-quality oral omega-3 supplements as well as lifitegrast and loteprednol topical therapy. I postponed measurements for lens calculations until her ocular surface was in better shape because hyperosmolarity of the tear film can lead to incorrect lens calculation.[49]

Dr O'Brien: The role of microbial colonization of the lids/lashes in the pathogenesis of MGD has been incompletely understood, yet as was mentioned, bacterial *lipases* play a role in the enzymatic saponification of meibum into free fatty acids and soaps. Thus, it is rational to reduce excessive microbial colonization of the lid margins. The use of lid-cleansing agents, including those containing hypochlorous acid or linalool, which have natural antimicrobial and anti-inflammatory effects, could be beneficial for such a patient. A preoperative pulse with systemic low-dose doxycycline or minocycline, not so much for antibacterial benefits, but for immunodulatory effects, could theoretically prove beneficial in reducing preoperative inflammation of the lid margins. Topical azithromycin, 1%, once daily has also demonstrated favorable effects on clinical symptoms and signs of MGD as well as on restoring the lipid properties of meibomian gland secretions toward normal.[50]

Dr Beckman: One additional point—it appears she may have a little bit of lower lid laxity, and her staining pattern supports some component of exposure. These eyes may be at increased risk of corneal infections. In addition to everything you did for her, I would have also considered some antibiotic ointment at night, both to lubricate during sleep and also to reduce the infection risk.

Dr McDonald: I agree with Dr Beckman; lagophthalmos and the resultant exposure keratitis appear to be present on the basis of her staining pattern and lid laxity. Lagophthalmos/Exposure keratitis is one of the most overlooked diagnoses in ophthalmology, and can negatively affect both preoperative measurements and postoperative recovery because the already-lax lids are stretched even further by the speculum.

Dr Beckman: How did this case turn out?

Dr Matossian: Upon return, her symptoms and lid margin appearance improved, as did her topography. With her ocular surface as optimized as possible, we proceeded with calculations and her surgery went smoothly, with a satisfactory visual outcome.

CASE 3. Dry Eye Disease in a Young Patient
—From the Files of Terrence P. O'Brien, MD

A 23-year-old Asian woman presented with the complaint that her eyes get really tired and her vision "jumps around". She had excellent systemic health, with some environmental allergies. Her medications included oral contraceptives, nonprescription antihistamines for allergy, and what she described as computer eyedrops. She consumes large quantities of coffee, does not smoke, and spends much time looking at computer monitors. On examination, her BCVA is 20/15 in the right eye and 20/20 in the left, with moderate myopic corrections in both eyes. Her external examination is shown in **Figure 9.**

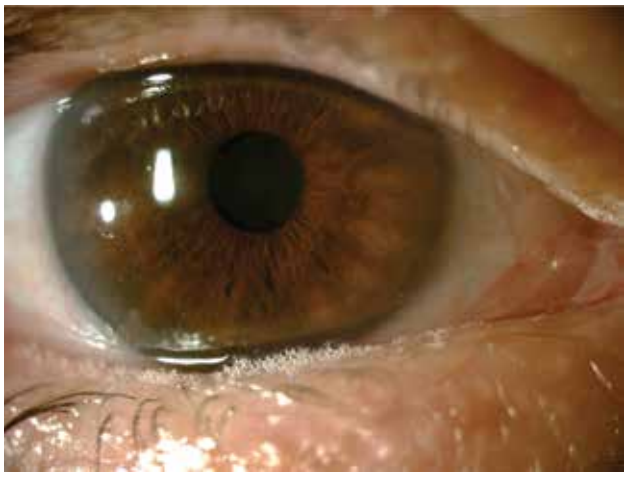

Figure 9. External examination of the patient presented in Case 3. Note the evidence of meibomian gland dysfunction, lid telangiectasia, and foamy tear film.

Image Courtesy of Terrence P. O'Brien, MD

Lissamine green revealed early staining of the conjunctiva more so than of the cornea. Her TBUT was 5 and 4 seconds in the right and left eye, respectively. Schirmer testing was 9 mm in both eyes. Her osmolarity was within normal limits, but her MMP-9 was positive in both eyes.

Dr Beckman: This case demonstrates the new face of DED that we are seeing in younger people. It seems that this patient might benefit from both pharmacologic as well as some behavioral interventions.

Dr O'Brien: Exactly right. We started with education so she would understand how her lifestyle and environment contributed to her symptoms. I asked her to take frequent breaks during screen time, cut back on her caffeine intake, eat a healthy diet supplemented with omega-3 essential fatty acids, and practice good lid hygiene, including both warm compresses and massage. We asked her to stop the frequent preservative-containing "computer drops" and rather to lubricate with preservative-free artificial tears during the day and to apply gel at night. I prescribed a 1-month pulse of loteprednol etabonate, 0.5%, with gradual taper and initiated chronic anti-inflammatory therapy with topical lifitegrast, 5%, twice daily. Topical cyclosporine A, 0.05%, is also an approved immunomodulatory alternative for maintenance anti-inflammatory therapy with a long track record of effectiveness and safety in management of patients with DED. It is important to address inflammation, both acutely and for the longer term, in this younger patient with aspects of both evaporative and aqueous-deficient DED.

Dr McDonald: I would add that not getting adequate sleep is a behavior that can aggravate DED. Some of my worst patients with dry eye are shift workers who are getting as few as 3 or 4 hours of sleep per night. This is another opportunity for behavior modification.

Dr O'Brien: Sleep is a precious and sometimes underappreciated commodity in systemic and ocular health. In a recent study of sleep and mood disorders in women with DED, sleep quality was significantly worse in women with than without DED. Mood disorders of depression and anxiety were major contributory factors, especially in the younger DED group.[51]

Summary and Take-Home Points

In this monograph, we have provided a modern framework for understanding the pathophysiology of DED as an inflammatory disease. New and emerging diagnostics provide excellent tools for identifying patients with DED, and an expanding array of therapeutics ensures that our patients with DED can find relief from their DED symptoms. The following take-home points provide a summary of our discussion:

- DED and ocular surface disease are increasingly prevalent in our modern multiscreen world and can be triggered and aggravated by the conveniences of modern society, including forced air heating and systemic medications
- DED affects our patients' visual function and their quality of life, and can have significant detrimental effects on issues such as contact lens wear and preoperative lens calculations for cataract surgery
- DED is a complex, multifactorial disease driven by inflammation, is both chronic and progressive, and often requires a multipronged therapeutic approach
- Given the inflammatory nature of DED, anti-inflammatory therapy should be instituted early to help control the underlying processes contributing to symptoms
- Innovative, new point-of-care testing can help us make the diagnosis of DED earlier in its course, before significant damage has been done to the ocular surface
- New and emerging therapeutics give us the most diverse array of treatment options to improve the health and quality of life of our patients with DED

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CME Post Test Questions

To obtain *AMA PRA Category 1 Credit*™ for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page. Alternatively, you can complete the CME Post Test online at http://www.tinyurl.com/CurrentOpinionsDryEye.

See detailed instructions at **To Obtain *AMA PRA Category 1 Credit*™** on page 2.

1. Which of the following has high-level evidence for establishing it as a risk factor for DED?
   a. Oral contraceptive use
   b. Menopause
   c. Radiation therapy
   d. Use of a systemic beta-blocker

2. The prevalence of DED in young adults is increasing. What is the likely cause of this observation?
   a. Higher rates of teen smoking
   b. Increased use of oral contraceptives
   c. Increased time spent staring at video screens
   d. Climate change

3. When evaluating a patient with symptoms of DED, _____ is a condition that often mimics these symptoms.
   a. Primary acquired melanosis
   b. Conjunctivochalasis
   c. Keratoconus
   d. Dacryocystitis

4. Which of the following is <u>not</u> a factor in the pathophysiology of DED?
   a. Increased tear osmolarity, cytokine release, and inflammation
   b. Allodynia
   c. Recuitment of T lymphocytes to the ocular surface
   d. Decrease in goblet cells

5. Foamy tears on the lid margin are a sign of _____.
   a. Corneal foreign body
   b. Allodynia
   c. Goblet cell loss
   d. Meibomian gland dysfunction

6. Which of the following tests can be helpful in diagnosing DED regardless of symptom severity?
   a. MMP-9
   b. TBUT
   c. Meibomography
   d. All the above

7. While cyclosporine A and lifitegrast have distinct mechanisms of action, they both work by interfering with _____.
   a. Evaporative tear loss
   b. The calcineurin phosphatase pathway
   c. T-lymphocyte activation and migration
   d. LFA-1

8. In clinical trials, symptoms of DED may show improvement in as early as _____ of therapy with lifitegrast.
   a. 3 days
   b. 2 weeks
   c. 3 months
   d. 6 months

9. A 60-year-old woman is referred for dry eye that has not improved with artificial tears. She complains of foreign body sensation, irritation, fluctuating vision, and grittiness. Visual acuity is 20/60 OD and 20/60 OS. Her TBUT is 2 seconds OU, and there is no staining of the cornea or conjunctiva and no scarring. Schirmer testing is 19 mm OD and 21 mm OS. What additional test would be optimal to target treatment?
   a. Nothing else needed to target treatment
   b. Tear osmolarity
   c. Sjögren titer
   d. Meibomography

10. A 45-year-old man, a stockbroker, wants LASIK. He has no relevant medical history, but spends a lot of time at work looking at computer and phone screens. His visual acuity is 20/40 OU; his tear film osmolarity is 321 mOsm/L OD and 331 mOsm/L OS; his TBUT is 4 seconds OD and 3 seconds OS. There is no corneal staining, but MMP-9 testing is positive OU. Which of the following treatments would be the most reasonable?
    a. Artificial tears alone
    b. Artificial tears plus an anti-inflammatory such as lifitegrast or cyclosporine
    c. Punctal plugs
    d. Amniotic membrane placement

Activity Evaluation/Credit Request

ORIGINAL RELEASE: JULY 1, 2017
EXPIRATION: JULY 31, 2018

CURRENT OPINIONS AND MODERN APPROACHES IN THE DIAGNOSIS AND TREATMENT OF DRY EYE DISEASE

To receive *AMA PRA Category 1 Credit*™, you must complete this **Evaluation** form and the **Post Test.** Record your answers to the **Post Test** in the Answer Box located below. Scan this completed page and return via e-mail to cme@nyee.edu or fax it to 212-353-5703. Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is e-mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

PARTICIPANT INFORMATION *(Please Print)* ☐ Home ☐ Office

Last Name _____ First Name _____

Specialty ☐ Ophthalmology ☐ Other Degree ☐ MD ☐ DO ☐ OD ☐ PharmD ☐ RPh ☐ NP ☐ RN ☐ PA ☐ Other _____

Institution _____

Street Address _____

City _____ State _____ ZIP Code _____ Country _____

E-mail _____ Phone _____ Fax _____

Please note: We do not sell or share e-mail addresses. They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.

Learner Disclosure: To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, **New York Eye and Ear Infirmary of Mount Sinai** Institute for CME requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. **CME certificates cannot be awarded unless you answer this question.** For additional information, please e-mail NYEE ICME at cme@nyee.edu. Thank you.

☐ Yes ☐ No I and/or my family member have a financial relationship with **New York Eye and Ear Infirmary of Mount Sinai** and/or refer Medicare/Medicaid patients to it.

☐ **I certify that I have participated in the entire activity and claim 2.0 *AMA PRA Category 1 Credits*™.**

Signature Required _____ **Date Completed** _____

OUTCOMES MEASUREMENT

☐ Yes ☐ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

_____

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

• Diagnose dry eye disease using at least 1 objective test, regardless of symptom severity	5	4	3	2	1
• Describe the implications of inflammation in dry eye disease on diagnosis and treatment approaches	5	4	3	2	1
• Describe clinically relevant results from clinical trials assessing anti-inflammatory drugs for the treatment of DED	5	4	3	2	1
• Select appropriate DED treatment based on individual patient characteristics and an appropriate approach	5	4	3	2	1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.

_____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes 1 = definitely will not make any changes

4 3 2 1

Please describe the change(s) you plan to make: _____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face? _____

4. Number of patients I see per week with dry eye ☐ 1–10 ☐ 11–20 ☐ 21–40 ☐ 41–60 ☐ More than 60

5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.
☐ Patient Care ☐ Practice-Based Learning and Improvement ☐ Professionalism
☐ Medical Knowledge ☐ Interpersonal and Communication Skills ☐ Systems-Based Practice

6. What other topics would you like to see covered in future CME programs? _____

ADDITIONAL COMMENTS _____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10

VISIT **HTTP://WWW.TINYURL.COM/CURRENTOPINIONSDRYEYE** FOR ONLINE TESTING AND INSTANT CME CERTIFICATE.

Current Opinions and Modern Approaches in the Diagnosis and Treatment of

DRY EYE DISEASE