CME Monograph

ADVANCES IN THE SCIENCE AND MANAGEMENT OF DRY EYE DISEASE

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CONTENT SOURCE
This continuing medical education (CME) activity captures content from a roundtable discussion held in May 2016 in Seattle, Washington.

ACTIVITY DESCRIPTION
Dry eye disease (DED) is a common global problem that can occur in adults of all ages. Early detection and management are important because mild dry eye can cause symptoms that affect daily function and quality of life, and DED can progress to become a serious condition. Understanding the pathogenesis of DED has led to innovations in diagnosis and therapy, but access to and use of these various modalities varies by country and practice setting. The purpose of this activity is to update ophthalmologists in the United States and Europe on developments in DED diagnosis and management.

TARGET AUDIENCE
This educational activity is intended for European and US ophthalmologists caring for patients with DED.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
- Evaluate and diagnose DED with appropriate assessment tools and techniques
- Describe the implications of inflammation in DED management
- Apply evidence-based approaches for the treatment of DED
- Describe clinically relevant results for newer treatments for DED

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ADVANCES IN THE SCIENCE AND MANAGEMENT OF DRY EYE DISEASE

The prevalence of dry eye disease (DED) is increasing as the result of a variety of factors. In recent years, clinicians have seen a growing array of diagnostic modalities designed to help identify and better characterize the disease. In addition, approaches to the management of DED have been changing based on emerging data, along with the recognition that meibomian gland dysfunction is a major cause of DED and that more product approvals are anticipated in the near future. However, access to diagnostic and treatment options varies, depending on the practice setting and location.

Recently, a panel composed of European and American ophthalmologists with expertise in DED gathered to discuss approaches to the evaluation and management of this common disorder. We hope their general insights and case-based reflections, which take into account the disease type and severity as well as the availability of different modalities, will be useful to readers.

Andrea Leonardi, MD

Definition and Epidemiology

Dr Leonardi: The International Dry Eye WorkShop (DEWS) introduced the currently accepted definition of DED in 2007, which states, "dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[1] Does this definition need to be revised?

Dr Messmer: I am participating in DEWS II, and I know the definition is being updated and modified. I think the current definition is too narrow because it fails to recognize certain important aspects of DED, such as the role of corneal nerves.

Dr Leonardi: If the new definition broadens the concepts of DED, are contemporary epidemiology studies necessary to determine DED prevalence based on this definition?

Dr Pflugfelder: Certainly, findings of studies investigating DED prevalence will depend on how DED is defined. This probably explains, in part, why estimates from available studies show such a wide range, from less than 1% to up to approximately 33% **(Table 1).**[2] I am not convinced that we need new broad surveys, but I think it is important to recognize that the prevalence of DED will be higher if the diagnostic criteria include symptoms and not just signs.

Table 1. Studies Evaluating the Prevalence of Dry Eye Disease[2]

Reference	Country	Population or Data Source	Prevalence, %*
McCarty et al, 1998	Australia	926 subjects aged 40-97 years	1.5-16.3
Bjerrum, 1997	Denmark	504 subjects aged 30-60 years	8-11
Clegg et al, 2006	France, Germany, Italy, Spain, Sweden, United Kingdom	Interviews with consultant ophthalmologists with a special interest in DED	0.02-0.07†
Shimmura et al, 1999	Japan	3500 subjects; 86% aged between 20 and 49 years	33
Schein et al, 1997	United States	2520 subjects aged ≥ 65 years	0.7-14.6
Moss et al, 2000	United States	3722 subjects aged 48-91 years	14.4
Yazdani et al, 2001	United States	10 million individuals in managed care plans	0.39-0.48
Schaumberg et al, 2003	United States	36,995 female health professionals aged 49-89 years	7.8
Miljanović et al, 2007	United States	25,444 male physicians aged ≥ 50 years	4.34

* Range reflects differences using different diagnostic criteria.
† Range reflects differences across countries.

Dr O'Brien: I believe that as we refine our definition of DED, according to advanced understanding, to encompass even more factors, prevalence data will demonstrate even higher numbers of affected individuals who are detected with greater sensitivity and specificity and perhaps uncover subpopulations previously underrecognized or entirely overlooked.

Dr Leonardi: Should people whose DED is a transient condition induced by certain tasks or environments be counted in studies of DED prevalence?

Dr Figueiredo: I think what is most important is for clinicians to recognize that DED can be a fluctuating condition and that individuals with intermittent dry eye should be identified and treated because their condition may become more serious.

Dr Leonardi: Is the prevalence of DED increasing?

Dr Messmer: It is increasing, and the reasons for this include worsening air pollution and more work being done at computers.[3,4] In addition, I think DED is being diagnosed more often because of increased awareness in the public and among practitioners.

Dr O'Brien: An important message here for clinicians is that they need to expand their perspective about who can be affected by DED. It is not just a problem in our growing older population; DED can develop in younger individuals and can affect the quality of life of people who are still active and working.

Classification and Pathogenesis

Dr Leonardi: Currently, DED is divided into 2 major classes defined by whether there is deficient aqueous tear production or increased evaporation from the ocular surface.[1] Does this classification need to be changed?

Dr Figueiredo: Tear quality is another factor to consider because even if tear production is adequate, DED can occur because of poor-quality tears and mechanisms other than increased evaporation.

Dr Messmer: I think the current classification provides a valuable foundation for choosing therapy. Treatment will be entirely different for a patient with a Schirmer score of 3 from that for someone who has a normal Schirmer score but fast tear film break-up time (TBUT) and blocked meibomian glands. However, when choosing therapy, it is important to keep in mind that many patients have a mixed presentation.

Dr O'Brien: In a study of more than 200 patients with DED, Lemp and colleagues found that approximately one-third had evidence of both meibomian gland dysfunction (MGD) and aqueous deficiency.[5]

Dr Leonardi: We now know that inflammation plays a major role in the pathogenesis of DED. Is it involved in all forms of DED?

Dr Pflugfelder: I think inflammation can be found in eyes with any type of tear dysfunction. In episodic dry eye, inflammatory mediators may come from epithelial cells or resident immune cells, whereas in more severe aqueous-deficient disease, there is an adaptive immune response involving T-helper cells that releases a different array of inflammatory mediators **(Figure 1).**[6] Consensus treatment recommendations developed by both DEWS and the International Task Force (ITF) Delphi Panel on Dry Eye were to add 1 or more anti-inflammatory therapies in patients with moderate signs and symptoms of DED (level 2 severity), particularly those without adequate relief from artificial tears.[7,8] There may be greater use of diagnostic inflammatory biomarkers in the future, which will identify specific mediators and guide more targeted therapy.

Dr O'Brien: I agree that *inflammation* in DED can sometimes be like "The Emperor's New Clothes" (with apologies to Hans Christian Andersen) in terms of being something we anticipate with great clinical expectations, yet of which we see no physical evidence

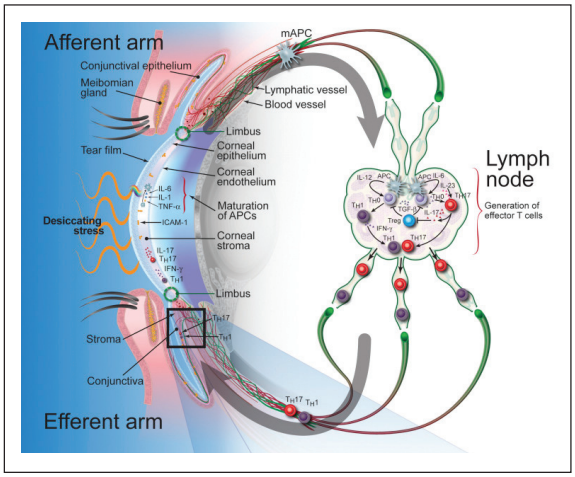

Figure 1. Tear hyperosmolarity secondary to dessicating stress activates intracellular signaling pathways within corneal and conjunctival epithelial cells, resulting in the release of proinflammatory cytokines, including interleukin 1, tumor necrosis factor, and interleukin 6. These cytokines activate cells of the innate immune system (macrophages and neutrophils), which release cytokines promoting the activation and maturation of immature antigen-presenting cells. Upon reaching the lymph nodes via the lymphatic vessels, mAPCs induce effector helper T-cell 1 and 17. These T cells, primed against ocular surface antigens, travel to the ocular surface through efferent blood vessels, bind to ocular surface antigens, and become activated. Chemical mediators released by the activated T cells perpetuate the inflammatory pathway and cause tissue destruction.

Abbreviations: APC, antigen-presenting cell; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; mAPC, mature antigen-presenting cell; TGF, transforming growth factor; T_H, helper T cell; TNF, tumor necrosis factor; Treg, regulatory T cell.

Reprinted from *Ocular Surface,* 14, Victor L. Perez, Stephen C. Pflugfelder, Steven Zhang, Amir Shojaei, Reza Haque, Lifitegrast, a novel integrin antagonist for treatment of dry eye disease, 207-215, Copyright 2016, with permission from Elsevier.

using our conventional methods of observation. As we become increasingly sophisticated in identifying and detecting markers of inflammation, the presence and role of inflammation in DED is no longer a fairy tale. With validated biomarker tools, we can more reliably confirm, provide targeted treatments for, and monitor response to therapies directed against inflammation.

Diagnostic Evaluation

Dr Leonardi: Diagnosis of DED is easy when a patient is very symptomatic and has significant ocular surface damage, but more challenging if there is only tear film deficiency or insufficient surface wetting. How is the diagnosis of DED approached in the United States?

Dr Pflugfelder: In terms of testing, I think a minimum assessment should include measurement of TBUT with fluorescein to look for tear film instability, assessment of symptoms and their severity using a formal questionnaire or by asking patients a few questions, grading of the severity of ocular surface damage according to staining with fluorescein and lissamine green, and assessment of tear volume/production with the Schirmer test and/or anterior segment optical coherence tomography (OCT). This information can be used to classify dry eye as aqueous deficient and/or evaporative and to grade severity to guide therapy, as recommended in the DEWS report.[1] These evaluations can be supplemented with assessments of tear composition, such as osmolarity and matrix metalloproteinase-9 as a marker of inflammation.

Dr Leonardi: Dr Figueiredo, would you please give us a European perspective?

Dr Figueiredo: Understanding the patient's symptoms is critical because symptom relief is an important treatment goal. I think symptoms should be assessed using a proper questionnaire, such as the Ocular Surface Disease Index (OSDI) or the Ocular Comfort Index.[9,10]

In addition, I consider the Schirmer test useful for understanding tear production, despite its limitations, and I also routinely perform TBUT with fluorescein and look at ocular surface staining with fluorescein and lissamine green, as recommended in the DEWS report and the Dry Eye Syndrome Preferred Practice Pattern of the American Academy of Ophthalmology.[11,12]

Lid margin assessment is also critical for identifying MGD. I often measure tear film osmolarity and use new technology, such as anterior segment OCT, to assess tear volume. The matrix metalloproteinase-9 assay is not part of my routine.

Dr Leonardi: What are some simple questions a busy general ophthalmologist can ask to understand the patient's symptoms?

Dr Messmer: The SPEED (Standard Patient Evaluation of Eye Dryness) questionnaire is fairly quick because it only asks patients to rate the frequency and severity of only 4 symptoms, along with a few additional questions.[13] Alternatively, I think it is very informative to ask patients to name their worst symptom. If I just say, "Tell me your symptoms," they may list 10 things, and then I am not sure what is really bothering them. Furthermore, I know that someone who complains most about burning in the morning has a different problem than someone who is bothered by tired eyes in the evening.

Dr O'Brien: We encourage evaluating symptoms with a formal, validated questionnaire, and use the OSDI. A reasonable alternative would be to ask patients the following 3 questions: Do your eyes ever feel dry or uncomfortable? Are you bothered by changes in your vision throughout the day? Do you ever use or feel the need to use eye drops? A positive answer to any of these questions is an indication for a more comprehensive examination for DED.

Dr Leonardi: Because some of the diagnostic tests mentioned may not be available to general ophthalmologists in the community, when should patients be referred for further evaluation with these modalities?

Dr Pflugfelder: Clinicians should refer patients whose conditions they are not comfortable dealing with. Often, these are individuals who are very symptomatic, regardless of the severity of any DED signs, or those with corneal epithelial disease associated with visual dysfunction. Certainly, consideration should be given to referring patients with more advanced DED that necessitates aggressive management.

Dr Figueiredo: In the United Kingdom, patients who have mild symptoms are usually treated in the community by their general practitioner, general ophthalmologist, or optometrist. The patients seen in tertiary care centers tend to be highly symptomatic, often not responding to initial therapy with artificial tears, or have developed some ocular surface changes, such as fluorescein staining of the cornea.

Dr O'Brien: Paradoxically, patients with moderate-to-severe ocular surface disease may have a paucity of symptoms, whereas others with minimal signs of DED may be experiencing disabling symptoms. Given the mismatch between symptoms and signs, treatment decisions for these patients can be challenging. I think anyone judged to have moderate-to-severe disease based on either signs or symptoms should be referred for a more comprehensive evaluation and aggressive management program.

Severity Grading

Dr Leonardi: Your comments raise the question of how we should grade DED severity.

Dr Pflugfelder: The 2006 ITF Delphi Panel on Dry Eye and DEWS developed grading schemes that classify DED into 4 severity levels based on signs and symptoms.[7,8] Applying these schemes can be challenging, however, because of the potential for discordance between signs and symptoms. I believe, therefore, that practitioners need to use their own discretion for severity grading, taking that paradox into account, while also considering how DED is affecting quality of life and function. Even if patients do not have significant objective findings, we want to treat DED so that patients are functional.

Dr Figueiredo: I completely agree that because of a mismatch between symptom and sign severity, it is uncommon to find patients who fit perfectly into 1 of the 4 severity levels of the DEWS or ITF classification schemes. Even patients who fit within the DEWS or ITF grading schemes, with agreement between signs and symptoms, may no longer be so easy to categorize once treatment is initiated because their DED signs and symptoms may not improve at the same rate. Signs of dry eye often respond to treatment faster than symptoms do.[14]

Dr O'Brien: The fact that we do not have a system that allows us to easily classify DED severity, taking into account possible discordance between signs and symptoms, has also created problems with assessing the efficacy of treatments in clinical trials. Going forward, it would be nice if we could validate the use of some objective tests for severity grading.

Dr Messmer: In terms of DED severity, it is important to me to identify patients who have severe disease and are at risk of developing complications. I think the ODISSEY (Ocular Dryness Disease Severity) European Consensus Group did a nice job creating an algorithm that makes it easy to identify patients with severe DED **(Figure 2).**[15] The diagnosis is based on 2 primary criteria: severe symptoms defined as an OSDI ≥ 33 and severe corneal fluorescein staining defined as ≥ 3 on the Oxford scale. If only 1 of these 2 criteria is met, then additional tests can be performed to establish whether or not the patient has severe DED.

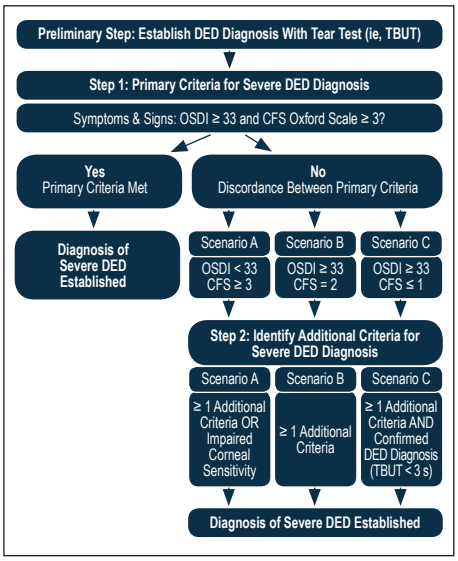

Figure 2. Scoring algorithm for severe DED diagnosis derived from the Ocular Dryness Disease Severity European Consensus Group[15]

Abbreviations: CFS, corneal fluorescein staining; DED, dry eye disease; OSDI, Ocular Surface Disease Index; TBUT, tear break-up time.

Reproduced from Baudouin C, et al. Diagnosing the severity of dry eye: a clear and practical algorithm. *Br J Ophthalmol.* 2014;98(9):1168-1176. doi:10.1136/bjophthalmol-2013-304619.

Dr Leonardi: I agree that the ODISSEY (Ocular Dryness Disease Severity) scheme is nicely done, but because additional testing may be needed to diagnose severe DED, it can still be complex. Is there an easier way for general ophthalmologists to distinguish patients with severe DED?

Dr O'Brien: Although uncommon, one particular situation to look for is a patient who is complaining of very severe pain who has minimal to no objective signs of DED. This may be a patient whose pain is mediated by some central nervous system mechanism rather than by that localized to the ocular surface, and who would be managed with other types of therapies targeting chronic pain syndromes.

Management

Dr Leonardi: As with any disease, successful management of DED requires that patients use the treatments prescribed. How do you encourage compliance?

Dr O'Brien: I think the importance of educating patients so they understand and accept their disease and its treatment, and thereby become aligned with the goals of treatment, is a larger aspect of DED management that is sometimes overlooked. At our center, technicians begin this educational process with counseling, which the physician then augments. I find that showing patients digital image evidence of DED is a compelling way to motivate their compliance with treatment. These visuals might include images from meibography or evaluation for MGD at the slit lamp, OCT evaluation of the tear meniscus, or vital dye staining.

Dr Messmer: I find the meibography and noninvasive TBUT images provided by 1 of the multifunctional diagnostic systems very helpful as educational tools **(Figures 3 and 4).** Meibography allows patients to see the loss of the meibomian glands and makes it easier to explain lid hygiene. By seeing the image of the unstable tear film, patients can understand problems they may be having with their vision when performing tasks like working at the computer.

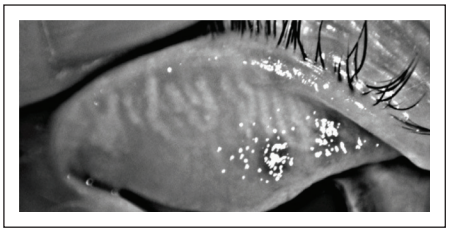

Figure 3. Meibography image shows loss of meibomian gland tissue associated with meibomian gland dysfunction in a patient with rosacea

Image Courtesy of Elisabeth M. Messmer, MD

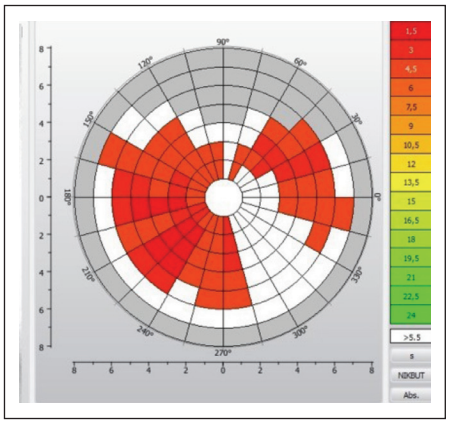

Figure 4. Noninvasive imaging shows decreased break-up time in a patient with evaporative dry eye

Dr Figueiredo: It also seems that patients are often interested to know their tear film osmolarity and other test results. I think it is nice for patients to have a number they can follow, which would help them better understand their disease and, more importantly, if their eyes are responding to treatment.

Dr Leonardi: Again, ophthalmologists in Europe might not have some of the devices you mentioned. Even though the Schirmer test is not that reliable, do you think showing patients its results can help them understand that DED is a condition of tear or tear film deficiency so they will comprehend the rationale for using tear substitutes?

Dr O'Brien: That is an excellent suggestion, especially for patients who require chronic treatment with topical cyclosporine to increase tear production. Showing increased wetting on the tear strips reinforces and assures the patient that the treatment is making positive progress.

Dr Leonardi: Ophthalmologists in the United States have had access to a commercially available cyclosporine product for more than a decade. European ophthalmologists had to use compounded formulations of cyclosporine until March 2015, when the 0.1% cyclosporine cationic emulsion received marketing authorization for the treatment of severe keratitis that has not improved with tear substitutes in adults with DED.[16]

Published results from the phase 3 SANSIKA trial showed that after 6 months, a 0.1% cyclosporine cationic emulsion was associated with greater improvement in most efficacy assessments than vehicle.[17] It was statistically superior to vehicle for reducing corneal staining and human leukocyte antigen DR as a marker of inflammation, and the benefit for improving corneal surface quality was seen by month 3 **(Figure 5).** The only adverse event reported more often with cyclosporine cationic emulsion than with vehicle was instillation site pain (29.2% vs 8.9%), but the pain was mostly mild. What advantages does this new cyclosporine product have compared with the compounded formulations being used by European ophthalmologists?

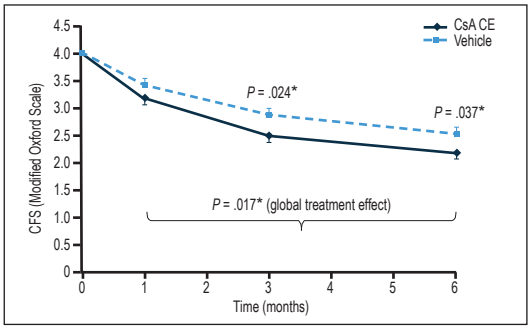

Figure 5. Change in corneal fluorescein staining over 6 months of randomized treatment with 0.1% cyclosporine A cationic emulsion or vehicle. Data represent mean corneal fluorescein staining values ± standard error of the full analysis set population. Sample size at baseline and months 1, 3, and 6: 154, 149, 140, and 132, respectively, with cyclosporine A cationic emulsion, and 91, 88, 89, and 93, respectively, with vehicle. Comparison between groups was performed using repeated-measures analysis of variance.

Abbreviations: CE, cationic emulsion; CFS, corneal fluorescein staining; CsA, cyclosporine A. * *P* values represent differences between CsA CE and vehicle.

Dr Figueiredo: It gives us access to licensed treatment. This is helpful because some patients resist the idea of using something that is off-label. In addition, the cationic oil-in-water emulsion formulation prolongs residence time on the ocular surface because the positively charged nano-sized droplets adhere electrostatically to the negatively charged mucins on the ocular surface.[18] Improving ocular retention improves absorption.[19]

I am still prescribing a compounded cyclosporine ointment for patients who have been using it for many years and are happy with the formulation. When initiating cyclosporine now, however, I am using the new cationic emulsion formulation for most patients.

Dr Messmer: I too have had problems getting patients to accept treatment with compounded cyclosporine, so I am glad to have a licensed product. In addition, I like that the cyclosporine cationic emulsion is recommended for once-daily dosing.

Some patients are still concerned about the risks of immunosuppression and infection with cyclosporine. Although the cationic emulsion contains a 2-fold higher concentration of cyclosporine than the anionic emulsion available in the United States, I am not concerned about systemic side effects based on clinical trial adverse event data and assays for cyclosporine in peripheral blood.[17,18] I discuss this information with patients.

Dr Leonardi: A high proportion of patients respond when treated with the 0.05% cyclosporine product that is commercially available in the United States, but it is not 100% effective. Dr O'Brien, do you think it would be helpful having the 0.1% product to use as an alternative?

Dr O'Brien: It would be useful to have an option that is better tolerated and that might provide the same or better efficacy with less frequent dosing. Sometimes we prescribe topical cyclosporine A, 0.05%, 4 times a day instead of the recommended twice-daily regimen in an effort to coax a better response, but the more frequent dosing can also lead to more side effects and greater intolerance.

The cyclosporine cationic emulsion is now in a phase 2 trial in the United States.[20] I am intrigued by its novel formulation, which provides a longer residence time on the eye because of electrostatic attraction between the cations and negatively charged mucins on the ocular surface. The formulation also contains triglycerides,[18] which may be beneficial for improving tear film stability.

Dr Leonardi: In fact, the vehicle in this formulation has been shown to be very effective for promoting corneal healing in an animal model.[21] In the United States, lifitegrast ophthalmic solution,

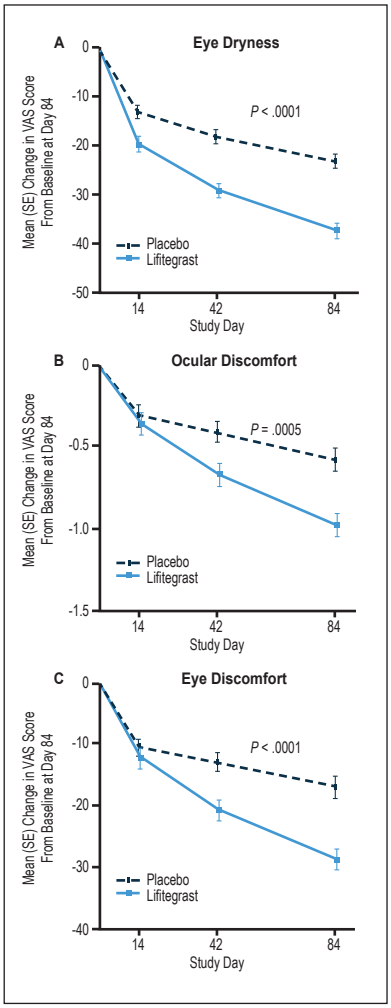

Figure 6. Change from baseline to day 84 in symptom scores in the placebo and lifitegrast groups in OPUS-2. Eye dryness was a coprimary end point.

Abbreviations: SE, standard error; VAS, visual analogue scale.

Adapted from Tauber J, et al.[23]

5%, was approved for the treatment of the signs and symptoms of DED.[22] Dr O'Brien, please tell us about this medication.

Dr O'Brien: We have been excited in the United States about having access to lifitegrast as a new immunomodulatory agent and alternative to cyclosporine. It is a lymphocyte function-associated antigen-1 antagonist that blocks both T-cell activation and the infiltration of T cells into ocular surface tissues.

The phase 3 trial results were encouraging and, in particular, showed the superiority of lifitegrast vs placebo for improving symptoms by day 14 in 2 studies **(Figure 6)** and in corneal and conjunctival staining in 1 trial.[23-25] The most common treatment-emergent adverse events associated with lifitegrast were instillation site irritation, dysgeusia, and instillation site reaction.

Dr Leonardi: Dr Figueiredo, do you think there is a role for combined immunomodulatory therapy in the management of moderate-to-severe dry eye involving cyclosporine plus another nonsteroidal agent?

Dr Figueiredo: It may be beneficial, and it might be reasonable to combine lifitegrast and cyclosporine because they have different mechanisms of action. Obviously, there is a need for clinical studies to assess efficacy and safety.

Dr Messmer: I think the combination of lifitegrast with cyclosporine is attractive because of the rapid symptom improvement that occurs with lifitegrast.[23]

Dr Leonardi: Currently, anti-inflammatory management for DED is initiated for more moderate disease. Would it be practical to prescribe the newer anti-inflammatory treatments at an earlier stage, with the aim of preventing disease progression, but recognizing that compliance with treatment may be poor among patients with mild DED, especially if they are not very symptomatic?

Dr Figueiredo: Moderate-to-severe DED started out as mild disease, so it is reasonable to think about preventive treatment. However, further study is needed to establish the efficacy and safety of anti-inflammatory agents, and it would also be helpful to find biomarkers to identify patients at risk for DED progression so we can target those most in need of early intervention.

Dr Messmer: I am starting immunomodulation earlier now than I did just a few years ago, and I expect we will see data in the future to show it is beneficial for preventing progression from moderate to more severe DED.

Dr Leonardi: Now I would like to present some cases from my files and see how you would manage these patients and how the approaches in Europe and the United States might differ.

CASE 1

A 55-year-old postmenopausal woman who works in an office presents with significant ocular discomfort, which is worse in her left eye. Her symptoms include blurred vision, foreign body sensation that worsens during the day, and a burning sensation that worsens when she is working on the computer or is in an air-conditioned environment.

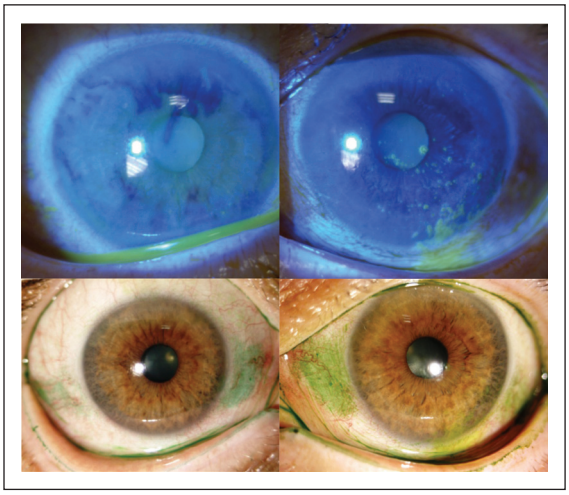

Figure 7. Findings from clinical examination

- Best corrected visual acuity: 20/20 OD, 20/20 OS
- Thin lacrimal meniscus OS
- Tear break-up time: 4-5 s
- Schirmer: 12 mm OD, 5 mm OS
- Corneal fluorescein staining: 0.5 OD, 2 OS (Oxford scale)
- Lissamine green: 1-0-2 OD, 3-1-2 OS (van Bijsterveld)

Images Courtesy of Andrea Leonardi, MD

She is on hormone replacement therapy (HRT), an antidepressant, and a beta-blocker for hypertension control. A systemic evaluation is negative for autoimmune disease. **Figure 7** shows the images and findings from her DED evaluation.

Dr Leonardi: How would you treat this patient? In particular, would you treat both eyes in the same way and would you choose any specific type of artificial tears?

Dr Pflugfelder: The primary problem in the right eye is a rapid TBUT, whereas the left eye shows aqueous deficiency and more severe ocular surface damage, so the approach to treating the 2 eyes may differ. Regarding artificial tears, I usually recommend preservative-free formulations if the patient feels the need to use them more than 4 times a day. I give patients samples of products with different viscosities so they can decide which ones they like. In addition to artificial tears, I think this patient needs anti-inflammatory therapy, in accordance with the DEWS recommendations.[7] I would use a low-dose corticosteroid for both eyes and cyclosporine for the left eye, which probably has more goblet cell loss associated with aqueous deficiency. I also recommend oral supplements containing omega-3 fatty acids and the omega-6 fatty acid gamma-linolenic acid, according to studies showing they provided a benefit for DED.[26,27]

Dr Figueiredo: For artificial tears, I tend to use what I call "low-viscosity drops." My preference is for 0.4% sodium hyaluronate, which is available in the United Kingdom. Although its viscosity is higher than that of some other artificial tears, it is lower than that of the carbomer gels and paraffin-based ointments that I use in my practice, in which many of the patients have more severe DED. To minimize the functional effect of gel-induced blurry vision, I recommend using the gel early in the morning, at lunchtime, and in the evening. Still, some patients will choose to use only the low-viscosity drop.

Patients with severe DED should use preservative-free products. They need to understand the importance of using such products because their general practitioner may recommend switching to a preserved artificial tear that costs less. I also highly recommend an ointment at bedtime for severe DED. For many years in the United Kingdom, we have been using a compounded cyclosporine ointment or some paraffin-based ointments.

Even though the right eye in this patient may not require anti-inflammatory treatment, I tend to treat both eyes in the same way. However, I would highlight to this patient the need to use artificial tears more often in the more severely affected left eye. For anti-inflammatory treatment, I would start with a topical corticosteroid and then introduce cyclosporine, 0.1%, cationic emulsion after approximately 1 month once the ocular surface inflammation is quieted down. Then, the cyclosporine will be better tolerated and patient compliance should be better.[28] I am aggressive with the corticosteroid to achieve rapid improvement, which will significantly encourage patient compliance. I start a preservative-free corticosteroid 6 times daily to every 2 hours for 7 to 10 days, and then taper it over 10 to 12 weeks, by which time there should be some degree of benefit from cyclosporine. Evidence from pivotal trials for both the 0.05% cyclosporine product and the 0.1% cationic emulsion show that it can take it can take 3 to 4 months to see a benefit.[17,29] Patients need to be educated about this delay so that they will not stop using their medication prematurely. Given their anti-inflammatory properties,[7] I also use oral omega-3 fatty acid supplements to support the management of DED, especially when it is associated with MGD.

Dr Messmer: I would treat both eyes in the same way, anticipating the potential for the right eye to worsen. I would recommend a hyaluronic acid artificial tear plus a preservative-free gel at night. In Germany, we will have a topical omega-3 product available soon, which I would prefer to use over an oral supplement, even though we need more evidence about its efficacy. I would also treat this patient with anti-inflammatory medications, starting with a corticosteroid and then adding cyclosporine, 0.1%, cationic emulsion.

Dr O'Brien: I do not have any additional recommendations beyond the excellent suggestions already outlined for treatment, but we also have to think about addressing contributing exogenous factors, including environmental issues and the effects of the oral medications this patient is taking. I would contact her mental health provider to see if she could be potentially switched to a less drying oral antidepressant without worsening her clinical depression. Recognizing the higher prevalence and effect of dry eye in women, we should step back and ask, "Which came first: the dry eye or the depression?"

Dr Messmer: I would speak to her internist about switching her to another antihypertensive medication.

Dr Pflugfelder: There are conflicting reports on the effects of HRT on DED.[30] I do not make any recommendations to patients on HRT, but counsel them to discuss it with their prescribing physician.

Dr Figueiredo: Patients need to be made aware that if they are using systemic medications that can increase ocular dryness, they may need to compensate by using more artificial tears.

Dr Leonardi: Although this patient could be considered to have mild or moderate DED, I might already consider her condition severe on the basis of the level of her symptoms and their functional effect. In addition, perhaps her problems with her vision are contributing to her depression. So this case may be more complicated than it seems in terms of choosing proper management.

CASE 2

A 38-year-old man presents with complaints about eye discomfort, irritation, tearing, occasional blurred vision, and crusting in the morning. He has had these symptoms for several months and has been using a tear substitute occasionally without finding relief. He works in a retail store, where he uses a computer occasionally.

Physical examination shows signs of seborrhea, along with mild redness on the lid margin and conjunctiva. He has no medical problems other than occasional bowel dysfunction, and is not on any medications. He reports exercising regularly by riding a bicycle. **Figure 8** shows the images and results from the DED evaluation.

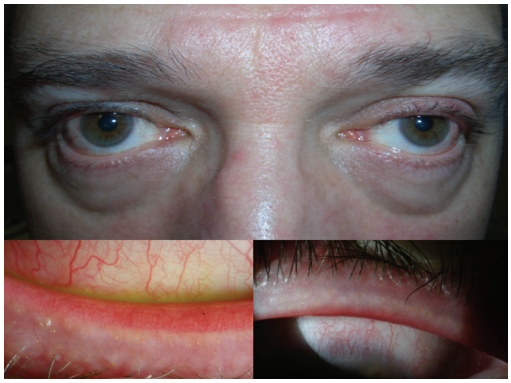

Figure 8. Findings from clinical examination

- Tear break-up time: 5-6 s
- Schirmer: 25 mm OD, 22 mm OS
- Corneal fluorescein staining: 1 lower cornea OD, 1 lower cornea OS (Oxford scale)
- Lissamine green: 1-0-1 OD, 1-0-2 OS (van Bijsterveld)
- Telangectasia on the lid margin
- Partially occluded meibomian glands, with swollen orifices and thick meibum

Images Courtesy of Andrea Leonardi, MD

Dr Leonardi: In this patient, we can tell a lot about his diagnosis by the appearance of his lids and facial skin. He obviously has MGD. Is standard lid hygiene with once-daily use of warm compresses and lid massage enough for this patient?

Dr O'Brien: I think not, and this is partly because lid hygiene is often done incorrectly. For example, patients may actually worsen their condition if they use scrubs containing detergents that break meibum down into byproducts that further destabilize the tear film, accelerating TBUT and contributing to ocular irritation.

Management of this patient's MGD should include a tear substitute to address the increased tear film evaporation, and a lipid-containing formulation may be beneficial. Use of antibiotics for MGD management is controversial. A report from the American Academy of Ophthalmology concluded there is a lack of high-level evidence supporting their efficacy.[31] In addition, the precise role of bacteria in MGD-related DED is unclear. Bacterial lipases break meibum down into free fatty acids and soaps, which are irritating to the ocular surface, so it is reasonable that an antibiotic that reduces bacterial colonization may be beneficial. However, chronic use of antibiotics will create a selection pressure and encourage the development of resistant organisms, not just in this patient, but in the global microbiosphere. I believe lid scrubs, such as those containing tea tree oil derivatives, which have antimicrobial properties, or those containing hypochlorous acid, a natural killer of bacteria derived from neutrophils not subject to the development of resistance, may be preferred. Still, I think there is a place for judicious use of both systemic and topical antibiotic therapy. The advantage of a systemic agent, such as low-dose doxycycline or infrequent azithromycin, is that it enters the meibomian glands and directly into meibum secretions, whereas topical antibiotics may not. Topical azithromycin has been shown to improve the lipid physicochemical properties of meibum, and it may also reduce bacterial lipase activity.[32,33]

Dr Pflugfelder: For this type of patient, I favor a systemic antibiotic because I find it works better than a topical agent. I use low-dose tetracyclines, such as doxycycline 20 mg twice daily or azithromycin 500 mg on day 1 and 250 mg daily for 4 days each month. I am getting very good responses with azithromycin, which was reported to give better results than doxycycline in a recent randomized controlled trial.[34]

Dr Leonardi: Those treatments are off-label and may not be eligible for reimbursement in some countries. What is the situation for using a systemic antibiotic to treat MGD in the United Kingdom?

Dr Figueiredo: I have not encountered any problems. Rather, the main concern is making sure the general practitioner does not discontinue the antibiotic, so it is important to explain the rationale to the patient. I certainly agree that a systemic antibiotic is appropriate for this patient because of his skin disease. Lately, we have been using lymecycline 408 mg once daily. It is popular among dermatologists in the United Kingdom as anecdotal treatment for rosacea, and it may be more effective than other tetracycline derivatives. Topical azithromycin only recently became available in the United Kingdom, so I have no experience with it.

I also recommend standard lid hygiene twice a day for patients with MGD. UK optometrists mostly use intense pulsed light therapy as well as the thermal and thermal pulsation devices for MGD management. I do not have any experience with these systems.

This patient also has signs of inflammation. I would start a topical corticosteroid, along with the artificial tears. I have not found any significant added benefit from using a topical lipid-based product in patients with MGD.

Dr Messmer: I would treat this patient as I would a patient with rosacea. In Germany, oral doxycycline is approved for rosacea.

Because lid hygiene is so difficult for patients to do properly, I started using a new device that has a disposable, high-speed rotating microsponge to support the effect of regular lid hygiene. The device cleans the lid margins mechanically and may help open blocked orifices of the meibomian glands. I do not have long-term experience with it yet, but my initial observations are that patients are benefiting.

In Germany, we have a number of lipid-containing artificial tears representing different formulations and viscosities. Having this variety increases the chance that patients will find something they like and will use.

Dr Leonardi: Dr O'Brien, what is the situation in the United States with the use of devices for MGD management? My impression is that these approaches are offered mostly by specialized centers, at which profit is the motive.

Dr O'Brien: In the United States, there is a subset of providers who are excessively promoting these devices. Some patients may indeed benefit significantly from such adjunctive physical therapy, but we need more studies to determine if this is true, exactly who these patients are, and if there is sufficient benefit to justify the cost. A published comparative study comparing a single 12-minute thermal pulsation treatment for MGD and standard lid margin hygiene found the thermal pulsation group had a significantly greater improvement in OSDI scores after 3 months, whereas improvement in expressible meibomian glands was similar in the 2 groups, and neither treatment led to significant improvement in any of the other objective parameters of DED that were measured.[35]

Dr Leonardi: Is anyone doing meibomian gland probing for MGD?

Dr Pflugfelder: I have done that using the Maskin probes. It can be painful and cause bleeding, and I am not convinced it provides a benefit. As Dr Messmer mentioned, I think debriding the orifices to clear some of the cornified epithelial cells may be better.

Dr Messmer: I used the Maskin probes in some patients, but perhaps it was too late in the course of the disease to provide benefit because these patients already had extensive gland atrophy. There are also no good studies showing long-term efficacy of meibomian gland probing.

Dr Leonardi: Is there a role for cyclosporine in the treatment of this patient?

Dr Pflugfelder: I have had poor results with cyclosporine in patients with MGD and normal tear volume, whereas those with aqueous-deficient DED who have moderate-to-severe ocular surface dye staining and goblet cell loss respond extremely well. I also find that cyclosporine burns more in patients who have sufficient aqueous in the tear film, and this leads to poor compliance.

CASE 3

A 43-year-old female office worker presents with severe symptoms of DED, which are poorly controlled with artificial tears. A systemic workup is negative for autoimmune disease. **Figure 9** shows the findings and images from the DED evaluation.

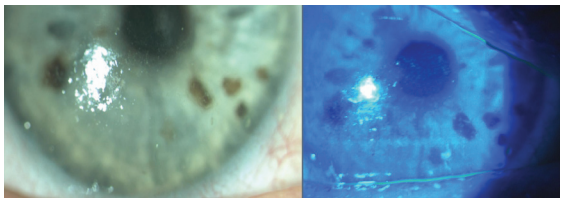

Figure 9. Findings from clinical examination

- Best corrected visual acuity: 20/20 OD, 20/20 OS
- Ocular Surface Disease Index: 45 (> 33)
- Thin lacrimal meniscus
- Tear break-up time: 2-3 s
- Schirmer: 4 mm OD, 3 mm OS
- Diffuse superficial punctate keratitis
- Corneal fluorescein staining: 4 OD, 4 OS (Oxford scale)
- Lissamine green: 2-2-3 OD, 3-3-3 OS (van Bijsterveld)
- Mild-to-moderate redness

Images Courtesy of Andrea Leonardi, MD

Dr Leonardi: This patient has a severe type of aqueous-deficient dry eye, but she does not have Sjögren syndrome. What type of artificial tears would you recommend for this patient?

Dr O'Brien: I prefer hypotonic tears to try to correct the hyperosmolarity of the tear film. I would also use a lubricant gel or ointment at night.

Dr Leonardi: This patient also requires anti-inflammatory treatment and should be started on cyclosporine. What other modalities can we offer patients with severe DED?

Dr Figueiredo: In more severe cases with aqueous deficiency, I initially use artificial tears and perform punctal occlusion using silicone plugs. It is my impression that punctal occlusion is used more aggressively in the United States and the United Kingdom than in other European countries. If the response to punctal occlusion is insufficient, I add autologous serum drops, and in the United Kingdom, we also have allogeneic serum that is supplied nationally by National Health Service Blood and Transplant and is available off-the-shelf for immediate use. Serum drops contain components, such as growth factors and vitamins, which support proliferation, migration, and differentiation of the corneal and conjunctival epithelium.[36] Despite the fact that we do not know the exact mechanism of action of serum drops, most of my patients with severe DED get a tremendous quality-of-life improvement when serum drops are started. Many patients can even reduce their need for other medications, and some use only cyclosporine once a day in combination with the serum drops.

Dr Leonardi: Serum contains many growth factors and is probably immunomodulating, but regulations in Italy require production by blood banks, so it is not so easily accessible.

Dr Messmer: In Germany, we have the same regulatory issues that limit the use of serum drops.

Dr O'Brien: In the United States, we are using an array of autologous blood products, including serum tears of varying concentrations that must be prepared and monitored very carefully, with the necessary regulatory infrastructure in place. Occasionally, we also use alternate immunomodulators, such as sirolimus and tacrolimus, in an off-label fashion, and we look forward to using lifitegrast and taking advantage of its rapid onset of action and multimodal targeted therapy. I think these different medications provide an opportunity to intervene at different points in the inflammatory cascade to achieve better control and clinical improvement.

Take-Home Points

The epidemiology of DED is changing:

- The prevalence is rising because of increased awareness and environmental and behavioral changes
- Dry eye disease is occurring more often now in younger patients and as an episodic condition because of factors such as ocular surgery and computer use

Dry eye disease is classified as being either an aqueous tear-deficient or evaporative disease:

- Understanding the DED type is important for choosing therapy
- Inflammation is important in the pathogenesis and progression of both types of DED

The diagnostic evaluation for DED should include the following:

- At a minimum, assessment of the presence and severity of symptoms, TBUT, vital dye staining for ocular surface damage, and lid margin evaluation
- Additional testing with newer instrument-based modalities, and point-of-care tests assessing tear composition may be considered according to product availability

Grading DED severity helps guide treatment decisions but is challenging:

- Severity levels in available rating schemes do not account for discordance in sign and symptom severity
- For practical purposes, clinicians might consider the severity of signs or symptoms

Artificial tears continue to be a mainstay in the treatment of DED:

- Patient preference may be the most important factor for product selection

Anti-inflammatory therapy is generally initiated for moderate or more severe DED:

- Approved medications include topical cyclosporine products (United States: cyclosporine emulsion, 0.05%; Europe: cyclosporine cationic emulsion, 0.1%), corticosteroids, omega-3 fatty acids (approval varies by country), and lifitegrast ophthalmic solution, 5.0% (United States)
- Medications used off-label include oral omega-3 and omega-6 fatty acids and antibiotics
- Cyclosporine cationic emulsion, 0.05%, is being developed for commercialization in the United States

Management of MGD may involve multimodal strategies with oral, topical, and physical treatments to improve meibum quality and clear obstructed meibomian glands.

Treatment for severe DED may include punctal occlusion and autologous or allogeneic serum drops.

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1. A basic evaluation to diagnose DED would include all the following, EXCEPT:
   A. Assessment of symptoms with a formal questionnaire
   B. Lid margin assessment
   C. Measurement of tear film osmolarity
   D. Measurement of TBUT

2. Inflammation in DED:
   A. Is involved in disease pathogenesis only in DED related to an autoimmune disease (eg, Sjögren disease)
   B. Is significant only because it can lead to permanent destruction of the lacrimal glands
   C. Is a concern only in chronic DED
   D. May be managed with certain topical or systemic antibiotics

3. Dry eye disease severity grading schemes from the DEWS and the ITF Delphi Panel on Dry Eye:
   A. Allow easy classification of disease severity in the vast majority of patients with DED
   B. Do not account for a possible mismatch between signs and symptoms of DED
   C. Have become more useful after an update, which incorporates tear film osmolarity
   D. Mainly consider the effects of DED on patient function

4. Cyclosporine cationic emulsion, 0.1%, is indicated for the treatment of adults with:
   A. Aqueous-deficient DED secondary to Sjögren syndrome
   B. DED with severe keratitis not improving with tear substitutes
   C. Evaporative DED secondary to MGD
   D. Neurotrophic keratitis

5. Lifitegrast:
   A. Is a mucomimetic agent and the first medication approved for treatment of MGD
   B. Is indicated for the treatment of DED-related symptoms on the basis of its superiority vs vehicle in 3 phase 3 trials
   C. Is indicated for the treatment of DED-related signs on the basis of its superiority vs vehicle in 3 phase 3 trials
   D. Prevents T-cell activation and infiltration into ocular surface tissues

6. Which of the following is a true statement about the role of omega-3 fatty acid treatment in DED management?
   A. Omega-3 fatty acids are a commercially available topical product that rapidly improves symptoms
   B. Oral supplementation is appropriate for consideration only in patients with MGD because they act only to improve meibum properties
   C. Oral supplementation may be considered for DED as part of an anti-inflammatory regimen
   D. There is no evidence to support a role for omega-3 fatty acids in DED

7. Meibomian gland probing for MGD:
   A. Has been demonstrated to provide a longer-term benefit than debriding the gland orifices
   B. Is comfortable, but may cause bleeding
   C. Is probably ineffective if there is extensive gland atrophy
   D. Was associated with significantly greater OSDI score improvement than standard lid hygiene in a randomized study

8. Antibiotics for the treatment of MGD:
   A. Are off-label, but may provide benefit through multiple mechanisms
   B. Should only be used topically to avoid systemic side effects
   C. Should only be given orally according to level 1 evidence establishing their efficacy and safety
   D. Are useful only in patients with staphylococcal blepharitis

9. A 62-year-old woman presents with a complaint of blurred vision. She is diagnosed with severe DED associated with MGD on the basis of evaluations that include a Schirmer test, TBUT, surface staining with fluorescein and lissamine green, tear film osmolarity measurement, lid margin assessment, and the severity of DED-related symptoms. Which of the following treatments would you likely NOT consider for initial therapy?
   A. Preservative-free artificial tears
   B. Topical cyclosporine drops
   C. Topical corticosteroid therapy
   D. Punctal occlusion

10. A 52-year-old postmenopausal woman presents with complaints of fluctuating vision. She is diagnosed with moderate mixed-type (evaporative and aqueous deficiency) DED. Which artificial tear would you recommend?
    A. A hypertonic formulation to correct tear film osmolarity
    B. A lipid-based formulation because MGD affects the lipid component of the tear film
    C. A preservative-free formulation if the patient finds it necessary to instill the drops more than 4 times a day
    D. An ointment because it has a longer retention time than a solution or gel and is preservative free

Activity Evaluation/Credit Request

ORIGINAL RELEASE: December 1, 2016
LAST REVIEW: September 19, 2016
EXPIRATION: December 31, 2017

ADVANCES IN THE SCIENCE AND MANAGEMENT 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. Mail or Fax this completed page to **New York Eye and Ear Infirmary of Mount Sinai**–ICME, 485 Madison Avenue, 17th Floor, New York, NY 10022 (Fax: 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 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

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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.
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☐ 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 1.5 *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:

• Evaluate and diagnose DED with appropriate assessment tools and techniques	5	4	3	2	1
• Describe the implications of inflammation in DED management	5	4	3	2	1
• Apply evidence-based approaches for the treatment of DED	5	4	3	2	1
• Describe clinically relevant results for newer treatments for DED	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. 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

5. 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