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CLINICAL PERSPECTIVES ON THE MANAGEMENT OF DRY EYE DISEASE

FACULTY

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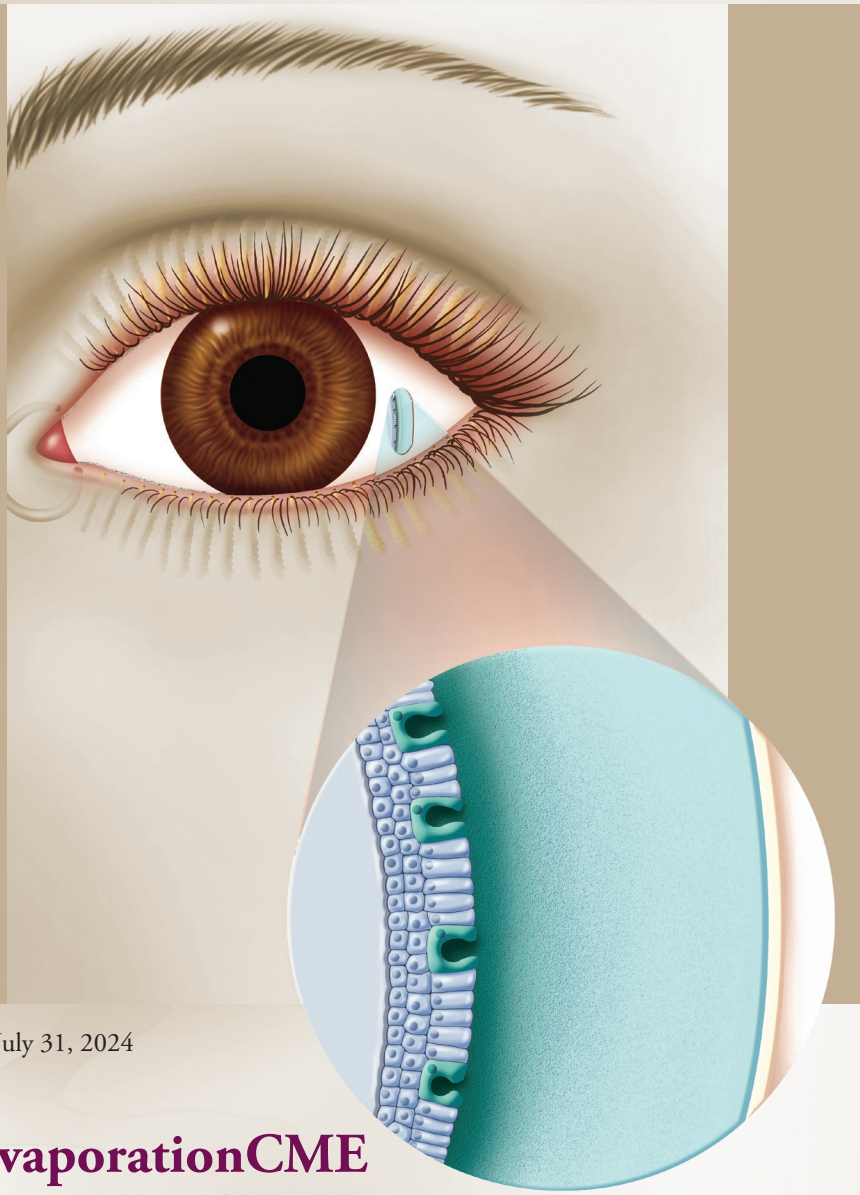

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Activity Description and Purpose

Dry eye disease is among the most common diseases affecting the eye, and its primary cause is meibomian gland dysfunction (MGD). MGD can be easily diagnosed by clinical evaluation of the quality of meibum expressed from meibomian glands. Although treatments are available to help manage the symptoms and signs of MGD, new and emerging therapies offer the opportunity to address several aspects of the underlying pathophysiology of MGD. In this educational activity, an expert panel will discuss the pathophysiology of MGD and MGD-associated dry eye disease, review current treatment options, and forecast the role of new and emerging therapies in the management of these conditions.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

After completing this activity, participants will be better able to:

- Review the function of the tear film in maintaining a healthy ocular surface
- Use diagnostic strategies that examine meibomian gland function in routine practice
- Discuss limitations of currently available treatment options for meibomian gland dysfunction–associated dry eye disease
- Evaluate clinical trial data for agents under development for the treatment of meibomian gland dysfunction–associated dry eye disease

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Cover Illustration: Illustration of the tear film (close up). The lipid layer is the outermost layer of the tear film and is produced by meibomian glands (yellow lid structures). A healthy lipid layer prevents excessive evaporative loss from the ocular surface.

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Expressions on Evaporation

CLINICAL PERSPECTIVES ON THE MANAGEMENT OF DRY EYE DISEASE

Introduction

The tear film is fundamentally important in maintaining the health and function of the ocular surface. Tear film abnormalities can cause significant discomfort and degradation of visual quality. Dry eye disease (DED) is among the most common diseases affecting the eye, and its primary cause is meibomian gland dysfunction (MGD). Meibomian glands (MGs) produce meibum, the chief component of the lipid layer of the tear film. In MGD, meibum production is impaired, leading to loss of the lipid layer and subsequent evaporative DED. MGD can be easily diagnosed by clinical evaluation of the quality of meibum expressed from the MGs. Although treatments are available to help manage the symptoms and signs of MGD, a paucity of quality data precludes the development of evidence-based treatment guidelines. New and emerging therapies offer the opportunity to address several aspects of the underlying pathophysiology of MGD. In this educational activity, an expert panel will discuss the pathophysiology of MGD and MGD-associated DED, review current treatment options, and forecast the role of new and emerging therapies in the management of these conditions.

Pathophysiology of Meibomian Gland Dysfunction

Dr Periman: We have learned a lot since the 2011 Tear Film and Ocular Surface Society MGD workshop, at which the following definition was developed by consensus: "Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease."[1] The pathophysiology of MGD is complex and involves many different pathways **(see Sidebar: The 6 Interrelated Mechanisms of Meibomian Gland Dysfunction)**, including obstruction of the MG orifices, hyperkeratinization of the duct system, increased viscosity of the meibum, microbial infection, and inflammation, all of which lead to gland dropout, reduced lipid secretion, and evaporative DED.[2]

Dr McDonald: Part of the complexity of the pathophysiology is that we do not have a full grasp of the many inciting events that initiate the disease process.

The 6 Interrelated Mechanisms of Meibomian Gland Dysfunction

Bacteria and bugs
Enzymatic compromise
Inflammation
Stasis
Temperature, altered, melting
Obstruction

Reference

1. Baudouin C, Messmer EM, Aragona P, et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. *Br J Ophthalmol.* 2016;100(3):300-306.

Dr Periman: In recognizing the multifactorial nature of MGD and its impact on DED, a double vicious circle concept has been developed to characterize the interplay between overlapping conditions of DED and MGD **(Figure 1)**.[3,4] There is no defined starting point in these cycles. For MGD, the 6 key interrelated events are microbial proliferation (bacteria, *Demodex*), altered biochemistry of the meibum, inflammation, stasis of meibum (thickened meibum and inspissation), abnormal melting temperature of meibum, and MG obstruction. For DED, the key interrelated events are tear instability, hyperosmolarity, inflammation, and damage to the ocular surface. The interactions between these 2 processes can overlap at every stage. The 2 processes drive one another, and both cycles are fueled by inflammation.

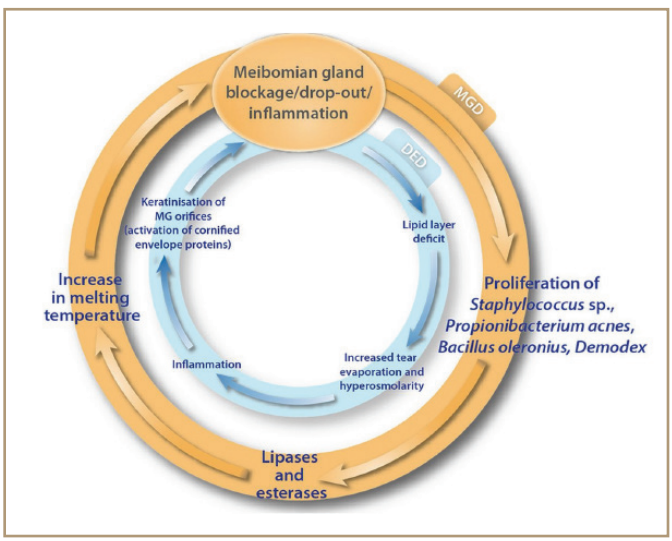

Figure 1. Double vicious circle of meibomian gland dysfunction and dry eye disease[3,4]

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Dr Nijm: This complexity—the multifactorial nature of the disease and the many pathways that lead to evaporative DED—provides multiple potential therapeutic targets for intervention. As a result, there are drugs that address the loss of the lipid layer or hyperkeratinization component and novel antimicrobials that combat common infectious etiologies.

Dr McDonald: Hyperosmolarity is an early finding in the cycle and disease process. Many patients have clinical signs of DED, such as hyperosmolar tears, before they have any clinical symptoms of DED.[5,6]

Dr Periman: That is a very important point. There are opportunities to identify and treat patients early in the disease process of MGD and DED. The focus on treating inflammation in DED has existed for a long time. By also addressing the evaporative load, we can stabilize the tear film and decrease this inflammatory driver.

Dr Trattler: I view inflammation as the end result of all these contributory factors. Low tear volume and rapid evaporation result in irritation to the eye, which results in inflammation.

Dr Nijm: Tear hyperosmolarity results from excessive evaporation, which is the inciting factor that drives inflammation.[7] Once hyperosmolarity is present, the rest of the double vicious circle will follow.

Dr Periman: The hyperkeratinization component is interesting. Why does it occur? We know that the addition of as little as 10% additional keratin into the meibum protein composition increases the rigidity of the meibum and destabilizes the tear film.[8] Keratin also raises meibum's melting point, increasing viscosity and contributing to stasis. Evidence suggests that enzymes released from the bacteria of the normal lid flora may contribute to hyperkeratinization.[2]

Dr McDonald: In-office procedures, such as microblepharoexfoliation, can address surface hyperkeratinization. These procedures, however, do not address hyperkeratinization within the ducts. This is an attractive therapeutic target that is the focus of at least 1 agent in development.[9,10]

Dr Trattler: The benefit of MG probing might be related to disruption of this hyperkeratinization covering the MG orifices, although it appears probing is not a popular treatment option at present.

Dr McDonald: I think probing is unpopular because it is time consuming and also because there is no code for it. If you do not perform it frequently, you may make the patient very uncomfortable and they may have swollen bloody lids for 2 or 3 days. As a result, probing has fallen out of favor, except in the hands of experts.

Dr Trattler: Key diagnostic and treatment opportunities exist during the preoperative assessment for ocular surgery. MGD and DED are common in eyes undergoing surgery. For example, MG atrophy has been reported in 56% to 95% of eyes at the time of preoperative cataract surgery evaluation.[11,12] With regard to DED, a prospective study of 272 eyes undergoing cataract surgery reported 63% had tear breakup time of ≤ 5 seconds, 77% had positive corneal staining, and 47% had Schirmer score of ≤ 10 mm.[13] Furthermore, a recent study found that 18% of 1404 patients undergoing refractive surgery had tear film hyperosmolarity (> 308 mOsm/L).[14]

Dr Periman: Proper management of these ocular surface issues are critical to optimizing the outcomes of surgical procedures.

Dr Nijm: It is remarkable how much of a difference treating the ocular surface can make in relation to outcomes. You can be an incredible surgeon, but if you ignore the ocular surface, your patient outcomes will suffer. It does not matter what type of surgery you are doing.

Dr Trattler: A perioperative course of topical cyclosporine has been shown to improve surgical outcomes following cataract surgery,[15] including when used in patients receiving multifocal intraocular lenses and in patients undergoing LASIK (laser-assisted in situ keratomileusis).[16,17]

Dr McDonald: The importance of managing lid disease preoperatively goes beyond optimizing the tear film for best postoperative optical quality. Patients with blepharitis have a higher bacterial load than those without.[18] These bacteria are what cause postoperative endophthalmitis. In several studies of patients with postoperative endophthalmitis, the bacteria that grew from the vitreous cultures matched the bacteria on the lid very closely.[19,20]

Tear Film Alterations in Meibomian Gland Dysfunction

Dr Periman: For decades, we embraced a 3-layer model of the tear film: an inner mucus layer, a middle aqueous layer, and an outer lipid layer.[21] A more contemporary view of the tear film is a biphasic model consisting of a mucin-aqueous glycocalyx gel with a decreasing mucin gradient from the ocular surface to the lipid layer **(Figure 2)**.[22] Note that the structure, location, and importance of the lipid layer remains unchanged as we shift to this new model. The lipid layer's role remains to prevent evaporation of the aqueous component of the mucin-aqueous layer. Loss of the lipid layer in eyes with MGD leads to evaporative DED. The goal of the new model is to underscore that the mucin and aqueous layers are not anatomically or functionally distinct.

The primary source of the lipid layer is the MGs. The quality of meibum is thus an important factor in the structure and function of the lipid layer. What types of events or conditions affect the quality of meibum? A recent study demonstrated that the presence of *Demodex* with MGD was associated with markedly altered differences in meibum composition compared with normal and MGD without *Demodex* present.[23]

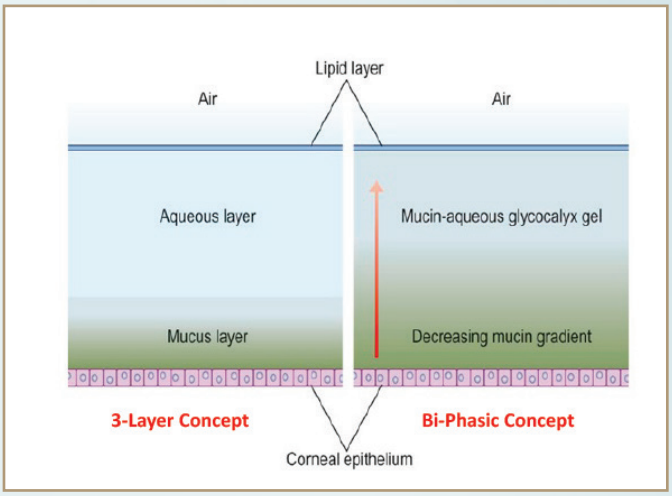

Figure 2. Historical 3-layer and more contemporary 2-layer (biphasic) model of the tear film[22]

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Dr Trattler: There are tear replacements with a lipid component that is meant to supplement the lipid layer. I have not been able to gauge their value in my patients.

Do you have any experience with these products?

Dr McDonald: In my experience, although most patients find a tear product that they like best, it seems like it is a different product for every patient. There does not seem to be one that most patients prefer over others.

Dr Periman: I find that tear product preference is highly individual. I have not been able to predict which tear product a patient is going to like best. With over-the-counter tears, who knows how long the lipid-containing components will stay on the ocular surface? Duration of effect matters as well.

Dr Nijm: I agree that tear product preference can be variable. I also think it is important for clinicians to take the lead in educating and recommending preservative-free products that have high-quality components and, ideally, studies that support their use. It is the one area for which the clinician's recommendation can make a big difference because, ultimately, it is the patient's choice, not one dictated by insurance.

Diagnosis of Meibomian Gland Dysfunction and Dry Eye Disease

Dr Periman: Diagnosing MGD can be problematic. As we discussed previously, there can be a significant mismatch between signs and symptoms of ocular surface disease.[5,6]

Patients can have mild or even moderate MGD and not have any symptoms. This is the ideal time to start treatment—before the ocular surface has been damaged enough to be symptomatic. Even among symptomatic patients, the diagnosis of MGD can be difficult because the symptoms are not specific to MGD. Other ocular surface conditions, such as DED and blepharitis, can have the same constellation of symptoms: burning, stinging, and blurring. MGD can also occur secondarily to other conditions, such as rosacea. Therefore, the first step to diagnosing MGD is to have a high level of clinical suspicion and assessment of risk factors, use patient symptom questionnaires, and to look for signs of MGD on the clinical examination.

My approach is to start with dermatologic inspection of the face. Are there signs of rosacea? I examine the lids for scurf, collarettes, or other signs of lid disease. I stain the ocular surface, and then evaluate the expressibility of the MGs. I pay attention to the quality and consistency of the meibum. Do you think the quality of the meibum matters in identifying MGD and selecting treatment?

Dr Nijm: I absolutely do. More than any other assessment, inspection of the meibum is the most direct and quickest way to detect MGD. If I express the glands and the meibum comes out in a toothpaste consistency or I cannot even get secretions, the MGs are severely dysfunctional and the MGD needs to be treated aggressively.

Dr McDonald: I also get tear osmolarity on most patients, and I will add meibography as needed. Meibography does not necessarily change my treatment plan, but it is a strong visual aid to help patients understand the disease and take it seriously.

Dr Periman: Do you grade the severity of MG dropout in your patients?

Dr McDonald: Yes. We should also discuss Schirmer testing. The US Food and Drug Administration (FDA) sees it as a valuable clinical trial end point, but I am less convinced of its clinical value. Its positive predictive value is less than that of other tests for DED. I do not perform it routinely. Plus, it is quite time consuming.

Dr Trattler: I evaluate the tear meniscus height. I also look for conjunctivochalasis at the same time.

Dr Periman: To summarize the evaluation, we inspect the face and lids, stain the ocular surface, express the glands, evaluate the tear meniscus, and note the presence of conjunctivochalasis. Meibography is an add-on to assess disease severity and help with patient education and motivation to adhere to therapy.

In the context of diagnosis, given the high degree of overlap between MGD and DED, how important is it to separate these 2 conditions in terms of diagnosis and treatment? Is it best to develop an integrated comanagement plan?

Dr Nijm: The 2 conditions are so intertwined that I tend to think of a Venn diagram. In each patient, I assess the degree of overlap and tailor treatment accordingly, depending on which condition is predominant.

Dr McDonald: When I see patients, I quickly grade their MGD and separately grade their DED. One study reported that 86% of 224 patients with DED also had MGD.[24] MGD is recognized as the most common cause of evaporative DED.[25] Although the conditions—DED and MGD—may be distinct, their overlap is substantial and comanagement is critical.

Dr Periman: My approach is to identify all the contributory components of MGD and DED at play in the vicious circle on a patient-by-patient basis, and then develop a treatment plan that addresses as many of them as possible.

Dr McDonald: I think the biggest obstacle for most clinicians is that they are uncomfortable facing the challenge of having patients with DED. Many are busy surgeons—cataract and refractive surgery—and the detection and management of ocular surface disease during the preoperative assessment is an unwelcome distraction. Studies have shown that surgical outcomes in these patients depend on successful management of DED.[15-17] I strongly advise that perioperative diagnosis and management of DED occur. If surgeons feel uncomfortable diagnosing and managing DED, they should consider referring these patients to providers who are. The patients can be treated and then sent back to the referring physician for surgery.

Current Treatments for Meibomian Gland Dysfunction

Dr Periman: There is a wide array of therapeutic approaches and options for MGD. As a general rule, I start with the simplest, least-invasive, and least-expensive options, which include warm compresses, artificial tears, and lid hygiene.[26] Patients are often receptive to over-the-counter artificial tears because they make sense to them. Their eyes are dry, so we have them put in lubricating drops to address the dryness. It is also an empowering approach—they can choose when they need to administer the drops. My preference is preservative-free artificial tears because we are all well aware of the adverse effects of preservatives on the health of the ocular surface.[27]

Dr McDonald: The downsides to preservative-free artificial tears are the added expense and packaging. Those single-use vials contribute to the burden of plastic-based pollution in the world. A few companies have come up with preservative-free products in multidose bottles, which significantly reduces both the cost and the wasted plastic.

Dr Nijm: The newer, multidose, preservative-free bottles have been a great addition for my patients. They prefer not having to carry individual vials, and the multidose bottles are more cost effective. It seems no matter what treatment we use, patients with DED still reach for tears to use.

Dr Trattler: Warming therapy can also be helpful.[26] Warm compresses are simple, but thermal therapy alone may not be as effective as thermal therapy with expression. This can be accomplished by adding digital massage after warming. Some products are available for in-home use by patients to warm and compress the lids to optimize meibum expression. For patients who do not respond well to in-home therapy, in-office systems provide thermal therapy with expression or intense pulsed light (IPL).[28] Gland probing, as discussed previously, is also available.

Dr Periman: Another in-office procedure is manual or mechanical microblepharoexfoliation, a procedure that removes debris, bacteria, and the bacterial biofilm from the lid margin. It has particular value in eyes with MGD related to *Demodex* infection and has also been reported to be helpful in eyes with chalazia.[29-31] It can be performed with a kit or a rotating brush that essentially buffs the lid margin free, but I prefer to do it manually using an okra-extract gel and sponge tip wand; you can actually feel the lid margin and eyelash bases becoming smoother as you do it. In this age of viral spread through tears and the potential for *Demodex* spread, I like the manual kit approach better than the mechanical rotating brush to limit the dispersal of microbes and debris.

Dr Trattler: Hypochlorous acid is also effective in reducing the bacterial load on the lids.[32] This can be easily applied by patients at home.

Dr Nijm: I have been using hypochlorous acid more frequently in the past 6 months. I think it makes a difference, especially in eyes with *Demodex*.

Dr McDonald: We do not yet have a drug specifically indicated for the treatment of *Demodex* infection, but there is one in development that we will discuss in the next section.

What do you tell your patients when you have diagnosed them with *Demodex*? How do you tell them that they have "bugs" in their eyes, but that you have no specific treatment to eradicate the bugs—without alarming the patients?

Dr Nijm: To minimize the shock and potential stigma, I tell patients that they have mites, similar to dust mites, but a few more than average.

Dr Periman: I show them the organisms under the microscope. Although we do not yet have a specific therapy to target *Demodex*, you can effectively control the load using microblepharoexfoliation and IPL.

Dr McDonald: I find that when I tell people that they have mites, they do not believe me and think I am crazy. I have decided to wait until we have an FDA-approved treatment before telling them again.

Dr Periman: In the meantime, we have nonspecific pharmacotherapies, including antibiotics such as azithromycin and doxycycline, anti-inflammatory agents such as cyclosporine and lifitegrast, and topical corticosteroids for acute exacerbations.

Dr Trattler: Doxycycline and minocycline have value beyond their antibiotic properties. These drugs alter the composition of meibum, making it less turbid and more liquid, thereby improving meibum flow and MGD symptoms.[33]

Dr Nijm: I think that is an excellent point. This is especially true for patients with rosacea whom I have treated many times with doxycycline, and who have seen their DED and MGD improve with their skin findings.

Dr McDonald: In terms of drug therapy for DED and MGD, there is also varenicline nasal spray. This drug acts on the trigeminal parasympathetic pathway to stimulate the production of natural tears from the lacrimal glands and goblet cells.[34] In recent studies, it is at least as effective and possibly more effective than cyclosporine and lifitegrast in improving the signs and symptoms of DED.[34,35] Patients tolerate varenicline well so long as you warn them about the tingle and sneezing that accompany dosing; pinching the nose and positioning the tongue to the roof of the mouth helps.

Dr Periman: What is the role of omega fatty acid supplementation? Do you talk to your patients about nutrition if they have DED and MGD?

Dr McDonald: Yes, and I do use omega-3 fatty acids. Some of my patients tell me that they do not need them because they eat fish 3 times a week. The reality is that eating fish *3 times a day* would not produce therapeutic blood levels. Supplementation is necessary.

Dr Periman: Neurostimulation is another therapeutic option. This approach has resulted in improvements in the signs and symptoms of DED.[36] I think neurostimulation is particularly valuable in postoperative patients, that is, after cataract or refractive surgery that involves the cutting of corneal nerves. This is an alternate pathway to stimulate the neurosensory pathway to complete tear production.

Dr Nijm: I agree. Neurostimulation, be it mechanical or pharmacological, offers patients a completely different mechanism of inducing tear production.

Dr Trattler: It is great that we have so many different treatment modalities for MGD. Despite this, we lack quality research to clarify the optimal order in which to use them, how to combine them, and to know which patients will best respond to which treatments. It is unclear to me how many different therapies I should start at the time of diagnosis. Too few, and patients get frustrated with their lack of progress and quit. Too many, and patients get overwhelmed and quit. It is often a matter of trial and error.

Dr Nijm: I completely agree. It is important to manage expectations from the start. I explain to patients that we have many different options and we will work through them until we find the treatments that work for them. In terms of in-home treatments, I make it clear up front that they only work if they do them at home.

Dr Periman: It helps to see these patients at short intervals during the initial treatment period and to reinforce the message at each visit. It is too much to take in all at once, but over time, if they hear the message repeatedly, it will stick better.

Dr McDonald: My approach depends on where the patients are in the diagnosis and treatment experience. For newly diagnosed patients, I start somewhat slowly, so as not to overwhelm them. If I am the seventh physician patients are consulting for their MGD, and they are miserable, I launch a comprehensive multitreatment approach from the start.

Dr Periman: One of the major limitations of current therapies for MGD/DED is the nature of the conditions themselves. They are so multifactorial that no single agent or treatment is going to cure every patient, and no 2 patients have the same experience or expectations. We have multiple treatment options, but we lack high-quality clinical practice studies to inform our treatment decisions. Customizing our approach to MGD on a patient-by-patient basis is the essence of practicing the art of medicine.

New and Emerging Therapies for Meibomian Gland Dysfunction

Dr Periman: A number of novel and innovative therapies for MGD and DED are in late-stage clinical development. The FDA recently approved one.[37] This newly approved therapy is perfluorohexyloctane, 100% (F6H8), an inert, anhydrous semifluorinated alkane.[38-40] Perfluorohexyloctane has a dual mechanism of action. It has low surface tension and spreads rapidly across the ocular surface to stabilize the tear film at the film-air interface to prevent evaporation. When placed over saline in vitro, it reduced evaporation by approximately 80%.[41] Secondly, it penetrates the glands and liquifies meibum to enhance meibum flow.[38,42,43] Its refractive index is similar to that of tears, so it has minimal effects on visual acuity.[39] Eye drops with an equivalent composition (100% F6H8) are already approved in Europe, Australia, and New Zealand for the treatment of evaporative DED mainly caused by MGD.[42]

Dr Trattler: Perfluorohexyloctane is very different from artificial tears. Artificial tears have a predominantly aqueous component, whereas perfluorohexyloctane is 100% alkane that will actually stay on the ocular surface and help patients feel more comfortable.

Dr Periman: The bead of water that forms on a newly waxed car happens because water has a high surface tension. In contrast, perfluorohexyloctane has a low surface tension, so it does not bead up. Instead, it spreads across the ocular surface and serves as a supplement to the lipid layer to prevent evaporation of the tear film.[38-40,42] Following encouraging results from a phase 2 study (SEECASE),[42] a pair of phase 3 randomized trials—GOBI and MOJAVE— were conducted and served as the basis for its approval for the treatment of DED.[39,40] Both studies randomly assigned 1199 patients 1:1 to receive either perfluorohexyloctane, 100%, or hypotonic saline 4 times daily for 8 weeks. The primary outcomes in both studies were changes from baseline in total corneal fluorescein staining (tCFS) and Visual Analogue Scale eye dryness score (EDS) (0-100 scale, with 100 being extreme dryness).

Both GOBI and MOJAVE met the primary end points, showing statistically significant differences favoring perfluorohexyloctane over control in change from baseline to week 8 in tCFS (mean treatment difference of -1.0 and -1.2, respectively) and in Visual Analogue Scale EDS (-7.7 and -105, respectively) ($P < .001$ for all comparisons) **(Figure 3)**.[39,40] Perfluorohexyloctane also demonstrated statistical superiority to control in both studies in the 4 key secondary end points, looking at changes from baseline in EDS and tCFS at week 2, burning or stinging score at week 8, and central corneal fluorescein staining at week 8.

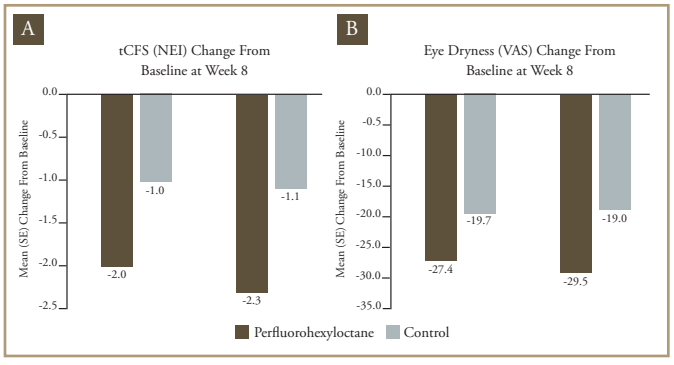

Figure 3. Mean change from baseline at week 8 for the primary efficacy end points in GOBI and MOJAVE[39,40]

Abbreviations: NEI, National Eye Institute; SE, standard error; tCFS, total corneal fluorescein staining; VAS, Visual Analogue Scale.

Perfluorohexyloctane was well tolerated in both studies, with only a single patient discontinuing treatment because of an adverse event (AE) (severe eye irritation).[39,40] Drug-related ocular AEs occurred in 6.3% of 303 patients receiving perfluorohexyloctane in GOBI and in 6.4% of 311 patients receiving perfluorohexyloctane in MOJAVE; all events but 1 were rated mild or moderate in severity. Blurred vision, affecting 3.0% of patients receiving perfluorohexyloctane in GOBI, was the only ocular AE in the perfluorohexyloctane groups occurring at a rate > 1.6% across both studies.

Dr Nijm: It is worth noting that the patients in the trials had significant disease.[39,40] At baseline, they had MGD and moderate to severe DED at study entry (adults with a tear breakup time of ≤ 5 seconds, Schirmer I test score ≥ 5 mm, MGD score ≥ 3 [range, 0-15], and tCFS score between 4 and 11 [range, 0-15]).

Understanding that this was their starting point, to see this much improvement in both signs and symptoms is impressive. The rapid onset of improvement will also have positive effects on the treatment adherence of patients.

Dr Periman: Perfluorohexyloctane is dosed 4 times a day.[37] Although that might seem like a high treatment burden for some diseases such as glaucoma, our patients with DED are used to putting in their artificial tears at least that often and will not have a problem with the dosing frequency, especially with treatments that work.

The control agent in both GOBI and MOJAVE was a hypotonic saline solution.[39,40] That is important because, to a greater extent than isotonic saline (which was the control in the phase 2 SEECASE study[42]), hypotonic saline can temporarily reverse the hyperosmolarity of tears in DED/MGD and may have a therapeutic benefit of its own.[44] Thus, the bar for demonstrating significantly greater benefit of perfluorohexyloctane, 100%, over control was higher in the phase 3 studies than in the phase 2 study, and investigators achieved it despite this higher bar.

Dr McDonald: The safety profile was favorable as well.[39,40] The only AE occurring in ≥ 2% of eyes in GOBI was blurred vision, which occurred in only 3% of patients receiving perfluorohexyloctane, 100%, vs 0.3% of patients receiving saline.[39] This translates to a shorter discussion with patients when prescribing the drug, and less for them to have to remember.

Dr Nijm: I think, naturally, we would like to know more about the nature of the blurred vision episodes. Were they transient upon instillation or continuous? Mild, moderate, or severe? That being said, importantly, only 1 of the 303 patients who received perfluorohexyloctane in GOBI discontinued therapy because of AEs compared with 3 in the saline group, so blurred vision did not seem to dissuade patients from using perfluorohexyloctane.[39] It is great to see such a strong safety profile.

Dr Periman: Which patients will you treat first with perfluorohexyloctane?

Dr McDonald: I believe perfluorohexyloctane could benefit a wide variety of patients. Because the clinical data support its quick action—with improvements in corneal staining within the first 2 weeks[39,40]—it will be particularly useful in preoperative patients to optimize the ocular surface before presurgical biometry.

Dr Trattler: On the basis of its mechanisms of action, this drug would be expected to work at all levels of dryness, from mild to severe. Because it replaces the lipid layer of the tear film,[38,42] it should work in people whose DED/MGD arises from multiple etiologies. Most patients would be expected to benefit from it. This may be one of those drugs for which you look for reasons not to use it rather than reasons to use it.

Dr Periman: Another drug currently under FDA review with possible approval in August 2023 is TP-03 or lotilaner.[45] Formulated as a 0.25% solution dosed twice daily for 6 weeks, this drug is a highly lipophilic antiparasitic that eradicates *Demodex* mites by selectively inhibiting parasite-specific gamma-aminobutyric acid chloride channels, effectively paralyzing and killing them.[46] In a phase 2b/3 study (SATURN-1) in patients with *Demodex* blepharitis, a greater percentage of patients receiving TP-03 (n = 209) vs placebo (n = 204) achieved complete collarette cure (a score of 0 on a 0-4 scale) (44.0% vs 7.4%, respectively; $P < .0001$) and mite eradication (0 mites/lash) (67.9% vs 17.6%, respectively; $P < .0001$).[46]

A second phase 3 study (SATURN-2) demonstrated similar results.[47] Collarette cure was achieved in 56% of 193 patients receiving TP-03 vs 12.5% of 200 patients receiving placebo, and mite eradication occurred in 52% of 193 patients receiving TP-03 vs 15% of 199 patients receiving placebo ($P < .001$). The most common AE was instillation-site pain/burning/stinging, which occurred in 7.9% of 203 patients receiving TP-03 and in 6.7% of 209 patients receiving control.

Dr Nijm: The clearance rate of 56% in eradicating the mites was something that I found notable because we are unable to accomplish that with any currently available treatments.[47] To be clear, we typically refer to collarettes as being associated with staphylococcal infections, and sleeves as pathognomonic for *Demodex*. In these studies, the term "collarettes" is being used in a broader sense to include sleeves, or what is often referred to as cylindrical dandruff.[46,47]

Dr Trattler: If the collarettes, or sleeves, are pathognomonic for *Demodex*, do you need to see the organism to start treatment? If there are sleeves, do you have to epilate the lashes and look for *Demodex* on the roots or can you just treat according to the sleeves alone?

Dr Periman: I think for busy clinicians, collarettes or sleeves alone support the initiation of treatment, but if you are a dedicated DED specialist, it is not unreasonable to go the extra mile, pull the lashes, and confirm the presence of the mite.

Dr McDonald: Once the mites are eradicated, the MGD improves significantly.

Dr Trattler: What is your current strategy for mite eradication?

Dr Periman: We use a combination of professional skincare, compounded topical creams with ivermectin and IPL treatments, to get control of the mite load.

Dr McDonald: Blepharoexfoliation and thermal pulsation therapy performed at the same sitting, and hypochlorous acid scrubs twice daily at home.

Dr Periman: There is 1 additional medication in development to discuss. AZR-MD-001 is a 0.5% selenium sulfide ophthalmic

ointment containing the active ingredient in shampoos used to treat seborrheic dermatitis. It is both keratolytic—breaking down the disulfide bonds in keratin to soften meibum—and keratostatic—slowing the production of abnormal keratin to prevent future MG blockage and to improve the quality of meibum.[9,10]

A phase 2 randomized trial was recently conducted to evaluate the effectiveness of AZR-MD-001 in eyes with MGD.[48,49] Patients (N = 245) with an MG expressibility score (MGS) of ≤ 12 and Ocular Surface Disease Index (OSDI) score of > 13 randomly received AZR-MD-001 (in concentrations of 0.5% or 1.0%) or vehicle applied to the lower eyelid twice weekly for 3 months. Outcomes included MGS, the number of MGs yielding liquid secretions, and OSDI. AZR-MD-001, 0.5%, met the coprimary end points, significantly improving the signs (number of MGs yielding liquid secretions, $P = .0005$) and symptoms (OSDI total score, $P = .02$) of MGD vs control at month 3.[48] Approximately 47% of 82 patients receiving AZR-MD-001, 0.5%, became completely nonsymptomatic (OSDI < 13) at 3 months compared with 28.2% of 80 patients receiving control ($P < .02$). Meibum quality (MGS) also improved significantly from baseline with AZR-MD-001, 0.5%, compared with control at month 3 (69% vs 44%, respectively; $P = .007$). Adverse events included application site pain, superficial keratitis, corneal staining, eye pain, and increased lacrimation; most were mild to moderate in severity.[49] Discontinuation rates due to AEs were 2.4% with AZR-MD-001, 0.5%; 1.2% with AZR-MD-001, 1.0%; and 0% with control. A phase 3 study of AZR-MD-001, 0.5%, for MGD is expected to commence in the second half of 2023.[50]

Dr McDonald: The role of hyperkeratinization in the pathophysiology of MGD is only recently coming to light. Many questions remain unanswered. Why does it occur? How deep into the glands does it occur? It is exciting to have a new way to think about the disease process, and even more exciting to have a treatment in development directed to this new therapeutic target.

Dr Trattler: I am encouraged that this new therapy may get right to the root cause of the MGD disease process. It will be interesting to examine serial meibography over time and see if we can demonstrate changes in the MG structure after therapy with this agent.

Dr Nijm: The twice-weekly dosing will be helpful in achieving adherence owing to ease of compliance.

Dr Periman: It is also helpful that selenium disulfide is a familiar molecule that has been used in dermatology for decades. The next few years could see a significant paradigm shift in our approach to MGD and DED. When I think of a typical patient who might present to me in 1 or 2 years, I can foresee starting with perfluorohexyloctane, 100%, to immediately stabilize the tear film while also treating with AZR-MD-001 to address the hyperkeratinization that is a common aspect of MGD. If there is a *Demodex* component, TP-03 can be added to effectively eradicate the mites. If the latter 2 drugs also gain approval, all 3 could immediately be integrated into our clinical practice patterns and reinvent the way we manage MGD.

Take-Home Points

- A healthy tear film consists of a mucin-aqueous layer and a lipid layer; in eyes with MGD, the lipid layer is compromised, leading to evaporative DED
- The most effective and efficient way to diagnose MGD is to express and grade the quality of meibum from the MGs
- Many treatments for MGD are available, but there are no clear evidence-based guidelines for the development of treatment plans for individual patients
- Newly approved and emerging therapies may offer the opportunity to address the underlying pathophysiology of MGD—including tear film lipid layer supplementation to prevent evaporative tear loss, reversal of hyperkeratinization that decreases meibum flow, and eradication of *Demodex* infestation

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References

1. Nichols KK, Foulks GN, Bron AJ, et al. The International Workshop on Meibomian Gland Dysfunction: executive summary. *Invest Ophthalmol Vis Sci.* 2011;52(4):1922-1929.
2. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The International Workshop on Meibomian Gland Dysfunction: report of the Subcommittee on Anatomy, Physiology, and Pathophysiology of the Meibomian Gland. *Invest Ophthalmol Vis Sci.* 2011;52(4):1938-1978.
3. Baudouin C, Messmer EM, Aragona P, et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. *Br J Ophthalmol.* 2016;100(3):300-306.
4. Geerling G, Baudouin C, Aragona P, et al. Emerging strategies for the diagnosis and treatment of meibomian gland dysfunction: proceedings of the OCEAN group meeting. *Ocul Surf.* 2017;15(2):179-192.
5. Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol.* 2014;92(2):161-166.
6. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea.* 2004;23(8):762-770.
7. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification report. *Ocul Surf.* 2017;15(3):276-283.
8. Gupta PK, Periman LM, Lain E, et al. Meibomian gland dysfunction: a dermatological perspective on pathogenesis and treatment outlook. *Clin Ophthalmol.* 2021;15:4399-4404.
9. Epstein-Barash H, Rapaport H, Alster Y, Rafaeli O. Keratolytic and keratostatic activity of selenium disulfide and its disease modifying role in meibomian gland disease. *Invest Ophthalmol Vis Sci.* 2021;62(8):692.
10. Alster Y, Epstein-Barash H, Rapaport H, Rafaeli O. Lipogenic activity of selenium disulfide and its role in enhancing lipid production in meibomian glands. *Invest Ophthalmol Vis Sci.* 2021;62(8):693.
11. Yeu E, Koetting C, Calvelli H. Prevalence of meibomian gland atrophy in patients undergoing cataract surgery. *Cornea*. Accepted manuscript. Published online January 12, 2023. doi:10.1097/ICO.0000000000003234

12. Cochener B, Cassan A, Omiel L. Prevalence of meibomian gland dysfunction at the time of cataract surgery. *J Cataract Refract Surg.* 2018;44(2):144-148.
13. Trattler WB, Majmudar PA, Donnenfeld ED, McDonald MB, Stonecipher KG, Goldberg DF. The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study: the effect of dry eye. *Clin Ophthalmol.* 2017;11:1423-1430.
14. Xuan R, Lawless M, Sutton G, Hodge C. Prevalence of tear film hyperosmolarity in 1150 patients presenting for refractive surgery assessment. *J Cataract Refract Surg.* 2022;48(4):387-392.
15. Hovanesian JA, Berdy GJ, Epitropoulos A, Holladay JT. Effect of cyclosporine 0.09% treatment on accuracy of preoperative biometry and higher order aberrations in dry eye patients undergoing cataract surgery. *Clin Ophthalmol.* 2021;15:3679-3686.
16. Donnenfeld ED, Solomon R, Roberts CW, Wittpenn JR, McDonald MB, Perry HD. Cyclosporine 0.05% to improve visual outcomes after multifocal intraocular lens implantation. *J Cataract Refract Surg.* 2010;36(7):1095-1100.
17. Salib GM, McDonald MB, Smolek M. Safety and efficacy of cyclosporine 0.05% drops versus unpreserved artificial tears in dry-eye patients having laser in situ keratomileusis. *J Cataract Refract Surg.* 2006;32(5):772-778.
18. Groden LR, Murphy B, Rodnite J, Genvert GI. Lid flora in blepharitis. *Cornea.* 1991;10(1):50-53.
19. Speaker MG, Milch FA, Shah MK, Eisner W, Kreiswirth BN. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. *Ophthalmology.* 1991;98(5):639-649.
20. Bannerman TL, Rhoden DL, McAllister SK, Miller JM, Wilson LA. The source of coagulase-negative staphylococci in the Endophthalmitis Vitrectomy Study. A comparison of eyelid and intraocular isolates using pulsed-field gel electrophoresis. *Arch Ophthalmol.* 1997;115(3):357-361.
21. Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II Tear Film report. *Ocul Surf.* 2017;15(3):366-403.
22. Cohen Y, Trokel S, Arieli Y, Epshtien S, Gefen R, Harris A. Mapping the lipid layer of the human tear film. *Cornea.* 2020;39(1):132-135.
23. Gao H, Chen H, Xie H-T, Xu K-K, Shi B-J, Huang Y-K. Changes in meibum lipid composition with ocular *Demodex* infestation. *Transl Vis Sci Technol.* 2021;10(14):6.
24. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea.* 2012;31(5):472-478.
25. Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The International Workshop on Meibomian Gland Dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. *Invest Ophthalmol Vis Sci.* 2011;52(4):1994-2005.
26. Geerling G, Tauber J, Baudouin C, et al. The International Workshop on Meibomian Gland Dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci.* 2011;52(4):2050-2064.
27. Goldstein MH, Silva FQ, Blender N, Tran T, Vantipalli S. Ocular benzalkonium chloride exposure: problems and solutions. *Eye (Lond).* 2022;36(2):361-368.
28. Beining MW, Magnø MS, Moschowits E, et al. In-office thermal systems for the treatment of dry eye disease. *Surv Ophthalmol.* 2022;67(5):1405-1418.
29. Epstein IJ, Rosenberg E, Stuber R, Choi MB, Donnenfeld ED, Perry HD. Double-masked and unmasked prospective study of terpinen-4-ol lid scrubs with microblepharoexfoliation for the treatment of *Demodex* blepharitis. *Cornea.* 2020;39(4):408-416.
30. Murphy O, O'Dwyer V, Lloyd-McKernan A. The efficacy of tea tree face wash, 1, 2-octanediol and microblepharoexfoliation in treating *Demodex folliculorum* blepharitis. *Cont Lens Anterior Eye.* 2018;41(1):77-82.
31. Zhu D, Gupta RR, Stein RL, et al. Randomized prospective evaluation of microblepharoexfoliation BlephEx as adjunctive therapy in the treatment of chalazia. *Cornea.* 2023;42(2):172-175.
32. Stroman DW, Mintun K, Epstein AB, et al. Reduction in bacterial load using hypochlorous acid hygiene solution on ocular skin. *Clin Ophthalmol.* 2017;11:707-714.
33. Aronowicz JD, Shine WE, Oral D, Vargas JM, McCulley JP. Short term oral minocycline treatment of meibomianitis. *Br J Ophthalmol.* 2006;90(7):856-860.
34. Visco DM, Hendrix LH, Sun L, Tam I, Macsai M, Gibson AA. Matching-adjusted indirect comparison of phase 3 clinical trial outcomes: OC-01 (varenicline solution) nasal spray and cyclosporine A 0.05% ophthalmic emulsion for the treatment of dry eye disease. *J Manag Care Spec Pharm.* 2022;28(8):892-902.
35. White DE, Hendrix LH, Sun L, Tam I, Macsai M, Gibson AA. Matching-adjusted indirect comparison of phase 3 clinical trial outcomes of OC-01 (varenicline solution) nasal spray and lifitegrast 5% ophthalmic solution for the treatment of dry eye disease. *J Manag Care Spec Pharm.* 2023;29(1):69-79.
36. Dieckmann G, Fregni F, Hamrah P. Neurostimulation in dry eye disease—past, present, and future. *Ocul Surf.* 2019;17(1):20-27.
37. Perfluorohexyloctane solution. Package insert. US National Library of Medicine. Updated May 18, 2023. Accessed June 30, 2023. https://dailymed.nlm.nih.gov/dailymed
38. Steven P, Augustin AJ, Geerling G, et al. Semifluorinated alkane eye drops for treatment of dry eye disease due to meibomian gland disease. *J Ocul Pharmacol Ther.* 2017;33(9):678-685.
39. Tauber J, Berdy GJ, Wirta DL, Krösser S, Vittitow JL; GOBI Study Group. NOV03 for dry eye disease associated with meibomian gland dysfunction: results of the randomized phase 3 GOBI study. *Ophthalmology.* 2023;130(5):516-524.
40. Sheppard JD, Kurata FK, Epitropoulos AT, Krösser S, Vittitow J; MOJAVE Study Group. NOV03 for signs and symptoms of dry eye disease associated with meibomian gland dysfunction: the randomized phase 3 MOJAVE study. *Am J Ophthalmol.* 2022;252:265-274.
41. Borchman D, Vittitow J, Ewurum A, Veligandla SR. Spectroscopic study of perfluorohexyloctane – human meibum interactions. *Invest Ophthalmol Vis Sci.* 2022;63(7):1525.
42. Tauber J, Wirta DL, Sall K, Majmudar PA, Willen D, Krösser S; SEECASE Study Group. A randomized clinical study (SEECASE) to assess efficacy, safety, and tolerability of NOV03 for treatment of dry eye disease. *Cornea.* 2021;40(9):1132-1140.
43. Schmidl D, Bata AM, Szegedi S, et al. Influence of perfluorohexyloctane eye drops on tear film thickness in patients with mild to moderate dry eye disease: a randomized controlled clinical trial. *J Ocul Pharmacol Ther.* 2020;36(3):154-161.
44. Baudouin C, Aragona P, Messmer EM, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. *Ocul Surf.* 2013;11(4):246-258.
45. FDA accepts Tarsus' new drug application for TP-03 for treatment of Demodex blepharitis. News release. Eyewire. November 9, 2022. Accessed June 30, 2023. https://eyewire.news/news/fda-accepts-tarsus-new-drug-application-for-tp-03-for-treatment-of-demodex-blepharitis?c4src=article:infinite-scroll
46. Yeu E, Wirta DL, Karpecki P, Baba SN, Holdbrook M; Saturn I Study Group. Lotilaner ophthalmic solution, 0.25%, for the treatment of *Demodex* blepharitis: results of a prospective, randomized, vehicle-controlled, double-masked, pivotal trial (Saturn-1). *Cornea.* 2023;42(4):435-443.
47. Gaddie IB, Donnenfeld ED, Karpecki P, et al; Saturn II Study Group. Lotilaner ophthalmic solution, 0.25% for *Demodex* blepharitis: randomized, vehicle-controlled, multicenter, phase 3 trial (Saturn-2). *Ophthalmology.* Accepted manuscript. Published online June 5, 2023. doi:10.1016/j.ophtha.2023.05.030
48. Nijm L, Craig JP, Hinds M, Alster Y, Bosworth C. AZR-MD-001 efficacy in resolving the signs and associated symptoms of meibomian gland dysfunction (MGD) in a phase 2 trial: responder status analysis. *Invest Ophthalmol Vis Sci.* 2023;64(8):5129.
49. Gupta P, Downie LE, Hinds M, Alster Y, Bosworth C. AZR-MD-001 restores gland function and improves signs and ocular symptoms of meibomian gland dysfunction (MGD). *Invest Ophthalmol Vis Sci.* 2023;64(8):5175.
50. Hutton D. Azura Ophthalmics presents positive results from phase 2b clinical trial of AZR-MD-001. *Ophthalmology Times.* December 10, 2022. Accessed June 30, 2023. https://www.ophthalmologytimes.com/view/azura-ophthalmics-presents-positive-results-from-phase-2b-clinical-trial-of-azr-md-001

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1. Evaporative dry eye is caused by deficiency in the _____ layer of the tear film.

   a. Basal
   b. Mucin
   c. Aqueous
   d. Lipid

2. Which diagnostic tool can help educate patients about MG loss and the need for treatment of MGD?

   a. Patient symptom questionnaire
   b. Schirmer test
   c. Meibography
   d. Tear osmolarity

3. For improvement in which primary end points did the phase 3 GOBI and MOJAVE trials show treatment benefits of perfluorohexyloctane?

   a. Conjunctival lissamine and corneal fluorescein staining
   b. EDS and tCFS
   c. Measures of meibum quality and quantity
   d. Schirmer I test score and EDS

4. A 52-year-old male presents with itch and contact lens intolerance. After examination, he is diagnosed with *Demodex* lid infestation, ocular rosacea, and DED associated with MGD. What is an appropriate treatment for this patient?

   a. Hypochlorous acid
   b. IPL
   c. Microblepharoexfoliation
   d. All the above

5. A 67-year-old woman scheduled for cataract surgery has MGD-associated DED affecting the quality of biometry to ascertain the optimal power of the intraocular lens implant. She wants surgery done as soon as possible. Which of the following investigational products has been shown in clinical trials to improve the ocular surface within the first 2 weeks of therapy?

   a. TP-03
   b. Perfluorohexyloctane
   c. AZR-MD-001
   d. None of the above