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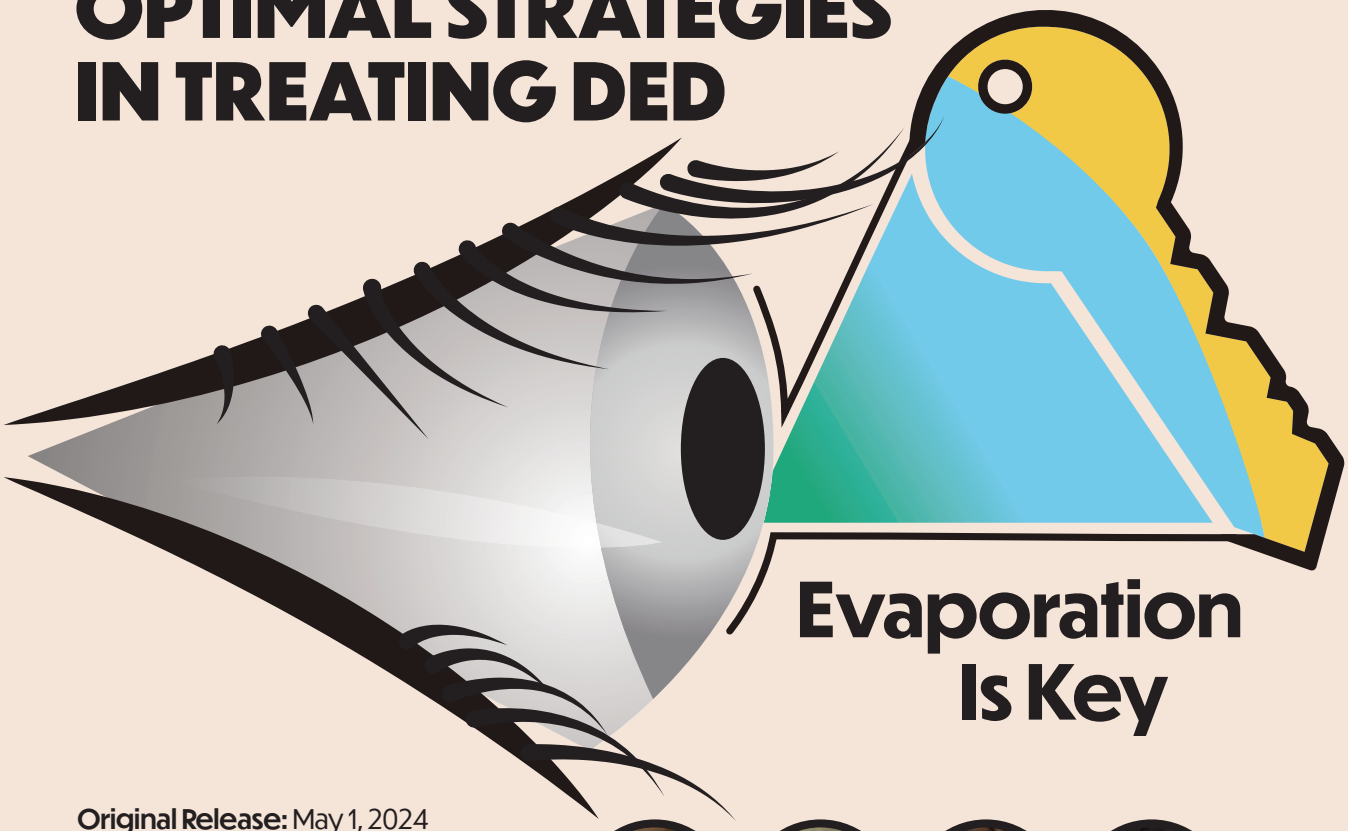
*A **Putting Evaporation Into Focus** Activity*

UNLOCKING OPTIMAL STRATEGIES IN TREATING DED



Evaporation Is Key

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FACULTY
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This continuing medical education activity is provided by MedEdicus LLC.

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This continuing medical education activity is supported through an educational grant from Bausch & Lomb Incorporated.

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Activity Description and Purpose

Dry eye disease (DED) is a common and multifactorial condition. The leading cause is meibomian gland dysfunction (MGD), which results in deficiency in the outer lipid layer of the tear film and increased evaporation. Advances in managing DED/MGD include the recent US Food and Drug Administration–approved perfluorohexyloctane with a novel mechanism of action. Lotilaner is a new option to address associated *Demodex* blepharitis. This educational activity presents an overview of DED/MGD pathophysiology and classification, results from clinical trials investigating new and emerging therapies, and case-based discussions in which experts share insights on developing targeted treatment regimens for managing DED/MGD. The desired results of this activity are to cement clinicians' knowledge of the role of evaporation in the pathogenesis of MGD and help them obtain practical strategies for screening, diagnosis, and effective treatment that can improve patient outcomes.

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
- Review clinical evidence of approved treatments for dry eye disease
- Design evidence-based treatment plans for patients with dry eye disease

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Introduction

A healthy, stable tear film is needed to maintain ocular surface health and quality vision.[1] Dry eye disease (DED) develops owing to disruption of tear film homeostasis that results from a deficiency of tear film quality and/or quantity.

The tear film is a complex structure that consists of 3 main layers: mucin, aqueous, and lipid.[2] Mucin is secreted mostly by conjunctival goblet cells and serves to coat the ocular surface. The aqueous layer comes from lacrimal glands and contains an array of proteins, electrolytes, and metabolites. The lipid layer is composed mostly of meibum secreted by the meibomian glands (MGs); it forms the outer layer of the tear film, provides a smooth optical surface, and serves to stabilize the tear film by protecting against evaporation. Imbalance between the rates of evaporation and tear supply results in tear hyperosmolarity, which is a core driver of DED development and progression.

Effective management of DED requires identifying the appropriate therapeutic targets, which relies on understanding the underlying pathophysiologic mechanisms in each case. Dry eye disease is broadly classified into 2 subtypes: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE).[3] There are multiple possible causes for EDE, but MG dysfunction (MGD) is the most common cause of EDE and of all DED.[1,3] MGD leads to deficiencies in meibum quality and/or quantity in the lipid layer of the tear film, which leads to increased evaporative loss and hyperosmolarity. ADDE develops when there is insufficient aqueous secretion by the lacrimal glands, which can occur as a result of inflammatory, neurogenic, or scarring disorders, and with aging.

CASE 1

Conventional and In-Office Treatments for Dry Eye Disease

From the Files of Nicole R. Fram, MD

A 52-year-old female who had Sjögren syndrome presented with concerns about ocular foreign body sensation, eyelid redness, and inability to tolerate air conditioning and wind. She was presbyopic and had rosacea, a history of hyperopic LASIK (laser-assisted in situ keratomileusis) OD and photorefractive keratectomy OS, and anatomically narrow angles with patent laser peripheral iridotomies OU. She was using lifitegrast, 5.0%, twice daily OU. Previous failed treatments for DED included topical cyclosporine, oral doxycycline, thermal pulsation, and autologous serum tears.

***Figure 1** shows images from the examination. Findings included trace inferior corneal punctate epithelial erosions OU; ocular rosacea with eyelid telangiectasias OU; MGD stage 3; tear breakup time (TBUT) < 3 seconds OU; Schirmer score of 3 seconds OD and 5 seconds OS; and tear osmolarity of 304 mOsm/L OD and 309 mOsm/L OS. There were no collarettes, keratinization, or LASIK flap striae or debris, and the conjunctiva and sclera were normal.*

The patient was treated with intense pulsed light (IPL), with application to the malar area of her face and lids followed by gland expression. She achieved noticeable benefit, including

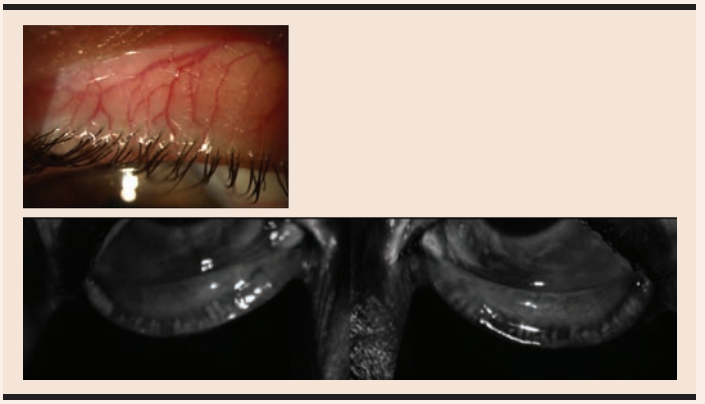

Figure 1. Slitlamp photography of the patient in Case 1 revealed large telangiectatic vessels in the left upper eyelid and meibography revealed > 66% loss of MGs OU (stage 3). Note the truncated remaining glands OU.
Images courtesy of Nicole R. Fram, MD

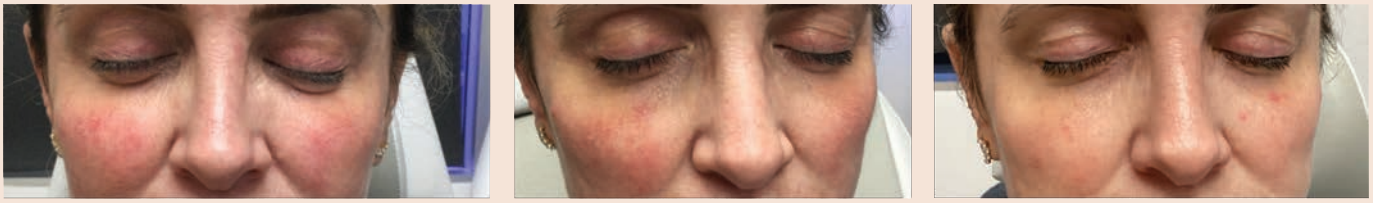

Figure 2. Treatment of the patient in Case 1 with intense pulsed light led to marked improvement in malar telangiectatic vessels and lid margin evaporative dry eye symptoms
Images courtesy of Nicole R. Fram, MD

improvement of DED symptoms and in the appearance of her facial and eyelid skin ***(Figure 2)****.*

Dr Fram: When I see new patients who tell me they failed topical cyclosporine, I wonder how long they used cyclosporine and if they were treated with a topical steroid before starting cyclosporine. Any medication placed onto an inflamed ocular surface can cause terrible burning. A short course of a topical steroid can quickly improve the inflammation and make cyclosporine more tolerable.[4]

What are your topline thoughts if you saw a patient with this type of history and examination findings?

Dr Donnenfeld: One thing I consider when I see a patient with DED-related concerns who has failed multiple treatments is whether the diagnosis is correct.

Dr Gupta: In addition to misdiagnosis, I think about whether a patient who failed multiple therapies or reports medication intolerance has very severe DED or even true allergy, although the latter is rare.

It is important to review the patient's history and examination findings carefully to see if anything was overlooked and/or needs to be better addressed. My suspicion in this case was that the patient's symptoms were mostly related to MGD, and the MGD was undertreated. I think that MGD is often overlooked when managing DED in patients with a chronic autoimmune disease because clinicians perceive DED in such cases as an aqueous-deficient disease and focus treatment only on controlling inflammation.

That said, I think a topical steroid could be very useful in this case **(see Sidebar: Treatment for Meibomian Gland Dysfunction)**. I would also suggest an in-office treatment for MGD.

Treatment for Meibomian Gland Dysfunction

Treatment for meibomian gland dysfunction (MGD) can be approached in a stepwise fashion, in which interventions are added with increasing severity.[1] As described by the management and treatment subcommittee of the International Workshop on Meibomian Gland Dysfunction, the regimen always includes lid hygiene with warming and gland expression to increase meibum flow and to clear meibomian gland (MG) obstruction. Ocular lubricants and treatments to address inflammation are added as MG severity increases. The latter can include oral tetracyclines, topical azithromycin, and steroids or the steroid-sparing immunomodulatory medications that are indicated for treating dry eye disease.

Multiple in-office interventional treatments for MGD designed to provide lid hygiene, clear obstructed MGs, and improve meibum secretion have become available since the report from the International Workshop on Meibomian Gland Dysfunction was published. These include microblepharoexfoliation, heat delivery with or without pulsation, and intense pulsed light (IPL). Other recent additions that can have a role in MGD management include perfluorohexyloctane, 100%, which targets increased tear evaporation, and lotilaner ophthalmic solution, 0.25%, which is indicated for the treatment of *Demodex* blepharitis.[2,3]

Thermal pulsation relieves MG obstruction by raising eyelid temperature to melt meibum and by applying pressure to the lid margins to express the glands.[4] Studies investigating thermal pulsation assessed a variety of end points and differed in length of follow-up. Overall, the results showed significant improvements in symptoms, MG severity score, MG function, and tear breakup time that occurred within a few weeks after a single treatment and were sustained for up to 12 months. The procedure is done under topical anesthesia and is safe. Devices from multiple manufacturers are available, but the applicator for some of the equipment does not fit well in patients with small fissures.

IPL is another in-office option used in the management of MGD. IPL delivers high-intensity light that is absorbed by chromophores in blood and converted to heat, leading to intravascular coagulation and ablation of vessels that are thought to secrete inflammatory mediators.[5,6] IPL may also act to liquefy thickened meibum and eradicate *Demodex*. Studies investigating IPL combined with MG expression show improvements in MG function, signs and symptoms of MGD, and levels of inflammatory markers in the tear film. Eyelid treatment with IPL is generally safe and well tolerated, but to protect against ocular complications, including iris damage, pupillary block, and secondary glaucoma, it should be done with a corneal shield in place.[5]

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Dr Fram: Tear osmolarity > 308 mOsm/L or an intereye difference > 8 mOsm/L is suggestive of DED.[5] I consider an elevated tear osmolarity level as an indication for anti-inflammatory treatment.

Dr Farid: How do you assess MGD severity? What is your counseling conversation with patients with MGD?

Dr Gupta: I like to do meibography for assessing MGD severity because I believe it is not possible to accurately evaluate the extent of MG atrophy in a slitlamp examination. Then, I use the information to rate MGD severity using the Meiboscale, which I consider the easiest MGD rating scale to use **(Figure 3)**.[6] The Meiboscale grades MGD on a 5-point scale, in which 0 indicates no gland loss and 4 represents > 75% loss. I consider patients with MG degree 3 or 4 on the Meiboscale as having severe disease and tell them I expect they will need multiple therapies to get them to a place in which they will feel less symptomatic. It is important to set realistic expectations because some patients expect that we have a cure for DED.

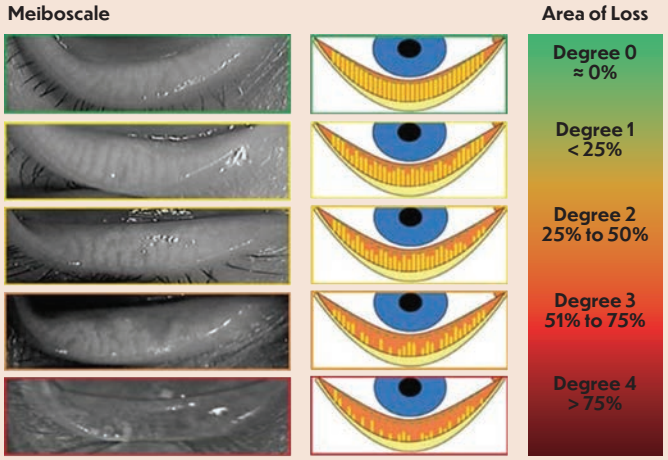

Figure 3. The Meiboscale rates severity of meibomian gland dysfunction on a 5-point scale according to percentage of meibomian gland loss[6]

Reprinted from *Contact Lens Anterior Eye*, 36, Pult H, Riede-Pult B, Comparison of subjective grading and objective assessment in meibography , 22-27, Copyright 2013, with permission from British Contact Lens Association.

Dr Fram: I agree. I try to temper the information about severity when talking to patients with advanced MG loss because I do not want to scare them. I tell these patients they have an issue, but many treatments are now available that can help.

When talking to patients with MGD-related DED, I explain that they are not producing enough lipids to maintain a normal outer tear film layer, and that is allowing the tear film to evaporate too fast. Therefore, although their vision may be clear immediately after they blink, it will soon begin to blur because the tear film is breaking down too rapidly and causing scatter of incoming light rays. I also like to talk about the interacting vicious cycles of MGD and DED and explain how tear film instability with MGD leads to and perpetuates DED, whereas DED causes inflammation that can cause or perpetuate MGD by affecting MG function **(Figure 4)**.[7,8] I agree with Dr Gupta's observation that many clinicians think of DED in patients with Sjögren syndrome as purely an aqueous-deficient disease. MGD is common and can develop because of the interacting pathophysiologic pathways of DED and MGD.

When patients tell me that their eyes are crusty in the morning, I explain to them that the crust is dry mucus from their tear film

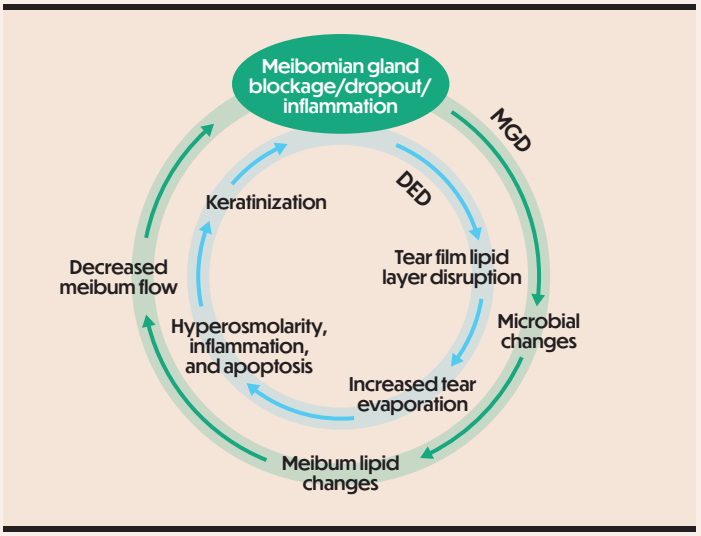

Figure 4. Significance of meibomian gland dysfunction in the vicious cycle of dry eye disease[8]

Abbreviations: DED, dry eye disease; MGD, meibomian gland dysfunction.

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and a sign that the tear film is unstable. I like to recommend in-office treatments for eyelid hygiene.

There are some conflicting reports about the benefit of in-office treatments for MGD for recanalizing atrophic MGs.[9] Nevertheless, they are useful for helping to maintain function of the remaining viable MGs.

Dr Donnenfeld: Oral doxycycline is my first-line choice for an anti-inflammatory treatment for MGD, but if a woman is pregnant or wants to become pregnant,[10] I prescribe topical azithromycin, with instructions to place a drop on the finger and rub it onto the lids once a day for several months.

What role does doxycycline have in your approach to managing MGD?

Dr Fram: I use oral doxycycline to treat patients with a large chalazion because of its activity against gram-positive organisms and anti-inflammatory effects on the MGs.[7,10] I use doxycycline rather than an oral cephalosporin antibiotic so long as the lesion is not suspicious for a more aggressive preseptal or orbital cellulitis. For acute chalazia, I typically prescribe doxycycline 100 mg twice daily for 7 days, followed by 50 mg daily as maintenance. I also start a course of antibiotic and anti-inflammatory drops. Doxycycline is also a go-to for me for treating ocular rosacea; for that indication, I prescribe 50 mg daily, alternating 3 months on and 3 months off. I tell patients that the 50-mg dose should not cause sun sensitivity, but they might experience some gastrointestinal adverse effects. If patients develop intolerable gastrointestinal adverse effects, I switch them to azithromycin 500 mg to 1 g once a week for 3 weeks as tolerated. If IPL treatment is planned, I have patients stop doxycycline 1 to 2 weeks prior to the IPL session because of the photosensitization concerns.

Dr Gupta: I have patients stop doxycycline just 3 days before IPL. I have used this approach for more than a decade and have not encountered any safety concerns. If I am doing IPL in a patient with a history of herpetic flares, I prescribe valacyclovir as prophylaxis, starting it a few days prior to IPL and continuing for 1 or 2 days post-IPL.

CASE 2

Treatment of Complicated Meibomian Gland Dysfunction That Failed Previous Therapy

From the Files of Preeya K. Gupta, MD

A 45-year-old female presented with concerns of chronic foreign body sensation, red eyes, and fluctuating vision when reading and especially with computer work. She had used topical cyclosporine for 6 months, with mild relief, and was using artificial tears, lid scrubs, and warm compresses. The patient had rosacea.

Findings on examination were matrix metalloproteinase-9 slightly positive OU, tear osmolarity of 290 mOsm/L OD and 298 mOsm/L OS, trace punctate epithelial erosions OU, TBUT of 4 seconds OU, and 2-3+ MGD, with moderate to severe MG atrophy, capped glands, and lid erythema ***(Figure 5)****.*

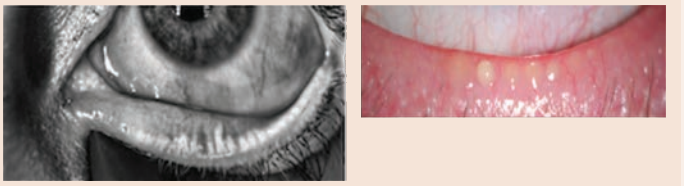

Figure 5. Diagnostic findings in evaporative dry eye disease: moderate to severe meibomian gland atrophy on meibography and capped glands
Images courtesy of Preeya K. Gupta, MD

Dr Gupta: There are many ways to assess MG function. Individual clinicians might have a personal preference that they find most efficient. What is your technique for MG evaluation?

Dr Farid: I press on the lids and try to assess both how many glands are secreting and the quality of the secretions, seeing if the meibum flows like olive oil or is thick like toothpaste or if there is no flow at all because the glands are blocked or totally atrophied.

Dr Fram: I do the same thing and also try to assess keratinization. Keratinization over the MGs will block them, which leads to increased bacterial colonization and inflammation.

Dr Donnenfeld: First, I simply apply pressure to the lids and stop if I see nice-quality meibum. If there is no secretion, I apply topical lidocaine gel on the lids and roll them using 2 cotton-tipped swabs. The rolling is diagnostic and can also be therapeutic.

Dr Gupta: There are approximately 30 to 40 glands in the upper eyelid and approximately 20 to 40 glands in the lower lid.[11] When I do the MG assessment, I like to see that at least one-third of the glands in each lid are functioning. It is not important how the MG evaluation is done, only that it is done.

How would you treat this patient?

Dr Donnenfeld: I would switch to another topical immunomodulator, suggest in-office MGD therapy, and start perfluorohexyloctane (PFHO), which is a new option **(see Sidebar: Perfluorohexyloctane)**.

Dr Gupta: I agree. One drawback of in-office MGD therapies is that they are not covered by insurance. I think they might be effective as standalone treatments for patients with mild MGD, but need to be used in conjunction with other treatments for anyone with moderate or more severe MGD. I also think in-office MGD treatments can be especially beneficial for patients who have failed multiple other modalities.

I was excited to see how quickly PFHO improved the dryness symptom in the pivotal trials, considering that with other prescription therapies, we have to tell patients that it can take up to 8 weeks until they start to feel better.

Dr Farid: The efficacy of PFHO for achieving the total corneal fluorescein staining end point is compelling,[12,13] and it is especially important when we are trying to improve the ocular surface condition to ready patients for cataract or refractive surgery.

Dr Gupta: There is a common belief that treatment with a steroid is needed to rapidly improve corneal fluorescein staining, but benefit was also seen for PFHO in the pivotal clinical trials.[12,13]

Dr Donnenfeld: When I evaluate a new drug for DED, I look at 3 basic concepts—efficacy, speed of onset, tolerability. On that basis, we can understand why many patients fail to continue treatment with a topical immunomodulator, because these products may be associated with relatively high rates of burning. It is impressive that < 1% of patients treated with PFHO in the pivotal trials reported burning and stinging.[12,13]

Dr Gupta: I tried PFHO myself and found that the drop had a smooth, slippery feel. There was no spillover onto my cheek. If I had not experienced some very temporary blurred vision, I would have wondered if the drop was even dispensed onto my eye because I barely felt anything.

Dr Fram: I have DED that can be particularly symptomatic toward the end of the day. I get immediate relief from a drop of PFHO. It does, however, blur my vision for 1 or 2 minutes. Therefore, I use it only when I am not operating.

Dr Donnenfeld: I consider PFHO the best single drug I have ever used for rapidly treating the signs and symptoms of DED. I think that it works equally well if the patient has ADDE or EDE. PFHO, however, does not treat the root cause of DED. Therefore, I prescribe it with the aim of helping patients feel more comfortable and to improve the ocular surface condition, but I use it in conjunction with other treatments that target the underlying cause of a patient's DED.

Insurance restrictions can make it difficult for patients to gain access to new prescription medications. The manufacturers of PFHO and of lotilaner, which recently became available to treat *Demodex* lid infestation,[14] have both contracted with specialty pharmacies that help overcome barriers to access and allow patients to get the medications at a reasonable cost. Working with these specialty pharmacies also lessens the burden to our office staff by eliminating calls from the patient's pharmacy about lack of coverage and handling of insurance denials.

Dr Gupta: There seems to be generally good insurance coverage for PFHO so that patients can get it at a reasonable cost. The manufacturer will also provide a free bottle to new users. Medicare, however, often does not cover any new medication.

Dr Farid: I let patients on Medicare know that they should be able to get the first bottle free or at a reduced cost, but then I continue to request refills because I think submitting prescriptions is important for letting Medicare know that we want all our patients to have access to new drugs.

Dr Fram: When trying to help insurance companies understand why this drug is necessary, it helps if you write in your note that the patient has failed other treatments. We have a relationship with a

Perfluorohexyloctane

Perfluorohexyloctane (PFHO) is a semifluorinated alkane compound that creates a monolayer at the air-tear interface that reduces tear evaporation.[1,2] The commercially available topical product is a preservative- and aqueous-free preparation containing 100% PFHO.[2] The dispensed drop volume is very small, only 10 µL.[3] PFHO has a low surface tension, spreads quickly over the ocular surface, and acts as a lubricant to reduce friction between the lids and the ocular surface.[1] PFHO also has a very long retention time on the ocular surface of at least 4 hours in preclinical studies, which is critical for its efficacy in controlling evaporation.[4]

PFHO was approved by the US Food and Drug Administration for the treatment of signs and symptoms of dry eye disease (DED) in May 2023 and is the first US Food and Drug Administration–approved treatment for DED that targets tear evaporation.[5] Compared with 3 commercially available artificial tear products, PFHO reduced the mean evaporation rate of saline in an in vitro model by approximately 80% ($P < .0001$).[6]

The efficacy and safety of PFHO were investigated in two phase 3 double-masked trials (GOBI and MOJAVE) that randomly assigned a total of 1219 adults with meibomian gland dysfunction–related DED to 4-times-daily treatment OU with PFHO or hypotonic saline (0.6%) for 8 weeks.[7,8] Change from baseline to day 57 in total corneal fluorescein staining and Visual Analogue Scale eye dryness score were evaluated as primary outcome measures, and were met in both trials **(Figure)**.[7,8] Secondary end point analyses showed both total corneal fluorescein staining and Visual Analogue Scale eye dryness score were significantly improved by PFHO at day 15.

PFHO was safe and well tolerated.[7,8] Overall, the percentage of patients with ≥ 1 ocular adverse event was similar in the PFHO and control groups. Blurred vision, which was reported by 3.0% of 303 patients using PFHO in GOBI and by 1.3% of 311 patients using PFHO in MOJAVE, was the only ocular adverse event in the pooled PFHO groups that occurred at a rate > 1%. Only 1 patient discontinued treatment because of an adverse event (severe eye irritation) in GOBI.[7]

Long-term use of PFHO for up to 52 weeks was investigated in the open-label KALAHARI trial, which enrolled 208 patients who completed GOBI.[9] Results from KALAHARI showed that patients originally randomly assigned to receive PFHO had continued improvement in corneal staining and eye dryness. Among patients in the control group in GOBI who started PFHO upon entry into KALAHARI, improvements in both corneal staining and eye dryness were achieved by 4 weeks and maintained throughout follow-up. Overall, 13.9% of patients had ≥ 1 ocular adverse event, which were mostly mild or moderate in severity.

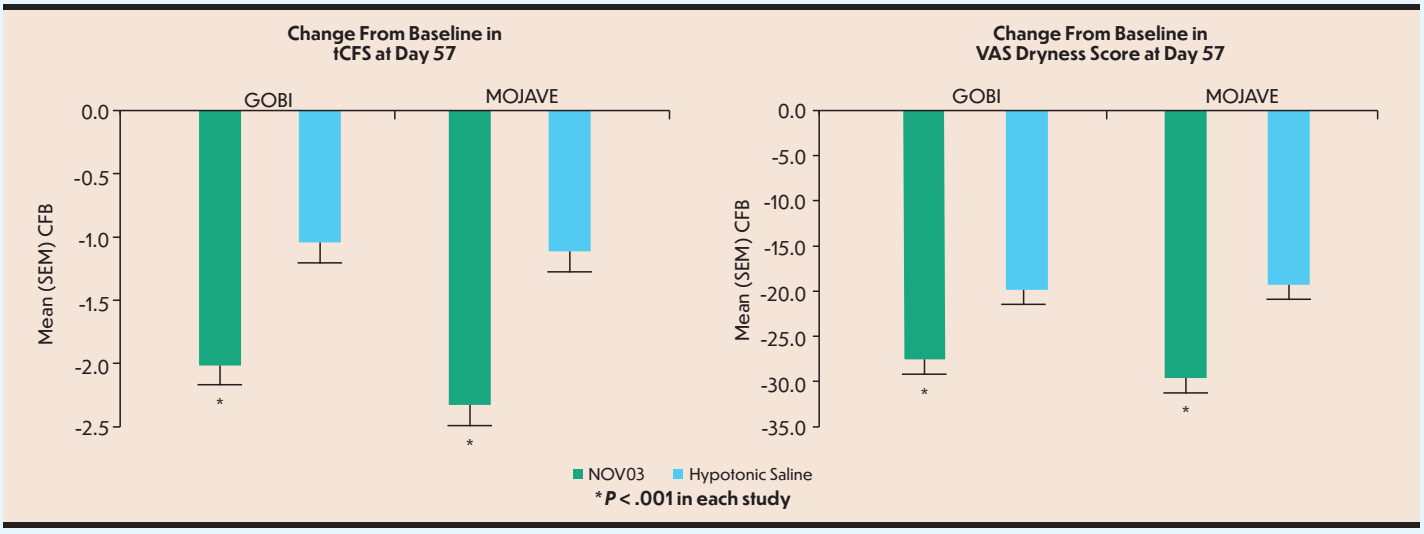

Figure. Pivotal trials investigating perfluorohexyloctane (NOV03) met their coprimary efficacy end points[7,8]

Abbreviations: CFB, change from baseline; SEM, standard error of the mean; tCFS, total corneal fluorescein staining; VAS, Visual Analogue Scale.

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specialty pharmacy that helps with the prior authorization process. This documentation helps us streamline the process.

Dr Donnenfeld: The patient in Case 2 had rosacea. Do you recommend hot compresses if a patient has rosacea, or do you have concerns that heat could worsen the inflammation?

Dr Gupta: Patients with rosacea may not tolerate hot compresses, but I usually tell them to do the best they can. I am not concerned about the risk of increasing inflammation.

Dr Donnenfeld: What do you think about using omega-3 supplementation? Are you concerned about an increased risk of prostate cancer?

Dr Gupta: The SELECT study that raised this issue has been criticized for having a number of flaws, and I do not hesitate to recommend omega-3 fatty acid supplementation to male patients with MGD who I think would benefit from it.[15] If patients are concerned about the risk, however, I will not try to change their mind or try to convince them to use a supplement.

Dr Donnenfeld: The important issue when recommending omega-3 fatty acid supplementation is to tell patients to choose a product that is in the triglyceride form, which has better bioavailability than an ethyl ester product.[16]

CASE 3

A Common Confounder – Recognizing and Treating *Demodex* Blepharitis

From the Files of Marjan Farid, MD

A 24-year-old female who worked as a software engineer presented reporting an inability to wear her soft contact lenses and recurrent chalazia. In addition to chronic or recurrent "stye" formation OU, she reported rapid redness and irritation with lens wear, difficulty working at the computer, feelings of irritation and grittiness, and lid redness. She had seen her optometrist multiple times and switched the brand of contact lenses she was wearing several times without improvement. Best spectacle-corrected visual acuity was 20/20 OU. Examination showed a small left upper lid chalazion, slow secretion of thickened meibum from the MGs, and diffuse collarettes along the base of the upper and lower lashes ***(Figure 6)****.*

Figure 6. Slitlamp image of the patient in Case 3 demonstrates *Demodex* blepharitis, evidenced by collarettes along the lash base
Image courtesy of Marjan Farid, MD

Dr Farid: Identification of mites through microscopic examination of epilated eyelashes is one way to detect *Demodex* infestation, but simply asking patients to look down when performing the slitlamp examination and looking for collarettes along the upper lid margin is an easy and practical method **(see Sidebar: *Demodex* Blepharitis)**.

When I diagnose patients with *Demodex* blepharitis, I recommend that they use a tea tree oil–based shampoo for washing their hair and tea tree oil lid wipes to cleanse their eyebrows.

Has anyone used ivermectin?

Dr Gupta: Before lotilaner was available, I was doing microblepharoexfoliation and adding oral ivermectin for patients with severe blepharitis associated with *Demodex*.

Dr Donnenfeld: I think microblepharoexfoliation is cost effective, simple, and gets to the root of the problem. We often use it in patients with MGD to remove biofilm that blocks the MGs and to remove the collarettes in patients with *Demodex* blepharitis. I think it is underused.

Treatment was initiated with mechanical microblepharoexfoliation along with at-home use of tea tree oil lid scrubs, warm compresses, and preservative-free artificial tears. The patient reported some symptomatic relief, but said she was too busy to keep up with the lid hygiene recommendations and that her persisting symptoms left her unable to wear her contact lenses for more than a few hours each day.

The patient was told to return every 3 to 4 months for blepharoexfoliation and was started on oral doxycycline and topical cyclosporine. At follow-up, she reported minimal improvement in symptoms. She expressed continued frustration because her symptoms were impacting her ability to work and quality of life, whereas her recurrent styes were affecting her appearance and preventing her from wearing makeup.

Dr Farid: Lotilaner is a highly lipophilic compound that is absorbed into the lash follicles and MGs.[17] Patients just need to instill a drop into each eye and do not have to scrub their lids. Lotilaner has a 6-week treatment course,[18] and the study data indicate that most patients maintain relief for at least 12 months.[19] Patients can be treated again if they are bothered by recurrent symptoms.

I do not think that all patients with MGD or DED have *Demodex* infestation, but lotilaner might change the landscape for managing patients who have chronic rosacea, significant collarettes, and inflammation along the lash margin.

What is your experience using lotilaner?

Dr Donnenfeld: I have been positively impressed using lotilaner in patients who come in with lid erythema and itching. I think that targeting *Demodex* might be the missing link for successful management of lid margin disease for many patients.

Dr Gupta: At first, I was reserving lotilaner for patients who had a lot of crusting on the lid margin. Realizing that collarettes are removed when patients perform lid hygiene, I began to focus more on symptom severity and started prescribing lotilaner even if patients had just a few collarettes because I thought they could benefit from mite eradication that would decrease the inflammatory load.

Demodex Blepharitis

Demodex blepharitis, characterized by the presence of collarettes at the base of eyelashes has been shown to affect 58% of 1032 patients in eye care clinics, regardless of demographics or hygiene habits, suggesting it is often underdiagnosed.[1] It is caused by 2 species of *Demodex* mites, leading to inflammation and symptoms such as itching, redness, and dry eyes through various mechanisms.[2] Traditional treatments have included lid hygiene and mechanical exfoliation, whereas off-label therapies, such as topical ivermectin/metronidazole gel and oral ivermectin, have shown efficacy in reducing mite counts and alleviating symptoms.[2,3]

Lotilaner is a potent noncompetitive antagonist of insect and arachnid gamma-aminobutyric acid chloride channels that causes paralysis and death of *Demodex* mites.[4] Lotilaner, 0.25%, ophthalmic solution was approved by the US Food and Drug Administration for the treatment of *Demodex* blepharitis in July 2023 and is recommended to be used twice daily for 6 weeks.[5,6]

The efficacy and safety of lotilaner ophthalmic solution for treating *Demodex* blepharitis was demonstrated in 2 pivotal trials—Saturn-1 and Saturn-2—that enrolled > 800 patients who had collarettes present on > 10 upper lid lashes, mild or worse erythema of the upper eyelid margin, and an average *Demodex* density, upper and lower eyelids combined, of ≥ 1.5 mites per lash.[7,8] The primary end point of complete collarette cure after 6 weeks was achieved by 44% of 209 patients treated with lotilaner and by 7% of 204 patients treated with vehicle in Saturn-1, and by 56% of 193 patients treated with lotilaner and by 12.5% of 200 patients treated with vehicle in Saturn-2 ($P < .0001$ for both comparisons) **(Figure)**. A statistically significant difference in complete collarette cure rates favoring the lotilaner groups vs vehicle was seen by day 15 in both studies **(Figure)**.[7,8] Statistically significant differences ($P \leq .0001$) favoring lotilaner were also achieved in secondary end points analyzing rates of clinically meaningful collarette cure, mite eradication, and lid erythema cure at week 6. At 1 year, rates of complete collarette cure and clinically meaningful cure in the lotilaner group remained > 50% and were significantly higher than those in the vehicle group.[9]

Lotilaner was generally safe and well tolerated.[7,8] Instillation-site pain was the most common treatment-emergent ocular adverse event and was generally very transient. Rates of instillation site pain in the lotilaner and vehicle groups were 11.8% and 7.7%, respectively, in Saturn-1 and 7.9% and 6.7%, respectively, in Saturn-2. More than 90% of patients in both studies rated lotilaner drop comfort as neutral to very comfortable.

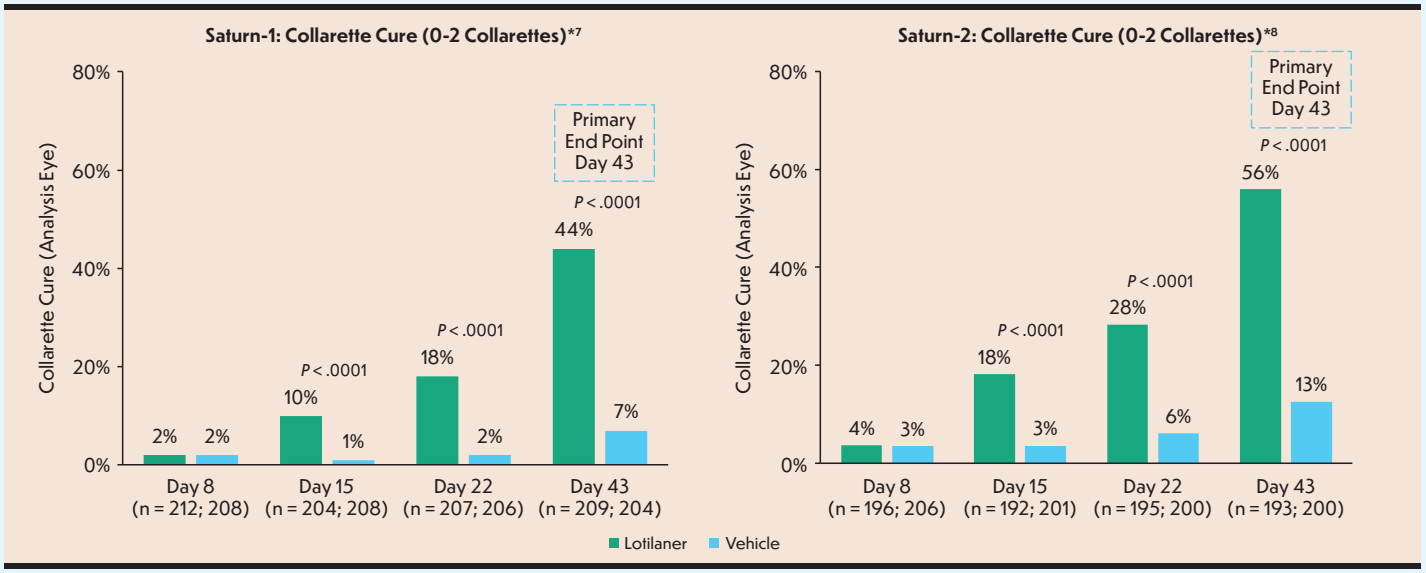

Figure. Percentage of patients achieving complete collarette cure at follow-up visits in Saturn-1 and Saturn-2[7,8]

* The primary efficacy end point was the proportion of patients achieving collarette cure (0-2 collarettes on the eyelid) compared with the vehicle control at day 43

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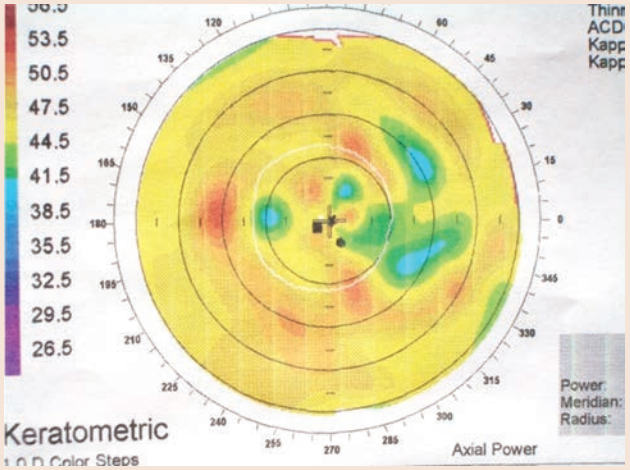

Figure 7. Corneal topography of the patient in Case 4 on presentation, with asymmetric corneal surface indicating irregular astigmatism and possible ocular surface disease

Image courtesy of Eric D. Donnenfeld, MD

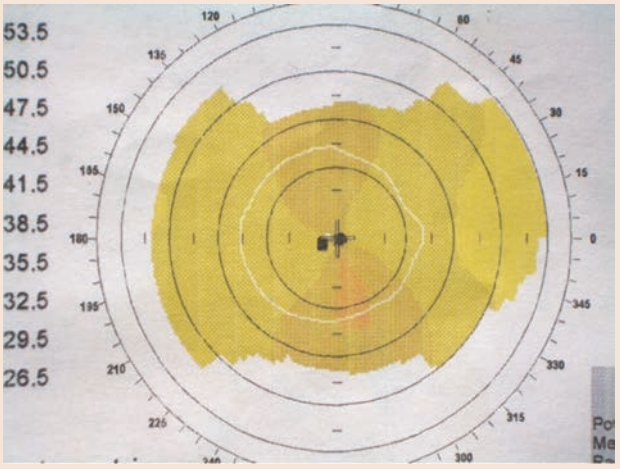

Figure 8. Corneal topography of the patient in Case 4 after treatment and before surgery

Image courtesy of Eric D. Donnenfeld, MD

CASE 4

Optimizing Surgical Outcomes for a Patient With Mixed Dry Eye Disease

From the Files of Eric D. Donnenfeld, MD

A 72-year-old male who presented with visually significant cataract wanted to have surgery as soon as possible and be spectacle free for distance postoperatively. He was a low hyperope (refraction +1.50 -1.25 × 173) and had Hashimoto thyroiditis and papulopustular acne rosacea. He had been treated for DED and was using lifitegrast, 5.0%, twice daily and nonpreserved artificial tears, but had persisting fluctuating vision, light sensitivity, and watering eyes.

Topography showed an irregular surface ***(Figure 7)****. The patient also had moderate corneal staining with lissamine green. Osmolarity was 318 mOsm/L OD and 320 mOsm/L OS, metalloproteinase-9 was positive, Schirmer score was 7 seconds OD and 10 seconds OS, TBUT was 5 seconds OU, and MGs were inspissated.*

Dr Donnenfeld: This patient's autoimmune disease raises suspicion for ADDE. We know from a study by Lemp et al, however, that most patients with DED have evidence of EDE.[1] In that study, 86% of 159 patients with DED had an evaporative component, including 36% with both EDE and ADDE, whereas only 14% had pure ADDE.

Currently, we have many treatments to offer patients with mixed DED, but the reality is that we cannot expect that they will use them all as directed if the regimen is too complex. How would you treat this patient?

Dr Fram: I think he needs treatment for his rosacea. I would prescribe oral doxycycline 100 mg twice daily for 2 weeks, then continue with 50 mg twice daily. I would also recommend IPL, having him stop the doxycycline 3 days prior, and add PFHO and a steroid pulse to control the inflammation.

Dr Farid: I think PFHO would be helpful for clearing up the corneal staining and allowing him to have cataract surgery sooner than later.

Dr Donnenfeld: I think treatment with both PFHO and a steroid will improve his ocular surface the fastest, but neither of those medications addresses the contribution of his lid margin disease to his DED. Although it is best to try to use the fewest number of treatments possible, this patient seemed to need more extensive intervention.

The patient was told to continue lifitegrast and was prescribed loteprednol, 0.5%, 4 times daily, PFHO 4 times daily, oral omega-3 supplementation, microblepharoexfoliation, thermal pulsation therapy, and oral doxycycline 50 mg daily. He was asked to return in 2 weeks, at which time his topography had improved ***(Figure 8)****. Preoperative biometry was performed. The patient had uneventful cataract surgery, followed by a smooth recovery.*

Emerging Therapies for Aqueous-Deficient and Evaporative Dry Eye

AZR-MD-001

AZR-MD-001 is an ophthalmic ointment containing selenium sulfide.[20] It targets hyperkeratinization within the MGs that causes MG obstruction and alterations in lipid quality.[21-23] Selenium sulfide has keratolytic properties, slows keratinocyte proliferation to help prevent future MG obstruction, and improves the quality of secreted lipids.[20-23] In CELESTIAL, a phase 2b trial, patients receiving AZR-MD-001, 0.5% or 1.0%, applied twice weekly to the lower lid at bedtime for 90 days achieved significantly greater improvements than controls receiving vehicle in coprimary end points assessing change from baseline in Meibomian Glands Yielding Liquid Secretion score (4.2 vs 2.4, respectively; $P < .0001$) and Ocular Surface Disease Index score (7.3 vs 3.8, respectively; $P < .05$).[20] Improvements in signs and symptoms of MGD were seen as early as day 14 after starting treatment with AZR-MD-001, 0.5%. Differences showing the superiority of AZR-MD-001, 0.5%, over vehicle were also achieved in key secondary end points looking at proportions of patients becoming asymptomatic, achieving a Meibomian Glands Yielding Liquid Secretion score ≥ 5, and having good meibum quality. The most commonly reported adverse event noted in patients receiving AZR-MD-001 was application site pain (11%).

Reproxalap

Reproxalap inhibits reactive aldehyde species that are precytokine mediators of inflammation and thereby acts earlier in the inflammatory cascade than steroids, cyclosporine, and lifitegrast.[24,25] A phase 3 DED chamber crossover clinical trial investigating reproxalap ophthalmic solution, 0.25%, met its

primary end points, showing statistical superiority over vehicle in analyses of ocular redness ($P = .0004$) and Schirmer test ($P = .0005$) after a single day of dosing.[26] Top-line results from a second chamber crossover phase 3 trial and new drug application submission to the US Food and Drug Administration are expected in the first half of 2024.[27]

OCS-02 (Licaminlimab)

OCS-02 is a topical ophthalmic formulation of the anti-tumor necrosis factor-α agent licaminlimab. Tumor necrosis factor-α is a proinflammatory cytokine that has been shown to be present in significantly increased concentrations in tears of patients with DED and to correlate with disease severity.[28] Results from a phase 2 trial showed that patients receiving OCS-02 had significantly greater improvement from baseline to day 29 in global ocular discomfort score than those receiving vehicle (8 vs 4, respectively; $P = .04$).[29] In addition, a significantly greater proportion of patients receiving OCS-02 achieved a > 20-point improvement in global ocular discomfort score than those receiving vehicle (18% vs 5%, respectively; $P = .02$).

Take-Home Messages

- A normal tear film is critical for maintaining ocular surface health and quality vision
- Disruption of tear film homeostasis leads to development of DED
- MGD is the leading cause of DED
  - MGD leads to deficiencies in meibum quality and/or quantity in the outer layer of the tear film, resulting in increased evaporative loss and hyperosmolarity, which is a core driver of DED
- Diagnosis of MGD requires MG expression during slitlamp examination
  - Examination should also include assessment for signs of contributing etiologies (eg, bacterial or *Demodex* blepharitis and ocular rosacea)
- Knowledge of the etiologies and pathophysiologic mechanisms of MGD and DED guides a targeted approach to management
- Management of MGD is based on severity and presence of contributing factors (eg, ocular rosacea and *Demodex* blepharitis)
- Current treatments for MGD encompass modalities for increasing meibum flow and addressing inflammation and microbial changes
  - In-office interventional treatments are designed to provide lid hygiene, clear obstructed MGs, and improve meibum secretion
  - PFHO, 100%, ophthalmic solution is the first FDA-approved treatment for DED/MGD that directly targets tear evaporation
  - Lotilaner, 0.25%, ophthalmic solution is the first FDA-approved treatment for *Demodex* blepharitis

Complete the CME posttest online at *https://tinyurl.com/treatingDED*

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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 primary end points improved with PFHO in the phase 3 GOBI and MOJAVE trials?
    a. Tear concentration of inflammation markers and MG score
    b. Total corneal fluorescein staining and Visual Analogue Scale eye dryness score
    c. Meibomian gland score and TBUT
    d. Global ocular discomfort score and TBUT

3. A 68-year-old male is scheduled for cataract surgery. During screening, he reports irritated eyes and blurred vision. He suffers from rosacea and arthritis and has difficulty administering eye drops. Examination shows no collarettes, blocked MGs, and grade 1+ corneal staining OU.

    Which of the following treatment options is the most appropriate?
    a. IPL
    b. Autologous serum eye drops
    c. Topical cyclosporine
    d. Punctal occlusion

4. A 35-year-old female complains of eye dryness and blurry vision that worsen during the day. Examination reveals inspissated meibum OU and no evidence of collarettes. Severe gland dropout OU is seen on meibography. Metalloproteinase-9 is negative OU. She has very little corneal staining OS.

    Which of the following treatment options is the most appropriate?
    a. Topical loteprednol etabonate, 0.25%
    b. Lid wipes and cyclosporine, 0.05%
    c. Warm compresses and PFHO, 100%
    d. Hyaluronic acid tears and omega-3 supplementation