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REVIEW

Dry Eye Disease Associated with Meibomian Gland Dysfunction: Focus on Tear Film Characteristics and the Therapeutic Landscape

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ABSTRACT

Meibomian gland dysfunction (MGD) is highly prevalent and is the leading cause of evaporative dry eye disease (DED). MGD is characterized by a reduction in meibum secretion and/or a change in meibum composition that results in the disruption of the tear film lipid layer and an increase in the tear film evaporation rate. Excessive evaporation causes tear film instability, desiccation, tear hyperosmolarity, inflammation, and apoptosis of ocular surface cells, resulting in a continuous cycle of DED. The primary treatment goal for DED associated with MGD is to restore the tear film lipid layer and decrease evaporation, thereby reducing ocular signs and symptoms. The management of MGD includes home care options (eyelid hygiene, warming eye masks, ocular lubricants) and office-based treatments (manual expression, microblepharoexfoliation, thermal pulsation, intense pulsed light, intraductal probing). Topical ophthalmic prescription medications attempt to alter various factors that may contribute to DED (e.g., inflammation, bacterial growth, inadequate tear production). In this review, clinical evidence regarding available treatments and emerging therapies from randomized studies in patients with DED associated with MGD is summarized. Although some treatment modalities have been evaluated specifically for DED patients with MGD, large-scale randomized controlled trials are needed to confirm efficacy and safety in this patient population. Currently, there are no approved prescription pharmacologic treatments specifically indicated for DED associated with MGD, and those medications approved for the treatment of DED do not target the key driver of the disease (i.e., excessive evaporation). NOV03 (perfluorohexyloctane; under review with the US Food and Drug Administration) is the most advanced emerging therapy for DED associated with MGD and has demonstrated statistically significant improvements in both signs and symptoms in randomized controlled trials. Development of novel pharmacotherapies will improve therapeutic options and allow for a more individualized approach for patients with DED associated with MGD.

Keywords: Clinical trials; Dry eye disease; Evaporation; Lipid layer; Meibomian gland

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dysfunction; NOV03; Perfluorohexyloctane; Pharmacotherapies; Tear film

Key Summary Points

Meibomian gland dysfunction (MGD), the leading cause of evaporative dry eye disease (DED), is characterized by a reduction and/or change in meibum secretion that results in the disruption of the tear film lipid layer and an increased rate of tear film evaporation.

Tear film evaporation causes tear film instability, tear hyperosmolarity, and ocular surface inflammation and cell apoptosis, resulting in a continuing cycle of DED.

Although a wide range of treatments are available for DED, the number of adequately powered, rigorously designed clinical trials evaluating the efficacy and safety of these treatments in patients with DED associated with MGD is limited.

There are no approved prescription pharmacologic treatments indicated for DED associated with MGD currently, and medications approved for the treatment of DED do not target the key driver of the disease (i.e., excessive evaporation).

NOV03 (perfluorohexyloctane; under review with the US Food and Drug Administration) is an emerging therapy for the treatment of DED associated with MGD and has demonstrated statistically significant improvements in both signs and symptoms of DED in randomized controlled trials.

INTRODUCTION

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by disruption of tear film homeostasis [1]. DED is commonly encountered in both ophthalmology and optometry clinical practice, with patient-reported symptoms that include dryness, grittiness, burning, stinging, light sensitivity, pain, visual fatigue, and blurred vision, as well as signs, observed on clinical examination, that include decreased tear fluid, tear film instability, and ocular surface damage [1–3]. In severe cases, corneal lesions and infections can occur [4]. DED can have a marked impact on patients' lives, including decreased physical and mental quality of life and interference with work productivity and other daily activities [5–7].

DED may be broadly classified as aqueous-deficient dry eye (in which lacrimal secretion is reduced), evaporative dry eye (in which evaporation from the tear film is excessive), or a combination of the two [8]. In early stages of DED, there may be excessive tearing due to sensory stimulation of the compensatory secretory tear response from lacrimal glands; however, this sensory response is thought to decrease as DED progresses [8]. It is estimated that aqueous-deficient dry eye by itself occurs in only 10–15% of patients with DED and that the vast majority of DED cases (more than 85%) have an evaporative component [9, 10]. Deficiency in ocular mucins can also play a role in the etiology of DED, although the prevalence of mucin deficiency is, as yet, unclear [11–13]. Meibomian gland dysfunction (MGD) has been identified as the primary cause of evaporative DED [1, 14, 15]. MGD is highly prevalent, with an estimated pooled prevalence of 35.9% in a recent meta-analysis of population-based studies, with rates observed in Asian countries generally being higher than those for other regions (e.g., United States, Australia, Europe) [16]. Among patients with DED, signs of MGD have been observed in 70–90% of cases [9, 17, 18].

DED and MGD are associated with a number of intrinsic (e.g., older age, female sex, Sjögren's syndrome, androgen deficiency, rosacea) and extrinsic (e.g., low-humidity environment, digital device use, contact lens use, topical and systemic medications) risk factors [2, 19, 20]. Although Sjögren's syndrome is strongly associated with aqueous-deficient DED, many patients with Sjögren's syndrome also exhibit signs of MGD, including meibomian gland loss

[21, 22]. Aging is generally associated with increased prevalence of clinical markers for DED and MGD [23]; however, a recent population-based study found that DED was also highly prevalent in the 20–30 year age group [24]. Use of digital displays is associated with abnormal blinking (i.e., reduced blink rate, incomplete eyelid closure), increased evaporation, and ocular surface alterations indicative of MGD, including reduced tear film stability and increased tear osmolarity [25]. Longer duration of exposure to digital displays may contribute to increasing rates of DED in pediatric and young adult populations [25].

In patients with DED due to MGD, disruption of the tear film lipid layer leads to excessive evaporation and associated signs and symptoms [26]. There is a need for safe, convenient, affordable treatments that effectively reduce the signs and symptoms of DED associated with MGD. The aims of this review are first to summarize the pathophysiology of DED associated with MGD, with a focus on the role of the tear film, and then to summarize the research evidence regarding available treatments and provide an overview of emerging therapies.

METHODS

Searches of the MEDLINE database were conducted in April 2022 for English-language articles, with no restriction on date of publication. An overall search was conducted using the terms "dry eye," "meibomian gland," and "tear film." Research evidence on specific treatments for DED associated with MGD was identified by conducting separate searches using the keywords "evaporative dry eye" or "meibomian" in combination with the following search terms for individual treatments: "lid cleanser" or "lid cleaning" or "lid hygiene," "warming," "artificial tears," "tea tree" or "terpinen-4-ol," "omega-3," "manual expression," "microblepharoexfoliation," "thermal pulsation" or "thermodynamic" or "LipiFlow" or "iLux" or "TearCare" or "eyeXpress" or "MiBo ThermoFlo," "intense pulsed light (IPL)" or "photobiomodulation," "probing," "tetracycline" or "doxycycline" or "minocycline," "azithromycin," "cyclosporine," "lifitegrast," "loteprednol," "varenicline," and "diquafosol." The output of each search was reviewed to identify prospective, randomized, placebo- or active-controlled clinical trials in patients with DED associated with MGD. Article bibliographies were reviewed to identify additional papers relevant to the assessment and treatment of DED associated with MGD. Emerging therapies were identified using searches including clinical trial registration databases, conference presentations, and company press releases. Studies of products in phase 2 or phase 3 development for the treatment of DED associated with MGD were selected for inclusion. This review article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

TEAR FILM

The tear film, a thin fluid layer (2–6 μm in thickness) covering the anterior surface of the eye, lubricates the eyes for comfort; protects against forces on the ocular surface during blinking; shields the eyes from environmental challenges such as extremes of temperature and humidity, pollutants, allergens, and infection; and maintains a smooth refractory surface to facilitate clear vision [27–29]. Tear turnover, evaporation, and blinking processes make the tear film a dynamic system [28]. Historically, the tear film has been thought to consist of three layers: an outer lipid layer, a middle aqueous layer, and an inner mucin layer that interacts with the corneal surface [27, 28]. More recently, the aqueous and mucin layers are thought of as a gel gradient and considered together as an aqueous-mucin layer (Fig. 1) [27, 30]. While the lacrimal glands and the conjunctival goblet cells mainly produce the aqueous and the mucin components of the tear film, respectively, the meibomian glands secrete most of the lipids in the tear film lipid layer [27]. The soluble mucins form a gel that

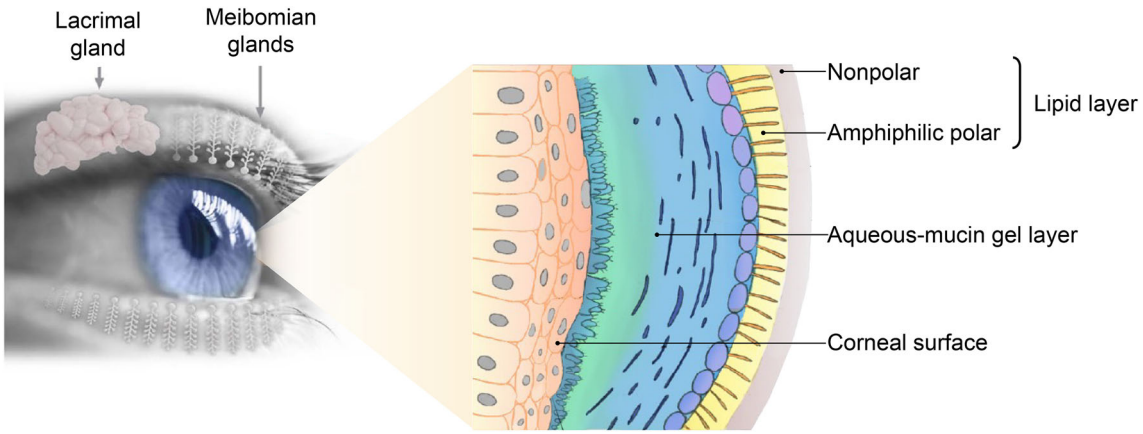

Fig. 1 Model of the precorneal tear film. Figure created with data from Khanna et al. [27]

maintains the wettability of the corneal surface, and the aqueous phase contains electrolytes, proteins, and metabolites that nourish and protect the eye [28, 30]. The lipid layer serves as a barrier against tear film evaporation, stabilizes the tear film by reducing surface tension, and assists with re-spreading the film after blinks [29, 31]. The balance between the lipid and aqueous layers is important for the stability of the tear film, and there is evidence that a compensatory system maintains this tear film homeostasis in response to changes in these components [32, 33].

It is thought that the tear film lipid layer is arranged in a duplex structural organization with nonpolar lipids at the air–tear interface and amphiphilic polar lipids adjacent to the aqueous-mucin layer [29, 30]. Cholesteryl esters, wax esters, and triglycerides (which constitute more than 80% of the total lipids in the tear film) are major components of the outer nonpolar lipid layer, while the amphiphilic polar layer is made up of phospholipids and omega-hydroxyl fatty acids (OAHFAs) [34]. The amphiphilic polar lipids are primarily responsible for the evaporation-resistant properties of the tear film lipid layer, although nonpolar lipids may also play a role [35–38]. In addition, the amphiphilic polar lipids serve as surfactant at the interface of the aqueous phase to allow uniform dispersion of lipid and aqueous layers [37].

MEIBOMIAN GLAND DYSFUNCTION: ROLE IN DRY EYE DISEASE

Meibomian glands, embedded in the upper and lower eyelids, are composed of acinar cells connected to a central duct that opens at the eyelid margin [8, 39]. Meibomian glands express a lipid-rich secretion called meibum that is spread onto the tear film on the ocular surface with each blink [39]. Meibum, the major source of lipids in the tear film, is composed of about 96% nonpolar lipids, mainly wax esters and cholesterol esters, and 4% amphiphilic polar lipids such as OAHFAs and phospholipids [29, 36, 37, 40]. The classes and ratios of lipids in the meibum are very similar to those of the tear film; however, the concentration of OAHFAs exceeds that of phospholipids in meibum, with the ratio being reversed in the tear film [41].

MGD is characterized by a chronic, diffuse abnormality of meibomian gland structures, terminal duct obstruction, and changes in meibum secretion [15]. A self-perpetuating adverse cycle has been postulated for the pathogenesis of MGD, wherein meibomian gland blockage, dropout, or inflammation, along with associated microbial proliferation and/or lipid deficiencies, decreases the flow of meibum from the glands (Fig. 2) [26]. A reduction in meibum secretion and/or a qualitative change in the meibum (e.g., increased viscosity,

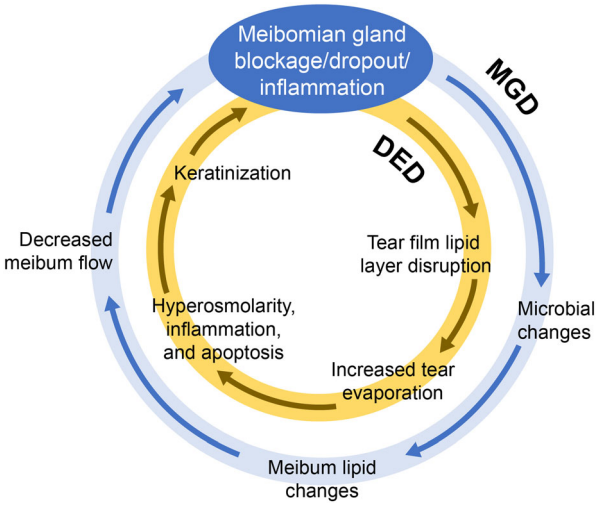

Fig. 2 Importance of MGD in DED pathology. *DED* dry eye disease, *MGD* meibomian gland dysfunction. Adapted with permission from Baudouin et al. [26] via a Creative Commons Attribution NonCommercial 4.0 International (CC BY-NC 4.0) license (https://creativecommons.org/licenses/by-nc/4.0/)

loss of OAHFAs, changes to the lipid profile) further disrupt the tear film lipid layer, thereby increasing the rate of tear film evaporation, prompting loss of ocular homeostasis and contributing to tear film instability [26, 36, 37, 42–46]. This excessive evaporation results in overall thinning of the tear film [47–50], which can lead to tear hyperosmolarity, ocular surface inflammation and cell apoptosis (including loss of goblet cells that secrete mucins), and clinical signs and symptoms of DED [13, 26]. Thus, increased evaporation and tear film instability are important underlying mechanisms of dry eye symptoms in patients with MGD.

Devices to Analyze Meibomian Gland Dysfunction and Tear Film Components

As the associations between DED signs and symptoms are low and inconsistent [3], the ability to accurately quantify ocular surface signs is important for diagnosing DED associated with MGD and assessing DED progression and response to treatment in clinical research and practice. Insights into the pathophysiology of DED associated with MGD can be gained by evaluating both the morphology of the meibomian gland (meibography) and the function of the secreted meibum (tear film breakup time [TFBUT], tear interferometry, tear osmolarity, tear film evaporation rate) [33, 51–53]. Meibography allows for direct visualization of meibomian glands using specialized illumination, thereby revealing any morphological distortions and/or gland loss related to ocular surface diseases [51]. Several commercial non-contact infrared meibography devices (CA-800 Topographer [Topcon Healthcare], LipiView® and LipiScan® [Johnson & Johnson Vision], Systane® iLux2® [Alcon], Keratograph® 5 M [OCULUS, Inc.], Meibox® [Box Medical Solutions Inc.]) are available that allow the capture of high-quality images that reveal meibomian gland abnormalities such as dropout, distortion, shortening, and thickening [51]. The recent development of in vivo laser scanning confocal microscopy and optical coherence tomography imaging can provide further anatomic details of the meibomian gland that may lead to a better understanding of MGD pathogenesis [54, 55].

Tear film instability is one of the important diagnostic criteria for DED diagnosis [53]. In addition to TFBUT, interferometry can also be used to assess tear film stability noninvasively, which allows visualization of the interferometric pattern of the lipid layer as well as quantitative evaluation of tear film lipid layer thickness (LipiView) [56]. The recently developed tear film imager (TFI; AdOM Advanced Optical Technologies, Ltd.) combines spectrometry and imaging, allowing the evaluation of the dynamic properties of the tear film (i.e., both temporal stability and spatial uniformity) [57]. In addition, the TFI can measure tear film inner layers with nanometer resolution. The tear film osmolarity test (TearLab® Osmolarity System [TearLab Corp], LacriPen® [LacriSciences Vision, Inc.]) is frequently used to diagnose DED and has demonstrated high correlation with disease severity [53, 58, 59]. Tear evaporation rate, another indicator of tear film stability, has been assessed in clinical research using a number of different methods (vapor pressure gradient, resistance hygrometry); however, these methods have been challenging to use as a diagnostic tool due to variability in

measurements influenced by the surrounding environment [53]. A handheld dermatology device modified to measure the tear film evaporation rate (Eye-VapoMeter®, Delfin Technologies Ltd.) has been shown to provide repeatable measurements; however, the diagnostic relevance of this device is yet to be established [53, 60].

A two-tiered approach to the diagnosis of DED has been recommended, in which the presence of DED is established first and then differential diagnosis is considered for MGD-related evaporative dry eye, aqueous-deficient dry eye, or a combination of the two [15]. The diagnosis of DED is based on patient-reported symptoms, a slit-lamp examination, and a series of tests that may include corneal fluorescein staining, the Schirmer test, and the measurement of blink rate, lower tear meniscus height, tear osmolarity, matrix metalloproteinase 9, TFBUT, and evaporation rate [15, 61, 62]. If results are suggestive of evaporative DED, the evaluation of meibomian gland function may include the quantification of lid morphology, the quantification of meibum expressibility and quality, and the quantification of meibomian gland dropout [15, 61]. Standardization is important both for diagnosing MGD and for monitoring treatment response [15, 61].

MANAGEMENT OF DRY EYE DISEASE ASSOCIATED WITH MEIBOMIAN GLAND DYSFUNCTION

The primary goal of treatment for DED associated with MGD is to restore the tear film lipid layer and decrease evaporation, thereby reducing ocular signs and symptoms. Management of DED associated with MGD often follows a stepwise approach starting with eyelid hygiene, warm compresses, and ocular lubricants and progressing to the use of office-based therapies and prescription medications when these initial steps fail to provide adequate improvement.

Home-Care Options

Eyelid Hygiene

It is recommended that patients with MGD practice eyelid hygiene twice daily, often in combination with use of warm compresses [63]. In a double-masked, randomized, contralateral eye study of lid hygiene for patients with blepharitis (n = 43), both an eyelid cleanser and diluted baby shampoo significantly reduced the signs and symptoms of DED and MGD, but only the cleanser improved the tear film lipid layer and reduced ocular inflammatory markers [64]. An investigator-masked, randomized trial in patients with MGD (n = 60) found comparable improvements in ocular symptoms with an eyelid cleanser and diluted baby shampoo [65]. To be effective in MGD treatment, long-term maintenance of eyelid hygiene is required [66]; however, many patients are noncompliant with the recommended procedure [66, 67].

MGD can be associated with *Demodex* mite infestation in some patients [68]. A solution of 50% tea tree oil was shown to kill *Demodex* mites during in vitro and in vivo studies [69]; however, there may be tolerability issues with ocular use [70]. Ocular wipes (Cliradex®, Biotissue, Inc.) have been formulated using terpinen-4-ol (the active ingredient of tea tree oil), but superior efficacy versus an unmedicated lid wipe has not been demonstrated in patients with blepharitis [71]. Ocular cleansing products containing hypochlorous acid may have antimicrobial properties [72] but have been evaluated in only one randomized controlled trial of patients with MGD [73].

Warming Eye Masks

The melting point of meibum is significantly higher (by ~4 °C) in patients with MGD than in healthy volunteers without dry eye symptoms, attesting to the qualitative changes in meibomian lipids in MGD [74]. The use of warm compresses is a common initial recommendation in the management of MGD [63], with the goal of heating the meibum sufficiently to increase liquification and flow. A number of products are available for this purpose (e.g., Bruder Moist Heat Eye Compress [Bruder

Healthcare Company], EyeGiene® [Eyedetec Medical], Blepha EyeBag® [previously MGDRx EyeBag, Théa Pharmaceuticals Ltd], Blephasteam® [Théa Pharmaceuticals Ltd]). In a longitudinal study, eyelid-warming treatments (EyeGiene, Blephasteam, or hot towel compress) administered for 12 weeks in a cohort of MGD patients altered the tear fluid lipidome, including significant reductions in lysophospholipids and increases in polyunsaturated fatty acid-containing phospholipids and OAHFAs [75]. These changes in tear lipids were correlated with reduced evaporation rate and improvement in ocular symptoms [75]. Several randomized trials also found that the use of warming devices improved tear film and meibomian gland function parameters in patients with MGD [76–78], although not all studies detected such changes [79]. As with lid hygiene, a key impediment to the effectiveness of home-use warming devices is lack of patient compliance [4].

Ocular Lubricants

Over-the-counter lubricating eye drops are a mainstay first-line therapy for DED and are widely available in multiple aqueous and lipid-based formulations. A randomized trial comparing lipid-containing versus aqueous eye drops in patients with DED (n = 99) found that lipid-containing eye drops provided greater benefits to patients with evaporative DED and that regular use may increase lipid layer grade [80]. Over a 6-month treatment period, symptom improvement preceded changes in the tear film and ocular surface, suggesting that long-term compliance is required to realize MGD-specific benefits [80]. Other randomized studies have demonstrated the superiority of lipid-based eye drops compared with non-lipid-based products for improving ocular signs associated with MGD [81–84]. However, the ocular surface retention time of lubricant eye drops, measured using fluorometry, was found to be limited in studies of patients with DED (22.4–40.8 min, compared with 17.6–22.7 min for saline) [85–87]. Many ocular lubricant products contain preservatives, which can cause inflammation and exacerbate DED, especially with frequent dosing and long-term use [88, 89]. Preservative-free products are available and may increase compliance, but the majority require single-use packaging, which increases cost.

Essential Fatty Acids

Multiple studies showed beneficial outcomes for oral omega-3 fatty acids in patients with DED, as illustrated by a meta-analysis of randomized, placebo-controlled trials reporting that omega-3 oral supplementation was associated with significantly greater improvements in TFBUT and Schirmer test results [90]. Further, supplementation of omega-3 and anti-inflammatory omega-6 (gamma linoleic) fatty acids for 6 months in postmenopausal women with DED improved ocular symptoms (Ocular Surface Disease Index [OSDI] score) and maintained corneal smoothness [91]. However, these findings are called into question by a more recent large, randomized study of patients with DED (n = 535) that compared 12 months of daily supplementation with 3000 mg of nonesterified omega-3 fatty acids to a placebo containing primarily oleic and linoleic acid (olive oil). This study found that, although both groups showed improvement, there were no significant differences in outcomes between the two groups [92]. A cross-sectional study of postmenopausal women (n = 322) found that high dietary intake of omega-3 fatty acids appeared to be protective against MGD [93]. In patients with MGD, several small randomized controlled trials have demonstrated significantly greater improvements with oral omega-3 supplementation versus control treatment in at least some of the signs and symptoms assessed, although findings were inconsistent across studies [94–98]. Larger controlled trials are needed to further evaluate the potential benefits of omega-3 fatty acid supplementation in the management of MGD specifically.

First-line treatment of MGD-related DED may include a combination of eyelid hygiene, home-use eyelid-warming devices, lubricant eye drops, and/or omega-3 supplementation. Combination treatments have been rarely studied in randomized trials [99], and additional, larger studies are needed.

Office-Based Treatments

Office-based therapies are typically used as second-line treatment in patients with inadequate response to self-management approaches. Options include manual expression of meibomian glands, microblepharoexfoliation, thermal pulsation devices (e.g., LipiFlow® Thermal Pulsation System [Johnson & Johnson Services, Inc.], iLux® [Alcon], TearCare® System [Sight Sciences, Inc.], MiBo ThermoFlo [MiBo Medical]), IPL, and intraductal probing of the meibomian glands (Maskin® Probe, Corza Medical).

Manual Expression

Manual expression of meibomian glands is achieved by careful but forceful squeezing of the eyelids to remove the ductal obstruction in the meibomian glands [100]. A wide variety of meibomian gland compression forceps and paddles are available for skilled clinicians to manually express meibomian glands. The efficacy of manual expression of meibomian glands has been assessed in small randomized trials for the treatment of patients with MGD [101, 102]. The findings include greater improvement in ocular symptom score, OSDI, TFBUT, and meibum quality and expressibility with manual expression used as an adjunct to conventional treatment versus conventional treatment alone. Many clinicians prefer to use warming eye masks prior to in-office manual expression for smooth secretion of the impacted meibum.

Microblepharoexfoliation

Microblepharoexfoliation devices remove bacterial biofilm and debris from the eyelids [71]. The BlephEx® (Alcon, Blephex LLC) system, a handheld device, has been evaluated in two small randomized trials as an adjunctive treatment to scrubs for *Demodex* blepharitis; in one study ($n = 81$), one microblepharoexfoliation session, followed by manual scrubs of the eyelids, was more effective in reducing *Demodex* counts and the OSDI score than manual eyelid scrubs alone [103]. However, in the other study ($n = 50$), microblepharoexfoliation with terpinen-4-ol-formulated ocular wipe scrubs or sham scrubs was effective in reducing *Demodex* counts but not in improving the OSDI score or meibomian gland secretion or dropout [71]. A separate study of 50 patients reported effectiveness of microblepharoexfoliation in conjunction with traditional lid hygiene versus lid hygiene alone in significantly resolving chalazia [104].

Thermal Pulsation

Thermal pulsation devices soften and express meibum by delivering a combination of heat and pressure to the eyelids. LipiFlow is the first and most studied in-office thermal device. A 2022 systematic review and meta-analysis of LipiFlow studies included 10 randomized clinical trials with a total of 761 patients [105]. Improvements in symptoms (e.g., OSDI score, Standard Patient Evaluation of Eye Dryness [SPEED] questionnaire score) and some signs (e.g., number of meibomian glands yielding liquid secretion, meibomian gland score) were significantly greater with LipiFlow versus control groups (lid hygiene, placebo therapy, or nontreatment); however, between-group differences were not significant in a more conservative analysis limited to studies using a contralateral eye design (or an average of the two eyes) to compare LipiFlow with lid hygiene [105]. The authors noted that the quality of evidence was generally low and that additional, rigorous, large-scale, randomized controlled trials are needed [105]. Prospective studies suggest that clinical effects of a vectored thermal pulsation treatment may be sustained for up to 1 year [106, 107], but these findings also require confirmation. Warming treatments (either vectored thermal pulsation or at-home devices) may reduce the conjunctival tear evaporation rate [78]; however, a study of patients with MGD ($n = 96$) did not find a significant change in tear osmolarity or lipid layer thickness 2–3 months after vectored thermal pulsation treatment [108].

There are a limited number of randomized studies evaluating other in-office thermal devices. The iLux system was compared with LipiFlow in two randomized, assessor-masked trials in patients with MGD and DED [109, 110]. At follow-up assessments conducted at 4 weeks ($n = 142$) [109] and 12 months ($n = 236$) [110],

significant improvements were observed in signs and symptoms for both treatments, with no significant differences between groups, such that iLux was considered noninferior to LipiFlow [110]. The TearCare procedure was compared with LipiFlow in a randomized, assessor-masked, noninferiority trial in patients with DED associated with MGD (n = 135), which demonstrated the noninferiority of TearCare across treatment outcomes assessed at 1-month follow-up [111]. MiBo Thermoflo was compared with LipiFlow in a preliminary, randomized, assessor-masked study (n = 54 patients [108 eyes]), which found significant improvements in signs and symptoms for both treatments at 1- and 2-month follow-up, with no significant differences between groups [112]. Across studies, in-office thermal treatments appeared to be well tolerated, with no device-related serious adverse events reported [105, 109–112]. As these treatments can be relatively expensive for some patients and are not covered by insurance, cost may be a barrier to access.

Intense Pulsed Light

IPL therapy is more commonly used in the treatment of dermatologic conditions, but several devices that deliver high-intensity visual light across a spectrum of wavelengths (400–1200 nm) have been developed for periocular use, and one (OptiLight, Lumenis Be, Inc.) has been authorized by the US Food and Drug Administration (FDA) for the management of DED signs due to MGD. The potential mechanism of action of IPL in MGD management is poorly understood but may involve warming (although observed eyelid temperature change is minimal [113]), thrombosis of abnormal blood vessels, inhibition of bacterial growth, and/or photomodulation effects on the meibomian glands [114]. It is possible that IPL may alter tear film lipids [115, 116] and tear cytokines [114, 117]. The efficacy of IPL for the treatment of MGD was evaluated in a meta-analysis that included nine studies (539 patients in total) and found that IPL combined with meibomian gland expression was superior to meibomian gland expression alone based on TFBUT and OSDI scores, but not SPEED scores [118]. The efficacy of IPL was correlated with the number of treatments received [118]. Also, the addition of meibomian gland expression appears to improve the efficacy of IPL [118–120]. While IPL appears generally well tolerated, it is contraindicated in patients with darker skin tones (e.g., Fitzpatrick type 5 or 6) due to potential skin depigmentation. Additional, well-designed, randomized controlled trials are needed to provide more definitive information about efficacy and safety. Cost is a consideration in the use of IPL, as it is not covered by insurance and maintenance treatments appear to be required to sustain observed effects.

Intraductal Probing

Intraductal probing of meibomian glands can mechanically open the gland orifices to allow meibum secretion in patients with obstructive MGD. An analysis of meibum before and after probing in patients with refractory obstructive MGD found improvements in lipid levels and meibum viscosity in all cases (n = 6 eyes) [121], and probing was associated with increased meibomian gland tissue area and growth of atrophied meibomian glands in a retrospective analysis of meibography results [122]. The efficacy of probing has been evaluated in small randomized trials of patients with MGD; findings include significantly greater improvement in TFBUT and meibum grade for probing plus 0.1% fluorometholone versus 0.1% fluorometholone alone [123], more rapid onset of improvement in signs and symptoms with probing plus conventional treatment (warm compress, massage, eyelid hygiene, omega-3 supplementation, and oral antibiotics) versus conventional treatment alone [124], and significantly greater improvement in symptoms but not signs (including number of meibomian glands yielding secretions) for probing plus post-procedural sulfacetamide/prednisolone ointment versus sham probing plus lubricating ointment [125]. Additional technologies, such as infrared meibography video, may improve visualization during meibomian gland probing and enhance research protocols [126]. Given the relatively invasive nature of meibomian gland probing relative to other treatments for MGD, analgesia used for this

procedure can be challenging for some patients, and additional clinical studies are needed to evaluate safety and efficacy.

Prescription Medications

Topical and Oral Antibiotics

The extent to which commensal bacteria contribute to the pathogenesis of MGD is unclear, but bacterial enzymes have been shown to alter secreted meibomian lipids [42, 63]. Bacteria colonizing the eyelid margin may also trigger proinflammatory processes [63]. Tetracyclines (e.g., doxycycline, minocycline) and macrolides (e.g., azithromycin) are antibiotics commonly used in the management of MGD. Tetracyclines, particularly at the lower doses possible with lipophilic compounds (i.e., doxycycline, minocycline), and azithromycin appear to have primarily anti-inflammatory effects in the treatment of MGD [63].

Evidence from randomized controlled trials of topical or oral antibiotics is limited. In a small randomized study, 2 weeks of topical azithromycin was shown to significantly improve meibum grade, tear osmolarity, and interferometric tear film pattern relative to preservative-free artificial tears in patients with MGD-associated posterior blepharitis (n = 36) [127]. The effects of topical azithromycin on meibomian gland function were not significantly different from those of oral doxycycline in a randomized, 4-week study of patients with newly diagnosed moderate-to-severe MGD (n = 169) [128], but oral doxycycline provided significantly greater improvement in meibomian gland plugging and corneal staining in a 3-week study in patients with moderate posterior blepharitis (n = 50) [129]. Results of a small study comparing topical versus oral azithromycin in patients with posterior blepharitis (n = 30) suggest that topical treatment may provide better stabilization of the tear film [130].

Randomized studies comparing oral antibiotics in patients with MGD indicate that azithromycin may be preferable to doxycycline [131, 132]. The rate of adverse effects was greater with higher-dose (200 mg twice daily) versus lower-dose (20 mg twice daily) oral doxycycline in a randomized placebo-controlled study of patients with MGD (n = 150), although efficacy was comparable in the doxycycline groups [133]. A randomized trial in patients with MGD (n = 28) found that vectored thermal pulsation was at least as effective as oral doxycycline for improving meibomian gland function and had a preferable tolerability profile [134]. In a randomized study of oral minocycline plus artificial tears versus artificial tears alone in patients with MGD (n = 60), clinical improvement (e.g., TFBUT, meibum quality, corneal fluorescein staining) after 2 months and reductions in some tear cytokine levels were significantly greater in the minocycline group [135]. Overall, study findings indicate that the use of antibiotics may reduce signs and symptoms in patients with MGD that do not respond adequately to over-the-counter or at-home therapies; however, there are safety concerns with repeated use of oral antibiotics. The use of topical compounds may improve tolerability and thereby increase compliance. Additional studies of oral or topical antibiotics, along with expression and/or eyelid treatments, are needed.

US Food and Drug Administration-Approved Treatments for Dry Eye Disease

No prescription pharmacologic products are specifically approved for the treatment of DED associated with MGD. Medications approved by the FDA for the treatment of DED include a cyclosporine 0.05% ophthalmic emulsion [136] and a cyclosporine 0.09% ophthalmic nanomicellar solution [137], which are indicated to increase tear production in patients with dry eye; and lifitegrast ophthalmic solution [138] and varenicline nasal spray [139], which are indicated for the treatment of the signs and symptoms of DED. In addition, a corticosteroid (loteprednol etabonate [LE] ophthalmic suspension 0.25%) is approved for short-term (up to 2 weeks) treatment of signs and symptoms of DED [140]. These medications were approved based on the results of clinical trials in patients diagnosed with DED [141–147], regardless of the presence of MGD. Few randomized controlled studies of these approved products have been conducted in patient populations diagnosed with MGD.

Cyclosporine A is a calcineurin inhibitor that mediates immunomodulatory effects by inhibiting T-cell activation and reducing subsequent cytokine release [148]. In a randomized study of patients with symptomatic MGD ($n = 33$), reductions in meibomian gland blockage and fluorescein staining were significantly greater for cyclosporine ophthalmic emulsion 0.05% compared with preservative-free artificial tears after 3 months of treatment [149]. In a study of patients with symptomatic MGD and TFBUT ≤ 8 s ($n = 70$), increase in TFBUT after 3 months was significantly greater for cyclosporine emulsion 0.05% versus preservative-free carboxymethylcellulose eye drops 0.5%. Meibomian gland expressibility was significantly increased from baseline at month 3 in the cyclosporine group (but was not significantly different from the control group), and corneal staining was not significantly different from baseline in either treatment group [150].

A novel cyclosporine product was formulated as a nanoemulsion in order to improve bioavailability [151]. Treatment with this cyclosporine topical nanoemulsion 0.05% (plus hyaluronic acid 0.15% eye drops four times daily and a warm compress twice daily) was compared to a control group (0.15% hyaluronic acid eye drops six times daily and a warm compress twice daily) in patients with obstructive MGD ($n = 52$); improvements in TFBUT after 3 months were significantly greater in the cyclosporine group, with comparable changes in dry eye symptoms (OSDI score) [151].

Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that blocks the binding of LFA-1 and intercellular adhesion molecule-1 to inhibit downstream inflammatory processes [152]. In a randomized study that compared 6 weeks of treatment with twice-daily lifitegrast versus one thermal pulsation treatment in patients with inflammatory MGD ($n = 50$), improvements in corneal staining and patient-reported eye dryness were significantly better with lifitegrast [153].

Loteprednol etabonate, a corticosteroid used in the treatment of inflammatory ocular conditions, was retrometabolically designed to have a lower risk of side effects (e.g., intraocular pressure) relative to other corticosteroids [154]. In a randomized study comparing topical LE 0.5% plus heat/hygiene (warm compresses and eyelid scrubs) with heat/hygiene alone in patients with moderate to severe MGD ($n = 60$), LE 0.5% significantly decreased certain inflammatory tear cytokines (interleukin-6, interleukin-8, monocyte chemoattractant protein-1) and improved TFBUT, meibum quality, meibum expressibility, and MGD stage [155]. The newest approved drug for the treatment of DED, varenicline nasal spray, stimulates aqueous tear production via activation of the trigeminal parasympathetic pathway [139]. Varenicline nasal spray has not been studied in a population of patients diagnosed with DED associated with MGD, although it is hypothesized that meibomian glands are also stimulated via the trigeminal parasympathetic pathway [156].

Diquafosol ophthalmic solution is widely used in Asian countries such as Japan, China, and South Korea for the treatment of DED but is not an FDA-approved treatment. Diquafosol, a $P2Y_2$ receptor agonist that increases tear fluid and mucin secretions directly onto the ocular surface, has been shown to significantly improve signs and symptoms of DED [157, 158]. Because $P2Y_2$ receptors are expressed in the sebaceous cells and ductal cells of the meibomian gland, it is hypothesized that diquafosol may be effective in the treatment of MGD [157]. However, only one small randomized study ($n = 57$) demonstrated that diquafosol significantly improved tear film lipid layer thickness and tear film stability compared with artificial tears in patients with DED and MGD [159]. These findings will have to be confirmed by larger clinical studies.

Thus far, only small studies have evaluated the use of FDA-approved treatments for DED specific to patient populations with MGD. Findings have not been confirmed in larger, well-designed, controlled trials.

Emerging Pharmacologic Treatments

Pharmacological agents in development for DED target one or more of the primary mechanisms of DED: reduced tear production, mucin deficiency, and MGD [4, 12]. Novel therapies to

Table 1 Topical pharmacologic agents in development for the treatment of dry eye disease associated with meibomian gland dysfunction

Compound	Company	Stage of development	Randomized clinical trials/ references	Active ingredient	Putative MOA
NOV03	Bausch + Lomb	Phase 3	NCT03333057 [160]	Perfluorohexyloctane	Functional meibum replacement or supplement
			NCT04139798 [161]		Inhibits evaporation
			NCT04567329 [162]		
AZR-MD-001	Azura Ophthalmics	Phase 2	NCT04314362 [163]	Selenium sulfide	Keratolytic
			NCT03652051 [164]		
AXR-270	AxeroVision	Phase 2	NCT04469998	Selective glucocorticoid receptor agonist	Anti-inflammatory with unique gene transactivation and transrepression profile
CBT-006	Cloudbreak Therapeutics	Phase 2	NCT04884243	Cyclodextrin	Cholesterol sequestration
HY-02	Hovione Scientia	Phase 2	NCT03888378	Minocycline	Antibiotic

MOA mechanism of action

restore mucin function have only been evaluated in preclinical and early clinical studies to date [12]. Several promising compounds are currently in late-stage (phase 2 or 3) clinical development for the treatment of DED associated with MGD (Table 1) [160–164].

NOV03 is a single-entity ophthalmic drop consisting of perfluorohexyloctane (an anhydrous, semifluorinated alkane). NOV03 has low surface tension, which enables it to spread rapidly across the ocular surface; in addition, it has a refractive index similar to that of water, and thus is expected to cause minimal visual disturbances [165, 166]. This nonaqueous drop does not require preservatives, which allows for the use of multidose containers. The NOV03 drop size is small, at a mean of 11 μL, and thus avoids the customary overflow from the tear lake that accompanies administration of traditional aqueous drops, which generally have a size of ~35–50 μL [165]. An in vitro study that evaluated the evaporation rate of physiological saline alone versus saline with NOV03 layered on top found that NOV03 reduced the evaporation rate of saline by ~80% [167]. It is thought that NOV03, which has amphiphilic properties [168], forms a layer on the tear film surface to prevent evaporation and could be a potential replacement or supplement for the dysfunctional tear film lipid layer in patients with MGD [167]. After ocular administration in rabbits, the residence time of NOV03 in tears was at least 6 h and even longer in the meibomian glands, suggesting that meibomian glands may serve as a depot; systemic exposure was minimal [169].

NOV03 has been evaluated in patients with DED associated with MGD in one phase 2 (SEECASE [NCT03333057]) and two phase 3 (GOBI [NCT04139798], MOJAVE [NCT045673

29]) randomized controlled trials [160–162]. In SEECASE, patients were randomly assigned to receive NOV03 four times daily (n = 114), NOV03 two times daily (n = 111), or a saline (0.9%) control two or four times daily (n = 111) for 8 weeks [160]. Both dose regimens of NOV03 demonstrated significantly greater reduction in the signs (e.g., total corneal fluorescein staining [tCFS]) and symptoms (e.g., eye dryness rated on a visual analog scale [VAS]) of DED versus saline as early as the second week of treatment, with continued improvement observed through week 8 [160]. NOV03 was shown to have a favorable safety and tolerability profile: the incidence of ocular adverse events was similar for the combined NOV03 (18/225, 8.0%) and control (13/111; 11.7%) groups. Additionally, only 4 patients withdrew from the study due to adverse events (3/225 [1.3%] receiving NOV03 and 1/111 [0.9%] in the control group) [160].

GOBI and MOJAVE were similarly designed, 8-week, randomized, double-masked, hypotonic (0.6%) saline-controlled trials in patients with DED associated with MGD (GOBI: NOV03, n = 303; control, n = 294; MOJAVE: NOV03, n = 311; control, n = 309) [161, 162]. In both studies, NOV03 demonstrated statistically significant reductions in both the primary sign (change from baseline in tCFS at week 8) and the primary symptom (change in VAS dryness score at week 8) relative to the control group [161, 162]. Similarly, NOV03 was superior to the hypotonic saline control based on all four key secondary endpoints (change from baseline in tCFS at week 2, VAS dryness score at week 2, central CFS at week 8, and VAS burning/stinging score at week 8) in both studies [161, 162]. The incidence of ocular adverse events was similar between treatment groups (8.3% for NOV03 and 5.1% for control in GOBI; 9.6% and 9.7%, respectively, in MOJAVE) [161, 162]. There were no serious ocular adverse events in either study; 1 patient in the NOV03 group and 2 patients in the control group (all in GOBI) discontinued study treatment due to an adverse event [161, 162].

AZR-MD-001 is an ophthalmic ointment containing selenium sulfide, which has demonstrated keratolytic [170] and lipogenic [171] activity in preclinical studies. Hyperkeratinization may play a role in meibomian duct obstruction in MGD [172]. In a small randomized study (NCT04314362), patients with MGD (n = 22) were randomly assigned to receive AZR-MD-001 1% or vehicle control ointment administered to the lower eyelid margin [163]. Evaluation at 2 weeks showed that AZR-MD-001 significantly decreased the tear evaporation rate and increased TFBUT and the number of meibomian glands yielding liquid secretion relative to the vehicle control group; however, there were no between-group differences observed in lipid layer thickness or DED symptoms (OSDI score) [163].

An ongoing phase 2, randomized, double-masked, vehicle-controlled study (NCT03652051) is evaluating three doses of AZR-MD-001 in the treatment of patients with MGD and evaporative DED. In a preplanned interim analysis that included 32 patients (AZR 0.1%, n = 9; AZR 0.5%, n = 7; AZR 1.0%, n = 7; vehicle control, n = 9), reduction in symptoms (OSDI score) and signs (meibomian gland score, meibomian glands yielding liquid secretion) at 3 months was significantly greater for AZR-MD-001 1.0% compared with the control group; the rate of adverse events with AZR-MD-001 appeared dose-related [164].

There are three additional compounds in phase 2 development for the management of MGD. AXR-270 is an ophthalmic selective glucocorticoid receptor agonist formulated as a cream, for which positive findings were reported in a phase 2 trial for the treatment of patients with posterior blepharitis associated with MGD (NCT04469998). Phase 3 trials comparing AXR-270 0.2% cream with vehicle are planned. CBT-006 is able to sequester cholesterol and is intended to improve meibum quality by dissolving lipids at meibomian gland orifices. A recently completed phase 2, randomized, double-masked, vehicle-controlled trial of CBT-006 (NCT04884243) enrolled approximately 90 patients with MGD; topline results were not available as of this writing. HY-02, a proprietary topical minocycline ointment to treat blepharitis-driven ocular surface disease, has been evaluated in a phase 2, vehicle-controlled study of patients with inflamed MGD (NCT03888378).

CONCLUSIONS

DED is a highly prevalent ocular condition that is characterized by alterations in the homeostasis of the tear film and the ocular surface. Most cases of DED have an evaporative component, and MGD is the leading cause of evaporative DED. Despite a wide range of available treatments for DED, there are a limited number of adequately powered, rigorously designed clinical trials evaluating efficacy and safety in patients with DED associated with MGD. Further evaluation of existing therapies and the development of pharmacologic agents targeted to the management of DED associated with MGD will improve therapeutic options and allow for a more individualized approach to treatment for patients with this ophthalmic condition.

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