White Paper

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Thermal Pulsation Systems and Topical Immunomodulators for Managing Meibomian Gland Dysfunction

Lyndon Jones, PhD, FCAHS, FCOptom, FAAO[1]

William Ngo, OD, PhD, FAAO[2]

Thao Yeh, OD, PhD, MPH, FAAO[3]

1. Professor / Director / University Research Chair, Centre for Ocular Research & Education, School of Optometry & Vision Science, University of Waterloo, Ontario, Canada

2. Head of Biosciences, Centre for Ocular Research & Education, School of Optometry & Vision Science, University of Waterloo, Ontario, Canada

3. Alcon Medical Affairs, North America, Fort Worth, TX

Key Messages

- Meibomian gland dysfunction (MGD) is an abnormality of the meibomian glands that results from duct obstruction and irregular meibum quality/quantity, leading to symptoms of dry eye. As MGD increases in severity, the more unstable the tear lipid layer becomes, resulting in increased tear evaporation, tear hyperosmolarity, and ocular surface inflammation.
- Clinicians have many options for managing MGD but must weigh many factors in developing their treatment plan, including comorbidities, efficacy and safety, time-to-onset, adverse side effects, patient psychology (potential for compliance/dropout), and convenience.
- Topical immunomodulators are indicated for and effective at reducing ocular surface inflammation. They have been shown to be effective in improving meibomian gland function within 4-12 weeks post-treatment.
- The mainstay of MGD therapy is a combination of eyelid heating and expression. The iLux® device is a thermal pulsation system that offers simultaneous heating and expression therapy and has demonstrated efficacy in relieving symptoms and improving gland function by as early as 1 week post-treatment.

Introduction

Meibomian gland dysfunction (MGD) is a complex and multi-layered disease that is often overlooked and challenging to manage. MGD has been defined as an abnormality of the meibomian glands characterized by duct obstruction and irregular meibum quality/quantity.[1] MGD causes evaporative dry eye, the leading cause of dry eye disease (DED), and results in decreased availability or change in composition of meibum on the ocular surface.[2,3] This leads to reduced protection of the underlying aqueous in the tear film, potentially leading to increased aqueous evaporation, tear hyperosmolarity, and ocular surface inflammation.[4]

Eyelid therapy (heating and expression) is the mainstay of MGD treatment, melting and facilitating outflow of meibum from the meibomian gland orifices and into the tear film.[5] Other MGD therapy options include lipid-based artificial tears, antibiotics (topical and oral), topical steroids, topical immunomodulators and omega-3 supplements, all of which target different manifestations of MGD.[5] It has been suggested that age-related meibomian gland changes in addition to the ocular surface inflammatory process result in hyposecretion of lipids from non-obstructed glands.[6,7] Since MGD and inflammation frequently appear together, several studies have explored the potential benefit of topical immunomodulators alone in improving gland function in MGD patients.[8-10]

To help bring clarity to the role of eyelid therapy and topical immunomodulators, we review the literature on the diagnosis and treatment of MGD below. We also discuss the mechanisms of action and efficacy of eyelid therapy and topical immunomodulators for improving clinical signs of MGD, and present other factors that can influence treatment selection from both eye care professionals and patients.

MGD Treatment Algorithms and Consensus Expert Opinion

Over the last decade, as researchers and clinicians have learned more about the pathophysiology of the disease, committees of experts have developed diagnosis and treatment algorithms to help clinicians better manage their patients. Below is a high-level summary of the recommendations set forth by the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), the Cornea, External Disease, and Refractive Society (CEDARS) Dysfunctional Tear Syndrome panel, and the American Society of Cataract and Refractive Surgery (ASCRS) Cornea Clinical Committee.[11-13]

Diagnosing MGD

According to the Report of the Diagnosis Subcommittee from the International Workshop on Meibomian Gland Dysfunction, the key clinical signs of MGD include changes in lid morphology, altered meibomian gland secretion, and meibomian gland dropout.[14]

Lid Morphology

Two key morphological features that characterize MGD are meibomian gland orifice (1) plugging and (2) positioning with respect to the mucocutaneous junction (MCJ).[14] Meibomian gland orifice plugging is considered a pathognomonic clinical sign of MGD and appears as elevations above the surface level of the lid due to obstruction and extrusion of a mixture of meibum and keratinized cell debris.[14] The other characteristic feature of MGD is the posterior positioning of meibomian gland orifices relative to the MCJ into the mucosa, eventually leading to orifice stenosis or obliteration and periductal fibrosis with progression.[14] Other clinical signs of MGD include rounding, notching, dimpling, telangiectasia, increased vascularity of the posterior lid margin, epithelial ridging between gland orifices, loss of orifice architecture, cystoid changes in the gland, formation of concretions within the acini and, possibly, the formation of chalazia.[14]

Meibomian Gland Secretion

Application of pressure to the eyelid margin releases meibomian gland secretions onto the lid margin. Meibum is presumed to be clear in normal patients and, as the disease progresses, becomes composed of altered lipids and keratinized debris that result in cloudy, opaque, inspissated, and eventually, toothpaste-like secretions.[14]

Meibomian Gland Dropout

Meibomian gland dropout refers to the visible loss of acinar tissue, which can be viewed on transillumination of everted eyelids or on infrared images (meibography). Appearance of visible glands suggest the presence of meibum in the ducts and a potential benefit from eyelid heating and expression.[14] The meibum are believed to reflect the infrared light, and when faded or missing, the glands are thought to contain little or no meibum.[14]

Treating MGD

Relieving chronic stasis and/or obstruction of meibomian glands is essential to successful treatment of MGD and improvement in DED symptoms.[12] Below we discuss indication and mechanisms of action for eyelid therapy, including thermal pulsation systems, and topical immunomodulators.

Heating and Massage – The Mainstay

Traditional at-home eyelid heating therapy may consist of various methods (e.g., warm towel, do-it-yourself pads, commercial masks) and regimens (e.g. frequency and duration).[5] Technological advancements in recent years offer more standardized in-office eyelid heating treatments (e.g., TearCare® (Sight Sciences, Inc., Menlo Park, CA), MiBo Thermoflo® (MiBo Medical Group, Dallas, TX)) and combination heating and expression therapy (e.g., iLux® (Alcon, Fort Worth, TX) and LipiFlow® (Johnson & Johnson Vision, Santa Ana, CA). Heat-only treatments require post-treatment gland expression to evacuate the glands, while thermal pulsation systems apply heat at a pre-specified temperature and duration to the eyelids, while simultaneously allowing the application of pressure to facilitate the outflow of meibum from the ducts.

Mechanism of Action of Thermal Pulsation Systems: The iLux® system (Figure 1) applies LED light-generated heat to the eyelids at 38-42°C (most meibum melt above 38°C) for up to 90 seconds. Typically, after 40 seconds of heating to melt the meibum, the eyelids are then compressed to facilitate the expression of meibum from the glands. The clearance of meibum from the orifices is visualized through the lens on the device. Additional heat and compression can immediately be applied for any glands observed that may need additional treatment. Another instrument, the LipiFlow®, applies heat at 42.5°C to the inner eyelids and automatically applies pulsed pressure for expression of the glands. Unlike the iLux®, gland expression cannot be visualized with the LipiFlow® during the treatment phase.

Figure 1: iLux® Thermal Pulsation System.

Topical Immunomodulators

MGD can lead to tear film instability, tear hyperosmolarity, and ocular surface inflammation. Topical immunomodulators can be used to control ocular surface inflammation associated with DED. The most commonly prescribed topical immunomodulators are cyclosporine A ophthalmic drops (CsA; Restasis® (0.05%) and Cequa (0.09%)) and lifitegrast ophthalmic solution (5%; Xiidra®) for use twice daily. CsA is an immunosuppressant indicated for *"...increasing tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation", and lifitegrast is indicated for "...the treatment of the signs and symptoms of dry eye disease."*[15,16]

Mechanism of Action: The DED immunopathophysiology involves an initial activation phase (release of acute phase cytokines) and an early amplification phase (early MMP-9 activity and dendritic cell activation).[17] This is followed by a T-cell differentiation and recruitment phase (a naive T-cell becomes an activated T-cell), a T-cell response phase with four parts: (1) adhesion, (2) migration, (3) activation and cytokine release, (4) and a chronic, self-perpetuating damage phase that trips the cycle of aberrant activation all over again in a chronic, downward spiral.[17] The pharmacologic strategies employed help to combat this cycle. CsA is a calcineurin inhibitor and acts by blocking T cell infiltration, activation, and the subsequent release of inflammatory cytokines (Figure 2).[18] Lifitegrast is a small molecule integrin antagonist that blocks the binding of the lymphocyte function-associated antigen 1 (LFA-1), which is an integrin expressed on T cells, with its native ligand, intercellular adhesion molecule 1 (ICAM-1) to disrupt the T cell mediated inflammatory cycle (Figure 3).[19] The exact mechanisms of action of both CsA and lifitegrast in DED are not known.

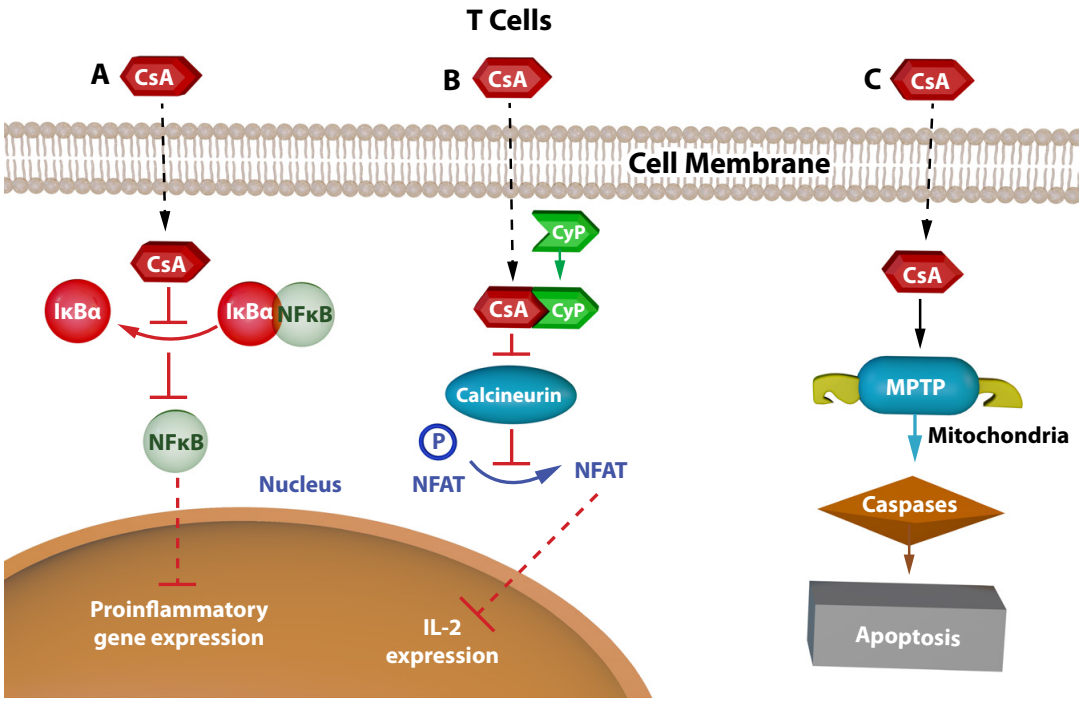

Figure 2: Mechanism of action of cyclosporine A. Prevents release of inflammatory cytokines through (A) inhibition of nuclear factor κB (NFκB), (B) inhibiting dephosphorylation of nuclear factor of activated T cells, and (C) inducing T cell apoptosis. [Adapted from Jerkins GW, et al. Clin Ophth 2019][18]

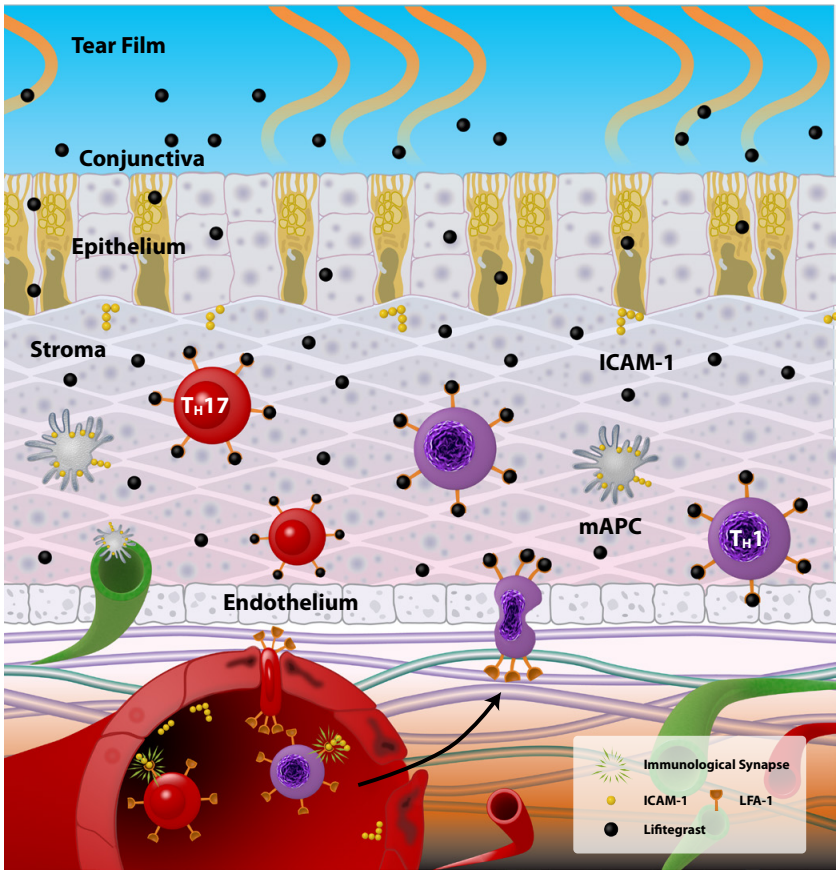

Figure 3: Mechanism of action of lifitegrast. Lifitegrast blocks the binding of ICAM-1 to LFA-1 to interrupt the T cell mediated inflammatory cycle. [Adapted from Perez VL, et al., The Ocular Surface 2016][19]

Efficacy of Eyelid Therapy and Topical Immunomodulators in Improving Signs and Symptoms of MGD

Eyelid Heating and Expression

Warm Compresses: In a one-month interventional study of moderate-to-severe MGD patients treated with a combination of eyelid scrubs, warm towel compresses, and gland expression, there were significant improvements in meibum quality and quantity, corneal and conjunctival staining, as well as a reduction in severity of dry eye symptoms ($p<0.001$).[20] While clinical trials have demonstrated effectiveness of traditional warm compresses, the lack of standardization of method (e.g., warm towel, do-it-yourself pads, commercial masks), regimen (e.g., frequency, duration), and follow-up schedule, as well as lack of compliance are all obstacles for achieving consistent success with at-home treatments in real-world populations.[5,12]

Thermal Pulsation Systems: In-office therapies offer structured and standardized care dictated by the technologies, manufacturer instructions, and clinical practices for pre- and post-treatment management. Thermal pulsation systems provide the added benefit of simultaneous heating and expression of the meibomian glands. The efficacy of LipiFlow® in treating signs and symptoms of MGD have been evaluated in two randomized clinical trials where LipiFlow® was compared to a warm compress regimen (control), and both studies reported significant improvements from baseline in the number of expressible meibomian glands and dryness symptoms score (Ocular Surface Disease Index (OSDI)).[21,22] When compared to the control group 3 months after treatment, the LipiFlow® group presented with similar number of expressible glands in one study and a higher mean change in number of expressible glands from baseline in the other study.[21,22] The iLux® (Alcon, Fort Worth, TX) is a newer thermal pulsation system that has demonstrated effectiveness in improving signs and symptoms of MGD. In a study comparing the efficacy of iLux® to LipiFlow® in 142 MGD patients, no significant difference was found between treatments, but both treatments yielded significant improvements in meibum quality, tear film stability, and symptoms at 2 and 4 weeks after a single treatment.[23] Furthermore, a single-arm study of 30 MGD patients with iLux® demonstrated significant improvements in meibum quality, tear film stability, and symptoms at 1-week and 1-month after treatment when compared to baseline.[24]

Treatment Considerations: In-office thermal pulsation systems offer the benefit of combined heating and expression therapy using standardized procedures and processes, but the procedures can be temporarily uncomfortable for some patients. Because the thermal pulsation systems require the insertion of a protective cover or heating pad behind the eyelids and provide a higher amount of heat and pressure to the eyelids compared to the traditional at-home methods, some patients have reported minor discomfort during treatment.[23] Side effects include conjunctival hyperemia and petechial hemorrhages on the conjunctiva and eyelids.[23,25] For patient comfort, a topical anesthetic should be instilled in the eye to be treated, following prescribing information supplied with the anesthetic.

Topical Immunomodulators

Cyclosporine A (CsA): Many studies have evaluated the efficacy of topical CsA in treating DED, but very few studies have evaluated its effectiveness in improving clinical signs of MGD. In a 3-month randomized, controlled trial of 33 symptomatic MGD patients, participants were randomized to receive treatment (CsA) or placebo (Refresh Plus® preservative-free artificial tears; Allergan, Inc.). Those in the CsA group showed a significant decrease in the number of meibomian gland inclusions after 2 ($p=0.02$) and 3 ($p=0.001$) months of treatment and in both lid margin vascular injection ($p=0.001$) and tarsal telangiectasia ($p=0.03$) after 3 months of treatment.[8] No significant differences between groups were found after 1 month for any study parameter, and no significant differences in dryness symptoms were found at any time point.[8] In another 3-month randomized, controlled trial of 70 symptomatic MGD patients, participants were randomized to receive treatment (CsA) or

control (Cellufresh®; Allergan, Inc.). Significant improvements from baseline in meibomian gland expressibility were reported after 1 (p=0.012) and 3 (p=0.048) months of CsA treatment and a difference in expressibility was found between study groups after 1 month (p=0.031).[9] However, means and variances were not reported, so it is unclear if these differences are clinically significant. Improvements in lid margin inflammation and tarsal conjunctival injection from baseline were reported for both study groups but were not significantly different between groups.[9]

Lifitegrast: As with CsA, many studies have evaluated the efficacy of lifitegrast ophthalmic solution 5% in treating inflammatory signs and symptoms of DED, but only three studies have reported on its efficacy in improving signs of MGD. In one retrospective study at Duke University Hospital, 121 lifitegrast patients were seen between September 2016 and March 2017 and had a follow-up visit 88.1 days, on average. After treatment initiation, there was no significant change observed in MGD score (0-3 scale) among all patients, those with moderate to severe DED, or those who used CsA concurrently.[26] In a phase IV, prospective, single-arm, open-label, 12-week study of 30 DED patients, there was no significant change in meibomian gland expressibility after treatment with lifitegrast for responders (≥ 5 mOsm/L change in tear osmolarity from baseline) or nonresponders (<5 mOsm/L change).[27] In a randomized, single-masked trial of 50 MGD patients, efficacy of lifitegrast was compared to LipiFlow® in reducing symptoms and various clinical signs, including lid redness, gland patency, and meibum quality score.[10] The study found that although symptoms of ocular discomfort (co-primary endpoint) improved from baseline for both study groups at days 21 and 42, there were no between-group differences at any time in the study.[10] There was also no difference in lipid layer thickness change at day 21 (co-primary endpoint) between study groups.[10] Finally, changes from baseline in eyelid redness and corneal staining at day 42 was greater in the lifitegrast group, but there was no significant difference between groups for all other clinical parameters.[10]

Treatment Considerations: An analysis of a prescription claim database suggests that over 60% of DED patients discontinue treatment within 12 months of initiation, with most discontinuations occurring at 3 months for CsA and 1 month for lifitegrast.[28] A subsequent survey of physicians and patients on their satisfaction with these topical anti-inflammatory medications for DED suggested that both doctors and patients reported overall satisfaction with the effectiveness of the medications.[29,30] However, physicians had a low-level of satisfaction with the time-to-onset and fewer than half considered either drug to be effective in managing symptoms.[30] Patients complained of dissatisfaction with time-to-onset (11% CsA, 29% lifitegrast) and ineffective relief of DED symptoms (31% CsA, 22% lifitegrast).[29] According to the authors, a "substantial" proportion of patients reported side effects to be common, including burning, itching, altered taste (dysgeusia; only for lifitegrast), blurred vision, and discharge.[29]

Conclusions

MGD is often overlooked and can be challenging to manage, but a routine and thorough eyelid examination evaluating lid morphology, gland secretion, and gland structure can identify MGD patients earlier in the disease process. Relieving chronic stasis and obstruction of meibomian glands is essential to successful treatment of MGD and improvement in DED symptoms. Heating and expression to melt meibum and clear the ducts, respectively, are the mainstay of MGD treatment. In-office thermal pulsation systems offer structured and standardized care dictated by the technologies, manufacturer instructions, and clinical practices for pre- and post-treatment management. The iLux® is a handheld thermal pulsation system that has demonstrated efficacy for relieving symptoms and improving gland function by as early as 1 week post-treatment.

Important Product Information

INDICATIONS: The iLUX® Device is indicated for the application of localized heat and pressure therapy in adult patients with chronic disease of the eyelids, including Meibomian Gland Dysfunction (MGD), also known as evaporative dry eye.

CONTRAINDICATIONS: Do NOT use the iLUX® Device in patients with the following conditions: Patients whose pupils have been pharmaceutically dilated; patients who have undergone ocular surgery within prior 12 months; patients with ocular injury or trauma, chemical burns, or limbal stem cell deficiency (within prior 3 months); patients with active ocular herpes zoster or simplex of eye or eyelid or a history of these within prior 3 months; patients with cicatricial lid margin disease; patients with active ocular infection, active ocular inflammation or history of chronic, recurrent ocular inflammation within prior 3 months; patients with an ocular surface abnormality that may compromise corneal integrity; patients with lid surface abnormalities that affect lid function in either eye; patients with aphakia; or patients with permanent makeup or tattoos on their eyelids.

WARNINGS/PRECAUTIONS: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner. The Disposable may not fit all eyes, such as eyes with small palpebral fornices. Use of the iLUX® device is NOT recommended in patients with the following conditions: moderate to severe allergic, vernal or giant papillary conjunctivitis; severe eyelid inflammation; systemic disease conditions that cause dry eye; in patients who are taking medications known to cause dryness; or patients with punctal plug.

POTENTIAL ADVERSE REACTIONS: Potential adverse effects may include eyelid/eye pain requiring discontinuation of the treatment procedure, eyelid irritation or inflammation, temporary reddening of the skin, ocular surface irritation or inflammation (e.g., corneal abrasion, conjunctive edema or conjunctival injection (hyperemia)), and ocular symptoms (e.g., burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light).

Attention: Please refer to the User Manual for a complete list of contraindications, instructions for use, warnings and precautions for the iLUX® Device.

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